as none of the other affected individuals, including the most severe, exhibited this finding.

Discussion. The modified Harding classification of ADCAs broadly sorts SCAs into 4 groups.[2] All of these designations allow for cerebellar ataxia where oculomotor abnormalities are nearly uniformly seen. Virtually all patients with SCA display gaze-evoked nystagmus and abnormalities of the slow visual-tracking systems which localize to the posterior vermis, flocculus, and paraflocculus.[7] These deficits are seen in ataxias due to both expanded repeats and point mutations.

The importance of accurate clinical classification of the various SCAs is increasing, as clinical trials are currently under way in an effort to finally provide relief in these debilitating conditions. Ultimately, molecular diagnoses will provide the genetic anchors allowing us to classify patients into homogeneous groups. However, this remains costly, forcing an appropriate step-wise approach when presented with a patient with acquired ataxia. The challenge for the clinician is prudence in ordering molecular testing which can be further economized by thoughtful consideration of the appropriate potential mutations. In evaluating the patient with clinical symptomatology of a spinocerebellar ataxia, the absence of striking oculomotor features may be consistent with the p.Arg420His allelic form of SCA13.

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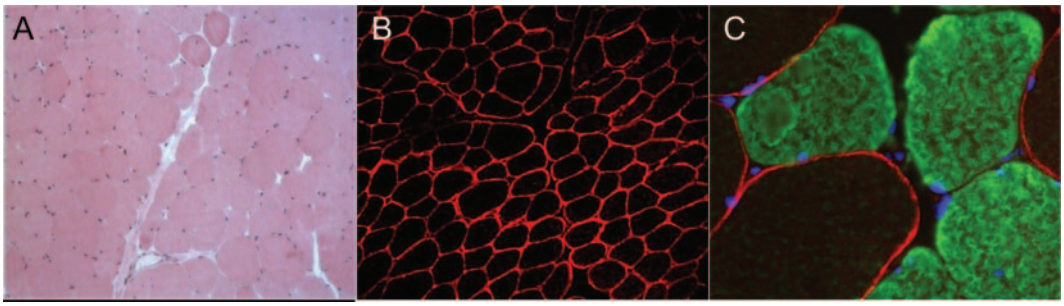
RECURRENT HYPERCKEMIA WITH NORMAL MUSCLE BIOPSY IN A PEDIATRIC PATIENT WITH NEUROMYELITIS OPTICA

Neuromyelitis optica (NMO) is a demyelinating disease of the CNS that preferentially affects the optic nerve and spinal cord.[1] The presence of circulating autoantibodies (NMO–immunoglobulin G [IgG]) having the water channel aquaporin-4 (AQP-4) as their target antigen is associated with NMO.[1] Outside the CNS AQP-4 is present in the distal collecting tubes of the kidney, in parietal cells of the stomach,[2] and in fast-twitch fibers of skeletal muscle.[3] Several findings support the idea that AQP-4 water channels may be associated to the dystrophin-glycoprotein complex (DGC) in skeletal muscle fibers and AQP-4 expression has been found altered in muscle diseases.[4]

We describe the case of a 13-year-old girl with NMO experiencing recurrent episodes of hyperCKemia.

Case report. The patient had been well until 2006, when she developed the first acute myelitis presenting with paraparesis, hypoesthesia, and paresthesias below the C7 level. MRI of the spinal cord showed the presence of a hyperintense lesion, extending from C7 to T9. Brain MRI was normal. A CSF analysis showed lymphocytic pleocytosis (85 cells/mm^3) and absence of oligoclonal IgG bands. She responded well to IV methylprednisolone (1 g daily for 5 days) and IVIg (0.4 g/kg body weight daily for 5 consecutive days). In 2007, a bilateral optic neuritis occurred. Brain MRI showed the presence of fluid-attenuated inversion recovery signal abnormality around the third ventricle. A repeat CSF analysis showed lymphocytic pleocytosis (10 cells/mm^3). Hematologic tests were normal as well as screening for autoimmune and infectious conditions (including testing for antinuclear antibodies, anti PM-Scl antibodies, antineutrophil cytoplasmic antibodies, lupus

Figure Patient's muscle biopsy



(A) Hematoxylin-eosin staining (×10) shows a normal histologic pattern. (B) A normal localization of AQP-4 (antibody purchased from Sigma-Aldrich, St. Louis, MO) at the surface of type 2 muscle fibers (×10). (C) Double immunofluorescence with anti AQP-4 (red) and anti-myosin heavy chain-slow (green) antibodies shows a preferential localization of AQP-4 around fast myofibers (unstained for myosin). Nuclei were visualized using DAPI-conjugated (blue) mounting medium (×40).

anticoagulant, anticardiolipin antibody, and anti-Borrelia, Treponema pallidum hemagglutination, and HIV serologies). NMO-IgG (on primate cerebellum) and anti-AQP-4 antibody (on AQP-4-transfected cells; Euroimmun, Lübeck, Germany) testings were positive (anti-AQP-4 antibody titer, 1:500). The patient was diagnosed with NMO. In the following year she experienced other clinical attacks (both optic neuritis and myelitis episodes), requiring IV methylprednisolone. In August 2008, the patient was admitted to the Section of Neurology, Perugia, Italy, because of a cervical myelitis. Laboratory tests demonstrated hyperCKemia (5,465 IU/L, normal values 0–180). In the following days CK rose to 15,818 IU/L. HyperCKemia was accompanied by a concomitant increase of lactic dehydrogenase (1,079 IU/L, normal values 225–450), glutamic-oxaloacetic transaminase (320 IU/L, normal values <45), and myoglobin (677.7 ng/mL, normal values 14.3–65.8). No significant alterations of CK-MB levels were demonstrated. No laboratory evidence of liver dysfunction/disease was found. After 5 days, CK declined to 1,386 IU/L, and then it remained mildly elevated (591 IU/L) in the following weeks. In September 2008, CK rose again to 14,163 IU/L. The patient was asymptomatic with the exception of mild myalgia. Repeat CK 30 days later was 340 IU/L. At the end of September 2008, therapy with azathioprine (2 mg/Kg) was started, with good clinical response. In November 2008, CK rose again to 4,068 UI/L, and then it progressively declined. A retrospective analysis of the patient's medical records also revealed another asymptomatic episode of moderate hyperCKemia in 2007 (1,985 IU/L) that occurred in association with a bilateral optic neuritis treated with methylprednisolone (1 g daily for 5 days). No clinical or laboratory evidence of muscle disease was found before 2007. During the second hyperCKemia episode, EMG was performed twice and it did not demonstrate myopathy or neurogenic changes. Muscle biopsy (taken from the vastus lateralis when CK levels were 7,828 UI/L) failed to show any major histopathologic alteration (figure, A). Immunofluorescent staining showed a normal sarcolemmal reactivity for dystrophin, dysferlin, and caveolin-3. Staining of AQP-4 was performed, ruling out a massive loss of AQP-4 at the surface of type 2 muscle fibers (figure, B and C). No other major causes of hyperCKemia, including medications,[5] were found.

Discussion. The occurrence of hyperCKemia episodes in 3 anti-AQP-4 antibody-positive NMO female patients has been recently described, suggesting the possibility of an anti-AQP-4 antibody-mediated attack to the sarcolemma.[6] This possibility is compatible with what we observed in our patient, particularly with the relapsing behavior of the hyperCKemia episodes. However, muscle biopsy findings excluded major histopathologic muscle alterations. In particular, both histopathologic and AQP-4-specific stainings reciprocally concurred to exclude inflammatory myopathy and significant losses of sarcolemmal AQP-4.

However, the utilized morphologic methods could not detect a partial loss of AQP-4 and the potential multifocality of the inflammatory pattern could have limited our potential to detect histopathologic abnormalities. Moreover, it is known that in about 30% of patients with pauci-asymptomatic hyperCKemia, muscle biopsy, even after comprehensive immunocytochemical and biochemical studies, is normal.[5] To date, the real prevalence and pathogenetic meaning of hyperCKemia in NMO remain unknown.

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