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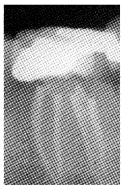

CLINICAL ARTICLE

Proposal for a standardized protocol for the systematic orofacial examination of patients with Hereditary Sensory Radicular Neuropathy

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Abstract

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Aim To apply a standardized protocol for the orofacial evaluation of two adult siblings (one male and one female) with Hereditary Sensory Radicular Neuropathy (HSRN) that presented with dental problems.

Summary The systematic evaluation consisted of (a) clinical questionnaire; (b) radiographs [orthopantomography and computarized tomography (CT)]; (c) orofacial psychophysical tests (pain, thermal, mechanical and electrical sensation); and (d) histology of gingiva and pulp (optical and transmission electronic microscopy). The female patient had complete insensitivity to orofacial pain and partial facial heat sensitivity, and received dental treatment without anaesthesia or pain. She had a severe and painless jaw infection due to pulp necrosis in tooth 37. The male patient had partial insensitivity to orofacial pain and required anaesthesia for dental treatment. Histological examination of gingivae and pulpal tissue revealed an altered proportion of unmyelinated and myelinated sensory nerve fibres.

Key learning points

- Patients with HSRN may present with significant, silent dental disease.
- A standard protocol is helpful when evaluating such patients.
- If the opportunity arises, evaluation of pulp tissue may reveal an altered proportion of myelinated and unmyelinated nerve fibres. This may avoid the more estabilished sural nerve biopsy.

Keywords: analgesia congenita, hereditary sensory radicular neuropathy, insensitivity-to-pain syndrome, orofacial pain, superficial sensitivity, toothache.

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Introduction

Hereditary sensory radicular neuropathy (HSRN) is a rare genetic disease that is characterized by insensitivity to pain. It is often discovered soon after birth, and presents with different degrees of sensory loss (Littlewood & Mitchell 1998). Genetic factors were identified by Mogil (1999) and new genes have been investigated since then (Nagasako *et al.* 2003). The loss of small fibres (C and Aδ) in the sural nerve was observed by Wood in 1996 (Nagasako *et al.* 2003), and possible causes of this feature include programmed cell death *in-utero* and incomplete development of nerve fibres (Littlewood & Mitchell 1998). The differential diagnosis may include assymbolia, hysteria and peripheral neuropathies (Person *et al.* 1977, Erdem *et al.* 2000). Absence of the sensory component is characterized by insensitivity and the absence of the affective component by indifference (Person *et al.* 1977, Nagasako *et al.* 2003). The consequences can be serious in terms of silent disease and unidentified injury.

Hereditary sensory radicular neuropathy can be classified into five subtypes, based on clinical rather than genetic findings (Nagasako *et al.* 2003) (see Table 1). Although HSRN is recognized as an important neuropathic issue, clinical research is rare (Nagasako *et al.* 2003).

Possible clinical findings in HSRN:

- Burning sensation in the extremities (including the hands) and joint injuries (Nagasako *et al.* 2003).
- Oral lesions after repetitive trauma (Erdem *et al.* 2000), that are often the first signs of disease (Chatrian *et al.* 1975, Rasmussen 1996, Karkashan *et al.* 2002).
- Severe, often silent infections such as osteomyelitis (Chatrian *et al.* 1975).
- Oral mucosa; scars and limitation of mouth-opening (Littlewood & Mitchell 1998).
- Self-dental extraction, dental infection and premature tooth loss (Chatrian *et al.* 1975).

Until now, microscopic studies have been conducted on sural nerve biopsies (Akai & Wakisaka 1990) and there are no previous studies on the innervation of dental or gingival tissues in such patients. Normally, unmyelinated fibres outnumber myelinated fibres by 3 : 1 in pulp tissues (Akai & Wakisaka 1990, Nair 1995). Teeth are often exposed to injury (Kerezoudis *et al.* 1993), and C fibres may retain sensory function during pulp inflammation and breakdown (Sessle 2000). C fibres may be involved in reparative mechanisms following pulp micro-exposure and such mechanisms may be compromized in HSRN patients (Fazekas *et al.* 1992, Kerezoudis *et al.* 1994). Patients with impaired responses may need careful evaluation during decision making processes for dental treatment.

Superficial sensitivity evaluation has been employed in the evaluation of neuropathies such as burning mouth syndrome (Grushka 1987), trigeminal neuralgia (Synai *et al.* 2003) and after trigeminal surgery (Siqueira *et al.* 2006), and may help to determine the nerve fibres affected.

The purpose of report is to describe a standardized protocol, with orofacial, clinical and sensory examinations, and histological examination of dental tissues in two patients with a preliminary diagnosis of HSRN type V.

Reports

Two adult siblings (one male of 22 years and one female of 16 years) with insensitivity to pain, and a preliminary diagnosis of HSRN type V, were referred to our pain service for orofacial evaluation. They had a number of dental problems and were seeking dental care. They had been indifferent to pain since birth and had multiple scars all over their bodies, including lips, tongue, oral mucosa, facial skin, feet and hands.

There was no known infectious or metabolic disease associated with the insensitivity,

Table 1 Classification of the hereditary sensory radicular neuropathies (HSRN)

HSRN I	Autosomal dominant; begins in the second through fourth decades of life with a distal loss of pain and temperature sensation that can progress to impairment across all sensory modalities (Nagasako *et al.* 2003). Slow rate of sensory neural transmission and low sensory action potential amplitude (Erdem *et al.* 2000)
HSRN II 'Morvan's syndrome of uncertain cause'	Autosomal recessive, onset in infancy; diffuse impairment of discriminative touch and pressure sensation, with variable involvement of other sensory modalities; severe loss of myelinated fibres with relative preservation of unmyelinated fibres (Nagasako *et al.* 2003). Superior and inferior limbs both affected, mostly in extremities (Person *et al.* 1977). No deep tendon reflex or perspiration is noted. Normal rate of motor neurone transmission in electrophysiological examination (Erdem *et al.* 2000)
HSRN III 'Riley-day syndrome'	Autosomal recessive, onset in infancy; widespread autonomic dysfunction combined with loss of pain and temperature, with difficulties in feeding and incidents of elevated body temperature, diarrhoeal attacks, fungiform papillae absent and Ashkenazic Jewish ancestry. Severe loss of unmyelinated fibres but not total absence of large-diameter myelinated fibres (Erdem *et al.* 2000, Nagasako *et al.* 2003)
HSRN IV 'Congenital insensitivity to pain with anhidrosis'	Autosomal recessive; pain insensitivity and autonomic deficits are present, touch and pressure sensitivity are unimpaired; mental retardation. Absence of unmyelinated fibres and losses of small myelinated fibres. Absence of epidermal innervation and loss of most dermal innervation, sweat glands with no innervation (inability to sweat) (Person *et al.* 1977, Nagasako *et al.* 2003). Hypotonic without any tendon reflexes, and neuromotor development retarded (Erdem *et al.* 2000). Mutation and polymorphisms in the TRKA gene on chromosome 1 that encodes the receptor tyrosine kinase for nerve growth factor (NGF) (Mardy *et al.* 2001)
HSRN V	Autosomal recessive (Karkashan *et al.* 2002), onset in infancy. Unaffected proprioception and sensitivity to touch, pressure, and vibration. Variable autonomic manifestations. Severe loss of small myelinated fibres with possible decrease in the number of unmyelinated fibres. They were considered cases of congenital indifference to pain before the ability to assess peripheral nerve morphology (Nagasako *et al.* 2003). Muscular rigidity, deep tendon reflexes are intact; mechanoreceptor and cutaneous neural junctional action potential are normal (Erdem *et al.* 2000)

and they presented no sweating abnormalities. Their parents, two brothers and one sister had no sensory abnormalities. The male patient and the parents of the female patient gave informed consent for a complete examination, including biopsies. Evaluation included, in summary:

- Clinical history and examination.
- Radiographic examination.
- Quantitative sensory tests (superficial sensitivity and gustative and olfactory examinations).
- Histological examination of dental tissues.
- Treatment of dental disease.

The standardized protocol

A standardized protocol was applied to both patients by a trained and calibrated dentist (Siqueira *et al.* 2006). This consisted of

1. The Orofacial Pain Clinic protocol (EDOF-HC) (Siqueira *et al.* 2004); a standardized orofacial pain questionnaire to detail: (a) chief complaint; (b) general pain characteristics when reported (location, intensity, quality, duration and worsening); (c) headache and body pain complaints; (d) medical history; and (e) evaluation of cervical, cranial, facial, dental and other oral structures. Routine orthopantomography was performed in both patients.

2. Clinical and quantitative sensory tests of face, teeth and oral mucosa (Siqueira *et al.* 2006). The face was divided in six areas, bilaterally (Fig. 1) and was evaluated by

(i) pinpricks for superficial pain evaluation with a digital device (IITC Life Science Electronic Anesthesiometer, Woodland Hills, CA, USA);

(ii) vonfrey filaments for superficial tactile evaluation with a digital device (IITC Life Science Electronic Anesthesiometer);

(iii) pen with a superficial plan area of 1 mm^2 for superficial facial hot and cold evaluation, and thermal examination of teeth with a digital device developed at the Functional Neurosurgery Division, Hospital das Clínicas, Medical School, University of São Paulo (dental results are outlined on Table 2).

(iv) electronic pulp tests (Endo Analyzer Model 8001; Sybron, Orange, CA, USA). Results are presented in Table 2.

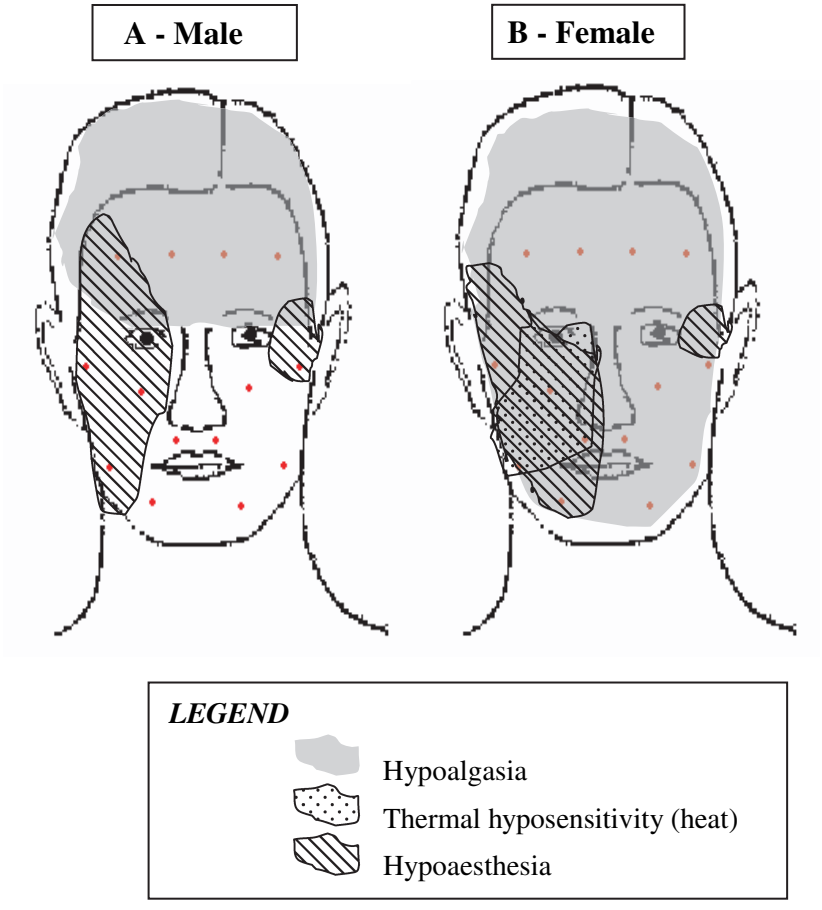

Figure 1 Facial sensitivity maps of the male and the female patient. Hypoalgesia was more extensive in the female patient (b); there was no involvement of the maxillary and mandibular trigeminal branches in the male patient (a); Case 1 did not present abnormalities in cutaneous cold and heat sensitivity. Hypoaesthesia in both was mainly in V2 and V3 territories, and mostly on the right side.

Table 2 Thermal and electrical sensitivity of the teeth

	Male patient	Female patient
Cold pain sensitivity	Teeth: 24, 32, 33, 41, 42, 44, 45, 47	Negative for all teeth Cold sensation without pain: teeth 11, 12, 15, 17, 22, 24, 26, 31, 32, 33, 34, 35, 41, 42, 43, 44, 45, 47
Heat pain sensitivity	Teeth: 23, 24, 31, 32, 33, 41, 42, 43, 47	Negative for all teeth
Electrical sensitivity	Negative: teeth: 12, 23, 43, 44, 45, 48 Positive (higher value than expected): teeth: 13, 31, 34, 41, 42 Positive (expected value): teeth: 15, 24, 32, 33	Negative for all teeth

(v) Gustative tests: different substances were applied in aqueous solution to the tongue, beginning with the smaller Molar concentration (Bartoshuk 1989): glucose (0.01, 0.032, 0.1, 0.32 and 1.0 mol L^{-1}) for sweet, sodium chlorate (0.01, 0.032, 0.1, 0.32 and 1.0 mol L^{-1}) for salty, citric acid (0.00032, 0.001, 0.0032, 0.01 and 0.032 mol L^{-1}) for sour, and urea (0.1, 0.32, 1.0, 3.2 and 10.0 mol L^{-1}) for bitter.

(vi) Olfactory tests: different concentrations of isopropanol were held at the nasal aperture for the olfactory threshold perception, beginning with the lower dilutions (0.09%, 2.59%, 7.78%, 23.33% and 70% of aqueous solution) (Cain 1989).

Clinical findings

The male patient had a history of painless facial trauma during a fight, with bone and tooth fractures, facial scars, and loss of tooth 11 (removed by the patient without pain) (Fig. 2a). He reported a headache 'when he was too much worried' (*sic*). He asked for local anaesthesia during dental treatment and reported severe toothache in his maxillary and mandibular posterior teeth. Since he also presented several past painless traumas and pain indifference in other regions of his body, a neurologist performed a biopsy of the sural nerve, and a reduced number of sensory nerve fibres was observed. He had gross crepitation of the left TMJ, but opening was not restricted. Orthopantomography revealed multiple residual dental roots and caries in many remaining teeth (Fig. 3a).

The female patient reported no need for local anaesthesia during previous dental treatment which had been painless. She also underwent biopsy of the sural nerve, and the number of sensory nerve fibres was reduced. Recently, she had experienced an 'itching' sensation from tooth 37. Clinical features are shown in Fig. 2b. A mandibular computarized tomography (CT) scan was taken with the purpose of clarifying the nature of diffuse radiolucy adjacent to tooth 37, which had extensive caries, dental pulp necrosis and apical periodontitis extending close to the mandibular canal. There was also deep caries in tooth 15, and smaller lesions elsewhere (Fig. 3b,c).

Sensitivity evaluation

The male patient presented hypoalgesia in the area corresponding to the ophthalmic branch of the trigeminal nerve (V1) bilaterally, and normal sensation in V2 and V3 distributions intra and extra-orally. There was normal thermal cutaneous sensitivity (cold and heat) in all branches; preserved corneal reflex bilaterally; hypoaesthesia mostly on the right side and insensitivity to pain stimuli during the evaluation with pinpricks in all three trigeminal branches bilaterally (Fig. 1a).

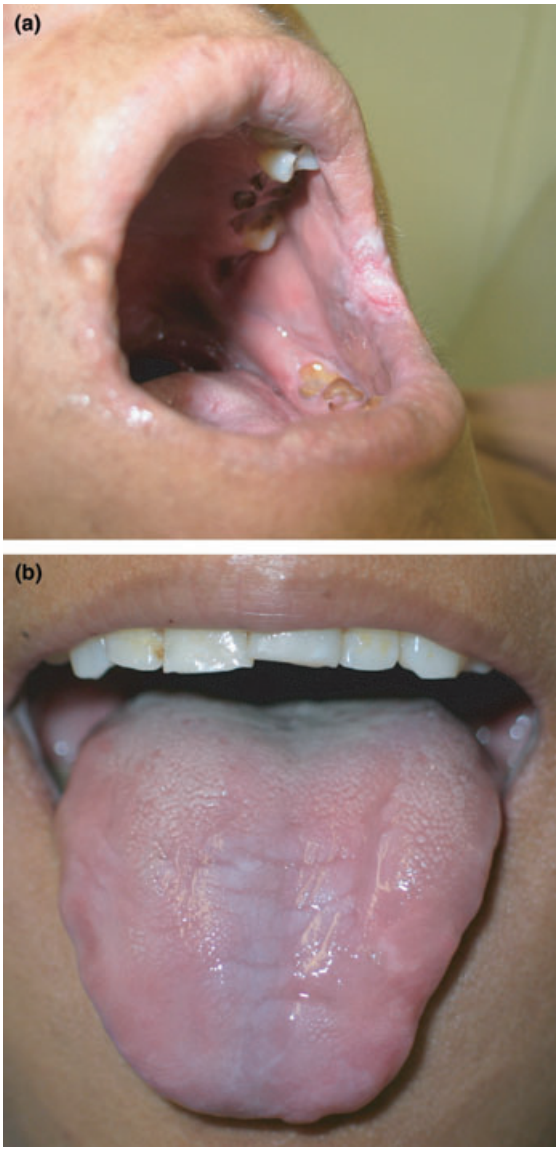

Figure 2 Multiple painless traumatic injuries. (a) Involvement of lips and mucosa of the male patient. (b) Lesions mainly on dorsum of the tongue, which was depapilated in the female patient.

The female patient had hypoalgesia in the distribution of all trigeminal branches intra and extraorally, normal cutaneous sensitivity to cold bilaterally, loss of thermal sensitivity to heat in V2 and V3 on the right side, preserved corneal reflex bilaterally, absence of gustative and olfactory abnormalities, hypoaesthesia in V2 (right side); insensitivity to pain in all trigeminal branches bilaterally (Fig. 1b). There were no gustative or olfactory abnormalities in either patient.

Dental treatment

Following clinical and radiographic examination, the following dental treatment was performed.

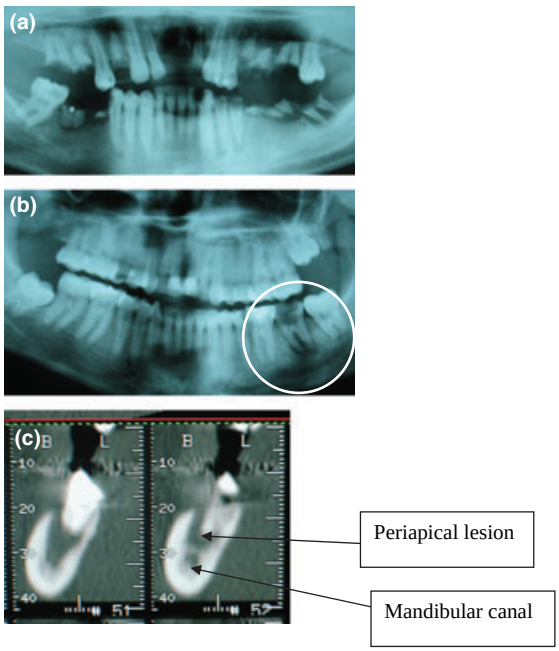

Figure 3 (a and b) Orthopantomography of the patients: (a) The male patient presented residual dental roots and extensive caries. (b) Tooth 37 of the female patient presented extensive caries with pulp necrosis and apical periodontitis. (c) Mandibular tomography of the female patient: the periapical lesion of the tooth 37 extended close to the mandibular canal.

Male patient

Extraction of teeth 15, 16, 17, 21, 22, 25, 26, 27, 36, 37, 46, under local anaesthesia and root canal treatment of teeth 34, 35 and 45 (without anaesthesia). During the dental extraction, small specimens of gingival tissue became available for histology. The necrotic state of the pulps in teeth 34, 35 and 45 ruled out histological examinations, and pulp tissue was not removed from the other extracted teeth. He was referred for prosthetic rehabilitation.

Female patient

Root canal treatment of tooth 37 and restoration with composite resin. Pulp exposure occurred during treatment of caries in teeth 15 and 35, and pulpectomy was performed without local anaesthesia or pain. The vital pulp tissue from tooth 35 was subjected to histological examination.

Other findings – histological examination

Histological examination of the number of peripheral sensory nerves in the gingiva of the male patient revealed no gross abnormalities (Fig. 4a). Examination of dental pulp tissue from tooth 35 by immuno-histochemistry with S-100 protein (Prozyn, Sao Paulo, SP, Brazil), and light microscopy revealed a reduced number of sensory nerve fibres (Fig. 4b). Transmission electron microscopy (TEM) showed normal ultra-structure of nerve fibres but a reduced proportion (almost 1 : 1) of unmyelinated (7.722 mm^{-2}) compared with myelinated (5.503 mm^{-2}) fibres (Fig. 4c).

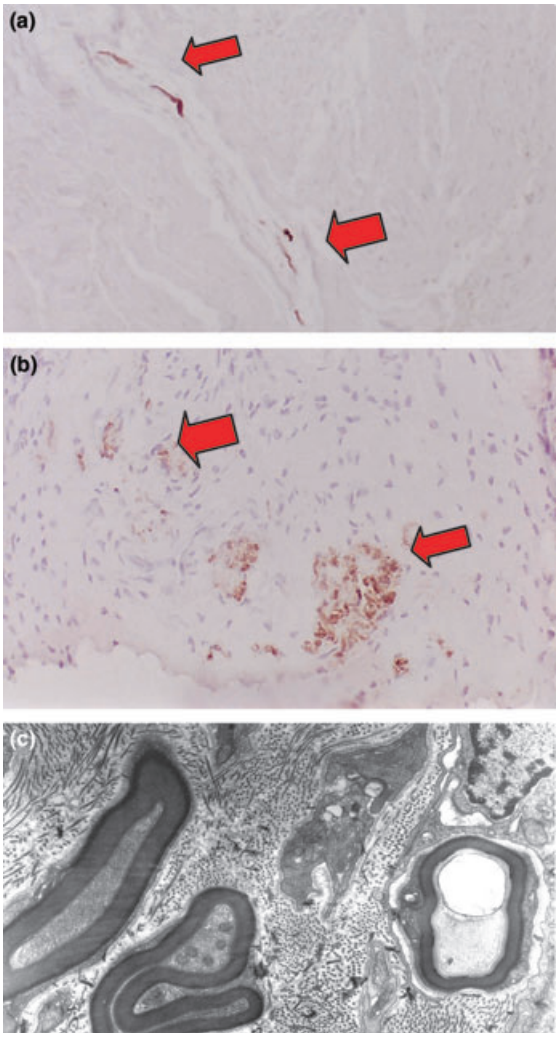

Figure 4 Histological examinations with immuno-histochemistry (S-100 protein) showing diminished nerve fibres: (a) gingival fragment removed during tooth extraction in the male patient; (b) pulp tissue removed after pulp exposure during caries removal in the female patient, tooth 15; (c) TEM from tooth 35 (female patient) showing normal ultra-structure of nerve fibres, but reduced proportion between myelinated (5.503 mm^{-2}) and unmyelinated (7.722 mm^{-2}) fibres.

Discussion

Histochemical and ultra-structural examination of dental pulp tissue from the female patient demonstrated that nerve fibre morphology was normal, but the proportion of unmyelinated relative to myelinated fibres was lower than usually expected in normal dental pulp tissue (Akai & Wakisaka 1990). Similar biopsy results were found in the sural nerve of the same patient (Erdem *et al.* 2000). This is the first report of oral tissue biopsy for level of innervation. Although the male patient also underwent endodontic treatment, the pulps were necrotic, and were inadequate for the histological analysis, but the gingival fragment showed apparently normal nerve fibre morphology and proportions. The female patient presented complete dental, oral and facial insensitivity, while the man presented partial sensitivity, and required local anaesthesia for the treatment. Whether the gross observations on the tissue specimens reflected different conditions is not known.

Both patients had already received preliminary diagnoses of HSRN type V after clinical and microscopic evaluation and the exclusion of infectious or metabolic diseases according to current diagnostic criteria (Person *et al.* 1977, Erdem *et al.* 2000, Nagasako *et al.* 2003).

Hereditary sensory radicular neuropathy must be differentiated from congenital indifference to pain, in which peripheral nerve histology and function is normal (Littlewood & Mitchell 1998, Nagasako *et al.* 2003). Sensory evaluation of these patients could be helpful in quantifying their abnormalities, and diagnosing and classifying their condition, since different clinical sensitivity tests may determine the degree of compromise of each kind of nerve fibre. Evaluating the trigeminal nerve (which is responsible for almost all facial sensitivity), and the dental pulp pain model (which presents almost exclusively nociceptive small diameter C- and Aδ-fibres) (Sessle 2000), by psychophysical methods may produce reliable data and well-defined insensitivity patterns. Electrical tests for dental pulp vitality are mostly negative in HSRN (Chatrian *et al.* 1975), and may be partial, as in the male patient, depending on the subtype of HSRN (Nagasako *et al.* 2003). The absence of nociceptive afferents in dental pulp tissue may result in being more prone to necrosis due to reduced neurogenic inflammation, which may be responsible for vessel-protection after injury (Fazekas *et al.* 1992, Kerezoudis *et al.* 1994). Regular clinical and radiographic review of such patients is necessary to exclude silent infection or inflammatory processes (Rasmussen 1996, Littlewood & Mitchell 1998, Karkashan *et al.* 2002), as with tooth 37 in the female patient. The TMJ abnormalities noted in the male are unusual in a patient of that age and may be related to previous facial trauma. A relationship with HSRN is another possibility, because bone and joint abnormalities are often attributed to painless trauma, and a gene related to HSRN has been described as involved in osteoblastic differentiation (Andria 2001).

The contradictory facts of absence of pain during dental treatment in the female patient and past 'itching' of tooth 37 could eventually be explained by diffuse patterns of some types of HSRN, such as type V. In the male patient, positive results in some dental pulp tests were also evidence of such a mechanism. All teeth in the female patient responded negatively to pulp tests, but the male patient presented different degrees of response, some normal or almost normal, some negative and others hypersensitive. This may show that there are different fibres supplying his teeth.

In evaluating different sensory modalities, small diameter fibres communicating cutaneous thermal sensitivity were not affected in the male but heat sensitive fibres were affected in the female patient. Moreover, the extension of superficial tactile loss was less than that of pain loss, indicating that large diameter fibres may have been less affected than small fibres. The right side was more severely affected in both cases though the explanation for this is unclear.

The fact that the patients were of different gender, but with the same parents, and with siblings free from abnormalities, reinforces the possibility of genetic recessive autonomic aetiology, possibly with variable, non sex-linked clinical patterns. Onset at infancy, genetic influence and loss mainly of small diameter fibres permits classification as HSRN type V.

Hereditary sensory radicular neuropathy is a rare disease, with a few published cases around the world. Its diagnosis is based on clinical findings, and confirmed by histological examination. The objective of this was to propose a model of orofacial investigation for these cases. It is less costly, easier and less invasive than other methods, such as biopsy, and could be useful to help in the diagnosis of such patients.

Conclusions

In conclusion, according to the methodology used.

- Patients with HSRN may present with significant, silent dental disease.

- A standard protocol is helpful in evaluating such patients.
- If the opportunity arises, evaluation of pulp tissue may reveal an altered proportion of myelinated and unmyelinated nerve fibres. This may avoid the more estabilished sural nerve biopsy.

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