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Electrophysiological evaluation of chronic neuropathic pain of spinal cord injury origin

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Abstract: The chronic neuropathic pain of spinal cord injury origin has been shown to be related to permanent neurochemical changes in the dorsal horn neurons thus producing spontaneous discharges of central nociceptive neurons resulting in chronic pain. There is a doubt, however, regarding the possible supraspinal neurogenic mechanism contributing to the generation of this chronic neuropathic pain phenomenon.

To address this issue we determinated the functional condition of the thalamocortical transsmission by obtaining somatosensory evoked potentials from the stimulation of median nerves in the group of 23 paraplegics suffering from chronic posttraumatic neuropathic pain. We prospectively collected and analysed data from 23 patients, 21 males and 2 females, aged from 22 to 59 years (mean age, 35.8 y) suffered from chronic neuropathic pain of the spinal cord and cauda equina injury origin who underwent neurophysiological investigation by obtaining somatosensory evoked potentials from the stimulation of median nerves. Somatosensory evoked potentials were defined according to three-grade scale: normal findings (C), slightly abnormal (B), abnormal findings (A). Our findings revealed pathological somatosensory evoked potentials in 17 patients (73.9%). Only 3 (13%) patients had normal findings, and 3 (13%) slightly abnormal according to our criteria. Pathological findings in a majority of our patients, with changes in the primary cortical complex N20-P25, could be indicative for the dysfunction of thalamocortical afferences in patients with paraplegic pain.

Keywords: neuropathic pain, spinal cord injury, somatosensory potentials

INTRODUCTION

The nature of the perception of pain mystified humans from the ancient times.

Scientific data regarding pain physiology accumulated during the XX century led to a comprenhensive definition of the pain sensation given by Bonica that goes:

‘ ’...pain provoked by injury or disease is the net effect of many simultaneously interacting biochemical, physiologic and psychologic mechanisms that involve activity in most parts of the nervous system concerned with sensory, motivational, and cognitive processes and psychodynamic mechanisms”[1]. It has been recognised that neither the sensation of pain is related to an oligosynaptic system nor there is definite pain center. Just on the contrary, the sensation of pain has been underlyed by the activity of the most sensory, motivational and cognitive parts of the nervous system. This definition refers to the nociceptive pain, provoked by the injury or disease, hence it avoids to help to understand the chronic pain that is expressed without provoking factors such as the chronic neuropathic pain of the spinal cord and cauda equina injury origin. To explain the pain sensation that appears as an independent phenomen neither provoked nor understendable in the causative meaning.

The paradoxical phenomenon of pain in the regions of the body rendered analgesic and/or anaesthetic occurs in about 10%-30% of the injured[2,3,4].

The final mechanism underlying this pain phenomenon is probably the result of a central neurogenic processes caused by the deafferentation shown to be related to the permanent neurochemical changes in the dorsal horn neurons, thus producing spontaneous discharges of central nociceptive neurons resulting in chronic pain[5]. However, there is a doubt regarding the possible supraspinal neurogenic mechanism contributing to the generation of paraplegic pain. In other words, the question is wheather the neural circuit responsible for the paraplegic pain or certain forms of that pain, includes central structures of sensory transmission and integration system or not. The long-term influence of the massive traumatic sensory loss on the functional status of the sensory transsmission and integration system is not known. To address this issue we determinated the

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functional condition of the thalamocortical transsmission by means of somatosensory evoked potentials (SSEP) in the group of patients suffering from chronic posttraumatic neuropathic pain of the spinal cord and cauda equina injury origin.

The aim of this study was to assess the functional status of the proximal structures of the sensory transsmission and integration system in the state of chronic pain suffering and to determine possible relations of the SSEP findings and the clinical pattern of the pain expression.

METHODS

We prospectively collected and analysed data from 23 patients 21 males and 2 females, aged from 22 to 59 years (mean age 35,8 y) suffered from the chronic posttraumatic neuropathic pain (as the sequela of spinal gunshot injuries) that underwent neurophysiological investigation by obtaining SSEP from stimulation of median nerves.

Chronic neuropathic pain was the sequela of spinal T9-L4 vertebral level gunshot injuries. All the participants underwent neurologic examination.

The patients were included in this investigation when they met the following criteria:

- the patient suffered from chronic neuropathic pain of the spinal cord and/or cauda equina injury origin that lasted for at least six months without relapse
- there was no evidence of the other neurological disease established by the somatic neurologic examination.

Actual neurological condition and functional classification of spinal injury was measured according to the American Spinal Injury Association Impairment Scale (ASIA)[6].

The ASIA Impairment Scale is used to determine the function of the key muscles and sensory points for respective myotomes/dermatomes thus providing data for the assessment of the level and degree of spinal neurological impairment according to the following gradation: A/ no sensory or motor function is preserved below the neurological level, B/ sensory but not motor function is preserved below the neurological level, C / and D-motor function is preserved below the neurological level and majority of key muscles have a muscle grade less from 3 (C), or equal/greater to 3 (D), E-sensory and motor function is normal.

DESCRIPTION AND ASSESSMENT OF PAIN

All the patients were interviewed by using Mc Gill-Melzack Pain Questionnaire, translated to the maternal language, with the list of 47 pain descriptors in order to assess the sensory structure along with the rhythm of the pain expressed. Two distinct qualities of the pain were noted: pain of thermal nature (*burning, boiling, baking, warm etc.*) and pain of different qualities of mechanical but not thermal nature (*cramping, stabbing, cutting, throbbing, shooting, sharp, incisive, constriction, distraction etc.*) The first was classified as a thermal pain, second as a mechanical nonthermal pain. The pain form consisted of thermal and other mechanical sensory equivalents was classified as combined mechanothermal pain syndrome[7]. The topography of the pain was delineated with the pain scheme drawn by the patients. The distribution of pain was either diffuse involving the whole body below the level of injury or the pain distribution was confined (Fig 1, Fig 2). Intensity of pain was measured by using Visual Analogue Scale (VAS)

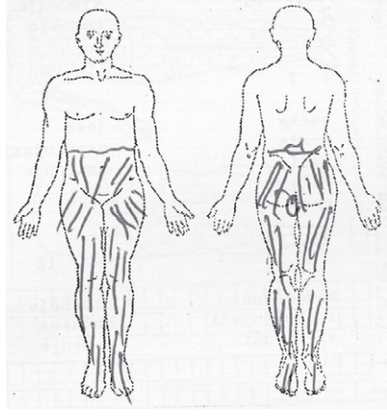

Fig 1: Pain scheme drawn by the patient: diffuse pain topography

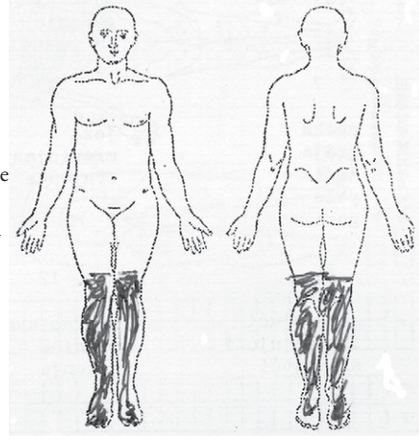

Fig 2: Pain scheme drawn by the patient: localised pain topography

SSEP investigation

The investigation was performed on the apparatus Premier-plus, Medelec MS20.

Stimulation of median nerves was performed by bipolar surface electrode in the region of the wrist ancle (Fig 3). Responses were recorded by monopolar needle electrodes above the Erb point, C7 and C2 vertebral level and contralaterally on the scalp above C3 and C4 point respectively with referent electrode Fz according to the electrodes distribution system "10-20" [8]. A total of 1024 single stimuli were delivered and, after that, averaged. Recordings was repeated from both hands two times in succsession for the purpose of the estimation of the reproducibility of the recordings. Wave form, synchronisation, amplitude and absolute and relative interwave latencies were anlyzed for all the responses recorded. Special attention was paid to the cortical responses N20-P25 ("primary cortical complex") having regarded that the wave N20 has been generated in the thalamocortical pathways.

SSEP were defined according to the three-grade scale originaly designed for this investigation:

- normal findings (C),
- slightly abnormal (not clearly shaped and synchronized waveforms, with reduced amplitudes and normal latencies of all cortical responses (B)

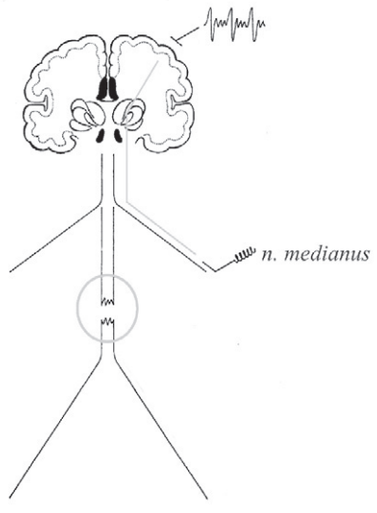

Fig 3: Scheme of the SSEP investigation, from stimulation of median nerves, that avoid cord injury (circle)

- abnormal findings (impressive changes of waveforms shape and synchronization, reduced amplitudes and prolonged latencies, especially cortical responses, including prominent changes of shape of primary cortical complex N20-P25, with total absence of N20 component) (A) (Table 1).

The SSEP findings were determined by the neurophysiologist blinded to the examiners condition.

STATISTICAL ANALYSIS

The differences of the SSEP findings as defined in our study was tested with respect to the certain characteristics of pain. Statistical analysis included Chi square test and Fishers exact test. Differences were considered significant at $p<0.05$. The investigation was approved by the Institutional Ethic Committee.

RESULTS

Clinical Characteristics of the Pain

There were 3 (13%) patients with diffuse infralesional pain of thermal quality.

Seven patients (30%) had intermittent pain of mechanical nature on the confined therritory.

Thirteen 13 (57%) patients suffered from pain of combined mechanical and thermal nature on confined therritory that described thermal pain component as background of continuous sensation of fluctuating intensity while mechanical pain component was superimposed and was intermittent. The pain theritory was billateral in all the patients.

SSEP findings

Our findings revealed pathological SSEP in 17 patients

Table 1: Classification of the SSEP findings

SSEP findings classification	Description of the SSEP findings
A	***Abnormal findings:*** Impressive changes of waveforms shape and synchronization, reduced amplitudes and prolonged latencies, especially cortical responses, including prominent changes of shape of primary cortical complex N20-P25, with total absence of N20 component.
B	*Slightly abnormal findings:* not clearly shaped and synchronized waveforms, with reduced amplitudes and normal latencies of all cortical responses
C	Normal findings.

(73,9. Only 3 patients had normal findings and 3 slightly abnormal, according to our criteria (Table 2).

Correlation Study Between SSEP Findings and Pain Characteristics

Intensity of pain

Intensity of pain was measured using the Visual Analogue Scale (VAS) and the three level of intensity were determined:

Very intensive/excruciating pain: VAS 9-10

Intensive pain: VAS 7-8

Moderate pain: VAS 5-6

Our results revealed that among 15 patients suffering from pain of excruciating intensity positive SSEP findings had 12 patients. While 2 patients had slightly abnormal SSEP and 1 had normal findings. In the group of 4 patients suffering intensive pain 3 had abnormal findings and 1 had slightly abnormal. In the group of 4 patients with moderate pain intensity 2 had positive findings and 2 normal findings (Table 3).

The average VAS index for the patients with pathological SSEP findings was 8, for those with slightly abnormal SSEP findings VAS was 7,5, and for the patients with normal SSEP findings the average VAS index was 5. This findings suggest that a positive correlation in between intensity of pain and incidence of pathological SSEP exists. This correlation reached a statistical significance for the intensity of excruciating pain ($p<0,001$) but not for the intensive and moderate pain .

Table 2: SSEP findings: results

SSEP findings	Patients
A	17
B	3
C	3

A: abnormal, **B:** slightly abnormal, **C:** normal SSEP findings

Table 3: Intensity of pain versus SSEP findings

Intensity of pain	SSEP-A	SSEP-B	SSEP-C
Excruciating (15)	12	2	1
Intensive (4)	3	1	
Moderate(4)	2		2

SSEP-A: abnormal, SSEP-B: slightly abnormal, SSEP-C: normal SSEP findings

SSEP versus rhythm of pain

Regarding the rhythm of pain our results revealed that 16 paraplegics suffered from steady pain. The steady rhythm of the pain in all the cases recorded was associated with thermal quality of the pain. The thermal pain equivalent was expressed as a pure thermal pain syndrome in three patients and as a part of a combined mechanothermal pain syndrome in 13 patients. The later group of 13 patients with combined m/t pain described thermal pain component as a background of continuous sensation while a mechanical pain component was superimposed and was intermittent. Among these 16 patients, that suffered from thermal steady pain either as a pure sensory equivalent or as a thermal component of combined m/t pain, SSEP were positive (SSEP-A) in 13 patients while in 1 patient SSEP was slightly abnormal (SSEP-B) and in 2 patients SSEP findings were normal (SSEP-C).

In the group of 7 patients suffering from intermittent pain of pure mechanical nature SSEP revealed 4 patients with pathological SSEP findings (A) and 2 patients with slightly abnormal findings (B) while 1 patient had normal (C) SSEP findings (Table 4).

The differences between the group with the pain of intermittent rhythm and the group with the pain of steady rhythm regarding the SSEP findings was not statisticaly significant ($p>0,05$).

Hovewer, comparing the group of 3 patients suffering from steady pain of pure thermal quality and the group of seven patients with intermittent pain of pure mechanical quality the differences between this two pain syndromes regarding the pathological SSEP findings were statisticaly significant ($p<0,05$). The analgesic taken by our patients correaltes closely with the intensity of pain. The intensive pain syndromes required opioids, while less intensive pain requires nonopioid analgesics. We did not note the relation between medication and SSEP findings since there were abnormal SSEP in group of patients used opioids as well as in those patients using

Table 4: Rhythm of pain versus SSEP findings

Rhythm of pain	SSEP-A	SSEP-B	SSEP-C
Steady (3)	2	1	
Intermittent (7)	4	2	1
Steady with intermittent(13)	10	1	2

SSEP-A: abnormal, SSEP-B: slightly abnormal, SSEP-C: normal findings

nonopioid analgesics. Having in mind that the SSEP remains unaffected by the narcothics[12], it is likely that analgesics used by our patients did not affect the pattern of SSEP findings.

SSEP versus neurological condition

Among the group of patients that suffered from pain of spinal cord and/or cauda equina injury origin there were 15 patients with complete neurological lesion and 8 patients with incomplete lesion (on ASIA - B level 5 patients and ASIA - C 3 patients, while there were no patients with lesion graded on ASIA - D and E level). Comparing the SSEP findings and the completeness of the neurological lesion revealed that among 15 patients with complete neurological lesion SSEP positive findings (SSEP-A + SSEP-B) had 14 of them and 1 patient was with normal SSEP finding. Among 8 patients with incomplete lesion (ASIA - B and C) there were 6 patients with positive SSEP and 2 patients with normal SSEP (Table 5).

Comparison of the SSEP findings and completeness of the neurological lesion showed that the incidence of the pathological SSEP findings in patients with complete neurological lesion was significantly higher than that incidence was in patients with incomplete neurological lesion (p=0,01).

DISCUSSION

By means of measuring the SSEP obtained by the stimulation of median nerves billaterally, in a paraparetic or paraplegic patient, we traced the signal transmission through the parts of the nervous system that were not subjected to injury (Fig 3).

Thus, any abnormality assessed in the thalamocortical system of transmission and integration, in the absence of neurological disease, could be considered as a functional consequence of the spinal cord and/or cauda equina injury itself.

Somatosensory evoked potentials are a reliable diagnostic test that provides an objective measure of function in its related sensory system. SSEPs are manifestations of the activity in the brain stem and other subcortical primary sensory tracts and nuclei recorded from the scalp. The close correlation between SSEPs waveforms and neural anatomy provides a view of the functional condition of the related neural generators of the waveforms[9].

Table 5: Neurological lesion versus SSEP findings

Neurological lesion	SSEP-A	SSEP-B	SSEP-C
Complete (15)	12	2	1
Incomplete (8)	5	1	2

SSEP-A: abnormal, SSEP-B: slightly abnormal, SSEP-C: normal SSEP findings

With the upper-limb stimulation recordable activity is generated in the thalamus, thalamocortical radiations, and cortex. The combined contributions from each of these structures produce a series of waveform peaks[10]. Thereafter the SSEP is capable of determining the functional status of the sensory transsmision and integration system[11].

As such, they have a high waveform consistency in normal subjects and are essentially unaffected even by general anesthesia or barbiturate levels sufficient to induce coma and flattening of the EEG[12]. The clinical utility of the evoked potentials is based on their ability to demonstrate abnormal sensory system function i.e. to reveal the presence of clinically unsuspected malfunction in a sensory system and to help to define the anatomic distribution of a desease process.

We were aware that the optimal design of the investigation should be the comparison of the SSEP findings established in the group of paraplegics suffering from chronic pain with the group of paraplegics without neuropathic pain. However we failed to provide a group of paraplegics that were not suffering from pain willing to accept such an investigation thus the investigation was completed in the group of paraplegics suffering from chronic pain.

The pathological SSEP findings in the majority of our patients, with the changes in the primary cortical complex N20-P25, could be indicative for the dysfunction of thalamocortical afferences in patients suffering from chronic neuropathic pain of spinal cord and cauda equina injury origin. There is a dilemma if the changes determinated by this investigation, i.e. dysfunction of the thalamocortical afferences, could contribute to the neurogenic mechanism of pain expression. The convulsive dorsal horn discharges of the deafferented cord segments, recorded in paraplegics[13], could be in a logical relation with the intermittent rhythm of the pain and favorably compare with the reported effectivness of the Dorsal Root Entry Zone lesion (DREZ) surgery in reliveing such form of the pain.

The DREZ operation aims at the selective destruction of the cord dorsal horn neurons for the selected cord segments, thus interrupting the underlying pain mechanism[14].

However, the diffuse infralesional steady, burning pain, escaped the expected effectiveness of the DREZ surgery [4, 7, 15, 16, 17, 18, 19].

Based on the experience in treating 127 patients with paraplegic pain R Tasker et al., 1992 reported the different response of steady and intermittent pain to destructive surgery. The spinal based destructive surgeries (DREZ, cordotomy, cordectomy) were effective for treating intermittent pain but not steady pain[4]. While those data indicates that pain of intermittent rhytm and confined theritorry is being generated by the convulsive discharges of the dorsal horn neurons it, at the same time, raises the question of the underlaying neurogenic mechanism of steady, diffuse neuropathic pain.

Considering the pain of steady rhythm, it is unlikely that the convulsive disharges of dorsal horn neurons of deafferented cord segments could produce the pain of steady rhythm. In other words said, it is likely that the pain expression corresponds to the underlying pain mechanism so that convulsive mechanism produces intermittent pain attacks, while the steady rhythm might be underlyed by the permanent disturbance in sensory transmission-perception system. We belive that the neurogenic mechanism of pain with steady rhythm might be related to a permanent functional disturbance of the structures involved in pain mechanism, comparing to the convulsive nature of the underlying mechanism of the intrermittent pain. The diffuse territory implyed the mechanism that was established in the regions of the CNS with broad representation of the body scheme such as the thalamus and thalamocortical afferences. Our findings confirmed the changes in the functional status of thalamocortical transmission but failed to clarify the dilemma if that changes contributed to the actual pain mechanism since the patients with steady, diffuse pain as well as those with intermittent, localised pain had a SSEP findings of thalamocortical dysfunction.

These findings suggested that the massive traumatic loss of sensory input altered functional status of the dynamic interactive system of sensory transmission and integration leading to the establisment of a new functional level of that system in the posttraumatic period.

Our findings correspond well to the hypothesis that deafferentation pain results from a posttraumatic dysfunction of the CNS[20] or from maladaptive reorganization following peripheral or central denervating lesions[21, 22] or that the pain is a product of disturbed information processing in the CNS[23].

Considering the steady pain in particular, our findings correspond to the postulate that this pain may be dependent upon a central process resulting from deafferentation, possibly in the final thalamocortical sensory path[24].

Plastic changes producing alterations of the integrative neuronal sensory processing is believed to be functional correlate of the chronic pain states[25, 26].

The processing of nociceptive (and inocuous) input to the forebrain my be altered in such a way as to permit or even cause the development of central pain in some patients[27].

The investigations on the function of human thalamus, related to the neuropathic pain states, revealed the different patterns and degrees of somatotopic reorganisation in human thalamus[28,29] or injury-induced alterations in metabolities in thalamic nuclei suggesting anatomic, functional and biochemical changes in thalamic region related to the posttraumathic neuropathic pain states[30]. There is evidence, established by means of functional brain imaging, of altered neural processing of sensory information following certain painful conditions, such as phantom pain[31, 32, 33]. The reduction in regional cerebral blood flow (rCBF), and the decrease in activity was noted in the thalamus while no significant change of rCBF was detected in somatosensory areas (Sl and Sll) in chronic neuropathic pain[34]. Hypoactivity in the thalamus has been even suspected to might be a specific signature for chronic pain[26]. Thalamocortical dysrhytmia was proposed as responsible for the development of neuropathic pain, also[35].The SSEP findings obtained in our investigation, with the absence of the thalamic wave, implicated the lower level of activity in the thalamus, too.

The fact that the steady diffuse pain below the level of injury is capable of modulation by the thalamic stimulation[24] corresponds favourably to the SSEP findings of the lower level of activity in the thalamus established in our investigation. The stimulation of the somatosensory pathway at the level of thalamus was based on the rationale that the state of neuropathic pain arise

in the absence of sensory input into the somatosensory thalamic nuclei[36]. Significant cortical reorganization after sensory deafferentation was seen in animal studies, too[21]. It raises the question whether the chronic neuropathic pain states share a pathophysiology linked to a common CNS plasticity?

We believe that the dynamic interactive functional nature of the system of sensory transsmission and integration, of necessity, imply functional adaptation in the posttraumatic period as a consequence of the impact of the massive traumatic loss of sensory input on that interactive system. We are more prone to belive that the thalamocortical disturbance contributes to the generation of the paraplegic pain sensation than to consider it as a coincidental findings insignificant for chronic pain state.

There is a lasting dilemma regarding the paraplegic pain phenomenon in general, that goes: why does one person suffering from paraplegia due to spinal cord trauma develop pain whereas an identical paraplegic with the same type of trauma remains pain free[37] ?

Our investigation imposed another doubt that goes: why does one injured suffering chronic neuropathic pain of spinal cord and cauda equina injury origin has a thalamocortical dysfunction in sensory transmission while the other, with the same form of pain, does not.

CONCLUSION

Further investigation is needed for the more objective assessment of the role of the thalamocortical sensory transsmission and integration system in the mechanism of neuropathic posttraumathic pain conditions. A question still remains to be answered.

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