SUMMARY

Scientific programme

Thursday May 26th afternoon

4.00 p.m. **Welcome and Opening**
M. Di Luca (Milano), F. Cattabeni (Milano)

4.30 p.m. **Plenary lecture**
Chairmen: U. Senin (Perugia), E. Grossi (Milano)

"PKC Isozymes: Molecular Convergence for the Regulation of Memory and Early Alzheimer's Disease Pathophysiology"
D. Alkon (Washington)

6.00 p.m. **Round table**
"Translational research: from bench to bedside and from bedside to bench"
In collaborazione con AIP
Chairmen: M. Trabucchi (Roma), P.L. Scapicchio (Roma)
Intervengono:
E. Garaci
(Presidente, Istituto Superiore di Sanità - Roma)
C. Caltagirone
(Università Tor Vergata e IRCCS Fondazione S.Lucia, Roma)
F. Cattabeni
(Dipartimento di Scienze Farmacologiche, Milano)
N. Ferrara
(Università degli studi di Napoli)
E. Pirfo
(Direttore Dipartimento di Salute mentale Giulio Maccacaro, asl3 Torino)

Friday May 27th morning

9.30 –12.30 a.m. **Symposium**
"Challenging Aß"
Chairmen: M. Di Luca (Milano), M. Memo (Brescia)

9.30 –10.00 a.m. **"Functions of the Fe65/APP complex in Caenorhabditis elegans"**
N. Zambrano (Napoli)

10.00 –10.30 a.m. **"Studies on the interaction of transthyretin and Aß"**
M. J. Saraiva (Porto)

10.30 –11.00 a.m. **"Alzheimer's Disease and Immunotherapy"**
B. Solomon (Tel Aviv)

11.30 –12.00 a.m. **"Role of Aß in Angiogenesis"**
M. Ziche (Siena)

12.00 –12.30 a.m. **Discussion**

Friday May 27th afternoon

2.30 –5.00 p.m. **Symposium**
"Preclinical Phases of Dementia"
Chairmen: C. Caltagirone (Roma), M. Musicco (Milano)

2.30 –3.00 p.m. **"Se il MCI amnesico si normalizza: sopravvalutazione iniziale o sottovalutazione successiva?"**
R. Perri (Roma)
"Quando il MCI non si trasforma in demenza: stabilità apparente o reale?"
L. Serra (Roma)

3.00 –3.20 p.m. **"Nuove prospettive patogenetiche negli stadi precoci di neurodegenerazione: ruolo dei processi infiammatori"**
P. Bossu'(Roma)

3.20 –3.40 p.m. **"Il deterioramento cognitivo su base vascolare e i suoi rapporti con la demenza di Alzheimer"**
M. Silvestrini (Roma)

3.40 –4.00 p.m. **"MCI: trattare e non trattare?"**
A. Cherubini (Perugia)

4.00 –4.20 p.m. **"MCI: Le prospettive farmacologiche"**
C. Mariani (Milano)

4.20 –5.00 p.m **Discussion**

5.30 –7.30 p.m. **Poster Session**
Chair of the evaluation committee
A. Padovani (Brescia), A. Bianchetti (Brescia)
10 prizes will be selected

9.00 p.m. **Gala Dinner and Ceremony of prizes for young neuroscientists**

Saturday May 28th morning

9.00 –11.20 a.m. **Symposium**
"Le demenze frontotemporali"
Chairmen: P. Mecocci (Perugia), M. Franceschi (Castellanza)

9.00 –9.30 a.m. **"Frontotemporal lobar degeneration: neuropathology and genetics"**
M. Tolnay (Basel)

9.30 –9.50 a.m. **"Genetic aspects of frontotemporal dementia"**
M. Riemenschneider (Münich)

10.20 –10.40 a.m. **"Inquadramento clinico delle demenze frontotemporali"**
A. Padovani (Brescia)

10.40 –11.00 a.m. **"Aspetti neuropsicologici e comportamentali delle demenze frontotemporali"**
G. Koch (Roma)

11.00 –11.20 a.m. **"Il trattamento dei sintomi comportamentali delle demenze frontotemporali"**
A. Bianchetti (Brescia)

11.30 –12.45 a.m. **Attività dei Gruppi di ricerca**

12.45 a.m. **Closing remarks**

Abstract list by topics

TOPIC A

Biology of Amiloyd, tau, inflammation, and other neurodegenerative mechanisms

TOPIC B

Epidemiology and risk factors

TOPIC C

Genetics and genetic testing

TOPIC D

Diagnosis, biomakers, neuroimaging and clinical course of AD and related disorders

TOPIC E

Therapeutic strategies

TOPIC F

Neuro Informatics

TOPIC G

Evidence-based patient management and social behavioural research / Neuropsychology

Poster
(in alphabetical order, poster's number is reported on left top page)

50

DISTURBO DEL LINGUAGGIO AD INSORGENZA SUB-ACUTA IN FORMA ENCEFALITICA VIRALE: CORRELATI ANATOMO-FUNZIONALI

***Erica Altamura*[1], *Pietro Annovazzi*[2], *Bruno Colombo*[2], *Vittorio Martinelli*[2], *Andrea Falini*[3], *Giancarlo Comi*[2], *Monica Falautano*[1].**

[1] Unità Funzionale di Psicologia, [2] Dipartimento di Neurologia e Neurofisiologia Clinica,
[3] Unità Operativa di Nuroradiologia, Università Vita-Salute Istituto Scientifico H. San Raffaele, Milano

Il Sig. A., di 50 anni e con un'elevata istruzione, giunge alla nostra osservazione per un disturbo del linguaggio, esordito subdolamente tre settimane prima.
Al primo esame neurologico obiettivo il paziente presenta afasia espressiva qualificata da anomie, circonlocuzioni e sporadiche parafrasie fonetiche. Ad una osservazione qualitativa emerge una corretta denominazione di oggetti di uso comune ed una mantenuta capacità di ripetizione, mentre la comprensione orale appare lievemente compromessa, come la capacità di lettura.
Non è evidente aprassia. L'impaccio ai movimenti fini delle dita della mano destra è lieve, in assenza di ulteriori deficit di forza. I riflessi osteo-tendinei sono presenti e simmetrici.
Si rileva una dismetria, più evidente a destra, alle prove indice/naso e, in misura minore, tallone/ginocchio. Non vi sono apparenti deficit delle sensibilità.
Durante la settimana di degenza si osserva una progressiva ingravescenza del quadro cognitivo.
L'indagine neuropsicologica, effettuata in due sessioni, mediante una batteria di test tarati e standardizzati su un campione normale di riferimento, rileva una seria compromissione delle funzioni linguistiche che configura un quadro di afasia globale, un marcato rallentamento psicomotorio, deficit di controllo attentivo, di categorizzazione logica, aprassia ideomotoria e buccofacciale. Tuttavia, il riscontro testistico evidenzia il mantenimento dell'efficienza della memoria visiva a lungo termine, della capacità di stabilire relazioni logiche mediante l'attivazione del pensiero inferenziale, delle competenze di prassia ideativa, costruttiva e di gnosia spaziale.
L'osservazione qualitativa rileva, inoltre, una mantenuta consapevolezza relativa al sé ed un corretto orientamento spazio-temporale.
Le indagini clinico-strumentali svolte presso il nostro Dipartimento comprendono una RM encefalo indicativa di un'alterazione focale corticale fronto-temporale sinistra, ripetuti EEG progressivamente più rallentati, più compromessi a sinistra, con anomalie epilettiformi in regione fronto-temporale sinistra ed un esame del liquor, risultato nella norma, anche per ricerche di DNA virali. Sono in corso studi per la valutazione della proteina prionica, arbovirus, enterovirus e coxakievirus. E' stata prevista, inoltre, una biopsia cerebrale.

24

GENETIC CORRELATES OF BEHAVIOURAL ENDOPHENOTYPES IN ALZHEIMER DISEASE: ROLE OF COMT, 5-HTTLPR AND APOE POLYMORPHISMS

***Silvana Archetti*[1]**, *Barbara Borroni*[2], *Mario Grassi*[3], *Michela Cossandi*[1], *Simone Franzoni*[4], *Carlo Caltagirone*[5], *Monica Di Luca*[6], *Luigi Caimi*[1], *Alessandro Padovani*[2].

[1] Department of Laboratory Diagnostics III Laboratorio Analisi, Brescia [2] Centre of Ageing Brain and Dementia, Department of Neurology, University of Brescia [3] Department of Health Sciences, Section of Medical Statistics and Epidemiology, University of Pavia [4]Alzheimer Centre, Palazzolo S/O, Brescia [5] Department of Neurology, IRCCS S. Lucia, University Tor Vergata, Roma [6] Centre of Excellence for Neurodegenerative Disorders and Department of Pharmacological Sciences, University of Milano.

To date, several studies have been conducted to understand the genetic correlates of Alzheimer Disease (AD)-related behavioural and psychological symptoms in dementia (BPSD). However, it has been suggested that targeting BPSD individually is too narrow of an approach if one wants to accurately define all of the associated risk factors, given that BPSD rarely occur in isolation.
Up to now, no work on genetic polymorphisms related to behavioural endophenotypes has been proposed.
The aim of the present study was to evaluate the relationship between behavioural endophenotypes in AD and genetic variations in dopamine- or serotonin-related genes, such as Cathecol-O-Methyltransferase (COMT) or 5-HTT gene linked promoter region (5-HTTLPR), and ApoE.
Two hundred thirty-two AD patients underwent clinical and neuropsychological examination, a behavioural and psychiatric disturbances evaluation, and ApoE, COMT, 5-HTTLRP genotyping; 66.4% of patients showed more than one behavioural symptom. By factor analysis and latent variables models, taking into account possible confounds (i.e. demographic characteristics, comorbidities, concomitant pharmacological treatments and disease severity) 4 endophenotypes were identified. These endophenotypes have been named “psychosis”, “moods”, “apathy”, “frontal”. In the adjusted model for covariates, COMT and 5-HTTLRP genetic variations correlated with “frontal” and “psychosis” endophenotypes, whilst ApoE genotype did not rule out a contribution in the development of non-cognitive cluster symptomatology in the disease.
These findings suggest the possibility of identifying distinct phenotypes on a genetic basis among AD patients and suggest that BPSD clustering into endophenotypes might provide a new strategy for guiding future research on this issue.

51

PERSONALITY CHANGES IN THE ALZHEIMER'S DISEASE: THE CASE OF APATHY

***Alessandra Barbieri*[1]**, *Erica Altamura* [1], *Monica Veronesi*[1], *Agnese Fiorino* [1], *Monica Falautano* [1], *Raffaella Mossini*[2], *Eliana Schiatti*[2], *Massimo Franceschi*[3] , *Giancarlo Comi*[2], *Giuseppe Magnani*[2]

[1] Functional Unit of Psychology,[2] Department of Neurology and Clinical Neurophisiology, Università Vita-Salute Scientific Institute Hospital San Raffaele, Milan, [3] Neurology Department, Casa di Cura Santa Maria, Castellanza.

Background: The Greek Stoic philosopher coined the term " Apathy" to refer to the condition of being free from emotions and passions. In the recent neuropsychiatric literature, apathy has been defined as the absence or lack of feeling, emotion or motivation; among neurological disorders apathy was reported to have high frequency in patients with Alzheimer's Disease and related conditions. The Alzheimer's Disease is a neurodegenerative disorder with cognitive and behavioural expressions. The cognitive domains become more serious during the course of the illness, on the contrary the behavioural and psychological symptoms of dementia (BPSD) appear to fluctuate and seem more heterogeneous. The BPSD may be present in the very early phase of the disease, and in some case before the first diagnosis, or in the late phase of the illness. The apathy has a high prevalence in the Alzheimer's disease and may be associated with severe impairments in activities of daily living and cognitive deficits.
The aim of this study is to evaluate the changes in personality with the Neuropsychiatric Inventory (NPI) across degrees and phases of the disease in consecutive AD outpatients, with a particular focus on the apathy.
Methods: The sample is made up of twenty patients (7 males, mean ages 72 $\pm$ 5) with neuropsychological assessment and clinical diagnosis of probable Alzheimer's disease according to DSM-IV and NINCDS-ADRDA criteria, referring to the Memory Impairment Center of Hospital San Raffaele. Exclusion criteria included a Mini Mental State Examination (MMSE) lower than 15, indicating that our cohort of patients were not in a late stage of dementia .
For this study the global cognitive impairment was defined by the MMSE, the functional status was measured by caregiver- informant rating scales commonly used to assess simplex and complex self-maintenance skills : Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) and the BPSD were assessed by the NPI. All 20 consecutive patients were assessed at three different phase of the illness: 2 months before the first diagnosis, at the moment of the first diagnosis and a year later.
Result: Apathy and depression were the symptoms most frequently reported by the caregivers. A clear trend towards increasing frequency with the severity of disease was found for apathy. A major effect of the duration of the disease was found in the probability of developing hallucinations and aberrant motor activity.
Conclusion: Changes in frontally-mediated behaviour are common in early and mild stages of cognitive impairment. These changes deserve a better understanding in order to improve the allocation and health resources and the quality of life of the patients with dementia.

52

NEGLECT IN ALZHEIMER DISEASE: A GENUINE SELECTIVE IMPAIRMENT OF SPATIAL EXPLORATION?

***M. Barone*#°,** *S. Basilico#°, G. Zanardi#°, A. Toraldo#°, M. Gandola#°, G. Bottini#°*

Dipartimento di Psicologia, Università degli Studi di Pavia
°Laboratorio di Neuropsicologia, Dipartimento di Scienze Neurologiche,Ospedale Niguarda, Milano

Introduction: unilateral spatial neglect (N) is a cognitive disorder mostly associated to right hemispheric lesion which denotes the impaired ability to respond to stimuli presented in the hemispace contralateral to the cerebral lesion (Kerkhoff, 2001). It has only occasionally been studied in patients with Alzheimer Disease (AD) (Venneri A., 1998; Freedman L., 1991). Contrasting evidence has been found in literature concerning both the frequency of N in AD and the side (right versus left) involved. (Venneri A., 1998; Bartolomeo P., 1998).
Aim of the study: to investigate the presence of personal and peripersonal N in AD by the means of tasks specifically apt to detect this neuropsychological condition.
Methods: *Subjects:* 60 patients with probable AD according to NINCDS-ADRDA criteria (McKhann et al., 1984) and 13 normal subjects (control group) matched for age and education.
Neuropsychological assessment: Memory, language, attention, frontal functions were explored. The evaluation also included the Albert and Diller tests, the horizontal line bisection and tasks of drawing and copying. A standard clinical neurological examination was also performed. The association of anosognosia and personal N was investigated with standardized interviews (Bisiach E., 1986). Data have been treated by cross tab analysis and with one-way ANOVA.
Results: 32 subjects (53.3%) showed N at least on one test. 17 subjects showed N for the right hemispace, 14 for the left hemispace, only one patient manifested bilateral N. A significant difference ($p=0.039$) has been found between AD patients and normal subjects on the line bisection test. This task is a sensible although not specific test to reveal N as for example does not distinguish a genuine N from a metric deficit which may be dissociated by the presence of N (Toraldo, 2004). Only a single case (AB) manifested a severe N, involving personal and peripersonal space.
Discussion: Compared to other studies we adopted specific tests to explore N in AD. We found that N / AD is a quite rare association. We propose that N should be properly investigated in AD in order to differentiate genuine selective deficit of personal and peripersonal space (such as in case AB) from a more general impairment of visuo-perceptive integration.

References

Bartolomeo P., Della Barba G.: Right-side neglect in Alzheimer disease. 1998 Neurology 51:1207-1209.
Bisiach, E., Vallar, G., Perani, D., Papagno, C. and Berti, A. 1986: Unawareness of disease following lesions of the right hemisphere: Anosognosia for hemiplegia and anosognosia for hemianopia. *Neuropsychologia*, 24, 471–82.
Freedman L., Dexter L. E.: Visuospatial Ability in cortical dementia. 1991 Journal of clinical and Experimental Neuropsychology 5: 677-690.
Kerkhoff G., Spatial hemineglect in humans. Progress in neurobiology 2001; 63: 1-27
McKhann G, D. D., Folstein M, et al. (1984). Clinical diagnosis of Alzheimer's disease: report of NINCSDS-ADRDA work group under the auspices of Department of Health and Human Services task force on Alzheimer's disease. Neurology, 34, 939-944.
Toraldo A., Mclntosh, RD, Dijkerman HC, Milner AD. A revised method for analysing neglect using the landmark task. 2004 Cortex, 40(3):415-31

Venneri A., Pentore R., Unilateral spatial neglect in the late stage of Alzheimer disease. 1998 Cortex, 34: 734-752

1

AN IN VITRO MODEL OF MITOCHONDRIA DECAY AND LOSS OF IRON METABOLISM: EFFECTS UPON CELLULAR AGING AND NEURODEGENERATION

***Luisa Benerini Gatta**, Maura Poli, Rosanna Verardi,Dario Finazzi*

Section of Chemistry, Faculty of Medicine, University of Brescia, Italy.

Background: The causes that underlie the neurodegeneration accompanying Alzheimer's disease (AD) are still unknown. Alteration of Amyloid Precursor Protein (APP) metabolism and beta-amyloid (A-beta) accumulation surely play an important role, but there is more and more evidence that other factors concur in determining the pathogenesis of the disease. It is well known that aging of the brain and AD neurodegeneration share some common features, such as the decline in mitochondrial function associated to decreased complex IV levels and activity, hypometabolism, oxidative stress and perturbation of iron homeostasis. We are attempting to establish an *in vitro* model of mitochondrial dysfunction associated to loss of iron metabolism in order to study their possible effects upon APP processing and cellular susceptibility to A-beta and other toxic stimuli. Our model is based upon the exposure of cells to ferrochelatase (FECH) siRNA. Ferrochelatase catalyzes the terminal step in the heme biosynthetic pathway, the insertion of ferrous iron into protoporphyrin IX. Ames' group (Atamna et al. 2002) has shown that blocking heme biosynthesis by NMP decreases mitochondrial complex IV, activates nitric oxide synthase, corrupts iron and zinc homeostasis and possibly alters APP metabolism. Interestingly heme synthesis declines with age and can be related to the age-associated loss of iron homeostasis. We intend to further pursue those finding in a more specific cellular model obtained by siRNA mediated FECH mRNA down-regulation. Preliminary results have been generated in HEK293 cells stably transfected with APP695wt or with APP695sw and transiently challenged with FECH siRNA. The same set of experiments will be performed in SH-SY5Y cells differentiated by exposure to retinoic acid. Together with the transient, "acute" model, we are also developing a "chronic" one, by producing cells with a stable/tetracycline inducible expression of the FECH siRNA.
Methods and results: Quantification of Ferrochelatase expression: We measured Ferrochelatase mRNA expression by real-time RT-PCR. When we transiently exposed HEK293 cells to FECH siRNA, we observed a specific and marked (about 90%) reduction of FECH expression level at 48, 72 and 96 h post transfection. We are producing a polyclonal antibody to FECH to monitor changes at protein levels. Assessment of mitochondrial function: We analysed the levels of COXII protein, a subunit of complex IV in the electron transport chain, by western blotting. COXII was selectively reduced in cells lacking FECH mRNA, thus suggesting that the assembly of cytochrome c oxidase was compromised. Mitochondrial function was also indirectly assessed by measuring variation in mitochondrial transmembrane potential by loading cells with the DiOC6 or JC-1 fluorophores and flow cytometry and microscopy analysis.. After treatment with FECH siRNA we observed a progressive decrease in mitochondrial transmembrane potential. We are measuring the production of ROS by exposing cells to H2–DCF-DA. *Our data show that FECH down-regulation induces mitochondrial shortfalls and we are now investigating the effects upon APP and iron matabolism and upon cell survival.* Iron metabolism: Cellular iron content and ferritin iron uptake will be analysed by coupled plasma spectrometry and 55Fe incorporation, respectively. Amyloid metabolism: HEK293 cells treated with FECH siRNA showed an altered electrophoretic migration pattern of APP, with the appearance of higher molecular mass species (200 kDa). The effects on APP processing and beta amyloid production are under investigation. Cell viability and apoptosis: we are investigating the effects of FECH down-regulation upon cellular viability; preliminary results show an increase of apoptotic cells upon exposure to FECH siRNA.

Conclusions: We believe that investigating the function of mitochondria and the mechanisms regulating iron metabolism in our cellular model can help in understanding the basic pathogenic processes of Alzheimer's Disease.

53

ANXIETY IN DEMENTIA: BODY AND EMOTION

***Miriam Benin*[1]**, *Monica Grobberio*[1], *Vanessa Raimondi*[1,2], *Federica Lucchelli*[3], *Paola Rizzi*[1], *Isabella Marchetti*[1], *Roberto Sterzi*[3]

[1]Laboratory of Neuropsychology and clinical Psychology – Department of Neurology, S.Anna Hospital (Como); [2]Department of Neurology, Bussolengo Hospital – USL 22 (Verona); [3]Department of Neurology, S.Anna Hospital (Como).

Background: According to cognitive-behavioural therapy (Beck, 1974; Wells, 1992), anxiety might be experienced as either somatic complaint (e.g., tachycardia) or emotional disturbance (e.g., I'm afraid, I'm in danger). Previous studies showed that anxiety is a common symptom in the elderly and in demented patients. Nevertheless anxiety assessment doesn't include an exhaustive analysis of this complex symptom range, underestimating somatic complains. This might lead to misdiagnose anxiety as a depressive symptom. In literature, in fact, anxiety in dementia is often assessed only by the specific subscale of the Neuropsychiatric Inventory (NPI) or by other questionnaires, such as Hamilton Anxiety Scale, which rely mainly on information provided not only by patient himself, but also by relatives and caregivers. Very little is known about how patients themselves experience anxiety. The aim of this study was to assess whether the use of a self reporting anxiety scale, such as Zung Self-rating Anxiety Scale (SAS), would allow identification of anxiety clusters in different dementias.
Methods: The SAS was administered to 23 Alzheimer's Disease patients (AD), 17 patients with Vascular Dementia (VaD), 15 patients with Depressive Pseudodementia (DPD), 13 patients with Fronto-temporal Dementia (FTD) and 17 non-anxious controls (N). They were all matched for age, education and severity of dementia (as measured by MMSE score). In all demented subjects cognitive impairment was sufficiently mild to allow self compilation of the scale. The SAS global score was divided into two subscores, corresponding to somatic symptoms (subS) and emotional symptoms (subE). Non parametric analysis of data was performed by within group Wilcoxon Signed Ranks Test and between groups by Mann-Whitney U-test.
Result: Severity of anxiety, measured as SAS global score, was comparable in all demented groups. Between groups analysis showed that AD and DPD patients performed significantly worse than VaD in subE ($p<0.042$); no significant difference emerged in subS. Within group analysis did not bring about any significant difference in N, AD, DPD, FTD; subS was significantly worse than subE in VaD ($p=0.002$).
Conclusion: Our data suggest that the somatic profile might represent a specific anxiety-subset across dementias, even when it's associated to more evident depressive symptoms. Nevertheless AD and DPD groups appear more sensitive to the emotional cluster. This might be explained by a different level of awareness: AD may be more alerted by their early cognitive impairment, a circumstance which triggers about their current condition, as in DPD. On the contrary subE but not subS might discriminate VaD patients among other dementias looking less troubled, maybe because of associated apathy. This might suggest a global impairment in perception of the specific emotional cluster rather than a greater influence of the somatic subset.

54

IN SEARCH OF THE EPISODIC BUFFER. A VOXEL-BASED MORPHOMETRY STUDY IN PATIENTS WITH DEMENTIA

M. Berlingeri*°, *S Basilico°#, G. Silani*°, G. Zanardi#°, R. Sterzi^, G. Bottini#°, E. Paulesu**

* Dipartimento di Psicologia, Università degli Studi di Milano-Bicocca, Milano
# Dipartimento di Psicologia, Università degli Studi di Pavia
°Laboratorio di Neuropsicologia, Ospedale Niguarda Cà Granda, Milano
^ U.O. Neurologia, Ospedale S.Anna, Como

Introduction: The working memory model (WM) proposed by Baddeley and Hitch (1974) is a multicomponent model of short-term memory. The basic model assumed three separable components, a central executive, and two material specific short-term memory slave systems: the phonological loop and the visuo-spatial sketch pad. The model successfully accounts for a number of phenomena that previous unitary models were unable to accommodate. However, the original WM model was also underspecified in a number of ways. For example it is not clarified whether its limited capacity arises from temporal constraints or stimulus complexity constraints (Carpenter, 2000), or what is the working memory component related to the ability to chunk connected information into smaller units (Vallar, 1999). In order to overcome these and other limits, Baddeley (2000) has recently proposed the existence of a new component of WM, the episodic buffer, i.e. a limited-capacity temporary storage system controlled by the central executive and connected with the episodic long term memory. To support this hypothesis Baddeley (2002) investigated AD patients and found that they were distinguishable in global AD showing an impaired performance at both immediate and delayed recall of a short story and selective AD who manifested a significantly more impaired performance at the delayed recall (Baddeley A, 2002). At the moment there are few anatomical evidences of this buffer from fMRI study on normal and young subjects (Prabhakaran V, 2000).
Aim of the study: - To explore the cause of low performance on immediate serial recall in AD patients
- To investigate the neuropathological correlate of the impaired episodic buffer in AD
Methods: Subjects: we studied 23 AD patients in agreement with NINCDS-ARDA criteria (McKhann G, 1984) divided in two groups (global AD; selective AD) on the basis of their performance on immediate short story recall test (Spinnler, 1987) and 22 normal subjects. - global AD (G-AD): patients whose difference "immediate recall-delayed recall" was between ± 1,5 SD compared to controls; - selective AD (S-AD): patients whose difference "immediate recall-delayed recall" was more than 1,5 SD compared to controls. Normal subjects and patients were studied with an extensive neuropsychological battery and had an MRI for the voxel-based-morphometry. MRI data were processed on the optimised VBM protocol as described by Good et al. (2001).
Statistical analysis: Neuropsychological data were treated by a one way ANOVA with Post-Hoc test. Anatomical data were analysed by Matlab 6.5 (MatWorks, Natick, MA, USA) and Statistical Parametric Mapping Software (SPM 2b, Wellcome Department of Imaging Neuroscience, London, UK, 2000).
Results: Behavioural results: no significant differences have been found between the two AD groups on neuropsychological tests. VBM: morphological data showed a different pattern of neural impairment between the two AD groups. The "selective AD" group presents a reduction of grey matter mainly in the right frontal and parietal lobes, whereas "global AD" patients present smaller regional volumes in the left fronto-temporal areas. A bilateral reduction of the grey matter density in the thalamus and in the hippocampus (BA 27) has been also found.

Discussion: Our results do not demonstrate any significant difference between the two groups at the neuropsychological evaluation. Executive functions and linguistic skills in particular do not differ across AD patients. Thus, the only significant cognitive difference is shown at the verbal memory level (immediate-delayed recall dissociation). Conversely the revealed anatomical dissociation fits with PET/fMRI data, suggesting the existence of an hemispheric asymmetry between encoding and retrieval processing as proposed by the HERA model (Tulving, 1994). In particular global AD patients seem to have an impairment of the encoding skills explaining their heavily impaired performance on immediate and delayed recall. On the other hand, the evidence of a selective atrophy of the cerebral areas monitoring retrieval processes explains the specific deficit mainly on the delayed recall in the other AD patients ("selective AD").

References:

Baddeley, A., Wilson B. (2002). Prose recall and amnesia: implications for the structure of working memory. Neuropsychologia, 40, 1737-1743.

Baddeley, A. D. (2000). The episodic buffer: a new component of working memory. Trends in Cognitive Science, vol.4, No.11.

Baddeley, A. D MA, Reichle ED. (2000). Working memory and executive function: evidence from neuroimaging. Current Opinion in Neurobiology, 10, 195-199.

Good, C. D., Johnsrude, I. S., Ashburner, J., Henson., Hitch G. (1974). Working memory. 47-89.

Carpenter, P., Just , R. N., Friston, K. J., & Frackowiak, R. S. (2001). A voxel-based morphometric study of ageing in 465 normal adult human brains. Neuroimage, 14(1 Pt 1), 21-36.

McKhann G, D. D., Folstein M, et al. (1984). Clinical diagnosis of Alzheimer's disease: report of NINCSDS-ADRDA work group under the auspices of Department of Health and Human Services task force on Alzheimer's disease. Neurology, 34, 939-944.

Prabhakaran V., N. K., Zhao Z., Gabrieli JDE. (2000). Integration of diverse information in working memory within the frontal lobe. Nature America Inc., 3(1), 85-90.

Spinnler, H., Tognoni G. (1987). Standardizzazione e taratura italiana di test neuropsicologici (Vol. Supplementum N.8). Milano: Masson Italia Periodici.

Tulving, E., Kapur S., Craick FIM., Moscovitch M., Houle S. (1994). Hemisperic encoding/retrieval asimmetry in episodic memory: Positron emission tomography findings. Proc. Natl. Acad. Sci. USA, 91, 2016-2020.

Vallar, G., Papagno, C. (1999). Neuropsychological impairments of verbal short term memory. In Handbook of memory disorders (second ed.): John Wiley and co.

25

PRESENILIN 2 MUTATION IN A LATE-ONSET ALZHEIMER'S DISEASE CASE: DOES A TRUE "SPORADIC" AD EXIST?

Livia Bernardi, *Carmine Tomaino, Maria Anfossi, A. Leotta [1], Maura Gallo, Silvana Geracitano, Angela Costanzo, Raffaele Maletta, Sabrina AM Curcio, Rosanna Colao, Gianfranco Puccio, Francesca Frangipane, Maria Mirabelli and Amalia C. Bruni*

Regional Neurogenetic Centre AS6 Lamezia Terme (CZ) Italy,
[1] Dept Phatology ASL 6 Lamezia.

Background: Mutations in the presenilin (PS1, PS2) and in the amyloid precurson protein (APP) genes cause autosomal dominant familial Alzheimer disease (FAD). PS1 mutations account for several FAD cases while the contribution of APP and PS2 is quite rare. Until now, mutations of the three genes have also been reported in few cases of early onset AD sporadic forms, while in sporadic late onset AD have never been described, thus showing that other genetic and environmental factors could be involved in the etiology.
Objective: To report a PS2 mutation in a sporadic late onset AD case.
Case report: Patient manifested his mild memory deficits, spatial disorientation and personality changes at 81. Two years later the family asked for a neurological evaluation due to the worsening of the illness. Patient was depressed, apathetic and showed memory disturbances (MMSE 22.1). Neurological examination was normal. CT scan revealed a mid temporal atrophy without any vascular lesions. During disease course a marked psychomotory agitation, delusions and language deficits were observed. Diagnosis of AD was performed. Familial history reported no cases of dementia but the father and one sister were referred as having a "Parkinson's disease", both deceased at 85 without any cognitive decline. Although it had no matter to the case, the family asked for a complete molecular genetic screening of the three FAD genes. Apolipoprotein E was also genotyped. Surprisingly, sequence analysis identified a PS2 Ser130Leu mutation in exon 5. The mutation was present in his son (aged 50) and in his 57 year old daughter, both healthy; it was absent in his wife, in his 59 year old daughter and in the only available proband's brother (aged 81).
Conclusions: We report a late onset sporadic AD patient aged 81 with Ser130Leu mutation in PS2 gene. The same mutation had already been described in a FAD autosomal dominant family whose index case developed AD at 65. Several considerations can be taken: (I) The first comment is related to the onset: it is confirmed the variability of age at onset for PS2 mutations (range 45-88 years). (II) PS2 mutations frequency could be underestimated; indeed, one can argue that in late onset AD the dominant transmission can be interrupted by the occurrence of death before the onset. (III) About the heritability of the mutation: we cannot determine its possible origin because parents were deceased, moreover we do not know whether and when the two sibs carrying the mutation (aged 50 and 57) will manifest an affected phenotype. It cannot be ruled out neither a de novo nor an inherited mutation; in this case, it remains unknown if the patient received it by his mother (referred as deceased at a very elderly age) or by the Parkinsonian father who transmitted also to his Parkinsonian daughter. If we assume the paternal origin of the mutation, this hypothesis points out that overlapping genetic factors could be involved in the disease progression, sharing possible common pathogenetic pathways. (V) Screening for Presenilin 2 mutations should be beneficial in characterizing a subgroup of genetically late-onset Alzheimer's disease in apparently sporadic patients.

33

VOXEL-BASED MORPHOMETRY AND 3D DIFFUSION TENSOR IMAGING STUDY IN PROGRESSIVE SUPRANUCLEAR PALSY

Borroni B. [a], *Brambati S.* [b], *Agosti C.* [a], *Broli M.* [a], *Alonso R.* [b], *Bellelli G.* [c], *Alberici A.* [a], *Gipponi S.* [a], *Gasparotti R.* [d], *Di Luca M.* [e], *Perani D.* [b], *Padovani A.* [a]

(a) Department of Medical Sciences, Neurology, University of Brescia, (b) Vita-Salute University, San Raffaele Institute, Milan, "Ancella della Carità" Hospital, Cremona, (d) Neuroradiology, University of Brescia, (e) Centre of Excellence for Neurodegenerative Disorders, University of Milan, Italy

Background: A comprehensive characterisation of grey and white matter changes in Progressive Supranuclear Palsy (PSP), the second most common extrapyramidal syndrome after Parkinson Disease, is still not available.
Objective: To evaluate grey and white matter changes in mild PSP patients by Voxel-Based Morphometry (VBM) and Diffusion Tensor Imaging (DTI), respectively.
Methods: Fourteen mild PSP patients and 14 healthy controls entered the study, and performed a clinical and neuropsychological evaluation according with a standardised assessment. Each subject underwent a structural Magnetic Resonance Imaging (MRI) study. Pre-processing analysis of MRI data were performed according to optimized VBM protocol, and fractional anisotropy was determined.
Results: By VBM, Significant clusters of reduced grey matter in PSP patients compared to controls were found at symmetrical loci in premotor cortex, frontal operculum, hippocampus and hippocampal gyrus ($P<0.005$, corrected for FDR). In regard to subcortical brain regions, pulvinar, dorsomedial and anterior nuclei of the thalamus, as well as cullicula were affected bilaterally. The white matter comparison did not show any significant difference between PSP patients and controls ($P<0.005$, corrected for FDR).
The inverse testing both for grey and white matter comparisons did not display voxels above threshold ($P<0.005$, corrected for FDR).
By DTI, a decrease in fractional anisotropy was found bilaterally anterior corpus callosum, left arcuate fascicolus, posterior thalamic radiations, in superior longitudinal fasciculus, and internal capsula, likely involving cortico-bulbar tract in PSP patients compared to controls ($P<0.005$, corrected for FDR).
Conclusions: The combination of the two technologies, i.e. VBM and DTI, firstly provided evidences of specific neural network associated to the disease onset. This approach opens a completely new insights to gain direct and in vivo information non brain tissue loss in PSP patients and may guide future research in this field.

2

NEW PATHOGENIC PERSPECTIVES IN THE EARLY NEURODEGENERATIVE PROCESS: ROLE OF INFLAMMATION

***Paola Bossù*[1], *Gianfranco Spalletta*[1,2], *Antonio Ciaramella*[1], *Maria Luisa Moro*[1], *Alberto Trequattrini*[3] *and Carlo Caltagirone*[1,2]**

[1]IRCCS Fondazione Santa Lucia, Roma; [2]Dipartimento di Neuroscienze, Università di Roma "Tor Vergata"; [3]ASL Città di Castello, Dipartimento di Salute Mentale, Perugia.

Background: Amyloid beta deposits are suggested to play a central role in driving Alzheimer's disease (AD) pathogenesis. Moreover, immune and inflammatory responses associated to amyloid burden seem to contribute to AD neurodegeneration. In the brains of afflicted individuals an amyloid plaque-associated chronic inflammation has been described, mainly due to microglia and astrocyte activation occurring in the early stage of the disease. Among the mediators of such persistent innate immune response, cytokines play a key role. Furthermore, recent findings indicate that the triggering of amyloid beta-specific immune response can result in a reduction of AD symptoms in vaccinated patients, probably due to the immune-mediated lowering of amyloid beta burden. Dendritic cells (DCs) are main players in orchestrating the immune response and pro-inflammatory cytokines are able to regulate them. In this context, great attention should be paid to key mechanisms controlling both brain inflammation and specific immune response against amyloid beta. The present study has been focused on interleukin (IL) -18, a member of the IL-1 cytokine superfamily and an important mediator of both innate and acquired immune response. IL-18 gene polymorphisms in AD patients and *in vitro* IL-18 activity on amyloid triggered DC have been analysed in the light of an IL-18 possible involvement in AD pathogenesis.
Methods: The distribution of two polymorphisms in IL-18 gene promoter (-137 G/C and -607 C/A) has been analysed in 308 late-onset Alzheimer's disease (LOAD) patients with respect to 138 control non-demented patients by amplification refractory mutation system (ARMS) PCR technique. Human myeloid DCs obtained from *in vitro* differentiation of donor's peripheral blood mononuclear cells (PBMC) in the presence of beta amyloid peptides, have been cultured with different pro-inflammatory cytokines (TNF alpha, IL-1 beta and IL-18). Phenotype and functional activity (antigen uptake and cytokine production) of mature DCs have been performed by flow cytometry analysis.
Results: The analysis of IL-18 promoter in AD patients and age-matched control subjects revealed differences in allele, genotype or haplotype distribution in tested patients when compared to frequencies found in control group. In particular, the -137 G/C polymorphism appeared in Hardy-Weinberg disequilibrium only as far as patient group, contrarily from controls. Moreover, the CC genotype at position -607 of the IL-18 gene was present with significant higher frequency in AD patients (36,4%) than in control subjects (26,8%). The logistic regression analysis evidenced that carriers of CC genotype were at increased risk of developing AD (OR=2.27; 95% C.I.=1.24-4.15; p=0.0076). Finally, the haplotypes resulted strongly associated to AD, being CA (the combination of the two less frequent alleles of both polymorphisms), significantly more present in patients than in controls (p = 0.007). In addition, data from *in vitro* analysis indicate that IL-18 appears to play a role in modulating the survival of amyloid beta-treated DCs.
Conclusions: These results indicate that IL-18 polymorphisms could be included among the genetic risk factors that determine AD susceptibility. Moreover, the likely altered IL-18 pathway in AD patients who have prevalent IL-18 gene variant, can modulate the activation of the immune system triggered by the 1-42 amyloid beta peptide. Therefore, the present data strongly support the hypothesis that a combined dysregulation of adaptive and innate immune mechanisms could be

implied in the pathophysiology of AD and that IL-18 can be a good candidate as an early component of the disease pathogenic process.

34

VOXEL BASED MORPHOMETRY MAY CONTRIBUTE TO PREDICT THE EVOLUTION FROM MILD COGNITIVE IMPAIRMENT TO ALZHEIMER DISEASE

***Marco Bozzali*[1]**, *Andrea Falini*[3], *Mara Cercignani*[2], *Massimo Franceschi*[5], *Raffaella Mossini*[4], *Monica Falautano*[4], *Giuseppe Scotti*[3], *Massimo Filippi*[4,5], *Giancarlo Comi*[4] *and Giuseppe Magnani*[4]

[1]Wellcome Department of Imaging Neuroscience, and [2]NMR Research Unit, Institute of Neurology, University College of London, London; [3]Department of Neuroradiology, [4]Department of Neurology and [5]Neuroimaging Research Unit, Scientific Institute and University Ospedale San Raffaele, Milan, Italy; [6]Department of Neurology, Multimedica-SantaMaria, Castellanza, Italy.

Background: Mild cognitive impairment (MCI) is associated with an increased risk for developing Alzheimer's disease (AD)[1]. Voxel based morphometry (VBM) is a spatially-specific and unbiased method of analysis of MR images reflecting the regional grey matter (GM) density at a voxel scale[2]. Aim of this study was to assess whether different patterns of regional GM loss could be associated to a different risk for evolving to AD over 2 years after diagnosis of MCI.
Methods: Twenty-one patients who met the diagnostic criteria for MCI took part in the study and underwent T1-weighted volumetric acquisition and 6 mm axial T2-weighted and fast fluid attenuated inversion recovery MR scans. Twenty-two patients diagnosed with probable AD and 24 healthy volunteers were also enrolled and studied as control groups. Subjects with radiological signs of concomitant cerebral vascular lesions on T2-wheighted and FLAIR scans were excluded from the analysis. T1 volumes from each subject were post-processed according to the optimized VBM protocol[2]. All the included patients with MCI have been clinically followed up for two years, and classified in two groups (converter to AD and non converter to AD). First, GM maps from converter MCI were compared with those from non converter MCI and AD patients. Next, GM maps from converter MCI, non converter MCI and AD patients were separately compared with those from healthy subjects.
Result: No areas of significantly different GM density were found when comparing directly converter and non converter MCI patients each other and with AD patients. When comparing AD patients with healthy subjects, widespread areas of reduced GM density were found predominantly in the insula, and in frontal, parietal and temporal lobes ($p_{corrected}<0.05$). When comparing converter and non converter MCI patients with healthy subjects, no areas of statistically significant abnormalities survived after correcting for multiple comparisons. However, before correction for multiple comparisons ($p_{uncorrected}<0.001$) converter MCI patients showed more widespread areas of reduced GM density compared to non converter (see Fig 1), with a pattern of distribution similar to AD patients.

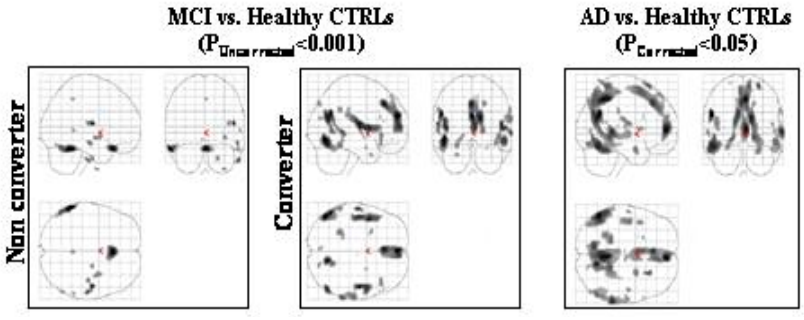


Fig 1. Areas of reduced GM density are superimposed on the SPM glass brain. Changes are more widespread in converter MCI patients vs healthy controls (centre) than in non converter MCI vs healthy controls (left). The pattern of distribution is also more similar to that observed when comparing AD patients with healthy controls

Conclusion: This study suggests that patterns of distribution of GM density reductions could predict a more rapid rate of evolution to AD in patients with MCI. If confirmed, the use of VBM in this kind of patients could increase our prognostic confidence and better address our therapeutic approach.

References

1. Petersen RC, et al., Arch Neurol 2001; 58:1985-92.
2. Good CD, et al. NeuroImage 2001; 14: 21-36.

18

EXTRAPIRAMIDAL SYNDROME ASSOCIATED WITH COGNITIVE DECLINE: ROLE OF PRIMITIVE REFLEXES EVALUATION

Marcella Broli*, *Chiara Costanzi*, Chiara Agosti, Stefano Gipponi, Nicola Gilberti, Barbara Borroni, Alessandro Padovani*

Centro per le Malattie Neurdegenerative e dell'Invecchiamento Cerebrale, Università degli Studi di Brescia, Brescia, Italy.

Background: The literature on Primitive Reflexes (PRs) in parkinsonian disorders has focused on the importance to determine their clinical value. However, only few studies on the prevalence of PRs in Parkinson's disease (PD), in Progressive Supranuclear Palsy (PSP) and in Corticobasal Degeneration are available.
Objective: To evaluate the incidence and the clinical significance of PRs such as glabellar, palmomental, snout and grasp reflexes in patients with extrapiramidal disorder diagnosis. To this purpose, we included also mild AD patients and age-matched control subjects for comparison.
Methods: 67 patients with extrapiramidal syndrome and cognitive decline were recruited (33 LBD, 21 PSP, 13 CBD). Moreover 70 patients with mild AD (MMSE>18), 57 with PD without dementia and 26 healty age-matched control subjects (CON) were enrolled. Each subject underwent a clinical and a neurological examination including the PRs evaluation, UPDRS III scale, and IADL and BADL recording. A standardised neuropsychological and behavioural assessment was also performed.
Results: Glabellar, snout, palmomental and grasp reflexes percentages are reported in table below as well as demographic and clinical characteristics of the 6 subgroups. Compared to CON, LBD showed are increased prevalence of glabellar reflex (R) (Chi-square test, p<.002), snout R (p<.005), grasp R (p<.05), while PSP of grasp R (p <.02). No significant differences in PRs % between CON and PD, CBD or mild AD were found. PRs>2 were present in the 83.9% of LBD. In the other groups, the 38.5% of CON, 46% of mild AD, 46% of CBD, 40.3% of PD, 61% of PSP showed PRs>2. The Odd Ratio (OR) of the risk of LBD in PRs > 2 was 27.9 (95%CI 2.9-269.0) compared to CON; the OR of the risk of LBD in PRs>2 was 14.6 (95% CI 2,7-79,6) compared to mild AD.

Table 1: Demographic and clinical characteristics, and Primitive reflexes in patients with PD, LBD, PSP, CBD, mild AD and in healthy age matched control subjects.

	CON	PD	CBD	PSP	LBD	MildAD
N	26	57	13	21	33	70
Age, y	73,4 ± 7,7	70,4 ± 9,8	63,4 ± 5.0	72,2 ± 6,4	72,7 ± 6,4	75 ± 6,4
Gender, F	8 (30%)	24 (42%)	2 (15%)	12 (57%)	20 (60%)	46 (66%)
MMSE	> 28	> 28	22,7 ± 4,2	26,4 ± 2,7	25,7 ± 14,2	22,5 ± 2,7
Glabellar.R	10 (38%)	26 (45%)	8 (61%)	13 (62%)	26 (79%)	45 (64%)
Snout R	14 (54%)	23 (40%)	7 (54%)	10 (48%)	28 (85%)	30 (43%)
Palmomental R	13 (50%)	18 (31%)	2 (15%)	12 (57%)	14 (42%)	22 (31%)
Grasp R	0 (0%)	0 (0%)	0 (0%)	4 (19%)	5 (15%)	0 (0%)

Conclusion: PRs evaluation can be helpful as an adjunctive tool for characterizing extrapiramidal syndromes with cognitive decline. PRs > 2 are strictly associated with LBD, and are less associated with AD, PSP or CBD.

*This authors contributed equally to this work.

3

PROTEIN PHOSPHORYLATION AND EXPRESSION IN RAT CULTURED HIPPOCAMPAL NEURONS AFTER ABETA (25-35) PEPTIDE TREATMENT: AN ATTEMPT OF NEUROPROTECTIVE RESPONSE?

***Alessandra Bulbarelli*[1]**, *Emanuela Cazzaniga*[1], *Elena Gatti*[1], *Tatsuro Mutoh*[2], *Massimo Masserini*[1]

[1]Dept. Experimental Medicine, University Milano-Bicocca, Via Cadore 48, 20052 Monza, Italy.
[2]Dept. Neurology, Fujita Health University School of Medicine, Toyoake, Aichi, Japan

Background: Amyloid beta-peptide, a 40-42 amino acid proteolytic fragment of the amyloid precursor protein (APP) is the major component of neuritic plaques and its 11 amino acid fragment (Abeta 25-35), can be neurotoxic. It is still unclear whether high levels of Abeta accumulation within the brain of AD patients represent a cause or a consequence of the neuronal damage. It has been shown that the addition of synthetic Abeta peptides to primary neuronal cultures resulted in a rapid increase in protein phosphorylation, including microtubule-associated protein Tau, in particular, Ser 199 is a specific Tau phosphorylation site for the proapoptotic enzyme, glycogen synthase kinase-3 (GSK-3 beta). TrkA expression, sparse or absent in hippocampal neurons, is up-regulated under pathophysiological conditions, and TrkA phosphorylation is provided by Nerve Growth Factor (NGF) against glutamate toxicity, through PI3K/Akt cell survival pathway activation. The PI3K/Akt cell survival pathway is involved in inhibition of GSK-3 beta by phosphorylation at Ser 9.
Methods: in this study, we analyse the effect of Abeta peptide (25-35) on phosphorylation and expression of proteins involved in neurosurvival, using primary hippocampal neurons obtained from day 18 rat embryos. Dissociated cells were maintained in culture in Neurobasal medium plus B27 supplement and at 7-8 DIV incubated for different times (3 min, 5 min, 15 min, 30 min,1 hour, 2-4 hours, 6-8 hours, 16 hours 24 hours and 48 hours) in complete medium containing 25microM Abeta peptide (25-35 fragment). Successively, proteins were submitted to SDS-PAGE and immunobloting analysis using the anti-phosphotyrosine monoclonal antibody (PY20, BD Transduction Laboratories) and specific polyclonal antibody raised against AKT, phospho-AKT and phospho-GSK-3 beta (Cell Signalling).
Moreover, we planned to analyze the expression of genes that could be activated as neuroprotective response, starting from total cellular mRNA isolated according to the TRIzol protocol and subjected to RT-PCR analysis with different primers: NGF, TrkA, TrkB, TrkC and GAPDH as housekeeping gene.
Results: preliminary results suggest that treatments with Abeta induce time-dependent modifications of protein phosphorylation pattern with changes, in particular, in the range of 75-150 KDa and 20-50 KDa. Interestingly, an increase of phosphorylated AKT and GSK-3 proteins forms after 1 hour of Abeta treatment was detected, indicating activation of survival pathways.
The RT-PCR experiments reveal an increased expression of NGF and TrkA after 1 hour incubation with Abeta, and no change of TrkB and TrkC expression.
Conclusion: it could be hypothesized that Abeta treatment activates neuronal survival mechanisms through modifications of protein phosphorylation and expression. Further studies will be carried out in order to identify the proteins involved.

4

IN VITRO ACTIVITY OF SYNTHETIC GROWTH HORMONE SECRETAGOGUES IN MICROGLIAL CELLS EXPOSED TO BETA AMYLOID FIBRILS

***Ilaria Bulgarelli*[1]**, *Laura Tamiazzo*[1], *Antonio Torsello*[1], *Elena Bresciani*[1] *e Vittorio Locatelli* [1]

[1] DIMESAB Università di Milano Bicocca

Background: Alzheimer's disease (AD) is characterized by the presence in the brain of amyloid plaques composed mainly of fibrils of beta-amyloid peptide, dystrophic neurites, activated microglia and astrocytes. The fibrillar forms of beta amyloid are able to bind the CD36, a class B scavenger receptor, and initiate a signalling cascade that regulates microglial recruitment and activation. The CD36 is also able to bind synthetic growth hormone secretagogues (GHS), a family of peptides that stimulates growth hormone secretion. We investigated whether GHS are capable to inhibit microglial activation induced in vitro by incubation with fibrils of beta-amyloid peptide, and promote cell survival.
Methods: We used the murine N9 microglial cell line activated by incubation with fibrillar amyloid peptide (25-35). The potential effect of GHS was studied coincubating the cells with increasing concentrations of hexarelin and one of its analogues. Cell activation was estimated by measuring with RT-PCR and real time PCR the mRNA levels for IL-1beta, IL-6 and TNF-alpha and CD36 in N9 cells. Neuronal survival in the presence of amyloid peptide and GHS was evaluated on SH-SY5Y, a human neuroblastoma cell line, after 24 and 48 hours incubation with amyloid beta fibrils and GHS and measured using MTT reduction assay.
Results: In N9 microglial cultures the amyloid peptide induced a significant rise of mRNA levels of IL-1beta and IL-6; treatment with hexarelin or its analogue blunted significantly this effect. The mRNA levels of TNFalpha and CD36 were not significantly modified by the different treatments. Incubation for 24 and 48 hours with the amyloid peptide induced a significant death in SH-SY5Y neuroblastoma cells, and this effect was clearly counteracted by the hexarelin analogue but not hexarelin.
Conclusions: these data indicate that GHS are capable to blunt the inflammatory process induced by amyloid beta fibrils in N9 microglial cells. Moreover, they suggest that GHS may play a neuroprotective role against cell death induced by beta amyloid, as demonstrated in the neuroblastoma cell line SH-SY5Y. These findings indicate that GHS may act against the inflammation and oxidative stress involved in the pathogenesis of the Alzheimer Disease.

46

DATA MINING OF BRAIN AGING DESCRIPTORS FROM THE NUN STUDY THROUGH NOVEL ARTIFICIAL ADAPTIVE SYSTEMS

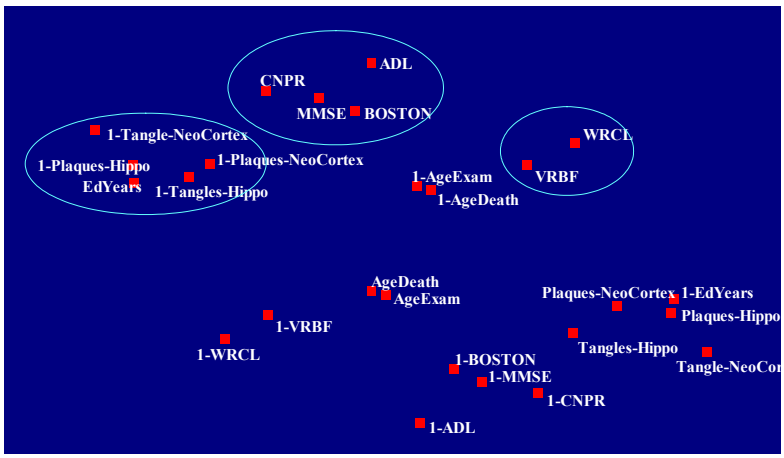
*M.Buscema, §D.Snowdon, §§P.Antuono, **E.Grossi.

*Semeion Research Center, of Sciences Communication, Rome.
**Bracco Imaging Medical Department, Milan, Italy.
§ University of Kentucky ,The Nun Study.
§§Department of Neurology, Medical College of Wisconsin, Milwaukee.

In this article we present a new algorithm able to perform non linear topographic mapping and its application to a dataset of AD subjects.
Topographic mapping is possibility to provide a visualization into 2 or 3 dimensions of multidimensional dataset, preserving the linear and non linear relationships among variables and/or among records.
Linear techniques cannot easily project into bi-dimensional space an high number of variables according to the matrix of their reciprocal distances, preserving all the keys information involved in the original dataset. In any case, linear techniques have to ignore non linear relationship.
The aim of this study is to discover hidden and the non linear associations among brain aging descriptors AIMS in a data set constituted by 117 participants in the Nun Study.
The mathematical system employed, called PST (developed by Semeion Research Centre), is able to find out the spatial distribution of N points which at best respects their reciprocal euclidean distances without exploring all possible combinations but "evolving" adaptively toward the best solution. In other words, given the reciprocal distances of the variables, this adaptive system identifies the emerging natural clusters.
We considered 26 input variables consisting in age, cognitive performances linked to memory, language, visuospatial ability, concentration, measured at the last examination before the death, and pathological key lesions of Alzheimer disease, measured after death in neocortex and hippocampus. In this way it could be possible to observe hidden "connections" or "associations" between descriptors that would have been overlooked relying only on their linear correlation.

13 Variables and their Complement: PST Map

Variables		Complement
1	AgeExam	1-AgeExam
2	AgeDeath	1-AgeDeath
3	EdYears	1-EdYears
4	ADL	1-ADL
5	WRCL	1-WRCL
6	CNPR	1-CNPR
7	BOST	1-BOST
8	VRBF	1-VRBF
9	MMSE	1-MMSE
10	TangleNeocortex	1-TangleNeocortex
11	TangleHippo	1-TangleHippo
12	PlaqueNeocortex	1-PlaqueNeocortex
13	PlaqueHippo	1-PlaqueHippo



Results:
-Two clusters of cognitive and functional tests emerged:1)MMSE, ADL, BOSTON, CNPR and 2)WRCL and VRBF.
-Years of Education resulted to be strongly associated with the absence of AD pathology features.

-Tangles in neocortex and plaques in hippocampus resulted to represent the most important variables in the data set as information load.

35

AUTOPSY PROVEN ALZHEIMER'S DISEASE PRESENTING WITH PRIMARY PROGRESSIVE APHASIA-PLUS SYNDROME: A CASE REPORT

***Annachiara Cagnin*[1,2] ,** *M. Graeber*[3], *F. Roncaroli*[3], *A.M. Chiamenti*[1], *A. Codemo*[1], *C. Ballarini*[1], *C. Gabelli* [1]

[1] Centro Regionale Invecchiamento Cerebrale (CRIC) Arcugnano (VI), [2] Dipartimento di Scienze Neurologiche Università di Padova; [3] Department of Neuropathology, Charing Cross London UK

Background: Primary progressive aphasia (PPA) is a dementia syndrome characterized by gradual dissolution of language with relative preservation of other cognitive domains for at least the first 2 years of illness. In rare cases, patients with PPA develop neurological signs of other boundary degenerative diseases such as the corticobasal degeneration (CBD): the so called PPA-plus syndrome. The neuropathological substrate of the disease is heterogeneous and mainly due to cortical neuronal loss and gliosis without distinctive histology.
Objective: To describe a pathologically proven Alzheimer's disease case presenting with PPA and evolved into a CBD-like syndrome.
Patient: We report a case of a 56-years-old man who died 6 years after presenting with the syndrome of progressive nonfluent aphasia and agrammatism with relative preservation of verbal comprehension and memory performance. MRI brain scan showed very mild atrophy of the left perisylvian regions and a SPECT study with a tracer for blood flow revealed a hypoperfusion of the left temporo-parietal regions. Biochemical screen and CSF analysis were unremarkable. Three years after aphasia onset he developed myoclonus of the right arm followed by ideomotor apraxia, digital agnosia, alien limb and asymmetrical parkinsonism. The clinical diagnosis was PPA-plus syndrome and a suspicious of a CBD with aphasic presentation was made. Autopsy examination revealed the presence of pathological hallmark typical of Alzheimer's disease with senile plaques and neurofibrillary tangles spread in the isocortex, hippocampus and subcortical regions. Genetic testing excluded the presence of mutations of the gene encoding for PS1.
Conclusion: Atypical sporadic early onset AD can present with PPA developing in the later stages clinical features of CBD. The clinical manifestation is sustained by an atypical regional distribution of the neuropathological hallmark of AD.

55

MIO NONNO NON SA FARE 2+2 MA CI VOGLIAMO BENE. IL CAFFE' ALZHEIMER: UNA PROPOSTA IN FASE DI ATTUAZIONE

Cristina Capellino (1), *Bruno Demichelis (1), Doriana Mambrin (1), Stefania Ghiglia (1), PierGiuseppe Zagnoni (1)*

Centro Abiotrofia Cerebrale Villa Fiorita – Peveragno

PREMESSA
I problemi dell'organizzazione socio-sanitaria rendono necessarie nuove forme di assistenza, riabilitazione e mantenimento del potenziale di autonomia per rispondere alle esigenze delle persone affette da demenza che richiedono un accudimento ed un'assistenza prolungata.
Il Caffè Alzheimer è uno spazio assistenziale coordinato da personale qualificato (nello specifico da due Educatori Professionali specializzati nel trattare con soggetti affetti da M.A.), coadiuvati da volontari costituiti dalla sezione femminile della CRI a da altri gruppi di volontari con finalità di auto mutuo aiuto. I familiari dei pazienti diventano una risorsa per se stessi e per gli altri pazienti e caregivers coinvolti.
La città di Dronero si è resa disponibile alla costituzione di uno spazio assistenziale denominato "Caffè Alzheimer" costituito da una rete multifunzionale in cui malati e parenti si ritrovano in uno spazio informale e "rilassato" per incontrarsi, bere una bibita o un caffè insieme, parlare dei problemi, ricevere informazioni e scambiarsi esperienze.
L'obiettivo è quello di creare un luogo di ritrovo, gratuito ed autogestito dai famigliari dei soggetti affetti da M.A., con l'aiuto di volontari e sotto la supervisione di operatori esperti, dove le persone che condividono lo stesso problema di salute si possano incontrare
MATERIALI E METODI
Alcuni incontri propedeutici con l'assessore all'assistenza hanno condotto ad un incontro con il Direttore della Casa di Riposo S. Camullo de Lellis e con il sindaco della città di Dronero nel corso del quale si è verificata la disponibilità dell'amministrazione civica a fornire in uso gratuito tre stanze all'interno della casa di riposo. Si è quindi proceduto a:
incontro con i MMG per informarli del progetto, chiedere supporto, iniziare la cernita dei pazienti;
tre incontri con la cittadinanza (il I° di informazione medica, il II° di proiezione di un film, il III° di informazione infermieristica ed educativa);
selezione dei criteri di inclusione (pazienti in stadio medio-grave con disturbi comportamentali) e dei soggetti;
creazione di materiale informatico di tipo educazionale, in via di pubblicazione sul sito del Comune di Dronero.
RISULTATI
Il Centro verrà inaugurato nel mese di Maggio 2005.
L'apertura sarà diurna dal lunedì al venerdì, dalle ore 9 alle 12 e dalle 15 alle 18.
Due educatori (C.C. e B.D.) saranno, a turno, quotidianamente presenti per 2 ore.
Un volontario della CRI, a turni mensili, sarà responsabile dell' apertura e chiusura dei locali.

COMMENTI
Il Caffè Alzheimer diviene importante: a) per il malato perché gli permette di entrare in contatto con persone competenti ed in grado di capire il suo problema e con altre che lo condividono, trovandosi nella stessa sua situazione; b) per il familiare che può confrontarsi con operatori del settore da cui ricevere informazioni su come comportarsi, sul significato della malattia e sulle possibili forme di assistenza attuabili.

Il ruolo dell'Educatore Professionale diviene di primo piano poiché è punto di riferimento per le persone (pazienti e familiari) che afferiscono al Caffè ed in quanto tale deve:
ACCOGLIERE → saper ospitare l'utenza con calore mettendola a proprio agio
COORDINARE → essere punto di riferimento sia per i malati che per i caregivers, responsabilizzare i volontari nelle ore in cui non è presente ed organizzare attività in base ai bisogni dei singoli
COINVOLGERE → lavorare in rete. La struttura è inserita nella realtà locale, per cui deve coinvolgere i vari enti locali, le associazioni di volontariato e la cittadinanza
CONSIGLIARE → diventare un occhio vigile sulla vita quotidiana e domestica del malato, offrire consigli su come relazionarsi a lui quando è a domicilio, riferire agli operatori sanitari l'insorgenza di patologie o problemi di loro competenza

19

L'USO DI FARMACI NEL PAZIENTE ANZIANO DEMENTE E NON DEMENTE: RISULTATI PRELIMINARI DEL PROGETTO ReGAl della SIGG

***M. Caputo*[1]**, *S. Ercolani*[1], *E. Mariani*[1], *F. Mangialasche*[1], *T. Ingegni*[1], *U.Senin*[1], *P. Mecocci*[1] *e il gruppo del Progetto ReGAl.*

[1]*Istituto di Gerontologia e Geriatria, Università degli Studi di Perugia*

Background: l'uso dei farmaci aumenta proporzionalmente con l'età in relazione all'aumento della comorbilità e delle malattie croniche nel paziente anziano. Tuttavia, come riportato in alcuni studi osservazionali, l'anziano è spesso sottotrattato per diverse patologie rispetto ai pazienti più giovani e non sempre questo è dovuto ad un maggior rischio di reazioni avverse legate alla polifarmacoterapia. Inoltre sono presenti pochi dati in letteratura sull'utilizzo di farmaci nella popolazione anziana affetta da demenza. Scopo di questo studio epidemiologico trasversale è quello di valutare, in un'ampia popolazione italiana di pazienti anziani dementi e non dementi, quali sono i possibili fattori che influenzano l'uso delle principali classi farmacologiche nelle diverse patologie osservate.
Methods: sono stati analizzati i dati del Progetto ReGAL (Rete Geriatrica Alzheimer). Dei 3467 soggetti, valutati in 39 centri italiani specializzati in disturbi della memoria dal gennaio 2001 al gennaio 2004, sono stati presi in considerazione i dati relativi a 2020 soggetti di cui l' 83% dementi, il 9% depressi e l' 8% cognitivamente, di età media di 77±7 anni. I pazienti assumevano in media 3±2 farmaci. Per valutare i fattori influenzanti l'utilizzo dei diversi farmaci in funzione di specifiche patologie, a parità di comorbilità, è stata utilizzata un'analisi di regressione logistica multivariata.
Result: dall'analisi preliminare dei dati è emerso che essere "oldest old" (> 85 anni) aumenta il rischio di essere meno trattati rispetto ai pazienti più giovani con anticoagulanti orali in corso di FA (OR=0,1) e con statine in caso di ipercolesterolemia (OR=0,1). Essere "oldest old" e per di più affetto da demenza, a parità di gravità della malattia, determina un minor trattamento con antidepressivi ed in particolare con gli SSRI (OR=0,3), ma un maggior rischio di essere trattati con antipsicotici tipici (OR=1,9) Inoltre con l'aumentare della gravità della demenza aumenta il rischio di essere trattato con antipsicotici tipici ed atipici (OR=2,9) così come vivere in una residenza e/o con assistenza (OR=1,8). L'essere demente determina un minor trattamento con inibitori dell'angiotensina II in corso di ipertensione arteriosa (OR=0,5) ed un minor trattamento con inibitori di pompa in corso di malattia peptica (OR=0,3). Essere depresso determina un maggior uso di ansiolitici rispetto ai soggetti dementi e controlli (OR=5,0).
Conclusion: dall'analisi emerge come l'età avanzata e la presenza di demenza influenzano l'uso di farmaci necessari per il trattamento di diverse patologie a parità di comorbilità.

5

EFFECT OF A-BETA (25-35) PEPTIDE ON LIPID METABOLISM IN RAT CULTURED HIPPOCAMPAL NEURONS. INVOLVEMENT OF THE PROTEASOME/UBIQUITIN SYSTEM

***Emanuela Cazzaniga*[1]**, *Elena Gatti*[1], *Alessandra Bulbarelli*[1], *Tatsuro Mutoh*[2], *Massimo Masserini*[1]

[1]Dept. Experimental Medicine, University of Milano-Bicocca, Via Cadore 48, 20052- Monza, Italy
[2],Dept. Neurology, Fujita Health University, Toyoake, Japan

Background: Interaction between Abeta, the major component of neuritic plaques, and neuronal membranes plays an important role in the neuropathology of Alzheimer's disease (AD). Abeta and its 25-35 fragment can be neurotoxic by a mechanism linked to peptide fibril formation. Abeta is able to insert into lipid bilayer, this ability is critically controlled by the ratio of cholesterol to phospholipids. Abeta recognizes GM1 ganglioside in membranes. Recognition is facilitated by the presence of cholesterol and sphingomyelin. Changes in the ganglioside composition have been reported in AD brains. A decrease of neuronal membrane cholesterol has been implicated in AD. The proteasome could contribute to the AD neuropathology and could control the physiopathological maturation of the Amyloid precursor protein. In vitro, Abeta peptide prevents ubiquitin-dependent protein degradation
Methods: Primary hippocampal neurons are established from day 18 rat embryos and are cultured in Neurobasal medium for 7 days. Cells were incubated for 16 or 72 hours with 25 microM of Abeta (25-35) peptide or with 1microM lactacystin, an inhibitor of proteasome. Endogenous lipid pattern has been assessed submitting the to lipid extraction and separation of gangliosides, phospholipids and cholesterol on silica gel TLC plates. Lipid biosynthesis has been investigated by evaluation of radioactivity incorporation after incubation with 16.6 microCi radioactive palmitic acid (47.5 Ci/mmol). After 48 hrs incubation, Abeta (25-35) was added directly into the medium for further 16 hrs. The radioactivity associated to total lipids, to gangliosides and to phospholipids, was determined by liquid scintillation counting. Separation of gangliosides and phospholipids was performed by TLC. Apoptosis was followed by analysis of caspases 1-9 activities using Sulforhodamine Multi-Caspase Activity Kit. Proteasome assay was performed by fluorometric assay of proteasomal chymotrypsin peptidase activity on a synthetic substrate.
Results: The content of endogenous gangliosides and phospholipids of cultured rat hippocampal neurons increases after cell treatment with Abeta during the first 16 h, then decreases. No differences are observed in the case of cholesterol. The effect is due to Abeta-induced increase of biosynthesis, as shown by the increased incorporation of tritiated palmitic acid into cellular lipids. Analogous results are obtained with treatment with lactacystin, a proteasome inhibitor. Proteasome enzymatic activity does not seem to be affected after Abeta treatment.
Conclusion: Abeta induces a temporary increase of phospholipid and glycosphingolipid biosynthesis, linked to the proteasome/ubiquitin system, and possibly due to an anomalous ubiquitination.

20

A PROPOSAL FOR AN ITALIAN TISSUE BANK FOR DEMENTIA

Andrea Maria Chiamenti, *Alessandra Codemo, Cristina Basso, Annachiara Cagnin, Patrizia Pagliari, Cristina Ruaro, Monica Rapattoni, Nicoletta Del Grosso Destreri e Carlo Gabelli*

Centro Regionale per lo Studio e la Cura dell'Invecchiamento Cerebrale (CRIC), Padova-Arcugnano (VI)

To verify the clinical diagnosis and to perform research on the metabolic or genetic alterations that causes neurodegeneration, it is essential to have access to a well characterized and organized collection of brain and other tissue specimens, as well CSF and blood samples. During the past four years, the Molecular Biology Laboratory of the CRIC collected blood samples from more than 2000 subjects whith neurodegenerative diseases and CSF from 60 patients. In selected cases neuropathological evaluation has been performed in collaboration with other institutions.
Our aim is now to develop a tissues bank to collect brain tissue, CSF, blood and fibroblasts samples of demented patients and controls from our clinic as well from other centers.
Main points of the plan:
- Selection of the partecipating units
- Standardization of the clinical data collection
- Selection of neuropathological procedures for diagnosis [1]
- Standardization of sample collection, handling and storage
- Evaluation of adherence to ethical guidelines [2]
- Analysis of starting up expenses and operating costs.

We estimate to collect biological samples from more than 300 patients/year, with neuropathological study in approximately 5-10 %. The organization of a network of clinics and other departments collaborating in patient selection and neuropathology studies is a crucial part of this initiative. In this respect our institution has already worked with 12 UVA in the Veneto region collaborating in sample collection and clinical characterization for a national genetic study on Alzheimer Disease.
Expected outcomes will be:
- to provide well characterized biological samples for research on neurodegenerative disorders and make possible the collaboration with other banks in different countries;
- to test the association of new polimorfisms or mutations with specific neurodegenerative phenotypes;
- to evaluate new biological markers in CSF or in plasma;
- to obtain neuropathological data to endorse the clinical diagnosis;
- to make possible farmacogenetic studies for a better therapeutic approach.

---

[1] See also specific guidelines of BrainNet Europe (www.brainnet-europe.org)
[2] See " Biobanche Genetiche – Linee Guida ", inserto ANALYSIS-N.5/6.2003 (www.snabi.it)

26

GENE POLYMORPHISMS OF INFLAMMATORY MOLECULES INFLUENCE COGNITIVE DETERIORATION IN THE COURSE OF ALZHEIMER'S DISEASE

***Martina Chiappelli*[1], *Emanuela Tumini*[1], *Elisa Porcellini*[1], *Massimo Franceschi*[3], *Nicola Canal*[2], *Elena Calabrese*[2], *Federico Licastro*[1].**

[1] Department of Experimental Pathology, University of Bologna, Bologna, Italy.
[2] Department of Neurology, IRCCS Don Gnocchi Foundation, Milan, Italy.
[3] Department of Neurology, Santa Maria Hospital, Castellanza , Milan, Italy.

Background: Several evidences suggest that inflammation or altered immune responses may play an important role in Alzheimer's disease. In fact, molecules with a regulatory role on the inflammation have often been found associated with neurodegenerative hallmarks in the brain of AD patients. Studies on the genetic variability of immune factors are showing that several polymorphic sites may influence the production of the cognate molecule. Other studies have also confirmed that the presence of these polymorphic alleles differentially influence the risk of developing AD. Genotypes of these immune molecules associated with an increased risk of AD may also be linked with the risk of developing cognitive deterioration in pre-clinical AD conditions. Moreover, these same polymorphic sites may affect the progression of cognitive alterations into emerging of clinical AD. Our previous study have already shown that subjects carrying the TT genotype of ACT, CC genotype of IL-6, AA genotype of IL-10, TT genotype of IL-1beta and APOE e4 allele have an increased risk of developing AD. In this study we investigated whether the polymorphisms of promoter regions of ACT, IL-6, IL-10, IL-1beta and APOE influenced the rate of cognitive decline, after the clinical appearance of the disease.
Materials and methods: *Subjects:* 109 patients (mean age 74±8) from Northern Italy with probable AD were followed up for two years. Cognitive performances were measured according to Mini Mental State Examination (MMSE). *DNA extraction and polymorphism detection:* genomic DNA was extracted from peripheral blood leukocyte. The ACT -51G/T, IL-6 -174G/C, IL-10 -1082G/A, IL-1beta -511C/T and APOE e4 polymorphisms were analysed by PCR, restriction endonuclease digestion and agarose gel electrophoresis.
Statistical analysis: slope comparison between linear regressions of MMSE score of AD stratified according to different genotypes was performed for each inflammatory molecule polymorphism.
Result: ACT TT genotype (the genotype associated with an increased risk of AD) was associated a faster cognitive decline than ACT GG genotype, when associated with the concomitant presence of APOE e4. On the contrary the IL-6 CC genotype was linked with a significant reduction of cognitive decline. In fact, subjects carrying the IL-6 GG genotype showed a faster decline than subjects with CC genotype. The IL-10 AA genotype was associated with a statistical significant lower MMSE score than the GG genotype at time 0, but the progression rate of cognitive decline was similar, indeed the two regression lines were parallel. The IL-1beta TT genotype or the APOE e4 allele, were not independently associated with a faster cognitive decline
Conclusion: From these results we can conclude that the allelic polymorphisms of the inflammatory molecules might exert differential effects on the risk of developing AD and the clinical progression of the disease. Therefore, inflammatory genes may be considered AD modifiers. These polymorphisms could predict the progression rate of cognitive decline in AD patients and relevance for pharmacological treatments of the disease.

6

EFFECT OF PRO AND ANTI-OXIDANT TREATMENT ON SHSY5Y NEUROBLASTOMA CELL LINE

***Elisa Conti*[1]**, *Gloria Galimberti*[1], *Fabrizio Piazza*[1], *Michela Zini*[1], *Roberta Rigolio*[1] *and Carlo Ferrarese*[1,2]

[1]Department of Neuroscience and Biomedical Technologies, University of Milano-Bicocca
[2]Department of Neurology, S.Gerardo Hospital, Monza (MI), Italy

Background: Alzheimer's Disease (AD) is known to be a multifactorial disorder; one of the main mechanisms involved in its pathogenesis is oxidative stress, which represents an imbalance between pro and anti-oxidant cell systems. High levels of Homocysteine (Hcy), a non essential aminoacid, well-known as a risk factor in different disorders such as cardio-vascular diseases, can contribute to oxidative damage. Several studies suggest the importance of anti-oxidant molecules to prevent this phenomenon. Among them Resveratrol (Rs), a polyphenolic compound constituent of red wine, has been demonstrated to have anti-apoptotic, anti-oxidant properties and to prevent excitotoxic insults. To investigate the influence of Hcy on oxidative stress and apoptosis in neuronal cells and the capacity of Rs to reverse these effects , we performed our study on human neuroblastoma cell line (SH-SY5Y).
Methods: We cultured differentiated (retinoic acid, RA, 10microM) and non–differentiated cells in presence of an acute Hcy stimulus of 24 hours and a "chronic" stimulus of six days (undifferentiated cultures only). For acute stimulus we used Hcy at concentrations ranging from 500microM to 5mM, supplemented or not with a defined $CuCl_2$; for chronic stimulus we used Hcy alone at lower concentrations, ranging from 15microM to 300microM. For both acute and chronic treatments we tested cell viability with MTT and LDH assays. To confirm the involvement of apoptotic pathways we studied the activation of caspase-3, and the presence of nuclear condensation by HOECHST staining method. To asses the alteration of redox status we analysed Reduced Glutathione (GSH) levels and production of Reactive Oxigen Species (ROS) by fluorimetric assays. At last, we preincubated cell cultures with Rs (1 microM and 10 microM) and then co-administered with Hcy, $CuCl_2$. Cell viability was evaluated by MTT assay.
Results: Hcy treatment induced low cellular mortality (about 10%) even at very high concentration. The contemporary addiction of Hcy and $CuCl_2$ decreased significantly viability from 20% ($p<0.05$) to 30% ($p<0.01$). The acute stimulus did not show any effect on differentiated cells, this is probably due to a known anti-oxidant effect of RA. Even the chronic stimulus didn't influenced cell viability. The activity of caspase-3 showed about 5 fold increase ($p<0.01$) in treated cells (Hcy 5mM + $CuCl_2$ 5microM) respect to control cells; moreover, treated cells demonstrated evidence of chromatine condensation and fragmentation, their number was reduced and about 12% of them was apoptotic. Incubation with Hcy and $CuCl_2$ induced slightly increase in ROS levels, and a significant decrease in GSH values ($p<0.05$, preliminary data). Pre-incubation with Rs 1microM followed by administration of Hcy and $CuCl_2$ showed a recovered viability till 50% ($p<0.05$ Hcy 1mM+$CuCl_2$ 5microM, $p<0.01$ Hcy 5mM +$CuCl_2$ 5microM).
Conclusion: Our results confirm the cytotoxic action of Hcy, and suggest a synergic effect with $CuCl_2$ in our cell model. Moreover, low GSH values confirm oxidative stress induced by our stimuli. Rs may prevent cell death not only inhibiting apoptosis pathways, but also reducing oxidative damage. We are now investigating the effect of other antioxidant molecules and testing fibroblasts as alternative cellular model. At last we can point out the validity of anti-oxidant substances and suggest their use for *in vivo* treatment, e.g. in AD, where oxidative stress plays a major role.

56

ACTION AND OBJECT NAMING IN THE TAUOPATHIES

***Maria Cotelli*[1]**, *Barbara Borroni*[2], *Antonella Alberici*[1], *Marcella Broli*[2], *Marco Calabria*[1], *Chiara Agosti*[2], *Analia Arevalo*[3, 5], *Valeria Ginex*[3;4], *Paola Ortelli*[4], *Alessandra Marcone*[4], *Michele Zamboni*[4], *Orazio Zanetti*[1], *Giuliano Binetti*[1], *Alessandro Padovani*[2] *e Stefano Cappa*[3;4]

[1]U.O. Alzheimer, IRCCS S. Giovanni di Dio–FBF; [2]Department of Medical Sciences, Neurological Clinic, University of Brescia, Italy; [3]Department of Psychology and Neuroscience, University Vita-Salute, Milan; [4] Neurology Unit, Ville Turro, Hospital San Raffaele Milan; [5]UCSD, San Diego, USA.

Background: The group of tauopathies includes frontotemporal dementia, (FTD), a neurodegenerative disease with different clinical presentations (Semantic Dementia -SD, the frontal variant- fV, and non fluent Primary Progressive Aphasia-NfPPA), Corticobasal Degeneration (CBD) and Progressive Supranuclear Palsy (PSP). These neurodegenerative conditions are variably characterized by language impairment; in particular, action naming has been found to be particularly affected in FTD (Cappa et al., 1998). The present study aimed to assess the ability to name objects and actions in different disorders belonging to the tauopathy group. Further, we wished to assess the effect of a particular conceptual dimension, i.e. manipulability, on the naming of object and actions.
Methods: Patients were recruited from the Department of Neurology University of Brescia, University Vita-Salute (Milan) and the IRCCS Memory Clinic (Brescia). Thirty-five were diagnosed as Frontotemporal Dementia (FTD), according to published criteria. Six patients had SD, 2 patients NfPPA, 12 fv-FTD; 7 diagnosed as PSP and 8 as CBD were also tested. The study also included ten patients diagnosed as probable Alzheimer Disease (AD) and 10 healthy volunteers, matched in age and education to patients sample. All patients underwent a detailed clinical and neurological evaluation. For each patient, a structural brain MRI excluded other causes of dementia. The stimuli used in the action-object picture naming (PN) task were taken from the Center for Research in Language-International Picture Naming Project corpus (CRL-IPNP, Bates et al., 2000). To assess the effect of manipulability (or the involvement of fine hand movements) the noun-verb stimuli were re-categorized into manipulable and non-manipulable items (i.e., objects which can or cannot be manipulated and actions which do or do not involve fine hand movements).
Results: Patients with PSP, CBD and AD were significantly more impaired in oral naming of verbs than nouns (*PSP*: T= 5,146 p=0,002 ; nouns mean 90,26; DS 7,55 vs verbs mean 67,14; DS 18,79 correct; *CBD*: T= 5,392 p=0,001nouns mean 93,12; DS 5,3 vs verbs mean 70,2; DS 10,3 correct. *AD*: T=3,614 p=0,006; nouns mean 77,86; DS 17,8 vs verbs mean 65,31; DS 11,34 correct). In addition, NfPPA patients showed a very large difference between nouns end verbs *(NfPPA*: nouns mean 71,65 ; DS 33,02 vs verbs mean 32,50; DS 27,15 correct $\chi 2$=30.496 ; p<0,0001). In contrast, there were no differences between noun- and verb-naming in patients with fvFTD and SD. The "manipulability" factor resulted impaired for object and action naming (manipulable action mean 6,56 DS 7,72 vs nonmanipulable action mean 4,91 DS 7,63 T=2,923 p=0,005; manipulable object mean 3,27 DS 5,32 vs nonmanipulable object mean 4 DS 5,3; T= -3,647 *p*= 0,001). The difference between manipulable actions and nonmanipulable actions was significantly different for CBD subjects (manipulable actions mean 4,49 DS 1,64; nonmanipulable actions 1,56 DS 1,48 T= 4,428 p= 0,003) and for AD subjects (manipulable actions mean 4,1 DS 1,58; nonmanipulable actions 3,09 DS 1,3 T= 2,891 p= 0,018). In addition, the difference between manipulable object and nonmanipulable object was significantly different only for AD subjects (manipulable objects mean 1,74 DS 1,6; nonmanipulable objects T= 3,1 DS 1,71 T= -4,197 p= 0,002) . The difference showed that for object naming, AD subjects make more errors on the non-manipulable objects.

Conclusion: Present study further supports the hypothesis of frontal lobe involvement in action naming. A simple language test may be helpful in distinguishing the different FTD variants in clinical practice. Further investigations will address the neural network associated to these mechanisms.

57

FRONTAL COGNITIVE DEFICIT MARKS MENTAL DETERIORATION IN SPINOCEREBELLAR ATAXIA 17

Sabrina AM Curcio, *Rosanna Colao, Gianfranco Puccio, Francesca Frangipane, Maria Mirabelli, Raffaele Maletta, Carmine Tomaino, Livia Bernardi and Amalia C. Bruni*

Regional Neurogenetic Centre AS6 Lamezia Terme, Italy

Background: Sca17 is an Autosomal Dominant Cerebellar Ataxia characterized by ataxia, psychiatric and extrapyramidal features, epilepsy and MRI findings of cerebral and cerebellar atrophy.
Evidence has shown that patients with cerebellar degeneration have cognitive dysfunction associated to the cerebellar disorder itself.
Several authors have reported a broad cognitive impairment in autosomal dominant cerebellar ataxias patients but the SCA17 neuropsycological profile is still unknown.
Objective: to characterize the first cognitive symptoms that occur in an Italian SCA17 kindred.
Materials and Methods: we administered a battery of neuropsycological tests assessing attention, short and long term verbal and visuospatial memory , executive functions, language, constructive abilities and intellectual abilities to 3 sca17 patients of this kindred who came to our observation in the first stage of the pathology.
Results: a selective early impairment of executive functions and phonological verbal fluency characterize the neuropsycological profile of patients studied while memory and constructive abilities are spared. This dysexecutive syndrome precedes clinical signs of ataxia and is associated with early behavioural disorders.
Conclusion: our results demonstrated frontal cognitive deficits in SCA17.
It is, in our knowledge, the first description of mental impairment in SCA17 and is in agreement with previous reports that highlighted frontal dysfunction in patients with cerebellar syndrome.

27

VEGF IS A NOVEL SUSCEPTIBILITY GENE FOR SPORADIC ALZHEIMER'S DISEASE

***Roberto Del Bo*[1]**, *Marina Scarlato*[1], *Serena Ghezzi*[1], *Filippo Martinelli-Boneschi*[2], *Chiara Fenoglio*[1], *Sara Galbiati*[1], *Roberto Virgilio*[1], *Daniela Galimberti*[1], *Gloria Galimberti*[3], *Carlo Ferrarese*[3], *Elio Scarpini*[1], *Nereo Bresolin*[1], *Giacomo Pietro Comi*[1]

[1] Department of Neurological Sciences, University of Milan, Milano.
[2] Department of Neurology, Scientific Institute and University, Ospedale San Raffaele, Milano.
[3] Department of Neuroscience and Biomedical Technologies, University of Milano-Bicocca, Monza.

Background. Converging evidence points to a pivotal role of Vascular Endothelial Growth Factor (VEGF) in neuronal protection and a lack of its activity in neurodegenerative disorders. From a genetic point of view, a number of polymorphisms localized in the promoter region of the VEGF gene have been associated with different diseases, including amyotrophic lateral sclerosis; besides, VEGF gene sequence variability might contribute to the inherited predisposition to VEGF-mediated pathological conditions. To date, there is no evidence supporting a role of the VEGF variability in the genetic susceptibility to Alzheimer's Disease (AD).
Methods. The VEGF gene was screened for well-known SNPs in a series of 249 Italian patients with sporadic AD, recruited from the Alzheimer Units of Ospedale Policlinico (Milan) and Ospedale San Gerardo (Monza). The control group consisted of 347 healthy subjects matched for ethnic background, sex and age to cases. Total DNA was isolated from peripheral blood and two genomic DNA regions containing specific portions of the VEGF promoter were analysed. Serum VEGF levels were assessed in 96 AD patients and 49 healthy controls.
Results. Genetic analysis revealed that frequencies of –2578A/A and –1198C/T genotypes were significantly higher in AD patients than in controls (respectively, 23.7% vs. 14.7% and 2.8% vs. 0%). The –2578A/A genotype was associated with an increased risk of disease (OR:2.03; p=0.003), independently of APOE genotype. Furthermore, the risk was significantly increased with respect to various VEGF genotype combinations. We observed a correlation between "at-risk" genotypes and increased serum VEGF levels in the group of AD patients, whereas no difference was detected between cases and controls, as a whole.
Conclusions. Our findings suggest that polymorphisms within the VEGF gene promoter confer greater risk for AD providing a new potential therapeutic target in AD and confirming the important biological role of VEGF in neurodegenerative processes.

58

TI RI-CONOSCO SENZA EMOZIONE": LA NECESSITÀ DEL PARADOSSO. SU UN CASO DI DELIRIO DI CAPGRAS

***G. Della Rocca*[1]**, *G. Conchiglia*[1], *A. Visciglio*[1], *P. Russo*[1], *D. Grossi*[2]

[1] "Villa Camaldoli", Napoli.[2] Dipartimento Psicologia S.U.N., Caserta.

Si presenta il caso di un uomo V. A., 76enne con scolarità superiore che improvvisamente al risveglio dichiarò che i figli erano stati sostituiti da altre persone simili con differenti caratteristiche comportamentali (antipatici, rozzi), tuttavia abbastanza affettuosi da meritare il termine di figli "putativi". Questo convincimento non coinvolgeva altri familiari e conoscenti. Ai nipoti chiedeva insistentemente dove fossero i loro genitori, nonostante questi fossero presenti. Tale convinzione era resistente ad ogni obiezione gli fosse posta. In una circostanza telefonò ad uno dei suoi figli sostenendo che il suo sosia gli insidiava la moglie. Riferì inoltre un frequente fenomeno di perseverazione visiva: i mobili della stanza appena lasciata continuavano ad essere visti per minuti in altri ambienti. La RM encefalo mostrò solo una diffusa atrofia cerebrale. L'esame neuropsicologico evidenziò: MMSE 16/30, deficit della memoria spaziale, dell'attenzione ed aprassia costruttiva, al Token-test ottenne 26/36. Fu rivelata difficoltà nel riconoscimento volti di personaggi famosi mentre allo specchio si riconosceva senza difficoltà. È rilevante sottolineare che il riconoscimento dei figli al telefono o in fotografia era perfettamente conservato. Tale delirio fu mantenuto per circa due mesi. L'ipotesi formulata era che la falsa credenza di V. A. fosse legata al mancato riconoscimento affettivo dei figli, su tale ipotesi fu suggerito ad uno solo dei due figli di enfatizzare l'affetto verso il padre, come se l'incontro avvenisse dopo molto tempo e si sollecitò lo stesso a ricordare con V. A. episodi del passato. L'effetto di questo tipo di "intervento" risultò efficace per il figlio che l'aveva attuato, mentre il delirio continuava a coinvolgere l'altro figlio che di fatto fungeva "da controllo". Successivamente anche il secondo figlio fu spinto ad attuare la stessa modalità comportamentale, ed anche in questo caso si ottenne lo stesso risultato. Al controllo clinico avvenuto circa un mese dopo questi eventi, V. A. dichiarò che i figli "putativi" erano partiti ed erano tornati i figli "veri". Alla domanda dell'esaminatore come fosse riuscito a capire quelli partiti erano i sosia, V. A. affermò: "sentivo che non erano i miei figli anche se erano del tutto simili". Il paziente rifiutò altre indagini neurofunzionali, tuttavia i dati clinici (perseverazione visiva) e neuropsicologici (disturbi della memoria spaziale, aprassia costruttiva, deficit del riconoscimento di volti noti, normale capacità linguistica) suggeriscono una prevalente compromissione dell'emisfero destro, pur in un contesto di moderato declino cognitivo globale. Il dato saliente è fornito dalla dissociazione mostrata dal paziente nel riconoscere i figli attraverso singole modalità percettive (riconoscimento dei figli in fotografia e della loro voce al telefono) e nel mancato riconoscimento degli stessi in condizioni realistiche. La difficoltà di elaborare contemporaneamente più modalità sensoriali, in questo paziente probabilmente ha impedito una adeguata reazione affettiva generando un paradosso: il delirio del sosia. È possibile ipotizzare che la falsa credenza si sia realizzata anche grazie al deficit dei "sistemi di controllo" così da permettere al paziente di accettare l'incongruenza logica. Il paradosso viene superato quando i figli riescono ad evocare nel padre una significativa reazione affettiva.

59

QUALE TRATTAMENTO PER I PAZIENTI MCI? UNO STUDIO PILOTA DI MEMORY TRAINING

***Francesca Dieci*[1], *Sandra Copelli*[1], *Sabrina Spaggiari*[1], *Giorgia Morini*[3], *Giovanni Messa*[1], *Pio Pelliccioni*[1,2] *e Paolo Caffarra*[1,3,4]**

[1]Consultorio Disturbi Cognitivi, Azienda USL, Parma
[2]Dipartimento Geriatrico Riabilitativo, Azienda Ospedaliera, Parma
[3]Dipartimento Neuroscienze, Università degli Studi di Parma, Parma
[4]Clinical Neuroscience Centre, University of Hull, UK

Background: Attualmente i soggetti con diagnosi di Mild Cognitive Impairment amnesico a-MCI) pur essendo considerati una popolazione a rischio per lo sviluppo di demenza, non sono sottoposti in maniera sistematica ad alcun trattamento fatta eccezione per alcuni trials che si occupano di investigare l'efficacia di interventi farmacologici nel ridurre la percentuale di conversione di MCI verso la demenza di Alzheimer (AD). La mancanza di linee guida relative all'uso di farmaci antidemenza per questa popolazione e la peculiarita' del disturbo amnesico, percepito come invalidante nella vita quotidiana, ha suggerito l'opportunita' di valutare l'efficacia di interventi di stimolazione cognitiva. Scopo del lavoro è stato, pertanto, attuare uno studio preliminare di memory training volto a migliorare la capacita' di apprendimento e rievocazione, valutando l'eventuale beneficio anche su indici comportamentali e del tono dell'umore in soggetti a-MCI rispetto ad un gruppo di controllo.
Methods: Sono stati inclusi nello studio 19 soggetti con diagnosi di Mild Cognitive Impairment amnesico su base degenerativa con MMSE ≥ 24 diagnosticati secondo i criteri di Petersen (Petersen et al., 1999). I soggetti venivano assegnati in modo casuale al gruppo sperimentale o di controllo quest'ultimo privo di trattamento. La durata del trattamento è stata di 4 settimane con sedute bisettimanali della durata di un'ora ciascuna (gruppo SPERIMENTALE: 10 soggetti di età media = 70±4,8; scolarità media = 6,4±2,3; MMSE = 26,7±1,4 - gruppo di CONTROLLO: 9 soggetti: età media = 74,9±5,7; scolarità media = 7,8±4; MMSE = 26,9±1,6). All'inizio e alla fine del trattamento veniva effettuata una valutazione cognitiva, comportamentale e della percezione soggettiva del deficit mnestico. Sono stati inoltre presi in esame l'andamento dell'apprendimento all'interno delle sedute e l'eventuale effetto di generalizzazione verso materiale non allenato. L'intervento di memory training ha previsto l'utilizzo di tecniche quali l'errorless learning e l'expanding reharsal (secondo la metodologia descritta da L. Clare 1999) con materiale di tipo ecologico (associazioni faccia-nome, luoghi-oggetti, appuntamenti e frasi generiche).
Results: Non sono emerse differenze significative fra il gruppo sottoposto a memory training ed il gruppo di controllo nel confronto fra la valutazione iniziale e finale degli indici cognitivi, comportamentali e del tono dell'umore, mentre si è osservato un miglioramento significativo (p=0,018) nel solo gruppo sperimentale per quanto riguarda la valutazione soggettiva dell'efficienza mnestica. L'andamento delle prestazioni all'interno delle sedute si è caratterizzato per una consistente variabilita' intra ed inter individuale con un indice percentuale medio di miglioramento tra prima e ultima seduta del 24%, (p=0,06, n.s.). Il ricordo di materiale non allenato ha, infine, messo in luce un miglioramento significativo tra la prestazione precedente e quella successiva al training (p=0,03).
Conclusion: L'intervento di memory training con la metodologia procedurale usata in questo studio, sembra aver favorito fondamentalmente due aspetti, quello legato alla percezione della propria efficienza mnestica e quello più propriamente oggettivo confinato all'effetto di generalizzazione su materiale non allenato. Una maggiore personalizzazione dei programmi di stimolazione, unita forse

ad un incremento della numerosità del campione potranno fornire migliori risultati in ambito cognitivo ed ecologico.

7

NEURONAL APOLIPOPROTEIN J IS UP-REGULATED BY OXIDATIVE STRESS

***Barbara Dozza*[1] ,** *Damiano Zaccheo*[2]*, and Paola Strocchi*[1].

[1]Department of Pharmacology, University of Bologna, Bologna, Italy; [2]Department of Experimental Medicine, University of Genoa, Genoa, Italy.

Apolipoprotein J / clusterin (apoJ) is a multifunctional glycoprotein up-regulated during various pathophysiological states and might represent a defence mechanism during cellular damage. An increase in either apoJ mRNA or protein expression is observed in numerous neurodegenerative conditions including Alzheimer's disease, Parkinson' disease, Pick disease, amyotrophic lateral sclerosis, and Huntington disease. Furthermore, these neurodegenerative disorders are characterized by intraneuronal abnormal filament accumulation associated with markers of oxidative injury.
To determine whether apoJ is affected by oxidative stress, we evaluated the effects of oxidative insult on the expression of apoJ as part of a cellular response in viable human neuroblastoma IMR-32 cells.
In our experimental model iron-ascorbate induced oxidative stress in IMR-32 cells without affecting cell viability, as detected by MTT-assay. It was found that IMR-32 cells express apoJ mature protein and that oxidative stress induced an up-regulation of apoJ level revealed by immunoblot analysis.
The results of the present study suggest that an increase in apoJ expression may be a physiological defence able to reduce cell damage and maintain cell viability during periods of increased radical production.
Supported by the University of Bologna, Funds for Selected Research Topics.

8

MACROMOLECULAR COMPLEXES IN ALZHEIMER DISEASE PATHOGENESIS: SEARCH FOR A PARTNER OF ACETYLCHOLINESTERASE

***Epis Roberta*[1]**, *Marcello Elena*[1], *Gardoni Fabrizio*[1], *Borroni Barbara*[2], *Padovani Alessandro*[2], *Cattabeni Flaminio*[1], *Toiber Debora*[3], *Soreq Hermona*[3], *Di Luca Monica*[1].

1.Dipartimento di Scienze Farmacologiche, Università di Milano, via Balzaretti 9-20133 Milano.
2.Dipartimento di Scienze Mediche- Unità di Neurologia- Università di Brescia, p.zza Spedali 1-25125 Brescia.
3. Department of Biological Chemistry and the Israel Center of Neuronal Computation, Institute of Life Sciences, The Hebrew University of Jerusalem, Jerusalem 91904, Israel.

Acetylcholinesterase (AChE) catalyses the rapid hydrolysis of acetylcholine (ACh) to acetate and choline, resulting in termination of neurotrasmission at cholinergic synapses. In addition, AChE is believed to play non-catalytic roles in nerve and muscle development and to be implicated in Alzheimer's disease (AD). The cholinergic hypothesis of AD suggests that the degeneration of cholinergic nerve terminals, and the concomitant decrease in ACh levels in the brain regions involved in cognition, together lead to the symptoms of AD. Consequently, AChE inhibitors are the most important currently available drugs for treating AD. However, molecular biology studies demonstrate that these drugs can induce AChE alternative splicing shift, and biochemical analyses show a selective loss of specific AChE molecular forms in AD. Therefore, detailed understanding of AChE's molecular polymorphism in AD is of great potential interest.
The human AChE gene contains 4 alternative first exons, of which only one encodes an in-frame extended N-terminus (hN-AChE). hN-AChE includes a 66 amino acids extension which precedes the signal peptide. This may prevent cleavage of the signal peptide, so that the amino terminal region plus signal peptide becomes a transmembrane domain of the hN-AChE protein. To challenge this hypothesis, a biochemical fractionation approach was taken to determine the distribution of AChE among the different subcellular compartments of murine hippocampal neurons. Immunoblot analysis of the biochemical fractions using anti-AChE antibodies revealed the presence of the predictably heavier N-AChE protein in purified synaptosomes as well as in the Triton-insoluble synaptic fraction. Confocal microscopy confirmed the existence of AchE in these fractions by immunofluorescence labeling. In view of this information, and because the extended hN-AChE primary sequence includes a proline-rich domain, we are currently searching for putative interactions between hN-AChE and the SH3 domain of candidate proteins involved in the assembly and function of the post-synaptic compartment.

28

COMORBILITA' E DISABILITA' NEI SOGGETTI DEMENTI: RISULTATI DAL PROGETTO ReGAl DELLA SIGG

Sara Ercolani, *Elena Mariani, Miriam Caputo, Francesca Mangialasche, Tiziana Ingegni, Umberto Senin, Patrizia Mecocci e il gruppo del Progetto ReGAl.*

Istituto di Gerontologia e Geriatria, Università degli Studi di Perugia

Scopo della ricerca Relativamente pochi studi hanno esaminato la prevalenza delle condizioni mediche concomitanti nei soggetti dementi. In questo studio epidemiologico trasversale abbiamo esaminato la prevalenza della comorbilità e il suo impatto funzionale nei soggetti anziani con deficit cognitivi e con demenza.
Materiali e Metodi Sono stati analizzati i dati provenienti dal Progetto ReGAL (Rete Geriatrica Alzheimer della SIGG). In particolare dei 3467 soggetti, valutati in 39 centri italiani specializzati in problemi di memoria dal gennaio 2001 al gennaio 2004, sono stati presi in considerazione i dati relativi a 3114 soggetti controllo, quelli con diagnosi di depressione, di MCI o di demenza. Ciascun paziente è stato valutato accuratamente secondo un protocollo standardizzato. Per quantificare la comorbilità è stata usata la Cumulative Illness Rating Scale (CIRS). Lo stato funzionale è stato valutato mediante le ADL (Activity Daily Living): da 0 (dipendenza completa) a 6 (indipendenza).
Risultati La popolazione presa in esame è formata da 2062 femmine (età media 77,4 ± 7,4 anni, scolarità 5,3 ± 3,4 anni e punteggio medio al MMSE 18,6 ± 5,9) e 1052 maschi (età media 76,1 ± 7,3 anni, scolarità 7 ± 4,4 anni e punteggio medio al MMSE 20,2 ± 6,4). In base alla diagnosi principale la popolazione risulta così suddivisa: controlli 7,8%, depressi 7,8%, demenza di Alzheimer (AD) 53,9%, Demenza fronto-temporale (FTD) 3%, demenza a corpi di Lewy (LBD) 1,1%, Parkinson Plus (PPD) 0,7%, Demenza vascolare (VaD) 7,3%, Demenza mista (Mix) 11,7% e Mild Cognitive Impairment (MCI) 6,9%. I soggetti con AD e FTD hanno una comorbilità significativamente più bassa rispetto agli altri tipi di demenza, al MCI ed ai soggetti cognitivamente integri ($p<0,001$). Le differenze più importanti sono soprattutto con i VaD e i Mix, ma è interessante notare che tali soggetti, rispetto agli AD e ai FTD, hanno significativamente maggiore sia la comorbilità vascolare (somma dei punteggi della CIRS della sfera vascolare: cardiologico, vascolare, ipertensione, endocrinologico) che quella non vascolare (somma dei restanti subitem della CIRS degli apparati non vascolari). Correggendo per sesso, età, scolarità e MMSE, la comorbilità (valutata sia come punteggio totale, che come comorbilità vascolare e non vascolare) e la comorbilità complessa (numero di subitem con punteggio ≥ 3) aumentano il rischio di disabilità grave (almeno una ADL persa) in tutte le classi diagnostiche considerate.
Conclusioni I soggetti con demenze di tipo degenerativo hanno la tendenza ad avere una comorbilità significativamente più bassa rispetto ai soggetti con forme vascolari o miste e ai soggetti con MCI e cognitivamente integri. Intervenire sulla comorbilità potrebbe ridurre la disabilità nei soggetti anziani con deterioramento cognitivo.

60

POSTERIOR CORTICAL ATROPHY: A CASE STUDY

***Agnese Fiorino*[1]**, *Erica Altamura*[1], *Alessandra Barbieri*[1], *Raffaella Mossini*[2], *Eliana Schiatti*[2] *Giuseppe Magnani*[2], *Giancarlo Comi* [2], *Massimo Franceschi*[3] *e Monica Falautano*[1]

[1] Functional Unit of Psychology, [2] Department of Neurology and Clinical Neurophisiology, Università Vita-Salute Scientific Institute Hospital San Raffaele, Milan,[3] Neurology Department, Casa di Cura Santa Maria, Castellanza

Background: Atypical presentation of neurodegenerative dementing disorders include the syndrome of progressive posterior cortical atrophy (PCA), first described by Franck Benson in 1988, involving selective early impairment of higher order visusospatial and gnosic functions in presence of relatively preserved episodic memory, insight and judgment.
This is a rare disease with unknown frequency in the population, but it's an easily recognizable clinical syndrome very distinct from Alzheimer Disease (AD), although some authors use the term "visual variant form of AD" to describe it.
Early symptoms of PCA include blurred vision, difficulties in reading (particularly following the lines of text while reading), and problems with depth perception. As the disorder progresses, other symptoms evolve such as getting lost while driving or walking in familiar places, misrecognition of familiar faces and objects, alexia, constructional apraxia, ideomotor apraxia, agraphia and rarely, visual hallucinations.
Brain Magnetic Imaging (MRI) shows bilateral atrophy in the parietal and temporal-occipital areas, which is more severe in right hemisphere.
Method: We sought to add one new case to the body of existing literature about patients with progressive dementia with prominent early visuospatial deficits.
This study reports a case of a 62-year-old right-handed female, A.C., who manifested outstanding predominant praxic, reading and objects recognition deficits, in spite of preserved semantic knowledge of their characteristics, judging and language.
We used a broad spectrum of tasks to investigate properly the cognitive profile of the patient. They can be clustered in 4 main groups:

1. Index of general functioning
2. Language
3. Gnosic and praxic abilities
4. Executive function and attention

Results: A.C. was impaired in recognizing visually presented objects (visual agnosia), and didn't show global perception and analysis of things; she showed severe ideomotor, ideative and constructional apraxia. AC was instead surprisingly good in task that stressed logical verbal abilities, also in the difficult ones such as the recognition of semantic absurdity, short term memory and working memory.
MRI revealed bilateral parietal and occipitotemporal atrophy, and SPECT showed bilateral parietal hypoperfusion.
Conclusions: Our findings support Benson's hypothesis that posterior cortical atrophy is a clinical syndrome distinct from the amnesic syndrome usually described in AD patients.

61

CLOSING-IN AS AN ALZHEIMER DISEASE (AD) NEUROPSYCHOLOGICAL MARKER: SENSITIVITY AND SPECIFICITY

***Giovanni Battista Flebus*[1],** *Stefano Zago*[2-3], *Alessia Monti*[2], *Barbara Poletti*[3]

[1]University of Milan, Bicocca, Milano, Italy
[2]Department of Neurological Science - University of Milan Medical School - IRCCS Ospedale Maggiore, Milano, Italy
[3]Dep. Neurology and Lab. Neuroscience - "Dino Ferrari" Center - University of Milan Medical School - IRCCS Istituto Auxologico Italiano, Milano, Italy

Background. The *closing-in* phenomenon, described first by Mayer Gross (1935, 1936) and then studied in detail in various pathological conditions by Muncie (1938) and Gainotti (1972), consists in the tendency to close-in to the model, copying as near as possible to the model or even into it, while performing constructive tasks (Gainotti et al., 1992). The aim of this study is to determine if the closing-in phenomenon is a good marker of dementia and to evaluate the sensitivity and the specificity of this behaviour as a diagnostic marker of Alzheimer Disease (AD).
Methods. The sample is made up of 52 patients (20 males and 32 females) with neuropsychological assessment, referring to the Alzheimer Valuation Unit (UVA) of Ospedale Maggiore in Milan. Different cognitive domains were investigated: global cognitive function, attention, executive functions, language, problem-solving, memory, visuo-spatial functions, praxis and visual recognition. Twenty-five of these subjects were diagnosed as AD (Alzheimer Dementia); 14 as MID (Multi-Infarct Dementia); 13 as other forms of dementia. Fifty-four normal subjects, not demented neither affected by focal or diffuse lesions (comparable to the groups of demented patients in terms of age and educational level) formed the control group.
Results. There is a significant statistical correlation with the presence of the closing-in phenomenon and low scores on the MMSE (Mini-Mental State Examination) and so its absences with the high ones (r_{pb}= -0.424 $p < 0.005$). The specificity of this marker was good (85%), although its sensitivity was only 20%. Even though this marker is capable to identify AD patient at an acceptable level of specificity it is not enough sensitive.
Conclusion. In summary this study showed that this marker is specific but not sensitive by itself to be considered as a good diagnostic marker for the early forms of cognitive impairment. A higher level of sensitivity and specificity has been reached considering more than one cognitive marker (as reported in Zago et al. in this poster session (*Cog-Markers*: standardizzazione e taratura di un nuovo strumento per la diagnosi e la stadiazione della malattia di Alzheimer).
References. Mayer Gross W. (1936) Further observation on apraxia. *Journal of Mental Science,*82,744-762.
Muncie W. (1938). Concrete model and abstract copy: a psychobiological interpretation of the 'closing-in' symptom of Mayer Gross. *Journal of Nervous and Mental Disease,*88,1-11.
Gainotti G., Parlato V., Monteleone D. and Carlomagno S. (1992) Neuropsychological markers of dementia on visuo-spatial tasks: a comparison between Alzheimer's type and vascular forms of dementia. *Journal of Clinical and Experimental Neuropsychology,* 14, 239-252.
Gainotti G., Marra C., Villa G., Parlato V., Chiaretti F. (1998). Sensitivity and specificity of some neuropsychological markers of Alzheimer Dementia. *Alzheimer Disease and Associated Disorders*,12, 152.

47

ON THE NATURE OF THE MEMORY DEFICIT IN PRECLINICAL AD: HINTS FROM THE SERIAL POSITION CURVE

***Elisabetta Forapani**, Valeria Isella, Francesca Piamarta, Ildebrando Marco Appollonio*

Neurology Section, S. Gerardo Hospital, Monza, DNTB, University of Milan Bicocca

Background: Anterograde verbal memory impairment deriving from mesial temporal lobe involvement represents the neuropsychological hallmark and the earliest manifestation of Alzheimer's disease (AD). Its basic cognitive underpinnings represent a long-standing dilemma: inefficient encoding, poor consolidation, accelerated forgetting or deficient retrieval may all hypothetically contribute to memory breakdown associated with AD pathology. One approach to the issue may be the study of the free recall serial position curve. Better recall of early and late items in a word list is a well known and awfully consistent phenomenon, thought to reflect the long-term (primacy effect) and short-term (recency effect) components of memory. In the present study we assessed the serial position curve in a particularly pure hippocampal amnesic syndrome, i.e. Mild Cognitive Impairment (MCI) with an isolated memory deficit.
Methods: We assessed primacy and recency effects at Rey's Auditory Verbal Learning Test (RAVLT) in 30 patients with amnesic MCI (defined according to Petersen's outlines), 30 patients with mild AD (diagnosed according to NINDS-ADRDA criteria) and 30 normal controls (NC) of comparable age, gender and education. Modelling of the serial position curve at the first immediate recall and comparison of forgetting rates from the different list positions passing from the fifth immediate to the delayed recall were the variables of interest.
Results: The three study groups had overlapping socio-demographic features. MMSE and RAVLT immediate recall scores were significantly different among the three study groups, with intermediate values for MCI patients, while RAVLT delayed scores were similar for AD and MCI patients and significantly worse than for NC subjects. At the first immediate recall, MCI and AD patients displayed a recency effect analogous to that of NC, while primacy effect was null in both cognitively impaired subgroups (Figure 1). Memory decay from the fifth immediate to the delayed recall was disproportionately large at the recency tract for MCI and AD patients with respect to healthy controls (Figure 2).
Conclusions: In line with previous literature data, in mild AD we found loss of the primacy effect, coupled with preservation of the recency effect, and a predominant memory decay from recency positions at delayed recall, suggesting lack of transfer of memories from short- to long-term stores. Interestingly, MCI patients showed exactly the same pattern of memory defects. Overall, these findings indicate that inefficient consolidation may account for amnesia in early AD. The potential contribution of these data to the diagnostic and prognostic work up of preclinical AD also deserve future verification.

Figure 1. Serial position curve at the first immediate recall for the three study groups.

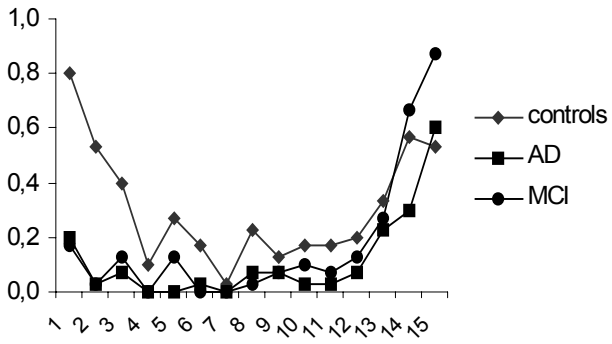
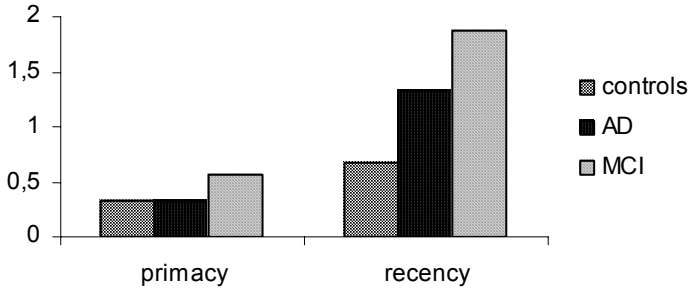


Figure 2. Memory decay (mean number of forgotten words) from primacy and recency positions for the three study groups.



29

CYP27 GENE MUTATION ASSOCIATED WITH COGNITIVE DETERIORATION AND PARKINSON'S DISEASE

***Carlo Gabelli*[1]**, *Giovanna Polesello*[2], *Patrizia Tarugi*[3], *Alessandra Codemo*[1], *Annachiara Cagnin*[1], *Elisabetta Gasparoli*[2], *Tommaso Scaravilli*[2], *Cristina Ruaro*[1], *Nicoletta Del Grosso Destreri*[1] *and Fulvio Bracco*[2].

[1]Centro Regionale per lo Studio e la Cura dell'Invecchiamento Cerebrale (CRIC)
[2]Dept. of Neuroscience, University of Padua
[3]Dept. of Biomedical Sciences, University of Modena

Cerebrotendinous xanthomatosis (CTX) is a rare autosomal recessive lipid storage disease caused by a deficiency of mitochondrial sterol 27-hydroxylase resulting in the accumulation of a bile alcohol and cholestanol in the nervous system, tendons and vessels. The heterogeneous phenotype includes juvenile cataract, Achilles tendon xanthomas, premature atherosclerosis, mental deterioration leading to dementia, pyramidal signs, cerebellar ataxia, peripheral neuropathy, and rarely parkinsonism.
Case report: the patient is a 42-year-old man, in his family there was three member with CTX and not consanguinity. His developed Achilles tendon xanthomas at the age of 32 and upon surgical removal of the xanthomas, was diagnosed CTX. Serum concentration of cholestanol was 3387 ug/dl, whereas serum total cholesterol concentration was quite normal (288 mg/dl: HDL 70 mg/dl, LDL 187.8 mg/dl). After four years of terapy with chenodeoxycholic acid, serum concentration of cholestanol decreased at 761 ug/dl. The diagnosis of CTX was cofirmed by mutation analysis of the sterol 27-hydroxylase gene (CYP27) mapped to chromosome 2. The patient is homozygote for a G → A transition at the first nucleotide of intron 7, a mutation causing the formation of minute amount of an abnormal mRNA, in which exon 6 joins directly to exon 8 with the skipping of exon 7.
The patient presented at the age of 40 years resting tremor and a rigidy and bradichinesia, akinetic hemisindrome gradually developed three years ago. Neurologic evaluation showed left side hemiparkinsonism, feexed posture, shuffling shortsteps on walking and mask-like oily face. There are not pyramidal or cerebellar signs. Neuropsycologic examination revealed a early stage of cognitive decline and a mild depression.
The RMI detected small diffuse cerebral atrophy, no abnormality was detected in basal ganglia or midbrain, the18F-FDG PET showed reduced uptake in the associative cortex, IBZM SPECT was normal, DaTscan showed reduced uptake in the right side of the basal ganglia. EMG and evoked potential was normal.
Given the young age of onset and despite the lack of family history, we excluded the presence of a Parkin mutation.
Liquor concentration of cholestanol was 31 ug/dl; Tau in the cerebrospinal liquor was 129 pg/mL, and protein 14-3-3 research was positive.
Apomorphine test with 3 mg s.c. moderately improved tremor and bradychinesia. The patient was treated with L-dopa-carbidopa 300 mg/day added of current terapy with chenodeoxycholic acid with improvement of the parkinsonian signs (UPDRS motor score of 50%). One year after the onset of this treatment the response is constant and motor fluctuations and dyskinesias are not present.
Discussion and Conclusion: The case reported confirms the wide phenotypic and molecular heterogeneity of CTX. The neurological presentation with predominance of extrapyramidal signs is atypical. In this patient, the clinical features, the good response to L-dopa therapy, suggest a presynaptic impairment of the dopaminergic nigrostriatal pathway with preserved postsynaptic D2 confirmed by DaTSCAN and IBZM SPECT. The early onset Parkinson could by a possible manifestation at exordia of CTX.

36

CSF CHEMOKINE LEVELS: DIFFERENCES AMONG MCI, AD AND FTLD PATIENTS. IMPLICATION IN AD PATHOGENESIS AND POSSIBLE RELEVANCE FOR EARLY DIAGNOSIS

***Daniela Galimberti*[1]**, *Niki Schoonenboom*[2a,b], *Philip Scheltens*[2a], *Chiara Fenoglio*[1], *Eliana Venturelli*[1], *Diego Scalabrini*[1], *Nereo Bresolin*[1], *Elio Scarpini*[1]

[1]Dept. of Neurological Sciences, "Dino Ferrari" Center, University of Milan, IRCCS Ospedale Maggiore Policlinico, Via F. Sforza 35,20122, Milan, Italy
[2]VU University Medical Center, [a]Dept. of Neurology and Alzheimer Center, [b]Dept. of Clinical Chemistry, Amsterdam, The Netherlands

A chronic inflammatory reaction plays an important role in the early pathogenesis of AD and a variety of inflammatory factors including cytokines and chemokines, have been detected in and around plaques and tangles. CSF TNF alpha, as well as MCP-1 and IL-8 levels, were found to be increased in AD patients, while IP-10 levels were increased only in a subgroup of patients, and correlated negatively with cognitive decline, suggesting a role of IP-10 in the early stages of the disease.
CSF IP-10, MCP-1 and IL-8 levels were determined in 36 subjects with MCI, 28 AD and 19 FTLD patients, as compared with 40 age-matched controls. IP-10 concentration was markedly increased in MCI and mild/moderate AD, but not in severe AD or in FTLD patients. MCP-1 and IL-8 levels were increased in all individuals studied, with highest peaks in MCI and mild AD patients.
Inflammation is likely to be a very early event in AD pathogenesis, preceding the clinical onset of the disease. While IP-10 is specifically increased in AD, MCP-1 and IL-8 are upregulated also in FTLD, suggesting a role in a common step involved in neurodegeneration. CSF chemokine evaluation could clarify AD pathogenesis, and in combination with A beta and tau determination, may represent a useful tool for early diagnosis.

21

ALZHEIMER'S DISEASE RISK FACTORS: ANALYSIS AFTER ONE YEAR TREATMENT

Gloria Galimberti[1], *Elisa Conti*[1], *Fabrizio Piazza*[1], *Tiziana Speranza*[2], *Daniela Belotti*[2], *Carmen Galbusera*[3], *Maurizio Facheris*[1], *Valeria Isella*[4], *Enrico Maria Pogliani*[2], *Marzia Galli-Kienle*[3] *and Carlo Ferrarese*[1,4].

[1]Department of Neurosciences and Biomedical Technologies, [2]Department of Clinical Medicine, Prevention and Sanitary Biotechnology, [3]Department of Experimental and Environmental Medicine, University of Milano-Bicocca, Milan, Italy. [4]Department of Neurology, S. Gerardo Hospital, Monza (MI), Italy.

Background: It is well known that various risk factors are involved in the development of Alzheimer's disease (AD). Among them high homocysteine (Hcy) plasma level, linked to low folate amount, represent a novel parameter which could be easily investigated. Increased Hcy plasma levels were found in AD patients with respect to Mild Cognitive Impairment (MCI) and control subjects (ctrls). Moreover, in vitro studies evidenced a role of this sulfur-containing amino acid in inducing oxidative damage and cell death. Based on this findings, we measured Hcy and folate plasma content in AD patients compared to MCI and controls subjects. On the same population we investigated other peripheral markers of oxidative stress and vascular damage in order to evidence possible correlations among them and/or the clinical features. The analyses were performed at the recruitment and after one year treatment with folate or vitamins C and E.
Methods: 84 AD patients, 34 MCI and 41 ctrls were recruited at the Department of Neurology (S. Gerardo Hospital, Monza), Department of Medical and Surgical Sciences (University of Brescia), Department of Neurological Science (University of Milan) and Department of Neuroscience (University of Roma "Tor Vergata"). After informed consent, blood samples were withdrawn and plasma was obtained by centrifugation. Hcy and folate levels were determined by each clinical centre following standard protocols. Thiobarbituric acid reactive species (TBARS) were measured by mass spectrometer after Copper incubation and Tissue Factor Pathway Inhibitor (TFPI) was detected by commercial ELISA kit. Among all patients and controls, a first subgroup was treated with vitamins C and E, a second one with folate and a third one didn't receive any therapy. After one year, all the analyses were repeated.
Results: Hcy basal levels were found significantly increased in AD (+58%, $p<0.05$) with respect to controls, however no differences were evidenced in folate amount. AD patients showed TFPI values significantly higher (+110%, $p<0.001$) than controls. TBARS levels seemed to increase following disease progression, but there were no relevant differences among categories. However, after one year vitamin treatment, AD and MCI subjects showed significant TBARS decreased (-60%, $p<0.01$). Hcy was lowered by folate therapy in subjects having out of range values, but seemed to be slightly increase by vitamins. Folate values followed a complementary trend. Generally, people with no treatment, showed no changes in all the analysed parameters.
Conclusions: Our studies suggested the importance of monitoring Hcy plasma level as a risk factor for AD and the possibility to lower its amount with folate therapy. Vitamins seemed to exert a positive action on peripheral marker of oxidative stress as TBARS. Moreover, elevated TFPI in AD patients confirmed the involvement of vascular damage in this degenerative disorder. These data suggested the importance to investigate these parameters in AD, but also in MCI who represents a pre-clinical stage of the disease. Vitamins and/or folate could be useful as a supporting therapy added to the traditional one.

9

ADENOSINE A2A RECEPTOR LEVELS IN DIFFERENT PERIPHERAL CELLS OF ALZHEIMER'S DISEASE PATIENTS

***Lorenza Galimberti*[1]**, *Beatrice Arosio*[1], *Carmen Calabresi*[1], *Silvia Scurati*[1], *Susanna Hamilton*[1], *Simona Delli Carpini*[1], *Giorgio Annoni*[2] *and Carlo Vergani*[1]

[1]Department of Internal Medicine, Chair of Gerontology and Geriatrics, IRCCS Foundation, Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, University of Milan, Milan, Italy;
[2]Department of Clinical Medicine, Prevention and Medical Biotechnology, University of Milano-Bicocca, Milan, Italy

Adenosine is an important endogenous purine neuromodulator of the central nervous system that mediates many important cellular processes. The physiological effects of adenosine are transduced through four different receptor types, A1, $A2_A$, $A2_B$ and A3. All adenosine receptors are G-protein coupled receptors (GPCR) of the type 1 variety which act by stimulating or inhibiting adenylyl cyclase. In particular the A2a receptor subtype seems to be implicated in neuroprotective mechanisms and interestingly one of its main function is to turn off the inflammatory response. The aim of this study was to investigate if an altered expression and/or function of A2a receptors, could contribute to the neurodegenerative mechanisms involved in Alzheimer's disease (AD). We analysed the expression of this receptor in platelets and Peripheral Blood Mononuclear Cells (PBMCs) from AD patients and sex- and age-matched healthy controls (HC); furthermore we analysed a T/C single nucleotide polymorphism (SNP) at position 1083 of exon 2 of the A2a gene that seems to be correlated with other neurodegenerative disorders. We found no statistical significative differences in the distribution of this SNP between AD and HC. By contrast the A2a mRNA levels in platelets were 25% higher in HC than AD (1.09 and 0.82 respectively; p=0.000). To confirm these data we analysed in a wider group of AD and HC the mRNA and protein expression of A2a in PBMCs. The preliminary results match with those obtained from platelets, suggesting a lower ability of AD subjects to terminate the inflammatory response and indicating a possible role of the A2a receptor in the pathogenesis of AD.

48

STUDIO DELLE CARATTERISTICHE DEI PAZIENTI AFFETTI DA MALATTIA DI ALZHEIMER E DA DEMENZA VASCOLARE, UTILIZZANDO LE SELF-ORGANIZING MAPS (SOM)

Maurizio Gallucci* , *Enzo Grossi**, Marco Intraligi***, Vittorio Carlei***, Francesco DiPaola[+], Stefano Curtolo[+], Monica Ronzon[+], Andrea Zanardo[¶], Massimo Buscema****

*Unità Valutativa Alzheimer Osp. Treviso, **Bracco SpA Milano, ***Centro Ricerche Semeion Roma, [+]Neuroradiologia Osp. Treviso, [¶]Laboratorio Chimica Clinica Osp. Treviso.

Le tecniche statistiche tradizionali non riescono facilmente a proiettare nello spazio bidimensionale soggetti descritti da un gran numero di variabili, senza operare selezioni basate sui parametri statistici usuali (varianza, correlazione lineare, media). L'uso di un particolare tipo di reti neurali non supervisionate chiamate Self-Organizing Map (SOM), permette di esprimere la clusterizzazione naturale dei soggetti in studio, utilizzando tutta l'informazione offerta dalle numerose variabili. L'obiettivo dello studio è stato, quindi, quello di applicare questa metodologia ad un database di soggetti dementi, afferenti all'Unità valutativa Alzheimer di Treviso, descritti da numerose variabili.
E' stato allestito un database composto di 190 soggetti (146 AD diagnosticati secondo i criteri NINCDS-ADRDA, 44 VD secondo i criteri NINDS-AIREN) con circa un centinaio di parametri completi per ciascun soggetto. Ogni soggetto è caratterizzato da dati generali [diagnosi, età, sesso, stato civile, lavoro, anni di istruzione scolastica, consumo d'alcool, familiarità per demenza, body mass index, fumo, incontinenza, ritmo sonno-veglia], da esami di laboratorio (i principali parametri ematochimici compresi omocisteina, TSH, folati e vit. B12), dal numero di malattie per ciascun apparato od organo, da dati neuroradiologici alla TAC (atrofia corticale, sottocorticale, ipodensità della sostanza bianca, lacune, infarti, emorragie e neoplasie, caratterizzati ciascuno per numero, grado, regione di appartenenza e lateralità) compresa la misura dell'ampiezza dei corni temporali dei ventricoli laterali, quale indice dell'atrofia della regione temporo-mesiale. L'orientamento della sezione alla TAC è stato di -20° rispetto alla linea orbitomeatale. Le misure sono state rilevate nella zona di massima ampiezza radiale in modo tale che riportassero una misura indiretta dell'atrofia ippocampale, dando un'indicazione riguardo la perdita neuronale a livello della "testa" dell'ippocampo.
I soggetti sono stati descritti attraverso una batteria di test neuropsicologici (*MMSE, Memoria di prosa, Digit Span, Parole di Rey, Matrici attentive, Fluenza verbale fonologica, semantica, Token Test*) e valutando l'autonomia nelle attività della vita quotidiana (*ADL, IADL*), la Hachinski Ischemic Scale, la gravità complessiva (*CDRS, Clinical Dementia Rating Scale*), la eventuale depressione (*GDS, Geriatric Depression Scale, HDRS, Hamilton Depression Rating Scale*) ed i disturbi comportamentali (*NPI Neuropsychiatric Inventory*).
Il sistema matematico utilizzato, la Self-Organizing Map (SOM), un algoritmo non supervisionato, correggendo i "pesi" dopo la presentazione di ogni ingresso auto-organizzandosi, realizza mappe bidimensionali di aggregazioni di parametri con un maggior dettaglio nelle regioni dello spazio di ingresso per le quali più alta è stata la frequenza dei valori di input. L'utilità è cogliere correlazioni sfumate che la statistica classica potrebbe trascurare.
La SOM ha separato nettamente la AD da VD. La analisi della distribuzione dei valori delle variabili nei due clusters permette di interpretare il contributo di particolari fattori alla distinzione dei due gruppi di appartenenza. Il fattore vascolarità è risultato ad esempio presente, anche se con valori lievi, anche nel cluster AD, confermando la presenza di un certo danno ischemico anche nel cervello AD(1).

Il parametro “fumo”, noto fattore di rischio per la patologia vascolare è, nella mappa SOM, completamente appannaggio della VD. L’assenza di lacune cerebrali è risultata tipica del cluster AD, mentre i parametri “lesioni vascolari dei gangli della base”, “presenza di una o due lacune” e “presenza di più di due lacune” sono risultati associati alla VD. L’atrofia del lobo temporale è strettamente correlata alla AD. L’omocisteina e la massima ampiezza tra i due corni temporali dei ventricoli laterali sono risultate legate tanto all’AD quanto alla VD.
In conclusione la SOM si presta nel cogliere interessanti relazioni tra AD e VD e può offrire un contributo importante alla più precisa caratterizzazione di questi pazienti. Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR. *Brain infarction and the clinical expression of Alzheimer disease. The Nun Study*. JAMA. 1997 Mar 12;277(10):813-7

37

FOLIC ACID AND ALZHEIMER DISEASE

***Elena Gatti*[1]**, *Emanuela Cazzaniga*[1], *Alessandra Bulbarelli*[1], *Massimo Masserini*[1]

[1]Dept. Experimental Medicine, University of Milano-Bicocca, Via Cadore 48, 20052- Monza, Italy

Background: Folate deficiency has long been implicated in cardiovascular disorders, and only recently it is becoming apparent that it also contributes to many neurological and psychological disorders including dementia, impaired cognition, depression, psychosis, and Alzheimer's disease. Low serum folate levels are strongly associated with atrophy of the cerebral cortex. Diminished folate levels are associated with a twofold increased risk in developing AD. The full range of mechanisms by which deficiencies in folate may contribute to neurodegeneration is unclear. The aims of this research are: (1) to establish a possible correlation between levels of folate (serum and red cells) and state of dementia (assessed by Mini Mental State Examination); (2) to ascertain possible differences in folate metabolism of AD patients and control subjects, by assaying folate binding of cultured fibroblasts.
Methods: We included 45 probable AD patients (age 79 ± 4,3 years) and 25 control subjects who were age-related (age 69 ± 3,36 years). Global cognitive function was assessed in AD subjects by using the Mini-Mental State Examination. Control subjects had neither active medical problems, nor personal or family history of neurological and psychiatric disorders. Serum and red cell folate were measured by Axsym system Kit (Abbott). Human skin fibroblasts were cultured with and without folate at 37°C in a humidified atmosphere of 95% air and 5% CO_2. To measure folate binding, on day 6th of cell growth, the medium was removed by aspiration and 1.5 ml of medium containing ^{3}H-folic acid (0,4x10 $^{-3}$microCi/ml) were added to each Petri dish. Experiments on AD and control fibroblasts were performed at the same stage of doubling in culture. After 4 hours incubation at 37 °C, cells were chilled on ice and the medium was removed by aspiration. After rinsing 3 times with ice-cold PBS, folate was released from the cells by washing rapidly for 2 minutes with 2 ml of ice-cold acid saline followed by a rinse with 1 ml of cold PBS. The radiolabeled folate in the acid saline, plus the 1 ml of cold PBS wash, represented acid-releasable folate and was measured by liquid scintillation counting. The cells were then detached from the culture dishes by incubating with trypsin-EDTA and then rinsing twice. The trypsin-EDTA suspension and washes were combined and the radioactivity, which corresponded to acid-resistant folate, was determined by liquid scintillation counting. Protein assay was performed according to Lowry protocol.
Results: AD patients have a lower concentration of serum folate than control subjects (AD 5,6 ± 4,6 ng/ml; Ctr 7,6 ± 3,2 ng/ml, p=0,02) while no difference in concentrations of red cells folate was remarked. MMSE and serum folate concentration are inversely correlated (p=0,0037) in AD patients. Fibroblasts of AD patients bind more tritiated folic acid than control subjects (Ctr 11,3 ± 8,8 dpm/microg prot ; AD 56,4 ± 54,6 dpm/microg prot; p=0,004)
Conclusion: AD patients have lower serum folate concentration than control subjects; the lower is serum folate, the higher is the stage of dementia. The great folic acid-binding ability of AD fibroblasts could explain the lower serum folate levels of AD subjects.

38

DEFICIT SPECIFICI E CIRCOSCRITTI DEL FLUSSO EMATICO CELEBRALE CARATTERIZZANO I VARI SOTTOTIPI DI MC

[1]***Caterina Ghetti,*** [2,3,5]*Paolo Caffarra,* [5]*Francesca Dieci,* [5]*Sandra Copelli,* [5]*Giovanni Messa,* [3,4]*Annalena Venneri*

[1]Fisica Sanitaria, Azienda Ospedaliera-Universitaria, Parma, [2,3]Dipartimento di Neuroscienze, Università di Parma, [3,4]Clinical Neuroscience Centre, University of Hull, UK, [4]Dipartimento di Neuroscienze, Università di Modena e Reggio Emilia, Consultorio Disturbi Cognitivi, AUSL, Parma.

Background: la definizione di Compromissione Cognitiva Lieve (Mild Cognitive Impairment, MCI) fu introdotta alcuni anni fa per descrivere un profilo cognitivo caratterizzato da un interessamento della memoria con prestazioni sostanzialmente inferiori rispetto a quelle rilevabili nei soggetti di età corrispondente, in assenza di altri deficit cognitivi e di demenza. Sebbene la compromissione della memoria rappresenti il sintomo principale, più recentemente sono comparse numerose osservazioni che testimoniano la presenza di deficit anche in altre funzioni (ad esempio di tipo esecutivo, prassico oppure deficit lievissimi rilevabili in più funzioni), in assenza di compromissione della memoria. Queste osservazioni hanno portato all'identificazione di distinti profili neuropsicologici che caratterizzano diversi sottotipi di MCI.
Tuttavia, nonostante il progredire delle conoscenze sulle varie tipologie dell'MCI, non sono ancora disponibili studi che comprovino se tali aspetti abbiano un substrato neuroanatomico oppure siano la conseguenza di artefatti psicometrici derivanti dall'uso di strumenti di valutazione poco affidabili e di scarsa sensibilità e specificità.
Studi di neuroimaging strutturale e funzionale condotti su pazienti affetti dalla variante amnestica dell'MCI hanno mostrato la presenza di alterazioni morfologiche e metaboliche cerebrali in sede temporale mediale, nel talamo, nella corteccia del cingolo ed in sede parietale.
Scopo del presente lavoro è stato quello di verificare se ai vari sottotipi neuropsicologici di MCI corrispondono pattern di ipoperfusione cerebrale diversi.
Methods: sono stati analizzati i profili di flusso ematico cerebrale di tre gruppi di soggetti con MCI (amnesici, disesecutivi e con deficit multipli) confrontati con quelli di 10 individui sani.
Il flusso ematico cerebrale è stato valutato mediante l'uso della Tomografia ad Emissione di Fotoni Singoli (SPECT), utilizzando il software Statistical Parametric Mapping 2 (SPM2; Wellcome Department of Imaging Neuroscience, London, UK) per i confronti statistici fra i vari pattern ematici cerebrali dei diversi sottotipi di MCI.
Result: i risultati mostrano la presenza di una riduzione significativa del flusso ematico cerebrale nelle regioni del giro paraippocampale e postcentrale a sinistra e nell'area fronto-temporale destra nel gruppo amnesico; nel giro frontale superiore e nella corteccia del cingolo a sinistra e nel giro frontale medio a destra nel gruppo disesecutivo ed infine nel giro angolare sinistro, nelle aree frontali destre e nella corteccia del cingolo bilateralmente nel gruppo con deficit multipli.
Conclusion: questi risultati confermano l'ipotesi che i diversi profili neuropsicologici che caratterizzano i sottotipi di MCI riflettono alterazioni funzionali cerebrali piu' o meno circoscritte alle aree cerebrali preposte alle competenze cognitive di cui si osserva un deficit nel profilo neuropsicologico. La natura del danno neurobiologico sottostante potrà essere chiarita solo dallo studio longitudinale della progressione del quadro clinico.

62

PATTERNS OF BEHAVIORAL SYMPTOMS IN ALZHEIMER'S DISEASE AND LEWY BODIES' DISEASE ACCORDING TO DEMENTIA SEVERITY

***Nicola Gilberti*[1], *Stefano Gipponi*[1], *Chiara Agosti*[1], *Chiara Costanzi*[1], *Marcella Broli*[1], *Barbara Borroni*[1], *Alessandro Padovani*[1]**

Department of medical Sciences, Neurological Clinic, University of Brescia, Italy

Background: Alzheimer's disease (AD) and Lewy bodies' disease (LBD) are characterized by different behavioural symptoms. AD patients exhibit a variety of behavioural alterations including agitation, apathy, depression, anxiety, delusions, irritability and disinhibition. Some studies have shown that behavioural changes become more frequent with advancing disease severity. No studies have evaluated the relationship between severity of the disease and behavioural alterations in LBD.
Objective: the aim of this study was to investigate whether different behavioural patterns exist between of AD and LBD in different stages of dementia severity.
Materials and Methods: patients were diagnosed according to published criteria for LBD and AD. 215 AD patients and 69 LBD patients were enrolled into the study. According to MMSE score, >19 for severe groups and ≤19 for mild groups, patients was divided in mild (AD= 111 patients; LBD= 52) and severe (AD=104 patients; LBD= 16). The Neuropsychiatric Inventory was administered to all patients.
Results: AD patients had a mean MMSE score =18,49 [±6,04] and mean NPI total score =23,08 [±16,68] while LBD patients a mean MMSE score =22,58 [±5,49] and mean NPI total score =26,85 [±17,44].
Mild AD patients had a mean MMSE score =23,15 [±2,53] and mean NPI total score =20,81 [±15,07] while mild LBD patients a mean MMSE score =25,13 [±2,89] and mean NPI total score =23,85 [±16,14]. Hallucinations and sleep disorders had a significant greater ($p<0,05$) prevalence in mild LBD versus mild AD. We have also found that sleep disorders and depression in mild LBD were more severe ($p<0,05$) than in mild AD.
Severe AD patients had mean MMSE score =13,52 [±4,55] and mean NPI total score =25,5 [±18,00] while severe LBD patients a mean MMSE score =14,12 [±2,89] and mean NPI total score =36,81 [±18,40]. The difference was significant ($p<0,05$) between mean NPI total score of severe AD patients versus severe LBD patients. Hallucinations and sleep disorders had a significant greater ($p<0,05$) prevalence and severity in severe LBD versus severe AD.
NPI total score, prevalence of agitation, wandering, sleep disorders and appetite disorders were significantly greater ($p<0,05$) in severe AD versus mild AD. In AD patients the severity of some symptoms such as apathy, appetite and sleep disorders increased significantly ($p<0,05$) with the severity of disease.
NPI total score, prevalence of delusions and hallucinations were significantly greater ($p<0,05$) in severe LBD versus mild LBD. In these patients the severity sleep disorders and hallucinations increased significantly ($p<0,05$) with the progression of disease.
Conclusions: Both AD and LBD patients present BPSD to high frequency across severity of dementia though with a differential pattern. LBD patients are more severely affected by hallucinations, sleep disorders and depression. These findings seem to suggest a differential neuropathologic involvement and might be of help in the diagnostic classification of the two most prevalent degenerative dementias.

10

FOLATE DEFICIENCY AND ALZHEIMER'S DISEASE: A LINK BETWEEN DIET AND NEURODEGENERATIVE DISORDERS

***Claudia Gravaghi*[1]**, *Anita Ferraretto*[1], *Elena Gatti, Emanuela Cazzaniga, Marina Pitto e Massimo Masserini.*

[1] Department of Medical Chemistry, Biochemistry and Biotechnology, University of Milan, via F. Cervi, 93, 20090 Segrate, Milan, and DIMESAB, University Milano-Bicocca, Monza.

Background: In recent years a growing body of evidence has supported the hypothesis that dietary deficiencies and genetic predisposition can influence age-related pathologies such as Alzheimer's disease and Parkinson's disease. At this regard, folate deficiency is linked to an increased cytosolic calcium concentration and oxidative stress due to high levels of homocysteine and a mitochondrial and DNA damage. All of these pathological conditions are also shared by Abeta peptide induced diseases at neuronal level. Thus, calcium homeostasis seems to be a central or, alternatively, a starting point for the events following the homocysteine accumulation in folate deficiency state and the Abeta peptide exposure of neurons. Abeta peptide is proven to impair intracellular calcium level in hippocampal neurons through different mechanisms acting across the plasma membranes and all providing an influx of calcium ions. In parallel, homocysteine accumulation is reported to increase cytosolic calcium level first via L-type channels, subsequently by NMDA receptors and efflux from internal source. For these reasons it appears of great importance to highlight the existing correlations between the folic acid deprivation during hippocampal neuron differentiation and Abeta peptide actions on plasma membranes.
Methods: Cultures of hippocampal neurons from embryonic day 18 of Charles River rats were prepared as described in literature. Folate-deprived cultures were obtained by growing neurons in folate-free medium. Intracellular calcium changes were monitored by fura-2 method on single cells through a High Speed Dynamic Video Imaging Systems. Abeta amyloid peptide (25-35) was dissolved in sterile ultrapure water at a final concentration of 1 mg/ml and kept frozen until use (at least one week).
Result: The hippocampal neurons, grown in a low density culture for 9 and 15 DIV, are different for morphology and number of cells, according with the presence or the absence of folate (+/-) in the culture medium. The folate (-) neurons show, already at 9 DIV, some thick neurites that become more evident at 15 DIV. Moreover, the number of surviving cells diminish with the days in culture in accordance with the fact that folate is an essential nutrient for brain tissue. We have previously demonstrated that the Abeta (25-35) peptide promotes a rapid intracellular calcium increase, triggering an influx through the plasma membrane, when is administered to the neurons folate +/- differentiated. The calcium influx, characterized for its kinetic and dose dependence, was now investigated in a Mg^{2+} free solution buffering the cells, to explore the NMDA receptor involvement. Both 9 DIV and 15 DIV neurons, folate (+/-), responded to Abeta (25-35) peptide with an elevated intracellular calcium rise and with an higher number of responsive cells compared to neurons examined in the presence of Mg^{2+}. The maximal effect was monitored in neurons cultivated in folate (+) medium from 9 to 15 DIV. Folate (-) hippocampal neurons are always less responsive compare to folate (+). The Abeta (25-35)-induced calcium influx emerges to be dependent from the NMDA receptor activation and, for a minor component, by the L-Type High Voltage calcium channel, expressed in a different way according with the DIV. The changes in cholesterol content at the level of plasma membranes are also involved in this Abeta induced effect, since the treatment with methyl-β̃ cyclodestrin to remove, or with the complex methyl-β̃cyclodestrin-cholesterol, to increase cholesterol, are followed by a lack of cytosolic calcium changes after Abeta peptide administration.

Conclusion: All of these results encourage to study the existence of a correlation between the neuronal plasma membrane structure, L-Type High Voltage calcium channel and NMDA receptors during the differentiation and the folate-deficiency consequences at this level.

49

PILOT STUDY ON THE USE OF ARTIFICIAL NEURAL NETWORKS IN PREDICTING COGNITIVE DECLINE FROM QUALITATIVE AND QUANTITATIVE FOOD CONSUMPTION IN EPIC-GREEK STUDY

E.Grossi*, *M.Buscema**, M.Intraligi**, A.Trichopoulou§§, D.Trichopoulos §§*
U.Cornelli§

*Bracco SpA Milano, ** Semeion Research Centre, Rome, § Loyola University Medical Center, Chicago, USA,§§ Department of Hygiene and Epidemiology, University of Athens.

The relationship between dietary intake and cognitive performance in elderly people are matter of controversy in the literature, especially as regards the role played by saturated fat and alcohol.
We have performed a pilot investigation on a random sub sample of EPIC Study, a population-based, prospective investigation involving 22,043 adults in Greece who completed an extensive, validated, food-frequency questionnaire at base line and have been followed for a median of 44 months. The data set consisted in 100 subjects(35 males; 75 females; mean age = 65 years ; range = 58-79) and by 104 independent variables describing demographic and lifestyle habits, quantitative intake of nutrients and qualitative intake of 72 different kinds of food classes.
The dependent variables were represented by two classes of Mini Mental State Examination (MMSE) scores: MMSE<26 (cognitive decline; N= 28), and MMSE_>26 (normal cognitive function; N=72)
No relevant differences were observed between the two groups in average quantitative daily intake of specific nutrients or foods and the linear correlation values between independent and dependent variables were extremely low. This gave the rationale for the use of Artificial Neural Networks (ANNs), able to compute highly non linear functions.
Two kinds of protocol were utilized for the classification problem**:**
Random protocol consist in 5 iterations of 2-fold cross-validation protocol (5x2 cross validation). The whole group of patients was five times randomly divided into 2 sub-samples, thus allowing 10 complete elaborations with the same type of ANN (the Back Propagation Standard). The same sub-samples were also used for the LDA (Linear Discriminant Analysis).
Optimized protocol: in this case, the whole group of patients was divided five times into 2 sub-samples using an Artificial Organism (T&T) created by Semeion.
Subsequently, each sub-sample couple was processed by a second Artificial Organism (I.S.) in order to reduce the number of input variables and, therefore, to select the most significant among the 94. In this experimentation Feed Forward ANNs, based on Back Propagation learning laws (FF_BP) were utilized. The table summarizes the results obtained.

EPIC GREECE - SUMMARY - AVERAGE RESULTS							
PROTOCOL	MODEL	Num	Cogn.Decline	Normal	A.Mean Acc	W.Mean Acc	Errors
RANDOM	LDA	10	60.00%	60.00%	60.00%	60.00%	20.0
	FF_Bp	10	73.57%	70.28%	71.93%	71.20%	14.4
T&T	FF_Bp	10	86.72%	86.91%	86.82%	86.12%	7.1
I.S.	FF_Bp	10	89.22%	86.23%	87.73%	86.35%	7.0

The analysis performed with linear models (discriminant analysis - LDA) reached unsatisfactory accuracy values(60%). The use of ANNs allowed very high predictive performances, with the possibility to classify in a correct way subjects developing cognitive decline with almost 90% of accuracy.

The following variables were always present in the best five predictive models created by I.S. system: age, gender, education years, BMI, waist circumference, diastolic pressure, saturated fat, alcohol and potatoes intake, while the following variables were present in 4 out of 5 models: smoke, physical exercise, monosaturated fat, vitamin E, vegetables, fruits, cereals, bread, coffee-tea.

Conclusions

These results underline the complex role played by of diet and nutrition habits in conjunction with demographic factors in the occurrence of senile dementia. The analysis of selected variables selected by I.S. system will allow to develop new hypotheses on the protective role or particular food elements on cognitive decline.

63

UNO STUDIO LONGITUDINALE SULLA FALSA MEMORIA IN SOGGETTI CON MCI

Daniela Leotta* , *Nada Puskaric°, Alberto Marchet*, Marcello Nobili*, Luigi Pernigotti*,Giuliano Geminiani °.*

* Ospedale Martini di Torino, centro U.V.A. presso R.S.A. Torino (Asl 2)
° Dipartimento di psicologia università degli studi Torino

Background: La presente ricerca è inserita nel filone di studio dei marker neuropsicologici in soggetti con mild cognitive impairment (MCI) come predittivi precoci di successiva evoluzione in malattia di Alzheimer. In particolare, si e' condotto uno studio longitudinale su soggetti MCI valutati in un compito di falsa memoria. Il fenomeno della falsa memoria e' presente anche in soggetti normali e puo' essere studiato sperimentalmente attraverso il paradigma DRM (Roediger & McDermott, 1995) che consiste nella presentazione di liste di parole semanticamente correlate che "convergono" verso una parola critica non presente nella lista; nella fase di rievocazione-riconoscimento vengono valutati gli item corretti, gli item critici (false memorie) e gli item intrusi. Studi sulla malattia di Alzheimer hanno evidenziato una relazione tra gravita' di demenza e produzione di false memorie (Balota et al, 1999).
Methods Uno studio longitudinale (durata del follow up 9-12 mesi) è stato condotto nel periodo Febbraio 2003 – Gennaio 2005, su pazienti afferenti al reparto di Neurologia dell'Ospedale Martini di Torino (ASL 2) e all' UVA (Centro Valutazione Alzheimer) presso RSA (Residenza Sanitaria Assistenziale) di Torino (ASL 2). Nella ricerca sono stati inclusi 26 soggetti MCI (16 maschi e 10 femmine con età media di 73,4 anni e scolarità media di 8 anni) diagnosticati secondo i criteri di Petersen et al. (1999), utilizzando come prove di memoria un test di memoria di prosa e il test di memoria verbale di Rey.
Il protocollo di valutazione neuropsicologica comprendeva: MMSE, MODA, Matrici attentive, Matrici di Raven, Cubi di Kohs, Digit Span, Corsi, Fluenza Semantica, Geriatric Depression Scale, e un test di Falsa Memoria secondo il paradigma DRM. Per il test sulla falsa memoria si è utilizzato un gruppo di controllo costituito da 25 soggetti di pari età e scolarità, senza segni di MCI o demenza, con un punteggio MMSE $\geq$ 26.
Results: Alla prima valutazione neuropsicologica i soggetti MCI nel test sulla falsa memoria producono più parole intruse rispetto al gruppo di controllo ($t=2.92$, $df=49$, $p=0.005$), mentre le loro prestazioni in parole corrette e parole critiche non sono significativamente differenti rispetto alle prestazioni del gruppo di controllo. Nella seconda valutazione nel gruppo MCI si rileva una significativa riduzione delle parole corrette ($t=2.54$, $df=24$, $p=0.018$), ma anche delle parole intruse ($t=2.19$, $df=24$, $p=0.038$), mentre si rileva un lieve ma non significativo aumento delle parole critiche; si sottolinea, tuttavia, un significativo aumento nella seconda valutazione del rapporto tra parole critiche e parole corrette ($t=3.02$, $df=24$, $p=0.006$). Solo nella prova di memoria verbale di Rey differita ($t=3.33$, $df=25$, $p=0.003$) e nel digit span ($t=2.54$, $df=25$, $p=0.018$) si rilevano altre significative differenze tra prima e seconda valutazione.
Conclusion: Il test sulla falsa memoria si e' rilevato un parametro sensibile al deterioramento nel tempo nella MCI, presentando un pattern di comportamento simile a quello evidenziato da Balota et al (1999) in soggetti con demenza di tipo Alzheimer. La sostanziale stabilita' delle parole critiche suggerisce una conservazione delle funzioni connesse con la memoria semantica.

22

POLYMORPHISMS OF Fas GENE ARE ASSOCIATED WITH AD RISK AND INFLUENCE COGNITIVE DECLINE

***Licastro Federico*[1]**, *Porcellini Elisa*[1], *Chiappelli Martina*[1], *Franceschi Massimo*[2], *Tumini Emanuela*[1], *Pinti Marcello*[3], *Nasi Milena*[3], *Troiano Leonarda*[3], *Cossarizza Andrea*[2],

[1]Dipartimento di Patologia Sperimentale, Università di Bologna, [2]Dipartimento di Scienze Biomediche, Università di Modena e Reggio Emilia, [3] Dipartimento di Neuroscienze, Castellanza (Varese) e Ospedale S. Raffaele, Milano

Background: The Fas antigen (CD95) is a cell surface receptor that mediates cell apoptosis signalling. Apoptosis controls a number of physiological functions and pathological processes. One of the major of pathological pathway is the one mediated by CD95 (Fas-Apo-1).
This is a trans-membrane protein belonging to the TNF receptor super family. Fas is a monomeric protein of cell membrane and its ligand is the Fas-ligand (FasL, CD178). Recent investigations have shown that Fas associated apoptosis is active in neuro-degenerative lesions of AD brain. The Fas gene is located in chromosome 10q24.1, a region shown to be in genetic linkage with late onset AD. Here we show data regarding the association of two polymorphisms of the Fas promoter region with patients with clinical Alzheimer's disease and cognitive deterioration.
Materials and methods: Genomic DNA was purified from peripheral blood leukocytes of 137 AD patients and 144 age comparable non demented controls. AD Patients were followed up for a two years intervals, MMSE recorded at 0, 12 and 24 months and the rate of cognitive deterioration was determined. Fas –1377 and Fas –670 were determined by DNA-PCR amplification and FRLP analysis or Real-Time PCR. Experimental data were analysed by χ^2 and its significance; Odds Ratio for AD risk was also computed.
Results: Polymorphism of Fas gene at position –670 was not associated with risk of developing Alzheimer's disease. On the other hand, the polymorphism in position –1377 was differentially distributed among patients and controls. In fact, the G carrier status was less frequent in AD patients (G carr 87.4 vs 97.2% p=0.003), the allele G being protective for AD (OR=0.198 p=0.003).
It is interesting to note that the percentage of AA homozygote subjects were higher in AD patients (12.6%) than in controls (2.8%), OR value being 5.060 p=0.0001.
The –1377 GG genotype appears also to be more represented among patients with a slow rate of cognitive decline during a 2 year follow-up.
Discussion: Our data confirmed previous report showing that the polymorphism at position –670 was not associated with AD risk. However present finding extends these observations, since the other polymorphism in the promoter region of Fas gene at position –1377 was indeed associated to the risk of developing the disease with the cognitive deterioration rate during the clinical history of the disease. We conclude that Fas gene is involved in pathological pathways controlling the neuro-degenerative deteriorations associated with AD.

64

REY-OSTERRIETH FIGURE B TEST: AN EASY AND SENSITIVE INSTRUMENT TO ASSESS SPATIAL MEMORY IN ALZHEIMER'S DISEASE

***Simona Luzzi*[1]**, *Martina Pesallaccia*[1], *Giovanna Viticchi* [1], *Marco Bartolini*[1] *e Leandro Provinciali*[1]

[1] Clinica Neurologica, Dipartimento di Neuroscienze, Università Politecnica delle Marche, Ospedali Riuniti di Ancona, Ancona, Italy

Background: long term memory impairment is the earliest and striking feature of Alzheimer's Disease (AD). Neuropsychologists tend mainly to focus on verbal memory and a few tests has been developed to examine spatial memory. The most used test in Italy is the Rey-Osterrieth Figure A. We used the more simplified Rey-Osterrieth Figure "B" to investigate spatial memory in a group of AD patients. It is an easy and ecological test, useful for old subjects with low level of education.
Methods: we used the Rey-Osterrieth Figure "B" to explore constructional praxis and short and long term spatial memory. Three different tasks were proposed to the subject: a) the copy of the figure b) the immediate reprodution from memory c) the delayed reproduction from memory after a delay of 15 minutes. The delay was filled with a distracting verbal task. The test was applied to 52 patients with AD and to 49 healthy subjects sharing similar demographical characteristics (sex, age, education) with AD patients. The test was administered again, after a 1-year interval, to a subgroup of 16 AD patients.
Result: the comparison (t test) between the performance of the AD patients and the controls showed that the AD patients obtained a significant lower score (t test) in all three tasks: copy of the figure ($t=4,43$; $p<0,001$); immediate reproduction from memory ($t=11,19$; $p<0,001$), delayed reproduction from memory ($t=15,70$; $p<0,001$). Within the AD patients group the comparison between the scores relative to the three tasks showed a significant loss of information in the two memory tasks (immediate and delayed reproduction from memory) versus the copy of the figure: copy vs immediate reproduction from memory ($t=17,94$; $p<0,001$); copy vs delayed reproduction from memory ($t=15,81$; $p<0,001$), immediate vs delayed reproduction from memory ($t=5,1$; $p<0,001$).
The follow-up study on AD patients showed further impairment in the three tasks.
Conclusion: the Rey-Osterrieth Figure B was able to detect the non-verbal memory impairment in a group of patients with Alzheimer's Disease when compared with a group of normal subjects matched for demographical variables. The 1-year follow-up in a subgroup of AD patients showed lower performance in the three tasks proposed. The test can be considered as a sensitive and useful instrument to detect the presence of spatial memory problems in AD and a sensitive instrument for neuropsychological follow-up. When normative values in a sample of Italian healthy subjects will be available it could be of use in the clinical practice as a valid alternative to the Rey-Osterrieth Figure A. It seems to be a rapid, easy and reliable test that can be performed by old persons, with low level of education.

11

DECREASED LEVELS OF ADAM 10 IN AD PATIENTS' PLATELETS ARE PARALLELED BY A DECREASE IN mRNA

***Lorenza Magno*[1]**, *Barbara Borroni*[2], *Elena Marcello*[1], *Fabrizio Gardoni*[1], *Flaminio Cattabeni*[1], *Alessandro Padovani*[2], *Monica Di Luca*[1]

[1] Dipartimento di Scienze Farmacologiche, Università degli Studi di Milano, via Balzaretti 9, 20133 Milano
[2] Brescia Dipartimento di Scienze Mediche-Unità di Neurologia- Università di Brescia, p.zza Spedali 1, 25125 Brescia

Amyloid peptide (Abeta) is derived by proteolytic processing of the amyloid precursor protein (APP). APP is subject to proteolytic cleavage by alpha-secretase (ADAM10), which occurs within the sequence of Abeta, thus precluding the peptide formation. Alternatively, APP can be cleaved by beta-secretase (BACE) and gamma-secretase to generate Abeta. These two pathways are differentially compartimentalised, therefore the molecular mechanisms regulating APP and secretase's intracellular localisation and trafficking towards neuronal membrane, may be central for Alzheimer Disease pathogenesis.
In our laboratory we have previously demonstrated, by means of western blot analysis, that ADAM 10 levels are decreased in platelets obtained from AD patient compared to control subjects and that the levels of sAPPalpha, the main metabolite derived from the enzymatic activity of this protein, are decreased in platelets and CSF of AD patient, suggesting that not only the protein but even the enzymatic activity of ADAM 10 are altered in AD.
Here we asked whether decreased protein levels of ADAM 10 in AD platelets are due to increased degradation or to reduced levels of its messenger. To this we performed RT-PCR experiments from platelets of controls (n=6) and AD affected patients (n=6). Using primers specific for ADAM 10 by means of RT-PCR we found that mRNA levels of ADAM 10 in AD platelets are markedly reduced compared to controls (AD *versus* C $p<0.005$)
Next we would like to investigate the way through which the messenger of ADAM10 is decreased, so we are developing an mRNA decay assay to demonstrate that stability of ADAM 10 mRNA is different in AD patient and control subjects.

12

SAP97 SCAFFOLDING PROTEIN MEDIATES ALPHA-SECRETASE ADAM10 TRAFFICKING AND DIRECTLY PROMOTES ITS ACTIVITY BOTH *IN VITRO* AND *IN VIVO*

Elena Marcello [1], *Fabrizio Gardoni* [1], *Daniela Mauceri* [1], *Martina Zimmermann*[1], *Barbara Borroni* [2], *Flaminio Cattabeni* [1], *Alessandro Padovani* [2], *Monica Di Luca* [1]

1. Dipartimento di Scienze Farmacologiche, Università di Milano, via Balzaretti, 9 – 20133 Milano
2. Dipartimento di Scienze Mediche-Unità di Neurologia- Università di Brescia, p.za Spedali 1, 25125 Brescia

Amyloid peptide (Abeta) is derived by proteolytic processing of the amyloid precursor protein (APP). APP is subject to proteolytic cleavage by alpha-secretase (ADAM10), which occurs within the sequence of Abeta, thus precluding the peptide formation. Alternatively, APP can be cleaved by beta-secretase (BACE) and gamma-secretase to generate Abeta. These two pathways are differentially compartmentalised, therefore the molecular mechanisms regulating APP and secretase's intracellular localisation and trafficking towards neuronal membrane, may be central for Alzheimer Disease pathogenesis.
In this study, we evaluate the interaction between ADAM10 and synapse-associated protein 97 (SAP97), a member of membrane-associated guanylate kinase protein family, involved in the processes of targeting ionotropic glutamate receptors at postsynapse. Confocal microscopy shows that SAP97 and ADAM10 display a high co-localisation pattern in hippocampal neurons. Moreover, both SAP97 and ADAM10 are enriched at the postsynaptic density.
Co-immunoprecipitation experiments, from postsynaptic densities purified from mouse brain tissue, demonstrate that SAP97 interacts with ADAM10 and pull down assays reveal that SAP97 SH3 domain recognizes proline rich motifs in ADAM10 cytoplasmic tail. Moreover SAP97 is responsible for driving ADAM10 to the postsynaptic membrane upon NMDA receptor activation and positively modulates alpha-secretase activity. Furthermore, perturbing ADAM10/SAP97 association *in vivo* decreases ADAM10 localization in postsynaptic membrane and consequently impairs physiological APP metabolism. Our findings indicate that glutamatergic synapse activation through NMDA receptor promotes the non-amyloidogenic APP cleavage, strengthening the correlation between APP metabolism and synaptic plasticity.

65

DEPRESSIONE E QUALITA' DELLA VITA IN PAZIENTI AFFETTI DA DEMENZA IN FASE LIEVE: UNO STUDIO MULTICENTRICO LONGITUDINALE

A. Margiotta, *A. Bianchetti, P. Scapicchio e M. Trabucchi per il Gruppo 5 ITINAD **

Introduzione: la valutazione della qualità della vita (QoL) è sempre più utilizzata per la determinazione dell'efficacia degli interventi nelle malattie cronico-degenerative. Ancora poco si conosce delle caratteristiche e della evolutività della QoL nel paziente demente, così come della relazione con le variabili cognitive, funzionali e psico-comportamentali.
Scopo dello studio: valutare le caratteristiche della QoL in pazienti con demenza in fase lieve (Mini Mental State Examination $\geq$ 18/30), le relazioni con le variabili cliniche e l'evoluzione nel tempo.
Pazienti e metodi: studio multicentrico longitudinale coinvolgente 12 Centri U.V.A. distribuiti su tutto il territorio nazionale. Il periodo di arruolamento (T_0) della durata di un anno si è concluso nell'ottobre 2004. Oltre allo stato cognitivo (MMSE), è stata valutata la consapevolezza di malattia (Clinical Insight Rating Scale: CIRS), la sintomatologia emotivo-affettiva (Geriatric Depression Scale: GDS), psicotica (Neuropsychiatric Inventory: NPI) e la comorbidità (Geriatric Index of Comorbidity: GIC). Il peso assistenziale e la sintomatologia depressiva nei caregivers sono state valutate attraverso il Caregiver Burden Inventory (CBI) e il Beck Depression Inventory (BDI). La qualità della vita è stata studiata attraverso due scale: la Quality of Life AD (QoL-AD) e la Cornell-Brown Scale (CBS). Vengono presentati i dati parziali relativi ai primi 6 mesi di follow-up (T_6).
Risultati: sono stati arruolati 202 pazienti (59% di sesso femminile); il 65% affetto da malattia di Alzheimer (AD), il 18% con diagnosi di AD + componente cerebrovascolare, il 13% affetto da demenza vascolare e il 4% affetto da demenza a corpi di Lewy. La durata media dei sintomi di malattia era 26 mesi; l'età media 77,2±6,7 anni. La media delle attività strumentali della vita quotidiana (IADL) perse era di 2,9±2,4; le attività di base (ADL) perse erano 0,9±1,5. Il MMSE 21,8±3,7; la GDS 10,1±5,9; l'NPI 18,9±19,3; il GIC 2,0±0,8. Le due scale di valutazione della QoL sono risultate ben correlate fra loro (r: 0,519; p=0,000) con punteggi medi alla QoL-AD pari a 31,0±5,1 e alla CBS di 7,0±13,0. La popolazione è stata suddivisa in base al livello di QoL stimato dal punteggio delle due scale; sono stati considerati ad elevata QoL i pazienti che avevano entrambi i punteggi di QoL-AD e CBS al di sopra della media delle rispettive scale (n=74) e a bassa QoL i pazienti i cui punteggi alla QoL-AD e CBS risultavano entrambi al di sotto dei valori medi di QoL-AD e CBS (n=68). Le differenze fra i due gruppi sono riportate in tabella.

	Alta QoL	**Bassa QoL**	**p**
Età (anni)	76,6 $\pm$ 7,2	77,9 $\pm$ 5,8	NS
Scolarità (anni)	7,1 $\pm$ 3,9	5,8 $\pm$ 3,0	0,021
BADL (funzioni perse)	0,5 $\pm$ 1,1	1,3 $\pm$ 1,6	0,000
IADL (funzioni perse)	2,2 $\pm$ 2,0	3,6 $\pm$ 2,4	0,000
Cognitività (MMSE)	22,2 $\pm$ 3,5	21,5 $\pm$ 3,6	NS
Depressione (GDS)	6,4 $\pm$ 3,9	13,5 $\pm$ 6,3	0,000
Insight (CIRS)	3,2 $\pm$ 2,5	3,1 $\pm$ 2,1	NS
Sintomatologia psicotica (NPI)	12,6 $\pm$ 17,1	27,8 $\pm$ 21,5	0,000
N° di farmaci assunti	2,8 $\pm$ 1,7	4,5 $\pm$ 2,3	0,000
Comorbidità (GIC)	1,9 $\pm$ 0,9	2,3 $\pm$ 0,8	0,012
Carico assistenziale (CBI)	13,1 $\pm$ 14,8	23,0 $\pm$ 18,0	0,000
Depressione del caregiver (BDI)	5,9 $\pm$ 5,4	8,3 $\pm$ 7,1	0,032

Conclusioni: in soggetti affetti da demenza in fase lieve, la qualità della vita risulta misurabile in maniera affidabile utilizzando strumenti dedicati. Rispetto ai soggetti con bassa QoL, i pazienti con

un'elevata QoL presentano una scolarità maggiore, una minore comorbidità, sintomi psicotici meno eclatanti e minor sintomatologia depressiva; il loro stato funzionale risulta meno compromesso. I caregiver dei soggetti con bassa QoL sopportano un carico assistenziale maggiore e appaiono maggiormente depressi.

* Gruppo 5 ITINAD: Bianchetti A, Margiotta A (Brescia); Padovani A, Vicini Chilovi B (Brescia), Neri M, Manni B, Sabbatini F (Modena), Fabbo A, Bonora A (Mirandola -MO), Menon V, Bergonzini E (Carpi - MO), Piccinini M (Firenze), Tripi G (Trapani), Putzu P (Cagliari); Testa A, Pierantozzi A (Ascoli Piceno), Trequattrini A, Perazzi A (Città di Castello - PG); Turrini G, De Bernardis M, Cugini G. (Ponticelli Terme – PR); Leotta D, Balla S, Capellero B (Torino); Vampini C, Peroli P (Verona).

30

INTERACTION OF CTSD AND A2M POLYMORPHISMS IN THE RISK FOR ALZHEIMER'S DISEASE

Elena Mariani[1]*, Davide Seripa*[2]*, Tiziana Ingegni*[1]*, Giuseppe Nocentini*[3]*, Sara Ercolani*[1]*, Antonio Metastasio*[1]*, Francesca Mangialasche*[1]*, Alberto Pilotto*[4]*, Umberto Senin*[1]*, Patrizia Mecocci*[1].

[1]Section of Gerontology and Geriatrics and [3]Section of Pharmacology, Department of Clinical and Experimental Medicine, University of Perugia, Perugia, Italy; [3]Pathology of Aging Unit, Research Department, and [4]Department of Geriatrics, IRCCS "Casa Sollievo della Sofferenza", San Giovanni Rotondo (FG), Italy.

Background: The proteins cathepsin D, coded by CTSD gene, and α_2-macroglobulin, coded by A2M gene, are involved in the biochemical pathways leading to deposition of beta-amyloid. In these proteins two amino acid polymorphisms (CTSD-*Ala/Val* and A2M-*Ile/Val*) have been associated with an increased risk for Alzheimer's disease (AD), but conflicting results have been reported.
Objectives: To study the association and the mutual interactions of the CTSD-*Ala/Val* and A2M-Ile/Val polymorphisms with sporadic AD
Design: Case-control study.
Settings: Referral center for aging and age-related disease in Umbria, central Italy.
Participants: One hundred patients with late-onset AD and 136 healthy elderly subjects as controls.
Results: The CTSD-Val allele and the CTSD-Ala/Val genotype are significantly more frequent in AD than in controls. The odds ratio (OR) for CTSD-Val subjects is 1.93 (95% confidence interval [CI], 1.00-3.76). The coexistence of the CTSD-Val with the A2M-Val allele synergistically increases the risk for AD to 2.69 (95% CI, 1.36-6.36), and to 3.29 (95% CI, 1.33-8.16) if estimated for the allelic combination. These associations remain significant after adjusting by age, sex and APOE epsilon4+ status.
Conclusions: The CTSD-Val allele of the CTSD-Ala/Val polymorphism is associated with an increased risk for late-onset AD, but no association was found for A2M-Ile/Val polymorphism. However, the combination of CTSD-Val with the A2M-Val allele seems to interact in increasing this risk.

66

NEUROPSYCHIATRIC FEATURES OF AMNESTIC AND SINGLE NON-MEMORY DOMAIN MILD COGNITIVE IMPAIRMENT. *RESULTS FROM THE REGAL PROJECT*

***Elena Mariani*[1]**, *Sara Ercolani*[1], *Miriam Caputo*[1], *Antonella Santucci*[2], *Roberto Monastero*[3], *Tiziana Ingegni*[1], *Patrizia Rinaldi*[1], *Antonio Metastasio*[1], *Patrizia Mecocci*[1]

[1]Section of Gerontology and Geriatrics and [2] Section of Ematology, Department of Clinical and Experimental Medicine, University of Perugia, Perugia [3] Institute of Neurology, University of Palermo

Mild Cognitive Impairment (MCI) has emerged as an identifiable condition preceding, at least in a clinical setting, diagnosable Alzheimer's disease (AD).
Neuropsychiatric symptoms (NPS) have been frequently described in patients with dementia and AD. Large prospective cohort studies with long-term follow-up suggested that depression and psychosis are risk factors for AD and dementia.
NPS have not been included in the diagnostic criteria of MCI, and only recently few comprehensive neuropsychiatric studies have been reported in MCI subjects.
We investigated the prevalence of clinically significant NPS, by means of the Neuropsychiatric Inventory (NPI), in subjects with MCI participating at a large multicentric clinical-based study (ReGAl project).
In particular, we sought to compare the frequency of NPS in two subgroups of subjects with MCI amnestic MCI (aMCI) (n=132) and single non memory domain (snmMCI) (n=75) to those of normal elderly controls (n=242) and patients with mild AD (n=99). The diagnosis of AD was based on the NINDS-ADRDA, whereas the MCI subjects met Petersen's criteria.
The most frequent clinically significant symptom in snmMCI was depression (22.7%), followed by anxiety (21.3%), irritability (16.0%), apathy (14.7%), and sleep disorders (13.3%). aMCI presented a similar spectrum of disturbances being depression and anxiety were the most frequent disturbances (28.8% and 21.2%, respectively), followed by sleep disorders (15.2%), apathy (14.4%), and irritability (10.6%).
The frequency of delusion, depression, aberrant motor behaviour and sleep disorders were significantly higher in MCI (both snmMCI and aMCI) and very mild AD compared to controls. Furthermore, AD showed also a higher prevalence of anxiety compared to controls. No statistically significant differences were found nor between snmMCI and aMCI groups, neither between each MCI subgroups and AD patients, except for delusion.
Our study underlines the importance of characterization of neuropsychiatric feature in MCI subjects, in order to evaluate the possible evolution to dementia. We suppose that neuropsychiatric symptoms may indicate a high risk of evolution to AD and could be used to help in prediction of long-term outcome; longitudinal studies are needed to explore this hypothesis.

39

A CASE OF SNEDDON'S SYNDROME PRESENTING AS MILD COGNITIVE IMPAIRMENT

Massimo Marianetti, *Concetta Mina*[1] *, Giuseppe Amadio Amabile*[1]

[1] Dipartimento di Neurologia e ORL , Università degli studi di Roma "La Sapienza"

Sneddon's syndrome(SNS) is characterized by the association of livedo reticularis and cerebrovascular disease . It mainly affects women between 25 and 35 years old (80% of cases) and has a chronic progressive course that cause many neurologic and systemic disorders. According to the presence or absence of antiphospholipid (aPL) antibodies it is possible to differentiate two distinct subsets of the disease: aPL negative and aPL positive SNS . At the moment the only diagnostic criterion with high specificity in support of the clinicl symptoms is the histological proof of the so called "intimal proliferation" of skin and brain arterioles . Although no prospective randomized controlled trials are available , a wide variety of treatments including antiplatelet agents and anticoagulants has been tried in these patients, often with good results . These patients often develop in the years cognitive dysfunctions and then dementia due to the cumulative effects of multiple cerebral infarcts. Concentration, attention and visuospatial construction are the most common cognitive deficits described . Cerebral ischaemia especially applies to the MCA and PCA territories. SPECT has high sensitivity in detecting perfusion abnormalities at an early stage of the disease, before they can be visualized by CT , MRI and conventional angiography .
Case Report: A 32 year old woman was admitted to our department for a progressive difficulty in topographic orientation. At onset, she referred some difficulties in moving from home to places she had never been before, but after a month the deficit worsened so much that sometimes she had problems in going from her bedroom to her kitchen, too. She said she felt as if she " could not create in her head the route". There was no evidence of behavioural abnormalitites. At neurological examination no motor, sensorial or cerebellar signs were present. She did not suffer from hypertension or diabetes, no other vascular risk factors was reported . Standard EEG, cranial CT scan and cerebral MRI (T1, T2, and Diffusion Weighted) were normal. Tc-99m ECD-SPECT scan showed a hypoperfusion of both the parietal lobes (left > right) . All hematological and biochemical examinations were normal , including VDRL, HBV, HCV, Borrelia, C3, C4, homocysteine, protein C, protein S, antithrombin III, ANA, ANCA , anti- DNA, anti- Sm, anti- SSA, anti SS-B, anti- RNP , LAC , anti-cardiolipin and anti-beta2 glycoprotein I antibodies(IgG and IgM). Factor V Leiden and prothrombin gene mutations were not present. She underwent a complete neuropsychological assessment . We used the MMSE , the Rey's 15 Words Test (immediate and delayed recall), the Rey's Complex Figure (copy, immediate recall and delayed recall) , the Judgement of Line Orientation Test (JLOT), the Attentive Matrices, the Raven's Progressive Matrices, the Phonological and Semantic Verbal Fluency Test and the Wisconsin Card Sorting Test . The patient had a selective involvement of visuo-spatial processing, strictly related with SPECT parietal hypoperfusion (Copy of the Rey's Complex figure test : score 31 , cut off 34.42 ; JLOT :score 11 , cut off 20). Fourteen months later , she returned to hospital for diffuse cutaneous livedo reticularis over the trunk and legs. A skin biopsy showed occlusion of arterioles by intimal proliferation. MRI showed some little parietal cortical-subcortical abnormalities suggestive of little arterial ischemic infarcts. All the other clinical and laboratory evidence was the same of the first observation. We made the diagnosis of aPL negative - SNS.
Our patient is the first SNS described presenting with an isolated neuropsychological deficit. Only the follow-up could clarify that it was a SNS related Vascular-Mild Cognitive Impairment. Sneddon's Syndrome should be always included in the differential diagnosis of neuropsychological

deficits in young adults. An early recognition could improve prognosis of a disease whose consequences can be devastating.

67

USO DI UN QUESTIONARIO BREVE SULLA AUTOVALUTAZIONE DEI DISTURBI DI MEMORIA IN SOGGETTI DI ETA' SUPERIORE A 50 ANNI

Lorenza Marino, *Oriana Pelati, Tiziana Tentorio, Marta Zuffi e Massimo Franceschi*

U.O. Neurologia, Multimedica Holding-Santa Maria, Castellanza (Va)

Introduzione: il presente lavoro nasce dall'osservazione clinica della frequenza con la quale viene riferito un disturbo soggettivo della memoria. Spesso tale disturbo appare essere effettivamente correlato con una misura quantitativa di iniziale deterioramento cognitivo, mentre in altri casi si inscrive in un'alterazione dell'umore o è l'espressione del normale invecchiamento.
Lo scopo del nostro lavoro è quello di osservare come una popolazione di soggetti sani di età superiore ai 50 anni percepisca il proprio funzionamento mnesico e ci siamo proposti di verificare se l'autopercezione della memoria sia coerente con una misura quantitativa di decadimento cognitivo.
Metodi: abbiamo estrapolato dal Subjective Memory Questionnaire (SMQ) di Bennett-Levy(1980) un questionario sull'autovalutazione della propria memoria e delle capacità di apprendimento di nuove abilità. Il questionario si compone di 17 items, così suddivisi: 11 items sulla valutazione soggettiva della memoria, 3 sulla valutazione soggettiva dell'apprendimento, 3 items riguardanti il tono dell'umore. Come misura globale del decadimento cognitivo è stato somministrato il Mini Mental State Examination (MMSE).
Vengono presentati i dati preliminari relativi a 90 soggetti sani (67F/23M) selezionati in modo casuale e scelti per lo più in centri di aggregazione sociale per anziani, di età compresa fra i 50 e gli 85 anni (69 ± 8), con una scolarità tra i 3 e i 17 anni (6.7± 3.1) e un MMSE tra 20.4 e 30 (26.3 ±.2.1). Il campione è stato quindi suddiviso in due sottogruppi in base all'età, gruppo "giovani" tra i 50 e i 70 anni (n = 47; età media 62.6 ± 5.6), gruppo "anziani" tra i 71 e 85 anni (n = 43; età media 75.8 ± 4.3) e successivamente è stata fatta anche una suddivisione in altri due sottogruppi in base alla scolarità, gruppo A con scolarità tra i 3 e i 6 anni (n = 57; media 4.8 ± 0.6) e gruppo B con scolarità tra i 7 e i 17 anni (n = 33; media 10 ± 3).
Nelle analisi statistiche abbiamo considerato, oltre al punteggio di MMSE corretto per età e scolarità, anche l'item di memoria incidentale. Oltre ad un'analisi descrittiva dei dati, abbiamo utilizzato una statistica non parametrica (Mann-Whitney U) di confronto tra i gruppi e un indice di correlazione (r-Spearman) tra ogni variabile raccolta.
Risultati: tra i due gruppi di soggetti divisi in base all'età emerge una differenza significativa del punteggio totale dell'autovalutazione della memoria (p = .048) (gruppo "giovani" media 25.5 ± 4; gruppo "anziani" media 27.1 ± 4.4), così come al sub-item di memoria incidentale del MMSE (p = .011) (gruppo giovani media 1.9 ± 1; gruppo "anziani" media 1.4 ± 1.1). Tra i due gruppi di soggetti divisi in base alla scolarità emerge una differenza significativa della memoria incidentale (p = .002). Non vi è alcuna differenza significativa nei due gruppi al punteggio totale del MMSE.
Sono risultate significativamente positive tutte le correlazioni tra il punteggio totale della memoria, dell'apprendimento e dell'umore e tutti i sub-items in entrambi i gruppi divisi nelle due fasce d'età e in tutti i soggetti;

- in tutti i soggetti e nel gruppo dei "giovani" il punteggio di autovalutazione della memoria totale correla con il punteggio totale del giudizio;
- il sub-item del MMSE di memoria incidentale non correla con il punteggio di autovalutazione della memoria totale; non sono presenti correlazioni significative tra il punteggio di memoria totale e il punteggio totale dell'umore in tutti i gruppi di soggetti esaminati.

Conclusioni: una prima conclusione che possiamo trarre da questi dati preliminari è che il campione di soggetti ha risposto in modo coerente a tutti i sub-item, potendo pertanto considerare il questionario come misura attendibile dell'autopercezione delle proprie capacità; tale osservazione potrebbe far ipotizzare che lo strumento da noi così utilizzato goda di una buona coerenza interna.
Il gruppo di soggetti compresi tra i 71 e 85 anni presenta un'autovalutazione soggettiva della memoria migliore rispetto a quella del gruppo dei soggetti tra i 50 e 70 anni, a fronte di una prestazione peggiore al sub-item di memoria incidentale. Tale dato suggerisce come non sembra esservi una reale corrispondenza tra il disturbo soggettivo di memoria e una misura quantitativa della stessa. Tale discrepanza potrebbe essere interpretata in più modi differenti: si potrebbe pensare che sia legato alla minor criticità dei soggetti anziani rispetto alla reale performance della loro memoria qualora questa risulti essere effettivamente deficitaria; d'altra parte potrebbe anche suggerire una maggior accettazione del disturbo di memoria come normale rispetto all'età; infine si potrebbe pensare che un contesto sociale altamente protettivo, quale quello dei centri di aggregazione sociale da noi visitati, produca una sorta di effetto di copertura delle reali difficoltà mnesiche (Cavallarin, 1990).

68

EFFICACIA DI UN TRATTAMENTO NEUROMOTORIO E COGNITIVO ASSOCIATO IN PAZIENTI ULTRASESSANTENNI

***Maria Vittoria Meraviglia*[1]**, *Costanza Bennardo*[1], *Anna Rita Loi*[1], *Alberto Nova*[2]

[1]Centro Rieducazione Motoria ASL - Milano
[2]Servizio Medicina Preventiva nelle comunità e nello sport

Obiettivi: Verificare l'efficacia di una trattamento neuromotorio e cognitivo combinato mirato al mantenimento dell'autonomia nelle attività della vita quotidiana, in pazienti di età superiore ai 65 anni.
Materiali e Metodi: Di 253 pazienti testati con Mini Mental State Examination (MMSE), sono stati presi in considerazione i 162 che hanno ottenuto un punteggio maggiore od uguale a 27 (sono pertanto stati esclusi quei pazienti con importanti deficit cognitivi e/o sensoriali). I 162 pazienti reclutati (125 donne e 37 uomini) di età media 69 ± 1.3 anni sono stati suddivisi in tre gruppi:
gruppo A: 56 pazienti sottoposti a rieducazione neuromotoria;
gruppo B: 52 pazienti sottoposti a rieducazione cognitiva;
gruppo C: 54 pazienti sottoposti a rieducazione neuromotoria e cognitiva associata.
Tutti i pazienti dei tre gruppi sono stati valutati prima dell'inizio del trattamento mediante visita neurofisiatrica, osservazione fisioterapica, test MODA e SELF scale. La rieducazione neuromotoria comprendeva sedute collettive (5/8 pazienti) bisettimanali della durata di 50 minuti articolate in due cicli di trenta sedute nell'arco di otto mesi. La rieducazione cognitiva è stata svolta in sedute di gruppo (5/8 pazienti) monosettimanali della durata di 40 minuti per un totale di trenta sedute nell'arco di otto mesi. Al termine del trattamento i pazienti sono stati rivalutati mediante la stessa procedura di valutazione iniziale.
Risultati: I pazienti del gruppo A hanno mostrato un miglioramento significativo sia delle abilità motorie che cognitive. I pazienti del gruppo B hanno mostrato un miglioramento significativo delle abilità cognitive in assenza di variazioni significative delle abilità motorie. I pazienti del gruppo C hanno mostrato un incremento sia delle abilità motorie che cognitive. Tutti i pazienti dei tre gruppi hanno mostrato alla SELF scale un sensibile aumento di punteggio.
Conclusioni: E' stato dimostrato un effetto sinergico tra apprendimento motorio e cognitivo: l'apprendimento motorio sembra costituire un canale preferenziale anche per l'apprendimento cognitivo ma non viceversa. Entrambe le modalità di apprendimento sembrano avere un effetto positivo sulla sfera affettivo-relazionale.

69

NEUROPSYCHOLOGICAL MARKER ON RAVEN'S CPM

***Alessia Monti*[1]**, *Stefano Zago*[1-2], *Barbara Poletti*[2], *Giovanni Battista Flebus*[3]

[1]Department of Neurological Science - University of Milan Medical School - IRCCS Ospedale Maggiore, Milano, Italy
[2]Dep. Neurology and Lab. Neuroscience - "Dino Ferrari" Center - University of Milan Medical School - IRCCS Istituto Auxologico Italiano, Milano, Italy
[3] University of Milan, Bicocca, Milano, Italy

Background. To improve the diagnostic accuracy in the early stages of dementia it is searched for in vivo markers capable of better differentiating AD from other forms of dementia (Gainotti et al.,1998). The Raven's Coloured Matrices (Raven, 1962) is a well-known test of visuo-spatial intelligence. There are three different categories of wrong responses on this test: the spatially wrong responses in which the correct form to complete the model is presented in a wrong spatial orientation; the globalistic responses which reproduce the whole shape of the model on a reduced scale; the odd responses which are completely different to the missing part and to the form of the model. Gainotti et al. (1992) have noted that globalistic and odd responses - *primitive answers* - are generally observed in conditions of severe brain pathology. The aim of this study is to determine if the tendency to give these *primitive answers* is a good marker of dementia and to evaluate the sensitivity and the specificity of this pattern of wrong responses as a diagnostic marker of Alzheimer Disease.
Methods. The sample is made up of 190 subjects (96 males and 94 females). Of these subjects, 160 were patients with neuropsychological assessment, referring to the Alzheimer Valuation Unit (UVA) of Ospedale Maggiore in Milan. Different cognitive domains were investigated: global cognitive function, attention, executive functions, language, problem-solving, memory, visuo-spatial functions, praxis and visual recognition. Seventy-one of these subjects were diagnosed as AD (Alzheimer Dementia), following the NINCDS/ADRDA criteria; 43 as MID (Multi-Infarct Dementia), following the NINDS-AIREN criteria; 18 as SCD (Sub-Cortical Dementia), following criteria suggested by Kalra et al.; 28 as DPD (Depressive Pseudo-Dementia), following criteria suggested by Reynolds et al. (1986). Thirty normal subjects, not affected by focal or diffuse lesions and not demented (comparable to the groups of demented patients in terms of age and educational level) formed the control group of the present research.
Results. A qualitative analysis of the tendency to give *primitive answers* on Raven's CPM showed that there were differences between demented and not demented patients and also between different etiological forms of dementia. The specificity of this marker is good (98%), although its sensitivity is only 4.2%. Even though this marker is capable to identify AD patient at an acceptable level of specificity it is not enough sensitive.
Conclusion. In summary this study showed that this marker is specific but not sensitive by itself to be considered as a good diagnostic marker for the early forms of cognitive impairment. A higher level of sensitivity and specificity has been reached considering more than one cognitive marker (as reported in Zago et al. in this poster session (*Cog-Markers*: standardizzazione e taratura di un nuovo strumento per la diagnosi e la stadiazione della malattia di Alzheimer).

References.
Raven J.C. (1962). *Coloured Progressive Matrices Sets A, AB, B*. London: H.K. Lewis (originally published in 1947, revised order in 1956).

Gainotti G., Parlato V., Monteleone D. and Carlomagno S. (1992) Neuropsychological markers of dementia on visuo-spatial tasks: a comparison between Alzheimer's type and vascular forms of dementia. *Journal of Clinical and Experimental Neuropsychology,* 14, 239-252.
Gainotti G., Marra C., Villa G., Parlato V., Chiaretti F. (1998). Sensitività and specificità of some neuropsychological markers of Alzheimer Dementia. *Alzheimer Disease and Associated Disorders*,12, 152.

13

THE AMYLOID BETA PEPTIDE 1-42 MODULATES THE IMMUNE FUNCTIONS OF DENDRITIC CELLS

***Maria Luisa Moro*[1]**, *Paola Bossù[1], Lorena Sanarico[2], Gianfranco Spalletta[1,3], Carlo Caltagirone[1,3] and Antonio Ciaramella[1]*

[1]IRCCS Fondazione Santa Lucia, Roma; [2]Istituto di Neurobiologia e Medicina Molecolare, CNR, Roma; [3]Dipartimento di Neuroscienze, Università di Roma "Tor Vergata";

Background: According to the largely accepted "amyloid cascade hypothesis", the key event of Alzheimer's disease (AD) pathogenesis is the production of amyloid beta peptides, which accumulate into fibrillar deposits and form the amyloid plaques, one hallmark of the pathology. Although the amyloid beta burden is mostly recognised as a central mechanism of AD neurodegeneration, the molecular pathways leading to AD are still muddled and an involvement of the immune system has been proposed by many authors, but its role is still controversial. A chronic inflammatory response has been frequently observed in AD brain, while a specific anti-amyloid beta peptide immune activation has been suggested to be dysregulated in AD patients only in few studies. However, this last observation has been further straighten by the results of some promising studies based on amyloid beta vaccination, indicating that vaccinated individuals are able to generate antibodies against amyloid beta and have a slow-down in the development of the disease, likely because of the immune-mediated clearance of amyloid beta. Taken together, all these observations indicate that further and deeper analysis of the immune mechanisms involved in AD pathogenic pathways are urgently needed. In this direction, particular attention should be devoted to dendritic cells (DCs), key regulators of immune responses. DCs, in fact, are capable of promoting or suppressing T-cell activation, producing regulatory cytokines, and, depending on the various circumstances, they can also induce tolerance. Moreover, according with their regulative nature, immature (or partially mature) dendritic cells (DCs) can protect the organism from excessive inflammation or the development of autoimmunity. In order to increase the knowledge regarding immune functions in AD pathogenesis, the present study was aimed to analyse *in vitro* the activity of amyloid beta peptides on DCs functions.
Methods: Human myeloid DCs obtained from *in vitro* differentiation of donor's monocytes cells, have been cultured for several days in the presence of beta amyloid peptides, in the attempt to mimic the pathological environment. After appropriate stimulation, DCs have been analysed in terms of phenotype and functional activity. Antigen uptake and cytokine production have been characterised by flow cytometry analysis and ELISA, respectively.
Results: The 1-42 amyloid beta peptide, differently from 1-40 and from its related inactive control peptide, was able to affect surface expression of DCs phenotype markers (HLA-DR, HLA-A,B,C, CD11c and CD86), and *in vitro* antigen uptake. Moreover, 1-42 amyloid beta peptide was effective in modifying both DCs aggregation in response to the TNF-alfa and in increasing the production of pro-inflammatory cytokines, such as IL-1 beta and IL-6.
Conclusions: These results demonstrate for the first time that 1-42 amyloid beta peptide can selectively trigger the immune system by affecting the differentiation pathways of human myeloid DCs. Probably, by recognising the accumulation of amyloid peptide as a "danger signal", the specialised immune regulatory DCs can activate certain mechanisms likely able to affect the balance between innate and adaptive immune response. The result of such activation could be at the basis of an increased brain inflammation and of a possibly reduced beta amyloid clearance, being both mechanisms responsible for neurodegeneration. Although further studies are needed to clarify the involvement of DCs in the complex scenario of AD pathogenesis, the present data provide a

further support to the belief that the immune system indeed plays an important role in this pathology.

40

POSTERIOR CORTICAL ATROPHY

***Raffaella Mossini*[1]**, *Eliana Schiatti*[1], *Monica Falautano* [1], *Alessandra Barbieri*[1], *Erica Altamura* [1], *Claudia Arcari*[1], *Massimo Franceschi* [2], *Giancarlo Comi*[1], *Giuseppe Magnani*[1].

Department of Neurology and Clinical Neurophysiology[1], University Vita-Salute, Scientific Institute Hospital San Raffaele, Milan, Neurology Department, Multimedica- Santa Maria, Castellanza [2].

Background: Posterior cortical atrophy (PCA) is an uncommon degenerative brain disease characterised by progressive dementia and disorder of cortical visual functions with predominant parieto-occipital atrophy. PCA patients display early deficits in visuo-spatial tasks including drawing, writing, calculating , finding their way around familiar places. Further possible deficits are visual agnosia for objects , faces and letters, visual field deficit and apraxia. Unlike typical Alzheimer disease memory, insight and judgement are relatively preserved. However when the disease progress, transition to global dementia regularly occurs.
In PCA visual association cortex damage is bilaterally but often more on the right side.
The most frequent pathologic findings of PCA are senile plaques and neurofibrillary tangles predominant affecting the visual association areas; it was so speculated that PCA is an atypical clinical variant of Alzheimer disease.
Methods: In our Memory Centre we identified 5 patients (3 females and 2 males) with possible PCA and followed up them for more then six months. All of them underwent clinical neurological examination, neuropsychological tests (attentive matrices; Token test; tests of phonological and semantic fluency; digit span; words pairs; logical memory; Corsi span; Rey figure copy and recall; Raven coloured matrices and constructive apraxia); CT scan or MRI and SPECT study.
Mean age at diagnosis was 61 years (range 53-73); mean MMSE 22 (range 17-26), mean history of symptoms 3.2 years.
Results: All the patients had the following criteria at diagnosis: 1) insidious onset of symptoms; 2) prominent visual dysfunctions in absence of visual ophthalmologic cause to explain the symptom;
3) progression of symptoms; 4) occipito-parietal atrophy at MRI / CT and posterior brain hypo perfusion on SPECT .
After the diagnosis all patients were treated with CHE inhibitors
Conclusions: All of our patients presented progression of the symptoms over six months after the diagnosis, and in latest neuropsychological assessments they have evidence of global cognitive impairment.

14

ELAV-LIKE PROTEINS AND PROTEIN KINASE C: A NEW CASCADE FOR MEMORY TRACE FORMATION AND ALZHEIMER'S DISEASE?

***Alessia Pascale*[1]**, *Marialaura Amadio*[1], *Cristina Lanni*[1], *Giovanni Scapagnini*[2], *Stefano Govoni*[1], *Daniel L. Alkon*[3] *and Alessandro Quattrone*[4]

[1]Experimental and Applied Pharmacology Dept, Pavia, Italy; [2]Institute of Neurological Sciences, CNR, Catania, Italy; [3]Blanchette Rockefeller Neuroscience Institute, Rockville, USA and [4]Laboratory of Functional Genomics, FiorGen Foundation, Sesto Fiorentino (FI), Italy.

Background: Modulation of mRNA decay appears to be an efficient post-transcriptional way of controlling local gene expression, since small changes in mRNA half-life can radically alter the abundance of a given mRNA and the amount of the relevant protein. ELAV-like proteins (ELPs) are ARE (adenine and uridine-rich elements)-binding factors able to stabilize and increase the translation of the bound mRNAs, thereby positively controlling gene expression. An involvement of neuronal ELPs in learning has been recently demonstrated (*Pascale et al, PNAS 101, 1217, 2004*). Within this general context, information are emerging on the possibility of mRNA stabilization through the activation of specific protein kinases. In particular, Protein Kinase C (PKC) activators, Ca^{2+} and phorbol esters, have been reported to modify the half-lives of some mRNAs. Moreover, experimental evidences point to a role of PKC in memory trace formation and to the impairment of this transduction system in aging and in Alzheimer's disease (AD). In accord with these premises, it was of interest to investigate the relationship between PKC activation and ELPs. In particular, we studied in a cellular model, human SH-SY5Y neuroblastoma cells, the influence of PKCα stimulation on ELPs, and on target proteins important for synaptic activity, coded by mRNA stabilized by ELPs, such as GAP-43. Finally, we evaluated the effect of Abeta treatment on ELPs levels.
Methods: Proteins were analyzed by Western blot and visualized by immunocytochemistry. Messenger RNA was evaluated with real-time quantitative PCR.
Results: We found that phorbol esters (PMA)-induced PKCalfa translocation is associated with an increase of ELPs levels (cytosol: +93%, $p<0.001$; membrane: +25%, $p< 0.05$; cytoskeleton: +59%, $p<0.001$); this effect was lost in PKCalfa-knock down SH-SY5Y. Moreover, the co-localization of PKCalfa and ELPs following PMA increases. In addition, PMA exposure induced a selective increase of GAP-43 protein levels in the cytoskeletal fraction (+38%, $p< 0.005$) that was lost in SH-SY5Y pre-incubated with Gö6976, a PKCalfa inhibitor. Finally, the treatment of SH-SY5Y cells with 1uM Abeta induced a decrease of cytoskeletal ELAV-like proteins (-53%, $p<0.05$).
Conclusions: The PKC pathway may participate to memory trace formation also by long term mechanisms acting through post-transcriptional control of substrate mRNAs involved in memory storage. Disease-associated modifications of this cascade may produce cognitive impairment.

70

SINGLE LETTERS READING IMPAIRMENT: *A CASE OF VISUAL DYSLEXIA IN DEMENTIA?*

S. Passoni° **,** *M. Berlingeri°, G. Zanardi#°, E. Paulesu^, G. Bottini#°*

°Laboratorio di Neuropsicologia, Dipartimento di Scienze Neurologiche Ospedale Niguarda, Milano
Dipartimento di Psicologia, Università degli Studi di Pavia
^Dipartimento di Psicologia, Università degli Studi di Milano-Bicocca, Milano

Introduction: letter-by-letter reading (Howard, 1991), attentional dyslexia (Saffran and Coslett, 1996; Hall, Humphreys and Cooper, 2001), neglect dyslexia (Warrington, 1991) and visual dyslexia (Lambon Ralph and Ellis, 1997) affect the initial recognition of letters and written word forms without necessarily affecting central semantic and phonological processes. In particular visual dyslexia is related with an impairment of the single letters recognition, identification and reading. In this case an impairment of the abstract letter identification units has been proposed (Howard, 1987; Hall, Humphreys and Cooper, 2001). Lambon Ralph and Ellis (1997) described a patient who made a very high proportion of visual errors in reading and showed a deficit of single letters' recognition and matching.
Aim of the study: To explore dyslexic deficits associated to a visuo-perceptual impairment in a 63 years old right-handed woman, GM, who had a cerebral stroke inducing bilateral parieto-occipital lesions.
Methods: Subjects: GM and a group of six normal control subjects. Cognitive assessment: subjects have been administered with tasks exploring single letters and single numbers reading, identification, recognition and writing abilities.Word / non word reading and dictation have also been explored. In order to distinguish semantic from visuo-perceptual levels' deficit subjects performed pictures and colours' naming tasks taken by the Aachener Aphasie Test (Huber, W. 1981) and the Pyramid and Palm Trees Test (Howard D, 1992). Data were treated by a T-test on each task score. Results: Compared to normal controls GM manifested a significantly more impaired performance on all the tasks with the exception of the single numbers' reading and the single numbers' copy. In particular she presented a significant difference between single upper-case letters (UC: the worse performance) and single lower-case letters (LC) identification ($p= 0,01$) and an impairment on matching upper-case to lower-case letters ($p= 0,01$). A significant difference between word and non-word reading ($p= 0,01$) with a worse performance on non-word reading was also evident. Discussion: GM impairment on single letters' recognition hardly may be ascribed to her more general deficit of visual integration as she is still able to read single numbers. Moreover she is also unable to write single letters under dictation and manifests a clear difference between word and non-word reading. Furthermore there is evidence of dissociations between agnosia and reading impairment (Buxbaum, 1999). GM differentiated performance suggests a specific impairment of the letter identification unit which may be distinguished by her more general visual integration deficit. Finally, GM dissociated performance on identifying and matching upper case and lower case letters suggests the existence of different stores for these linguistic items.
References
Buxbaum LJ, Glosser G, Coslett HB. Impaired face and word recognition without object agnosia. Neuropsychologia, 1999, 37: 41-50
Hall DA, Humphreys GW, Cooper ACG. Neuropsychological evidence for case specific reading: multi-letter units in visual-word recognition. The Quart. J. Exp. Psyc. 2001, 54 (2): 439-467
Saffran EM, Coslett HB. "Attentional dyslexia" in Alzheimer disease: a case study. Cognitive neuropsychology, 1996, 13 (2): 205-228

Lambon Ralph MA, Ellis AW. "Patterns of parelexia" revisited: report of a case of visual dyslexia. Cognitive neuropsychology, 1997, 14(7): 953-974

Howard D. Reading without letters? In Coltheart M, Sartori G, Job R (Eds). The cognitive neuropsychology of language. Hove, UK. Lawrence Erlbaum associated Ltd. 1987: 27-58.

Howard D, Patterson K. The pyramids and Palm trees test. Bury St Edmunds, U.K., Thames Valley test Co; 1992

Huber W, Poeck K, Weninger D, Willmes K. The Aachener Aphasia Test: reliability and inter-rater agreement 1981 May;52(5):269-77. German.

71

WHAT MILD COGNITIVE IMPAIRMENT IS? DEBATING THE NOSOLOGICAL ISSUE

Oriana Pelati, *Stefania Castiglioni, Marta Zuffi, Lorenza Marino, Tiziana Tentorio and Massimo Franceschi*

Neurology Dept, Multimedica Holding-Santa Maria, Castellanza (Varese)

Background: Mild Cognitive Impairment (MCI) represents a pathology largely recognized in the literature, but not yet nosologically defined. Previous classifications defined as MCI an isolated impairment of memory (amnestic MCI: aMCI) or other cognitive domains (non-amnestic MCI: naMCI). Several studies demonstrated that aMCI patients are at higher risk for developing Alzheimer's Desease (AD) with an estimated conversion rate of 10-15% per year. Much less studied is the clinical evolution of naMCI. Furthermore, MCI is a heterogeneous entity characterized by differences in cognitive profile, and it may be associated with other neurological disturbances as movement or behavioral disorders. At the present there is no clear consensus as how to consider these associated factors.
During the meeting of the ITINAD First Group in Rome on 16 december 2004, researchers from Niguarda and Castellanza proposed to follw-up naMCI patients, in order to clarify the rate of progress and the fate of this category.
In the following study two centres specialized in the neuropsychological assessment of mental deterioration present the results of a feasibility study, conducted retrospectively using two different classification criteria.
Aim of the study is a preliminary observation of the prevalence of the phenomenon and to compare its prevalence with two different diagnostic criteria.
Methods: we present an "epidemiologic" analisys of all patients with suspected or clear dementia (first diagnosis or controls) evaluated during 2004 with an exensive neuropsychological battery. Following the MCI classification proposed by the Italian Neurological Society guidelines (Neurol Sci 2004), we retrospectevely defined as MCI patients with MMSE ≥ 24 (adjusted score) and no evidence of functional decline in every day life at a clinical analisys. Behavioral and movement disorders, as well as cerebro-vascular impairment have not been considered as exclusion criteria, but as associated features to MCI.
We distinguished patients with isolated memory impairment, patients with memory impairment plus one or more other cognitive deficits, patients with one cognitive function impaired (not memory) and pts with more cognitive functios impaired except memory.
Results: 368 pts have been evaluated: 302 (82%) showed a MMSE score < 24 (usually corresponding to a dementia diagnosis). 45 pts (12%) were identified with MMSE ≥ 24 and at least one cognitive deficit; 18 of them have been previously evaluated in 2003. Finally 21 pts (6%) had no evidence of cognitive impairment.
The following table shows the distribution of different categories of cognitive impairment and of different associated factors.

Impairment of: Associated with	Only memory	More cognitive functions (not memory)	One cognitive function (not memory)	Memory and one or more cognitive functions	Tot.
Nothing	5	1	3	1	**10 (22%)**
Vasculophaty	4	1	6	6	**17 (38%)**
Movement disorder	0	2	2	0	**4 (9%)**
Behavioral or psychitric disorders	3	3	6	2	**14 (31%)**
Tot.	**12 (27%)**	**7 (16 %)**	**17 (37%)**	**9 (20%)**	**45 (100%)**

Conclusions: this retrospective feasibility study conducted in two different departments revaled that:

- naMCI patientsare commonly seen
- naMCI is even more prevalent than aMCI in a sample of pts with suspected cognitive deficit

We will propose to all ITINAD Centres a longitudinal follow-up study of naMCI pts according to a common clinical and neuropsychological protocol.

72

RIABILITAZIONE DELLA MEMORIA E DEL LINGUAGGIO IN PAZIENTE CON DANNO CEREBRALE VASCOLARE

Clara Pelizzari

Fondazione Benefattori Cremaschi, Crema (CR)

Dopo una fase di pessimismo sulla possibilità di rieducare i disturbi della memoria, numerose sono state le recenti ricerche atte a verificare le effettive possibilità che la memoria possa essere "rieducata"; circa la scelta dei metodi applicabili si è posta l'esigenza di una attenta specificità a seconda delle caratteristiche del disturbo e della scelta degli obiettivi, che devono essere stabiliti con molto realismo in rapporto alla gravità del disturbo. Ben più consolidata la storia della riabilitazione dell'afasia, dalla fine del diciannovesimo secolo agli anni '70 in cui si è andato sviluppando un approccio totalmente innovativo, quello cognitivista. Una definizione oggi condivisa è quella che considera il deficit lessicale come un disturbo determinato dal danno ad una componente lessicale, cioè ad uno/ più meccanismi ritenuti coinvolti nell'elaborazione delle parole.
Il caso di seguito riportato è quello di una donna di 57 anni, S.D. con 8 anni di scolarità, coniugata e madre di otto figli. Luglio 2003 ricovero ed intervento in neurochirurgia per emorragia subaracnoidea da rottura di aneurisma cerebrale. Maggio 2004 S.D. viene sottoposta a derivazione ventricolare esterna frontale destra e test di infusione ventricolare. Agosto 2004 somministrazione test neuropsicologici: emerge un quadro di grave decadimento cognitivo su base organica. Compromissione generale delle capacità cognitive superiori; in particolare grave difficoltà nella memoria a breve termine, disorientamento temporale e personale, importante anomia, agrafia e dislessia. Si segnala anosoagnosia, rallentamento psico-motorio, tratti di perseverazione e labilità emotiva. Valutazione logopedica: difficoltà di lettura (usa molti neologismi), di denominazione orale, di comprensione di ordini complessi, parafasia semantica, non vengono segnalate difficoltà di ripetizione e comprensione delle consegne orali.
Progetto riabilitativo: per riabilitazione memoria: uso di ausili esterni, mnemotecniche (metodo delle iniziali, metodo delle parole associate) e metodi cognitivi (verbalizzazione dei punti, visual imagery, categorizzazione…); per riabilitare il linguaggio: rieducazione dei lessici di input (riabilitare il lessico ortografico) e dei lessici di output (produzione fonetica e categoriale con costruzione di un vocabolario); esercizi per riabilitare la lettura, l'attenzione e l'orientamento temporale/personale.
Dopo sei mesi di costante e giornaliero lavoro si è potuto osservare un miglioramento cognitivo generale ed in particolare della memoria (verbale, visiva, topografica) dell'orientamento (temporale e personale), dell'attenzione e della denominazione (anche se vi sono presenti ancora perifrasi e parafasia). Migliorate le capacità di lettura e di ragionamento ed i tempi di ritenzione delle informazioni acquisite. Migliorata anche la gestione dell'autonomia quotidiana e della deambulazione per l'esercizio fisioterapico effettuato quotidianamente. Ripetuta la somministrazione dei test neuropsicologici a tre mesi e a sei mesi dalla prima valutazione.

	Agosto 2004	**Novembre 2004**	**Marzo 2005**
MMSE	10	16	19
MODA	37.7	62.6	68.1

In questa mia piccola esperienza si è notato un miglioramento cognitivo generale, riportato anche dai familiari, anche se la valutazione dell'efficacia dei trattamenti è ancora un problema aperto in

molte aree della neuroriabilitazione a causa delle molte difficoltà metodologiche. Essendo quindi le conferme sperimentali su tale efficacia scarse, i suggerimenti in letteratura sono stati presi come generali indicazioni da applicare al caso in questione e da modellare lungo il percorso terapeutico.

44

DETERMINANTS OF GOOD RESPONSE TO CHOLINESTERASE INHIBITORS IN A COHORT OF CONSECUTIVE PATIENTS SEEN IN AN ALZHEIMER CENTER OF NORTHERN ITALY

C.Pettenati [1,2], *D.Perotta* [1], *C.Campanello* [1], *M.Barbieri* [1], *S.Feller* [3], *M.Musicco* [4]

[1]: Centro Regionale Alzheimer AO G.Salvini Passirana Rho (MI) Dipartimento di Riabilitazione, [2]: Università Milano-Bicocca, Scuola di Specialità in Neurologia, [3]: UOC Neuroriabilitazione Dipartimento di Riabilitazione AO G.Salvini Garbagnate M.se (MI), [4] CNR ITB Segrate Milano

Cholinesterase inhibitors (Ache-i) are drugs effective in patients with Alzheimer's disease but, in clinical trials, only 20-30% of them are considered "responders" showing an improvement on cognitive scales. Also in clinical practice some patients have a good response whereas other show no benefit from treatment with these drugs. It might be interesting to know the characteristics of the patients, which predict a good response to Ache-i treatment. From the starting of Cronos Project in october 2000 up to December 2004 we have seen 1768 patients in our Alzheimer Center in Passirana di Rho (Mi) of these 428 initiated a treatment with Ache-i. 53 patients interrupted the treatment due to adverse events occurring in the first three months of treatment (35 T1, 28 T4) and the remaining 375 were included in the present study. The median follow-up was 16 months. After six months of follow up 260 patients did not show any worsening at Mini Mental Status Examination, the corresponding figure for longer follow-ups of 12 and 18 months were 170 and 122. Considering these patients as good responders their occurrence is 50% after six months and 52.3% and 47,5% after 12 and 18 months respectively. The characteristics of good responders have been compared with those of poor responders and from preliminary analyses it seems that age and the presence of behavioral and psychological symptoms might be significant predictors of the response to Ache-i treatment. The role of other variables as disease severity and rate of progression is under investigation.

73

ASSESSING AD PATIENTS' ABILITIES IN A MONEY DECISION-MAKING TASK

***Barbara Poletti*[1]**, *Alessia Monti*[2], *Stefano Zago*[1-2], *Vincenzo Silani*[1]

[1]Dep. Neurology and Lab. Neuroscience - "Dino Ferrari" Center - University of Milan Medical School - IRCCS Istituto Auxologico Italiano, Milano, Italy
[2]Department of Neurological Science - University of Milan Medical School - IRCCS Ospedale Maggiore, Milano, Italy

Background. Decision-making ability has been reported to be declined in some healthy older person (Denburg et al., 2005). Decision-making ability is involved in many instrumental skills, for example in handling money, usually compromised in Alzheimer's Disease (AD) patients. The purpose of this study was to analyze AD patients' money decision-making ability with an adapted version of the Iowa Gambling Task (Bechara et al., 1994). This task, contemplating the concrete use of money, better reflects the actual money decision-making ability in AD patients and the awareness of future consequences about their actions, thus simulating everyday life situations. This could be a fundamental instrument in medico-legal context where clinicians are often asked to assess AD patient's daily living independency, thus arising legal and ethical issues.
Methods. Ten patients with neuropsychologically assessed and clinically diagnosed probable AD, following the NINCDS/ADRDA criteria were enrolled. The Mini Mental State Examination (MMSE) score of these patients ranged 21-23, defined as mild AD patients, according to Magni et al. (1996) classification. Twenty-one healthy control volunteers closely matched with patients for age and educational features were selected. We administered an adapted version of the Iowa Gambling Task based on the original as described in Bechara et al. (1994). The only difference of our version concerned the currency (euro instead of dollar). The Gambling Task procedure evaluates decision-making by measuring the participant's ability to choose between high gains with a risk of extremely high losses and low gains with a risk of smaller losses. Participants were instructed to win as much money as possible by picking one card at a time from each of four decks (A, B, C and D) in any order until they were instructed to stop (after the selection of the 100th card). While performing the task participants were informed of the amount of money they had left after each card was selected. They could also ask for another loan.
Results. ANOVA was carried out in order to show different patterns in the two groups. No significant differences were found in cards choosing patterns (mean number of cards from the advantage decks vs mean number of cards from the disadvantage decks). AD patients performed significantly worse than controls in time asking for a new loan. Normal subjects who started with the disadvantageous decks learned to pick from the advantageous decks. Even though statistically not significant our results show a trend, in AD patients, to ignore future consequences showing a behaviour driven by immediate reward and less motivated by uncertain future loss or gain.
Conclusion. Our data are not conclusive. This might be probably ascribed to the small sample of the study. However this issue needs further studies involving other groups of cognitive impaired patients, such as FTD patients and focally neurological ones. The assessment of decision-making ability in AD's patients is of basilar importance in planning adequate support for patients and their caregivers, in designing targeted training programs and for its legal and ethical consequences.
References

Bechara, A., Damasio, A. R., Damasio, H., Anderson, S.W. (1994). Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition*, 50, 1-3, 7-15.
Denburg, N.L., Tranel, D., Bechara, A. (2005). The ability to decide advantageously declines prematurely in some normal older persons. *Neuropsychologia*, 43, 7, 1099-1106.

Magni, E., Binetti, G., Bianchetti, A., Rozzini, R., Trabucchi, M. (1996). Mini Mental State Examination: a normative study in italian elderly population.
European Journal of Neurology, 3, 1-5.

15

MOLECULAR MECHANISMS REGULATING NMDA RECEPTOR LOCALIZATION AND FUNCTION IN NEURONS; ROLE IN NEURODEGENERATIVE DISORDERS

Polli Federica, *Mauceri Daniela, Gardoni Fabrizio, Cattabeni Flaminio, Di Luca Monica.*

Dipartimento di Scienze farmacologiche, Università di Milano, via Balzaretti, 9 – 20133 Milano

The N-methyl-D-aspartate (NMDA) type glutamate receptors are abundant, ubiquitously distributed throughout the CNS, fundamental to excitatory glutamatergic transmission and critical for normal brain function. To date, although molecular basis of glutamate toxicity remain uncertain, there is general agreement that NMDA subtype of ionotropic glutamate receptors plays a key role in mediating at least some aspects of glutamate neurotoxicity, and have been implicated as a mediator of neuronal injury associated with neurodegenerative disorders.
On this view, it is important to notice that, NMDA receptors are not, however, fixed at the synapse: a large fraction of synaptic NMDA receptors can move laterally to extrasynaptic sites. Interestingly, there are strong evidences that activation of extrasynaptic NMDA receptors is implicated in neuronal death while synaptic receptors play a role in mediating neuronal survival. Notably, the mechanism responsible for the subcellular localization of NMDA receptors in hippocampal neurons remains to be identified although targeting of the receptors to different locations may involve the large carboxy-terminal tails of the NR2 subunits.
In the last few years, binding of various post-synaptic density (PSD) proteins to NMDA receptor NR2 subunits has been extensively described. In particular a large number of studies identified the NMDA receptor complex as a target for specific enzymes, i.e. □CaMKII and for scaffolding proteins, i.e. PSD-95 family underlining the central role played by NMDA receptor in building up the complex network of PSD proteins.
To this, we tested whether NMDA receptor NR2 localization was affected by acute dissociation of the PSD-95-NMDA receptor interaction. Membrane-permeable peptides were used to disrupt the NMDA receptor-PSD-95 interaction in different experimental systems as tested by immunoprecipitation and subsequent immunoblotting. In addition, how and if CaMKII activity can govern stuctural organization of the NMDA receptor NR2 subunits at the excitatory synapse has been analysed. Our results will add knowledge to the understanding of the molecular mechanisms regulating NMDA receptor localization and function in the hippocampal glutamatergic neuron.

31

HMG-COA REDUCATSE GENE POLYMORPHISM INFLUENCES CONGNITIVE DECLINE IN ALZHEIMER PATIENTS

***Elisa Porcellini*[1]**, *Martina Chiappelli*[1], *Emanuela Tumini*[1], *Nicola Canal*[3], *Elena Calabrese*[3], *Giuliana Salani*[2], *Massimo Franceschi*[2], *Luigi Maria Edoardo Grimaldi*[2], *Federico Licastro*[1]

1 Università di Bologna, Dipartimento di Patologia Sperimentale, 2 Ospedale San Raffaele, Milano, 3 Fondazione Don Gnocchi, Milano.

Background: the association between cholesterol and AD has recently receive much attention and several investigations report a link between cholesterol and the disease. It is interesting to know that intracellular cholesterol levels might contribute to neuronal degeneration associated with AD by modulating the production of soluble amyloid and increasing deposition of the insoluble Abeta peptide. The hydroxy-metylglutaryl-coenzyme A (HMG-CoA) reductase is the rate limiting enzyme in the cholesterol biosynthesis and we have investigated whether a polymorphism in this gene might be a genetic marker of AD and/or clinical progression of the disease.
Materials and methods: 337 patients with probable sporadic AD (mean age 74±9 SD year) and 586 non demented subjects (mean age 73±7 SD year) from Northern Italy was included in the study. Diagnosis of probable AD was performed according to standard clinical procedures and followed the National Institute of Neurological Communicative Disorder. AD patients were stratified according the rate of cognitive decline in three different groups following method previously described (Doody RS et al, Arch Neurol, 2001). Polymorphisms in the promoter region of the HMG-CoA and in the APOE (epsilon 2,3,4) gene were detect by PCR-DNA amplification and agarose gel electrophoresis. HMG-CoA polymorphism is in the promoter region of the HMG-CoA gene in position –911 and consists in a transversion (C->A).
Results: Frequency of A allele was higher in patients than in controls and the Odds Ratio for AD in A carrier was 2.759. The presence of A allele influenced also the clinical progression of disease. In fact, patients carrying the A allele showed a faster cognitive impairment than those without the A allele of HMG-CoA reductase polymorphism, in other words the percentage of A carrier patients was higher in the group with fast cognitive decline than that in the group of patients with slow cognitive decline deterioration.
Longitudinal records of MMSE was available during a two year follow-up and regression lines of MMSE score at 0, 1 and 2 years were plotted. MMSE scores at time 0 from patients with or without A allele were comparable. However the slop of regression line from A carrier patients was different from that of non A carrier patients, being deterioration rate higher in patients with A allele. Therefore, our findings showed that the HMG-CoA genotypes influenced the risk of developing AD and the progression of disease .
Conclusion: Our findings indicated that the polymorphic region at the promoter of the HMG-CoA reductase gene is a genetic risk factor for the disease. The HMG-CoA A alleles affects also the rate of cognitive decline. from our findings we conclude that HMG-CoA red. is a key enzyme affecting pathogenetic mechanisms influencing the neurodegeneration associated with AD.

74

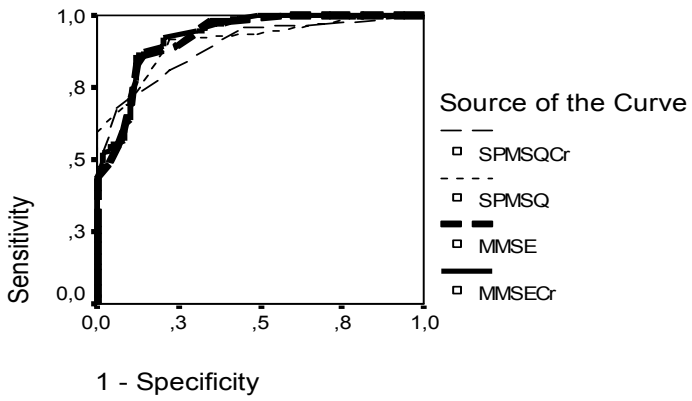
A COMPARISON OF THE MINI-MENTAL STATE EXAMINATION AND THE SHORT PORTABLE MENTAL STATUS QUESTIONNAIRE IN INSTITUTIONALISED ELDERS

Pradelli, S(1,2) ; *Vettor, S(1); Bencivenga, S(1); Pinarello, A(1); De Vreese, LP(2)*

[1] ISRAA, Treviso [2] RSA IX Gennaio, Modena

Background: To verify the sensibility and specificity of two commonly used measures of cognitive status: the Mini-Mental State Examination (MMSE) and the Short Portable Mental Status Questionnaire (SPMSQ) and to assess their correlation in elderly people with and without dementia living in a Nursing Home.
Methods 165 (142 females) institutionalised elders participated in the study: 54 cognitively intact residents and 111 patients with a clinical diagnosis of dementia (DSM-IV-TR, 2000). All residents were administered separately and in a blind manner both the MMSE and SPMSQ. First, we assessed the ability of the two cognitive measures to differentiate between subjects with and without dementia by means of the Receiver Operating Characteristic (ROC) curve. Second, we applied the Pearson's correlation matrix to the two scores. Third, we computed multiple regression analyses to probe the predictive power of each cognitive measure.
Results: The ROC curve (Fig. 1) showed that the corrected MMSE score (MMSECr) is better than its raw score, which in turn is better than the SPMSQ, both for its raw and corrected scores. The correlation between the two tests was -0.85. The regression analyses indicated that the predicted MMSECr score equals 28.16 - 1.98×SPMSQ. The 95% CI for the coefficient representing SPMSQ was -2.18 to -1.79 ($p<0.001$). The predicted SPMSQ scores equals 11.47 - 0.364×MMSECr (95% CI, -0.40 to -0.33, $p<0.001$). The R^2 for the regressions was 0.72. There was no evidence of a lack of linear fit between the models.

Figure 1. – The Receiver Operating Characteristic curves for the MMSE and the SPMSQ.



Conclusions: Taken together, these findings confirm that MMSE and SPMSQ highly correlate with each other also in institutionalised elderly. Moreover, and most importantly, the best cut off points for MMSECr and SPMSQ appeared to be 24 and 3, respectively. Finally, the good prediction of one

score based on the other may allow for reliable comparisons of data derived from different studies that use one but not the other measure.

41

FRONTAL VARIANT IN PS1 MUTATED FAMILIES: DOES THE PURE CLINICAL PICTURE OF AD EXIST?

Gianfranco Puccio, *Rosanna Colao, Sabrina AM Curcio, Francesca Frangipane, Maria Mirabelli, Raffaele Maletta, Carmine Tomaino, Livia Bernardi, Nicoletta Smirne and Amalia C. Bruni*

Regional Neurogenetic Centre AS6 Lamezia Terme (CZ) Italy

Background: Alzheimer's disease (AD) is typically marked at onset by memory loss, later followed by a global cognitive decline. Only in the late stage of the disease are behavioural disturbances manifest. On the contrary, Frontotemporal dementia (FTD) usually starts with behavioural disturbances and patients present only later with overt cognitive decline.
The rare, genetic form of early onset AD (FAD) may be caused by mutations of presenilin 1, presenilin 2 or APP genes and generally presents with a classical picture of the cognitive disorder. In a minority of cases, familial forms of FTD may be caused by mutations of tau. Binetti et al (2003) recently reported that an atypical dementia with behavioural disorder at onset was caused by mutation of PS2 gene, but absence of neuropathological control precluded a better knowledge of this unusual disease. Interestingly, PS1 mutations have already been associated with FTD and in one case were shown to be the cause of a neuropathologically confirmed Pick's disease.
Therefore, evidences do exist of overlapping symptoms and etiologic causes for both AD and FTD, suggesting that a common pathway might underlie neurodegenerative disorders.
We have been studying for several years two large Calabrian FAD families (family N and family To), that were instrumental in the cloning of PS1 gene. Both families share the same rare mutation (Met146Leu), thus confirming *a posteriori* their common origin.
Our aim is to study the beginning of the disease during the first two years from onset to verify whether behavioural disorders may characterize the onset phenotype in a classical case of FAD.
Patients and Methods: Among the 130 FAD affected subjects identified over 15 generations, we studied 15 individuals (mean age at onset 41 ± 3.8) during the last years. Together with neurological examination, neuropsychological tests, neuroradiology and molecular genetic analysis of PS1, a checklist of symptoms and signs, relying on Lund and Manchester clinical criteria, was filled out for each patient.
Results: A behavioural pattern marks the onset in 7 out 15 patients. Reduction of interest and of motor initiative, apathy, depression and emotional blunting precede memory loss. The course of the disease in this subgroup is more aggressive and within two years the patients present with a complete impairment of all cognitive functions even as age at onset and disease duration are not different compared to the "cognitive" subgroup. All of "behavioural" patients belong to Family To whereas family N patients show a "cognitive" pattern.
Conclusion: Althouth both branches of the Calabrian kindred carry genetically and and neuropathologically confirmed FAD, a pattern of behavioural changes at onset has been evidenced in one branch only. The number of the patients studied is not high but the group is pure. Some explanations can be suggested. We can hypothesize that different topographic locations of AD lesions could determine the different phenotypical pattern; however the fact that the behavioural picture belongs to family To, suggest that additional genetic or environmental factors could be involved. Our data are in agreement with the recent findings that frontal pictures can be determined by PS mutations. Presenilin analyses may be helpful to characterize kindreds with familial dementing illnesses regardless of the phenotype, particularly if no tau mutation is present. A common pathway might underlie neurodegenerative disorders and deep research on factors modulating gamma secretase activity have to be further investigated.

75

STIME COGNITIVE: CONFRONTO TRA PAZIENTI CON DEMENZA DI ALZHEIMER E CON DEMENZA FRONTO-TEMPORALE

Vanessa Raimondi*° *, Monica Grobberio°, Antonino Sergi*, Renzo Bassi**

*Laboratorio di Neuropsicologia, U.O. Neurologia Ospedale "Orlandi" ULSS 22, Bussolengo (VR)
°Laboratorio di Neuropsicologia, U.O.Neurologia, Ospedale S. Anna, Como

Background: l'effettuazione di stime cognitive è una capacità che richiede processi cognitivi di selezione e regolazione (Luria, 1973). Nell'articolo di Shallice and Evans (1978) emerge come questa abilità sia legata all'integrità dei lobo frontali. Non tutti gli studi però sembrano confermare tale ipotesi. Taylor (1995) infatti, in un lavoro che ha messo a confronto pazienti neurologici con una lesione anteriore vs pazienti neurologici con una lesione posteriore, non trova differenze significative nella loro prestazione in un compito di stima cognitiva. Altri studi dimostrano come pazienti con demenza di Alzheimer (AD) (Goldstein, 1996) e con malattia di Parkinson (Bullard, 2003) abbiano dei disturbi nell'effettuazione di stime cognitive. Lo scopo del presente lavoro è valutare se un test di stima cognitiva verbale breve e di semplice somministrazione (tratto dall'Esame Neuropsicologico Breve – ENB di Mondini e coll., 2003) possa discriminare pazienti con AD e pazienti con demenza Fronto-temporale (FTD) da un gruppo di controllo e se esistono differenze trai due gruppi di pazienti neurologici studiati.
Method: il test di stima cognitiva che è stato utilizzato consiste di cinque domande che richiedono un valutazione di quantità:

1. Quanto costa un litro di latte?
2. Quanta distanza c'è tra Milano e Roma?
3. Quanto è lunga una chitarra?
4. Quanto dura una messa?
5. Quanti canguri ci sono in Olanda?

Il punteggio totale va da "0" a "5". Per ogni risposta il soggetto può ottenere un punteggio di "0", "0,5" o "1". Il test è stato somministrato ad un gruppo di controllo (N=27, età media=72, MMSE medio=28), un gruppo di pazienti con AD (N=27, età media=73, MMSE medio=22) ed un gruppo di pazienti con FTD (N=27, età media=70, MMSE medio=24). Tutti i gruppi sono confrontabili per età e scolarità, i due gruppi di pazienti sono confrontabili anche per punteggio al MMSE. Sono state effettuate statistiche descrittive e analisi non-parametriche trai gruppi (Mann-Whitney U.Test).
Results: emergono differenze significative tra i punteggi nel test di stima cognitiva tra il gruppo di controllo e i gruppi di pazienti neurologici, per AD p=0,002 e per FTD p=0,029. Non ci sono differenze tra le prestazioni di pazienti con AD e con FTD. In particolare il punteggio medio nell'effettuazione di stime del gruppo di controllo è "3,8", quello degli AD "2,8" e degli FTD "3,1".
Discussion: da questo studio emerge come la prestazione nella prova delle stime cognitive dell'ENB sia utile nel discriminare soggetti senza patologie neurologiche da soggetti con demenza di Alzheimer e con demenza Fronto-temporale in fase iniziale. Emerge inoltre come non esistano differenze significative trai due gruppi di pazienti con demenza. Tali dati sembrano indicare che l'iniziale deterioramento cognitivo, sia esso di origine prevalentemente temporo-parietale (AD) o fronto-temporale (FTD), comprometta in qualche modo la capacità di effettuare stime cognitive. Rispetto alla correlazione tra effettuazione di stime cognitive e funzionalità frontale da questo lavoro non sembrano emergere conferme in tal senso. Ad ogni modo occorre fare delle osservazioni circa la complessità dell'operazione di effettuazione della stima e circa il tipo di strumento utilizzato in questo e in precedenti lavori. L'effettuazione di stime richiede infatti l'utilizzo della working memory, di abilità di analisi del problema, di ragionamento e di giudizio. Tali funzioni, nel test utilizzato nel presente lavoro, agiscono sulla base dell'accesso a informazioni enciclopediche,

sulle quali viene poi effettuata la stima. Quindi, per un'ipotesi più esplicativa circa il coinvolgimento dei lobi frontali nell'effettuazione di stime cognitive potrebbe essere utile valutare il peso di questa variabile.

16

NMDA RECEPTOR MIGHT MEDIATE BETA-AMYLOID AND GLUTAMATE EFFECTS IN HUMAN FIBROBLASTS

Chiara Riva, *Chiara Paola Zoia, Simona Andreoni and Carlo Ferrarese*

University of Milano-Bicocca, Department of Neuroscience and Biomedical Technologies, Monza (MI), Italy

Background: Abnormal extracellular accumulation of both beta-Amyloid (Abeta) and glutamate is associated with neuronal degeneration occurring in Alzheimer's disease (AD). It has also been suggested that Abeta, as well as excitotoxic aminoacids, may interact with NMDA receptor to exert its neurodegenerative action. In fact, Abeta gives rise to a variety of toxic events, including extracellular glutamate accumulation which, in turn, induces hyperactivation of glutamate receptors with consequent increase of intracellular Ca^{2+} concentration, oxidative stress, damage to glutamate transporters and free radical production.
In order to study the role of Abeta and glutamate in AD, we proposed to characterize NMDA receptor and to investigate glutamate uptake modifications after Abeta, glutamate and NMDA treatments, in human fibroblasts as *ex vivo* peripheral model.
Methods: Fibroblasts were differently treated with 5microM Abeta (1-42) for 2h, glutamate and NMDA for 1h. High affinity, sodium- and energy-dependent glutamate uptake was evaluated as [^{3}H]-glutamate cellular incorporation. Glutamate transporters and receptors were studied by western blot and RT-PCR. LDH extracellular release, apoptosis by Hoechst nuclear staining and mithocondrial activity by MTT assay were also assessed.
Results: In Abeta and glutamate treated control fibroblasts, we observed a glutamate uptake reduction similar to that found in fibroblasts from AD patients. However, while previous results showed an EAAT1 protein decrease and an increase of its mRNA in AD fibroblasts, we demonstrated no significant EAAT1 molecular alterations in control fibroblasts after Abeta and glutamate exposure. On the other hand, treated cells showed a decrease in MTT reduction rate, without increase in LDH extracellular concentration or induction of apoptosis.
To clarify if glutamate and Abeta may interact with the same receptor, we first investigated the presence of glutamate receptors in human fibroblasts. RT-PCR analysis gave the expected size amplification product for NMDA receptor 2A/B subunits, even if western blot showed a positive signal at lower molecular weight, indicating a possible post-transcriptional modification. Other studies are in progress to verify the presence of the NMDA receptor 1 subunit. Moreover, we are studying the effect of NMDA on glutamate uptake in treated and untreated control fibroblasts. Preliminary results indicate a comparable glutamate uptake reduction in fibroblasts treated with NMDA, glutamate and NMDA+glutamate. A similar decrease was also observed after NMDA+Abeta treatment. Since no addictive effect was observed in fibroblasts treated with glutamate+Abeta, NMDA+glutamate and NMDA+Abeta, we may hypothesize that these drugs act on the same receptor.
Conclusion: Our results suggest the presence of NMDA receptor also in fibroblasts and indicate that Abeta might decrease glutamate uptake through NMDA receptor and consequently induce different intracellular signaling cascades. Moreover, Abeta glutamate uptake inhibition which we observed in fibroblasts is similar to that showed by other Authors in astrocyte cultures and it confirms that fibroblasts could be a suitable *ex-vivo* peripheral model to investigate possible pathogenic mechanisms in AD.

76

VISUAL MENTAL IMAGERY AND EXECUTIVE FUNCTIONS DIFFERENTIATING AMONG DEMENTIA: THE VISUAL – COGNITIVE ESTIMATION TEST

***Paola Rizzi*[1]**, *Monica Grobberio*[1], *Vanessa Raimondi*[1,2], *Miriam Benin*[1], *Carlo Umiltà*[3], *Roberto Sterzi*[4]

[1]Laboratory of Neuropsychology and Clinical Psychology – Department of Neurology, S.Anna Hospital (Como); [2]Department of Neurology, Bussolengo Hospital – USL 22 (Verona); [3] University of Psychology, Padua – Italy; [4]Department of Neurology, S.Anna Hospital (Como).

Background: Cognitive estimation is a complex executive function associated to the frontal lobes involved in selection and regulation of cognitive processing (Luria, 1966). There are specific stages to allow good cognitive estimations: problem analysis (planning), matching with similar stored problems (working memory), generation of hypotheses accessing to semantic representations from high-level information (reasoning and abstraction), correction of wrong answers (self-correction). Several ways to evaluate this skill has been studied, such as the original cognitive estimation test by Shallice and Evans (1978), but all of them used only verbal stimuli even when the aim was to assess a general numerical judgment. The aim of the study is to propose a new computerized test to assess cognitive estimation in visuo-spatial domain and to define whether this visual-cognitive estimation test (V-CET) should differentiate among dementias.
Methods: The V-CET has been composed by 10 slides: 5 slides shows a number of items between 5 and 10 (S1) and 5 shows between 10 and 25 items (S2). A mixed presentation of slides has been made and presentation-time was 0,5 msec. Subjects were required to define how many stimuli appear in each slide to obtain three different scores: mean of estimated stimuli in V-CET (TV-CET), in S1 (V-CET1) and in S2 (V-CET2). Mean answer time of every score was also calculated. 56 normal controls (N, aged from 25 to 85), 35 patients with mild to moderate Alzheimer's Disease (AD, aged from 70 to 85) and 14 patients with mild to moderate Fronto-Temporal Dementia (FTD, aged from 70 to 85) have been administered with V-CET. The N group has been subdivided in three subgroups: controls aged less than 60 years (N1), from 60 to 70 years (N2) and from 70 to 85 (N3). N3, AD and FTD were matched for age and education; AD and FTD were matched for severity of dementia (as measured by MMSE score). We studied whether age, sex or education interfere in estimation and answer times in N subgroups. Then we compared data obtained by N3, AD and FTD. Non-parametric analysis has been performed by within groups Wilcoxon Signed Ranks Test and between groups by Mann-Whitney U-Test.
Results: In N subgroups we found no differences due to sex or education. On the contrary, age seems to interfere in accuracy of estimation: N3<N1=N2. No differences were found about answer times. Between groups: N3=AD in every V-CET score but AD>N3 in V-CET and S1 answer times. N3>FTD in TV-CET ($p=.003$) and V-CET2 ($p=.007$) but N3=FTD in every answer times. AD>FTD in V-CET2 ($p=.030$) but no differences in answer times. Within groups: in N3 V-CET1=V-CET2; in AD V-CET1>V-CET2 ($p=.008$) while in FTD V-CET2>V-CET1 ($p=.035$). No differences in answer times.
Conclusion: The worse performance obtained by FTD group whether in total number of items estimated in both conditions and in the estimation of the condition with more than 10 items suggests a general underestimation of visual stimuli in spite of a preserved answer time, that means good information processing and identification of few visual information. On the contrary, AD slowness just in answer time of the condition with less than 10 items seems to show a more specific lack in processing visuo-spatial items. According to literature, the result highlights impairment in turning perceptual information into visual mental imagery (Tippet et al.,2003) which allow to process representations, count up the items and answer.

In conclusion, V-CET might be a useful tool to discriminate FTD from AD patients because it seems to asses either specific skills required for cognitive estimation or abilities involved in visual mental imagery.

77

DEPRESSIONE CRONICA E DEMENZA: UNO STUDIO NEUROPSICOLOGICO

Elena Sartorio[1] , *Stefano F. Cappa[1], Paola Ortelli[1], Valentina Cucumo[1], Giada Caramatti[1], Marco Catalano[2], Adelio Lucca[2], Enrico Smeraldi[2]*

[1] Istituto Scientifico San Raffaele, Milano
[2] Dipartimento di Scienze Neuropsichiche Ville Turro San Raffaele, Milano

Background. E' comune osservazione clinica che un significativo deterioramento cognitivo possa manifestarsi in pazienti affetti da disturbo bipolare I e II, particolarmente in un sottogruppo di pazienti anziani con episodi multipli di malattia o cronici, suggerendo un possibile effetto demetigeno della malattia (*Lars Vedel Kessing et al., 2001*; *Ariel G. Gildengers et al. , 2004*). Secondo il modello neuropsicologico della depressione di *Mayberg et al.* (*1999*), le regioni prefrontali, parietali e il giro del cingolo anteriore dorsale sarebbero implicate nella regolazione dell'attenzione e delle funzioni esecutive, mentre il giro del cingolo anteriore e ventrale e le strutture sottocorticali governano gli aspetti circadiani e vegetativi del tono dell'umore . Il modello riceve conferma anche dagli studi di brain imaging di Fossati et al. (2002). Quindi, una disfunzione nel sistema fronto-striatale diventa critico anche per funzioni cognitive quali le funzioni esecutive, l'attenzione, la velocità dell'information processing, l'apprendimento, la memoria (*Carrie E. Bearden et al., 2001*).
Obiettivo. Valutare se il decadimento cognitivo, in un campione di pazienti anziani (>65 anni) affetti da disturbo dell'umore da più di 10 anni e attualmente in fase eutimica, sia condizionato dal decorso della malattia o da altre variabili considerate nell'anamnesi.
Ipotesi. Ci aspettiamo, in primo luogo, che il paziente con una storia di disturbo dell'umore pregresso presenti un processo oggettivabile di decadimento cognitivo indipendente dalla comorbilità con un disturbo organico che comporti una degenerazione corticale.
Ci aspettiamo, inoltre, di osservare un deterioramento cognitivo delle funzioni cognitive sottese alle regioni cerebrali disfunzionali.
Materiali e metodi. Sono stati selezionati 32 soggetti, secondo i seguenti criteri: almeno 65 anni d'età, una storia clinica pregressa di disturbo dell'umore secondo i criteri dell'Asse I del DSM-IV (APA, 1995), fase eutimica al momento della valutazione, assenza di gravi condizioni mediche internistiche o neurologiche.
Ogni paziente è stato sottoposto ad uno screening iniziale sulla base di una raccolta anamnestica dettagliata e della Psychogeriatric Assesment Scales (PAS, Jormet & McKinnon, 1995) ed è stato valutato tramite un'apposita batteria testale neuropsicologica costituita dai seguenti test: Mini Mental State Examination (MMSE; Folstein et al., 1975), Token Test (Test dei gettoni; De Renzi & Vignolo, 1962), fluenze fonemiche, fluenze semantiche, digit span diretto e inverso, Test di Corsi, Test della memoria di prosa, Figura complessa di Rey-Osterrieth (CFT; Rey & Osterrieth, 1959), test delle matrici attentive, Matrici Progressive di Raven (Raven, 1938), Weigl's Sorting Test (Weigl, 1927), Trail Making Test, Cognitive Estimation Task (CET; Della Sala et al., 2003), scala delle attività di base della vita quotidiana (BADL; Katz et al. 1963), scala delle attività strumentali della vita quotidiana (IADL; Lawton et al. 1969).
Risultati. il campione è costituito dal 72% da donne e dal 28% da uomini, con un'età media di 71±5 anni, una durata media di disturbo dell'umore di 22±2 anni e una durata di normotimia di 14±3 anni. Il 43% dei soggetti presenta una licenza di scuola elementare e il 31% una licenza di media inferiore. Il MMSE risulta sotto i valori normativi per il 25.1% dei soggetti. Assai frequente è la compromissione per il digit span diretto (31.3%), la memoria a lungo termine visuo-spaziale (CFT, 46.9%), le abilitá visuo-percettive e prassico-costruttive (CFT, 78.1%); seguono il Weigl's Test (31.3%), il CET (37.5%), il Token Test (31.3%), il Test di Corsi (28.1%) e la memoria di prosa

(21.9%). Meno frequente la compromissione per gli altri test: 6.3% per le fluenze fonemiche e semantiche, il 15.6% per le matrici attentive, il 3.1% per le Matrici Progressive di Raven, il 12.5% per il TMT(A) e il 6.3% per il TMT(B-A).
Conclusioni. Questa prima analisi ci permette di osservare che a fronte di una valutazione globale del profilo cognitivo lievemente compromessa, si osserva una più frequente compromissione della memoria a breve termine che della memoria a lungo termine. Questo dato rappresenta una differenza rilevante rispetto al profilo cognitivo caratteristico dei pz con AD (in cui la MBT risulta una delle funzioni più resistenti anche a livelli avanzati del decadimento). Si osserva, inoltre, una compromissione della memoria di lavoro, delle funzioni esecutive e delle abilità visuo-spaziali e prassico-costruttive. Si può quindi concludere che i pazienti con lunga storia di disturbo dell'umore presentano un pattern di deficit cognitivi polisettoriali, che non risulta essere quello caratteristico della malattia di Alzheimer, aprendo prospettive di diagnosi differenziale tra le due patologie.

23

FATTORI PROGNOSTICI DEL DECORSO DEL DETERIORAMENTO COGNITIVO IN UNA COORTE DI UTENTI AFFERENTI A CENTRI U.V.A.

***S. Scalmana*[1]**, *A.Mastromattei*[1], *D. Di Lallo*[1], *A. Capon*[1], *V. Mattia*[1], *G. Guasticchi*[1]

[1] Agenzia di Sanità Pubblica, Regione Lazio. Per il gruppo di lavoro "Progetto Alzheimer": Prof. C.Caltagirone (IRRCS Fondazione Santa Lucia, Roma); Prof.ssa M.G. Marciani (Università di Tor Vergata, Roma); Dott. C. Marra (Università Cattolica del Sacro Cuore, Roma); Prof. P.M. Rossini (Afar Fatebenefratelli, Roma).

Background: Il decorso del deterioramento cognitivo e gli ambiti cognitivi maggiormente compromessi si differenziano in relazione a diversi fattori: clinici, assistenziali, ambientali ed individuali. Lo studio, collocato all'interno del Progetto di ricerca finalizzata del Ministero della Salute, coordinato dall'Agenzia di Sanità Pubblica del Lazio, "Un modello di stima dell'occorrenza della malattia di Alzheimer", si propone di valutare in una coorte di utenti afferenti a centri UVA l'evoluzione nel tempo del deterioramento cognitivo, in relazione alla diagnosi iniziale e ad altri determinanti (sesso, età, scolarità) . Methods: Attraverso l'analisi dell'archivio di 4 UVA della città di Roma sono stati selezionati pazienti con diagnosi di demenza, distinta tra Malattia di Alzheimer, Demenza vascolare, Forme miste, Demenza frontotemporale, Demenza a Corpi di Lewy. Tutti i soggetti hanno ricevuto una prima valutazione neuropsicologica ed una valutazione di follow up a 12 mesi con il test del MMSE, il Test delle 15 Parole di Rey, e delle PM 47. Per confrontare la variazione tra la prima e la seconda valutazione è stato utilizzato il test sign-rank di Wilcoxon per misure appaiate. Per valutare i possibili determinanti della variazione del punteggio continuo del MMSE tra le due valutazioni, sono stati eseguiti dei modelli di regressione lineare univariata rispetto ai seguenti fattori: sesso, età (>75 o ≤75), scolarità, diagnosi (AD/ non AD), UVA di riferimento. È stato infine eseguito un modello di regressione lineare multivariata con i fattori maggiormente associati alla variazione del MMSE (età, sesso, diagnosi, interazione sesso - età). Results: Il campione è costituito da 332 soggetti, 202 donne (61%) e 130 uomini (39%), di età compresa tra i 45 e i 92 anni (il 20,5% di età inferiore a 65 anni ed il 24,1% di età superiore a 80 anni), con una scolarità compresa tra 0 e 19 anni. Il 74% dei pazienti presentava diagnosi di Alzheimer, il 15% demenza vascolare e forme miste, l'8% demenza fronto-temporale, il 3% demenza a corpi di Lewy. Il test di Wilcoxon ha evidenziato una variazione significativa (aggravamento del deterioramento) tra la prima e la seconda valutazione solo per i test PM 47 (tutte le diagnosi: p=0,0039, AD: p=0,0065) e per il MMSE (tutte le diagnosi: p<0,0005, AD: p<0,0005). La tabella 1 mostra la variazione del punteggio del MMSE stimata dal modello di regressione multivariata per classe di età, sesso e diagnosi. Si evidenzia una variazione del MMSE maggiore nelle donne rispetto agli uomini, ad eccezione dei soggetti con AD ultrasettantacinquenni. La variazione maggiore si osserva nel gruppo di donne di età inferiore a 75 anni con AD (n=68, 20% del campione).

Tab 1. Modello di regressione lineare multivariata : stima della variazione del punteggio al MMSE a 12 mesi dalla prima valutazione, per sesso, età e diagnosi.

ΔM	**Donne**		**Uomini**	
	Alzheimer		**Alzheimer**	
Età	*Si*	*No*	*Si*	*No*
< 75	2,01977	0,73882	0,6169	-0,6640479
> 75	1,55706	1,87	1,74977	0,4688261

ΔM=mmse1val-mmse2val

Conclusions: Nella AD l'età più giovane e il sesso femminile costituiscono importanti fattori prognostici di un più rapido decorso del deterioramento cognitivo. Ciò suggerisce l'importanza di attivare per tempo specifici percorsi terapeutico-riabilitativi volti a ridurre il peggioramento del quadro cognitivo in tali soggetti.

45

ACTIVE INTERNALIZATION OF A Mn-SOD IN LIVING TUMOR CELLS

***Antonella Schiattarella*[1]**, *Antonella Borrelli*[1], *Antonella Occhiello*[2], *Alessandra Pica*[2] *and Aldo Mancini*[1]

[1]Istituto Nazionale dei Tumori-Napoli;
[2] Dipartimento di Biologia Evolutiva – Università di Napoli, Federico II.

Manganese superoxide dismutase (MnSOD) is the primary antioxidant enzyme that protects cells from oxidative stress by catalyzing dismutation of superoxide anion to hydrogen peroxide and oxygen in mitochondria of eukaryotic cells. The MnSOD is composed of four homologous 24 kDa subunits. After being synthesized in the cytoplasm, a 2 kDa leader-sequence drives the MnSOD into the mitochondrial matrix, where this peptide is cleaved and the protein becomes mature and hence enzymatically active. MnSOD was reported to protect cells from a variety of insults and to suppress apoptosis in cultured rat ovarian follicles, new cell lines and transgenic mice. By generating H_2O_2 MnSOD may also give rise to oxidative stresses associated with inflammatory reactions and neoangiogensis. Protection from apoptosis and stimulation of vascularization are prerequisites for tumor progression to which MnSOD may thus contribute in a positive fashion. Yet, SOD may also be deleterious to neoplastic cells, as shown by the capacity of ecSOD from muscle cells to suppress the growth of melanoma cells *in vitro*, upon transduction via recombinant adenoviruses. SODs therefore appears to control multiple reactions, the orchestration of which will determine the fate of cancer cells. The data show that the human liposarcoma cell line LSA secrets a protein which was identified as a polymorphic variant of MnSOD. This production and release takes places in absence of detectable LSA cell death, suggesting that MnSOD is externalized through a genuine secretion process. This possibility was supported by visualization of multiple SOD containing vesicles in cytoplasm of LSA cells. The fate of Mn-SOD remains normally confined to the mitochondrial matrix and the only example of extracellular SOD reported until now in the literature concerns a Cu/Zn dependent species distinct from LSA product. Functional assays using both purified MnSOD from LSA cells, and recombinant Mn-SOD led us to assign another unique property to Mn-SOD namely its oncotoxicicty. Incubation with rec. Mn-SOD efficiently killed tumor-derived human epithelial cells under conditions in which equivalent non-transformed cells survived. Most interestingly, our current work indicates that the oncotoxicity of Mn-SOD is directed against a variety of other human tumor cells, including the Glyoblastoma cells. Although the cytotoxic mechanisms is presently matter of speculation, we think that Mn-SOD needs to be internalized by target cells in order to became intoxicated. This uptake would allow Mn-SOD to be processed and or meet appropriate conditions, in order to gain functionality. This scenario would be consistent with our observations showing that exogenous Mn-SOD is indeed taken up by target cancer cells, and its activity is dependent on the state of these cells. It can be assumed that internalized Mn-SOD will lead to the production of hydrogen peroxide (H_2O_2) in target cells. Knowing that catalase, the enzyme responsible for H_2O_2 detoxification into molecular oxygen is present in 10-50 times lower amounts in many tumor cells compared with their normal progenitors, the treatment with rec.Mn-SOD may lead to an especially high accumulation of H_2O_2 in these neoplastic cells resulting in their preferential killing, while the normal cells result oxygenated. These data suggest that MnSOD deserve not only to be considered for the treatment of cancer, but also to prevent or to restore the degeneration of normal cells, having a therapeutic potential against other pathological condition known to be associated with oxidative stresses, such neurodegenerative diseases and aging.

42

DEMENZA FRONTALE DEGENERATIVA O SECONDARIA A ELETTROCUZIONE? DISCUSSIONE DI UN CASO CLINICO

***Francesco Scoppa*[1], *Paola Di Salvo*[2], *Vincenzo Saporito*[3]**

[1]UVA n°4 UO Neurologia e Neurofisiopatologia Università di Palermo.
[2]Servizio Dipartimentale Anziani e ADI AUSL n°6 Palermo
[3]Servizio Neurologia Distretto di Bagheria AUSL n°6 Palermo

La sindrome da elettrocuzione è un disturbo caratterizzato da deficit cognitivi persistenti e turbe psicocomportamentali dovute a folgorazione naturale (fulmini) o artificiali (scariche di corrente elettrica). I disturbi cognitivo-comportamentali sono molto simili a quelli osservati nei traumatismi cranio-encefalici lievi e moderati. I disturbi psicocomportamentali vanno da specifiche fobie a disturbi depressivi maggiori e sono spesso associati con svariati disturbi somatici di natura funzionale. I meccanismi di danno encefalico da elettrocuzione sono al momento speculativi e molto probabilmente multifattoriali. Pazienti che non migliorano a distanza di circa 3 mesi dal trauma sono da considerarsi a rischio per esiti invalidanti. La valutazione clinica di questi casi può essere interdisciplinare in quanto sono spesso indicati farmacoterapia, psicoterapia e riabilitazione neuropsicologica.
Caso Clinico:
Sogg. Maschio di 40 anni.
Forte fumatore, modico bevitore. Nel 1986 episodio depressivo della durata di circa un anno e mezzo con attacchi di panico. Dal 1991 al 2002 temperamento di tipo ipomaniacale. Nel mese di giugno ‘98 episodio di elettrocuzione con conseguente frattura della testa omerale sinistra da trazione con successivo intervento in anestesia totale. Circa un anno e mezzo addietro in un periodo di stress particolare il paziente ha iniziato a notare dei disturbi della memoria di fissazione con afasia nominum ed anomia. Per tali disturbi il paziente sotto consiglio di uno specialista neurologo ha eseguito i seguenti esami: RMN encefalo: atrofia corticale temporo-parietofrontale bilaterale con mielomalacia lungo i corni frontali. Il dosaggio della vit. B12 e dei folati nonchè la funzionalità tiroidea sono risultati nei limiti. Un controllo ECG è risultato nei limiti e così pure la Rx del torace.
Es. Neurologico: Hoffman a dx. ROT vivaci e simmetrici agli arti inferiori e lievemente asimmetrici a quelli superiori per prevalenza destra. Epstein e palmomentoniero assenti.
Es. Neuropsicologico: MMSE: 28/30; Corr. 25.2; ACE: 89/100; ADL:6/6; IADL:5/5. Capacità logico-astratte nei limiti.
PET cerebrale qualitativa: Ipocaptazione a carico della corteccia cerebrale a livello del giro frontale superiore bilateralmente con più spiccata compromissione della regione interemisferica.
Sospetta degenerazione frontale in paziente con personalità ciclotimica.
Dosaggio ADH : in corso.
Terapia: Depakin chrono 300 c., 1c ore 20 dopo cena.
Il nostro caso pone un problema di diagnosi differenziale molto interessante in quanto, sebbene la storia e il decorso clinico indirizzino verso un disturbo conseguente ad elettrocuzione, non si può escludere che si tratti di una demenza fronto-temporale a esordio assai precoce (37 anni) preceduto da prodromi di tipo psichiatrico (perseverazione, logorrea, marcata giovialità), ipotesi peraltro supportata dal neuroimaging funzionale che rivela un deficit perfusivo caratteristico “della corteccia cerebrale a livello del giro frontale superiore bilateralmente con più spiccata compromissione della regione interemisferica”. D’altro canto è anche suggestiva l’ipotesi che lo shock elettrico possa avere agito da stimolo slatentizzante il che spiegherebbe l’ esordio in così giovane età della malattia. Il paziente resta in osservazione e certamente il risultato del dosaggio dell’ADH nelle 24 ore e il tempo saranno elementi determinanti nella chiarificazione del caso.

78

INTERVENTI INTEGRATI DI ATTIVAZIONE COGNITIVA, PSICOSENSORIALE E AFFETTIVO-COMPORTAMENTALE IN SOGGETTI AFFETTI DA MCI

Secchiaroli Roberta, *Lorusso Sebastiano*

Lab. di Neuropsicologia U.O. Neurologia, Ospedale Infermi Rimini, Ass Alzheimer RiminiOnlus

Obiettivo: il presente intervento aveva lo scopo di verificare se il miglioramento dello stato "di benessere" raggiunto attraverso un approccio integrato potesse incidere sulle prestazioni del soggetto in una fase di compromissione cognitiva non ancora a grado demenziale.
Metodo: Si è utilizzato un approccio globale che ha coinvolto la persona in tutte le sue componenti (cognitiva, emotiva e corporea). Si è integrato il metodo Sociodrammatico (che "impegna tutti i mezzi di espressione dell'individuo, considerato nella sua situazione all'interno del gruppo" - Lebovoci et al, 1958), con tecniche basate sulla terapia di Reminiscenza ed esercizi di stimolazione cognitiva e sensoriale.
Gli incontri, effettuati settimanalmente per tre mesi, erano suddivisi in una prima fase di Attivazione psicosensoriale attraverso canali multipli (modalità tattile, gustativa, olfattiva ed uditiva) ed Attivazione mnestica (expanding rehearsal: apprendimento di coppie di parole). La seconda fase, invece, riguardava l'elaborazione affettivo-comportamentale ed era dedicata alla messa in scena di vissuti personali partendo da aneddoti raccontati dai partecipanti o prendendo spunto da fotografie del loro passato (reminiscenza attuata in maniera psicodrammatica) oppure dalle difficoltà da loro vissute (sociodramma) a causa del disturbo mnestico.
Soggetti: 5, 2 maschi e 3 femmine (età media: 73.2; range: 65 – 79, scolarità media: 9.6; range 5 - 17); diagnosi di compromissione cognitiva lieve (MCI), di tipo amnesico in tre casi, con memoria più altre funzioni coinvolte negli altri due casi (tutti avevano precedentemente eseguito un iter diagnostico comprendente neuroimaging ed esame neuropsicologico esteso). In due casi era presente anche depressione. E' stata somministrata la Scala CBI (Caregiver Burden Inventory) ai familiari (tab. 2).
Risultati:
Tabella 1: Risultati alle Scale di valutazione dei soggetti al T0 (prima dell'intervento) e al T1 (entro un mese dalla fine)

Soggetti	Mini Mental State Examination (MMSE)		Wechsler Memory Scale 1 e 2 (WMS)				Beck Inventory Depression Scale (BDI)		Scala valutazione clinica dell'Insight (CIRS)	
	T0	T1	T0 P.C. Q.M		T1 P.C. Q.M.		T0	T1	T0	T1
V.C.♀ (74 anni)	19,7	20,7	86	83	88	86	6	5	6	6
R.C.♂ (65 anni)	21,9	21,9	88	86	91	90	6	5	5	4
G.N.♂ (79 anni)	21,1	22,1	82	77	85	81	3	1	6	5
G.P♀ (75 anni)	25,7	27,7	96	97	96	97	4	1	3	3
C.R.♀ (73 anni)	20,3	21,4	75	67	75	67	16	14	7	7

Tabella 2: riepilogo risultati al CBI familiari (punteggi totali del gruppo)

	Carico oggettivo T0 T1		Carico Evolutivo T0 T1		Carico Fisico T0 T1		Carico Sociale T0 T1		Carico Emotivo T0 T1		TOTALI T0 T1	
n.5 Familiari	20	19	21	13	11	11	7	6	14	10	73	59

Osservazioni e conclusioni: Per quanto riguarda i dati "quantitativi" sopra riportati, è chiaro che, visto l'esiguo numero di partecipanti, il trend di miglioramento riscontrato nelle scale cognitive, timiche e dello stress dei familiari va inteso solo come una indicazione ed un incoraggiamento a proseguire nella direzione intrapresa. Per quanto riguarda l'aspetto qualitativo , i risultati sono da considerare buoni. Le persone, attraverso atti creativi sorprendenti, hanno mostrato una voglia straordinaria di creare un gruppo coeso all'interno del quale aiutarsi e "ripararsi".

43

THE INFLUENCE OF CEREBRAL WHITE MATTER HYPERINTENSITY ON COGNITIVE FUNCTION IN THE MILD COGNITIVE IMPAIRMENT SUBJECTS

Micaela Sepe Monti, *Giuseppe Bomboi, Patrizia Pantano, Antonella De Carolis, Valentina Bianchi, Luigi Bozzao, Franco Giubilei.*

Dipartimento di Scienze Neurologiche. Università "La Sapienza" - Roma

BACKGROUND: The value of white matter hyperintensity (WMH) as a predictor of Alzheimer's Disease (AD) in subjects affected by amnestic Mild Cognitive Impairment (aMCI) has not yet been elucidated. The WMH might be caused by AD neuropathology itself or it might be a consequence of either chronic cerebral ischemia or comorbid medical condition in the elder ones. The goal of the present study was to evaluate the influence of cerebral WMH on aMCI clinical course.
METHODS: We enrolled 21 subjects (mean age ± SD, 72.6 ± 4 years, range 61-81 years) affected by aMCI according to Petersen Criteria. At baseline, patients underwent the screening for dementia, including brain MRI (Philips, 1,5 T) and neuropsychological evaluation (MMSE, Token, Raven, Prose Memory, Phonological and Semantic Fluency, Visual Search and Constructional Apraxia). The mean MMSE score ± SD was 27.1 ± 2.8. The presence/absence of vascular risk factors (hypertension, diabetes, cardiopathy, cholesterol, trygliceride, smoke) was assessed from patients and informants. The volume of vascular lesions (vascular load) were evaluated on MRI FLAIR sequences using a semiautomatic lesion-detection program. None of the patients had abnormalities on MRI other than WMH or incidental small lacunar lesions (<5 mm). All subjects had a clinical follow-up every year.
RESULTS: At two year follow-up, 10 subjects converted to AD according to NINCDS-ADRDA criteria, while the MCI diagnosis was confirmed in 11 subjects. No differences in age, sex, level of education, vascular load and vascular risk factors were found between the two groups.. However, subjects who developed dementia tended to be more affected by hypertension, diabetes and cardiopathy. Vascular load was related to age ($r = 0.408$, $p = 0.04$; Pearson correlation) but not to vascular risk factors. The baseline score of MMSE, Prose Memory, Semantic Fluency and Visual Search were significantly different ($p=0.032$, $p = 0.002$, $p = 0.008$, $p = 0.03$, respectively; Mann Whitney test) in subjects who developed dementia at follow-up compared to subjects who had a confirmed aMCI diagnosis.
CONCLUSION: Our results suggest that neuropsychological evaluation might predict conversion to AD in aMCI subjects. On the contrary, cerebral WMH doesn't seem to influence the development of dementia in aMCI subjects and it isn't related to vascular risk factors. This suggests that the cognitive deterioration in aMCI subjects is mainly caused by the proper degenerative neuropathologies and that, especially in the early phase of disease, the vascular load doesn't influence the cognitive performance.

79

IL FENOMENO DEL CLOSING-IN NELLE PATOLOLOGIE NEURODEGENERATIVE CORTICALI E SOTTOCORTICALI

[1]Serra Laura, *[1,2]Fadda Lucia, [1]Costa Alberto, [1]Perri Roberta, [1,2]Carlesimo GA, [1]Peppe Antonella, [1,2]Caltagirone Carlo.*

[1]IRCCS Fondazione Santa Lucia; [2]Università Tor Vergata, Roma

Introduzione: Il fenomeno del closing-in è definito come la tendenza ad accollarsi ad un modello durante l'esecuzione di un compito costruttivo. Tale fenomeno sembra caratteristico degli stadi più avanzati del deterioramento cognitivo nella Malattia di Alzheimer (AD) e si ritiene che possa essere determinato da una disfunzione visuo-spaziale o da un deficit della working memory visuo-spaziale. La disintegrazione delle abilità visuo-spaziali è tipica sia delle patologie neurodegenerative corticali che di quelle sottocorticali. Scopo di questo lavoro è indagare i correlati neuropsicologici del fenomeno del closing-in nei pazienti affetti da AD e Malattia di Parkinson (PD).
Metodo: 14 pazienti con AD (F/M 7/7; Età 68,8± 12; Scolarità 8,1± 3,8) diagnosticato secondo i criteri NINCDS-ADRDA, e 10 pazienti con PD e demenza di grado lieve (F/M 3/7; Età 74,5± 5; Scol. 5,2± 2,4) che presentavano closing-in in un compito di Copia libera di disegni. Inoltre sulla base dei risultati di un recente lavoro che ha definito la presenza di diverse tipologie di closing-in le caratteristiche qualitative del nostro campione risultavano così distribuite: gruppo AD near era presente in 3 casi (21%), adherent in 5 casi (35%), overlap in 3 casi (21%). In 3 casi (21%) si aveva una tipologia mista di closing-in; gruppo PD near 3 (30%), adherent 4 (40%) overlap 3 (30%). I due gruppi sono stati confrontati in una serie di compiti verbali e visuo-spaziali che valutavano differenti abilità cognitive: memoria a breve termine (Digit Span; Corsi Span), memoria a lungo termine verbale (15 Parole di Rey; Test del Breve Racconto) e visuo-spaziale (Rievocazione immediata e differita della Figura Complessa di Rey); working memory (Digit Span Backword; Corsi Span Backword), ragionamento logico deduttivo visuo-spaziale (Matrici di Raven Colorate), abilità prassico-costruttive (Copia a mano libera di disegni; Copia di disegni con elementi di programmazione; Copia della Figura Complessa di Rey), funzioni esecutive (Fluidità verbale fonologica; Modified Sorting Card) e linguaggio (Costruzione di frasi).
Risultati: i pazienti AD e PD differiscono significativamente per scolarità ($F=4,42$ $p<0.05$) e per MMSE (AD 16,4 ±1,4; PD 22,1 ± 3,5; $F=29,1$ $p<0.00$). Come atteso i pazienti AD hanno prestazioni significativamente inferiori rispetto ai PD nella prova di long-term memory visuo-spaziale ($F=12,3$ $p<0.05$), nella short-term memory verbale ($F=4,45$ $p<0.5$) nella working memory verbale ($F= 4,52$ $p<0.05$), nel problem-solving ($F=4,48$ <0.05) e nella prassia a mano libera ($F=5,28$ $p<0.05$). Mentre i due campioni sono comparabili per età e nelle prove cognitive non differiscono significativamente nella long-term memory verbale, nella short-term memory verbale e visuo-spaziale, nella working memory visuo-spaziale, nelle funzioni esecutive e nel linguaggio. Inoltre sia nel gruppo degli AD che dei PD il punteggio del MMSE non correlava con il punteggio della prassia costruttiva.
Conclusioni: il nostro lavoro evidenzia che il fenomeno del closing-in non è specifico dell'AD ma è riscontrabile anche in altre patologie neurodegenerative. Tale fenomeno nei due gruppi non è correlato con la gravità di demenza misurata dal MMSE. Inoltre a fronte di una significativa differenza in un compito che richiede capacità di elaborazione visuo-spaziale i due gruppi evidenziano una equiparabile compromissione della working memory visuo-spaziale, in accordo con l'ipotesi che il closing-in sia prodotto da un deficit a carico della working memory visuo-spaziale.

80

A NEW TEST FOR THE STUDY OF SEMANTIC MEMORY: APPLICATIONS TO DIFFERENT DEGENERATIVE DEMENTIAS

Chiara Spartà§*, *Claudio Luzzatti§, Stefania Castiglioni*, Marta Zuffi*, Massimo Franceschi*.*

*Neurology Dept., Multimedica Holding S.Maria, Castellanza (VA);
§ Psychology Dept. Università degli Studi, Milano-Bicocca.

Background: Semantic memory is our knowledge of the world; it contains permanent representations of concepts, words and their meanings, as well as of objects and other stimuli perceived through the senses. Shallice argues that the semantic system may be conceived as a distributed net, in which regions tend to be more specialized for analysing certain aspects of a concept (e.g. the more perceptual features vs. the more conceptual ones); such specialization depends on the different patterns of connections subserving each process. Thus, a single concept would be most strongly represented in the activity of those pathways most involved in its identification and use. It seems to be resonable that also different types of association between concepts are made on different basis, being, therefore, selectively impaired by brain damage.
The aim of the project was to study semantic memory impairments in different degenerative dementias. In particular, our purpose was to verify if a new picture-to-picture matching test (called "the TAS" test) was a reliable measure of semantic memory in demented patients. A secondary aim was to study the presence of different patterns of response at the TAS subtests between groups of patients.
Methods: 40 patients with Alzheimer's Disease (AD), with mild to moderate degree of cognitive deficit, (MMSE score = 18.9 ± 4.1); 6 patients with Fronto-Temporal Dementia (FTD); 4 patients with Progressive non-fluent Aphasia (PA), and 2 patients with Semantic Dementia (SD) have been studied. A control group has been also recruited, including 37 healthy subjects. Patients did not differ significantly for age and education from the control group.
The "TAS" test is a new picture-to-picture matching task, made of 76 stimuli. It has been built considering 4 different types of relationship between concepts: "Categorical"associations (C), "Encyclopaedic" (E), "Functional" (F), and "Visual- Encyclopaedic" ones (VE). Each category included 19 items.
All subjects were administered a battery including: the MMSE, the VOSP test, the TAS test, an Object Decision task, a task assessing Visual Imagery, and the Naming sub-test of the AAT (DEN-AAT). Moreover, patients were administered an extensive neuropsychological evaluation.
All scores have been converted into z-points, in order to identify the pathological scores, and to compare scores obtained on different tasks. For each group, comparison analyses have been made using the t-test. Moreover, correlations between the TAS sub-tasks scores, and between the overall TAS score and the other tests of the battery, have been calculated within each group.
Results: 1) AD and SD patients obtained a pathological score on the TAS test; the FTD and PA groups' performance was in the normal range. 2) overall TAS score showed significant correlation with the MMSE score, in the AD and FTD groups; it was correlated with the DEN-AAT score in the AD group, but not in the FTD group. In the PA group, the overall TAS score did not correlate neither with the MMSE score, nor with the DEN-AAT one. 3) as for comparisons between groups, AD pts showed a significant difference with the Control group in all the TAS sub-tasks ($p<0.001$); AD pts also differed from the FTD group in the overall TAS score ($p<0.05$) and in some of the TAS sub-tests (C, E, $p<0.05$; VE, $p<0.001$); they did not differ from the PA pts in any of the semantic association task. The other groups (FTD, PA and Control group) did not significantly differ from each other in any of the semantic tasks.

SD pts also showed differences in the pattern of semantic impairments, suggesting possible dissociations.

Discussion: The TAS test seems to be a suitable tool to assess semantic memory in the dementias, since it is applicable even to patients with a low MMSE score, and with verbal comprehension impairment. Moreover, it seems to be a valid tool for semantics, since it is not necessarily correlated to the degree of cognitive disfunction, or to the performance in the other language tasks. Different patterns of semantic impairments have been found, in the different groups of patiens. Moreover, a first qualitative analysis on single-cases' performances suggests the presence of dissociations between different types of semantic relationship; thus our purpose for the future is to analyse single-cases, in order to verify current models of semantics.

81

M.DI ALZHEIMER: VERIFICA DELLA CORRELAZIONE TRA NPI-STRESS E SCALA GREENE ED INDIVIDUAZIONE DEI DETERMINANTI SOGGETTIVI DELLO STRESS DEL CAREGIVER

C.Tenconi [1,2], *C.Pettenati* [1,3], *D.Perotta* [1], *C.Campanello* [1], *M.Barbieri* [1], *S.Feller* [4], *M.Musicco* [5]

[1]: Centro Regionale Alzheimer AO G.Salvini Passirana Rho (MI) Dipartimento di Riabilitazione, [2]: Università Milano-Bicocca Facoltà di Psicologia [3]: Università Milano-Bicocca, Scuola di Specialità in Neurologia, [4]: UOC Neuroriabilitazione Dipartimento di Riabilitazione AO G.Salvini Garbagnate M.se (MI), [5] CNR ITB Segrate Milano

Introduzione: L'assistenza quotidiana del paziente Alzheimer (AD), svolta per più del 90% in famiglia, prende convenzionalmente il nome di caregiving. Esistono numerose evidenze di come il caregiving sia in grado di indurre modificazioni della storia naturale di AD, ma fattore limitante le potenziali capacità terapeutiche è il burn-out determinato dallo stress che l'attività di assistenza induce sul caregiver stesso. E' per questo che grande interesse è rivolto nella letteratura medica e psicologica allo stress del caregiver e ai suoi determinanti.
Razionale e scopo dello studio: L'NPI-stress misura lo stress indotto dai disturbi del comportamento del paziente AD, la scala Greene invece indaga lo stress su aspetti inerenti la vita del caregiver quali modificazioni dell'attività lavorativa o la sua vita sociale. In questo studio abbiamo voluto verificare quali fossero i principali determinanti di stress del caregiver ed in particolare se fossero predominanti le caratteristiche del paziente o quelle dello stesso caregiver. Abbiamo inoltre voluto valutare se le misure dello stress derivate dalle due scale misurassero lo stesso fenomeno o se fossero dipendenti dagli strumenti di misura utilizzati.
Metodi e campione: Lo studio è stato condotto presso il Centro Regionale Alzheimer di Passirana-Rho (MI). Sono stati inclusi 150 pazienti ambulatoriali consecutivi in modo stratificato: 50 con AD lieve (MMSE ≥16) 50 con AD moderato (16> MMSE ≤ 10) e 50 con AD severo (MMSE < 10). Le caratteristiche principali del paziente indagate per questo studio sono state: età, sesso, scolarità, professione premorbosa, gravità dell'AD al MMSE, livello di disabilità alle scale BADL e IADL, gravità della sintomatologia psichica e comportamentale alla NPI. Le caratteristiche del caregiver indagate sono: età, sesso, professione, convivenza con il paziente AD, livello di stress NPI e Greene, ore dedicate al paziente, tipo di supporto di cui usufruiva (famiglia, amici, badante, supporto religioso), bisogni dichiarati (pausa-vacanza, assistenza domiciliare, centro diurno, aiuto economico) e salute autopercepita (ottima, buona, discreta, pessima).
Risultati: Anche se statisticamente significativo il coefficiente di correlazione fra l'NPI stress e la Greene è particolarmente basso ($r=0.122$ $p<0.01$). Nessuna variabile (sociodemogafica e di malattia) relativa al paziente influenza in modo statisticamente significativo il punteggio di stress alle due scale. In particolare vi è assoluta assenza di correlazione fra gravità del decadimento cognitivo misurato con il MMSE e il livello di stress del caregiver misurato con la Greene ($r= -0,19$ $p<0.05$). Vi è ovvia e significativa correlazione lineare fra punteggio all'NPI del paziente e punteggio all'NPI-stress del caregiver ($r=0.808$ $p<0,01$). I cluster della Greene (personale distress, life upset, negative feelings) sono tra loro solo parzialmente correlati misurando quindi componenti in parte differenti dello stress del caregiver ($r=0.7$). In ogni caso ciascun cluster è altamente correlato al punteggio totale della scala ($r= 0.8$). Tra le variabili relative al caregiver solo la stato di salute autopercepito (ANOVA $F(3,146)$ 5,285 $p=0.002$), ed i bisogni riferiti (ANOVA $F(3,146)$ 10,00 $p=0.000$) sono risultati significativi. L'NPI stress per entrambe queste variabili non è risultata significativa (rispettivamente ANOVA $F(3,146)0.750$ $p=0.524$ e $F(3,146)0,206$ $p=0,892$). I caregiver che autoriportano una salute ottima hanno punteggi alla Greene significativamente

inferiori rispetto a coloro che riportano livelli meno soddisfacenti di salute. Il tipo di supporto in atto è risultato significativamente associato al punteggio di stress misurato con l'NPI-stress (ANOVA F(3,146)4,656 p= 0.004).
Conclusioni: il nostro studio suggerisce che lo stress del caregiver sia influenzato più da fattori soggettivi del caregiver che da fattori obiettivi inerenti il paziente. Più in dettaglio si può poi concludere che il livello di stress dipende in modo rilevante dalle scale di misura utilizzate, per il fatto che NPI-stress e Greene mostrano una correlazione poco soddisfacente. I cluster della Greene mostrano tra di loro una non completa correlazione, e ciò suggerisce che i cluster misurino effettivamente componenti diverse dello stress del caregiver che andranno separatamente indagate anche in studi futuri. Tra le variabili del caregiver sembra emergere che le sue caratteristiche psicologiche e di personalità influenzino in modo rilevante anche la sua risposta al carico assistenziale in termini di stress. Ciò significa che vi è ampio spazio per un intervento di tipo psicologico e che con una adeguata integrazione fra servizi assistenziali e supporto individuale al caregiver è possibile stendere un progetto di cure più efficace per i malati di Alzheimer.

82

STUDIO COMPARATIVO DEL DISAGIO E DEI BISOGNI DI DUE GRUPPI DI CAREGIVER PROVENIENTI DA DUE DIVERSE AREE GEOGRAFICHE ITALIANE

Tiziana Tentorio* , *Rosaria Laura Marzullo§, Stefania Castiglioni*, Marta Zuffi*, Massimo Franceschi**

* U.O. Neurologia, Multimedica Holding - Santa Maria, Castellanza - Varese
§ U.O: di Geriatria I.N.R.C.A. Istituto di ricovero e cura a carattere scientifico, Sede di Fermo (AP).

Introduzione: sulla base di uno studio pilota precedentemente svolto presso l'U.V.A. di Castellanza (T.Tentorio et al., VIII Annual Meeting ITINAD, Sorrento 2004) che riguardava l'espressione di disagio da parte dei famigliari di pazienti affetti da Malattia di Alzheimer, ci siamo proposti di estendere il campione di studio, ed in particolare di confrontare tale realtà così come viene percepita in due diverse aree geografiche italiane (province di Varese e Ascoli Piceno).
Metodi: abbiamo ampliato i dati precedentemente raccolti presso il centro di Castellanza, distribuendo il medesimo questionario anche presso l'I.N.R.C.A. di Fermo. Il questionario si compone di una prima parte di raccolta dei dati anagrafici del caregiver, di una seconda di informazioni sul malato (es. durata di malattia) e sul tempo ad esso dedicato, ed una parte composta dalla Relative Stress Scale a sua volta divisa in tre sottoscale (1: disagio psicologico; 2: modificazioni abitudini; 3 : sentimenti negativi verso il malato).
Presso entrambi i centri il questionario è stato distribuito, presso gli ambulatori U.V.A., a serie consecutive di caregiver di pazienti inseriti nel progetto cronos da almeno sei mesi. Vengono presentati i dati relativi a 35 soggetti presso il centro di Castellanza e 45 soggetti presso il centro di Fermo.
I dati relativi a tutte le variabili indagate sono stati sottoposti alle comuni statistiche descrittive. Le stesse variabili sono state confrontate tra i due gruppi attraverso una statistica non parametrica (Mann-Whitney U). Inoltre, all'interno dei due gruppi è stato calcolato l'indice di correlazione (r-Spearman) tra tutte le variabili in oggetto.
Risultati: 1) I dati anagrafici risultano così distribuiti nei due gruppi:

- Castellanza: età media dei carer 54 ± 10,7 anni; 11,4% (4) maschi, 88,6% (31) femmine; 25,7% (9) coniugi, 57,1% (20) figli, 14,3% (5) nuore, 2,9% (1) sorelle.
- Fermo: età media 50 ± 10,9 anni; 23,8% (10) maschi, 76,2% (32) femmine; 11,9% (5) coniugi, 52,4% (22) figli, 26,2% (11) nuore, 4,8% (2) sorelle, altro 4,8% (2).

Centro di riferimento	**Esordio malattia (in mesi)** Media D.S.	**Data diagnosi (in mesi)** Media D.S.	**Si occupa direttamente del malato ?**	**Possiede informazioni sufficienti sulla malattia ?**	**Riceve aiuto ?**	**Adeguatezza dell'aiuto**	**Contatti con i servizi sociali**
Fermo	40 22,5	28,7 20,0	SI = 26 (61,9%) NO = 15 (37,5%)	SI = 25 (59,5%) NO = 17 (40,5%)	SI = 22 (52,4%) NO = 20 (47,6%)	Insuff = 2 (10%) Suff = 10 (45,5%) Adeguato = 9 (40,9%)	SI = 5 (11,9%) NO = 37 (88,1%)
Castellanza	44,8 15,8	30,3 19,2	SI = 25 (71,4%) NO = 9 (25,7%)	SI = 22 (62,9%) NO = 13 (37,1%)	SI = 13 (37,1%) NO = 21 (60%)	Insuff = 3 (23%) Suff = 8 (61,5%) Adeguato = 2 (15,4%)	SI = 5 (11,9%) NO = 37 (88,1%)

2) I due gruppi differiscono significativamente nella distribuzione del grado di parentela, nella fonte primaria di informazioni sulla malattia e nel grado di stress. In particolare, i caregiver di Ferno ottengono punteggi più elevati ($p < 0,01$) sia nel punteggio totale che alle singole sottoscale della RSS.
3) Nel gruppo di Castellanza il tempo trascorso con il malato correla positivamente con età del carer (r = 0,454*), con la durata della malattia (esordio r = 0,398*; data diagnosi r = 0,375*) e con la gestione diretta del malato (r = 0,492**), ma non con il grado di stress. Correlano positivamente

con il grado di stress: il sesso del carer (RSS tot. r = 0,452**; Sottoscala 1 r = 0,402*; Sottoscala 3 r = 0,456**) e la gestione diretta del malato (RSS tot. r = 0,376*; Sottoscala 2 r = 0,442*); negativamente con l'aiuto ricevuto (RSS tot. r = -0,486**; Sottoscala 2 r = -0,55**).
Nel gruppo di Fermo il tempo trascorso con il malato correla con la gestione diretta del malato (r = 0,426**) e con la Sottoscala 2 della RSS (r = 0,316*), ma non con i dati di durata della malattia. Inoltre correla positivamente con il grado di stress, l'esordio della malattia (RSS tot. r = 0,312*; Sottoscala 1 = 0, 364*).
Conclusioni: Nei due gruppi diversi pattern di correlazione con il grado e la tipologia di stress sembrano suggerire l'influenza di differenze di natura socio-culturale a determinare il disagio nelle due aree. Sembrerebbe che a Fermo la presa in carico dal parte del caregiver non sia modulata né dalla gravità di malattia (come generalmente indicato dalla durata della stessa) né dall'utilizzo di servizi assistenziali sul territorio, dando luogo nel tempo a un maggiore livello di disagio percepito.

83

CENTRO DIURNO ALZHEIMER: IMPATTO SULLA GESTIONE DEI PAZIENTI

Trequattrini A., *Spadoni L., Petturiti F., Alunni S., Picchi C., Meloni F., Perazzi A., Ciappi F.*

Dipartimento Tutela Salute Mentale, ASL1 Umbria, Città di Castello (PG).

Background: il Centro Diurno per pazienti affetti da malattia di Alzheimer "Luigi Coli" si trova a Città di Castello (PG) e costituisce un servizio a carattere intermedio fra l'assistenza domiciliare e la residenzialità, dove è prevista una durata dell'inserimento dei pazienti a tempo determinato e a giorni alterni. Persegue scopi assistenziali e riabilitativi nei confronti dei pazienti, nonché sostegno e supporto ai loro familiari.
Methods: lo studio, osservazionale, ha raccolto longitudinalmente dati relativi al consumo di risorse sanitarie per il trattamento di 21 pazienti affetti da demenza tipo Alzheimer probabile (secondo i criteri NINCDS-ADRDA), di grado medio-grave, durante un periodo di otto mesi: alla baseline (T0), all'ingresso nel Centro Diurno (T1, 2 mesi), alla dimissione dal Centro Diurno (T2, 6 mesi) ed alla fine dello studio (T3, 8 mesi). Scopo della ricerca è stato definire il carico assistenziale e l'andamento clinico dei pazienti prima, durante e in seguito alla frequentazione del Centro Diurno. Inoltre, si è cercato di evidenziare l'impatto che l'assistenza del Centro Diurno può avere sugli interventi sanitari nell'immediato e fino a due mesi dalla dimissione. L'evoluzione clinica dei pazienti è stata monitorata con visite programmate nel protocollo, durante le quali venivano somministrati i seguenti test clinici: MMSE (Mini Mental State Examination), ADL (Activity of Daily Living), IADL (Instrumental Activity of Daily Living).
Results: i risultati del nostro studio evidenziano che, a fronte di un lieve e non significativo peggioramento delle condizioni cliniche dei pazienti, durante i primi due mesi di osservazione sul territorio, si è avuta un'inversione significativa di andamento dei punteggi totali di tutte e tre le scale, con un notevole miglioramento, durante i 4 mesi di accesso al Centro Diurno. Dopo la dimissione dal Centro Diurno le condizioni cliniche medie del campione sono peggiorate nuovamente. L'omogeneità dell'andamento dei tre diversi strumenti di valutazione clinica conferma la positiva influenza dell'intervento del Centro Diurno sul decorso delle demenze nel gruppo osservato. Sia l'impiego di farmaci per il sistema nervoso centrale, che il numero di interventi sanitari totali nei tre momenti dello studio, dimostrano che la frequentazione del Centro Diurno porta ad una significativa riduzione delle risorse impiegate. Nel periodo di frequentazione, inoltre, si assiste ad una riduzione importante del carico di assistenza familiare e privata giornaliera. L'andamento positivo delle variabili cliniche ed economiche indotto dalla frequentazione del Centro Diurno, tuttavia, non si protrae a lungo successivamente alla dimissione, in seguito alla quale, infatti, si verifica un incremento rilevante dell'assistenza privata, in termini di ore mensili.
Conclusions: il nostro studio evidenzia come la frequentazione del Centro Diurno abbia influenzato positivamente la performance mentale (MMSE) e le abilità dei pazienti (ADL e IADL), riducendo anche significativamente la necessità di assistenza familiare e privata. Il Centro Diurno ha una sua valenza terapeutica intrinseca ma l'entità dei benefici che se ne può trarre dipende da una costellazione di altri fattori interdipendenti: l'inserimento di un paziente presuppone, infatti, una vera e propria presa in carico e la strutturazione di un progetto terapeutico individuale. Inoltre, questo tipo di struttura, per poter avere un impatto significativo sul decorso della malattia e per alleggerire i carichi dei caregivers, deve poter garantire l'accesso dei pazienti per periodi di tempo prolungati.

32

THE *T-786C* NOS3 POLYMORPHISM IN ALZHEIMER'S DISEASE: ASSOCIATION AND INFUENCE ON GENE EXPRESSION

***Eliana Venturelli*[1]**, *Daniela Galimberti*[1], *Carlo Lovati*[2], *Chiara Fenoglio*[1], *Diego Scalabrini*[1], *Claudio Mariani*[2], *Gianluigi Forloni*[3], *Nereo Bresolin*[1], *and Elio Scarpini*[1]

[1]Dept. of Neurological Sciences, "Dino Ferrari" Center and CEND, University of Milan, IRCCS Ospedale Maggiore Policlinico, Milan, Italy
[2]Dept. of Neurology, University of Milan, Ospedale L. Sacco, Milan, Italy
[3]Dept. of Neurosciences, Istituto di Ricerche Farmacologiche M. Negri, Milan, Italy

Alzheimer's disease (AD) is considered a multifactorial disease, caused by both, genetic and environmental factors. Beta-Amyloid (ĄBeta) deposits in AD brains can lead to the production of superoxide radicals, that, combining with nitric oxide (NO), form peroxynitrite, which in turn induce cellular injury. NO is produced by the activity of three isoforms of Nitric Oxide Synthase (NOS). So far , one of them, the endothelial form (NOS3), has been widely studied and the corresponding gene, located on chromosome 7q35, has been proposed as candidate gene. A common polymorphic variant in NOS3 gene, a single nucleotide polymorphism (SNP) consisting in a T→C transition (T-786C), is located in the promoter region of the NOS3. This SNP has been reported to be associated with vascular pathologies, but at the present, no information are available on a possible association with AD.
T-786C genotype was determined by RFLP in an Italian population of 432 AD patients compared with 360 healthy controls, matched for ethnic background, age and gender.
Peripheral blood mononuclear cells (PBMC) from 22 subjects (11 AD and 11 controls) carrying different genotypes were isolated. Total RNA was extracted and analyzed by Real-Time PCR. Fisher's exact test was used for differences in allele distribution between the groups. Expression levels were compared using the Mann-Whitney U-test. No significant differences either in allelic or genotypic frequencies of the T-786C polymorphism between AD and normal population were observed. Stratifying AD patients by age at onset, gender, or the presence of the ApoE e4 allele, no differences were observed as well. However, expression of NOS3 in PBMC seems to be influenced by the presence of the C mutated allele, as demonstrated by a tendency towards a decrease in mRNA levels in C carriers, assessed by Real-Time PCR assay. This effect was observed both in patients and controls, independently from the cognitive impairment, and is likely to be dose-dependent, being mostly evident in CC homozygous.
In conclusion, the T-786C SNP doesn't seem to be a risk factor for sporadic AD, but its presence correlates with a trend toward lower NOS3 expression rate, although the potential importance of this reduced gene transcription on neurodegeneration needs further elucidations.

84

ALZHEIMER'S DISEASE ASSESSEMENT SCALE AS A USEFUL TOOL TO PREDICT PROGRESSION TO DEMENTIA IN MILD COGNITIVE IMPAIRMENT

Barbara Vicini Chilovi, *MD, Luca Rozzini, MD, Erik Bertoletti, MD, Alessandro Padovani PhD, MD.*

Clinica Neurologica, Università degli Studi di Brescia.

Background: the insidious onset of Alzheimer Disease (AD) suggests that many, if not all, patients with AD pass through a prodromal stage of Mild Cognitive Impairment (MCI) before overt dementia is diagnosed. To date, efforts to differentiate those who will progress to dementia from those who will not have, proved inconclusive, and while grades of risk have been identified, their generalizability for practicing physicians is not clear.
Objective: to develop reliable and practical tools that aid in identifying patients at risk of developing Alzheimer Disease among heterogeneous populations with MCI.
Methods: longitudinal and retrospective comparison of neuropsychological performance in: subjects meeting criteria for amnestic Mild Cognitive Impairment who, after one year follow-up, developed probable or possible AD, and subjects from the same group who did not progress towards dementia. A sample of 70 subjects referring memory complaints, corroborated by an informant, underwent a multidimensional assessment to verify the absence of dementia and to exclude other possible causes of cognitive decline. Moreover they were administered a comprehensive neuropsychological battery at baseline and after one year follow-up.
Results: of the 70 subjects revaluated after one year, 23 (32,8%) were progressed to dementia of Alzheimer type (*converters*), while 47 (67,2%) remained in a condition of MCI (*stable* MCI). Gender, age and education were equal among *converters* and *stable* MCI, and the groups were clinically similar. Psycho-behavioural symptoms, referred and self reported, were presented in both groups, with a relatively more frequent presence of depressive symptoms in the *stable* MCI, even not significant. Global cognitive performances were little more impaired, but not significantly, in *converters* when assessed by Mini Mental State Examination (MMSE), while there was a significant difference in mean Alzheimer's Disease Assessment Scale-cognitive part (ADAS-Cog) total score, that was found to be an independent predictor for developing dementia within one year. As regards subscores of the ADAS-Cog, *stable* MCI gained 2,9 error points on non-word list items compared with a gain of 4,8 points for *converters*. In terms of z scores (SD units), *converters* performed on average 1,3 SD higher on the immediate word list recall test and 2,1 SD higher on the delayed word list recall test compared to 0,8 SD and 1,5 SD, respectively, in the *stable* MCI (scores compared to normal controls). Moreover *converters* performed on average 2,9 SD higher on the orientation test and 0,6 SD higher on the constructional praxis, compared to 0,6 SD and no differences in the *stable* group. In a logistic regression model higher ADAS-Cog score, without word list items, was independently associated to a major risk of conversion to dementia within one year.
Conclusions: among patients with amnestic MCI those with a greater impairment in cognitive domains other than memory, were at higher risk to develop dementia of Alzheimer type within one year. ADAS-Cog, had revealed a useful and practical tool to discriminate between subjects with MCI those more impaired on memory and non memory tasks, and was a significant predictor for progression towards AD.
Table. MMSE and ADAS-Cog baseline scores in MCI patients who converted in AD within one year or remained stable.

	Converters (n 23)		Stable (n 47)		
	Mean	SD	Mean	SD	p.
MMSE	25,9	2,1	26,8	1,8	ns
ADAS-Cog total score	11,89	3,5	8,4	4,4	.001
ADAS-Cog without word list items	4,8	2,8	2,9	2,3	.004
Word list immediate recall	6,4	1,1	5,6	1,2	.008
Word list delayed recall	8,4	1,7	7,3	2,1	.05
Word list recognition	4,2	1,6	3,3	2,1	.04

85

TASSO DI CONVERSIONE VS. ALZHEIMER DI PAZIENTI CON MILD COGNITIVE IMPAIRMENT E CON DEPRESSIONE INVOLUTIVA

Elena Viganò; *Michele Perini; Antonella Carnicelli; Fiorella Tavernelli; Francesca Bollini; Davide Zarcone.*

U.O. Neurologia - U.V.A.- Azienda Ospedaliera S. Antonio Abate di Gallarate,

Background: Negli ultimi anni l'interesse per le fasi precoci della demenza è notevolmente aumentato. In particolare, da più autori l'attenzione è stata rivolta a pazienti affetti da Mild Cognitive Impairment (MCI) e a pazienti con quadro depressivo involutivo, entrambi considerati ad alto rischio di sviluppare demenza.
Scopo del lavoro è valutare il tasso di conversione vs AD in pazienti con MCI e con disturbo depressivo involutivo nell'arco di 18 mesi.

Methods: Tra i pazienti afferiti all'U.V.A. di Gallarate dal settembre 2000 (tot. 1430), ne sono stati arruolati e seguiti nel tempo 2 gruppi:
50 pazienti diagnosticati come depressi dopo valutazione clinica e neuropsicologica. L'esame neuropsicologico, oltre al MMSE e alla parte cognitiva dell'ADAS (i cui punteggi sono risultati per tutti i pazienti nella norma) ,includeva il questionario di valutazione della depressione di Zung (indice SDS : M = 59,06). Tutti questi pazienti sono stati sottoposti a terapia antidepressiva.
50 pazienti diagnosticati come MCI nei quali il disturbo cognitivo lieve non si accompagnava a criteri clinici di demenza. Tutti i pazienti rispondevano ai criteri proposti da Petersen et al.(1999) per l'MCI . In questo campione n°12 pazienti (24%) mostravano alla prima valutazione un deficit cognitivo isolato che coinvolgeva la sola memoria (MCI AMNESTICO) e n°38 pazienti (76%) con compromissione della memoria e di almeno un'altra funzione cognitiva (QUESTIONABLE DEMENTIA).
Result : Il follow-up eseguito a 18 mesi di distanza dalla valutazione basale ha mostrato quanto segue:
Dei 50 pazienti diagnosticati come depressi, 44 si sono presentati all'ambulatorio per essere rivalutati. Di questi, 23 (52,2%) hanno risposto alla terapia antidepressiva con miglioramento del quadro cognitivo e scomparsa del sintomo depressivo (indice SDS: M = 48,69); 8 (18,1%) sono rimasti invariati con persistenza del disturbo depressivo senza peggioramento della sintomatologia cognitiva; 13 (29,5%) invece hanno risposto a terapia antidepressiva (o almeno in parte) ma sono peggiorati cognitivamente, rispondendo così ai criteri clinici per la messa in atto di terapia anticolinesterasica.
Il follow-up di 40 pazienti con diagnosi MCI ha evidenziato quanto segue : 27 pazienti (67,5%) sono rimasti stabili cognitivamente o hanno avuto un lieve peggioramento non risultato significativo per A.D. ; 2 (5%) sono tornati nel range di normalità; 11 (27,5%) hanno mostrato una progressione verso malattia di Alzheimer. Di questi 11 pazienti: 3 (27%) appartenevano al sottogruppo con MCI amnestico; 8 (73%) erano pazienti con altre funzioni cognitive compromesse oltre alla memoria.

Conclusion: I nostri dati confermano l'aumentato rischio sia per i pazienti con MCI sia per i pazienti con depressione involutiva di sviluppare demenza. Inoltre abbiamo stimato nei due gruppi di pazienti percentuali abbastanza sovrapponibili (29,5% nei depressi e 27,5% nei MCI) nell'evoluzione dei sintomi cognitivi in A.D. nell'arco di 18 mesi .

86

COG-MARKERS: STANDARDIZZAZIONE E TARATURA DI UN NUOVO STRUMENTO PER LA DIAGNOSI E LA STADIAZIONE DELLA MALATTIA DI ALZHEIMER

***S. Zago*[1,2]**, *B. Poletti*[2], *A. Monti*[1], *R. Ferrucci*[1]

[1]Dipartimento di Scienze Neurologiche, IRCCS Ospedale Maggiore-Policlinico, Milano
[2]U.O. di Neurologia, Dipartimento di Scienze Neurologiche, Università degli studi di Milano, IRCCS - Istituto Auxologico Italiano, Milano

I markers neuropsicologici rappresentano segni caratteristici di fallimento evidenziabili in malati di Alzheimer (AD) durante l'esecuzione di prove testistiche di varia natura (Gainotti, Marra, Parlato e Chiaretti, 1998). Tra i markers cognitivi più noti vanno menzionati il closing-in in prove visuocostruttive, la presenza di risposte globalistiche e/o strane alle Matrici Progressive di Raven, gli errori di intrusione, i falsi riconoscimenti e gli effetti di posizione seriale rilevabili al test di memoria delle 15-parole di Rey, l'incapacità nell'esecuzione a memoria del quadrante di un orologio, gli errori nella transcodificazione di numeri.
La misura di validità di un marker viene qualificata in termini di sensibilità e specificità. Per *sensibilità* si intende la capacità del marker di identificare il maggior numero di pazienti affetti da AD (è tanto più elevata quanto meno sono i *falsi negativi*), mentre per *specificità* si intende la capacità del marker di identificare come AD solo i pazienti effettivamente tali e non affetti da altre forme di demenza o da un declino cognitivo fisiologico (è tanto più elevata quanto meno sono i *falsi positivi*). Si può affermare che un marker affidabile per l'AD dovrebbe raggiungere i livelli di sensibilità/specificità attualmente ottenibili con l'intero iter diagnostico (combinazione di dati anamnesici, ematochimici, neurologici, neuropsicologici e neuroradiologici) che secondo alcuni autori si aggira attorno all'85-90%. Un marker cognitivo dovrebbe inoltre essere di semplice esecuzione e individuare il più precocemente possibile la malattia.
Lo scopo del presente lavoro è stato quello di sviluppare una nuova batteria, denominata *Cog-Markers*, che accorpando diversi markers presenti in letteratura possa fornire livelli di sensibilità e specificità maggiori, rispetto a quando i markers vengono considerati singolarmente. Già Gainotti et al., (1998) avevano rilevato la possibilità di incrementare il valore diagnostico mediante l'assemblamento di più markers. Nella presente batteria sono stati considerati 8 markers che nell'ordine di presentazione all'interno della batteria risultano: (1) orientamento temporale, personale e spaziale, (2) transcodificazione scritta di numeri, (3) rievocazione di 15-parole (test simil-Rey), (4) il closing-in e l'accollamento al modello, (5) il test dell'orologio, (6) test di memoria (adattamento del Free and Cued Selective Reminding Test), (7) test della matrici (test simil-Raven), (8) test delle stime cognitive e assurdità.
La batteria è stata somministrata ad oggi a due gruppi (52 soggetti normali e a 31 pazienti con diagnosi probabile di AD) comparabili per età (70-89 anni), scolarità (3-13 anni) e sesso. Dall'analisi dei risultati emerge una netta separazione tra le performance prodotte dal gruppo AD rispetto a quelle del gruppo di anziani normali. Considerando come *soglia discriminante* il valore ottenuto dalla sottrazione di due deviazioni standard alla prestazione media dei soggetti anziani normali (95.6/164) si rileva che nessun paziente AD ottiene un punteggio al di sopra di tale valore. Tra i pregi evidenziati dal Cog-Markers vanno anche menzionati la praticità, il tempo di esecuzione contenuto (30-45 minuti) e l'assenza di fenomeni *soffitto* e *pavimento*.
Per concludere, la batteria qui presentata sembra essere particolarmente promettente ed è attualmente in corso un ampliamento del campione sia normale che patologico finora esaminato.

Riferimenti Bibliografici

Gainotti, G., Marra, C., Parlato, V., e Chiaretti, F. (1998). Sensitivity and specificity of some neuropsychological markers of Alzheimer dementia. *Alzheimer Disease and Associated Disorders*, 12, 152-162.

87

WHAT MCI IS?
DEBATING THE NOSOLOGICAL ISSUE

Gabriele Zanardi *°, *Stefania Basilico*°, Ambra Mazzola° , Serena Passoni°, Gilda Pesenti^°, Stefano Panzeri°, Martina Gandola*°, Gabriella Bottini*°.*

*Dipartimento di Psicologia Università di Pavia
° Laboratorio di Neuropsicologia Dipartimento di Scienze Neurologiche Ospedale Niguarda, Milano
^Dipartimento di PsicologiaUniversità di Milano-Bicocca, Milano

Introduction: The MCI represents a well defined pathology largely recognized in the literature. However the classification of this pathological condition is still controversial. Previous classifications in fact, consider MCI an isolated deficit of episodic verbal memory with a duration of at least six months, without other cognitive dysfunctions and not associated to depression (Petersen RC, 1999). Nowadays many authors propose to include in the MCI also other categories of patients manifesting various cognitive, behavioural and neurological disturbances (Luis C.A., 2003).
Aim of the study: To perform a retrospective analysis of a population of patients who had a neuropsychological assessment to investigate a referred MCI in the presence of a normal global cognitive functioning. We wanted to explore whether in this population a more extensive nosographical classification could be applied in order to improve the neuropsychological support to the clinical diagnosis.
Methods: 74 patients (51 females; 23 males; age range: 52-84 yrs; education range: 3-18 yrs) have been assessed along two years (2002-2004). 23 of them had also a neuropsychological follow-up within one year from the first evaluation. Subjects were administered with tests to identify memory, language, attention, visuo-constructive ability, executive functions' deficits. All the subjects had a normal MMSE score.
Results: Subjects have been classified in three categories: 1) MCI with isolated deficit of long-term verbal memory (A MCI), 2) MCI with isolated deficit of long-term spatial memory (S MCI), 3) MCI characterized by one or more cognitive dysfunctions (F+). Table 1 illustrates the distribution of patients into these categories.

Tab 1

Pts	Number	Sex	Age	Education
A MCI	9 – 12,16%	5 male-4 female	54aa - 79aa	6 - 17
S MCI	22 – 29,73%	6 male-16 female	53aa – 80aa	3 – 18
F+	43 – 58,11%	12 male-31 female	52aa – 84aa	3 – 15

Table 2 illustrates the percentage distribution of dysfunction in the different cognitive domains in the F+ category.

Tab 2

Cognitive Domain	Neuropsychological Test	
Verbal production_frontal function	Semantic and phonemic fluency	4,7%
Verbal episodic memory	Short Story Recall	30,2%
Short term verbal and spatial memory	Digit Span / Corsi Span	2,3%
Verbal comprehension	Token Test	16,3%
Constructive apraxia	Rey figure copy	44,2%
Long term spatial memory	Rey figure recall	86%
Divided attention	Attentional Matrices	4%
Sustained attention	Trail Making A– B	51,2%

A preliminary descriptive analysis of a two years follow-up study on this restricted group of patients shows: *Tab 3*

Initial diagnosis	Pathological evolution after 24 months	Percentage
S MCI	SMCI	28,5%
	F+	28,5%
	AD	14,5%
	NORMAL	28,5%
F+	SMCI	14,3%
	F+	35,7%
	AD	35,7%
	NORMAL	14,3%

Conclusions: Our results demonstrate that many patients with MCI although maintain a normal MMSE score for a considerable time, develop various dysfunctions in different cognitive domains. As a consequence these patients may be considered as MCI to be differently classified. As centres specialized in cognitive deterioration diagnosis may utilize different clinical approaches, a multicentric study with the aim to better define the methodological aspects of MCI classification and the adequate parameters to identify the MCI categories that more frequently evolve in AD, may be helpful to clarify the actual scenario.

Refereces:

- Petersen RC, Smith GE, Waring SC (1999) “Mild Cognitive Impairment: Clinical characterization and outcome.” Arch Neurol 56: 303-308
- Luis CA, Loewenstein DA, Acevdo A (2003) “Mild Cognitive Impairment: directions for future research” Neurology 61: 438-444
- Dementia Study Group of the Italian Neurological Societt (2000) “Guidelines for diagnosis of dementia and Alzheimer’s disease” Neurol Sci 21: 187-194
- Jacobs DM, Sano M, Doonelef G, Marder K (1995) “ Neuropsychological detection and caracterization of preclinicla Alzheimer’s disease” Neurology 45: 957-962
- Perri R, Carlesimo GA, Ca<ltagirone C e il gruppo di studio “ diagnosi precoce della malattia di Alzheimer” dell’Italian Interdisciplinary Network of Alzheimer’s disease(2001) “Mild Cognitive Impairment: studio multicentrico italiano” Rivista di Neurologia 11: 65-72

88

TRAIL MAKING TEST'S SUBCOMPONENTS EXPLORED BY A TOUCH

G. Zanardi* ° , *M. Berlingeri°, I. Curti*, M. Picascia*, V. Servodio*, R. Ursillo*, F. Pasotti°, S. Jan#, G. Bottini*°*

*Dipartimento di PsicologiaUniversità di Pavia
° Laboratorio di Neuropsicologia Dipartimento di Scienze NeurologicheOspedale Niguarda, Milano
^Dipartimento di Psicologia Università di Milano-Bicocca, Milano
#Divisione di Neurologia, Dip. Scienze Neurologiche, Ospedale Niguarda, Milano

Introduction: The Trail-Making Test (TMT) is widely-used in clinical practice. Both parts, A and B, involve visual scanning, visuo-motor coordination and visuo-spatial ability; part B is characterized by a more demanding shifting set as it involves numbers and letters (Bradford D.T., 1992). However the lack of standardisation of presentation and scoring makes comparison across different patient groups problematic, as there may be considerable procedural variation. It is not clear for example if patients with Mild Cognitive Impairment (MCI) show a defective performance at the TMT.
Aim of the study: to investigate whether fractionating the various cognitive components of TMT may stress performance's differences between MCI patients and normal controls (young adult and elderly).
Methods: 20 elderly subject (10 females; 10 males; age range: 50-84 yrs; education range: 5-18 yrs) 30 young subject (25 females; 5 males; age range: 21-40 yrs; education range: 10-18 yrs) and 5 MCI patients (2 females; 3 males; age range: 61-81 yrs; education range: 5-15 yrs) were administered with the canonical TMT A - B and with a series of subtests exploring the different cognitive components supposed to be involved in the classical TMT: Concept Shifting Test (CST) (Vink & Jolles, 1985) exploring visual scanning, visuo-motor coordination and shifting abilities; Visuo-Motor Speed Test (VMST); Reticular Planning Task (RPT) exploring visual scanning shifting ability; Visuo-Motor Task (VMT) exploring visual perception and oculo-motor coordination abilities; Visuo-Motor Spatial Abilities (VMSA) exploring visual scanning of numerical and literal stimuli. Tests were administered by a touch screen platform. Data (overall time implied to ending a task, in second) were analyzed by a non parametric test (Wilcoxon).
Results: No difference between the three groups has been revealed on the VMT.
Elderly subjects have been found to be slower than young subjects ($P<0,001$) on all the other tasks. The same difference has been detected in the comparison between young subjects versus MCI patients ($P<0,001$). Furthermore MCI are significantly slower than elderly subjects on the following tasks: TMT-B, CST A-B, VMST-B, RPT A-B, VMSA A-B ($p<0,050$).
Conclusions: these results show that young subjects are faster than elderly subjects and MCI at almost the all tasks. MCI compared with elderly normal subjects appear to be impaired when tasks become more demanding in terms of cognitive strategies. This result suggests that MCI patients may show frontal dysfunction. The exploration by the means of TMT subcomponents allows to exclude other cognitive deficits such as visual perception and scanning, visuo-motor coordination and set-shifting abilities when investigated separately.
References
Bradford D.T., "Interpretive reasoning and the Halstead-Reitan test", Clinical Psychology Publishing Company, inc. (1992)
Vink M., Jolles J.,. "A new version of trail making test as an information processing task." Journal of Clinical Neuropsychology, (1985), 7, 162
Corrigan JD, Nancy SH, "Relationships between Parts A and B of the Trail Making Test", Journal of clinical psychology, (1987), 43, 402-409

Reitan RM, “category test and Trail Making Test as measures of frontal lobe functions” The clinical neuropsychologist, (1995), 9, 50-56

17

DIFFERENT MODULATION OF ERK AND $_{P}$38 KINASES BY GLUTAMATE AND BETA-AMYLOID TREATMENTS IN HUMAN FIBROBLASTS

Chiara Paola Zoia, *Chiara Riva, Elena Tagliabue, Proserpio Paola e Carlo Ferrarese*.

University of Milano-Bicocca, Monza, Department of Neuroscience and Biomedical Technology, Laboratory of Neurobiology.

Background: Several pathological conditions such as perturbation of intracellular calcium homeostasis, increased oxidative stress, excitotoxicity, aberrant expression of APP and exposure to amyloid-beta protein (Abeta) cause modifications of MAP kinases signaling pathways and play an important role in the pathogenesis of Alzheimer's disease (AD). However, the relationship between these and other events, associated with disease pathogenesis, is still unknown. p38 activation has been shown both in neuritic plaques of AD patients and in glutamate and Abeta treated cell line. Also MEK1/ERK is activated in degenerating neurons in AD and it plays an important role in Abeta processing and secretion. On the other hand, *in-vitro* Abeta treatment involves the generation of hydrogen peroxide that leads to the down-regulation of ERK. Furthermore, ERK phosphorylation was also blocked by NMDA receptor antagonists in rat CNS.
To investigate AD-specific and systemic mechanisms, we tested modulation of MAPK pathways in skin fibroblasts (fb) from patients and controls. Moreover, to reproduce MAPK modifications similar to those we observed in fb from AD patients, we treated control fb with sublethal Abeta and glutamate concentrations.
Methods: Cell lines, obtained after skin biopsies, were maintained in 5% CO_2 humidified incubator at 37°C. Experiments were undertaken with consent of each recruited subject. Fb cultured cells were pelleted for biomolecular studies. Protein extract were run into 7.5% SDS-PAGE and analyzed by western blot or they were subjected to specific phospho-Elisa kits. We investigated the MAPKs activation in control and AD fb, with or without 5uM glutamate and $Abeta_{1-42}$ at basal conditions and after incubation with specific kinase inhibitors (SB 203580, PD 98059).
Results: In fb from AD patients, p38 phosphorylation is shown while, in control fb, it appeared only after glutamate and Abeta exposure. Our previous data showed ERK phosphorylation in fb from moderate/severe AD patients compared to control fb, as it was observed in CNS from AD patients, while they indicated ERK de-activation in mild AD fb. Since we obtained these different results, we treated control fb with glutamate and Abeta and, as we observed in mild AD patients, ERK down-regulation was demonstrated. To better investigate Abeta and glutamate involvement in MAPK pathways, we are now testing effects of p38 and MEK/ERK inhibitors (SB 203580 and PD 98059). Since these inhibitors displayed different behaviors, we hypothesize that Abeta and glutamate explain similar effects on p38 phosphorilation and ERK down-regulation but they act through different steps of cell signaling cascade.
Conclusion: These different behaviors in e*x-vivo* fb may be useful to investigate the specific regulating mechanisms of these signaling pathways, i.e. Raf family proteins and stress-responsive or mitogen-activating protein kinase phosphatases. Elucidating the MAPK pathways, that regulate APP processing and modulate glutamatergic system, may be of potential therapeutic utility for this neurodegenerative disease.

List of authors