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RISK FACTORS FOR UNPLEASANT PARESTHESIAE INDUCED BY PARESTHESIAE - PRODUCING DEEP BRAIN STIMULATION

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ABSTRACT - Paresthesiae-producing deep brain stimulation (stimulation of ventrocaudal nucleus - VC, medial lemniscus - ML or internal capsule - IC) is one of the few procedures to treat the steady element of neural injury pain (NIP) currently available. Reviewing the first 60 patients with NIP submitted to deep brain stimulation (DBS) from 1978 to 1991 at the Division of Neurosurgery, Toronto Hospital, University of Toronto, we observed that 6 patients complained of unpleasant paresthesiae with paresthesiae-producing DBS, preventing permanent electrode implantation in all of them. Such patients accounted for 15% of the failures (6 out of 40 failures) in our series. In an attempt to improve patient selection, we reviewed our patients considering a number of parameters in order to determine risk factors for unpleasant paresthesiae elicited by paresthesiae-producing DBS. The results showed that this response happenned only in patients with brain central pain complaining of evoked pain, secondary to a supratentorial lesion. Age, sex, duration of pain, quality of the steady pain, size of the causative lesion and site (VC,ML,IC) and type (micro or macroelectrode) of surgical exploration were not important factors. Unpleasant paresthesiae in response to dorsal column stimulation, restricted thalamic lesion on computed tomography and the occurrence of associated intermittent pain were considered major risk factors in this subset of patients and the presence of cold allodynia or hyperpathia in isolation and the absence of sensory loss were considered minor risk factors. It is our hope that the criteria here established will improve patient selection and so, the overall results of DBS.

KEY WORDS: pain, analgesia, deep brain stimulation, electrical stimulation, paresthesiae, stereotaxis, thalamus, thalamic nuclei, medial lemniscus, internal capsule.

Fatores de risco para parestesia dolorosa induzida por estimulação cerebral profuda em sítios produtores de parestesia

RESUMO - A estimulação cerebral profunda (ECP) de sítios cuja estimulação elicita parestesia (núcleo talâmico ventrocaudal - VC, lemnisco medial - LM e cápsula interna - CI) é um dos poucos métodos atualmente disponíveis para o tratamento do elemento constante da dor por injúria neural (DIN). Revendo os primeiros 60 pacientes com DIN submetidos à ECP na Division of Neurosurgery, Toronto Hospital, University of Toronto, no período 1978 / 1991, observamos que 6 destes pacientes apresentaram parestesia dolorosa à estimulação de VC / LM / CI, prevenindo a definitiva implantação do sistema em todos eles e totalizando 15% (6 dentre 40) das falhas em nossa série. Em uma tentativa de se melhorar a seleção de pacientes para a ECP e, com isto, seus resultados globais, revimos nossos casos, considerando uma série de parâmetros, de modo a determinar os fatores de risco para parestesia dolorosa. Os resultados mostraram que esta resposta à estimulação de VC / LM / CI é exclusiva de pacientes com dor central cerebral, secundária a lesão supratentorial, apresentando dor evocada como parte do quadro doloroso. Nem todos os pacientes com estas características, porém, apresentavam parestesia dolorosa.

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O estudo comparativo destes dois subgrupos (dor central cerebral + dor evocada + parestesia dolorosa e dor central cerebral + dor evocada + parestesia dolorosa) permitiu definir que: 1. Parestesia dolorosa à estimulação da coluna dorsal da medula espinhal, lesão restrita ao tálamo à tomografia computorizada e dor intermitente como parte do quadro doloroso são fatores de risco maiores para parestesia dolorosa à estimulação de VC / LM / CI; 2. Alodínia ao frio ou hiperpatia isoladamente e ausência de deficit sensitivo ao exame neurológico são fatores de risco menores; e 3. Idade, sexo, duração da dor, qualidade da dor constante, dimensões da lesão causal e sítio (VC, LM ou CI) ou tipo (macro ou microeletrodo) da exploração cirúrgica não parecem ser fatores de risco relevantes. O autor sugere também os prováveis mecanismos fisiopatológicos envolvidos na gênese da parestesia dolorosa à estimulação de VC / LM / CI.

PALAVRAS-CHAVE: dor, analgesia, estimulação cerebral profunda, estimulação elétrica, parestesia. estereotaxia, tálamo, núcleos talâmicos, lemnisco medial, cápsula interna.

Neural injury pain (NIP) is still a poorly understood disease. It presents with a steady element, always present and usually burning or tingling in character and with two other elements, intermittent pain and evoked pain, which occur, respectively, in 41.7% and 56.7% of the patients[7]. The steady element is best treated with modulatory procedures such as paraesthesiae-producing deep brain stimulation (thalamic ventrocaudal nucleus, the most frequently used target, medial lemniscus and internal capsule)[3,7], dorsal column stimulation[3,7] and more recently, motor cortex stimulation[8]; destructive procedures directed to the reticulothalamic tract (medial mesencephalic tractotomy and medial thalamotomy) may also be effective[3,7]. On the other hand, the intermittent and evoked elements are best treated with periventricular-grey (PVG) stimulation or with destructive procedures directed to the nociceptive fibers, spinothalamic tract or reticulothalamic tract[3,7].

As it usually happens with the majority of techniques to treat poorly understood diseases, the successful rate of deep brain stimulation (DBS) is not very high: in our series of 60 patients with NIP, just 20 obtained successful ongoing relief of their pain[7]. Other possible explanations for the relatively low successful rate of DBS are the incomplete knowledge of the mechanisms by which DBS yields pain relief[9,10] and poor patient selection.

PVG stimulation seems to induce pain relief by activation of the descending serotonergic and noradrenergic pathways. Our data, obtained from patients with cord central pain harboring complete cord transection in whom PVG stimulation was unsuccessful in alleviating their intermittent pain, support this hypothesis[10]. The way thalamic ventrocaudal (VC) stimulation achieves relief of pain is a controversial matter. Vilela Filho[9] and Vilela Filho & Tasker[10] have recently presented strong evidence against most of the mechanisms previously proposed and suggested that VC stimulation produces pain relief by activation of an inhibitory multisynaptic pathway to the medial thalamic nociceptive neurons, having as relays the somatosensory cortex, motor cortex, anterior putamen, substantia nigra reticulata and compacta, and globus pallidus internus; the neurotransmitters involved were also suggested.

Tasker et al[1-6] have reported painful and burning responses with stimulation mainly of medial thalamus and medial mesencephalon and, less frequently, VC nucleus (at this site these responses were intermingled with by far the commonest paresthetic responses) in patients predominantly with NIP. We now describe another response with VC stimulation, unpleasant paresthesiae, reported by 6 (10%) of our 60 patients with NIP and preventing permanent electrode implantation in all of them[7]. Since it is a very time-consuming, expensive and not too effective and free of risk procedure[7], it would be important to know the risk factors for unpleasant paresthesiae, which was the cause of failure of DBS in 15% of our patients (6 out of 40 failures; just 20 out of 60 patients obtained successful ongoing relief of their pain). Such knowledge would improve patient selection for VC (and other paresthesiae-producing sites) stimulation. This paper addresses this subject.

PATIENTS AND METHODS

Between June 1978 and July 1991, 62 patients with intractable chronic pain were admitted to the Division of Neurosurgery, Toronto Hospital, University of Toronto, to undergo DBS. There were 25 female and 37 male,

mean age of 57.2 years (29-80 years), mean interval between causative event and onset of pain of 11.3 months (0-240 months) and mean duration of pain of 79.1 months (3-504 months). Two patients presented nociceptive pain and 60 patients, neural injury pain (NIP), of which 17 presented brain central pain, 16 cord central pain and 27, peripheral neuropathic pain. All 60 patients with NIP complained of a steady element, burning in 76.7%, tingling in 28.3% and aching in 21.7%; 56.7% of the patients had evoked pain (hyperpathia = 79.4%, touch allodynia = 61.8% and cold allodynia = 26.5%) and 41.7%, intermittent pain. Evoked pain was present in 82.3% of the patients with brain central pain, 48.1% of peripheral neuropathic pain and 43.7% of cord central pain. Intermittent pain was present in 59.3% of those with peripheral neuropathic pain, 43.7% of cord central pain and 11.8% of brain central pain[7].

The surgical technique used has already been described elsewhere[7,10].

The sites surgically explored were: ventrocaudal nucleus (VC), 91.9%, medial lemniscus (ML), 11.3%, internal capsule (IC), 4.8% and PVG, 67.7% of the patients[7].

In 6 patients VC stimulation, as well as associated ML stimulation in one of these patients, induced unpleasant paresthesiae, preventing electrode insertion for trial stimulation in 4 patients and internalization of the system after electrode insertion and trial stimulation in 2 patients[7]. All these patients had evoked pain (17.6% of the patients with evoked pain) and a brain lesion (infarct) as cause of their pain (35.3% of the patients with brain central pain and 42.9% of the patients with brain central pain presenting evoked pain). However, there were another 11 patients with brain central pain, 8 of them also complaining of evoked pain, who did not report unpleasant paresthesiae with VC, ML or IC stimulation.

In an attempt to find out the factors responsible for unpleasant paresthesiae induced by paresthesiae-producing deep brain stimulation (VC, ML, IC), we divided the patients with brain central pain complaining of evoked pain into two groups: those with unpleasant paresthesiae - UP (6 patients) and those with "normal" paresthesiae - NP (8 patients) and compared the two groups regarding sex, age, duration of pain, quality of steady and evoked pain, presence of associated intermittent pain, degree of sensory loss, type (macroelectrode or microelectrode) and site (VC, ML or IC) of surgical exploration, results of dorsal column and trigeminal stimulation when performed and the findings on computed tomography (the lesions were classified as infrathalamic, thalamic, suprathalamic and thalamosuprathalamic and as small (< 0.5 cm), medium (0.5 to 3.0 cm) and large (> 3.0 cm).

RESULTS

I. Sex:

UP: 3 male / 3 female
NP: 4 male / 4 female

II. Age:

UP: mean age = 60.8 years (52 - 68 years)
NP: mean age = 61.2 years (37 - 77 years)

III. Duration of pain:

UP: mean duration of pain = 48 months (4 - 120 months)
NP: mean duration of pain = 44 months (12 - 82 months)

IV. Steady pain:

Steady pain was present in all patients.

UP: all patients (100%) of this group complained of burning pain and one third (33.3%) of them also complained of tingling, aching and/or cold pain.

NP: 75% of these patients had burning pain, 37.5% tighting pain and 12.5% cold, tingling, aching, throbbing and/or sharp pain.

V. Intermittent pain:

Only two patients complained of intermittent neuralgic pain. Both of them belonged to the UP group.

VI. Evoked pain:

All patients under study presented evoked pain.

UP: 83% of the patients complained of hyperpathia and 67% of allodynia (touch allodynia in 50% and cold allodynia in 50% of the patients). Two patients (33%) presented hyperpathia as the

only feature of evoked pain, 1 patient (16.7%) complained only of cold allodynia, 1 patient (16.7%) of both hyperpathia and touch allodynia and 2 other patients (33%) presented simultaneously hyperpathia, cold and touch allodynia (both had associated intermittent pain).

NP: 62.5% presented hyperpathia and 87.5%, allodynia (touch allodynia in 87.5% and cold allodynia in 50%). Touch allodynia alone was present in 2 patients (25%), hyperpathia alone in 1 (12.5%), touch and cold allodynia in 1 (12.5%), hyperpathia and touch allodynia in 1 (12.5%) and hyperpathia, touch and cold allodynia in 3 patients (37.5%).

VII. Sensory examination:

Sensory examination was normal in 2 patients. In the other 12 patients, spinothalamic tract (pain and temperature) and medial lemniscus (touch, vibration and position) loss was proportional.

UP: normal in 2 patients (33%) (one of them with intermittent pain), moderate loss in 4 patients (66%).

NP: mild loss in 3 patients (37.5%), moderate loss in 4 patients (50%) and severe loss in 1 patient (12.5%).

VIII. Type of surgical exploration:

UP: 1 patient (16.7%) was explored with macroelectrode, 3 (50%) with microelectrode and 2 (33%) with both.

NP: 1 patient (12.5%) was explored with macroelectrode, 6 (75%) with microelectrode and 1 (12.5%) with both.

IX. Site of exploration:

UP: VC and PVG were explored in all patients and medial lemniscus (ML), in 1 patient. Both VC and ML stimulation produced unpleasant paresthesiae.

NP: VC was explored in 7 patients, PVG in 5, ML in 2 (associated with VC and PVG in 1 patient and with internal capsule - IC - in the other) and IC in 1 (associated with ML).

X. Results of dorsal column stimulation (DCS) and trigeminal stimulation (TS):

UP: technically adequate DCS (paresthesiae in the painful area) was performed in 2 patients (both without intermittent pain), before VC stimulation in 1 patient and after unsuccessful VC stimulation (unpleasant paresthesiae) in the other. It produced unpleasant paresthesiae in both patients.

NP: technically adequate DCS was performed in 2 patients and did not relieve their pain. Two other patients were submitted to TS, which was unsuccessful in 1 patient (no relief of pain) and partly successful in the other, who is still using TS associated with VC stimulation.

XI. Findings on computed tomography (CT):

UP without intermittent pain: the 4 patients presented clinically supratentorial infarct. CT was normal in 1 patient and showed thalamic infarct (posterior thalamus) in 3 patients, which was small in 2 patients and medium in 1.

UP with intermittent pain: CT showed suprathalamic infarct in both patients, which was small in one and large in the other.

NP: 7 patients presented clinically supratentorial infarct (1 of them also presented infratentorial infarct - Wallenberg's syndrome, but CT demonstrated only the supratentorial lesion, which was compatible with the patient's pain) and 1 patient, infratentorial infarct. CT was normal in 3 patients (2 with supratentorial infarct and 1 with infratentorial infarct) and showed suprathalamic lesion in 2 patients (1 large and 1 medium) and thalamosuprathalamic lesion in 3 (2 large and 1 medium).

DISCUSSION

In patients without neural injury pain (NIP), stimulation of the mesencephalon medial to 8 mm from the midline or the thalamus medial to 12 mm rarely elicits any response and stimulation of VC usually produces paresthetic responses and, only rarely, isolated burning or, even more unusually, painful responses, which is different of the pain complained by patients with nociceptive pain[2,3,5,6].

On the other hand, in patients presenting NIP, burning and painful responses are quite common. They occur in clusters in the mesencephalon medial to 8 mm from the midline and in the medial thalamus medial to 12 mm, being by far the commonest response at these sites, which are usually silent in patients without neural injury pain[2,3,5,6]. These responses are referred contralaterally and non-somatotopographically to deafferented areas of the body, resembling the patient's own pain both in quality and distribution. Burning and painful responses were also reported in patients with NIP by stimulation of the spinothalamic tract in the spinal cord[2,5] and mesencephalon[2,5,6], VC[1,3,4], thalamic radiations and somatosensory cortex[1,3], being the responses at these sites frequently intermixed with the more common normal paresthetic (VC, thalamic radiations and somatosensory cortex) or warm, hot and cold (spinothalamic tract) responses and somatotopographically organized, resembling the patient's pain. The vast majority of patients presenting such responses with VC or medial thalamic/mesencephalic stimulation complained of evoked pain[1,3,4].

Now, we describe another response with VC stimulation: unpleasant paresthesiae, which was reported by 6 out of 60 of our patients with NIP[7].

Deep brain stimulation, despite its shortcomings, is, many times, the last or even the unique resource for treating patients with NIP. Since unpleasant paresthesiae is a risk factor for unsuccessful paresthesiae-producing deep brain stimulation (it accounted for 15% of our failures), knowing in advance which patients would present such response could avoid the performance of the procedure in these patients and so, improve patient selection.

In an attempt to determine the risk factors for unpleasant paresthesiae, we reviewed our first 62 patients who underwent DBS.

The first and most important observation was that unpleasant paresthesiae occurred only in patients (6 patients) with evoked pain (6 out of 34 patients -17.6%- with evoked pain), the same way the painful and burning responses above described did. The second and equally important observation was that it curiously, differently of the painful and burning responses, occurred only in patients with brain central pain (6 out of 17-35.3 %-patients) in whom the evoked element was present (6 out of 14 -42.9%- patients with brain central pain harboring evoked pain). It never occurred in patients with cord central or peripheral neuropathic pain, regardless the presence of evoked pain.

On the other hand, there were another 8 patients with brain central pain presenting evoked pain who did not complain of unpleasant paresthesiae with VC/ML/IC stimulation. Then, our next step was to separate the patients with brain central pain presenting evoked pain (14 patients) into 2 groups and compare these groups taking into account a number of parameters. One group, composed of 6 patients, presented unpleasant paresthesiae with VC/ML stimulation and was named UP and the other group, made of 8 patients, presented only "normal" paresthesiae with VC/ML /IC stimulation and was called NP.

Sex, age, duration of pain, site (VC,ML or IC) and type (macro or microelectrode) of surgical exploration, the size of the lesion observed on computed tomography and the quality of the steady pain were not significant risk factors, since they were quite similar in both groups.

Intermittent pain, although relatively frequent in patients with peripheral neuropathic (59.3%) and cord central (43.7%) pain, is unusual in patients with brain central pain. Only 2 out of our 17 patients (11.8%) in this category complained of intermittent pain, associated with steady and evoked pain in both cases. Interestingly, both patients complained of unpleasant paresthesiae. If the numbers were not too small, we would be tempted to state that 100% of the patients with brain central pain presenting evoked and intermittent pain report unpleasant paresthesiae with paresthesiae-producing DBS, regardless all other parameters.

Dorsal column stimulation (DCS) was performed in 2 patients of UP and in 2 patients of NP and trigeminal stimulation (TS) in 2 patients of NP. DCS produced unpleasant paresthesiae in the 2

patients of UP (both without intermittent pain), but produced only normal paresthesiae and was ineffective in the 2 patients of NP. TS was ineffective in 1 patient and was partly effective in the other, both of NP.

DCS was performed in 26 other patients (1 of which, with peripheral neuropathic pain, after failed DBS) of this series, 9 with cord central pain, 16 with peripheral neuropathic pain and 1 with nociceptive pain; 8 of these 26 patients presented evoked pain[7]. DCS produced unpleasant paresthesiae in 2 patients (both had evoked pain), one with peripheral neuropathic pain, in whom VC stimulation produced excellent pain relief and the other with cord central pain, in whom VC stimulation was ineffective, but in none VC stimulation elicited unpleasant paresthesiae. TS was performed in 4 other patients; 3 of them had evoked pain. TS induced unpleasant paresthesiae only in one patient, who presented peripheral neuropathic pain and in whom VC stimulation was ineffective but did not produce unpleasant paresthesiae (this patient also had evoked pain).

So, in a patient with brain central pain harboring evoked pain, if DCS elicits unpleasant paresthesiae, VC stimulation is at high risk (100% of our patients) of producing unpleasant paresthesiae as well; this correlation was not observed in patients with cord central, peripheral neuropathic or nociceptive pain.

CT was performed in all patients with brain central pain. It showed a thalamic infarct in 3 patients and was normal in 1 patient of UP without intermittent pain and demonstrated suprathalamic infarct in the 2 patients of UP presenting intermittent pain. As for the patients of NP, CT was normal in 3 patients and showed a suprathalamic infarct in 2 patients and a thalamosuprathalamic infarct in 3 patients. Summarizing, in a patient with brain central pain presenting evoked pain but not intermittent pain, if s/he presents a thalamic lesion on CT s/he is at high risk (100% of our patients) for unpleasant paresthesiae with VC stimulation. A normal CT, however, does not rule out the possibility of unpleasant paresthesiae. Another interesting observation is that all patients of UP had clinically supratentorial infarcts as well as all but one patient of NP, who presented infratentorial infarct (CT was normal in this patient). Based on these observations, one might assume that unpleasant paresthesiae occurs just after supratentorial lesions, maybe for the same reason it did not occur in any of our patients with central cord and peripheral neuropathic pain.

Evoked pain occurred in all patients under study. Hyperpathia occurred more frequently in patients of UP (83%) and touch allodynia, in patients of NP (87.5%). Cold allodynia alone happened just to one patient who belonged to the group of UP. Hyperpathia alone was more frequent in patients of UP and touch allodynia in isolation occurred only in patients of NP. These results suggest that patients with hyperpathia and/or cold allodynia are at higher risk of unpleasant paresthesiae than patients with touch allodynia, especially if in isolation.

All patients of both groups but one patient of NP presented none to moderate sensory loss. Severe sensory loss, however, occurred just with one patient of NP and no sensory loss happened just with 2 patients of UP (both patients had an infarct demonstrated by CT compatible with subclinical sensory loss in the area of distribution of their pain).

Summarizing, in patients with brain central pain secondary to a supratentorial lesion and presenting evoked pain, the following parameters correlated very well with unpleasant paresthesiae elicited by VC stimulation and were named major risk factors: presence of intermittent pain, CT showing a confined thalamic lesion in patients without intermittent pain and unpleasant paresthesiae produced by DCS. Other parameters seemed not too important and were denominated minor risk factors: the presence of cold allodynia or hyperpathia as the unique modality of evoked pain and the absence of sensory loss.

Now, how different is this response, unpleasant paresthesiae, from previously reported responses to DBS?

Tasker et al[2,3,5,6] described painful and burning responses by stimulation of the medial thalamus/ mesencephalon. These are probably other types of response since they were elicited by stimulation of the reticulothalamic pathway and not of the spinothalamic and medial lemniscus relay, as in the present series; electric current spread could not be at play because of the low intensity of the electrical stimulation used.

On the other hand, Tasker et al[1,3,4] also described painful and burning responses by stimulation of VC; microelectrode recording at these sites revealed tactile neurons representing the same part of the body as that to which the response was referred. Could the response we now report represent a mere choice of words for the same phenomenon? It is a reasonable explanation. However, despite more oftenly happening among patients with evoked pain, painful and burning responses occurred indistinctly in patients with brain central, cord central or peripheral neurophatic pain. In the present series, unpleasant paresthesiae occurred only in patients with brain central pain, preventing permanent electrode implantation in all of them. It is this author's guess that this response could represent a high concentration of painful and/or burning responses in a single and wider area, which would happen associated with thalamic lesions and where stimulation would give rise to unpleasant paresthesiae.

One has to consider that the conclusions here reported were drawn from a relatively small number of patients and not for even one minute they were intended to be absolute. Quite the contrary, it is this author's intention to elicite other author's interest in this very interesting matter in order to, by refusing or supporting the criteria here established, improve patient selection and the overall results of paresthesiae-producing deep brain stimulation.

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