

Sea wave-induced internal carotid artery dissection

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Internal carotid artery dissection has been associated with trivial trauma.¹ We report a patient with internal carotid artery dissection related to a severe sea wave trauma to the cervical region.

Case report. A right-handed 56-year-old man presented to the emergency room because of a 15-minute episode of dysarthria and left-hand numbness. Earlier that day, he had been in the sea. There was heavy surf with waves that were 0.5 to 1 m high. When he was distracted and with his neck turned to the left, a wave struck him, knocking him over. When he returned to shore, his wife noticed that he was disoriented and confused. These symptoms lasted approximately 30 minutes, and he later presented to the hospital with a transient neurologic deficit (outlined above) and right-sided headache. He never smoked and had no personal or family history of arterial dissection, connective tissue disease, hypertension, or migraine. On neurologic examination at admission, he was alert and fully oriented and had a right ptosis and miosis. The rest of the examination was normal. There were no clinical signs suggesting hereditary connective tissue disease, such as hypermobile joints, other limb and dermal abnormalities, or blue sclera. Complete blood count and routine biochemistry were unremarkable. Head CT was normal. MRI study (fluid-attenuated inversion recovery, diffusion, and T1- and T2-weighted sequences and MR angiography) showed an acute ischemic stroke in the right middle cerebral artery territory and a hematoma in the wall of the right internal carotid artery along with internal carotid artery narrowing, consistent with arterial dissection (figure). The patient was diagnosed with TIA (although there was radiologic evidence of infarction) secondary to a right carotid artery dissection. He was treated with sodium heparin for 7 days and then discharged with oral warfarin.

Discussion. This patient experienced an internal carotid artery dissection probably related to the wave trauma, as there was a clear relationship between this trauma and the onset of the neurologic symptoms.

Traumatic dissection of the internal carotid artery has been described in diverse situations: blunt trauma in road traffic accidents,¹ sports (taekwondo, French horn, kickboxing, softball, etc.),² airbag or seatbelt trauma,^{3,4} and strangulation.⁵ Occasionally, dissection is an incidental finding during radiologic screening of the cervical spine and brain in severely injured patients.⁶

In our patient, the intensity of the injury may have been high, as the patient presented a period of concussion. The energy that a sea wave can produce can be calculated using the formula $E = \frac{1}{2}(\rho g H^2)$, where ρ is the density of the sea water, g is the acceleration of the gravity, and H is the height of the wave.⁷ With this formula, a sea wave of 0.5 m corresponds to energy of approximately 315.4 J/m². This energy is a crude approximation because it would be necessary to introduce multiple modifying factors as part of complex engineering calculations. Whether the dissection is a result of the direct trauma of the sea wave over the anterolateral part of the neck or secondary to a sudden and forced neck twist is not certain.

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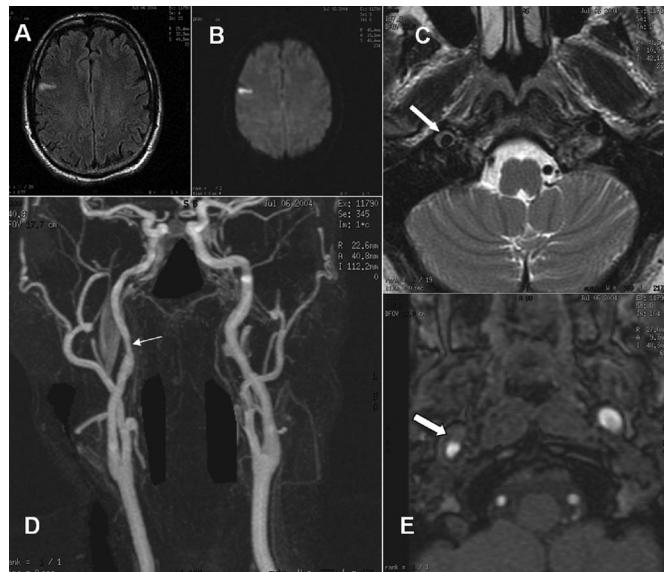


Figure. (A and B) Axial fluid-attenuated inversion recovery and diffusion-weighted sequences showing a middle cerebral artery territory acute ischemic stroke. (C and E) Axial T2 (C) and T1 (E) sequences showing a hematoma (arrows) in the wall of the right internal carotid artery. (D) MR angiography study showing narrowing of the right internal carotid artery.

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Pseudo-ulnar sensory loss in a patient from a small cortical infarct of the postcentral knob

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A wide spectrum of sensory syndromes with different topographic patterns have been described in patients with cerebral infarction.¹⁻⁴ The sensory abnormalities may be limited to small areas, mimicking a radicular or trunk distribution, mainly for lesions in sensory cortex and thalamus.

Case report. A 31-year-old man suddenly had a right arm pain, numbness, and burning sensation on his right forearm and hand, predominant on the ulnar side. He also reported an expressive aphasia that resolved in a few minutes. There was no history of previous strokes. Two hours later, at admission, neurologic examination revealed a full sensory loss for pinprick and temperature modalities restricted to the V digit, the lateral side of the IV digit, the lateral palm, and the dorsal area of his right hand (figure, A and B). Lemniscal sensory modalities were normal. The hypoesthesia strictly coincided with the sensory distribution of the ulnar nerve. Moreover, the patient had a fastidious hyperalgesia for brush, touch, and pinprick stimuli. There was no evidence of motor impairment; specifically, the ulnar-dependent movements were normal. The rest of the neurologic examination was normal.

Noncontrast cerebral CT was normal, whereas a brain MRI performed 3 days later revealed a small ischemic lesion at the level of the midportion of the postcentral gyrus in the territory of a parietal branch of the middle cerebral artery (see figure, C and D). Despite the presence of a notable sensory loss, sensory and motor nerve conduction studies of ulnar, median, and radial nerves were normal. Somatosensory evoked potentials (SEPs) from median and ulnar nerve at the wrist and from the V digit were normal. MRI of the cervical spine was unrevealing.

Conventional vascular risk factors were absent. Carotid and vertebral arteries were normal at duplex ultrasonography and MRI angiography. Transesophageal echocardiography revealed a large patent foramen ovale, with spontaneous flow of >20 microbubbles/beat. Even though lower limb compression ultrasonography failed to reveal deep vein thrombosis and coagulation tests were normal, we hypothesized a paradoxical embolism as stroke mechanism. Seven days later and 4 months after discharge, the

pseudo-ulnar sensory distribution was still present; the hypoesthesia was milder if compared with that at admission, involving mostly pinprick sensation and associated with a marked hyperalgesia.

Discussion. Our patient presented a highly restricted sensory loss in a distribution mimicking the ulnar nerve. At the onset, only a transient expressive aphasia suggested the presence of a cerebral lesion. The sensory loss was restricted to the ulnar side of the hand; the splitting of the IV digit suggested an ulnar rather than a radicular (C8) disease. Notably, the hypoesthesia clearly resembled the sensory pattern observed in the compression of the ulnar nerve at the elbow. In patients with thalamic and cortical infarction, neurologic deficits involving both sensory and motor functions in the distribution pattern of the ulnar nerve have already been described.¹⁻⁴ Unlike several reports on pseudo-ulnar palsy,^{1,2,4} our patient had no impairment of the motor functions of the ulnar nerve.

The evidence of a pseudo-ulnar pinprick and temperature hypoesthesia in a patient with a postcentral infarction raises some questions regarding the underlying pathophysiologic mechanism. It is well known that human primary sensorimotor cortex is organized in an orderly somatotopic way (the so-called "homunculus" described by Penfield and Boldrey).

Several studies on sensorimotor cortex with SEPs have pointed out that cortical representations for the human hand in the postcentral gyrus have a clear somatotopic organization, from medial superior to lateral inferior, in the following order: ulnar nerve, median nerve, and then lip.⁵ The splitting of the IV digit resembling an ulnar distribution suggests that a peripheral nerve representation is already present at the cortical level.

Remarkably, our patient's sensory loss concerned the spinothalamic modalities (pinprick and temperature sensation), while deep lemniscal sensations were preserved. The somatosensory cortex is organized into vertical columns, spanning all six layers from the cortical surface to the white matter; all neurons within a single column receive signals from the same skin area and can be elicited by one modality only (either touch, pressure, temperature, or pain). This happens because anatomically separate pathways convey different somatosensory modalities.⁶ Although each of the four areas of the primary somatosensory cortex (3a, 3b, 1, and 2) receives inputs from all areas of the body surface, one modality tends to dominate in each area.⁷ Moreover, the normality of SEPs is in agreement with the preservation of deep lemniscal sensory modalities, which mostly contribute to the cortical response.

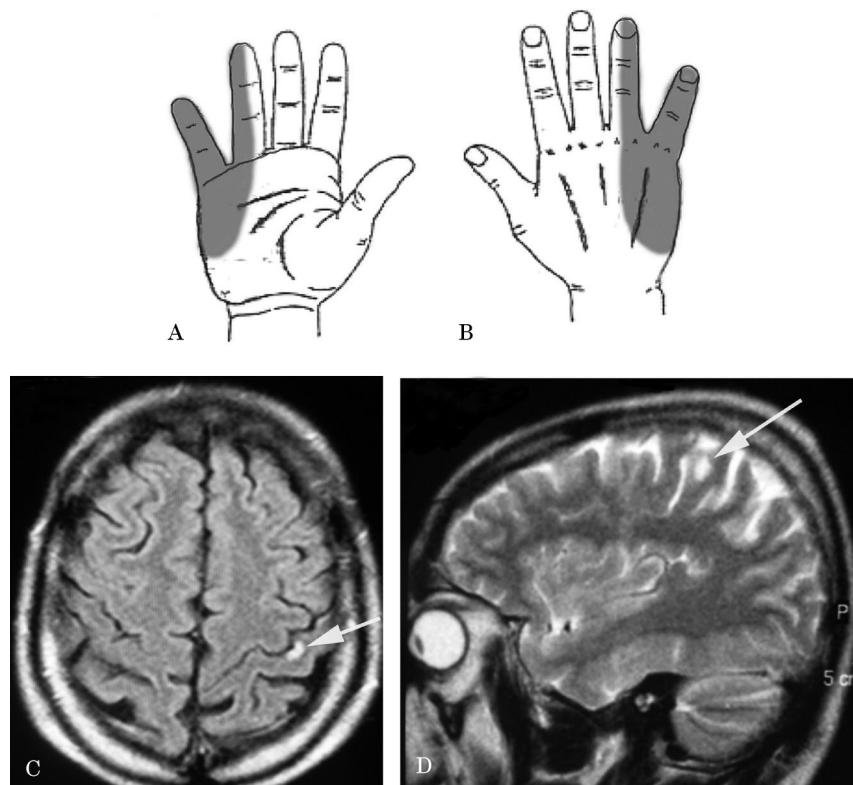


Figure. Neurologic examination of a 31-year-old man with right arm pain, numbness, and burning sensation on his right forearm and hand, predominant on the ulnar side. The examination revealed a full sensory loss for pinprick and temperature modalities restricted to the V digit, the lateral side of the IV digit, the lateral palm, and the dorsal area of his right hand (A and B). Noncontrast cerebral CT was normal, whereas a brain MRI performed 3 days later revealed a small ischemic lesion at the level of the midportion of the postcentral gyrus in the territory of a parietal branch of the middle cerebral artery (C and D).

Our case highlights the importance of suspecting cerebral ischemic lesions in patients with peripheral sensory loss when neurophysiologic investigations are normal.

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Seizures following reduction in phenytoin level after orally administered folic acid

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Phenytoin reduces folate levels and may be responsible for the development of a macrocytic anemia. This may be avoided by prophylactic administration of folic acid to patients with seizure who will be on long-term anticonvulsant treatment. The relationship between folate and phenytoin metabolism, however, is a dual and interdependent one and the addition of folic acid to a stable anticonvulsant regimen predictably lowers serum phenytoin levels.¹ We report a case of recurrent seizures in a patient after the addition of folic acid for treatment of macrocytic anemia. The reduction in drug levels was substantial and resulted in several seizures in a patient previously well controlled.

Case reports. A 52-year-old man was admitted to the hospital for repair of an acute hip fracture. There was a history of cerebrovascular disease complicated by stroke, hemiparesis, and generalized tonic-clonic seizures. He had been free of seizures for the 3 years previous to admission and all outpatient phenytoin levels were consistently between 12 and 18 µg/mL on a stable regimen of 300 mg/day. He did not consume alcohol. Three weeks before admission, his serum level was 12.4 µg/mL. At the time of initial hospital evaluation, a mild macrocytic anemia was noted with Hgb 12.1 and MCV of 104. The patient was started on five mg of oral folate and his usual daily phenytoin dose of 300 mg/day was continued. An interview with his caretaker confirmed that no doses of phenytoin had been missed and the patient consumed no alcoholic beverages. On preoperative evaluation the patient's cardiopulmonary status was judged to be normal as was hepatic function on laboratory testing. The only other new medication administered was morphine for pain control. The following day he had a grand mal seizure with full recovery in 45 minutes. A phenytoin level was 4.5 µg/mL. He was given 500 mg of fosphenytoin with continued oral dosing of 300 mg/day. His level 18 hours later was essentially unchanged (4.8 µg/mL) and he had another generalized tonic-clonic seizure. One gram of fosphenytoin was then given and the folic acid dose was reduced to 1 mg per day. All further seizure activity was suppressed and phenytoin levels were measured at 17.6 µg/mL the following day. A subsequent prednisone trough level 24 hours later was 11.3 µg/mL on 1 mg of folic acid and 300 mg of phenytoin per day.

Discussion. Folate has been shown to be a coenzyme necessary for red blood cell development, normal gastrointestinal integrity, and maintenance of normal neurologic function. Proposed mechanisms by which phenytoin causes a decrease in serum and RBC folate levels include decreased gastrointestinal absorption of folate with impairment of folate transport in tissues² and depletion due to phenytoin induced increase in hepatic metabolism.³ New, lowered, steady state folate levels occur within 2 to 3 weeks of the initiation of phenytoin.

The impact of adding folic acid to a stable phenytoin regimen in an effort to correct folate deficiency is often underestimated. A

number of studies have investigated the effect of folic acid on serum phenytoin concentrations. The mean decrease in total serum phenytoin after the addition of 1 mg of folic acid in four folate-deficient men aged 30 to 43 years was 20.6% on day 15 in one study⁴ and in a second study of seven folate-deficient men, there was a similar 22.6% drop in phenytoin levels.⁵ Literature review suggests that the effect of 5 mg of oral folic acid (the dose our patient received) will result in a 39.1% drop in drug levels.⁶ Pharmacokinetic studies of this interaction strongly suggest that folic acid is a cofactor in the metabolism of phenytoin. While the effect that folic acid has on the nonlinear and dose-dependent pharmacokinetics of phenytoin is cumbersome to delineate, several authors have demonstrated significant changes in the Michaelis-Menton parameter (K_m) for phenytoin when folate levels were manipulated.^{5,7} Higher levels of folate appear to increase the affinity of metabolizing enzymes thus greatly increasing the efficiency of phenytoin degradation.

Our case is a vivid reminder that the relationship between folic acid and phenytoin is a dual and interdependent one. The use of folic acid in clinical medicine has increased dramatically in recent years, underscoring the need to disseminate this pharmacologic relationship. Clinicians adding folic acid to the regimens of folate deficient patients should make anticonvulsant adjustments that anticipate significant reductions in phenytoin concentrations and potential loss of seizure control.

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Familial polyneuropathy with anti-myelin-associated glycoprotein antibodies

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We describe the occurrence of the anti-myelin-associated glycoprotein (anti-MAG) syndrome, a well-recognized variant of chronic inflammatory demyelinating polyneuropathy (CIDP) with distinct clinical and electrophysiologic characteristics, in two brothers.

Case 1. A 70-year-old man presented with symmetric numbness distal to his knees, followed by progressive imbalance and gait unsteadiness that developed over 2 years. His similarly affected brother is described below (Case 2); there was no other relevant family history. On examination he had mild distal weakness in both lower limbs and symmetric vibration and proprioceptive loss distally in all four limbs. Muscle stretch reflexes were absent. Gait was severely ataxic and Romberg's sign was present. Nerve conduction studies revealed a severe demyelinating polyneuropathy with disproportionate distal slowing, prolongation of F waves without evidence of conduction block, and met criteria for CIDP.¹ Immunoglobulin M (IgM) kappa monoclonal gammopathy was identified; IgM was 235 mg/dL (normal, 50 to 200 mg/dL) of which 50% to 90% was monoclonal and anti-MAG reactivity was positive at a titer of 35 U/L (normal, <16 U/mL; Focus Technologies Inc., Cypress, CA). CSF analysis revealed an elevated protein of 92 mg/dL (normal, <45 mg/dL) with no cells. Genetic tests for hereditary motor sensory neuropathy type 1A and 1B were negative as was connexin 32 DNA sequencing (Athena Diagnostics, Worcester, MA). The patient received plasma exchange and IV immunoglobulin with no sustained benefit. Rituximab (375 mg/m² weekly for 4 weeks) led to an improvement of his gait: the modified Rankin disability scale improved from 4 (moderate-severe disability) to 3 (moderate disability). The patient has received rituximab (375 mg/m² weekly for 4 weeks) at 6 monthly intervals for 2 years.

Case 2. The 72-year-old older brother of the first patient developed numbness and mild bilateral lower-limb weakness over 2 years. On examination, he had bilateral foot dorsiflexor weakness with prominent vibration and proprioceptive loss in the distal lower limbs. Muscle stretch reflexes were absent. His gait was wide-based and ataxic and Romberg's sign was present. He had mild disability, graded on the modified Rankin Scale as 2. EMG revealed a severe demyelinating polyneuropathy with disproportionate distal slowing, prolongation of F waves without evidence of conduction block, and met criteria for CIDP.¹ An IgM kappa monoclonal gammopathy was identified with total IgM of 638 mg/dL (normal range: 40 to 230 mg/dL). Anti-MAG reactivity was positive at a titer of 1:25,600 (normal <1,600, Athena Diagnostics). CSF protein was 61 mg/dL (normal, <45 mg/dL) with no cells. Genetic tests for hereditary motor sensory neuropathy type 1A and 1B and connexin 32 DNA sequencing were negative (Athena Diagnostics). A sural nerve biopsy demonstrated demyelinating and axonal features with focal linear IgM deposition (figure). The patient had no benefit with IVIg and received rituximab (375 mg/m² once each week for 4 weeks) with stabilization of symptoms.

Discussion. This is a report of two siblings with clinical and electrophysiologic features typical for an anti-MAG-associated demyelinating neuropathy. Although there are three reports of the familial association of monoclonal gammopathy and polyneuropathy, none was associated with the presence of anti-MAG antibodies.²⁻⁴ Genetic factors may also be operative in the development of monoclonal gammopathy and multiple myeloma.⁵ Monoclonal gammopathies of unknown significance are identified in 3% of individuals over age 70 years and occur in 10% of patients with peripheral neuropathies of unknown etiology, although the association may be fortuitous.⁶ Up to 50% of patients with IgM monoclonal gammopathies develop polyneuropathy.⁶ Anti-MAG antibodies occur in patients with IgM kappa monoclonal gammopathy, although there are rare reports of the occurrence of anti-MAG antibodies without detectable monoclonal gammopathy. These antibodies are thought to have a pathophysiologic role; they intercalate within the layers of myelin leading to widening of lamellae and architectural derangement, resulting in demyelinating polyneuropathy.⁶

Patients with CIDP who have monoclonal gammopathy (CIDP-MGUS) are distinct from classic CIDP.⁶ CIDP-MGUS patients tend to be males over 60 years, with a progressive, sensory-

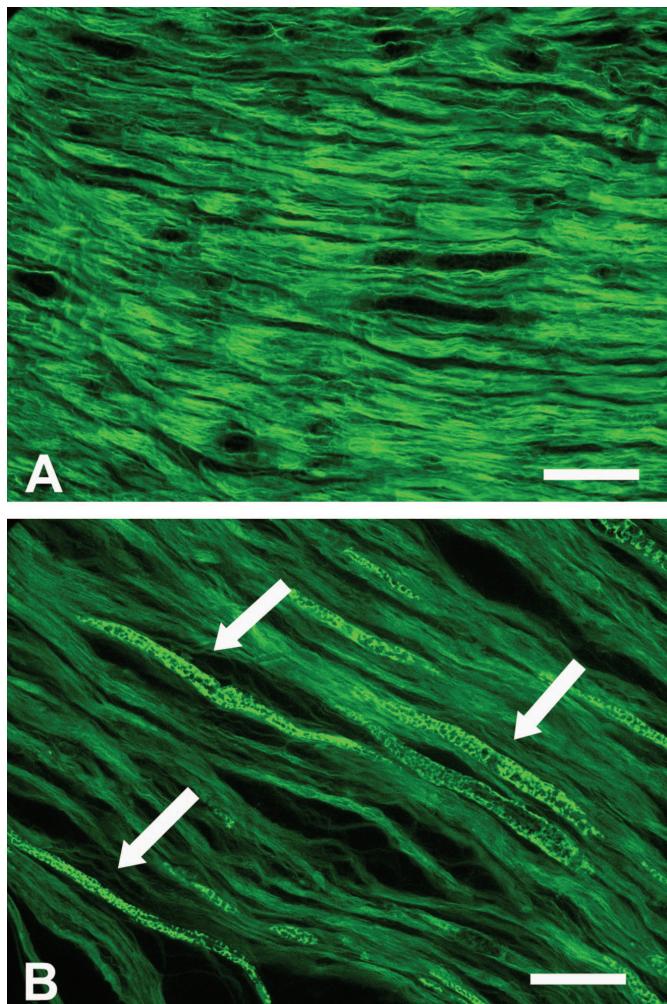


Figure. (A) Immunofluorescence staining specific for human immunoglobulin G displays diffuse, nonspecific pattern. (B) Immunofluorescence staining specific for immunoglobulin M displays focal, linear pattern, which probably represents staining of the few remaining myelinated axons of this sural nerve biopsy. (Bar measures 100 μ m.)

predominant demyelinating polyneuropathy.⁶ Immunomodulatory therapies are characteristically unsuccessful in these patients.⁶ Patients with anti-MAG antibodies and demyelinating neuropathy are a select subset of the CIDP-MGUS. On electrodiagnostic studies they have disproportionate distal slowing on nerve conduction studies. The anti-MAG syndrome does not respond to standard immunomodulating therapies including plasma exchange, IV immunoglobulin, corticosteroids, or cyclophosphamide.⁶ Rituximab, a monoclonal antibody directed against the B cell surface membrane marker CD20, is well tolerated and early reports suggest that this may be a promising agent in the anti-MAG neuropathy syndrome; our experience to date is similar.⁷ We recommend evaluation for monoclonal gammopathy and anti-MAG antibodies in symptomatic relatives of patients with acquired demyelinating polyneuropathy.

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Hemiplegic ALS: Mills syndrome

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Originally described in 1900,¹ progressive hemiplegia, also known as Mills syndrome, is a rare motor neuron disease. However, the existence of this entity has been subject to debate.^{2,3} A more recent report suggested that it could represent a variant of primary lateral sclerosis (PLS).² We describe a patient with progressive hemiplegia with electrophysiologically confirmed and exclusively unilateral lower motor neuron involvement who was later also found to have Waldenstrom macroglobulinemia (WM).

Case report. A 69-year-old man presented with a 12-year history of very slowly progressive right lower limb weakness and wasting. Ipsilateral upper limb involvement started about 5 years after onset. He denied any sensory symptoms or sphincter involvement. His past medical history was unremarkable, as was his family history. On examination, he presented distal (Medical Research Council [MRC] grade 2 to 3) more than proximal (MRC grade 4) right lower limb weakness affecting all muscle groups. The right upper limb was also weak, again more distally (MRC grade 3) than proximally (MRC grade 4). Tone was moderately increased on the right. Reflexes were pathologically brisk in all four limbs, more on the right. Hoffmann sign was present bilaterally. Plantar responses were flexor. There was severe atrophy without visible fasciculations mainly of the distal muscles of right upper and lower limbs. Sensation was entirely normal bilaterally to all modalities, including vibration and joint position. Cranial nerve functions were unimpaired, coordination and vision were normal. Routine blood investigations (full blood count, inflammatory markers, electrolytes, renal function, liver enzymes, calcium, creatine kinase, thyroid function) revealed a moderately raised white cell count (11,300/ μ L). Anti-GM1 antibodies were negative. Serum and urinary lead levels were within normal limits as was parathormone level. Serum protein electrophoresis revealed a raised IgM level of 16.5 g/L with an IgM lambda monoclonal band of 10.3 g/L. Bone marrow aspirate and biopsy showed an increase of up to 70% of the lymphocyte population and was consistent with a diagnosis of WM. Skeletal survey was normal. CSF examination

showed a normal protein of 0.33 g/L, and normal cytology. Motor and sensory nerve conduction studies showed no significant abnormality (table). Needle EMG showed, exclusively in right-sided muscles, a combination of abundant spontaneous fasciculations, fibrillation potentials, and positive sharp waves in the upper and lower limb, proximal and distal muscles (right first dorsal interosseous, deltoid, tibialis anterior, and quadriceps femoris), and large, long duration, polyphasic potentials with reduced recruitment on voluntary contraction. Acute denervation was not detected in the same four muscles investigated on the left side, with only rare, isolated fasciculations being recorded. Repeat nerve conduction was refused by the patient, who, however, agreed to undergo a second EMG 6 months later. No significant changes were observed, with persistent, exclusively unilateral signs of denervation being present in all tested right-sided muscles. A brain MRI scan showed mild periventricular ischemic changes and a cervical MRI was normal. A diagnosis of clinically probable ALS according to the El Escorial criteria⁴ was made.

Discussion. Since Mills' original description,¹ few additional cases have been reported.² The scarcity of reports and lack of pathologic data raised doubt about the authenticity of this syndrome, since all the published cases except for two² dated back to times when it was not possible to exclude definitely a structural abnormality as the underlying cause.^{2,3} WM has occasionally been reported in association with anterior horn cell disease, although whether the gammopathy plays any role in the pathophysiology of motor neuron involvement is unclear.⁵ Because it was diagnosed 12 years after the onset of the neurologic problems, and having remained asymptomatic for years as can be the case,⁶ the implication here of the lymphoproliferative disease in relation to the motor neuron disorder remains uncertain. A common cause explaining both disorders remains plausible.

Few if any similar cases have been reported since 1994,² indicating the rarity of idiopathic progressive hemiplegic syndromes. However, the two previous cases had PLS rather than ALS and the authors suggested Mills syndrome could be considered a PLS variant.² Mills had initially described eight cases of a very slowly advancing form of hemiplegia starting in the lower limb and then spreading to the ipsilateral upper limb.^{1,2} Reports through the

Table Nerve conduction study results

Motor nerve	Site	Latency, ms	Amplitude, mV	Amplitude, %	Velocity, m/s	Minimum F-wave latency, ms
Right median-recorded APB	Wrist	3.9 (normal <4)	7.3 (normal >5)	100		25.60 (normal <30)
	Elbow	8.50	6.0	81.5	58.2 (normal >48)	
Right common peroneal-recorded EDB	Ankle	5.25 (normal <6.5)	4.0	100		61.65 (normal <55)
	Fibular neck	13.60	3.5	86.6	40.1 (normal >44)	
Left common peroneal-recorded EDB	Ankle	4.60	5.2	100		56.80
	Fibular neck	12.55	3.3	63.4	42.8	

Sensory conduction studies: right median potential: 11.3 μ V (normal >10), velocity: 44.0 m/s (normal >40); right sural potential: 6.9 μ V (normal >5), velocity: 41.6 m/s (normal >38).

APB = abductor pollicis brevis; EDB = extensor digitorum brevis.

early 1950s described cases with very slow progression, ascending weakness, pyramidal tract signs, amyotrophy without fasciculations, and occasional facial weakness, with rare sensory disturbances. A family history of similar problems was rarely reported. Most cases had persistent unilateralism after 15 years, although spread to the contralateral side was reported in a third.

The features present in our patient with ALS resemble those of these earlier cases, as did those of the previously described two patients who had PLS.² This report suggests that progressive hemiplegia or what has been known as Mills syndrome can correspond not only to hemiplegic PLS, but also in some cases to hemiplegic ALS. The natural course of this mild unilateral motor neuron disease variant seems, in either case, identical, suggesting a different pathophysiologic basis for neuronal death in this form of the condition.

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