Fragile X Tremor Ataxia Syndrome With Rapidly Progressive Myopathy

In this report, we describe a patient with clinically definite fragile X-associated tremor/ataxia syndrome (FXTAS) who experienced rapidly progressive, painless, noninflammatory proximal and distal myopathy after surgery with general anesthesia.

Report of a Case | A right-handed man in his 60s presented with a 10-month history of rapidly progressive motor impairment. His medical history was significant for type 1 diabetes mellitus, peripheral neuropathy, diabetic amyotrophy of the lower extremity, and complex partial sei-

zymes. He also reported a 20-year history of slowly progressive, bilateral hand tremor with action and intention. Family history was significant for fragile X syndrome in his sister’s son.

Ten months earlier, he had undergone total left hip arthroplasty under general anesthesia. After this, he developed rapidly progressive gait and limb ataxia, diffuse muscle weakness and atrophy, impairment of manual dexterity, head tremor, increased hand tremor, dysarthria, mild dysphagia, myoclonic jerking, and frequent falls. He reported orthostatic lightheadedness, nocturia, and erectile dysfunction but no myalgias or muscle cramps and no changes in cognition, motivation, or mood.

Examination showed moderate bilateral dysdiadochokinesis; dysmetria on finger–nose–finger and heel–knee–shin tests; and overshoot on finger follow. There was also mild dysarthria, titubation with standing, and mild-moderate gait ataxia. Extraocular movements were significant for saccadic pursuits and hypometric saccades; square wave jerks and nystagmus were absent. A bilateral jerky hand tremor was present with action and intention; no rest or postural tremor was observed. There was also mild cervical dystonia with left head turn, right head tilt, and a positional yes–yes head tremor. There was no parkinsonism. Diffuse proximal and distal muscle atrophy was noted in all 4 extremities. There was bilateral scapular winging, and right greater than left weakness (4− to 4+ power) in the biceps, finger extensors, and intrinsic hand muscles, particularly the right opponens digitig minimi. There was also weakness (4− to 4+ power) in the left greater than right iliopsoas, of bilateral plantar flexion, and of left ankle and great toe dorsiflexion. Spasticity and fasciculations were absent. There was diffuse hyperreflexia but the ankle jerks were absent. The plantar responses were flexor. There was mild impairment of distal vibratory sensation. The Montreal Cognitive Assessment score was 26 of 30, with impairment of repetition, abstraction, and delayed recall.

Genetic testing showed a fragile X premutation, with 90 CGG repeats in the fragile X mental retardation 1 gene. Brain magnetic resonance imaging showed mild cerebral and cerebellar volume loss and mild T2/fluid-attenuated inversion recovery hyperintensities in the pons and periventricular white matter. The middle cerebellar peduncle and corpus callosum splenium signs were absent. Electrodiagnostic testing of the right arm and leg showed evidence of a clear noninflammatory myopathy affecting the proximal and distal muscles and a moderate to severe large-fiber axonal peripheral myopathy. No active denervation was found. Muscle biopsy from the right quadriceps showed findings consistent with myopathy, including fiber size variation, but no definite signs of mitochondrial dysfunction (Figure). The following test results were all normal: complete blood cell count; electrolytes; renal, hepatic, and thyroid function tests; creatine kinase; erythrocyte sedimentation rate; anti-glutamic acid decarboxylase antibodies; celiac laboratories; other autoimmune and paraneoplastic serologies; vitamin B12 level; heavy metal testing; human immunodeficiency virus test; Lyme antibody; VDRL; serum protein electrophoresis;
immunofixation electrophoresis; and cerebrospinal fluid studies. The rheumatoid factor level was 54 IU/mL. Magnetic resonance imaging of the cervical and thoracic spine; computed tomographic scan of the chest, abdomen, and pelvis; and testicular ultrasonography were unrevealing. DaTscan (GE Healthcare) showed no evidence of a dopaminergic deficit.

Discussion | To our knowledge, this is the first report of documented myopathy in FXTAS. Prior studies have described leg weakness in FXTAS1 and fibromyalgia symptoms in female carriers of the FXTAS premutation4,5; however, the current study is the first to demonstrate the presence of myopathy. The myopathy observed in this case was not an incidental finding, but rather one of the major and most disabling features of his presentation. Together, these observations broaden the spectrum of clinical manifestations of FXTAS6,6 and underscore the potential risks of surgery with general anesthesia1,7 in this population.

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COMMENT & RESPONSE

Subthalamic Nucleus Deep Brain Stimulation in Parkinson Disease

To the Editor We read with interest the article by Jung et al1 reporting the effects of subthalamic nucleus deep brain stimulation (STN DBS) on pain characteristics in patients with Parkinson disease (PD) after an 8-year follow-up. These findings provide new insights into the mechanisms by which DBS improves pain and its long-term effects.

Despite the beneficial long-term effects of STN DBS on pain in patients with PD, some considerations should be pointed out. Although the overall pain intensity improved, pain prevalence increased from 67% to 83%, and new-onset pain developed in most of the patients during the 8-year follow-up. Common reasons associated with chronic pain incidence in the general population (eg, diabetic neuropathy and osteoarthritis) were largely ignored in the article.1 Nevertheless, the number of patients reporting fluctuations in pain with motor symptoms (fluctuating pain) decreased significantly after surgery, suggesting that DBS could improve motor fluctuations and pain by different mechanisms.2 In addition, while dystonic pain responded well to DBS (usually presenting during off periods), other syndromes, such as neuropathic and musculoskeletal pain, did not seem to do so. The authors concluded that musculoskeletal pain does not respond to STN DBS.1 We found strikingly different data 1 year after DBS in a group of 41 patients with PD prospectively assessed for the effects of DBS in nonmotor symptoms.2 These differences probably resulted from a lack of validation and specificity of current classifications of pain in PD. There is currently no validated pain classification system for PD pain that takes into account the various aspects of pain,1 its impact on daily activities,4 the presence of neuropathic pain as it is presently defined,5 or standardized information on the presence of pain fluctuation according to motor symptom swings. Also, secondary hyperalgesia in areas of referred pain from myofascial trigger points are frequently overlooked6 and may lead to the overdiagnosis of central pain, which itself does not have formal diagnostic criteria or a validated definition.

It is unlikely that a single intervention will relieve all types of pain that patients with PD may present with, so it is imperative to better define and classify the different pain syndromes related to PD. We believe the time has come to consider that improving the classification of pain in patients with PD is a major unmet need in the care of these patients and it would constitute the backbone of future evidence-based trials of its treatment.

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In Reply We thank Cury et al for their interest in our article.1 In our study, we included any type of pain that the patients reported, irrespective of its presumptive causes, which is more relevant to clinical situations than excluding pains that may have causes other than Parkinson disease (PD). As a result, in contrast to the study by Cury et al,2 the prevalence of pain increased during the 8-year follow-up primarily owing to the development of new pain, despite the improvement in the severity of pain. However, our short-term results showed that the prevalence of pain decreased at 2 years after subthalamic nucleus deep brain stimulation (STN DBS) compared with baseline as shown in Figure 1B of our article,3 which is in line with Cury et al.

Our study did not indicate that musculoskeletal pain does not respond to STN DBS. Rather, it showed that STN DBS has a beneficial effect on musculoskeletal pain in patients with PD. Curry et al2 surveyed the prevalence of each type of pain; however, we evaluated the effect of STN DBS on pain in terms of prevalence and severity. Although the magnitude of improvement was smaller than other types of pain, musculoskeletal pain also improved after STN DBS by 29% in severity after 8 years, despite the fact that most of the newly developed pain was the musculoskeletal type. Fur-