Glossopharyngeal Neuralgia as Onset of Multiple Sclerosis

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Objectives and Methods: Glossopharyngeal neuralgia is a painful condition, affecting the ninth cranial nerve, rarely described in the course of multiple sclerosis. Here we describe a case of multiple sclerosis presenting with glossopharyngeal neuralgia.

Results and Discusion: We suggest the presence of demyelinating areas at the nerve root entry zone as principal trigger mechanism.

Key Words: glossopharyngeal neuralgia, multiple sclerosis, facial pain, demyelinization, ephaptic transmission

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Pain is a common problem of persons with multiple sclerosis (MS), the most common central nervous system demyelinating disease, and it has been recently recognized as an important factor in their overall health-related quality of life.[1,2] Nevertheless, estimates of pain prevalence can vary widely from 29% to 86% lifetime, whereas at the onset of disease its prevalence ranges from 11% to 23%.[3] One of us (P.B.C.) already found that 57% of MS patients reported pain syndromes at some time during the MS course, whereas 21% reported pain as a symptom at onset of MS.[4] The type of pain more frequently affecting MS patients are headache (12% to 22%), back pain (10% to 16%), Lhermitte sign (9% to 13%), and trigeminal neuralgia (TN; 1% to 2%).[3] In contrast, glossopharyngeal neuralgia (GPN), a condition originally described in 1910,[5] represents a rarer manifestation of pain during MS.

The glossopharyngeal nerve exits the brainstem out from the sides of the upper medulla. It supplies motor fibers to stylopharyngeus muscle and it contributes to the pharyngeal plexus. It also supplies parasympathetic fibers to the parotid gland through the otic ganglion. Finally, it receives sensory fibers from the posterior one-third of the tongue, tonsils, pharynx, middle ear, and carotid sinus.

GPN is characterized by recurring attacks of severe pain in the back of the throat and tongue, in the area near the tonsils, and part of the ear. Pain lasts for seconds to minutes in duration. Attacks may be triggered by particular actions, such as chewing, swallowing, talking, coughing, or sneezing. In some cases, even sudden movements of the head or raising the arm on the side of the pain could precipitate GPN.[6] It affects the left side more frequently and symptoms usually begin in people above the age of 40 years,[7] with a peak-age at onset between 40 and 60, and left-side involvement predominates in females.[6] With time, the features of pain may become more atypical, with greater areas of more enduring and dull pain and occasionally bilateral, rarely on both sides simultaneously. As regard the natural history of GPN, patients can experience a remission of pain, even though clusters have an irregular course.[8]

In the general population, incidence of GPN seems to be 0.7 per 100,000/y (0.9 in men and 0.5 in women),[9] 0.7% to 1.0% of that of TN.[10] GPN has also been rarely described in the course of MS; in MS patients, its incidence is about 0.5 per 1000, in contrast to that of TN, which has an incidence of 40 per 1000.[11] GPN may be associated with TN, accounting for 8% to 11%.[8]

Treatment of pain in MS icludes the use of anti-epileptic drugs, muscle relaxers/antispasmodic agents, and anti-inflammatory drugs. Minagar and Sheremata[11] reported 4 cases of MS complicated by GPN. Relief of symptoms was obtained after the administration of carbamazepine, 1000 mg daily.

In our study, we describe a case of MS presenting with GPN. The appearance of GPN as onset of the pathology is an original description. The patient, a 41-year-old woman, came at our observation at the Department of Neurological Sciences of the University of Naples "Federico II," Naples, Italy. She described paroxysm of excruciating, knife-like pain, referred to back of the tongue, pharynx, and part of the ear, exclusively to the left side. Each paroxysm started or worsened with swallowing, coughing, brushing her teeth, or eating and usually lasted for seconds to a few minutes. After each episode, there was usually a refractive period during which stimulation of the trigger zone did not induce pain. The attacks occurred several times a day and had started 1 month earlier. An otolaryngologist concurred with a diagnosis of GPN. She had no history of previous diseases, except for blood hypertension treated with nifedipine 30 mg/d. Neurologic examination was normal. The brain gadolinium-enhanced magnetic resonance imaging (MRI) scan, performed to investigate the causes of GPN, showed some small rounded areas of increased signal on T2-weighted images in the centrum semiovale and periventricular regions. MR angiography (MRA) of the cerebellopontine angle had been also performed and revealed no pathologic elements. Blood tests were normal.

We treated our patient with carbamazepine (up to 800 mg/d) with partial relief of pharyngeal pain after 30 days from the beginning of treatment. Three months later, the patient spontaneously reduced the dosing of carbamazepine with the reactivation of pain, which responded to the rechallenge with therapy. After 6 months, the patient developed weakness in the left leg and widespread paresthesia. Neurologic examination revealed paraparesis with brisk tendon reflexes in the legs, especially in the left one, with a clear extensor plantar response; the expanded

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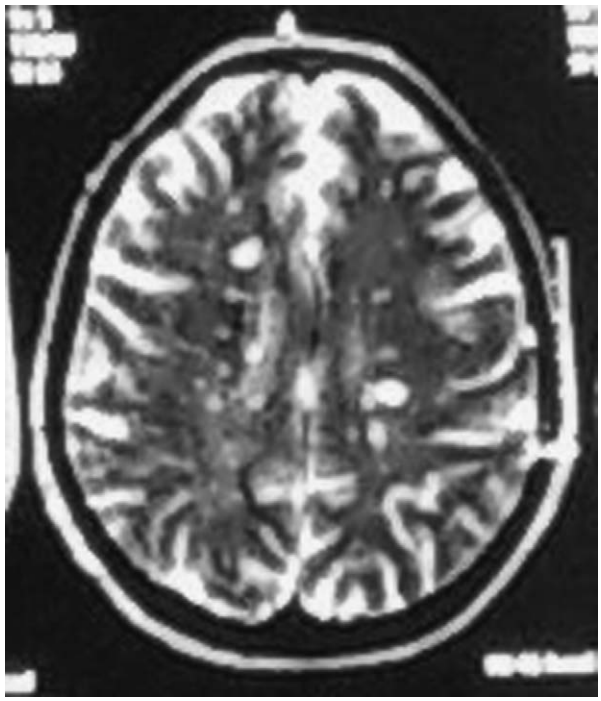

FIGURE 1. Magnetic resonance imaging scan of multiple rounded demyelinating areas in the white matter of the periventricular regions and in the centrum semiovale in a T2-weighted image.

disability status scale was 3.5.[12] A new MRI showed further demyelinating lesions on T2-weighted scans in the centrum semiovale, periventricular regions, white matter of left temporal lobe (Fig. 1), and dorsal spine (Fig. 2), with enhancement after intravenous injection of gadolinium. Cerebrospinal fluid (CSF) examination showed normal glucose, protein, and cell count, but oligoclonal bands were present (Fig. 3). Albumin and IgG in the CSF and serum were measured with Behring Nephelometer analyzer (Dade Behring, Germany).

The method we used for the detection of oligoclonal bands is isoelectric focusing (IEF), performed as previously described by Keir et al.[13] Briefly, IEF gel was prepared with IEF agarose, Pharmalyte pH 3 to 10, and Pharmalyte pH 8 to 10.5 (Amersham Biosciences); and focusing was performed on a Multiphor II apparatus (Amersham Biosciences). The electrode strips were soaked with 1M NaOH and 0.05M SO_4H_2, and paired serum and CSF samples (3 μL) were applied on the anodic side of the gel. After focusing, the proteins were transferred to a nitrocellulose membrane (Millipore). The membrane was then incubated with alkaline phosphatase-conjugated rabbit antihuman IgG and, finally, stained using nitro blue tetrazolium and bromo-chloro-indoleyl phosphate. We made diagnosis of MS according to McDonald et al[14] criteria.

A trial of intravenous methylprednisolone (1000 mg/d for 3 d, followed by 500 mg/d for 2 d) resulted in relief of the patient's neurologic symptoms, including GPN. After 1 month, the patient started the β-interferon-1a (Rebif 44 3 times weekly) treatment to prevent further relapses. To date, after 12 months from the beginning of treatment, the patient shows no relevant neurologic alterations and no GPN.

FIGURE 2. Magnetic resonance imaging scan of dorsal spine: a small rounded demyelinating area in a T2-weighted image.

GPN has different causes, but, in some cases, the source of irritation of the ninth cranial nerve is not found. The most common causes of GPN are vascular compression of nerve roots entering the lateral medulla or neck tumors. In particular, vascular compression is thought to cause pain through demyelination and ephaptic transmission.[15] To find out whether a blood vessel is pressing on the nerve, pictures of the brain arteries may be taken using the MRA or conventional angiography. GPN can also be related to a neoplasia injuring the glossopharyngeal nerve in the neck or in the skull base, such as medullary, laryngeal, or nasopharyngeal cancer. To identify tumors at the base of the skull, computed tomography or MRI scan of the head might be performed.

In our patient, MRA was normal and MRI showed no tumors; therefore, the cause of GPN could be related to a demyelinating plaque next to the nucleus of the ninth nerve—too small to detect—or, especially, in the nerve root entry zone. Also Paty and Ebers[16] hypothesized that the potential cause of the closely related TN in MS patients could be appearance of demyelinating plaques at the root entry zone of the trigeminal nerve. Our hypothesis was supported by other studies, as well, demonstrating how frequent and underrated is cranial nerves involvement in

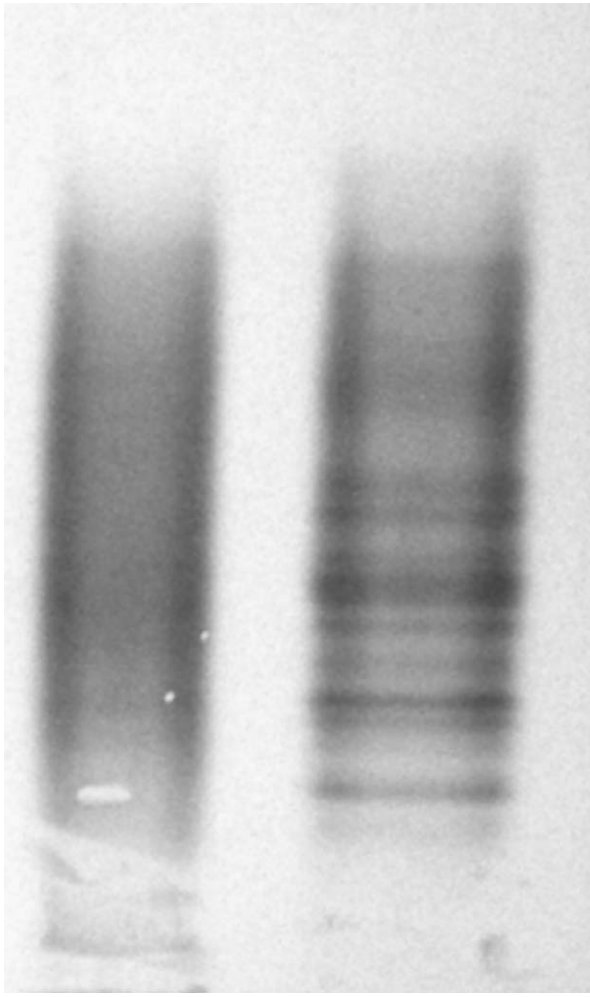

FIGURE 3. Isoelectric focusing in agarose gel. Presence of oligoclonal bands in cerebrospinal fluid (right) but not in serum (left).

MS. Pichiecchio et al[17] showed MRI enlargement of both trigeminal nerves at the root entry zone, with gadolinium enhancement of the cisternal portion in a MS patient with sudden right TN. This is the first description of peripheral involvement of the trigeminal nerve in MS supported by instrumental findings. In addition, Kenner et al[2] suggest that the pathophysiology of GPN in MS may be linked to certain plaque location with the disruption of pain pathways and abnormal impulses through motor axons, or to the development of an acquired channelopathy in affected nerves.

According to our observation, the injury of a cranial nerve as onset of MS seems more frequent. In fact, the involvement of other cranial nerves, such as the sixth, was described as the initial manifestation of MS and related to a demyelinating lesion in the pons.[18,19]

In conclusion, although cranial nerves are very small structure, modern MRI has all options to reveal or rule out their involvement. Therefore, the appearance in healthy people of GPN, even without other neurologic abnormality, justifies a brain MRI examination and also every cranial neuralgia should be depth investigated. In our opinion, demyelinating area at the root entry zone of the glossopharyngeal nerve could be a potential cause of GPN in MS patients, perhaps associated with ephaptic conduction.

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