CLINICAL/SCIENTIFIC NOTES OPEN ACCESS

Blended phenotype of adult-onset Alexander disease and spinocerebellar ataxia type 6

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Neurol Genet 2020;6:e522. doi:10.1212/NXG.0000000000000522

Alexander disease is an autosomal dominant hereditary disease characterized by progressive spastic paraplegia, ataxia, and bulbar symptoms caused by mutations in the glial fibrillary acidic protein (*GFAP*) gene. Previous nation-wide surveillance revealed that the prevalence rate in Japan is estimated at 1 in 2.7 million people.[1] Meanwhile, SCA6 is an autosomal dominant spinocerebellar ataxia characterized by adult-onset pure cerebellar ataxia. The prevalence of SCA6 is estimated to be 1 in 100,000 people in Japan.[2] Here, we report an extremely rare case presenting with a blended phenotype of adult-onset Alexander disease and SCA6.

Clinical report

The patient was a 57-year-old woman presenting with progressive ataxia, facial and limb numbness, dysarthria, and dysphagia. Familial history showed that her father was genetically diagnosed with SCA6 (figure, A). At age 35 years, the patient experienced clumsiness in her right hand. At age 45 years, she developed rotation vertigo and visited our department. Her familial history suggested the diagnosis of SCA6, which was genetically confirmed. She gradually developed mild dysarthria since then, although she did not experience difficulty in verbal communication. At age 54 years, numbness appeared in both upper limbs and the lower face. At age 55 years, she developed dysphagia and noticed rapid exacerbation of dysarthria to the point that verbal communication became difficult. Neurologic examination showed cerebellar ataxia, dysarthria, dysphagia, spastic paraplegia, and sensory disturbance in all modalities in the extremities and lower face. MRI showed severe atrophy of the medulla oblongata and cervical spinal cord with preserved basal pons, which is called tadpole appearance. The anterior portion of the medulla oblongata showed high-intensity signals on T2-weighted MRI. The midbrain tegmentum and the cerebellum were also atrophic (figure, B–D). All these MR findings are characteristic of Alexander disease.

Her DNA sample was obtained with IRB-approved informed consent. PCR-based fragment analysis was performed to detect triplet repeat expansions in *CACNA1A*. Direct nucleotide sequencing analysis was conducted for whole exons of *GFAP* with specific genomic primers (supplemental method e-1, links.lww.com/NXG/A326). The mutational analysis revealed both an expansion of the CAG repeat (23 repeats) in *CACNA1A* and a known heterozygous point mutation in the *GFAP* gene (c.827G>T, p.R276L) (figure, f).

Her mother had developed difficulty in walking at age 66 years and was diagnosed clinically with amyotrophic lateral sclerosis. However, her brain MRIs were also suggestive of Alexander disease (figure, e), although cerebellar atrophy was less severe than in the proband. Based on the clinical radiologic findings and genetic data, we concluded that the proband inherited Alexander disease from her mother and SCA6 from her father and presented with a blended phenotype of both diseases.

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The Article Processing Charge was funded by the authors.

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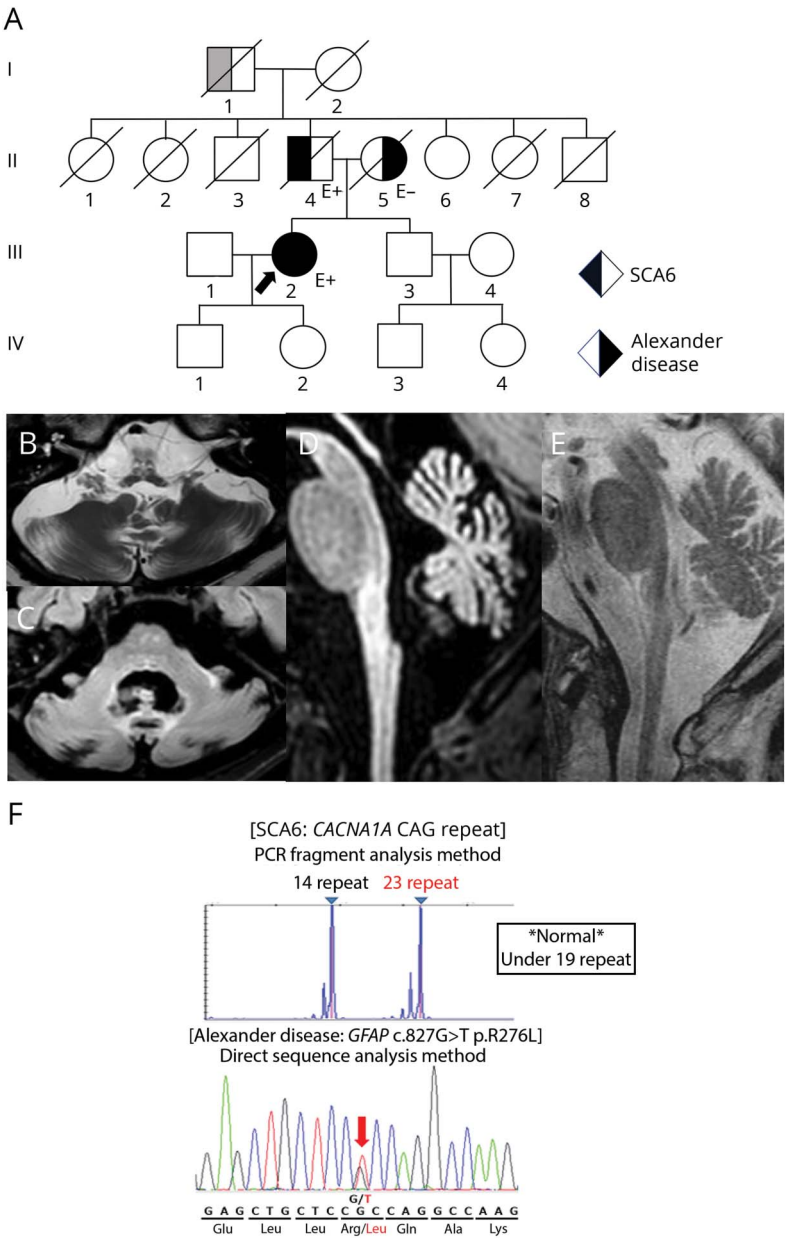
Figure Genetic data of the proband and brain MRI of the proband and his mother



(A) Pedigree chart of the family. The proband is shown with an arrow. Those who underwent genetic tests are indicated as E+ and not as E−. Patients whose diagnosis was established as corresponding diseases are shown in black and suggestive but not established in gray. Her paternal grandfather developed a progressive gait abnormality suggestive of SCA6. Her mother was diagnosed as Alexander disease based on typical brain MRI findings, although she did not undergo genetic tests. (B–E) Brain MRIs. T2-weighted images of the proband (B) and her mother (E) and fluid-attenuated inversion recovery (FLAIR) images of the proband (C, D) showed atrophy of the midbrain, cerebellum, medulla, and upper cervical spinal cord, the latter 2 designated as tadpole appearance characteristic for Alexander disease. High-intensity signals were observed in the dentate nucleus (C) and medulla oblongata (B, D) in the proband. Cerebellar atrophy was more severe in the proband than in her mother (D, E), presumably due to concomitant SCA6. (F) Mutational analysis of the proband. The upper row: PCR fragment analysis for the triplet repeat expansion in the SCA6 locus. The lower row: an electropherogram of a *GFAP* mutation c.827G>T (p.R276L). An arrow shows the heterozygous mutation in *GFAP*. *GFAP* = glial fibrillary acidic protein.

Discussion

Alexander disease is divided into 3 types based on location: type 1 is the cerebral dominant type, type 2 is the medulla oblongata/spinal cord dominant type, and type 3 is the mixed type. According to clinical symptoms and imaging findings, our patient was classified as type 2. Previous reports have shown that patients with the mutation also presented with type 2 phenotypes, predominantly bulbar and pyramidal signs with minimal cerebellar ataxia. In these individuals, brain MRI revealed typical T2-weighted high-intensity lesions in the medulla oblongata and cervical lesion and mild cerebellar atrophy.[3,4] In contrast, our patient developed ataxia as the initial symptom, suggesting that concomitant SCA6 played a major role in the symptomatic onset with the subsequent rapid deterioration caused by the *GFAP* mutation. Whether the underlying degeneration process of SCA6 triggered the rapid deterioration caused by the *GFAP* mutation is an intriguing issue to be discussed. In the animal model of SCA1, activation of astrocytes with increased expression of GFAP occurred early in the absence of neuronal death. This suggests that expanded polyglutamine stretches per se are the trigger of astrocyte pathology.[5] Likewise, astrocytic expanded polyglutamine affected glial glutamatergic clearing and caused neuronal dysfunction in Huntington disease model mice.[6] Therefore, it is plausible to hypothesize that accumulation of expanded polyglutamine stretches and dysfunction of GFAP proteins might confer synergistic effects on the clinical course in our patient. Accumulation of similar patients or model animal

experiments using double-transgenic mice would be warranted to investigate the hypothesis. Comprehensive gene analysis using next-generation sequencers has occasionally revealed pathogenic mutations of multiple mendelian inherited diseases, and the concept of blended phenotype has been proposed.[7] This report describes a blended phenotype caused by an extremely rare combination of Alexander disease and SCA6. A take-home message is that in cases in which clinical course and physical examination are atypical or complicated, and multiple familial history exists, the possibility of blended phenotypes should be taken into consideration.

Acknowledgment

The authors thank Shoko Watanabe, PhD, for technical assistance including mutational analysis.

Study funding

No targeted funding reported.

Disclosure

The authors report no disclosures. Go to Neurology.org/NG for full disclosures.

Publication history

Received by *Neurology: Genetics* June 1, 2020. Accepted in final form August 19, 2020.

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