Secretariat

General Inquiry : SIDS Family Association Japan
6-20-209 Udagawa-cho, Shibuya-ku, Tokyo 150-0042, Japan
Phone/Fax : +81-3-5456-1661 Email : englishcontact@sids.gr.jp

Registration Secretariat : c/o Congress Corporation
Kosai-kaikan Bldg., 5-1 Kojimachi, Chiyoda-ku, Tokyo 102-8481, Japan
Phone : +81-3-5216-5551 Fax : +81-3-5216-5552 Email : sids2006@congre.co.jp

The 9th SIDS International Conference June 1-4 2006 in YOKOHAMA Program and Abstracts

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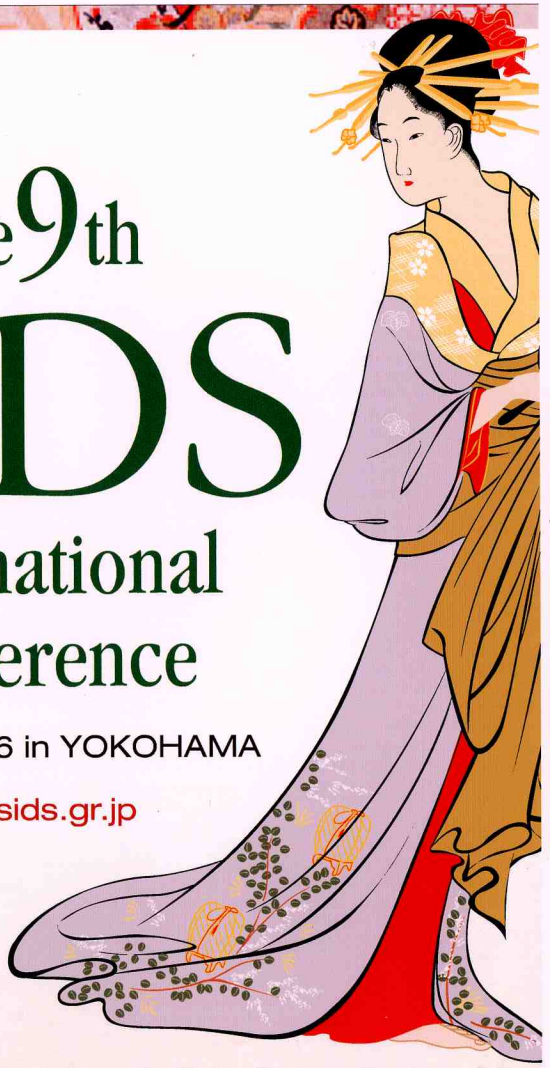

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Meeting with

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PROTECTING LITTLE LIVES, PROVIDING A GUIDING LIGHT FOR FAMILIES

examination, routine autopsy dissection and ancillary tests to suggest any definite cause of death. Due to the ß-APP staining the possibility of previous episodes of occult trauma, apparent life threatening events (ALTEs), and accidental or inflicted suffocation were raised in the autopsy report and his death was classified as 'undetermined'. As detailed analyses and investigations provided no supportive evidence for trauma or inflicted injury, hypoxia was considered the most likely cause. Because of these concerns, sleeping oxygen saturation levels were monitored following the birth of a subsequent sibling who had normal APGAR scores and no evidence of any health problems. Oxygen desaturation to 70% occurred in association with a colour change while on the postnatal ward, and a subsequent polysomnogram showed multiple episodic significant desaturations to around 80% in association with central apnea. Other testing was unremarkable. This report highlights the importance of undertaking immunohistochemical staining of the brains of infants who die unexpectedly, as it may not only assist with the evaluation of possible mechanisms of death in an individual infant, but may also help with the clinical management of subsequent siblings.

144 (S)

ß-APP IMMUNOREACTIVITY IN SUDDEN UNEXPECTED DEATH IN INFANCY

Colin Smith, Jeanne E Bell, Jean W Keeling
University of Edinburgh, UK

Sudden Infant Death Syndrome (SIDS) affects infants under the age of 1 year and has an incidence of approximately 1 per 1000 live births. By definition the cause of death remains unexplained after a thorough investigation including post-mortem with examination of the brain. While the underlying cause remains uncertain neuropathological examination has revealed a number of subtle abnormalities including brainstem scarring, cerebral white matter gliosis, and focal hypomyelination. While the lesions described are non-specific many are thought to be secondary to hypoxia-ischaemia. ß-Amyloid Precursor Protein (ß-APP) immunoreactivity is an early marker of neuronal stress and a marker of axonal damage, secondary to a number of insults including ischaemia.
This study looked at early neuronal injury in a group of SIDS cases (n=50) using ß-APP immunohistochemistry and found only a small subset of cases to exhibit significant ß-APP immunohistochemistry. Within this group no specific patterns of neuronal injury were seen. These cases were compared to a group of infant death cases in which a pathological cause for death was found (n=40).
The neuropathological distinction between SIDS and non-accidental injury (NAI) can, in some cases, be very difficult and there is a realisation that occasionally, despite extensive investigations, cases of NAI are missed and diagnosed as SIDS. ß-APP immunoreactivity can be useful in assessing cases of possible non-accidental injury (NAI), as diffuse traumatic axonal injury is a marker of significant traumatic brain injury. However, axonal damage can be seen in cases of hypoxia-ischaemia, particularly in cases of cerebral swelling, leading to diagnostic confusion. Cases of NAI (N=3) were studied with ß-APP immunohistochemistry in conjunction with SIDS cases. One SIDS case showed a pattern of white matter injury which could not be distinguished from NAI pathological. Although uncommon a pattern of ß-APP immunohistochemistry which mimics NAI may be seen in the setting of SIDS and needs to be interpreted with caution.

145 (S)

SIDS AS A RESULT OF MUTATIONS IN LONG QT SYNDROME GENES

Marianne Arnestad[1], Lia Crotti[2,3], Torleiv O Rognum[1], Roberto Insolia[2], Matteo Pedrazzini[2], Chiara Ferrandi[2], Ashild Vege[4], Peter J Schwartz[2,3]
[1]Institute of Forensic Medicine, University of Oslo, Norway, [2]Molecular Cardiology Laboratory, IRCCS Policlinico S. Matteo, Pavia, Italy, [3]Department of Cardiology, University of Pavia and IRCCS Policlinico S. Matteo, Pavia, Italy, [4]Department of Laboratory Medicine, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway

Background: Long QT Syndrome (LQTS) is a genetic disorder caused by mutations in ion channel genes. LQTS can cause cardiac arrhythmia and sudden death in the absence of structural heart disease. Based on a study of neonatal ECGs in over 33.000 infants where 12/24 later SIDS victims were found to have prolonged QT interval, as well as molecular studies of a small number of SIDS victims, LQTS has been suggested to cause a proportion of SIDS cases. We performed a molecular study of a large number of SIDS cases in order to determine the actual role of LQTS in SIDS.
Material and method: Cases of sudden unexpected deaths 0-3 years old from the south-eastern region of Norway, investigated at the institute of Forensic Medicine between 1988-2004 were included: 201 SIDS and 45 non-SIDS deaths. Non-SIDS deaths were treated as controls. As additional ethnically matched controls we used 137 adult cases dead from non-cardiac causes. The samples were screened for mutations in the LQTS genes KCNQ1, KCNH2, SCN5A, KCNE1 and KCNE2. DNA was prepared from blood and tissue samples, and PCR performed to amplify DNA products. DHPLC was used as a screening technique. Mutations, rare variants and common polymorphisms were confirmed by sequencing. Possible functional effects of mutations or rare variants (not found in Norwegian controls and reported in < 0.7% of white populations) were confirmed by electrophysiological studies.

Results: We found 11 mutations and 8 rare genetic variants in 24/201 SIDS cases (11.9%), while there were non in the 45 infant or 137 adult controls. Based on their functional effect we considered the genetic variants found in 17/201 SIDS cases (8.4%) as likely contributors to SIDS. Thirteen (76%) of the mutations were found in SCN5A.
Discussion: The present study, based on the largest data set of DNA samples from SIDS victims so far, provides evidence that a relatively high proportion of SIDS cases can be caused by cardiac arrhythmia due to mutations in LQTS genes. Taking into account that in 35-40% of patients affected by LQTS the responsible mutation is still not found, the present findings suggest that the number of SIDS cases accounted for by LQTS may be even higher.

146 (S)

SEROTONIN TRANSPORTER GENE VARIATION IN SIDS

Siri H Opdal[1], Ashild Vege[1,2], Marianne Arnestad[1], Torleiv O Rognum[1]
[1]Institute of Forensic Medicine, University of Oslo, Norway, [2]NTNU, Trondheim, Norway

Serotonin influences a broad range of physiological systems, including regulation of breathing, the cardiovascular system, and the immune system. Several studies indicate that serotonin might play a regulatory role in sudden infant death syndrome (SIDS). The system is under bottleneck control of a single protein, the serotonin transporter (5-HTT), which regulates the re-uptake of serotonin from extracellular space. Expression of the 5-HTT gene is regulated by two polymorphic regions, both of which have been investigated in different SIDS populations. These studies indicate an association between the long alleles of the gene and SIDS.
In the presert study, the 5-HTT gene polymorphisms in the promotor and intron 2 have been investigated in 219 SIDS cases, 33 cases of infectious death, and 93 controls. The promoter genotypes are denoted SS, SL and LL. In the SIDS cases 15% were SS, 49% SL and 36% LL. In the cases of infectious death, 12% were SS, 39% SL and 49% LL. In the controls, 18% were SS, 52% SL and 30% LL. There were no differences in genotype distribution between the groups (p=0.4), even though there was a tendency that the cases of infectious death were more likely to have the LL genotype and the L allele (p=0.05 and p=0.08 respectively) compared to the controls.
In the intron 2 polymorphism the different alleles are denoted 9,10 and 12, the genotypes detected were 9/10, 9/12, 10/10, 10/12 and 12/12. In the SIDS cases 3% were 9/10, 2% 9/12, 11% 10/10, 44% 10/12 and 40% 12/12. In the cases of infectious death 3% were 9/10, 9% 9/12, 18% 10/10, 37% 10/12 and 33% 12/12. In the controls 13% were 10/10, 56% 10/12 and 31% 12/12. There was a significant difference between the groups in both genotype and allele distribution (p=0.04 and p=0.03, respectively), with the SIDS cases more likely to have the 12 allele and the 12,12 genotype than the controls.
The results from this study confirms the previous reported association between the long alleles of the 5-HTT gene and sudden infant death. The fact that, in addition to beeing a neurotransmitter, serotonin is an important inflammatory mediator is of special interest since several studies reports an activated immune system in SIDS victims. It may be speculated that the combination of an abberant immune response and a dysregulation of the serotonergic network is a part of the death mechanism in these cases.

147 (S)

STILLBIRTH VERSUS SIDS. PATHOLOGY OF THE AUTONOMIC NERVOUS SYSTEM AND DNA POLYMORPHISMS IN SIUD AND SIDS

Luigi Matturri[1], Giulia Ottaviani[1], Francesco Nonnis Marzano[2], Anna M Lavezzi[1]
[1]Institute of Pathology, Lino Rossi Research Center, University of Milan, [2]Dipartimento di Biologia Evolutiva e Funzionale, University of Parma, Italy

Pathogenesis of sudden intrauterine unexpected death (SIUD) and sudden infant death syndrome (SIDS) seems to privilege, in most cases, autonomic nervous dysfunction. Neurogenic factors are interplaying in all the driving pathogenic hypotheses (the cardiac, the respiratory, and the visceral dyskinetic), as well as in the cardiac-arrhythmogenic one, in which the conduction system is subject to strict autonomic control. Therefore, histological substrates for SIDS should be looked for in a wild field of neuropathology, which include the autonomic nervous system, central and peripheral, and the cardiac conduction system. The studies we have conducted on a large series of victims of SIDS, of unexpected neonatal and late fetal deaths, revealed analogous and frequent lesions of the autonomic structures that control the respiratory activity, as well as the cardiovascular, upper digestive and arousal functions. The research upheld a new approach to SIDS by analogical link with late fetal stillbirth which has a six-fold greater incidence than SIDS. The common denominator of all these deaths was the absence of neurological symptoms, generally associated with the presence of congenital anomalies and in some cases of acquired lesions. Particularly frequent is the hypoplasia and/or agenesis of the arcuate nucleus involved in the central chemoreceptors, observed with the incidence of about 50% both in stillbirth and in SIDS victims. In stillbirth this anomaly is frequently associated with hypoplasia of the reticular formation, lung hypoplasia and chronic hypoxia. Hypoplasia of the parabrachial K?lliker-Fuse complex was detected in about 50% of our term fetuses and neonates dying suddenly and unexpectedly. Congenital anomalies are detected also in other nuclei (solitary tract, hypoglossus, vagus nuclei) as well as astrogliosis and functional alterations of the neurotransmitters, such as catecholamines in the locus coeruleus.

Regarding the cardiac conduction system, accessory atrio-ventricular pathways (mainly Mahaim fibers) were seen in 30% of SIDS cases. Under particular conditions and autonomic neuronal stimulation, these accessory pathways can trigger potentially lethal arrhythmias, generally due to junctional reentry.
The chronic prenatal exposure to cigarette smoke was significantly associated with brainstem and cardiac conduction abnormalities, as well as early coronary lesions.
The research was extended to the detection of DNA mutations and polymorphisms potentially involved in SIDS etio-pathogenesis. Analysis of SCN5A and MCAD genes allowed exclusion of LQTS and deficiency of fatty acids b-oxidation in our samples, while detection of the promoter long (L) allele of 5-HTT gene resulted more frequent in SIDS infants (75%) than in controls (30%).

148 (S)

LIPOCALIN-TYPE PROSTAGLANDIN D SYNTHASE LOCALIZES SPECIFICALLY TO NEURONS IN BRAINSTEM OF SUDDEN INFANT DEATH SYNDROME VICTIMS

Hidetoshi Taniguchi[1], Ikuko Mohri[1,3], Akihito Kimoto[2], Takahisa Kanekiyo[1], Keiko Matsuoka[2], Kazuko Wada[1], Yoshihiro Urade[3], Keiichi Ozono[1], Masahiro Nakayama[2], Masako Taniike[1]
[1]Department of Developmental Medicine (Pediatrics), Osaka University Graduate School of Medicine, [2]Department of Pathology, Osaka Medical Center and Research Institute for Maternal and Child Health, [3]Department of Molecular Behavioral Biology, Osaka Bioscience Institute, Japan

Prostaglandin (PG) D_2 is the most abundant PG in the brain. It is invoved in induction of sleep in the CNS and mediates inflammatory reaction in peripheral tissues. Lipocalin-type PGD synthase (L-PGDS) is responsible for biosynthesis of PGD_2 in the brain and is a unique bifunctional protein which catalyzes biosynthesis of PGD_2 and also functions as lipocalin. We have previously reported that expression of L-PGDS was progressively increased in perineuronal oligodendroglia(OL)s in mouse models for genetic neurological disorders and in OLs and astrocytes which were positive for aß-crystalline, a stress protein, in demyelinating plaques of human brains with multiple sclerosis. These lines of evidence suggest that L-PGDS is induced as a stress reaction.
In this study, we investigated whether upregulation of L-PGDS also occurred in brains from sudden infant death syndrome (SIDS) victims. Six infants diagnosed with SIDS in Osaka prefecture during 1981 to 1996 were eligible for the study. The age of SIDS victims ranges from 2 to 11 month-old and 4 non-SIDS age-matched autopsied brains were used as control. Immunostaining of L-PGDS was performed in all samples and examined its expression in relation to activation of astroglia and microglia as detected with glial fibrillary acidic protein (GFAP) and CD68 respectively as well as TdT-mediated dUTP nick-end labeling (TUNEL) positive apoptotic cells.
In the SIDS brains, immunoreactivity for L-PGDS was observed in OLs and neurons. In the brainstem, however, L-PGDS was confined to neurons and its immunoreactivity was by far intense when compared with those in the cerebral cortex and brainstem of control brains. These L-PGDS-positive neurons compose inferior olivary nuclei, hypoglossal nuclei, and cuneiform nuclei in the medulla. L-PGDS immunointensity was intense in SIDS brainstem irrespective of activation of astroglia and microglia as well as the number of apoptotic cells.
Together with our pervious works, these findings suggest that induction of L-PGDS occurs as a result of recurrent hypoxia-ischemia and its timing is much earlier than activation of astrocytes or cell death. Moreover, up-regulated L-PGDS may produce extra amount of PGD_2, which exerts inflammatory reactions in brainstem or otherwise, reduces arousablily in SIDS victims. This study implies that PGD_2, produced by L-PGDS, may play a crucial role in the pathogenesis of SIDS.

149 (S)

PULMONARY HEMORRHAGE IN SUDDEN AND UNEXPECTED DEATH IN CHILDREN: NATURAL DEATH OR HOMICIDE?

Caroline Rambaud[1], Elisabeth Briand-Huchet[2], Michel Durigon[1]
[1]Service de medecine legale - Hopital Raymond Poincare AP-HP - GARCHES and Faculte de medecine Paris-Ile de France Ouest - Universite Versailles, [2]Centre de reference pour la MSN - Hopital Antoine Beclere - CLAMART, France

Introduction: The presence of siderophages within lung alveoli means that a bleeding occurred at least 3 days prior to death. We reviewed a series of pediatric autopsies to know in which amount and frequency siderophages are found.
Methods: A Perls staining was performed on at least one (right inferior lobe) of the 8 systematically made lungs' slides in 173 consecutive autopsies: 147 sudden unexpected natural deaths (13 neonates < 28 days; 17 children > 12 months; 117 infants) and 26 non natural deaths (2 neonates < 28 days; 3 children > 12 months; 21 infants). The number of siderophages was counted on 80 fields (x40) for each case. The classification was made in 4 grades according to their number: G0 = no siderophage; G1 = 1 to 30; G2 = 31 to 400; G4 > 400.
Results: The majority of cases had no (G0) or only a few (G1) siderophages. There were 35 children in grades G2 and G3: 7 out of the 26 non natural deaths (27%) and 28 out of the 147 natural deaths (19%) (not significant). The death causes found in each group were compatible with repeated pulmonary bleedings: the non natural deaths were 5 child abuses (2 Shaken Baby Syndromes, 2 upper airway obstructions and 1 repeated thoracic traumas) and 2 accidents (1 overlaying co-sleeping and 1 bedding accident related to a retrognathism). The natural deaths with siderophages were of cardiac (n = 6) and pulmonary causes (2 pulmonary hypertension), 15 infections with a pulmonary localization, 1 Di Georges syndrome with hypocalcemia (laryngospasm) and 1 neurological disease with numerous loss of consciousness and apneas.
Conclusion: If the presence of numerous pulmonary siderophages cannot be explained by a medical cause, child abuse or negligence such as repeated upper airway obstructions, Shaken Baby Syndrome or thoracic traumas must be considered.

150 (S)

UNDERSTANDING ONE OF THE THREE RISK FACTORS OF SIDS: A CRITICAL PERIOD OF DEVELOPMENT IN BRAIN STEM NUCLEI INVOLVED IN THE CONTROL OF RESPIRATION

Margaret Wong-Riley[1], Qiuli Liu[1], Ralph A Franciosi[2]
[1]Medical College of Wisconsin, Department of Cell Biology, Neurobiology and Anatomy, [2]Children's Hospital of Wisconsin, Department of Pathology, USA

In 1994, Filiano and Kinney proposed the Triple Risk Model for Sudden Infant Death Syndrome, which states that SIDS occurs, and only occurs, when (a) a vulnerable infant encounters (b) an external stressor or stressors during (c) a critical period of postnatal development. All three factors have to be present simultaneously for death to occur. The first factor can result from diverse causes, such as prenatal exposure to nicotine and other drugs, organic airway defect, and non-lethal genetic defect. The second factor precipitated the Back to Sleep Campaign and has significantly reduced, though not eliminated, the incidence of SIDS. The third factor, though suspected, has not been well studied and characterized. Using the rodent as a model, we performed in-depth analysis of neurochemical and metabolic development of several brain stem respiratory nuclei from postnatal day (P) 0 to 21. We found that the developmental trends did not follow a predicted progression, but rather, exhibited a dramatic change at P12. Specifically, the level of cytochrome oxidase activity, a marker of neuronal energy metabolism and functional activity, exhibited a prominent reduction at P12. This was accompanied by a distinct drop in the expression of excitatory neurotransmitters and receptors (glutamate and NMDA receptors) and a sharp rise in the expression of inhibitory neurotransmitters and receptors (GABA, GABAB receptors, and glycine receptors). Moreover, GABAA receptors in the rat pre-Botzinger complex and the ventrolateral subnucleus of the solitary tract nucleus exhibited a switch in subunit dominance from alpha 3 to alpha 1 around P12, suggesting that the same neurotransmitter, GABA, may have different physiological effects before and after the switch. The implication from these studies is that the brain stem respiratory nuclei under study experience a transient inhibitory dominance within a narrow postnatal window. If such a critical window exists in the human, and if a vulnerable infant is exposed to exogenous stressors during this sensitive period, then it is conceivable that the infant is unable to overcome the challenge, and catastrophic events, such as SIDS, may result. (Supported by Children's Hospital and Health System Foundation, Wisconsin, USA).

151 (ST)

PLACENTAL ETIOLOGIES OF FETAL GROWTH RESTRICTION AND STILLBIRTH

Halit Pinar, Fusun Gundogan
Brown Medical School, USA

Learning Objectives
1.Review of current knowledge in placental growth
2.Review placental conditions that are associated with growth restriction and stillbirth
Abstract/Summary
The placenta is a unique organ which forms during gestation and looses its utility after parturition. Although hosted by the mother and supports the fetus, it originates from the embryo thus of fetal origin. The interface of maternal tissues and the developing placenta is complex. Recent developments describing some of the basic molecular pathways have contributed significantly to our understanding of normal placental growth.
Between 1994-2005, we examined 737 stillbirth and their placentas at Women and Infants Hospital, Brown Medical School. There were 471 cases that showed findings consistent with established cause/strong association with stillbirth such as amniotic fluid infection syndrome, placental abruption, fetal vascular compromise, twin-twin transfusion syndrome, maternal fetal hemorrhage, multiple congenital malformations with/without aneuploidy. 266 cases did not show an established cause or association with stillbirth.
When growth restriction was analyzed as an independent variable, 28% (131) of the 471 cases had impaired fetal and/or placental growth. In contrast, 58% (158) of the cases in the undetermined group were growth restricted.
Placental findings in this group included abnormalities of placental shape, lesions that might compromise fetal circulation such as abnormal umbilical cord insertions, villous remodeling abnormalities, abnormal vasculogenesis and impaired trophoblast turnover.