Appendix e-3

Differential diagnosis of trigeminal neuralgia

Trigeminal Neuralgia (TN) is distinct from other craniofacial neuralgias by its strict distribution within the innervation territories of the trigeminal nerve branches. There is little anatomical overlap with the innervation by glossopharyngeal nerve, the intermedius branch of the facial nerve or occipital nerves. The unique paroxysmal character of TN and evidence of trigger zones or manoeuvres further exclude alternative causes of orofacial neuropathic pain or nociceptive pain caused by a disease primarily involving the jaw, temporomandibular joints or teeth, eyes, ears, nose or throat.

Herpes zoster and postherpetic neuralgia. Herpes zoster develops in the trigeminal innervation territory in a quarter of the patients. The acute pain preceding or directly associated with the rash is typically constant, but approximately 30% of the patients report superimposed paroxysmal pain.[1] Skin lesions and spontaneous resolution in the majority of patients allow for easy differentiation from TN except for rare cases without a rash (*sine herpete*). These patients may pose a diagnostic challenge if they develop chronic postherpetic neuralgia (PHN). However, patients with trigeminal PHN typically complain of continuous burning pain and mechanical allodynia that affects skin areas larger than the trigger zones. They typically also exhibit sensory deficits.[2,3] Unlike TN, PHN is distributed in the ophthalmic branch of the trigeminal nerve more often than in the second or third divisions of the nerve.[4,5]

Painful trigeminal neuropathy. Trigeminal neuropathy caused by a connective tissue disease or hereditary disorders is usually bilateral but may begin asymmetrically and occasionally present with paroxysmal pain similar to TN.[6,7] Indeed trigeminal neuralgia may be the first symptom of an underlying connective-tissue disease.[8,9] The patients will eventually develop bilateral sensory deficits and continuous pain, which clarifies the diagnosis. MRI is normal, but trigeminal reflexes are invariably delayed or absent.[7]

Pain following trigeminal nerve trauma. Facial trauma, dental procedures, or maxillofacial surgery may damage branches of the trigeminal nerve. Sometimes these focal neuropathies present with episodes of paroxysmal stabbing or burning pain. The pain attacks are usually longer than those associated with TN and most patients also describe continuous pain.[10,11] The trauma or the

intervention should not escape medical history. Abnormal findings in quantitative sensory testing and neurophysiological tests support the diagnosis of traumatic trigeminal neuropathy.[12]

SUNCT/SUNA. The latest International Classification of Headache Disorders[13] classifies SUNCT (short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing) and SUNA (short-lasting unilateral neuralgiform headache with cranial autonomic symptoms) as trigeminal autonomic cephalalgias. However, the paroxysmal character of the pain associated with these conditions has prompted speculation that they are in fact neuralgias and variants of TN.[14,15] However, there are clear phenotypic differences between the two conditions and TN. Pain attacks last 5–240 seconds in SUNCT and between 2 seconds and 10 minutes in SUNA. Unlike the pain paroxysms associated with TN, the pain typically involves the eye and periorbital part of the face. The pain may be triggered by innocuous stimuli,[16] but a refractory period between paroxysms is very rare.[17] MRI shows neurovascular contact of the trigeminal nerve root in 17% of the patients, who may benefit from microvascular decompression.[18] Autonomic features are defining criteria for SUNA and SUNCT and include eyelid edema, lacrimation, conjunctival injection, nasal congestions and rhinorrhea. Mild ipsilateral autonomic symptoms, e.g., tearing, are reported by 21% to 31% of patients with TN, whereas marked signs of autonomic nervous system involvement as it is seen in SUNA and SUNCT are rare.[11,19]

Cluster-*tic*. Opinions on cluster-*tic* are divided. Cluster-*tic* may represent a subtype of trigeminal autonomic cephalalgia, which occurs in approximately 5% of patients with cluster headache.[20] Other investigators argue that cluster-*tic* results from a coincidence of cluster headache and TN and does not constitute an independent clinical entity.[21] Patients typically report periods of paroxysmal pain that follow a temporal pattern similar to cluster headache. As in TN, the pain may be triggered by distinct stimuli. Autonomic signs such as tearing or reddening of eye and face, which are pathognomonic for cluster headache, may be minimal or absent. The only feature differentiating cluster-*tic* from TN is indeed the particular pattern of symptomatic periods.

Non-neuropathic, non-neurological pains. TN may mimic dental pain, and up to a quarter of patients with TN will initially consult a dentist.[22] It is noteworthy though, that even intraoral TN is never located in a tooth.[23] And unlike dental pain, TN is not evoked by heat. Unfortunately, some dentists are not familiar with the differential diagnosis of TN.[24] Dental pain is in fact the most common misdiagnosis of TN, resulting in unnecessary removal of teeth in up to 48 % of patients.[19,22,25,26] Dental pain, e.g. from acute pulpitis, can present with extremely painful attacks that

occur either spontaneously or triggered by thermal stimuli or chewing, should be ruled out be a dentist or orofacial pain specialist.

Atypical odontalgia, also termed persistent dentoalveolar pain, is non-paroxysmal pain in a tooth or the jaw that is not explained by dental or bone pathology.[27,28] Most patients report persistent, moderately intense oral pain that frequently starts after a dental procedure, e.g., a tooth extraction. Atypical odontalgia does not resemble the paroxysms of pain in TN.

Temporomandibular disorder (TMD) is a common cause of orofacial pain. TMD typically produces bilateral pain, but when it starts on one side of the face and occurs episodically, it may raise the suspicion of TN. However, the pain is located around the temporomandibular joint and jaw muscles area and usually extends outside the trigeminal territory. It is mostly a diffuse, dull pain that lasts for hours.[29,30] TMD is not associated with trigger zones.

Pain secondary to obstruction of a salivary duct has a colic rather than paroxysmal character, and is always linked to eating. It is usually of aching character. Palpation of a tender, swollen parotid or submandibular gland typically reveals the cause without the need to perform a sialography.

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