



Aneurysmal subarachnoid leak with normal CT and CSF spectrophotometry

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Subarachnoid hemorrhage (SAH) can be identified in 95% of patients with CT performed within 1 day of the ictus. If CT scanning is negative, but the clinical suspicion of SAH remains, then lumbar puncture (LP) after 12 hours with appropriate spectrophotometric analysis for bilirubin in CSF is recommended. Xanthochromia, defined as spectrophotometric absorption measurements exceeding 0.023 at wavelength 415 nm or a peak in the absorption curve in the 450- to 460-nm range or both, was identified in all CT-positive patients with SAH when the CSF was analyzed within 2 weeks of SAH.¹ The authors concluded that an LP performed after 12 hours and within 2 weeks of symptom onset would identify all of the CT-negative patients with SAH.¹

Case report. A 29-year-old man developed sudden, severe pain around his neck and throat while defecating. The pain radiated down to his shoulders and up to his vertex. He described the pain as the "worst pain" he had ever experienced. By the next morning, he described his neck as "stiff." During the following week, he had ongoing headache with episodes of vomiting and sweating. There was a previous history of migraine, which was different from his presenting complaint (occipital pain, nausea, and vomiting, which resolved within 2 days). He was admitted to the hospital on day 7.

Blood pressure on admission was 170/125 mm Hg. CT scan of brain with and without contrast agent revealed no abnormality. LP on day 8 revealed <1 white cell/ μ L, 6 red cells/ μ L, 0.39 g/L protein, and 3.3 mmol/L glucose. CSF net bilirubin absorbance was <0.007, suggesting no evidence of SAH.

The patient's blood pressure was investigated and treated. On day 13, he was referred to a neurologist. He still had headache with exacerbations. Neurologic examination was normal. MRI of the brain including fluid-attenuated inversion recovery sequences was normal. An MR angiogram demonstrated a 4-mm aneurysm of the right middle cerebral artery. After discussing treatment options, the patient consented to surgical clipping of the aneurysm. At operation, there was evidence of an old hemorrhage in the form of yellow discoloration of the arachnoid in the sylvian fissure. The aneurysm was thin walled, and there was a remnant of a thin small clot capping the dome. The patient had an uneventful postoperative recovery. Six months later, he was asymptomatic, had returned to work, and was normotensive on treatment.

Discussion. Warning headaches have been reported in 30 to 60% of patients who have had SAH. Although unruptured aneurysms can cause symptoms due to thrombosis, embolism, or mass effect,² sentinel headache due to hemorrhage has rarely been documented. In one autopsy report, there was leakage of blood through a previous small tear in the wall of a saccular aneurysm as well as a fresh fatal rupture at the fundus of the aneurysm.³ In many patients, however, rebleeding may occur at the same tear as the putative sentinel leak, rendering it impossible at autopsy to distinguish sentinel hemorrhage from rehemorrhage. The lack of definitive evidence of sentinel leaks, other potential mechanisms

for aneurysms to cause symptoms, and the lack of focal hemorrhage recorded at surgery have led to "sentinel hemorrhage" skepticism. Patients with first-ever acute, severe headache presenting with SAH without loss of consciousness or focal deficits had no clinical or radiologic differences from SAH patients who had a preceding bout of headache. Some of these headaches may be due to recall bias.⁴ Long-term follow-up of patients with thunderclap headache investigated with negative CT and CSF findings suggests a benign outcome.

There are a few reports of thunderclap headache in patients with an unruptured aneurysm.^{2,5,6} In some patients, vasospasm has been identified at angiography. No evidence of old or recent hemorrhage was found on CT or CSF analysis or at operation.^{5,6}

"Minor leak" aneurysmal hemorrhage was documented in 8 of 46 Japanese patients with a normal CT scan of the brain.⁷ Seven of the eight patients had headache for >24 hours. They all had a "normal CSF color." Our findings suggest that a false-negative CSF bilirubin determination (which is more sensitive than visual inspection) can occur within the recommended investigative time-frame with a history suspicious for SAH. The location of the aneurysm, particularly within the sylvian fissure, loculation of blood, and the small amount of hemorrhage are possible explanations for this finding.

Most patients with SAH but negative CT appear to be accurately diagnosed with appropriately timed CSF bilirubin determination.¹ Our observation is insufficient per se to alter current management protocols for patients with suspected SAH, although neuroimaging advances may improve detection of small SAHs.

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"Levodopa phobia": A new iatrogenic cause of disability in Parkinson disease

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Two recent research directions have raised question about the role of levodopa in treating Parkinson disease (PD). First is evidence that levodopa is toxic in nigral neuronal cell cultures.¹ Second are clinical trials showing that compared to beginning therapy with a dopamine agonist, initial treatment with levodopa is associated with earlier appearance of dyskinesias and wearing-off fluctuations.^{2,3} There has been much publicity about these potential negative aspects of levodopa. I report two patients with PD who

became disabled because their treating neurologists were fearful of prescribing levodopa because of the widespread publicity.

Case reports. Case 1. A 72-year-old man had been diagnosed with PD 3 years earlier. He was initially treated with ropinirole and required steadily increasing dosages up to 24 mg/day. Due to ongoing bradykinesia and gait difficulties, amantadine 300 mg/day and deprenyl 10 mg/day were added. Visual hallucinations and episodes of confusion developed but resolved after discontinuation of amantadine and deprenyl. The patient was functionally disabled by unsteady gait with freezing, overall slowness, and impaired dexterity for daily activities such as dressing and eating and was referred to the University of Rochester PD Program by the treating neurologist "since there are no other medication op-

tions." Examination was compatible with moderate idiopathic PD. Ropinirole was reduced to 9 mg/day and levodopa (with carbidopa) was titrated over 3 weeks to 600 mg/day. Gait, bradykinesia, and other motor function improved substantially and this improvement has been maintained for 9 months with no tolerability problems.

Case 2. A 62-year-old man had been diagnosed with PD 6 years earlier. He was treated with deprenyl 10 mg/day and levodopa (with carbidopa) 300 mg/day and did well for 4.5 years. He then developed "wearing off" motor fluctuations, start hesitation, and gait imbalance. The addition of entacapone 600 mg/day produced mild but unsatisfactory benefit. Levodopa was adjusted to 150 mg at 7:00 AM, 150 mg at 10:00 AM, and 100 mg at 2:00 PM. The patient was slow but had adequate mobility most days from about 8:00 AM to 3:00 PM but was bedridden in an akinetic "off" state at all other times. He stopped working due to this medical disability. He was referred to the University of Rochester PD Program by the treating neurologist "because I don't want to use more than 400 mg/day of levodopa and I know it's best to use as little medication as possible." Examination was compatible with moderate idiopathic PD. Over the next 6 weeks, levodopa was adjusted to 150 mg every 3 hours (7:00 AM to 10:00 PM; 900 mg/day), entacapone 200 mg and pramipexole 0.25 mg were given with each levodopa dose, and deprenyl was reduced to 5 mg/day. Motor fluctuations largely resolved and there was substantial improvement in overall function that has been maintained for 6 months. The patient has returned to work.

Discussion. While recent research regarding levodopa appears to have influenced treatment practices, it remains controversial and it is unclear if its effects on clinical practice are justified. While the *in vitro* study suggested levodopa neurotoxicity, there is no current evidence that this translates to the human disease.¹ A recently published trial found no clinical or neuroimaging evidence that early use of levodopa, even in high dosages, adversely impacts the illness.⁴ Several commentaries with different interpretations of the early levodopa vs dopamine agonist trials have been published^{5,6} and the Practice Parameters Committee of the American Academy of Neurology concluded that

initial symptomatic treatment with a dopamine agonist or levodopa is appropriate.⁷

Currently available scientific data do not appear to justify the practice of neurologists withholding adequate levodopa therapy, particularly for patients with substantial functional disability. The "Sinemet scare" has become an unjustified iatrogenic cause of disability in PD. Similarly, the fear of levodopa induced by publicity has led some disabled patients with PD to avoid the drug inappropriately.

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Palatal myoclonus in a patient with a lateral thalamic infarction

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Palatal myoclonus (PM) is characterized by rhythmic involuntary jerking movement of the soft palate and the pharyngopalatine arch, often involving the diaphragm and laryngeal muscles.¹

The two distinct clinical entities, symptomatic PM and essential PM, arise from different pathophysiologic mechanisms.²

Symptomatic PM is usually associated with lesions located in the myoclonic triangle (the Guillain–Mollaret triangle). It consists of the red nucleus, inferior olive, contralateral cerebellar dentate nucleus, and the connecting pathways, namely the central tegmental tract, the inferior cerebellar peduncle, and superior cerebellar peduncle.³ Symptomatic PM may be isolated or more rarely associated with movements of the extremities such as tremor, choreoathetosis, and myoclonus.^{4,5}

Case report. A 64-year-old man was referred for acute onset of motor impairment of the right arm. On admission neurologic examination revealed clumsiness of the right arm and right dysmetria on finger-to-nose test. On the fifth day the patient developed myoclonic movements of his right arm consisting of rhythmic flexion of the hand over the forearm. The myoclonus was absent at rest and was elicited only with right hand outstretched. In the meantime rhythmic involuntary jerking movements of the soft palate and the pharyngopalatine arch (palatal myoclonus) were noted. The patient was unaware of his PM. Myoclonic movements of the right hand were synchronous with the PM and had a frequency of 0.5 Hz.

On admission a cranial CT scan and extracranial Doppler ultrasonography were normal. Three days later, a brain MRI revealed two ischemic lesions involving the lateral portion of the left thalamus (figure) and the medial temporal lobe in the territory of

the deep (thalamogeniculate pedicle) and superficial branches of the posterior cerebral artery. No medullary lesions were present.

We performed an EEG-polygraphic recording including 16 EEG channels, EKG recording, 4 EMG channels (flexor and extensor muscles of both forearms) that revealed the presence of rhythmic contractions involving simultaneously the flexor and the extensor muscles of the right hand, without related EEG abnormalities. Back averaging of myoclonic jerks was performed, confirming the absence of a cortical potential time locked with EMG potentials. No features of negative myoclonus were present at the polygraphic study. Somatosensory evoked potentials were normal. An EKG revealed the presence of atrial fibrillation while transthoracic and transesophageal echocardiograms showed a slight dilatation of the left atrium. Routine blood and coagulation tests were normal. At discharge, both PM and the upper limb myoclonus were still present. Two years after the stroke, PM was still evident while the extremity myoclonus had disappeared.

Discussion. We describe PM in a patient with a lateral thalamic infarction, which was associated with a synchronous upper limb myoclonus. Several abnormal involuntary movements have been reported in patients with thalamic infarction,^{6,7} particularly involving the lateral portion. PM (either isolated or associated to extremity myoclonus) has almost exclusively been described in patients with lesions involving the Guillain–Mollaret triangle.⁵

The presence of a complex myoclonus in a patient with a lateral thalamic infarction raises some questions regarding the pathogenetic mechanism. If the upper limb myoclonus might be explained by the impairment of the cerebellar efferent pathway at the level of the ventrolateral nucleus, it is difficult to explain the PM in absence of brainstem or cerebellum lesion. It is well known that the central tegmental tract descending in the dorsal brainstem from the red nucleus to the inferior olive is relevant for the occurrence of the PM. Moreover the impairment of the CTT may cause a disinhibition of the inherent activity of the cells within the inferior olive which, according to animal studies, expose a spontaneous activity at a frequency between 0.5 and 3 Hz. In our pa-

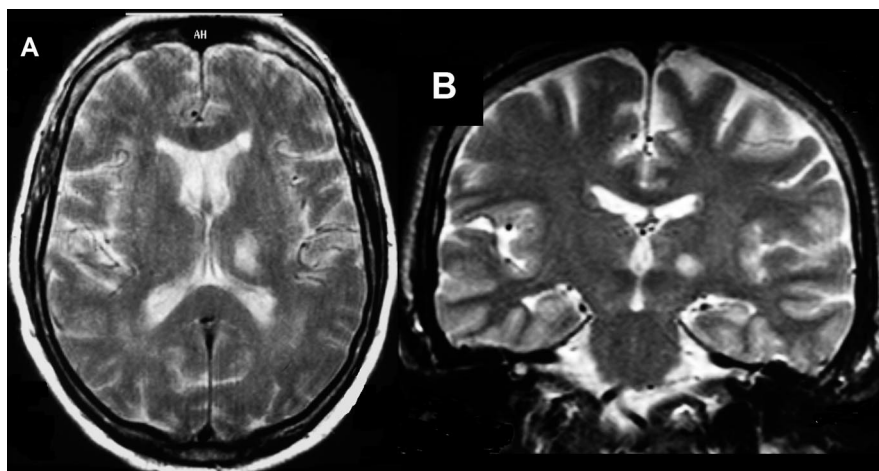


Figure. Magnetic resonance scan, (A) axial, T2-weighted (3,800/120/2 repetition time/echo time/excitations) and (B) coronal, T2-weighted (3,800/120/2). A round hyperintense lesion is located in the lateral portion of the left thalamus (A). The ischemic lesion involves the lateral thalamus (B) in the territory of the thalamogeniculate arteries arising from the posterior cerebral artery.

tient, we hypothesize an influence of the lateral thalamus on the red nucleus located in the upper mesencephalon. Indeed the presence of descending thalamo-rubral fibers has been reported in old neuroanatomic studies but not in the more recent investigations and is in contrast with the accepted notion that there is an absence of any descending fibers from the thalamus to the brainstem.

However, the concomitance of upper limb myoclonus, cerebellar signs, and PM may suggest a unique pathogenetic mechanism related to the lesion of the ventrolateral thalamus and the cerebellar circuit.

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Different pain patterns in patients with vertebral artery dissections

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Spontaneous or traumatic cervical artery dissections are an increasingly recognized cause of stroke in young adults.¹ The internal carotid artery (ICA) is more frequently involved than the vertebral artery (VA).¹ Headache and neck pain are common and suggestive symptoms of VA dissection (VAD).² However, their clinical characteristics and their relationship with focal neurologic symptoms have not been extensively analyzed.

Methods. We prospectively analyzed 10 consecutive patients admitted to our hospital with diagnosis of VAD from 1995 to 2003. In all cases, the dissection was confirmed by magnetic resonance angiography (MRA), conventional angiography, or both. The presence of headache, neck pain, or both at the time of the dissection, their characteristics, and their association with neurologic signs and symptoms were registered by direct interview. The history of headache was classified according to the International Headache Society criteria.³ Headache at the time of arterial dissection was classified into that occurring before, during (within 30 minutes of the focal symptoms), or after other clinical manifestations.

Case report. A 48-year-old man with no history of migraine was admitted to the hospital because of thunderclap headache with left hemicranial and posterolateral neck pain and clinical signs of Wallenberg syndrome. He reported three previous episodes of severe left hemicranial headache lasting 2 hours in the last 48 hours before admission. MRI showed left lateral medullary infarct, and MRA revealed left V1 to V4 VAD.

Results. Ten patients fulfilled diagnostic criteria of VAD (six men; mean age 54.3 years, range 30 to 67 years). Dissection was traumatic in only one patient. Pain (headache, neck pain, or both)

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was present in all patients; it was the first symptom of VAD in six patients. It affected the posterolateral aspect of the neck in eight. Headache was present in eight patients; it was hemicranial in four, occipital in three, and frontoparietal in one. Headache preceded other clinical manifestation in five patients, was simultaneous with other manifestations in two, and developed after neurologic deficit in the remaining patient. Only one patient had a history of migraine. No patient had subarachnoid hemorrhage. All patients were anticoagulated.

We identified two groups according to the temporal pattern of pain:

Group 1 (continuous pain pattern). In five patients (mean age 59.6 years), pain was continuous: bioccipital in two, located in the neck in one, and headache and neck pain in two. Mean pain intensity was 6 of 10, and mean pain duration was 26.4 hours. Mean time from pain onset to VAD diagnosis was 3.1 days (range 0 to 9 days). Dissection affected the V4 segment in two patients. Three patients experienced a cerebellar infarct, and the remaining two developed a Wallenberg syndrome. All patients recovered completely.

Group 2 (intermittent pain pattern). In five patients (mean age 49 years), pain attacks were separated by pain-free periods. Four patients had hemicranial headache associated with neck pain, and one patient had neck pain only. Mean pain intensity was 7 of 10 with a mean duration of 4.6 hours. Mean time from pain onset to VAD diagnosis was 7.7 days (range 0.5 to 15 days). Mean number of pain attacks was 5.4, and pain-free periods lasted up to 34 hours. Dissection affected the V4 segment in all patients. Three patients showed a Wallenberg syndrome, and the remaining two experienced a cerebellar infarct. Two patients had disabling sequelae.

Discussion. Headache is a cardinal manifestation of ICA and VA dissections.² The most common syndrome in VAD is unilateral, typically occipital headache with or without ipsilateral neck pain

followed by ischemic symptoms in the vertebrobasilar distribution.^{2,4} Pain may be explained by the fact that dissection affects the upper cervical nerves that innervate the vasculature of the posterior fossa.⁵ Nevertheless, asymptomatic progression of the arterial dissection in the acute phase¹ and asymptomatic recurrences have been reported.⁶

The main finding of our study is that 50% of our patients with VAD showed a headache pattern consisting of recurrent pain attacks separated by pain-free periods.

ICA dissection may occur in steps.⁷ Pain in the neck may be present for days or may recur days or even weeks later, accompanied by TIAs or strokes. The explanation proposed is that the initial tear extends and intramural bleeding enlarges when the symptoms worsen.⁷ It is likely that the same mechanism might be implicated in VAD with a pattern of recurrent pain attacks, as suggested by our results.

Although the small number of patients is a shortcoming of this study, our findings suggest that intermittent pain pattern is not infrequent in VAD and might be associated with hemicranial headache, younger age, delayed diagnosis (probably due to the presence of pain-free intervals), intracranial extension of VAD, and worse prognosis.

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Severe sensory neuropathy associated with long-term linezolid use

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Linezolid is an antibiotic used for treatment of drug-resistant gram-positive micro-organisms. It is recommended to treat patients with linezolid for up to 28 days,¹ but sometimes it is used for a longer period of time in the treatment of bone infections. It is usually well tolerated, and few patients develop myelosuppression, diarrhea, or nausea.¹ However, recent reports indicate a risk of a potentially irreversible neuropathy following prolonged use.^{2–5} We report an additional patient with severe sensory polyneuropathy following a 6-month course of linezolid.

Case report. A 42-year-old, otherwise healthy woman sustained left ankle, tibia, femur, pelvic, and rib fractures in a motor vehicle accident in December 1999. Subsequently, she underwent multiple orthopedic surgeries, complicated by treatment-resistant staphylococcal osteomyelitis. In May 2001, she was treated with linezolid 600 mg bid orally. This drug was continued until November 2001. In June 2001, she had lower extremity numbness. Electrodiagnostic studies showed absent medial and lateral plantar and sural sensory responses and were otherwise unremarkable. However, a few months later, she gradually developed progressive weakness and numbness of the lower and upper extremities, ac-

companied by right facial numbness and blurred vision. She was admitted to the hospital in November 2001. By that time, her vision had improved, and she had severe acral burning pain and numbness. She did not abuse alcohol, and there was no family history of neuropathy. On examination, she had severe sensory loss to all modalities extending up to the knee and elbow levels. Vibration sense and proprioception were more severely affected than sensation to light touch, cold, and pinprick. Deep tendon reflexes were 1 of 4 in the upper extremities and absent in the legs. Strength examination was limited by orthopedic instrumentation, but she had only mild distal weakness of right foot dorsiflexors and bilateral finger extensors (Medical Research Council 4/5). Coordination was normal. She was ambulating with crutches. Fundoscopy revealed retinal vein engorgement, and visual acuity was 20/40 bilaterally.

Laboratory studies included normal CSF studies, normal vitamin B₁₂ and glucose levels, and negative anti-Hu, anti-Yo, and SS-A/B antibody titers. Lip biopsy was negative. MRI studies of total spine, brain, and optic nerve were normal. Electrodiagnostic studies demonstrated severe sensory neuropathy (or ganglionopathy) (table), without motor involvement and with a normal needle examination. The patient declined a nerve biopsy. Outpatient and electrodiagnostic follow-up over 20 months revealed no changes.

Discussion. Toxic neuropathies usually improve after the offending agent is removed or after a period of “coasting.” However,

Table Nerve conduction studies

| Sensory nerves | Amplitude (normal), μ V | | Peak distal latency (normal), ms | |
|----------------------|-----------------------------|-----------------------------|-----------------------------------|-----------------------------|
| Sural | NR | | NR | |
| Superficial peroneal | NR | | NR | |
| Median | 1 (>20) | | 3.6 (<3.4) | |
| Ulnar | NR | | NR | |
| Radial | NR | | NR | |
| Motor nerves | Amplitude (normal), mV | Distal latency (normal), ms | Conduction velocity (normal), m/s | F-wave latency (normal), ms |
| Peroneal | 5.7 (>2.5) | 4.3 (<5.5) | 41 (>40) | 46.9 (<55) |
| Tibial | 15.1 (>8) | 3.5 (<6.0) | 41 (>40) | 45.9 (<57) |
| Median | 6.6 (>6) | 3.3 (<3.9) | 54 (>50) | 26.7 (<31) |
| Ulnar | 9.1 (>7) | 2.2 (<3.1) | 56 (>50) | 26.2 (<33) |

NR = no response.

if the dorsal root ganglia are affected, sensory neuro(no)pathy may be irreversible.⁶ Eighteen cases of possible toxic linezolid-associated peripheral neuropathy have been described in the literature,³ but it is probably more common as more cases were reported to drug-monitoring agencies or electronic mailing lists.^{2,3} The severity and persistence of sensory neuropathic symptoms following linezolid treatment indicate possible ganglionopathy.^{2,5} Notable is the frequent occurrence of optic neuropathy, suggesting common mechanisms of neurotoxicity.^{2,3,7} Concomitant optic neuropathy may improve before peripheral neuropathy.² Our patient might also have had optic neuropathy, but her visual symptoms had already improved.

Peripheral neuropathy associated with linezolid has predominant sensory involvement with profound loss of vibration sense and proprioception, burning pain, and only minor weakness. In most patients, symptoms do not improve after medication is stopped. Electrodiagnostic studies are consistent with axonal or ganglion cell injury, affecting predominantly sensory nerve fibers. Affected patients were treated with linezolid for 4 to 6 months, much longer than the recommended 28 days, suggesting a threshold effect.¹⁻⁵ Mechanisms of nerve injury by linezolid remain unclear. Linezolid blocks bacterial protein synthesis by binding to ribosomal proteins; it has been speculated that neurotoxicity may be related to mitochondrial dysfunction, but histopathologic studies are lacking.^{3,7}

Our case expands the spectrum of sensory neuro(no)pathy and demonstrates the need to closely monitor patients treated with long-term linezolid therapy as neuropathy may be irreversible.

Further studies are needed to fully elucidate the pathophysiology and mechanisms of linezolid-related nerve injury.

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Electrophysiology extends the phenotypic spectrum of X-linked myopathy with excessive autophagy

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X-linked myopathy with excessive autophagy (XMEA) (MIM 310440) is an X-linked recessive boyhood-onset disorder of skeletal muscle with a slowly progressive course toward wasting of proximal muscles of the lower extremities and wheelchair dependency by the fifth decade of life. Involvement of distal leg muscles and upper extremities is clinically evident late in the disease.^{1,4} Skeletal muscle pathology is characterized by a constellation of rare and unique features. Autophagic vacuoles containing cellular debris are present in the sarcoplasm, and at the sarcolemma extruding their contents to the extracellular space. Myofibers containing vacuoles have multiple layers of basement membrane. Intense calcium accumulation is seen at the myofiber periphery, in the absence of necrosis. Extensive deposition of complement membrane attack complex (MAC) is present at the myofiber surface, without resultant cell lysis. Finally, class I major histocompatibility complex is expressed, despite the absence of inflammation.^{1,4} Nerve conduction studies (NCS) are normal but EMG reveals myopathic changes, including striking myotonic and high-frequency discharges, in the absence of any clinical myotonia, in all muscles, even clinically unaffected facial, bulbar, and distal limb muscles.⁵ In the present work, we demonstrate that XMEA can manifest with the EMG abnormalities alone, without the clinical syndrome.

Methods. Two apparently unrelated American families (Families E and B; see figure E-1 on the *Neurology* Web site at www.neurology.org) with XMEA have been followed by one of the authors (J.T.K.) for 20 years. All eight clinically affected members of these families (black squares in figure E-1) are following a similar clinical course with onset of weakness in mid to late childhood, obvious lower limb girdle muscle atrophy by mid to late adolescence, and severe wasting requiring Gower's type maneuvers to rise from a seated position, and ambulatory walking aids by the

30s. One patient in his 50s is wheelchair-dependent. The creatine kinase (CK) levels in these patients, including the oldest, range from 2 to 10 times the upper limit of normal. Their biopsies and EMG exhibit the classic features of XMEA.⁶

The XMEA gene maps to one of the most gene-dense regions of the genome, a 4.37 Mb region containing at least 110 genes, in chromosomal band Xq28⁷ (see figure E-1). We genotyped this region in Families E and B and noticed that the haplotypes of affected individuals (boxed section, see figure E-1) are identical in the two families, indicating a likely common founder, and common mutation, in these two families. Genealogic review revealed that each family had an ancestor who had migrated to the American state of Ohio from present-day Slovakia in the 19th century. Work is under way to determine whether a familial relationship exists between these two individuals.

Results. The disease-associated haplotype was present in all affected individuals, but surprisingly it was also found in two apparently unaffected members of Family E (III-7 [58 years old] and III-11 [41 years old]; see figure E-1). We reexamined these two individuals clinically and found minimal, questionable, weakness in hip flexion and quadriceps function in Patient III-11 and a CK three times higher than the upper limit of normal. The older individual, III-7, continued to have normal strength in all muscle groups with CK at the upper limit of normal. We then examined both electrophysiologically, and obtained a quadriceps biopsy from Patient III-11. NCS were normal, and needle examination (Vastus Medialis and Lateralis and Tibialis Anterior) demonstrated increased insertional and abnormal spontaneous activities, and complex repetitive and myotonic discharges. As negative controls, we performed EMG studies in two unaffected age-matched male relatives who do not carry the disease-associated haplotype, and found no abnormalities. Pathologic analysis in Patient III-11 revealed very rare abnormal fibers (<5%), with telltale XMEA features: vacuolation and sarcolemmal and vacuolar staining with MAC and dystrophin antibodies.

Discussion. In this study, we have documented clinical nonpenetrance, while demonstrating penetrance of the electrophysiologic phenotype in XMEA. Absence of the clinical phenotype in some XMEA patients invokes the presence of modifier genes, outside the XMEA gene region, with protective effects against XMEA myopathology. Presence of the EMG phenotype in all individuals with the disease-associated haplotype suggests that it is an essential component of the syndrome. The EMG findings indicate myofiber membrane irritability throughout tested muscles despite the rarity of pathologically affected fibers, supporting previous theories^{3,5} of a primary myofiber surface abnormality in the pathogenesis of XMEA.

Additional material related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for the March 8 issue to find the title link for this article.

Refinement of the XMEA phenotypic spectrum will impact future genetic studies, including the correct assignment of affected status to male subjects with recombinant chromosomes, necessary to the narrowing of the XMEA gene region.

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