EUR J PHYS REHABIL MED 2015;51:725-36

Pain in stroke patients: characteristics and impact on the rehabilitation treatment. A multicenter cross-sectional study

I. APRILE [1, 2], C. BRIANI [3], C. PAZZAGLIA [2], F. CECCHI [4], S. NEGRINI [1, 6], L. PADUA [1, 5]
for the Don Carlo Gnocchi Pain-Rehab Group*

[1]Rehabilitation Department, Don Carlo Gnocchi Onlus Foundation, Milan, Italy
[2]Rehabilitation Department, Don Carlo Gnocchi Onlus Foundation, Rome, Italy
[3]Department of Neurosciences: Sciences NPSRR, University of Padova, Italy
[4]Rehabilitation Department, Don Carlo Gnocchi Onlus Foundation, Massa Carrara, Italy
[5]Institute of Neurology, Catholic University, Rome, Italy
[6]Department of Clinical and Experimental Sciences, University of Brescia, Italy

Background. **Post-stroke pain (PSP) is a common and disabling complication, difficult to treat, that often decreases patients' quality of life (QoL). The hypothesis is that PSP may negatively affect rehabilitation treatment.**
Aim. **The aim of this paper was to quantify and characterize pain in a sample of post-stroke patients undergoing rehabilitation and to investigate the impact of pain in slowing down or discontinuing the rehabilitation program.**
Design. **Multicenter cross-sectional study.**
Setting. **Inpatients and outpatients of rehabilitation department.**
Population. **One hundred and six subacute and chronic stroke patients.**
Methods. **Pain intensity was measured with the NRS or the PAINAD (if cognitive/language impairment was present); pain characteristics were assessed with the DN4, and NPSI questionnaire. QoL was measured with the SF-36. A clinical assessment and a semi-structured questionnaire on pain occurrence, impact, and management was administered by the physiotherapist in charge of the patients and by the physician.**
Results. **Nearly 1/3 of the patients (32.9%) with normal cognitive functions and language reported pain occurrence after stroke; 81.8% of them had NRS≥3 and 31.8% DN4≥4 (meaning neuropathic origin of pain). In about 20% of the patients the PAINAD was used to measure pain; 17.4% of them presented a score ≥3. In 24.5% of our sample, pain influenced rehabilitation treatment. In 16% of the whole sample, pain influenced patients' attention during rehabilitation session. Patients with hypoesthesia presented significantly higher neuropathic pain scores than patients with normal sensory function. Regarding QoL, we found that patients with higher neuropathic pain showed more severe deterioration of mental aspects of QoL, where patients with higher nociceptive pain presented more severe deterioration of physical aspects of QoL.**
Conclusion. **The results from this multicenter study showed that in about ¼ of the patients, pain negatively influenced the rehabilitation program delaying the recovery and likely increasing the cost of rehabilitation.**
Clinical Rehabilitation Impact. **Clinicians should pay more attention to pain, especially neuropathic pain, in post-stroke patients. Tailored pharmacological therapy, to treat and prevent pain, might improve patients' compliance during the rehabilitation process.**

KEY WORDS: Stroke - Pain - Rehabilitation - Quality of Life.

**List of collaborators.*—S. Brancaccio (Sant'Angelo dei Lombardi), L. Brambilla (Parma), L. Callea (Rovato), R. Caprioli (Palazzolo), G. Devalle (Palazzolo), F. De Santis (Roma), C. Di Blasi (Roma), E. Di Sipio (Roma), M. Diverio (Sarzana), M. Forni (Sarzana), S. Galeri (Rovato), M. Germanotta (Roma), G. Giordano (Palazzolo), G. Melchiorri (Roma), S. Misciagna (Roma), A. Paperini (Firenze), A. R. Pellegrino (Roma), M. Ricca (Rovato), G. Rinaldi (Roma), B. Rizzi (parma), M. Rossi (Parma), A. E. Ruggeri (Roma), I. Santoro (Sant'Angelo dei Lombardi), C. Schiaffini (Roma), G. Spannocchi (Palazzolo), A. Testa (Rovato), F. Trecate (Palazzolo).

Corresponding author: I. Aprile, Rehabilitation Department, Don Carlo Gnocchi Onlus Foundation, Piazzale Morandi 6, 20100, Milan, Italy. E-mail: iaprile@dongnocchi.it

Rehabilitation is a complex process where the attempt to restore function is strongly influenced by several interrelated variables. While many variables depend on the patient (age, type and site of damage, personality), others depend on the technical skills of the therapists as her/his ability to relate with the patient. For patients and health system (high cost of rehabilitation) a major effort of the scientific community is underway in order to find the most efficient rehabilitation strategies. The definition of efficiency includes the concepts of time and result ("result in a given time").

Post-stroke pain (PSP) is a common and disabling complication, that often decreases patients' quality of life (QoL).[1-9] It can be nociceptive and/or neuropathic, persistent and often treatment-refractory. It can be a central post-stroke pain (CPSP), a post-stroke shoulder pain (PSSP) or a Complex Regional Pain syndrome (CRPS). CPSP is a neuropathic pain resulting from a primary lesion or dysfunction of the central nervous system.[2] It is characterized by pain and sensory abnormalities in the body parts corresponding to the brain territory injured by the cerebrovascular lesion.[3] PSSP is a common complication after stroke, whose etiology is largely unclear; it is related to central post-stroke pain, complex regional pain syndrome type 1, depression and sensory abnormalities and may be caused and maintained by various pain mechanisms.[4] CRPS is a debilitating complication of hemiplegia that affects a significant number of moderate to severely impaired stroke survivors. There is emerging consensus that biomechanical factors and microtrauma to the hemiparetic shoulder contribute significantly toward the genesis of CPRS among stroke survivors. The exact pathophysiology that explains how these triggers translate to the disease manifestation remains to be elucidated.[10]

PSP may be associated with peripheral nociceptive pain due to abnormal posture, reduced shoulder movement and spasticity.[5] In fact symptoms and signs of central sensitization in PSSP may be due to both neuropathic and (ongoing) nociceptive pain mechanisms which may coexist.[4]

PSP is often difficult to treat, increases in the months following the stroke, and the treatment response is mostly insufficient or moderate.[3]

The hypothesis is that PSP may negatively affect rehabilitation treatment: for the fear of pain, stroke patients might reduce compliance to passive and active movement, and may be not motivated and depressed, with negative effects on their recovery.

This hypothesis also arose from the recent observation of the negative impact of pain on rehabilitation treatment in orthopaedic patients.[11]

No studies on the influence of the PSP on the rehabilitation program have so far been reported.

The aims of the current paper were to evaluate, through a cross sectional study, occurrence and characteristics of PSP (nociceptive/neuropathic) and its impact on the rehabilitation program (slowdown or delay or discontinuation of rehabilitation process due to pain).

Material and methods

In this cross sectional study all patients undergoing rehabilitation after stroke from October 2011 to February 2012 in 8 Centers of the Don Gnocchi Foundation were considered (see below inclusion and exclusion criteria).

The study was approved by the Ethic committee of each center participating in the study.

Information regarding patients' demographic characteristics (age, sex, BMI), historical and clinical data (type of stroke, localization of the stroke lesions according to Bamford classification, affected side, time from stroke onset less than or more than six months), clinical setting, previous rehabilitation treatment, associated comorbidities (diabetes, hypertension, cardiovascular disease, hypercholesterolemia) and other risk factors (such as smoking), drug therapies for pain were recorded.

In order to evaluate whether the pain occurred after stroke and interfered with the rehabilitation plan, data derived from a specifically designed structured questionnaire (developed by the physicians) were acquired from the physiotherapist (Figure 1).

Patients

One hundred-six consecutive patients were enrolled in this study.

Inclusion criteria: inpatients and outpatients, subacute and chronic stroke patients, aged>18 years, who had suffered from a unilateral stroke and had been performing rehabilitation treatment for at least 1 week (4-5 sessions weekly of neuromotor training, and, when indicated, 3 sessions weekly of lan-

guage/cognitive training; each rehabilitation session lasted 1 hour).

Exclusion criteria: non adhesion to the study, comorbidities causing severe pain (such as tumors, trauma or fractures), signs of possible concomitant neurological condition (such as radiculopathies, polyneuropathies). Cognitive/language impairment was not an exclusion criteria (see below).

All participants (or close relatives, if cognitive impairment was present) gave a written informed consent prior to participation.

Somatosensory assessment

A clinical examination was performed on both the affected and unaffected side at upper and lower limbs.[12] Differences in the sensory function (normal/hypoesthesia, hyperesthesia or allodynia) between the affected and non-affected side in response to the application of a cotton wool (light touch), a cold metal object (cold sensation) and a Semmes Weinstein filament size 6.65 (sharpness) were recorded.

The filament was applied perpendicularly and briefly (<1 second) with even pressure. The patients were examined with eyes closed and were asked to say if they felt the tactile stimulus. This procedure was repeated 10 times. Eight affirmative responses out of 10 were considered normal, while 0 to 7 responses were considered abnormal. Proprioception was tested on thumbs and big toes. The tactile detection threshold was determined using Semmes Wein stein filaments (Touch-Test Hand Kit, North Coast Medical, Inc., UK).

Outcome measures

The following clinical and disability standardized measures were used: National Institutes of Health Stroke Scale (NIHSS), Barthel Index (BI), Deambulation Index (DI), Motricity Index (MI) for upper and lower limbs, Trunk Control Test (TCT), and Ashworth Scale (AS for upper and lower limb).

Pain was assessed in patients without cognitive/language impairment using usual patient-oriented measures: Numeric Rating Scale (NRS), Douleur Neuropathique en 4 Questions (DN4) and Neuropathic Pain Symptom Inventory (NPSI). In patients with a cognitive/language impairment (abnormal production and/or comprehension, that gave concerns about the reliability of self-report from these individuals), the pain was assessed using proxy measures: the Pain Assessment in Advanced Dementia (PAINAD).

1. After the stroke did you have pain which you never had experienced before the stroke? Yes ☐ No ☐
2. Did pain have a negative effect on the rehabilitation program? Yes ☐ No ☐
3. Did pain interrupt the rehabilitation program? Yes ☐ No ☐
4. Did pain slow down the rehabilitation program? Yes ☐ No ☐
5. Did pain modify the rehabilitation program? Yes ☐ No ☐
6. Did the patient refuse/interrupt a rehabilitation session? Yes ☐ No ☐
7. Did pain influence the patient's attention during rehabilitation treatment? Yes ☐ No ☐

Figure 1.—Questionnaire about the pain interference on rehabilitation plan.

NRS is a generic and widely used pain measure, DN4 is a screening tool able to differentiate neuropathic from nociceptive pain, and NPSI quantitatively assesses neuropathic pain symptoms.

The primary outcome measure of the study was NRS (for patients without cognitive/language impairment) and PAINAD (for patients with cognitive/language impairment).

QoL and depression were assessed in patients without cognitive/language impairment using SF-36 and Beck Depression Inventory (BDI).

The QoL and depression scales have been included in the study design because pain has an important effect on QoL and a strong relationship has been observed between pain and depression.

All outcome measures were previously developed and validated.

Clinical scales

The National Institutes of Health Stroke Scale (NIHSS) is a systematic assessment tool that provides a quantitative measure of stroke-related neurologic deficit. The NIHSS was originally designed as a research tool to measure baseline data on patients in acute stroke clinical trials. The scale is widely used also as a clinical assessment tool to evaluate severity of stroke patients, determine appropriate treatment, and predict the patient's outcome. The stroke scale

is valid for predicting lesion size and can serve as a measure of stroke severity. The NIHSS has shown to be a predictor of both short and long term outcome of stroke patients. Additionally, the stroke scale serves as a data collection tool for planning patient care and provides a common language for information exchanges among healthcare providers.[13] The NIHSS has established reliability and validity for use in prospective clinical research, and predictive validity for long-term stroke outcome.[14]

Disability evaluation

To assess disability we used Barthel Index (BI), Deambulation Index (DI), Motricity Index (MI) for upper and lower limbs, Trunk Control Test (TCT), and Ashworth Scale (AS).

The BI [15] was developed to assess change in functional status in individuals with neurological or musculoskeletal disorders who undergo rehabilitation. It provides a measure of ability, measuring what an individual 'can do'. The BI ranges from 0 (dependence) to 100 (independence). It is the most widely used measure to assess functional status, having great validity, reliability and sensitivity. The DI is an adapted form (8-point scale) of the physical therapy part of the Patient Evaluation Conference System. The 8-point scale ranges from 0 (not assessed) to 7 (within normal limits, functionally independent).[16]

MI (for upper and lower limbs Index), measures the overall stroke patients' impairment. Arm and leg score were separately calculated as sum (points for the 3 arm tests) + 1 (minimum score: 0; maximum score: 100). It is a simple, brief measure of general motor function that can predict the mobility post-stroke outcome.[17]

The Trunk Control Test (TCT) [18] examines four axial movements: rolling from a supine position to the weak side (T1) and to the healthy side (T2), sitting up from a lying-down position (T3), and sitting in a balanced position on the edge of the bed with feet off the ground for 30 seconds (T4). The scoring is as follows: 0, unable to perform movement without assistance; 12, able to perform movement but in an abnormal manner; and 25, able to complete movement normally. The TCT score is the sum of the scores obtained on the four tests (range 0-100).

The Ashworth Scale was used to evaluate upper (shoulder, elbow and wrist) and lower (hip, knee and ankle) limbs. This is a five-point ordinal scale that grades the resistance during passive muscle stretching [19] as follows: 1: no increase in muscle tone; 2: slight increase in tone giving a "catch" when the affected part is moved in flexion or extension; 3: more marked increase in tone but the affected part is easily flexed; 4: considerable increase in tone; passive movement difficult; 5: the affected part is rigid in flexion or extension.

Pain measures

The intensity of pain was assessed with the Numeric Rating Scale (NRS) that ranges from 0 (no pain) to 10 (the worst imaginable pain).[20] Moreover, pain features were dissected through DN4, a screening tool [21] already used in stroke patients.[4] DN4 is a clinician-administered questionnaire consisting of 10 items: 7, concerning the quality of pain, were obtained by interviewing the patients, whereas 3 items were based on clinical examination assessing the presence or absence of touch or pinprick hypoesthesia and tactile allodynia. A score of 1 was given to each positive item and a score of 0 to each negative item. Scores ≥4/10 were considered indicative of neuropathic pain. The DN4 questionnaire has very good sensitivity (83%) and specificity (90%) for identification of chronic pain associated with a lesion in the nervous system (either peripheral or central) and it is frequently used to evaluate pain in stroke patients.[22] The neuropathic pain symptom inventory (NPSI) was designed to evaluate the different symptoms of neuropathic pain [23] and it allows discrimination and quantification of five distinct clinically relevant aspects of neuropathic pain, and it is also able to measure changes due to treatment.

The pain assessment in advanced dementia (PAINAD) is based on a 0-2 scale for five items yielding a score ranging from 0 to 10.[24] Psychometric properties of PAINAD were previously assessed and it was used for evaluating pain in nonverbal patients.[25]

Impact of pain on rehabilitation program was assessed using a specifically developed form (Figure 1). The form included dichotomous questions: the first question concerned the onset of pain after stroke and was administered by physiotherapist to patient; the others questions investigated if pain had a negative effect on the rehabilitation program, if pain caused discontinuation of the rehabilitation program (STOP rehab), if pain had slowed down the rehabilitation program (SLOW rehab) or if pain had modified the

rehabilitation program (MOD rehab) and were completed daily for one week by each patient's therapist. Patients who had discontinued 2 or more consecutive rehabilitation sessions because of persistent pain were included in the STOP rehab group; patients who have given up only one rehabilitation session were included in the SLOW rehab group; and patients who have modified 2 or more consecutive rehabilitation sessions because of persistent pain were included in the MOD rehab group. The modification of the rehabilitation program consisted in a reduction of active and passive exercises on painful segment (upper and/or lower limb) and reduction of walking training in patients with lower limb pain.

The criteria for categorizing patients in STOP, SLOW and MOD rehab groups had been agreed on with all physicians of the participating centers before the beginning of the study. Physicians performed the categorization of the patients and physical therapists were blinded to categorization criteria.

Quality of life and depression

The health-related QoL was measured using the validated Italian version of the SF-36,[26] a self-administered short instrument scoring 0 to 100, including 4 physical and 4 mental dimensions. This questionnaire assesses eight specific categories of physical and emotional functioning (Physical Function, Physical Role, Bodily Pain, General Health, Vitality, Social Function, Emotional and Mental Health Role), which are summed to generate two main scores: the Physical Composite Score (PCS) and Mental Composite Score (MCS). The score for each category ranges from 0 to 100. A low PCS value indicates severe physical dysfunction, distressful bodily pain, frequent tiredness and unfavourable evaluation of health status. A low MCS indicates frequent psychological distress, and severe social disability due to emotional problems.

The beck depression inventory (BDI) is a 21-item, self-report rating inventory that measures characteristic attitudes and symptoms of depression.[27]

SF-36 and BDI were applied only to patients without cognitive/language impairment.

Data analysis

The occurrence of pain in our sample was calculated according to the following cut-offs: NRS Score ≥3 (or PAINAD Score ≥3), and DN4 Score ≥4.

The influence of pain on rehabilitation was investigated comparing the pain measure values (NPSI, NRS, PAINAD and DN4 scores) between patients whose pain had an impact on rehabilitation and patients whose pain did not interfere with rehabilitation.

In the evaluation of the relationship between pain and sensory function sample was classified in patients with and without hypoesthesia, and a comparison of the pain scores between these two groups was performed.

In the analysis of the impact of pain on QoL the relationships among SF36 (scores and subcores) NRS and NPSI were investigated. With respect to DN4, a comparison of the SF36 scores between patients with DN4<4 and patients with DN4≥4 was performed.

Statistical analysis

All statistical analyses were performed using the STATSOFT (Tulsa, OK, USA) package. Because of ordinal or nominal measures, non-parametric analyses were performed. We used the Spearman's rank correlation coefficient for the correlation between the validated pain and QoL measures; we used the Mann Whitney U test for the comparison between two groups (for example patients with DN4<4 and those with DN4≥4). For the comparison between patients with normal sensory and patients with hypoesthesia (in all 4 sensory modalities) we used Mann-Whitney U Test and two-sample means test. We used χ^2 Test to compare two dichotomous values (for example abnormality of presence/absence hypoesthesia in patients with/without pain).

To better understand what factors might interfere with rehabilitation, it was created a binary variable assuming value 1 for those patients in whom pain had a negative effect on the rehabilitation program and 0 for all those patients in whom pain did not a negative effect on rehabilitation. We also assessed if other covariates, besides pain, had any influence on rehabilitation. We investigated the influence of the following factors on the probability of negatively influence the rehabilitation program: gender (male/female), age (in years), previous rehabilitation experiences, stroke duration (measured in days), pain medication, pain scores (measured using NRS score).

TABLE I.—*Patients' characteristics, historical data, risk factors.*

Sample (N.)			106
Patient characteristics	Age (mean, SD)		70.9±13.0 (32-91)
	Sex (male, %)		52.6%
	BMI (mean, SD)		24.9+5.5
	Kind of stroke	Ischemic	70.3%
		Hemorrhagic	29.7%
	Localization (Bamford classification)	LACS	16.9%
		PACS	42.7%
		TACS	27.0%
		POCS	13.4%
	Affected side	Right	58,8%
		Left	41.2%
	Post-stroke phase	Sub-acute	80%
		Chronic	20%
Risk factors	Smoke (%)		31.6%
	Diabetes (%)		30.3%
	Arterial hypertension (%)		83.7%
	Atrial fibrillation (%)		42.6%

LACS: Lacunar syndrome; PACS: Partial Anterior Circulation syndrome; TACS: Total Anterior Circulation syndrome; POCS: Posterior Circulation syndrome.

TABLE II.—*Clinical, disability, pain and QoL evaluation*

Clinical scale	NIHSS (mean, SD)	9.4±5.6
Depression scale	BDI (score 0-39) (mean, SD)	13.8±10.4
Disability measure	Barthel Index (score 0-100) (mean, SD)	34.4±28.0
	Deambulation Index (score 0-7) (mean, SD)	2.7±3.1
Motricity Index	Trunk Control Test (score 0-100) (mean, SD)	43.5±32.0
	Upper limb MI (mean, SD)	41.5±31.5
	Lower limb MI (mean, SD)	43.4±31.3
Ashworth Scale	Shoulder (score 0-5) (mean, SD)	1.0±1.2
	Elbow (score 0-5) (mean, SD)	1.1±1.2
	Wrist (score 0-5) (mean, SD)	1.1±1.2
	Hip (score 0-5) (mean, SD)	0.9±1.1
	Knee (score 0-5) (mean, SD)	1.0±1.2
	Calf (score 0-5) (mean, SD)	1.1±1.2
Pain tools	NPSI (score 0-100)	7.2±9.0
	NRS (score 0-10) (mean, SD)	4.2±2.9
	DN4 (score 0-10) (mean, SD)	1.9±2.6
QoL tool	SF-36 *PCS* (score 0-100) (mean, SD)	32.4±7.9
	SF-36 *MCS* (score 0-100) (mean, SD)	42.9±9.8

An alpha level of 0.05 was set for all statistical tests.

Results

Patients' characteristics, historical data and risk factors are reported in Table I.

Regarding pain medications, 30% of our patients did not take medications, 30% were on gabapentin or pregabalin, 20% took antidepressant drugs, 5% took pregabalin in addition to antidepressants, 5% were on opioids and 10% took opioids accompanied by supplemental non-opioid analgesic.

Mean of clinical, disability, pain and QoL measures score are reported in Table II.

Pain occurrence and features

About eighty percent (78.3%, 83/106) of the patients had no cognitive impairment and filled in self-reported questionnaire to assess pain.

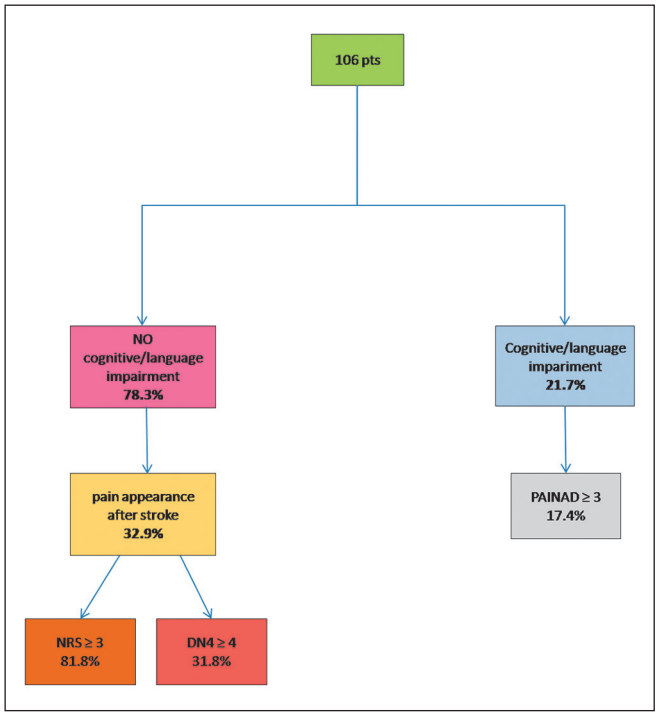

Figure 2.—Physician interview.

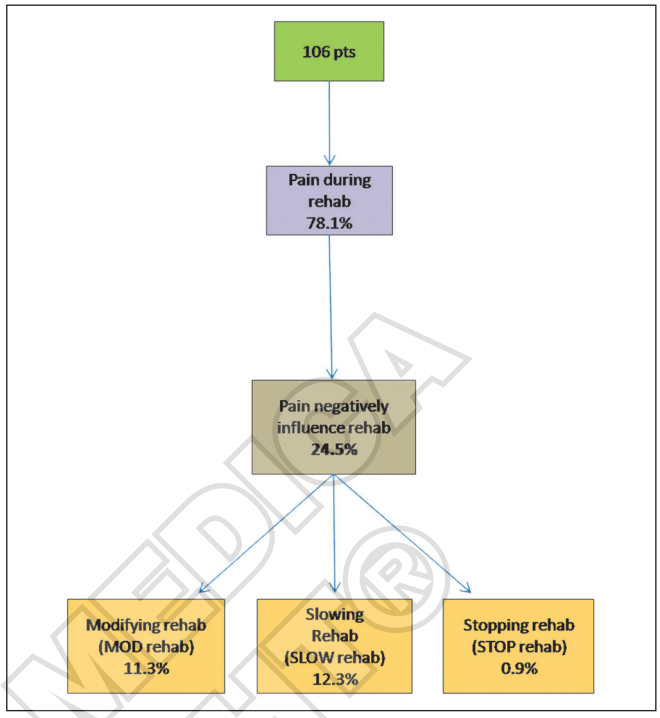

Figure 3.—Therapist interview.

About twenty percent (21.7%, 23/106) of patients had cognitive/language impairment and pain was assessed through PAINAD.

Patients without cognitive impairment (N.83)

Approximately 1/3 of patients (32.9%) reported pain that they had never experienced before stroke. Pain occurred about 1 month after the stroke (mean: 17.3 days; SD: 13.8). In this group 81.8% of patients had a NRS ≥3 and 31.8% had DN4≥4 (Figure 2).

Note that 90.9% of patients who complained of pain showed abnormality at the clinical somatosensory assessment, while only 25.6% of patients without pain had abnormal somatosensory function (χ^2 Test P<0.0000).

Patients with cognitive impairment (N.23)

About 1/5 of the patients (4/23; 17.4%) had PAINAD Score ≥3 (Figure 2).

In our sample complained of clinically relevant pain (NRS ≥3 or PAINAD Score ≥3): 20% of patients enrolled within 1 month after stroke; 41% of patients from 2 to 6 months after stroke; and 42% of patients from more than 7 months after stroke.

Influence of pain on rehabilitation

The rehabilitation program (as reported by the therapists) was negatively influenced by the presence of pain in 24.5% of the whole sample. In particular rehabilitation program was modified in 11.3% of patients, slowed down in 12.3% and discontinued in 0.9%. According to the therapists, in 16% of the whole sample pain influenced patient's attention during rehabilitation session (Figure 3). Note that 7% of patients without cognitive impairment reported no pain in the interview although they complained of pain during rehabilitation session.

As expected, patients reporting impact of pain during rehabilitation had higher degree of pain when compared with patients whose pain did not interfere with rehabilitation: NPSI P<0.05; NRS P<0.02 (Figure 4), PAINAD P<0.04 (Figure 5); only DN4 did not show significant different values between the two groups.

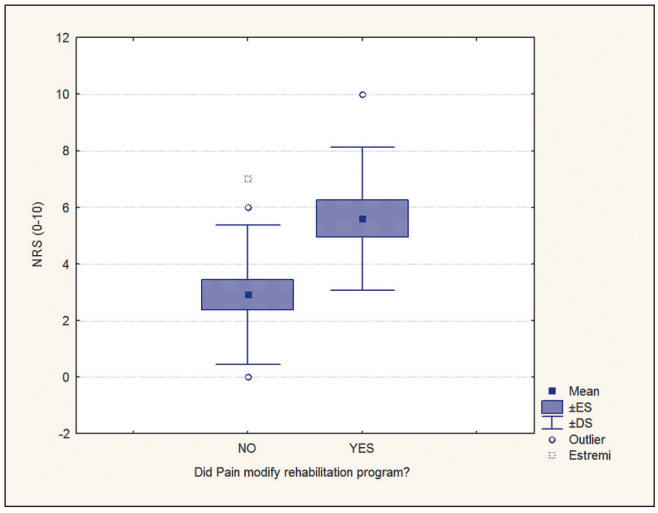

Figure 4.—Comparison of the NRS score between patients with and without negative influence on rehabilitation for pain.

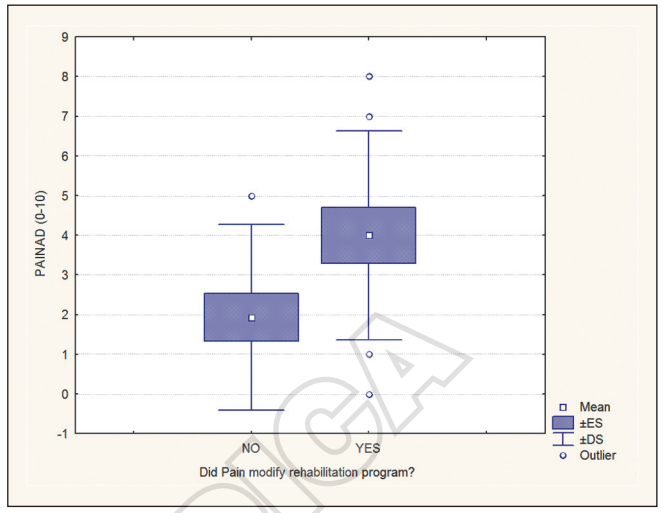

Figure 5.—Comparison of the PAINAD score between patients with and without negative influence on rehabilitation for pain.

TABLE III.—*Comparison of the pain scores in the two groups: patients with normal sensory and patients with hypoesthesia (in all 4 sensory modalities) using Mann-Whitney U Test and two-sample means test.*

Sensory modalities	Statistical test	DN4	NPSI	NRS	PAINAD	Bodily-Pain_SF36	BDI
Light touch	Two-sample means test	t=-5.551; P=0.000	t=-7.105; P=0.000	NS	NS	NS	NS
	U Mann-Whitney	U=11.5; P=0.002	U=0.000; P=0.005	NS	NS	NS	NS
Cold sensation	Two-sample means test	t=-3.427; P=0.003	t=-4.505; P=0.001	NS	NS	t=3.582; P=0.001	NS
	U Mann- Whitney	U=17.0; P=0.016	U=0.000; P=0.019	NS	NS	U=21.50; P=0.010	U=27.50; P=0.018
Sharpness	Two-sample means test	t=-5.422; P=0.000	t=-6.872; P=0.000	NS	NS	NS	NS
	U Mann- Whitney	U=9.5; P=0.005	U=0.000; P=0.007	NS	NS	NS	NS
Proprioception	Two-sample means test	t=-3.427; P=0.003	t=-4.505; P=0.001	NS	NS	NS	NS
	U Mann- Whitney	U=17.0; P=0.016	U=0.000; P=0.019	NS	NS	NS	NS

Relationship between pain measures and clinical data

NRS showed a significant relationship with BMI (P<0.03; r:0.4): patients with higher BMI reported more pain. NPSI showed a significant relationship with Ashworth scale (P<0.02; r:0.6) at the elbow (and a trend at the shoulder: (P=0.06; r:0.5): the higher the spasticity at the upper limbs the more severe the neuropathic pain.

NPSI was significantly higher (P<0.05) in hemorrhagic than in ischemic stroke. No significant difference was observed between the side of stroke.

NIHSS, Motricity Indexes (upper and lower limbs), Ashworth scale (referred to shoulder, elbow and wrist) were not related to NRS and PAINAD. No relationship was found between measures of pain and age or gender.

Relationship between pain measures and sensory function

Table III shows pain (neuropathic and nociceptive) and depression (BDI) in patients with and without hypoesthesia. Concerning neuropathic pain measures (DN4 and NPSI), patients with hypoesthesia presented significantly higher neuropathic pain scores than patients with normal sensory function as represented in Figures 6, 7. In our sample of patients, 3.8% presented with hyperesthesia and 2.8% with allodynia. Due to the very low number of cases showing increase of sensitivity or allodynia, we decided to compare only the most represented groups (Table IV).

Relationship between pain measures and QoL

In addition to the expected relationship between the pain domain of SF36 (Bodily pain) and the NRS

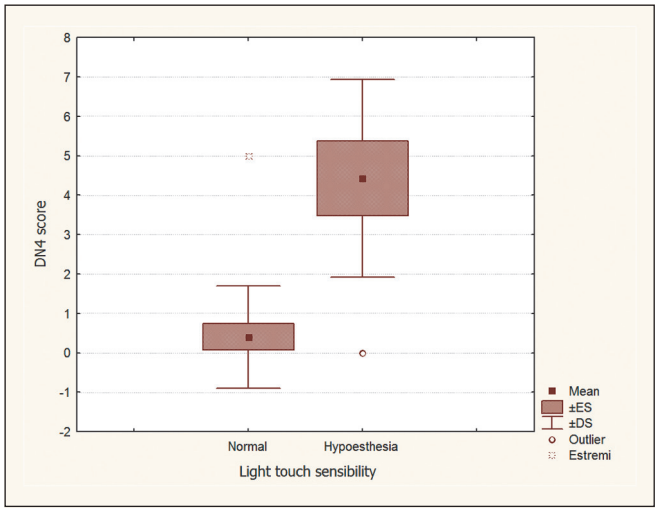

Figure 6.—Comparison between patients with and without hypoesthesia.

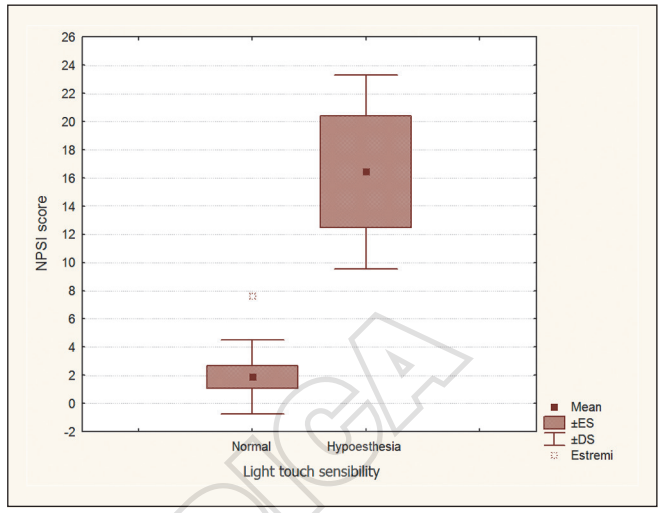

Figure 7.—Comparison of the NPSI score between patients with and without hypoesthesia.

TABLE IV.—*Normal and abnormal sensitivity (diminished/increased and allodynia) in our sample (n°72 cases).*

Modality of sensitivity		Percentage (N. cases)
Light touch	Normal	47.2% (34)
	Diminished	45.8% (33)
	Increased	4.2% (3)
	Allodynia	2.8% (2)
Cold	Normal	62.5% (45)
	Diminished	34.7% (25)
	Increased	2.8% (2)
	Allodynia	0% (0)
Proprioception	Normal	58.3% (42)
	Diminished	38.9% (28)
	Increased	2.8% (2)
	Allodynia	0% (0)
Sharpness	Normal	50.0% (36)
	Diminished	41.7% (30)
	Increased	5.5% (4)
	Allodynia	2.8% (2)

(P<0.02; r:-0.4), a significant correlation was found between physical aspects of QoL and NRS (Physical Function and Physical Composite Score: P<0.02; r:-0.4 and P<0.003; r:-0.5 respectively). Moreover, significant correlations between NPSI and two subscores of SF36 (Mental Health and Bodily Pain, P<0.04, r:-0.7 and P<0.03, r:-0.7, respectively) were found: the higher the neuropathic pain the more severe the deterioration of QoL related to pain and mental health. No significant differences were observed in all QoL scores and subscores of the patients with DN4<4 and patients with DN4≥4.

Logistic analysis results

The variables with a significant pain-related negative effect on rehabilitation program resulted to be higher NRS and previous rehabilitation experiences. The logistic model showed that higher NRS score increased the probability of having negative effect on the rehabilitation program. In particular, as the NRS score increased by one unit, the odds of this outcome increased by 1.4 (95% confidence interval: 1.1-1.8), namely the probability that pain negatively influences the rehabilitation program increased by 40%. In the same way patients with history of previous rehabilitation experiences had a higher probability that pain negatively influences the rehabilitation program (odds ratio: 12.3, 95% confidence interval: 2.1-72.4).

Discussion

Pain may significantly affect functionality and negatively influence physical activity of post-stroke patients but very few data on this topic are available.[28, 29]

This is the first study in which the impact of pain (nociceptic and/or neuropathic) on the rehabilitation treatment was evaluated.

In this study a heterogeneous sample of stroke patients who are representative of the rehabili-

tative stroke population was analyzed, through validated and commonly used outcome measures focused mainly on disability and pain. The sample had a mild/moderate clinical impairment and depression, a moderate/severe disability and mild spasticity.

About 30% of the patients complained of post-stroke pain, in agreement with literature data.[6-8] However, the degree of pain in the population might have been influenced (namely reduced) by the pain therapy that 70% of patients was taking during data collection.

Recently O'Donnell *et al*. reported a lower frequency of post-stroke pain compared to our results, probably because they evaluated patients within 4 months from the stroke, while 30% of our sample had suffered from stroke more than 4 months before enrolment.[9]

The complete sensory assessment, using several pain measures (distinguishing neuropathic and nociceptive pain) strengthen previous data on the association between pain and clinically assessed sensory impairment.[4] Roosink *et al*. showed that sensory function is reduced in patients with DN4≥4, without a statistical significance probably due to the small sample size. Niessen *et al*. had already shown, studying post-stroke shoulder pain, a relationship between shoulder proprioception, kinematics, and pain.[30] In our study, having used pain measures able to differentiate neuropathic from nociceptive pain, we showed the strong relationship between neuropathic pain and sensory impairment: patients with hypoesthesia showed a significantly higher NPSI and DN4 score than patients with normal sensory function. This is an expected result because neuropathic pain and sensory impairment are usually related.[4] Note that NPSI had been previously used in central pain but not in a wide sample of stroke patients. In this first study on post-stroke patients, NPSI showed a strong correlation with sensory impairment. The results of our study suggest the need: 1) to assess neuropathic pain (and not only nociceptive pain) in stroke patients and 2) to pay more attention to neuropathic pain occurrence in stroke patients with clinical sensory abnormality.

Moreover, as expected and observed in other neurological diseases,[31] a higher neuropathic pain is related to a more severe deterioration of QoL.

Interestingly the frequency of pain in patients with cognitive impairment is lower than that in patients without cognitive impairment. This difference has made us question the validity of the behavioral measures of pain, which may overlook the incidence of pain in cognitively-impaired patients. Moreover, the higher the spasticity at the upper limb the more severe the neuropathic pain.

Theoretically we expected that shoulder spasticity would be a cause of nociceptive pain. The association between spasticity and neuropathic pain suggests to reevaluate the role of spasticity in the pathogenesis of post-stroke pain and to consider that abnormal brain plasticity may develop after spasticity. Further studies focused on the relationship between spasticity and pain will help better define this issue. Accordingly, a recent consensus stated that there is good quality scientific evidence to treat spasticity by using botulinum toxin not only because it reduces muscle over-activity due to central nervous system diseases but also because it improves some pain syndromes, including neuropathic pain.[32]

As we had previously observed in a study on post-surgical orthopedic patients, pain confirms its crucial role on the rehabilitation process. In about ¼ of the patients, pain negatively influenced the rehabilitation program delaying the recovery and likely increasing the cost of rehabilitation.

The results from this multicenter study showed that pain has a relevant role in the rehabilitation treatment of stroke patients. In fact, as the logistic model showed, the pain intensity negatively influenced the rehabilitation program. Likewise, also previous rehabilitation experiences increased the probability that pain negatively influenced the rehabilitation program. Note that patients with previous rehabilitation experiences had not only a longer duration from stroke ($P<0.0001$) but also a stronger pain (NRS $P<0.03$). These data suggest that pain in stroke patients might induce a vicious cycle: patients with more pain underwent many rehabilitation therapies but they had also a higher probability that pain negatively influenced their rehabilitation program. Likely these patients would not gain the best result from rehabilitation program increasing rehabilitation cost. The results of our study underlined the importance to treat and prevent pain in stroke for the possible negative effect on rehabilitation path.

The few available data on pain and rehabilitation

programs open a debate on the following question: "Should we treat and prevent pain not only for QoL aspects but also to speed up rehabilitation?"

Everything that slows the rehabilitation process has a negative impact on patients, their families and Health System.

This study has some limits: we recorded information about the use of drug medications but we did not acquired data about the duration or the effect of pharmacological treatment (drug medications or botulinum toxin) on pain, and further studies focused on the impact of the pharmacological treatment on pain in stroke patients should be carried out; moreover the cross-sectional nature does not allow to confirm if patients with more pain actually have a lower ability to reach their maximum functional potential, and longitudinal studies are necessary to compare the results of rehabilitation in patients with or without pain.

Nevertheless, our study confirms the hypothesis that PSP has negative effects on the rehabilitation program.

Conclusions

Clinicians should pay more attention to pain, especially neuropathic pain, in post-stroke patients. Tailored pharmacological therapy, to treat and prevent pain, might improve patients' compliance during the rehabilitation process.

References

1. Kim JS: Post-stroke pain. Expert Rev Neurother 2009;9:711-21.
2. Kumar G, Soni CR. Central post-stroke pain: current evidence. J Neurol Sci 2009;284:10-7. Review.
3. Klit H, Finnerup NB, Jensen TS. Central post-stroke pain: clinical characteristics, pathophysiology, and management. Lancet Neurol 2009;8:857-68.
4. Roosink M, van Dongen RT, Renzenbrink GJ, Ijzerman MJ. Classifying post-stroke shoulder pain: can the DN4 be helpful? Eur J Pain 2011;15:99-102.
5. Roosink M, Geurts AC, Ijzerman MJ. Defining post-stroke pain: diagnostic challenges. Lancet Neurol 2010;9:344; author reply 344-5.
6. Jönsson AC, Lindgren I, Hallström B, Norrving B, Lindgren A. Prevalence and intensity of pain after stroke: a population based study focusing on patients' perspectives. J Neurol Neurosurg Psychiatry 2006;77:590-5.
7. Lundström E, Smits A, Terént A, Borg J. Risk factors for stroke-related pain 1 year after first-ever stroke. Eur J Neurol 2009;16:188-93.
8. Naess H, Lunde L, Brogger J, Waje-Andreassen U. Post-stroke pain on long-term follow-up: the Bergen stroke study. J Neurol 2010;257:1446-52.
9. O'Donnell MJ, Diener HC, Sacco RL, Panju AA, Vinisko R, Yusuf S, *et al*. Chronic pain syndromes after ischemic stroke: PRoFESS trial. Stroke 2013;44:1238-43.
10. Chae J. Poststroke complex regional pain syndrome. Top Stroke Rehabil 2010;17:151-62.
11. Padua L, Aprile I, Cecchi F, Molino Lova R, Arezzo MF, *et al*. Pain in postsurgical orthopedic rehabilitation: a multicenter study. Pain Med 2012;13:769-76.
12. Cruccu G, Anand P, Attal N, Garcia-Larrea L, Haanpää M, Jørum E, *et al*. EFNS guidelines on neuropathic pain assessment. Eur J Neurol 2004;11:153-62.
13. Goldstein LB, Bertels C, Davis JN. Interrater reliability of the NIH stroke scale. Arch Neurol 1989;46:660-2.
14. Kasner SE. Clinical interpretation and use of stroke scales. Lancet Neurol 2006;5:603-12.
15. Shah S, Vanclay F, Cooper B. Improving the sensitivity of the Barthel Index for stroke rehabilitation. J Clin Epidemiol 1989;42:703-9.
16. Korner-Bitensky N, Mayo N, Cabot R, Becker R, Coopersmith H. Motor and functional recovery after stroke: accuracy of physical therapists'–predictions. Arch Phys Med Rehabil 1989;70:95-9.
17. Demeurisse G, Demol O, Robaye E. Motor evaluation in vascular hemiplegia. Eur Neurol 1980;19:382-9.
18. Collin C, Wade D: Assessing motor impairment after stroke: a pilot reliability study. J Neurol Neurosurg Psychiatry 1990;53:576-9.
19. Ashworth B: Preliminary trial of carisoprodol in multiple sclerosis. Practitioner 1964;192:540-2.
20. Young IA, Cleland JA, Michener LA, Brown C. Reliability, construct validity, and responsiveness of the neck disability index, patient-specific functional scale, and numeric pain rating scale in patients with cervical radiculopathy. Am J Phys Med Rehabil 2010;89:831-9.
21. Bouhassira D, Attal N, Alchaar H, Boureau F, Brochet B, Bruxelle J, *et al*. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain 2005;114:29-36.
22. Perez C, Galvez R, Huelbes S, Insausti J, Bouhassira D, Diaz S, Rejas J. Validity and reliability of the Spanish version of the DN4 (Douleur Neuropathique 4 questions) questionnaire for differential diagnosis of pain syndromes associated to a neuropathic or somatic component. Health Qual Life Outcomes 2007;5:66.
23. Bouhassira D, Attal N, Fermanian J, Alchaar H, Gautron M, Masquelier E, *et al*. Development and validation of the neuropathic pain symptom inventory. Pain 2004;108:248-57.
24. Warden V, Hurley AC, Volicer V. Development and psychometric evaluation of the Pain Assessment in Advanced Dementia (PAINAD) Scale. J Am Med Dir Assoc 2003;4:9-15.
25. Paulson-Conger M, Leske J, Maidl C, Hanson A, Dziadulewicz L. Comparison of two pain assessment tools in nonverbal critical care patients. Pain Manag Nurs 2011;12:218-24.
26. Apolone G and Mosconi P. The Italian SF–36 Health Survey: translation, validation and norming. J Clin Epidemiol 1998;51:1025-36.
27. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561-71.
28. Widar M, Ahlstrom G, Ek AC. Health-related quality of life in persons with long-term pain after a stroke. J Clin Nurs 2004;13:497-505.

29. Widar M, Samuelsson L, Karlsson-Tivenius, S, Ahlstrom G. Long-term pain conditions after a stroke. J Rehabil Med 2002;34:165-70.
30. Niessen MH, Veeger DH, Meskers CG, Koppe PA, Konijnenbelt MH, Janssen TW. Relationship among shoulder proprioception, kinematics, and pain after stroke. Arch Phys Med Rehabil 2009;90:1557-64.
31. Cocito D, Paolasso I, Pazzaglia C, Tavella A, Poglio F, Ciaramitaro P, *et al*. Pain affects the quality of life of neuropathic patients. Neurol Sci 2006;27:155-60.
32. Esquenazi A, Novak I, Sheean G, Singer BJ, Ward AB. International consensus statement for the use of botulinum toxin treatment in adults and children with neurological impairments--introduction: Eur J Neurol 2010;17 Suppl 2:1-8.

Acknowledgments.—We would like to thank Enrico Di Stasio for his help in statistical analysis.

Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Received on November 3, 2014.
Accepted for publication on February 25, 2015.
Epub ahead of print on February 26, 2015.