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J. GORDON MILLICHAP, MD. EDITOR
JOHN J. MILLICHAP, MD. ASSOCIATE EDITOR

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HEREDO-DEGENERATIVE DISORDERS

SPINOCEREBELLAR ATAXIA 21 WITH RETARDATION

Investigators at Universite de Lille Nord de France, and other centers in France, report the identification of a novel causative gene for spinocerebellar ataxia 21, an autosomal dominant disorder, initially mapped to chromosome 7 and designated as SCA21. The gene, TMEM240, has various mutations in eight SCA families. The ataxia was first described in a large French family with slowly progressive cerebellar ataxia, mental retardation, and severe cognitive impairment in two young children. The present researchers identified a coding mutation in the TMEM240 gene in the original SCA21 pedigree. To date, 37 different genetic loci have been associated with SCA subtypes, and 22 causative genes have been identified. Screening by whole exome sequencing of 368 French families from the SPATAX network of hereditary paraplegias and cerebellar ataxias detected the causative mutation in two other unrelated families.

The clinical features of patients with TMEM240 mutations are as follows: 1) early onset with delayed cognitive and motor skills; 2) mental retardation with frontal behavior disorders (impulsivity, aggressive, apathy); 3) clumsiness presenting age 2 to 20 years; and 4) cerebellar ataxia. Cognitive impairments in 3 children tested at age 9-13 yrs and 3 adults (25-54 yrs) involved abstract reasoning, visual working memory, visual episodic memory, executive functions, visuospatial functions, speed of information processing, and selective attention. MRI shows cerebellar atrophy of the vermis and hemispheres with sparing of brainstem. Mild iron overload is noted in several cases, most severe in red nucleus and pallidum. (Delplanque J, Devos D, Huin V, et al. TMEM240 mutations cause spinocerebellar ataxia 21 with mental retardation and severe cognitive impairment. **Brain** 2014 Oct;137(Pt 10):2657-63).

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COMMENTARY. Childhood onset SCAs and their clinical features in addition to ataxia include dentatorubropallidoluysian atrophy (chorea, dystonia, seizures, dementia), SCA13 (mental retardation), SCA with tremor, cognitive defects, and facial dyskinesia, and Friedreich ataxia variant [1]. Testing for SCA21 is recommended in families with early onset mild or slowly progressive ataxia, particularly when associated with moderate to severe cognitive impairment. The causative gene in SCA21, TMEM240, is highly expressed in the cerebellum, dentate gyrus, putamen and caudate nucleus. The authors note that another transmembrane protein (TMEM237) is involved in Joubert syndrome-related disorders, characterized by midbrain malformation with hypoplasia of the cerebellar vermis [2].

References.
1. Ropper AH, Samuels MA. Adams and Victor's Principles of Neurology. 9th ed. New York: McGraw Hill Medical; 2009. Chapter 39, Table 39-5; p. 1052.
2. Huang L, et al. Am J Hum Genet. 2011 Dec 9;89(6):713-30.

COGNITIVE IMPAIRMENTS IN ATAXIA-TELANGIECTASIA

Investigators from Massachusetts General Hospital, Boston, and centers in Frankfurt, Germany, examined 22 patients with the classic phenotype of ataxia-telangiectasia for neurocognitive features, and compared patients with early stage cerebellar disease (group AT-I) versus those with late stage cerebrocerebellar disease (group AT-II). Group AT-I patients scored low average compared with standard norms on all tests and were significantly impaired compared with healthy controls for verbal IQ, vocabulary and comprehension, processing speed, visuospatial processing, and working memory. Group AT-II patients scored below average on all tests for attention, working memory, and abstract reasoning. Comprehension scores were lower for patients in AT-II than in AT-I, whereas vocabulary scores showed no difference between groups. Cognitive impairments in ataxia-telangiectasia present early, coinciding with cerebellar pathology and are characteristic of the cerebellar cognitive affective syndrome. Cognitive impairments worsen in later stages of ataxia-telangiectasia, and correlate with development of supratentorial, noncerebellar pathology. (Hoche F, Frankenberg E, Rambow J, et al. Cognitive phenotype in ataxia-telangiectasia. **Pediatr Neurol** 2014 Sep;51(3):297-310).

COMMENTARY. The cerebellar cognitive affective syndrome (CCAS) associated with acquired cerebellar lesions is characterized by cognitive impairment, disorders of executive and visuospatial function, and expressive language and affective disorders. The behavioral developmental profile of patients with congenital cerebellar malformations is variable but similar to the CCAS. Malformations affecting the cerebellar vermis induce affective and social disorders, evolving to an autistic symptomatology, whereas malformations of cerebellar hemispheres are associated with selective neuropsychological deficits involving executive functions and visuospatial and linguistic abilities [1]. Patients with ataxia-telangiectasia, a neurodegenerative disorder, display a cerebellar motor phenotype during their first to third year of life and later, with involvement of noncerebellar or cerebrocerebellar circuits, the progression of cognitive and behavioral disorders is apparent. Functional neuroimaging studies during the phase of