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Schwannoma of the posterior tibial nerve in a patient with schwannomatosis and a novel mutation of the *LZTR1* gene☆

Schwannoma del nervio tibial en un paciente con schwannomatosis asociada a una nueva mutación en el gen *LZTR1*

Dear Editor:

Schwannomatosis is the third most frequent type of neurofibromatosis, after neurofibromatosis types 1 and 2 (NF-1 and NF-2). The disease is characterised by the presence of multiple non-intradermal schwannomas in the absence of bilateral vestibular schwannomas, and was first described in the 1990s in a clinical-pathological study of patients with multiple schwannomas not meeting criteria for NF-2.[1] Various genetic alterations have since been implicated in the disease; significant examples are germline mutations of the tumour suppressor gene *SMARCB1* and loss-of-function mutations in *LZTR1*; both genes are located on chromosome 22.[2,3] From a clinical viewpoint, schwannomatosis presents a significant overlap with NF-2, which greatly hinders the correct diagnosis of these patients; therefore, genetic studies are an important diagnostic tool in case of uncertainty.[4]

We present the case of a patient with schwannoma of the posterior tibial nerve in whom we detected a novel loss-of-function mutation in *LZTR1*, underscoring the importance of clinical suspicion of this type of disease in specific cases.

The patient was a 54-year-old man with history of schwannoma of the left median nerve, treated surgically; he was receiving enalapril to treat arterial hypertension. The patient visited the neurology department due 3-year history of neuropathic pain in the left heel and plantar surface, in the territory of the posterior tibial nerve. The patient reported no family history of neurological disease,

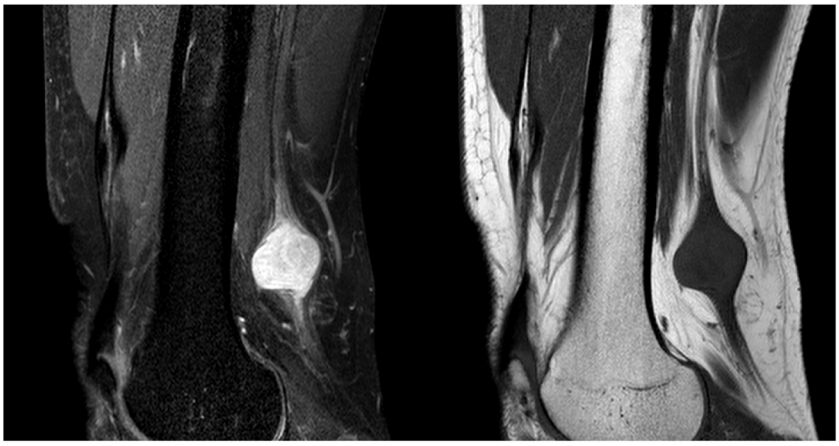

Fig. 1 Fat-suppressed proton density—weighted and T1-weighted sagittal MRI sequences showing a lesion to the superior popliteal fossa, involving the posterior tibial nerve. The lesion is isointense on T1- weighted sequences and presents heterogeneous hyperintensity on proton density—weighted sequences. The entering and exiting nerve can be seen.

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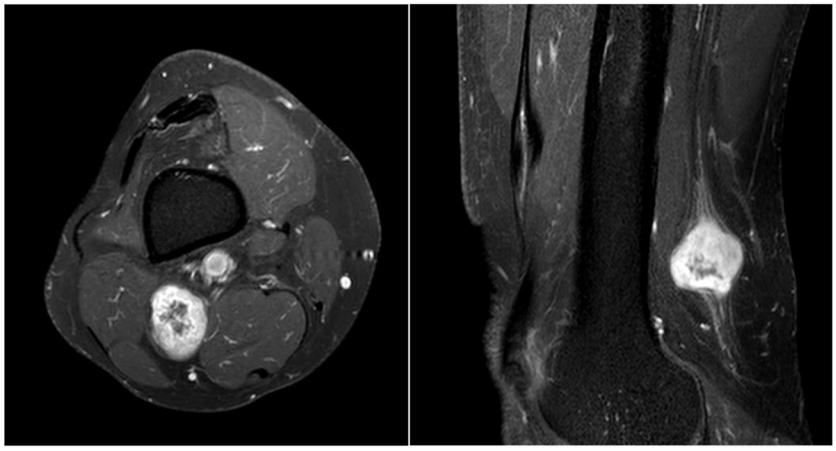

Fig. 2 Fat-suppressed T1-weighted axial and sagittal MRI sequences with contrast administration, showing marked peripheral contrast uptake with heterogeneous central areas not displaying contrast uptake.

and his daughter was healthy. Physical and neurological examination revealed no abnormalities, with negative Tinel sign and no palpable masses in any region. The patient provided an MR image of the lumbar spine and an EMG recording, which showed no relevant alterations, and had been assessed on several occasions by the emergency and traumatology departments, with a clinical diagnosis of non-specific pain in the left foot. Based on clinical suspicion, we ordered an MRI study of the left lower limb, which revealed a tumour involving the initial segment of the posterior tibial nerve (Fig. 1 and 2); an anatomical pathology study performed after resection of the mass confirmed the diagnosis of schwannoma. We also requested a high-resolution brain MRI study focusing on both internal auditory canals, which detected no evidence of vestibular nerve involvement. The patient met clinical criteria for schwannomatosis,[5] but we were unable to rule out NF-2, which has prognostic and therapeutic consequences. For these reasons, and with a view to providing genetic counselling to his family members, we requested a study of the genes *ENG*, *GDF2*, *GLMN*, *GNAQ*, *HRAS*, *LZTR1*, *NF1*, *NF2*, *PIK3CA*, *PTEN*, *SMAD4*, *SMARCB1*, *TEK*, *TSC1*, *TSC2*, and *VHL*. The genetic study revealed that the patient was heterozygous for a previously undescribed *LZTR1* mutation (c.1203C > G) (p-Y401), which results in a premature stop codon; this finding is compatible with diagnosis of *LZTR1*-related schwannomatosis.[3] The alteration was confirmed with Sanger sequencing; the patient's family members have not yet been tested.

This case demonstrates the need to consider atypical or rare causes in patients presenting chronic pain of unknown aetiology; nerve sheath tumours constitute one such cause. Diagnostic delay is common in patients with schwannomatosis due to the rarity of the disease[6] and the non-specificity of its symptoms: pain not associated with a palpable mass is the most common symptom.[7] Furthermore, family history does not usually provide valuable information, as only 13% of patients have family history of the disease.[7] We should also stress the importance of genetic studies for correct diagnosis, as schwannomatosis presents a broad spectrum of phenotypes and is often indistinguishable from NF-2. The latter condition is usually associated with germline mutations, which are detected in over 90% of patients without mosaicism,[4] and presents poorer prognosis than schwannomatosis.[6] Moreover, both entities usually manifest as multiple cranial meningiomas exclusively; this has given rise to controversy about the need to broaden diagnostic criteria to include genetic testing in the basic diagnostic study.[8]

This case report contributes a novel *LZTR1* mutation, expanding the genetic spectrum of the disease.

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Posterior interosseous nerve syndrome as an isolated symptom of haemorrhagic stroke: the central mimicking the peripheral☆

Cuando lo central parece periférico: síndrome del interóseo posterior como manifestación aislada de ictus hemorrágico

Dear Editor:

The term ''pseudoperipheral palsy,'' coined by Jean Lhermitte, refers to weakness predominantly affecting the hand (pseudoulnar, pseudomedian, or pseudoradial nerve palsy)[1] associated with a central nervous system lesion, mimicking a lesion to the peripheral nervous system.[2,3] Pseudoperipheral palsy is rarely caused by ischaemic stroke (< 1% of cases),[2] and association with haemorrhagic stroke is even rarer.

We present the case of an 82-year-old right-handed man with no known vascular risk factors. He went to bed with no symptoms and when he awoke at 03:00 to urinate, he presented lack of coordination in the left hand, with no headache, neurovegetative symptoms, or any other neurological symptoms. He reported no pain or sleeping on the left limb. Upon arrival at our centre, blood pressure was 150/90 mm Hg. The neurological examination revealed weakness (4/5) in extension of the left fingers, thumb, and wrist, and normal strength (5/5) in finger flexion. The biceps, brachioradialis, triceps, and wrist flexor muscles showed normal strength. The intrinsic muscles of the hand and the opponens pollicis, adductor pollicis, and flexor pollicis longus muscles showed normal strength; pronosupination and proximal muscles also showed normal strength. Sensitivity and all other areas of the neurological examination were normal. Although these findings are compatible with posterior interosseous nerve syndrome, we requested a head CT scan given the lack of evident nerve compression and the normal strength of the finger flexors; the study revealed a small haematoma in the right precentral gyrus (Fig. 1). A blood analysis yielded no relevant findings. A brain MRI scan performed 3 months after the event revealed subacute/chronic haematoma in the right precentral gyrus and no intracranial aneurysms, fistulas, or arteriovenous malformations (Fig. 2). The patient was prescribed rehabilitation treatment at discharge; a 3-month follow-up examination revealed improvements in mobility of the distal extensor muscles, with complete functional recovery.

According to the Penfield homunculus model, the cortical neurons that innervate the upper limbs are located in the lower third of the dorsolateral surface of the precentral gyrus, corresponding with Brodmann area 4.[1,3–5] Advances in brain imaging have led to an improvement in the characterisation of the cortical representation of the hand. The hand motor cortex has an inverted omega shape in most cases (90%), with some individuals (10%) displaying a horizontal epsilon shape on the axial plane and a hook shape on the sagittal plane.[3,4] However, finger movement is controlled by a profusely distributed neuronal network, rather than by spatially and functionally separated bundles of neurons.[1]

Our patient presented signs of posterior interosseous nerve syndrome associated with a small haematoma in the precentral gyrus. The literature includes several cases of ischaemic stroke associated with isolated hand palsy without sensory involvement[6,7]; however, the association with haemorrhagic stroke has not previously been reported. In addition to the precentral gyrus, pure motor involvement of the hand may be associated with lesions to the angular gyrus, the ventral posterolateral nucleus of the thalamus, the internal capsule, the corona radiata, and the base of the pons.[8]

Differential diagnosis should include C7 radiculopathy, radial nerve dysfunction, vasculitis associated with hyperacute mononeuropathy, spinal cord disease, hereditary neuropathy with liability to pressure palsy,[7] and atypical lacunar syndromes.[9] Diagnosis of this entity requires a high level of clinical suspicion due to its clinical and therapeutic implications and the non-specificity of examination findings. Sudden onset with no trauma or nerve compression, lack of pain, presence of cardiovascular risk factors, and normal neurophysiological study results may assist in diagnosis.[3,6,7] Synkinetic wrist extension following fist closure is a useful exploratory sign for differentiating central from peripheral radial nerve palsy: a slight elevation of the clenching hand (with the arm held out and palm facing the floor) is observed in patients with central radial nerve palsy, whereas further wrist drop is observed in patients with peripheral radial

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