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Role of the Qst-Testing for the Determination of the Nervus Intermedius Neuralgia Phenotype – Case Report

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Abstract: Background and Objectives: Nervus Intermedius neuralgia is a rare and difficult to suspect entity. This study aims to present the case of intermedius neuralgia, discusses the implications of the phenotype in the patient approach, as well as the role of quantitative susceptibility testing (QST), as an important tool in the diagnosis and therapeutic management. Case report: 40-year-old female patient, smoker, accompanied by neurology (generalized tonic-clonic seizures), in use of carbamazepine. During one of the seizures, she said fall from height, resulting in fracture of the left temporal bone and ipsilateral facial paralysis. After to optimal the therapy, she had no more seizures, but evolved with paroxysmal pain, shock-like, located in the groove between the ear and scalp at high intensity, with shooting area in the wall of the external auditory channel. Reports that had more crisis with the arrival of winter. The examination revealed mechanical hyperalgesia and "wind-up" phenomenon on the affected side. CT mastoid with evidence of temporal fracture to the left crossing the mast cells. Electroneuromyography corroborating with peripheral facial paralysis. Other tests without changes. It was submitted to the QST-test, evidencing hyperalgesia to cold in the region corresponding to the pain complaint. Lamotrigine was associated with the treatment regimen with 90% improvement of symptoms. Conclusion**:** This is a rare etiology and difficult diagnosis. The QST-test was extremely important, as well as aid in the diagnosis also allows us to identify the great variability of phenotypic profile within each etiology, which may reflect distinct pathophysiological mechanisms, with different therapeutic responses. There is evidence that lamotrigine assist in the treatment of neuropathic pain associated hyperalgesia to cold.

Keywords: QST, Nervus Intermedius, Neuropathic Pain, Lamotrigine, Phenotype

1. Introduction

The intermediate nerve (NI) was identified by Eustachius (1563), but was only described by Heinrich August Wrisbergn at the University of Göttingen in 1777. In 1857, John Nottingham introduced the term "painful ear tic" to describe sudden paroxysms of pain In 1876, Webber described the pain phenomenon observed in six cases of facial paralysis, in which the pain was located inside the ear and the mastoid regions, with irradiation to the face and occipital region. In 1909, Orbison observed a case of herpes zoster of the tympanic membrane with ear pain, tinnitus, deafness, without facial nerve paralysis James de Ramsay Hunt acknowledges the involvement of the intermediate nerve in ear pain, based on clinical observations of herpes zoster [1].

O NI emerges from the bulb-pontine sulcus, near the facial nerve. They then penetrate the internal acoustic meatus, in which the intermediate nerve loses its individuality, forming a single nerve trunk that penetrates the facial canal and is commonly described as a sensitive root of the facial nerve.

Neuralgias are usually pains emanating from sensory nerve trunks and distributed in all or part of the area supplied by these nerve structures. They are characterized by painful paroxysms, of short duration. The character of the pain is

described as lancinating or as a sensation of shock [2]. Regarding semiotics, they can be described as typical (when they respect the anatomical limits of nerve structures, as well as the paroxysmal nature of pain) and atypical (when part of these requirements is not respected). These are examples of neuralgias: the trigeminal, the herpetic, n. glossopharyngeal; of n. occipital and n. intermediate

Intermediate neuralgia is a rare syndrome and its etiology is still unknown. Since 1968, about 50 cases have been published on the intermediate nerve [3]. It is believed that the etiology of this syndrome is analogous to trigeminal neuralgia [4]. Calvin et al concluded that both central and peripheral mechanisms are necessary for [5]. Fromm and associates proposed that a peripheral nerve injury (at the trigeminal or distal root) is the first event leading to central synaptic changes [6].

The International Headache Society defined the following criteria as criteria for diagnosis: (A) Paroxysmal pain felt deep in the ear, for seconds or minutes, of intermittent occurrence; (B) Presence of a firing area on the wall of the posterior external auditory canal; (C) Exclusion of a structural lesion. In cases of intermediate nerve section or compression, there may be loss of tear function, decreased sensitivity in the posterior region of the external auditory canal. [7-9].

The vast majority of effective pain treatments produce clinically meaningful improvements only in a minority of the patients that receive them. Many authors have suggested that one factor contributing to this state of affairs is the prevailing approach to pain classification [10–13]. At present, pain diagnosis is based primarily on signs and symptoms, sometimes combined with evidence of disease, structural damage or injury. However, the clinical diagnosis typically provides limited information regarding the pathophysiological mechanisms underlying the pain experience that may guide choice of treatment. Because treatments exert their clinical benefits by impacting the mechanisms underlying pain, an important goal for enhancing pain care is to incorporate assessment of pain mechanisms into the patient evaluation. One potentially promising method for assessing the mechanisms that contribute to the development and/or maintenance of chronic pain is quantitative sensory testing (QST). Over the last two decades, QST protocols have been developed to complement and extend the bedside neurological examination [14–18]. QST collectively refers to a group of procedures that assess the perceptual responses to systematically applied and quantifiable sensory stimuli for the purpose of characterizing somatosensory function or dysfunction. QST assesses the integrity of the entire neural axis from receptor to brain and complements clinical neurophysiological studies (e.g. nerve conduction) which can only assess sensory large fiber function. Thus, QST can provide information regarding large myelinated A-beta, thinly myelinated A-delta and small unmyelinated C fiber function and their corresponding central pathways, although it cannot provide information on the exact source of somatosensory dysfunction. QST represents a useful, non-invasive method to assess both loss and gain of sensory function that may contribute to our understanding of pathophysiological mechanisms. It can be also used to evaluate a condition natural history and may predict and/or reflect treatment responses. Although QST provides quantifiable sensory measures, similar to other psychophysical methods it can be affected by variations in the subject's concentration, attention and disposition and by procedural variability [19].

Emerging evidence suggests that QST measures may have value for predicting future experiences of both acute and chronic pain. [20-22]

In the case in question, the QST not only was configured as an important diagnostic tool, but also contributed to the therapeutic conduct. The sensorial quantification test (QST) for temperature and pain evaluates in a non-invasive way the entire nociceptive pathway, from the thermal receptor to the verbal manifestation of the patient, by determining the thresholds for different sensations [23-25].

Thus, the objective of the present study is to report a case of intermediate neuralgia, and the role of the QST test in determining the phenotypic profile and its impact on therapeutic management.

2. Case Report

A 40-year-old female patient, smoker, accompanied by neurology (generalized tonic-clonic convulsive seizures), using carbamazepine 200 mg orally twice a day. She reports that she suffered a fall of her own height, resulting in a fracture of the left temporal bone and ipsilateral peripheral facial paralysis. The dose of carbamazepine was optimized for 200 mg orally divided every 8 hours + fludrocortisone 0.1mg twice a day.

The patient reported no further seizures, but she presented paroxysmal left temporal headache. MRI of the skull without evidence of expansive, vascular or demyelinating disease. EEG: No pathological changes. In physiotherapy since 2014. It was evaluated by otorhinolaryngology, during an painful crisis in the left ear, with no evidence of active infection, being referred to the pain clinic, with suspected neuropathic pain.

Performed mastoid CT with evidence of left temporal fracture crossing the mastoid cells (Figure 1). Electroneuromyography revealing amplitude decrease, compatible with peripheral facial paralysis. The patient reports short-term paroxysmal pain, well located in the furrow between the auricle and the scalp, after a severe left temporal bone fracture (Numeral Verbal Scale: 10), with a firing area in the wall of the auditory canal external. Reports that had more crisis with the arrival of winter. Pain was alleviated with the use of tramadol 50 mg and ketorolac 10 mg. At the examination: Presence of left peripheral facial paralysis, mechanical hyperalgesia and "wind-up" phenomenon in the left preauricular region. She performed a QST-test, showing cold hyperalgesia on the affected side of the face. Lamotrigine 25 twice a day + carbamazepine 600

mg / day + tramadol 50 mg orally daily every 8 hours was associated with a 90% improvement in pain.

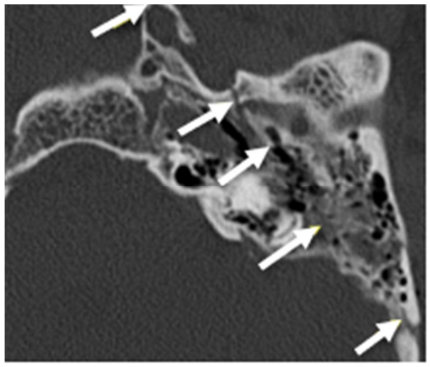

Figure 1. *Mastoid CT with evidence of left temporal fracture crossing the mastoid cell.*

3. Methods

The patient is followed up at the pain clinic of our institution and allowed to perform the referred tests. The tests were performed in our sensitivity laboratory. The patient was instructed about the test, and a pilot test was performed. The devices were properly calibrated and previously tested, in order not to cause tissue lesions in the patient.

Description of tests

The hot and cold detection thresholds and the cold and heat pain thresholds were estimated with a computerized thermal test apparatus (Medoc TSA-2001; Medoc Ltd., Ramat Yishai, Israel) with a peltier device with an active surface of 16 x 16 mm. The apparatus was filled with water, which can be heated or cooled, the temperature being transmitted to the device in contact with the patient's skin. The stimulus intensity was gradually increased from 32°C (1°C / sec, cutoff limits: 10 ° and 52°C) until the patient pressed the response button at a given temperature, which recorded the temperature, returning to the baseline value (32°C). Four tests were performed for each sensitivity and the value considered was the average of these values.

The thermodo was positioned in the furrow between the scalp and the auricular region, comparing the right side (control) with the left side affected (test) of the face. At the end of the test, the results were generated as graphs, with the mean values of the respective trials. Cold and heat detection thresholds, respectively, by means of 4 measurements for each stimulus. Then, the pain thresholds were evaluated for cold and heat, respectively, by means of 3 measurements for each of the stimuli.

4. Results

The figure 2 shows the measurements on the right side of the face (healthy side). There is a homogeneous distribution of detection thresholds for cold and pain for cold: Averages of 29.3°C and 9.79°C, respectively. The same procedure was performed on the left side (affected side), figure 3. Reductions were detected in the detection thresholds in the cold, as well as in the cold pain thresholds (Averages 30.67°C and 29.59°C), respectively, justifying the patient's report on pain symptoms worsening during the winter (cold hyperalgesia).

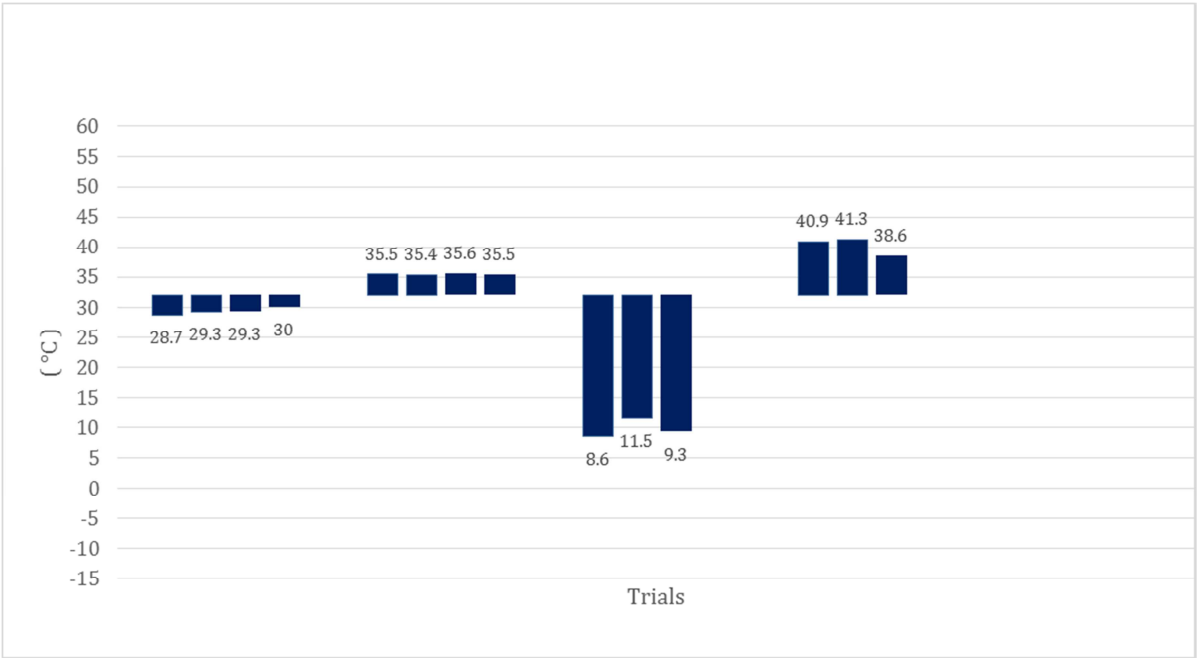

Figure 2. *Result of thermal thresholds of detection and pain (cold and heat) - Right side (Test Graph). The thermodo was positioned in the groove between the auricle and the scalp on the right. The temperature averages were taken into account (Celsius scale) of each stimulus. The results were generated as a graph, arranged in four sequences (from left to right): Cold detection threshold (CS): 29.3°C; Heat detection threshold (WS): 35.4°C. Cold pain threshold (CP): 9.79°C. Heat pain threshold (HP): 40.27°C. The values are within normal limits AVG: Average value of the sequences. STD: Standard Deviation.*

Table 1. *Test Results.*

Modality	Baseline	Rate	Trials	AVG	STD
CS	32	1	4	29,32	0,56
WS	32	1	4	35,47	0,12
CP	32	1,5	3	9,79	1,56
HP	32	1,5	3	40,27	1,5

The Von Frey Filament was used to evaluate the mechanical detection threshold and the threshold of mechanical pain, being these within normality. The repetitive stimulus (10 times) with the filament 26 g was used to determine the *wind up* phenomenon, being present. The occurrence of this phenomenon is related to the process of mechanical hyperalgesia and central sensitization. The mechanical allodynia was evaluated with the aid of a brush, and was not present.

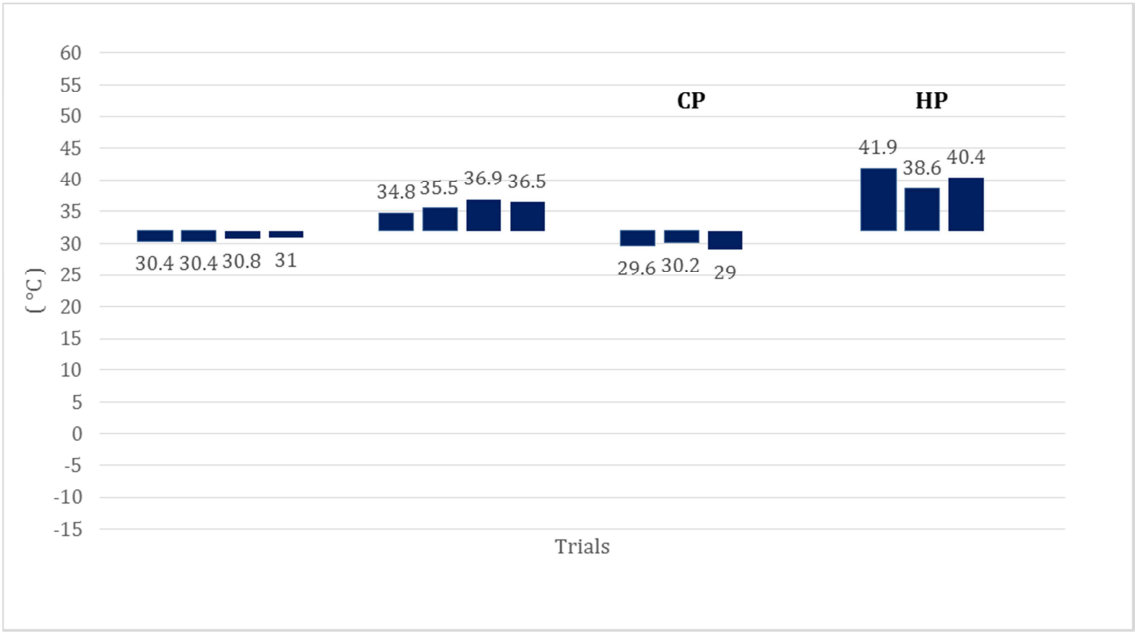

Figure 3. *Result of thermal thresholds of detection and pain (cold and heat) - Left side (affected) Test Graph. The thermodo was positioned in the furrow between the auricle and the scalp on the left. The temperature averages were taken into account (Celsius scale) of each stimulus. The results were generated as a graph, arranged in four sequences (from left to right): Cold detection threshold (CS): 30.67°C; Heat detection threshold (WS): 35.94°C. Cold pain threshold (CP): 29.59°C. Heat pain threshold (HP): 40.3°C. There were reductions in the detection thresholds in the cold, as well as the pain thresholds in the cold, justifying the patient's report on the pain symptoms worsening during the winter (cold hyperalgesia). AVG: Average value of the sequences. STD: Standard Deviation.*

Table 2. *Test Results.*

Modality	Baseline	Rate	Trials	AVG	STD
CS	32	1	4	30,67	0,29
WS	32	1	4	35,94	0,93
CP	32	1,5	3	29,59	0,63
HP	32	1,5	3	40,3	1,69

5. Discussion

Neuropathic pain syndromes develop after a lesion or disease affecting the somatosensory nervous system [26]. Despite advances in understanding the complex neurobiology of pain, the pharmacological management of these syndromes remains insufficient and several promising drugs have failed in late stage development [27].

Thus, there is a need to predict treatment responders both for clinical practice, in which even first-line treatments are beneficial in less than 50% of patients, and for clinical trial design, in which a negative outcome maybe due to a low responder rate rather than uniform inefficacy of the treatment.

Recent studies on neuropathic pain emphasize the fact that individuals with the same etiology (as in diabetic neuropathy) may present themselves in different ways, from asymptomatic patients to those with severe symptoms [28]. This corroborates a multifactorial mechanism that determines the existence of different phenotypic profiles.

Several trials in neuropathic pain have used baseline QST profiling to identify predictors of treatment response [29-30] that can be tentatively assigned to the 3 clusters: Patients with a baseline QST profile (“thermal hyperalgesia”) exhibited a higher efficacy in a prospective randomized placebo-controlled trial with oxcarbazepine, [31] in a preplanned analysis of a placebo-controlled trial with

botulinum toxin, [32] and in a retrospective analysis of a study using topical capsaicin patches without a placebo arm [33]. A retrospective analysis of a placebo-controlled trial with topical lidocaine demonstrated lower efficacy [34]. Patients with a baseline QST profile ("sensory loss") exhibited a higher efficacy in a retrospective analysis of a placebo-controlled trial with oral opioids [35]. A prospective randomized placebo-controlled trial with oxcarbazepine demonstrated lower efficacy [36]. Patients with a baseline QST profile ("mechanical hyperalgesia") exhibited a higher efficacy in retrospective analyses of placebo-controlled trials with oral pregabalin, [37] topical lidocaine, [38] lamotrigine, [39] or intravenous lidocaine [40].

Some studies have demonstrated the safety benefit of lamotrigine (200-400 mg) safely in the treatment of patients with incomplete spinal cord injury who presented areas of evoked pain, providing a lower pain score when compared to the control group [39].

An experimental model that induced cold hyperalgesia by means of ciguatoxin, demonstrated statistically significant improvement with lamotrigine. [41].

Lamotrigine is an antiepileptic drug that acts on voltage-sensitive sodium channels and stabilizes the neuronal membrane to inhibit the release of excitatory neurotransmitters, mainly glutamate, mediated by sodium influx. [42-47]. Adverse effects associated with the use of lamotrigine include: dizziness, nausea, headache, fatigue and other CNS-related symptoms. Special attention should be given to the occurrence of Steven Johnson syndrome. For this reason, dose escalation is recommended until a satisfactory effect is achieved. A dose of 25 mg / day was used, with a good tolerance, being gradually increased to 50 mg of 1 twice a day, with improvement of 90% of the symptoms.

6. Conclusion

It is a rare etiology in our country and difficult to diagnose. The QST test is extremely important in the approach to cases such as this, as it also helps to identify the great variability of the phenotypic profile within each etiology and, therefore, may reflect different pathophysiological mechanisms, with therapeutic responses differentiated for each patient. A better understanding of these profiles allows for an individualized and more effective therapeutic approach.

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