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The first Korean case of adult-onset Alexander disease

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Abstract

Alexander disease (AxD) is a progressive neurodegenerative disorder caused by mutations in the gene encoding the glial fibrillary acidic protein (GFAP). Three subtypes of AxD have been identified based on the age of onset: infantile (under age 2), juvenile (age 2 to 12) and adult (over age 12). The adult form is rare and presents with unique clinical features different from those of the infantile forms. Here, we present the first Korean case of adult-onset cerebellar ataxia with typical tadpole-like brainstem atrophy on the magnetic resonance imaging (MRI). Molecular genetic analysis revealed a heterozygous missense mutation (c.1246C>T, p.R416W) in the GFAP gene.

INTRODUCTION

Alexander disease (AxD)[1] is a progressive neurodegenerative disorder caused by mutations in the gene encoding the glial fibrillary acidic protein (GFAP).[2,3] The pathologic hallmark is the accumulation of ubiquitinated intracytoplasmic inclusions in astrocytes, called Rosenthal fibers, which are composed of GFAP.[2,3] Three subtypes of AxD have been identified based on the age of onset: infantile (under age 2), juvenile (age 2 to 12) and adult (over age 12).[2,3] The adult form is rare and clinically characterized by slowly progressive signs of brainstem and spinal cord involvement.[2,3] Here, we report the first Korean case of adult onset AxD with characteristic MRI findings confirmed by GFAP mutation analysis.

CASE REPORT

A 28-year-old man presented with a 10 year history of progressive gait disturbance and dysarthria. On neurologic examination, bilateral upbeat nystagmus was revealed when the man lay down. There were cerebellar dysarthria and dysphagia but no palatal tremor. The tone of the limb muscles was spastic, and the reflexes of the legs were brisk, but the plantar responses were flexor. He was ambulatory, but his gait was unsteady due to ataxia. He had difficulty in tandem walking. Although his early intellectual development was normal and there were no complaints of cognitive impairment, the mini-mental examination score was 27/30. There were no known neurologic disorders in his family, but the familial history was limited.

Laboratory tests, including routine hematology, blood chemistry and analysis of urine, were unremarkable. Genetic testing for spinocerebellar ataxia (SCA)-1,-2,-3,-6,-7 and -17 revealed no abnormalities. The enzyme activities of arylsulfatase A and ß-galatocerebrosidase in leukocytes were within normal limits. No prominent abnormalities were found in the concentration of very long chain fatty acids and their respective ratios. Mutations in the SPG3A and SPG4 genes were not found.

The brain MRI showed a tadpole like brainstem atrophy, consisting of marked atrophy of the medulla oblongata and the cervical spinal cord with an intact pontine base in combination with mild cerebellar atrophy. In addition, severe thinning of the anterior body of the corpus callosum was present. (Figure 1 a-d) Fluid attenuation inversion recovery (FLAIR) images revealed abnormal hyperintensities around the fourth ventricle and bilateral periventricular white matter. (Figure 1 e-g)

With informed consent, molecular genetic analysis of GFAP was performed. Sequence analysis revealed a heterozygous c.1246C>T mutation in exon 8 that causes a substitution of arginine for tryptophan at amino acid position 416 (p.R416W). This mutation has been already described in a patient with pathologically proven

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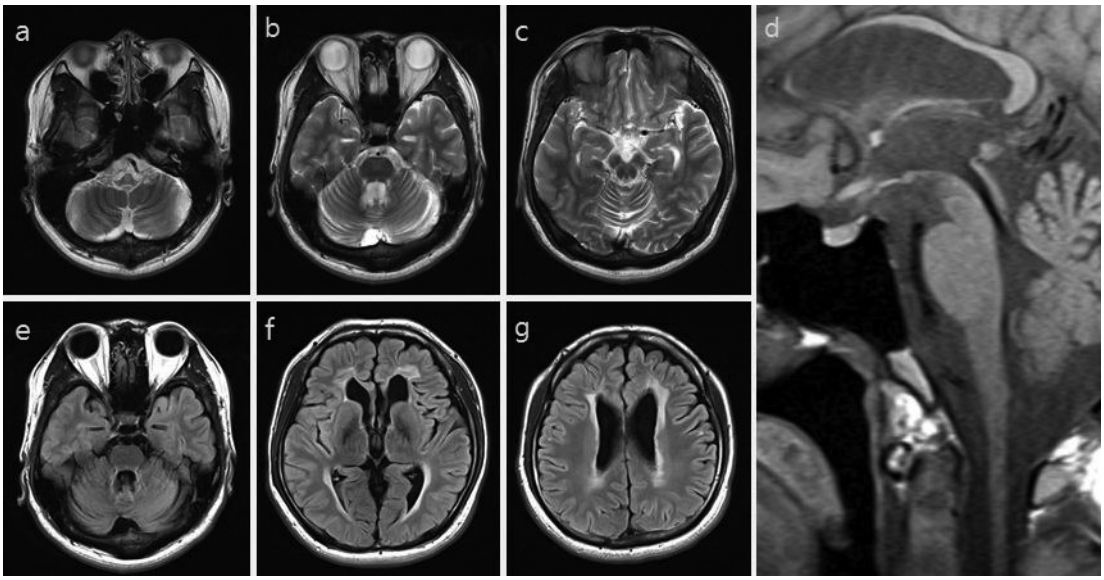

Figure 1. T2-weighted axial images showing marked atrophy of the medulla (a) but little atrophy of the pontine base (b) and atrophy of the midbrain (c), T1-weighted sagittal images showing tadpole-like brainstem atrophy with cerebellar atrophy and thinning of the anterior body of the corpus callosum (d) FLAIR axial images showing abnormal hyperintensities around the fourth ventricle (e) and bilateral periventricular white matter (f, g)

adult-onset AxD (case 5)[4] and has been found in all three forms of AxD.[5-8] The R416W mutation is one of the four common mutations reported in both familial and sporadic cases (2).

DISCUSSION

Herein, we report a patient with adult-onset AxD with an identified heterozygous missense mutation in the GFAP gene, c.1246C>T (p.R416W), which was already described in a pathologically proven adult-onset AxD case (4). Although the infantile AxD has been previously reported in Korea[9], this is the first Korean case of adult-onset AxD to our knowledge.

Dominant GFAP missense mutations are the primary underlying cause of all three forms of AxD, and several mutations associated with adult-onset AxD have been found, but the genotype-phenotype relation has been poorly understood.[2] Adult forms comprise a very small portion of affected individuals and present with unique clinical features different from those of infantile forms.[2,3] While infantile forms are typically characterized by megalencephaly, seizures, spastic paresis and psychomotor retardation leading to death within a few years, adult forms usually present with slowly progressive bulbar dysfunction such as dysarthria, dysphagia and dysphonia, pyramidal signs, ataxia and palatal myoclonus.[2,3]

The tadpole-like appearance of the brainstem in this case is strongly suggestive of adult onset AxD, and these characteristic MRI findings allowed us to perform a molecular analysis of the GFAP gene. Diagnostic MRI criteria were proposed for the diagnosis of AxD in 2001.[10] Fulfillment of four out of the five criteria was required for a diagnosis of AxD[10], but it is difficult for an MRI-based diagnosis because only one criterion was fulfilled (brainstem abnormalities), and one criterion could not be assessed (no contrast administered) in this case. Adult and some juvenile forms cannot always meet these criteria, and MRI patterns are different from those of infantile forms.[11] The radiologic features of adult onset AxD are atrophy and signal changes in the medulla oblongata and upper cervical cord and minimal to moderate supratentorial periventricular abnormalities.[11]

In a recent study, the authors proposed revised subtypes of AxD based on clinical and neuroimaging features: type I was characterized by early onset, seizures, macroencephaly, and typical MRI features, and type II with a later onset characterized by brainstem features and atypical MRI findings.[12] After that, MRI findings in type II AxD were examined in another study.[13] The authors said that the middle cerebellar peduncle and pial FLAIR changes as well as atrophy and

signal change of the medulla and spinal cord were important diagnostic clues of type II AxD.[13]

In conclusion, AxD should be considered in cases of progressive adult-onset ataxia, especially combined with the characteristic MRI findings, regardless of the presence of family history. Clinical and radiologic suspicion is most important and molecular analysis of the GFAP gene is essential to make a diagnosis of AxD.

DISCLOSURE

Conflict of interest: None

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