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OCULOMOTOR AND VISUAL AXIS SYSTEMS SPARING IN SPINOCEREBELLAR ATAXIA TYPE 13^{R420H}

Spinocerebellar ataxia type 13 (SCA13) has been described to have both neurodevelopmental and neurodegenerative phenotypes. Three distinct mutations, all occurring in the KCNC3 voltage-gated potassium channel, have been shown in vitro to have unique biophysical properties.¹ The p.Phe448Lys and p.Arg423His mutant alleles share a profound developmental phenotype with delayed motor milestones, mental retardation, and epilepsy.

In contrast, p.Arg420His shows a neurodegenerative phenotype reminiscent of other SCAs. Onset ranges from the second to fourth decade. Once clinical symptoms declare, there is a slow though relentless progression with prominent truncal and appendicular ataxia, gait instability, and dysarthria. The electrophysiologic properties of this mutant allele are consistent with a null mutation. Coexpression with wild-type *Shaw* alleles demonstrates a subtype-specific dominant negative effect.¹

The description of SCA types has grown considerably in the last decade, as have their attendant etiologies. Though many SCAs are trinucleotide repeat diseases, several are now attributable to point mutations. Historically, the differential diagnosis of these disorders has been difficult. There is considerable phenotypic overlap among the SCAs and clinical heterogeneity within single genotypes.^{2–4} Often, patients presenting for evaluation are so advanced as to mask subtle phenotypic features obfuscating identifying characteristics of particular subtypes. Though molecular diagnostics are available, pan screening is prohibitively expensive. Though no current effective treatments exist, accurately identifying each SCA is imperative in designing clinical trials toward treatment development.

We examined a Filipino kindred harboring the SCA13^{R420H} mutation to investigate phenotypic features that may assist in differentiating this disease from other SCAs.

Methods. Forty-one members of a 3-generation Filipino kindred segregating the *KCNC3*^{R420H} allele were comprehensively examined. Of these individu-

als, 21 were affected and 20 were unaffected. The affected individuals ranged in age from 10 to 82 years old. Of this group, 7 were presymptomatic, 2 were minimally affected with a Scale for the Assessment and Rating of Ataxia (SARA) score⁵ of 1–1.5 and Functional Stage⁶ of 0.5–1, and the remainder had SARA scores ranging from 4 to 32.5, Functional Stages from 2 to 5, and a disease duration ranging from 5 to 48 years. Due to examination conditions, formal direct-current electro-oculography including horizontal optokinetic nystagmus drum and vestibulo-ocular reflex testing were not performed, allowing that electrophysiologic examinations may have revealed more subtle findings. However, particular attention was given to oculomotor pathologies as well as other defining characteristics along the visual axis representative of what would be available to a community-based neurologist. This examination included assessments for gaze-evoked horizontal/vertical nystagmus, slow/hypometric/hypermetric saccades, fragmented smooth pursuit, square wave jerks on fixation, horizontal/vertical ophthalmoplegia, diplopia, abnormal visual acuity, and optic nerve atrophy.

Standard protocol approvals, restrictions, and patient consents. University of Florida institutional review board approval for this study and signed informed consents for all patients examined have been retained.

Results. The 20 unaffected individuals in this pedigree demonstrated no clinical signs of oculomotor abnormalities. Surprisingly, of the 21 affected individuals, 14 of whom were symptomatic, marked oculomotor abnormalities were also absent. This was observed in spite of the fact that 10 of these individuals had SARA scores ≥ 8 . The 2 most severely affected individuals (SARA 29 and 32.5) were also spared.

Two patients did demonstrate slight delay in initiation of ballistic saccades, 1 showing increased eye-blink during this delay. These patients were at a median regarding disease severity and duration with SARA scores of 8 and 10.5 and Functional Staging of 2 and 3. Disease duration in this subgroup was 10 and 23 years. This finding is of unclear significance

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/mm³) 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/mm³). 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