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A Case of Metachromatic Leukodystrophy Confirmed by Molecular Genetic Analysis

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= Abstract =

Metachromatic leukodystrophy (MLD) is the rare neurometabolic disease caused by the deficiency of the enzyme arylsulfatase A resulting in a deficiency of sulfatide degradation and the target gene is ARSA gene. We report a case of the late infantile form of MLD that was confirmed by means of enzyme assay and gene analysis with typical brain MRI and MR spectroscopy finding.

Key Words : Metachromatic leukodystrophy, Arylsulfatase A, ARSA gene, MRI, MR spectroscopy

Introduction

Metachromatic leukodystrophy (MLD) is the typical white matter disease which belongs to the lysosomal sphingolipid storage group, and it is inherited in the autosomal recessive way[1]. MLD is caused by the deficiency of enzyme arylsulfatase A resulting in the deficiency of sulfatide degradation and the target gene is ARSA gene. The accumulation of sulfatide triggers leukodystrophy. The incidence of MLD is reported as about 1 per 100,000 live births in the European population, and is found at even lower rate in Asia[2, 3]. Clinically, it shows a wide range of spectrum with respect to the age of onset, the rate of progression and the initial symptoms. The suggested classification is as following: (i) the late infantile form of disease that starts before the age of 2 or 3 years, (ii) the juvenile form that starts between 2 or 3 and 16 years, and (iii) the adult form that presents its first symptoms after the age of 16 years[4-6].

There rarely have been confirmed cases of MLD in South Korea. So here we report a case of the late infantile form of MLD that was confirmed by means of enzyme assay and gene analysis.

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Case Report

Two year and six month old male patient was transferred for developmental delay and generalized rigidity which developed since he was 18 months old. He had no specific birth history and showed normal pattern of development including independent walking before the onset of symp-

toms. The regression progressed continuously. Nothing unusual was found in his family history.

The brain MRI done after his admission revealed increased white matter signal in both hemisphere on T2 weighted image and tigroid stripes appearance which is a typical finding of metachromatic leukodystrophy (Fig. 1). MR spectroscopy also showed the elevation of choline and reduction of N-acetylaspartate (Fig. 2).

Laboratory tests, including those for muscle enzymes, lactate, pyruvate, amino acid and organic acid assays, showed no specific findings. Arylsulfatase A enzyme activity checked was decreased down to 7.3% of normal control value. Direct sequencing of ARSA gene using blood as a sample showed homogeneous c.296G>A (p.Gly 99Asp) mutation. Thus, the patient was confirmed to have metachromatic leukodystrophy (Fig. 3).

Patient was treated with general supportive care. He developed seizure at the age of 2 years

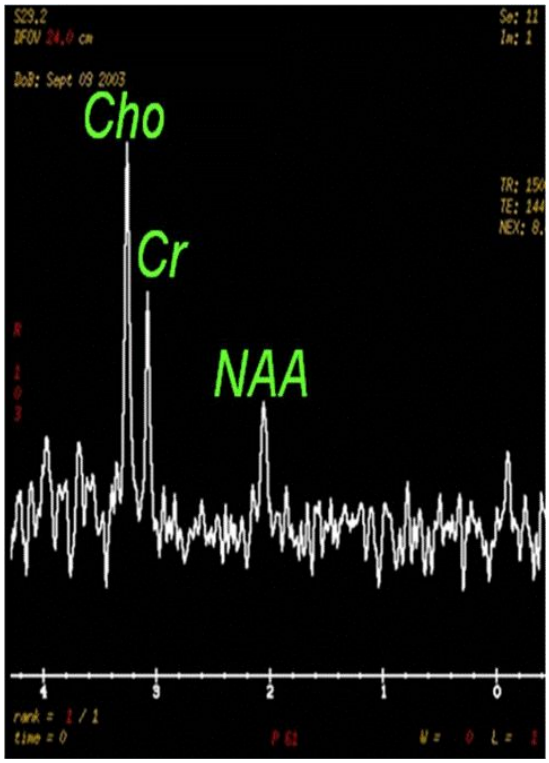

Fig. 2. MR spectroscopy shows elevation of choline and reduction of N-acetylaspartate.

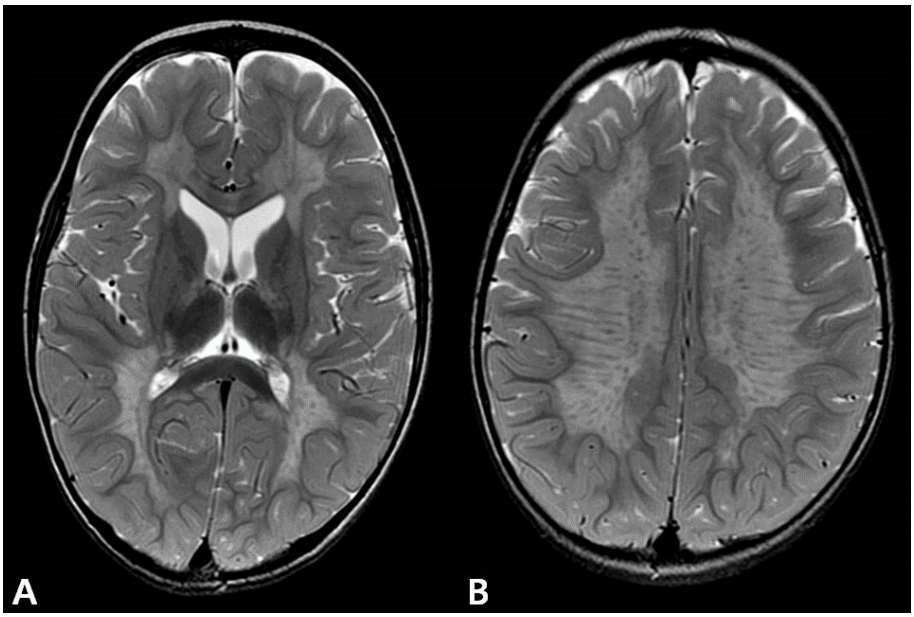

Fig. 1. Brain MRI shows tigroid stripes appearance and diffuse increased white matter signal in both hemisphere on T2 weighted image.

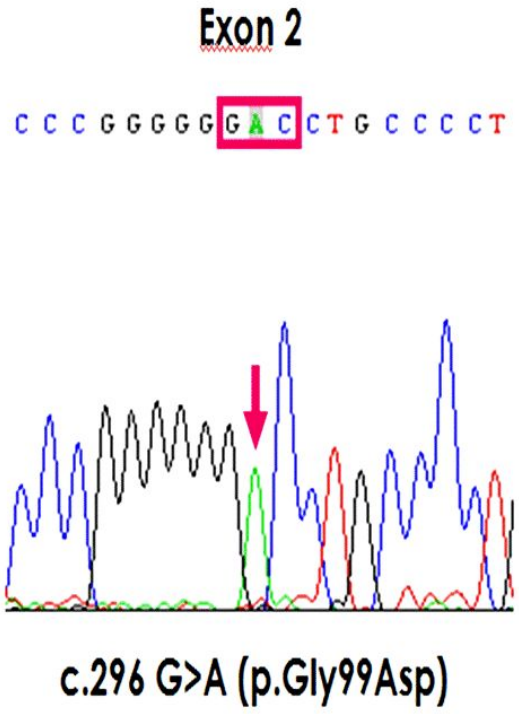

Fig. 3. Direct sequencing of ARSA gene reveals homogeneous c.296G>A (p.Gly99Asp) substitution mutation.

and 8 months and started taking antiepileptic drug. Developmental deterioration kept on progressing. Spasticity was aggravated and he had to stay at bed-ridden state when he became 3 years old. At 5 years of age, gastrostomy was performed for feeding to maintain nutrition. Eight months later, respiratory difficulty manifested and he received ventilator care at intensive care unit, followed by tracheostomy. The patient was discharged after being applied with home venti lator. General condition continuously deteriorated leading him to repeated hospital admissions. The patient expired at the age of 7 due to sepsis and respiratory failure.

Discussion

Our case presented the late infantile form of MLD with symptom onset at 18 months old and followed progressive deterioration. Studies agreed that most children with a rapid early course are the ones who developed symptoms in their second year of life, and children with an onset after 3 years of age have a rather protracted course. European surveys reveal 40-50 % of patients have a late infantile form, 30-40 % a juvenile form, and around 18-20% an adult form[2, 6, 7].

In brain MRI of our case tigroid stripes could be seen in the way of extending radially within the abnormal white matter frequently low density. Though this is the typical finding of MLD, it is not very specific as it can also be observed in other leukodystrophies[8, 9]. The proton MR spectroscopy of our patient was consistent with reported findings of MLD patients. In MR spectroscopy, elevation of choline can be interpreted as a sign of enhanced membrane turnover associated with demyelination, and reduction of N-acetylaspartate in gray and white matter as the result of neuronal and axonal loss[10]. Since brain MRI and MR spectroscopy of the patient made us suspect MLD, arylsulfatase A enzyme activity and ARSA gene analysis were carried out to confirm it. Brain MRI and MR spectroscopy can serve as the very useful tools for performing the screening test of MLD when only not-specific neurological manifestations are provided.

MLD is known to be very heterogeneous when it comes to genetics. Among Caucasians, only 3 alleles are frequently referred as the cause of MLD. There is the splice donor site mutation of the exon2/intron 2 border (IVS459+1 A>G) with

a frequency between 15% to 43%, a missense mutation causing a Pro426Leu amino acid substitution with a frequency between 16% to 25% of all MLD alleles, and a missense mutation causing an Ile179Ser substitution with a frequency of 12 to 13% in European patients[11, 12]. We found homogeneous c.296G>A (p.Gly99Asp) mutation in our case, not the type of mutation commonly found. This type was also reported as the most common one in Japanese patients[13]. One could suggest that racial differences might play a role here.

We feel sorry for not having performed ARSA gene study on the family members of our patient. If gene study was done in his parents and siblings, the carrier state could have been identified more clear and have enabled us to provide a better genetic counseling. But still, our case has the clinical significance as the confirmed case of MLD by biochemical enzyme assay and molecular genetic analysis. More active approach to the cases showing leukodystrophy in neuroimaging is recommended. Further studies on clinical features and prognosis of patients with these kinds of neurometabolic disease, including the collection of knowledge as much as possible, would certainly benefit the development of medical science for rare disease.

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유전자 검사로 확진 된 이염색 백색질 장애 환아 1례

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이염색 백색질 장애(metachromatic leukodystrophy, MLD)는 arylsulfatase A 효소의 결핍에 의해 sulfatide의 분해가 이루어지지 못하여 초래되는 드문 중추신경계 대사질환으로 원인 유전자는 ARSA이다. 저자들은 뇌 MRI, MR spectroscopy에서 전형적인 양상과 더불어 효소검사와 유전자 분석에서 확진 된 후기 영아기 이염색 백색질 장애를 경험하였기에 보고하는 바이다.

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