

Carotid artery dissection and middle cerebral artery stroke following methamphetamine use

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Methamphetamine use may be associated with increased risk of stroke in young adults. We describe two cases of carotid artery dissection and ipsilateral middle cerebral artery (MCA) stroke following methamphetamine use.

Case reports. Patient 1. A 36-year-old right-handed woman had sudden onset of speech difficulty and right-sided weakness while eating lunch. She presented to the emergency department within 30 minutes. Her medical history was significant for migraine and oral contraceptive and methamphetamine use. She was smoking methamphetamine with some left neck pain over the preceding two nights. Her initial examination was remarkable for global aphasia, left gaze preference, and right hemiplegia without Horner syndrome. The NIH Stroke Scale (NIHSS) score was 21. The initial head CT was unremarkable. IV tissue plasminogen activator (tPA) was started within 80 minutes of symptom onset. She improved significantly with only moderate expressive aphasia and mild right hemiparesis 8 hours after tPA therapy. A follow-up diffusion-weighted MRI of the brain showed a small infarct in the left frontal lobe (figure, A). MR angiography revealed a focal narrowing in the left internal carotid artery (ICA). There was an intimal flap on carotid ultrasound (figure, B) and an intramural thrombus on fat-saturation T1 MRI of the neck, indicative of dissection. Extensive workup, including fasting lipid panel and transesophageal echocardiogram, was only significant for methamphetamine in the urine. No cocaine or other illicit drugs were detected. She was treated with IV heparin. A cerebral angiography 3 days later showed minimal irregularity in the left ICA suggestive of resolving dissection. The patient was discharged on warfarin 5 days after stroke. She recovered with only mild expressive aphasia and returned to work within 4 months. Warfarin was replaced with aspirin 81 mg/day at 8-month follow-up. She has remained well on aspirin.

Patient 2. A 29-year-old right-handed woman with a history of methamphetamine use for 10 years developed sudden right-sided weakness and speech difficulty 4 days after her last use of methamphetamine. She was taken to a local hospital where the initial head CT was normal. A subsequent MRI showed a large left MCA infarct. She was discharged home on aspirin 4 days after stroke. Due to worsening deficit, she was brought to our center the next day for further evaluation. Her examination was remarkable for global aphasia and right hemiparesis without Horner syndrome. Her NIHSS score was 17. A repeat MRI confirmed large left MCA infarct (figure, D). Transesophageal echocardiography and hypercoagulability state (lupus anticoagulants, antithrombin III activity, protein C and S activity, prothrombin gene mutation, factor V Leiden mutation, and homocysteine level) were all unremarkable. The urine toxicology screen was not performed at outside hospitals or our medical center. MR angiography showed significant narrowing of the left proximal common carotid artery. Diagnostic cerebral angiography demonstrated a large intimal flap and severe stenosis with a filling defect (clot) underneath the flap (figure, E), indicative of dissection. There was no evidence of aorta involvement. Due to large MCA infarct with hemorrhagic transformation, the dissection was treated with stent-assisted angioplasty rather than anticoagulation. The patient was discharged home with aspirin (325 mg) and clopidogrel (75 mg). She recovered with only moderate expressive aphasia and mild right hand weakness within 4 months. Follow-up angiography at 7 months showed no restenosis.

Discussion. Both patients had stroke from carotid artery dissection following methamphetamine use. Neither had history of recent trauma, infection, connective tissue disorders, miscarriages, or other illicit drug use. Despite a history of migraine and contraceptive use, Patient 1 developed left neck pain without regular migraine headaches. Her urine was positive for methamphetamine at the time of carotid dissection and stroke. Patient 2

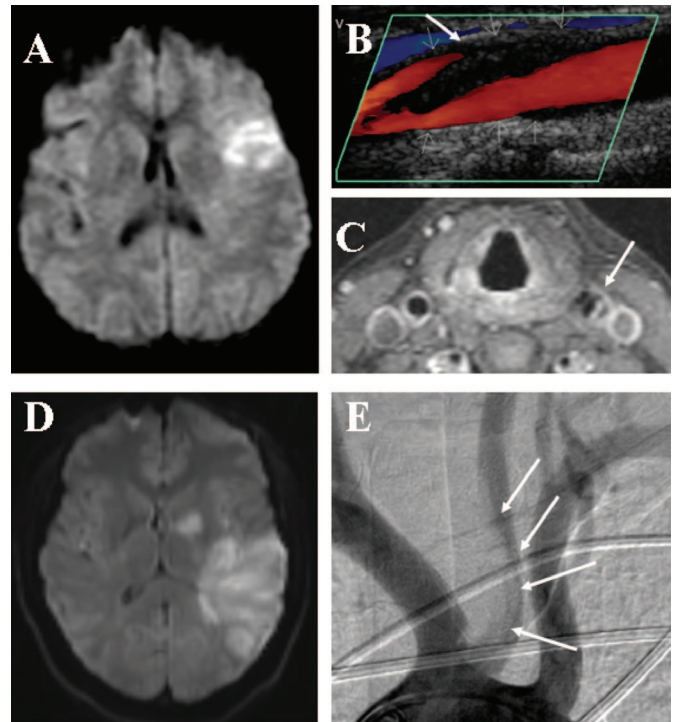


Figure. Diffusion-weighted MRI of the brain shows a small left frontal infarct in Patient 1 (A). Carotid ultrasound reveals an intimal flap (B), and fat-saturation T1 MRI of the neck demonstrates an intramural thrombus that is pathognomonic of arterial dissection (C). MRI of the brain shows a large left MCA infarct in Patient 2 (D). The angiography reveals a large intimal flap and severe stenosis with a filling defect (clot) underneath the flap (E), indicative of arterial dissection.

developed stroke a few days after her last use of methamphetamine. Extensive workup failed to reveal any other risk factors. Methamphetamine may induce vasospasm, hypertension, vasculitis, or direct vascular toxicity.^{1,4} Methamphetamine abuse has been associated with aortic dissection.⁵ Carotid artery occlusion or segmental narrowing described in a previous case report, appeared to be consistent with carotid artery dissection.² Cocaine has similar effects and has also been implicated in carotid artery dissection.⁶ Therefore, it is likely that cervicocephalic dissections may be secondary to a drug class effect rather than a specific drug.

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ALS in a patient with hereditary neuropathy with liability to pressure palsy

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Hereditary neuropathy with liability to pressure palsy (HNPP) is infrequently diagnosed, although epidemiologic data suggest the prevalence may be as high as 16/100,000.¹ HNPP is associated with a 1.5-Mb deletion on chromosome 17p11.2-12 bearing the peripheral myelin protein 22 (PMP22) gene. There is a possible association between HNPP and CNS demyelinating lesions. We present a patient with a 1.5-Mb deletion in the PMP22 gene who presented with symptoms, signs, and electrophysiologic findings of ALS in addition to multiple mononeuropathies.

Case report. A 51-year-old woman presented in 2005 with a 4-month history of increasing weakness in the right upper limb and deteriorating gait due to a sensation of "heaviness" in her legs. There was no history of falls, incontinence, or visual symptoms. She had a previous diagnosis of left-sided carpal tunnel syndrome.

On examination, she had a mildly spastic gait and increased tone in four limbs. There was wasting evident in the muscles of the right hand, with fasciculations seen in the right triceps, biceps, and quadriceps muscles bilaterally. There were increased reflexes throughout, with patellar clonus and positive Hoffmann's sign. Our patient had pes cavus, and she informed us that her daughter and three sisters also had high-arched feet. No other relevant family history was known.

EMG revealed marked acute and chronic denervation changes in both upper limbs, involving the right more severely. Milder chronic neuropathic features were evident in both lower limbs, with no evidence of bulbar denervation. Nerve conduction studies demonstrated normal sural nerve sensory action potentials (SAPs), but reduced radial and median nerve SAPs bilaterally. There was marked slowing of the median motor nerve conduction velocities bilaterally at the wrist, with very severe slowing of the ulnar nerves bilaterally at the elbow and moderate slowing of the right common peroneal motor nerve conduction velocities at the fibular head. There was no evidence of proximal conduction blocks in the four limbs.

The conclusion from neurophysiologic studies was that these findings might represent dual pathology, consistent with widespread anterior horn cell disease, with a background compressive neuropathy such as HNPP.

MRI of the brain and spinal cord was normal. CSF analysis was normal, with no oligoclonal bands found. Other investigations included normal full blood count, routine biochemistry, serum lead levels, and negative HIV (1 and 2) and syphilis serology. Antineuronal antibodies, human peripheral nerve, and spinal cord antiganglioside antibodies were negative. Genetic analysis for HNPP was positive, demonstrating a deletion at the chromosome site 17p11.2.

Clinical follow-up at 6 months after our patient's initial presentation revealed progression of symptoms and signs. She is now markedly dysarthric, with prominent fasciculations and wasting in the muscles of all limbs. Her weakness has progressed, and the deep tendon reflexes remain brisk, with bilateral extensor plantar responses. She now fulfills the revised El Escorial research diagnostic criteria for definite ALS.² Muscle biopsy was not deemed necessary, given the clinical and neurophysiologic findings.

Discussion. HNPP is a demyelinating neuropathy, clinically characterized by recurrent painless focal neuropathies, which occur mainly at common entrapment sites.³ Prolonged neurologic deficits are uncommon, as symptoms tend to improve within days to weeks.³ Electrophysiologic examinations of patients with HNPP reveals two characteristic findings, namely, a generalized sensorimotor neuropathy and superimposed focal conduction abnormalities preferentially located at common entrapment or compression sites.⁴ The disease is autosomal dominantly inherited and is associated with a 1.5-Mb deletion on chromosome 17p11.2-12 bearing the peripheral myelin protein 22 (PMP22) gene.³ PMP22 is localized in the compact part of peripheral nerve myelin and accounts for about 2 to 5% of the total myelin.⁵ PMP22 has an essential role in the formation and maintenance of compact myelin, but its role outside the peripheral nervous system is uncertain.⁵ Previous case reports and a single larger family study have demonstrated that a possible association exists with HNPP and CNS lesions.^{5,6} The CNS lesions identified consisted of MRI findings of possible demyelination, with clinical evidence on history or examination consistent with CNS lesions in some patients.

Although cases of neuropathies such as motor neuropathy with conduction block have been shown to mimic ALS,⁷ to our knowledge there has been no description of HNPP associated with ALS to account for our patient's mixed upper and lower motor neuron signs and her electrophysiologic findings. Whether our patient's syndrome represents a coincidental co-occurrence of two uncommon conditions or a possibly new CNS manifestation of HNPP is unknown.

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An acute, life-threatening, hypersensitivity reaction to riluzole

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Riluzole is the only Food and Drug Administration–approved treatment of ALS that has been shown to modestly prolong survival.¹ Riluzole is generally well tolerated. Serious drug-related side

effects occur in fewer than 2% of subjects.² Approximately half of these are attributable to elevations in liver transaminases.² Long-term follow-up studies have not suggested any long-term toxicity of this drug.³ Adverse events in general are thought to be minor and reversible with discontinuation of the drug. We report a severe, life-threatening systemic inflammatory reaction to riluzole in a patient with ALS.

Case report. A healthy 50-year-old man was diagnosed with ALS after presenting with 1 year of progressive asymmetrical hand weakness. He fulfilled the El Escorial Criteria for clinically definite ALS at the time of his presentation. He began riluzole therapy at 50 mg twice daily. Concurrently, he was started on zolpidem tartrate to assist with his sleep. Fourteen days later, he began to complain of myalgias and fevers to 40°C. His liver enzymes at that time demonstrated a modest elevation: AST of 92 (normal, 12 to 31), alanine aminotransferase of 166 (normal, 10 to 45), alkaline phosphatase of 140 (normal, 45 to 115). His baseline liver enzymes had been normal before starting the riluzole. His riluzole was held because of the elevated enzymes, but his zolpidem was continued. His symptoms continued to progress during the next 48 hours to include prominent nausea and diffuse pruritic rash. His admission examination revealed the diffuse rash, generalized lymphadenopathy, and atrial fibrillation. Evaluation included chest x-ray, demonstrating diffuse interstitial infiltrates; echocardiogram, demonstrating constrictive pericarditis; and a bone marrow biopsy, demonstrating hypercellular marrow with several granulomas. Infectious disease work-up was unremarkable. The patient's atrial fibrillation required rate control with metoprolol and amiodarone. He was otherwise treated supportively. His symptoms improved spontaneously and he was discharged after a 16-day hospitalization. By 3 months, his liver enzymes returned to normal and his skin rash resolved. His cardiac medications were discontinued, and he has remained in normal sinus rhythm. Follow-up echocardiogram demonstrated resolution of his pericarditis, and his lymphadenopathy was no longer apparent on clinical examination. The patient was not rechallenged with riluzole. He has continued to use the zolpidem intermittently as a sleep aid. He has now been observed for 1 year, and there has been no recurrence.

Discussion. A number of idiosyncratic reactions have been reported with the use of riluzole. The reported cases to date have demonstrated isolated organ involvement without a systemic reaction. These include case reports of acute hepatitis and pancreatitis caused by riluzole therapy.^{4,5} There have been two cases of hypersensitivity pneumonitis.^{6,7} These cases all had a focal inflammatory component. Liver biopsy in one case demonstrated an inflammatory reaction with the presence of mononuclear cells and plasmacytes.⁴ Lung biopsy in one of the cases of hypersensitivity pneumonitis also demonstrated a mononuclear infiltrate and loose epithelioid granulomas.⁷ In each of these cases, the inflammatory reaction was limited to a single organ and resolved with stoppage of riluzole. One case was rechallenged with riluzole after resolution of the patient's hepatitis with recurrence.⁴

The present case is an example of a rare idiosyncratic reaction that can occur with the riluzole in ALS. This is the first case report of a severe systemic inflammatory reaction occurring

within 2 weeks of beginning riluzole therapy. Secondly, this patient's reaction is atypical for the usual allergic hypersensitivity reaction. The previously reported adverse reactions have suggested a localized inflammatory component with involvement isolated to a single organ. Interestingly, in this case and in one previous case, there was a prominent granulomatous reaction. Finally, this is the first case to report life-threatening cardiac involvement as an acute reaction to riluzole.

Without a rechallenge with riluzole, one cannot conclude definitively that this reaction is caused by this medication. This was unlikely caused by zolpidem. The reaction resolved without stopping the zolpidem, and we are unaware of previous similar reactions attributable to zolpidem. Given the temporal onset within 2 weeks of the riluzole's initiation and the spontaneous resolution of the symptoms after the withdrawal of the medication, it is likely that riluzole was the cause. This case highlights the need to consider drug reaction with the occurrence of any single or multiorgan inflammatory reaction after the initiation of riluzole therapy. Although our case began acutely after the initiation of therapy, others have reported occurrences late as an idiosyncratic reaction.

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Ptosis as a feature of late-onset glycogenosis type II

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Glycogenosis type II, or acid maltase deficiency, is an autosomal recessive lysosomal storage disease caused by a deficiency of acid alpha-glucosidase. Diagnosis of glycogenosis type II is suspected in patients with a progressive proximal muscle weakness in combination with myopathic discharges on electromyogram and a raised serum creatine kinase. Diagnosis is confirmed by mutation analysis and muscle biopsy.¹

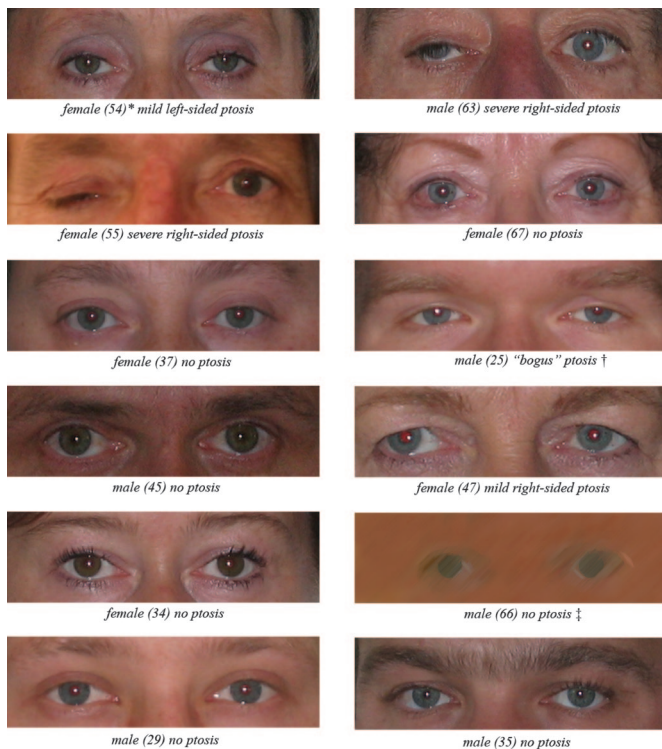
We investigated the association between glycogenosis type II and ptosis in a 37-year-old woman diagnosed with glycogenosis type II who initially presented to our neurologic center with unilateral ptosis and decreased levator function. Proximal,

truncal, and facial muscle weakness are common symptoms in glycogenosis type II. Weakness of the levator palpebrae muscle, however, is not a known feature of glycogenosis type II. Ptosis in patients with late-onset glycogenosis type II has incidentally been reported.^{2,3}

Methods. Twelve patients with biochemically proven late-onset glycogenosis type II were enrolled from the Dutch population: eight patients from the Radboud University Nijmegen Medical Centre and four patients from the Erasmus Medical Centre, Rotterdam. In all 12 patients, diagnosis of glycogenosis type II was confirmed by mutation analysis of the GAA gene, revealing compound heterozygosity for IVS1-(13T>G). Patients were excluded in cases of congenital ptosis or known comorbidity associated with ptosis, such as myasthenia gravis, mitochondrial myopathy, or cranial nerve III palsy. Patients underwent ophthalmologic examination including standardized photography of the eyes.

Ptosis is present when the upper eyelid is less than 2.0 mm from midpupil or when there is more than 2.0 mm of asymmetry between the left and right upper eyelid.⁴ Severity of ptosis is divided into mild (1.5 to 2.0 mm), moderate (0.5 to 1.5 mm), and severe (–0.5 to 0.5 mm) ptosis. The maximal upward deflection of the eyelid was measured to determine the levator palpebrae function. For statistical analysis, the Fisher exact test was used.

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* age in years

† the elevation of the lower lid suggests orbicularis oculi action as the cause of the apparent ptosis

‡ patient did not approve of publication of photograph

Figure. Standardized photograph of the eyes of 12 patients with glycogenosis type II.

Results. All 12 patients were willing to participate. Patients were compound heterozygous for IVS1-(13T>G) in combination with del exon18, delT525, Trp516Stop, Trp772Arg, or IVS2-4(C>G) mutation (table E-1 on the Neurology Web site at www.neurology.org). The average age was 46 years (range, 25 to 67). None of the patients had congenital ptosis or comorbidity that could have caused ptosis.

Four of 12 patients (33%) with glycogenosis type II had ptosis (figure). The average age of the patients with ptosis was 55 years (range, 47 to 63). In the general population (ages 50 to 59 years), a ptosis prevalence of 2.4% has been reported.⁵ This indicates a prevalence difference of 31% ($p = 0.018$). In three patients, ptosis initially was the first feature of glycogenosis type II. In the normal population, the levator function is 14 mm, with a range of 12 to 18 mm.⁶ In 6 of 12 patients (50%) with glycogenosis type II, the levator function was decreased. A correlation of 0.84 was found

between the occurrence of ptosis and a decreased function of the levator muscle ($p = 0.000$).

Discussion. We found a significantly higher prevalence of ptosis in late-onset glycogenosis type II compared with the general population. In three patients with glycogenosis type II, ptosis was the first feature of the disease. The correlation between ptosis and a decreased function of the levator muscle was 0.84, indicating a muscular cause of the ptosis. We conclude that ptosis is a feature of glycogenosis type II. Until now, glycogenosis type II was not a known cause of myogenic ptosis. Other causes of myogenic ptosis are mitochondrial myopathies, oculopharyngeal muscular dystrophy, oculopharyngodistal myopathy, and myotonic dystrophy. Myogenic ptosis is relatively uncommon and should be differentiated from other progressive forms of ptosis, including aponeurotic, neurogenic, traumatic, and mechanical causes. Ptosis of a myogenic cause should be suspected in any case with decreased levator function, particularly if muscular weakness in the extraocular muscles, face, or body is present.

This year, enzyme replacement therapy has become available for the treatment of glycogenosis type II.⁷ Early start of treatment is required because the effect depends on residual muscle function. Therefore, diagnosing glycogenosis type II in an early stage has become more important. Because ptosis is an easily recognizable feature and can be a presenting symptom of glycogenosis type II, identifying ptosis as a symptom of glycogenosis type II can facilitate early diagnosis.

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Unusual features in a boy with the rapsyn N88K mutation

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Fluctuating or episodic weakness starting in infancy is seen in congenital myasthenic syndromes (CMSs), periodic paralyses, and a disorder precipitated by febrile illness mapped to Xp22.3.¹ Mutations in rapsyn (*RAPSN*) cause congenital myasthenia and more

than 20 mutations with three different clinical phenotypes have been identified.^{2–4}

Case report. The patient, now 19 years old, developed cyanotic spells at age 3 days. He was hypotonic with a weak cry, but had no persisting respiratory difficulties. He received nasogastric feeding and antibiotics, despite normal infection parameters, and was discharged well after 3 days. At age 6 months, fever developed again, possibly due to a respiratory infection; he also had problems swallowing saliva and one episode in which he became cyanotic and increasingly hypotonic. His leukocyte count fell from 36.8 to 9.2 (normal 3.5 to 11.0 × 10⁹/L); chest x-ray, cerebral ultrasound, and EEG were normal. He was treated with oxygen and ephedrine and discharged well 5 days later.

During the next 5 years, he had five more attacks, all preceded by fever and characterized by generalized weakness, including facial and tongue muscles, ptosis, and diplopia. He became briefly respirator dependent on three occasions. Episodes lasted between 1 and 2 weeks, and he was healthy between attacks. After 5 years

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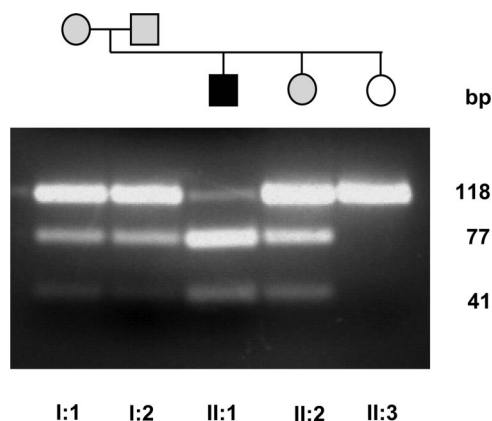


Figure. Restriction enzyme analysis for the N88K mutation in the family. To detect the RAPSN mutation N88K (264C>A), a PCR fragment of 118 bp containing exon 2 was amplified. Because the mutation creates a new BseNI site, the wild-type allele remains undigested, whereas the mutant allele yields two fragments (77 bp and 41 bp). The patient (II:1) is homozygous for the mutation, whereas the parents (I:1 and I:2) and one healthy sister (II:2) are heterozygous, and another sister does not carry the mutation (II:3).

of age, he had no more attacks. Currently, he participates in normal physical activities, but experiences occasional muscle cramps and transient diplopia during hard exercise, especially when it is hot. His mother has observed weak facial muscles when he is tired. Neurologic examination is normal, and there are no other members of the patient's immediate family with neurologic disease.

The following were normal or negative: serum potassium on admission; potassium and lactate after oral glucose loading with insulin; respiratory and cardiac responses to exercise; urine mass spectrometry during attacks; EEG; visual, auditory, and sensory evoked potentials; cerebral MRI, CT, and ultrasound; pyruvate dehydrogenase activity in fibroblasts; edrophonium test; acetylcholine receptor; citric acid; and titin antibodies.

Muscle biopsy showed occasional Z-line streaming only. Neurophysiologic testing (table E-1 on the *Neurology* Web site at www.neurology.org) showed transient minor myopathic changes aged 12, but no other evidence of neuromuscular dysfunction until aged 19 when single-fiber EMG showed increased jitter, but no neuromuscular transmission block. The entire coding region, promoter region, and adjacent intronic regions of the RAPSN gene were sequenced and the 264 C>A mutation leading to the amino acid exchange N88K identified (figure).

Discussion. Episodic muscular weakness associated with fever and the lack of any positive supplementary tests suggested that our patient had the X-linked disorder described in one Australian family.¹ Typically, however, these individuals have severe weakness that resolves spontaneously over weeks to months. Young patients are normal between episodes, although fatigability is seen and respiratory weakness is not a feature. A periodic paralysis was considered unlikely as exacerbation due to illness is uncommon and the pattern of weakness is different.

A CMS was considered from the onset. Our patient was, however, symptom free between attacks, had normal serologic and edrophonium tests and normal age-appropriate electrophysiologic

tests including no decrement following a conditioning train of 5 to 10 minutes of 10-Hz stimulation or exercise (table E-1). In the absence of another explanation, our patient was tested and found to be homozygous for the RAPSN N88K mutation.⁵ Mutations of the CHAT gene were excluded by direct sequencing of the entire CHAT gene.

Patients with RAPSN N88K typically present early or late.^{3,6} Late-onset disease starts between 13 and 48 years and is frequently mistaken for seronegative myasthenia gravis (MG). Patients have no bulbar or respiratory symptoms, but proximal weakness with marked weakness of ankle dorsiflexion that is unusual in MG. Two patients only had mild ptosis, and all had normal eye movements. Response to anticholinesterases is usually good. Symptoms are present from birth in the more common early-onset phenotype. Most show bulbar dysfunction, respiratory difficulties, and minor facial malformation. Arthrogryposis multiplex congenita is frequent, especially in compound heterozygotes with a truncated allele.⁶ More than half have worsening precipitated by febrile illness leading in many to episodic crises or apnea or both. Most have abnormal repetitive nerve stimulation or single-fiber EMG or both and a good response to acetylcholinesterase inhibitors, some with additional improvement with 3,4-diaminopyridine. Clinical symptoms generally improve with age, although ptosis is evident in half of the patients. Some muscle fatigability usually remains, but limb strength is often normal.³

Our patient expands the spectrum of phenotypes caused by RAPSN mutation. Despite an early onset, our patient shows no dysmorphic features or arthrogryposis and no ptosis or fatigability between attacks. During attacks, he had ptosis and diplopia, whereas patients with RAPSN mutations often have strabismus, but otherwise normal eye motility. Repetitive nerve stimulation was normal both during and between attacks, and there was no response to acetylcholinesterase inhibitors.

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