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MYOGLOBINURIA AND MUSCLE PAIN ARE COMMON IN PATIENTS WITH LIMB-GIRDLE MUSCULAR DYSTROPHY 2I

Fukutin-related protein (*FKRP*; OMIM #606596) is critical for the appropriate glycosylation of α -dystroglycan, a component of the dystrophin-glycoprotein complex. The 12-kb *FKRP* gene is composed of 3 noncoding exons and 1 exon encompassing the entire open reading frame.¹ Mutations in *FKRP* cause autosomal recessive muscular dystrophy with a wide range of clinical severity. A common missense mutation, c.826C>A (p.L276I), has been identified. Generally, individuals homozygous for this mutation have a mild form of limb-girdle muscular dystrophy (LGMD) 2I, compound heterozygotes with 1 c.826C>A allele have a more severe form of LGMD 2I, and those with 2 unique alleles are most severely affected, including some with congenital muscular dystrophy.^{1,2}

We report a high incidence of myoglobinuria and muscle pain in a retrospective study of patients with LGMD 2I.

Methods. *Standard protocol approvals, registrations, and patient consents.* Institutional Review Board approval was obtained for all recruitment and data collection. Written informed consent was obtained from all participants or their legal guardians. This study was posted on clinicaltrials.gov (NCT00313677). All patients with *FKRP* mutations were eligible for enrollment from 2006 to the present.

Genetic testing. *FKRP* mutations were confirmed in the University of Iowa Molecular Pathology Laboratory using an amplification-refractory mutation system (ARMS) assay, direct sequencing, or both. The ARMS assay identifies the c.826C>A *FKRP* variant and common point mutations in *SCGA* (c.229C>T in LGMD2D) and *SCGB* (c.341C>T in LGMD2E). Primer sequences and technical details are provided in appendix e-1 on the *Neurology*[®] Web site at www.neurology.org.

Clinical evaluation. Participants completed a questionnaire and interview regarding medical history and activities. Medical records were reviewed and selected items including age at onset, presenting symptoms, comorbidities, and laboratory testing were abstracted to a secure database. All participants were

specifically asked about any episodes of “cola-colored” or brown urine, and details surrounding the event.

Results. Twenty-six LGMD 2I patients have enrolled. Fourteen (54%) are homozygous for the c.826C>A mutation and 12 (46%) are heterozygous with 1 c.826 C>A allele and 1 other pathogenic allele. Self-reported age at onset of weakness was 13.6 ± 8.5 years for c.826C>A homozygotes, compared to 4.3 ± 3.5 years for patients with only 1 copy of the c.826C>A allele. Serum creatine kinase (CK) levels not associated with myoglobinuria ranged from 1,193 to 18,474 IU.

Seven patients (27%) have had at least 1 episode of myoglobinuria by self-report. Six of these 7 (86%) are homozygous for the c.826C>A mutation. Clinical features of those with myoglobinuria are summarized in the table. In 3 cases, the first bout of myoglobinuria led to the diagnosis of muscular dystrophy. In other patients, myoglobinuria occurred many years prior to diagnosis of muscular dystrophy, usually because patients did not report the problem to medical personnel (see the table). The first episode of myoglobinuria occurred before age 18 years in 6 individuals, and was precipitated by physical activity. No one in this group is known to have sustained renal damage. Serum CK as high as 56,000 IU was recorded in association with myoglobinuria.

Sixteen patients (61%) of the cohort reported significant muscle pain or cramps as part of their symptom complex, including 6 with myoglobinuria and 10 without. Eleven patients (69%) with myalgia are homozygous for c.826A>C and 5 (31%) are compound heterozygotes. Muscle pain, like myoglobinuria, was typically associated with physical exertion.

Discussion. Myoglobinuria and muscle pain were common features of the LGMD 2I phenotype in our series. Other series have variably reported myalgia¹⁻⁵ but 2 large series found a strikingly similar incidence of myoglobinuria (~25% of patients).^{4,5}

Of the patients with myoglobinuria described here and in the literature, all but 2 are homozygous for the common c.826C>A allele. These patients, with a milder phenotype, may engage in more vigor-

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Table Clinical characteristics of patients with myoglobinuria

Patient	Genotype	Age at diagnosis of muscular dystrophy, y	Age at onset of pain, y	Age at onset of myoglobinuria, y	No. of lifetime episodes of myoglobinuria	Precipitants of myoglobinuria
1	Homozygous c.826C>A	14	13	13	>15	Swimming, hiking, weight lifting
2	Homozygous c.826C>A	20	6	11	>50 ^a	Physical education class, weight lifting
3	Homozygous c.826C>A	7	9	6	4	Swimming, cold exposure
4	Homozygous c.826C>A	9	9	9	1	Wrestling match
5	Homozygous c.826C>A	32	10	16	3	Square dancing, sky diving
6	Homozygous c.826C>A	42	Cannot recall	8	>50 ^a	Running, playing basketball, football
7	Compound heterozygous c.826C>A and c.1141delG	11	None	8	2	Squats, step-ups

^a Two patients reported tea- or cola-colored urine associated with most athletic workouts over many years. (One viewed this as a sign that he had a good workout.)

ous activity (see activities listed in the table) and thus precipitate rhabdomyolysis. A similar pattern is seen in dystrophinopathy, where up to 37% of minimally symptomatic patients reported myoglobinuria,⁶ compared to rare reports in typical Duchenne muscular dystrophy.

We note that one of our patients, and at least 3 others in the literature,^{5,7} experienced anesthetic reaction suggestive of malignant hyperthermia. It will be important to clarify the frequency of this potential complication in future series.

Myoglobinuria can be precipitated by a wide variety of insults in healthy muscle or can be associated with myopathy. An underlying *FKRP* mutation should be considered in patients presenting with childhood-onset myoglobinuria who have sustained elevation of CK (>5× normal). In addition, management of patients with LGMD 2I should include specific questions about myalgia and myoglobinuria.

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MOTOR NEURON DISORDER WITH TONGUE SPASMS DUE TO PYRETHROID INSECTICIDE TOXICITY

Pyrethroids are widely used insecticides because of their high potency and relatively low toxicity to mammals.¹ Symptoms of acute pyrethroid neurotoxicity in humans include numbness, dizziness, muscle fasciculations, and, in more severe cases, hypersalivation, seizures, and coma.¹ Recently, 2 cases of partly or completely irreversible motor neuron disorder (MND) secondary to chronic pyrethroid inhalation were reported.^{2,3} We report a case of reversible MND and involuntary tongue movements (ITMs) secondary to transient pyrethroid overexposure.

Case report. A 60-year-old farmer presented a 3-month history of slurred speech due to ITMs, preceded by a burning sensation of the tongue and palate associated with facial paresthesias. ITMs were continuous without any clear triggering or alleviating factor. The patient denied traumatic event, infectious episode, or neuroleptic intake. Family history was unrevealing. He reported a similar episode 2 years earlier that resolved spontaneously over a few months. He admitted having used type II pyrethroid insecticides (λ -cyhalothrin and cypermethrin) disregarding the recommended precautions. He regularly manipulated (about 10 times per year for several years) the volatile liquid without protective gloves or mask, before pulverizing the product on his crop. The process exposed him to repeated low-dose exposure through inhalation and probably the dermal route.

His examination had normal results except for slightly slurred speech and continuous, irregular spasms of the tongue, lasting 0.2 to 2 seconds, equally present at rest and during tongue protrusion (videos 1 and 2 on the *Neurology*[®] Web site at www.neurology.org). No other orofacial territory was affected, including the palate.

Concentric needle EMG (CNEMG) revealed a neurogenic pattern of recruitment limited to the lower facial muscles bilaterally. Motor evoked potentials (MEPs) to transcranial magnetic cortical stimulation were altered in the tongue and lower facial muscles, normal in the limbs. The triple stimulation technique (TST)⁴ yielded a 50% loss (or dysfunction) of cortico-motor projections to the left hand.

Morphologic brain MRI was normal. Diffusion tensor imaging (DTI) revealed bilateral thinning of the corticospinal tracts (CSTs) with a reduced number of visible fibers (figure). CSTs were reconstructed

by using a well-established streamline method based on the fiber assignment by continuous tracking (FACT) algorithm.⁵

The patient was recommended to avoid pyrethroid exposure and was re-examined 4 months later. Tongue spasms had completely regressed (video 2), MUP recruitment markedly improved in facial CNEMG, except in the left mentalis muscle, and TST ratio and DTI-FACT returned to normal (figure).

Discussion. Our patient presented ITMs associated with neurophysiologic and imaging evidence of MND that resolved a few months after cessation of pyrethroid exposure. Repeated exposure to weak levels of pyrethroids induced neuronal death in animals, namely in the primary motor cortex.¹ This could explain the finding of irreversible motor neuron loss observed in the previously reported cases of pyrethroid-induced MND.^{2,3} By contrast, MND symptoms were reversible in our patient. We speculate that pyrethroids in our patient induced functional motor neuron impairment rather than cell death, manifesting as altered motor neuron excitability.

Pyrethroids prolong the open state of voltage-dependent sodium channels in nervous tissue, leading to axonal hyperactivity and repetitive discharges.¹ Pyrethroid neurotoxicity, especially that of type II, can manifest with chorea and hypersalivation, as signs of neuronal hyperactivity.¹ In our patient, paresthesias and ITMs suggested pyrethroid-induced axonal hyperactivity in the orofacial region. Interestingly, the specific action of pyrethroids on the excitability of hypoglossal motor neurons has been experimentally demonstrated.⁶ Conversely, we speculate that abnormal axonal excitability resulted in loss of function, explaining reversible MND symptoms. Functional motor neuron impairment may precede cell death due to irreversible “cellular” or “synaptic” excitotoxicity. “Cellular” excitotoxicity relates to intra-axonal Na⁺ overload due to prolonged sodium channel opening that in turn leads to increased Ca²⁺ influx. “Synaptic” excitotoxicity relates to an increased Ca²⁺ influx due to excessive glutamatergic neurotransmission in which non-NMDA receptors could play the major role.⁷ In both cases, excessive Ca²⁺ load activates neuronal cell death. In our patient, these events were probably prevented by the cessation of exposure.

Our case is an example of “functional,” reversible MND. It also illustrates that DTI-FACT is sensitive to fiber dysfunction and abnormalities do not necessarily imply fiber loss. The rapid normalization of CST

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(A) At initial presentation. (B) Four months after cessation of exposure to pyrethroids. Note the marked thinning of the bilateral corticospinal tracts (arrow) on the initial examination as compared to the follow-up investigation.

aspect on successive examinations favored reversible axonal dysfunction rather than axonal regrowth.

Pyrethroid neurotoxicity should be considered in orofacial movement disorders, especially if preceded by sensory symptoms and followed by signs of upper or lower MND. Our patient had an unusual overexposure to pyrethroids, and in practice pyrethroid-induced MND is probably rare. Nevertheless, it may be valuable to include the search for pesticide exposure in the diagnostic workup of MNDs.

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