OBSERVATION

Cerebellar Ataxia With Progressive Improvement

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Background: Nonprogressive cerebellar ataxias are characterized by a persistent, nonprogressive ataxia associated with cognitive impairment. Cerebellar hypoplasia on imaging is variable but is not predictive of the degree of ataxia or cognitive impairment.

Objective: To describe a family with a nonprogressive cerebellar ataxia associated with cognitive and motor impairments that improve with age.

Design: Genetic study in a family with nonprogressive cerebellar ataxia. Clinical and imaging features are also described.

Setting: Community hospital.

Patients: Both parents and 3 children from an affected family.

Main Outcome Measures: Clinical features, magnetic resonance imaging findings, and genetic findings.

Results: A genome-wide single nucleotide polymorphism screen did not show clear linkage to known spinocerebellar ataxia loci, in particular spinocerebellar ataxia type 15. Repeat spinocerebellar ataxia loci expansions were excluded. Magnetic resonance images of all affected individuals demonstrated cerebellar vermian abnormalities.

Conclusions: These findings suggest that nonprogressive cerebellar ataxia is genetically heterogeneous and, when associated with gradual improvement in cognition and motor skills, likely represents a separate, distinct clinical entity.

Arch Neurol. 2006;63:594-597

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NONPROGRESSIVE CEREBELLAR ataxias (NPCAs) are characterized by a congenital ataxia, which is persistent, nonprogressive, and associated with cognitive impairment.[1] Cerebellar hypoplasia on imaging is variable, presenting in half of the affected children, but is not predictive of the degree of ataxia or cognitive impairment.[2] Although this disorder is largely sporadic, families with NPCA have been reported to exhibit autosomal recessive,[2,3] autosomal dominant,[4-6] and sex-linked recessive[7,8] modes of inheritance. A recent study[6] suggested that the rare autosomal dominant form of this disorder overlaps with the spinocerebellar ataxia type 15 (*SCA15*) locus. We describe a family with a form of NPCA that improves with age and that does not localize to the *SCA15* locus or the repeat expansions in known SCA regions.

REPORT OF A CASE

The 34-year-old gravida 4 para 3 mother (I:2 in **Figure 1**) was born after 55 hours of labor, was given a diagnosis of cerebral palsy, and had learning difficulties in school, having been held back for 3 different grades. As a child she noted difficulty walking, which was attributed to limb-length discrepancy and scoliosis. Her neurologic examination now reveals only mild gait ataxia that has improved since childhood. Magnetic resonance imaging of the brain was notable for a small vermis, a mega cisterna magna, thinning of the splenium of the corpus callosum, and possible heterotopic gray matter (**Figure 2**A).

All the children were born after uncomplicated pregnancy and vaginal delivery and had normal birth weights. The 9-year-old boy (II:1 in Figure 1) was referred at age 2 years because of developmental delay. His parents noticed that he did not begin walking until age 20 months and then that he did not walk well until age 24 months. At that time he had gait ataxia, had normal muscle tone, and was uncoordinated in the use of his hands to grasp objects, with fine motor skills estimated to be at the 12.5-month level. Subsequently he continues to have developmental delay but is improving symptomatically. Neurologic examina-

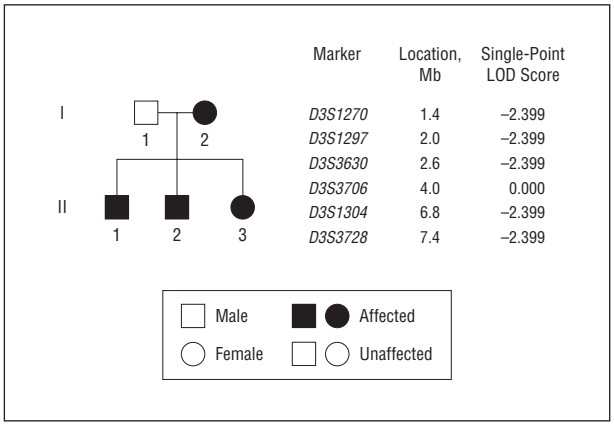

Figure 1. Pedigree of a family with an autosomal dominant, nonprogressive cerebellar ataxia that improves with age. The disease does not seem to map to chromosome arm 3p by single-point logarithm-of-odds (LOD) score. Database is National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/ and http://genome.ucsc.edu/).

tion now reveals normal speech and language except for alexia. He can recognize and write individual letters and can follow 3-step commands. There is no dysarthria. He has a slightly ataxic gait but normal finger-to-nose and fast finger movements. Magnetic resonance imaging of the brain was notable for callosal and vermian dysgenesis, a mega cisterna magna, and band heterotopia around the lateral ventricles posteriorly (Figure 2B and C).

The 5-year-old boy (II:2 in Figure 1) was referred at age 14 months because of developmental delay. His parents noticed that, like his brother, he was slow to develop language. At that time his examination showed central and truncal hypotonia with normal extremity tone. Subsequently he was slow to begin walking (22 months) and preferred to use his toes while walking with an ataxic gait. He has continued to have developmental language delay but is improving. His neurologic examination now reveals normal speech and language except for alexia. There is no dysarthria. He can follow 2-step commands. He has a slightly ataxic gait but normal finger-to-nose and fast finger movements. Magnetic resonance imaging of the brain demonstrated a slightly small cerebellar vermis, a diffusely thinned corpus calosum, and a mega cisterna magna (Figure 2D).

The 3-year-old girl (II:3 in Figure 1) was referred at age 7 months because of developmental delay. At that time her examination showed generalized truncal and limb hypotonia. Subsequently she began walking at age 24 months and preferred to use her toes while walking with an ataxic gait. She has developmental language delay but is improving. Her neurologic examination now reveals normal speech using 2- to 3-word sentences without evidence of dysarthria. She cannot read letters but can follow 1-step commands, can pass objects between her hands, and reaches for objects without evidence of dysmetria or dysdiadochokinesia. The reflexes are normal and symmetric, but with plantar responses bilaterally. Her gait is ataxic. Magnetic resonance imaging of the brain demonstrated mild dilatation of the occipital horns, partial agenesis of the posterior aspect of the corpus callosum, a mega cisterna magna, and a hypoplastic cerebellar vermis (Figure 2E and F).

The 35-year-old father (I:1 in Figure 1) had normal findings on neurologic examination and brain imaging. The family history is notable only for a maternal uncle with mental retardation and seizures.

MOLECULAR STUDIES

This study was reviewed and approved by the Children's Hospital, Boston, institutional review board, and informed consent was obtained from the participants. Genomic DNA was extracted from peripheral whole blood lymphocytes using standard techniques (Qiagen, Valencia, Calif). Repeat expansions at *SCA1*, *SCA2*, *SCA3*, *SCA7*, *SCA8*, *SCA10*, *SCA12*, *SCA17*, and dentatorubral-pallidoluysian atrophy (*DRPLA*) loci were investigated by polymerase chain reaction using commercial laboratories. For a genome-wide screen, single nucleotide polymorphism analyses were performed on the affected individuals using the 10K Array Xba 142 2.0 set (Translational Genomics Research Institute, Phoenix, Ariz) according to the manufacturer's instructions. The DNA chip data were analyzed using DNA-Chip Analyzer software.[9] Additional linkage studies were performed using microsatellite markers (Applied Biosystems, Foster City, Calif) that localize to chromosome arm 3pter, the *SCA15* locus (*D3S1270*, *D3S1297*, *D3S3630*, *D3S3706*, *D3S1304*, and *D3S3728*). Statistical calculation of single-point logarithm-of-odds scores was performed using the Allegro or DNA-Chip Analyzer program, assuming $\theta = 0$, an autosomal dominant mode of inheritance, and a disease frequency of 1:10 000; given the early onset of disease, penetrance was set at 1.00.

RESULTS

No repeat expansions at the *SCA1*, *SCA2*, *SCA3*, *SCA7*, *SCA8*, *SCA10*, *SCA12*, *SCA17*, and *DRPLA* were detected by polymerase chain reaction. Negative logarithm-of-odds scores were obtained by a single nucleotide polymorphism genome-wide screen for *SCA1*, *SCA4*, *SCA6*, *SCA7*, *SCA8*, *SCA10*, *SCA12*, *SCA13*, *SCA14*, *SCA16*, *SCA19*, *SCA22*, *SCA24*, and *DRPLA*. Analysis of microsatellite markers for chromosome arm 3p excluded this region as a potential locus. The pedigree size was too small to definitively identify a gene locus.

COMMENT

No clear clinical and radiographic criteria have been established for NPCA. Families with NPCA uniformly show mild-to-moderate early-onset nonprogressive ataxia and delayed motor milestones. However, cognitive impairments and learning problems are only demonstrable in approximately half of the affected individuals.[6] Other clinical findings, such as dysarthria, nystagmus, dysmetria, and brisk tendon reflexes, are not consistent in members of the same family. Moreover, the radiographic finding of cerebellar hypoplasia is variable, and the degree of cerebellar dysgenesis does not correspond to the level of cognitive or motor impairment. Boys have been reported to be more affected in another previous study.[10]

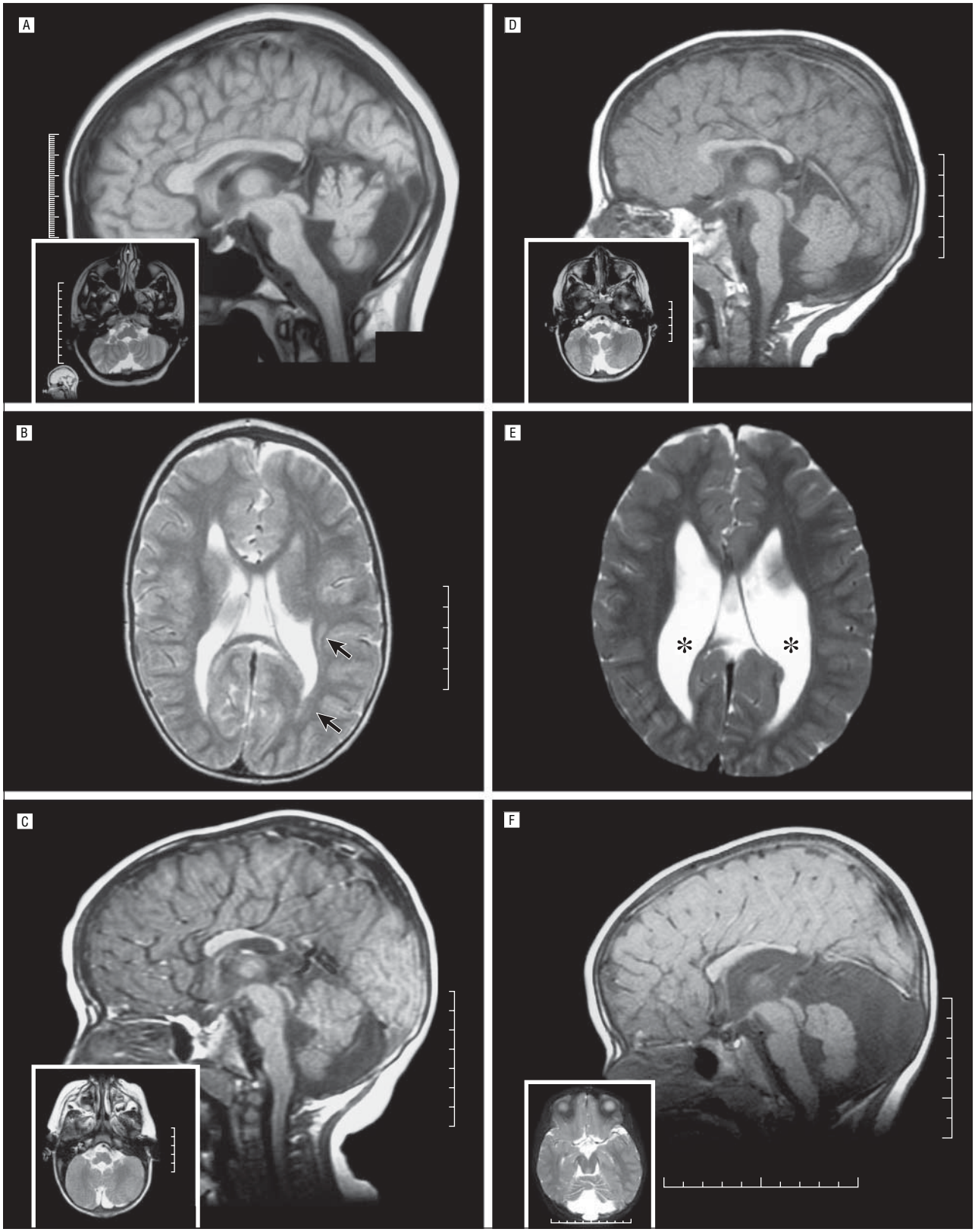

Figure 2. Magnetic resonance images (MRIs) of the brain of affected individuals. Insets represent axial MRIs at the level of the cerebellum and brainstem that show the uniform finding of vermian atrophy in all affected individuals. The scales are in centimeters. A, Sagittal T1-weighted MRI of the mother (I:2) demonstrates cerebellar vermian atrophy, a mega cisterna magna, and collosal thinning. B, Axial T2-weighted MRI of the oldest affected son (II:1) shows subcortical heterotopia (arrows) along the lateral ventricles. C, Sagittal T1-weighted MRI of the same individual is also notable for inferior vermian hypogenesis, a mega cisterna magna, and callosal thinning. D, Sagittal T1-weighted MRI of the middle child (II:2) is remarkable for a cerebellar vermian hypoplasia, decreased white matter volume, and a mega cisterna magna. E, Axial T2-weighted MRI of the youngest child, a girl (II:3), demonstrates mild ventriculomegaly (asterisks). F, Sagittal T1-weighted MRI of the same individual reveals hypoplasia of the cerebellar vermis, a mega cisterna magna, and dysgenesis of the posterior aspect of the corpus callosum.

Three previously described families with NPCA have been found to have cerebellar hypoplasia, delayed cognitive and motor development, and progressive improvement of coordination and ataxia with increasing age.[4,5,11] Exclusion of known SCA gene expansions or linkage to known SCA loci has not been performed in these families. The present study describes a fourth family with these same characteristics. Taken in this context, the forms of NPCA can be classified into at least 2 subtypes—disorders that show improvement of coordination and ataxia with increasing age (possibly due to maturation of the cerebellar system) and disorders that show only no progressive worsening of clinical deficits.

These forms represent a group of genetically heterogeneous disorders. No identified repeat expansions in or clear linkage to the known SCA regions and exclusion of the *SCA10* and *SCA15* loci in the current family with NPCA (that improves with age) suggest a possible new genetic basis for this disorder. The possible patterns of transmission are autosomal dominant, mitochondrial, and X-linked dominant. In addition, the findings in this family further support the idea that many adults previously labeled with cerebral palsy in childhood have imaging findings of brain malformations, with associated genetic implications.

Further classification of the different forms of congenital NPCA are necessary to identify causative genes. Consistent radiographic findings (vs variable findings) of cerebellar vermian abnormalities in any given pedigree may represent one basis for distinguishing the different disorders. Clinical recognition of improving cognitive and motor deficits vs nonprogressive cognitive and motor deficits may serve as a secondary basis for classification.

Accepted for Publication: December 5, 2005.
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Funding/Support: This study was supported by grant R37 NS35129 from the National Institute of Neurological Disorders and Stroke (Dr Walsh), grant 6-FY00-132 from the March of Dimes (Dr Walsh), grant 1KO8MH/NS63886 from the National Institute of Mental Health (Dr Sheen), and the Milton Fund (Dr Sheen). Dr Walsh is an Investigator of the Howard Hughes Medical Institute. Dr Sheen is a Charles A. Dana fellow and Beckman Young Investigator.
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Additional Information: Because the boys initially appeared more severely affected (suggesting at that time an X-linked mode of transmission), the *OPHN1* gene was sequenced and found to be normal by Laurent Villard, PhD, at the University of Marseilles, France.
Acknowledgment: We thank the family members for their cooperation.

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