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Adult-Onset Adrenoleukodystrophy with Frontal Lobe Symptoms: A Case Report

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Abstract

ALD, which is the X-linked adrenoleukodystrophy (X-ALD), is a rare inherited metabolic disease caused by an enzyme deficiency leading to accumulation of saturated very long chain fatty acid (VLCFA), especially in brain and adrenal cortex. Its prevalence is currently estimated at 1:30,000 to 50,000 in males in Japan. We report a 34-year-old man, who acts of theft, peep and obscenity with adult onset cerebral adrenoleukodystrophy (ALD). An elevated VLCFA and a point mutation in the ABCD1 gene confirmed the diagnosis of ALD. Diffusion-weighted MRI revealed a high intensity area in the white matter of the frontal lobes. T2-weighted image revealed diffuse high signal intensity in the deep white matter. MR diffusion-weighted image revealed high signal intensity area in the white matter of the frontal lobes. Proton magnetic resonance spectroscopy (H-MRS) of the white matter of the frontal lobes revealed an extreme decrease of N-acetylaspartate (NAA) and an increase of the choline (Cho)/creatinine (Cr) ratio. The mild hypoperfusion was detected in the both cerebral hemispheres by the single photon emission CT (SPECT). The genetic phenotype was detected and he was diagnosed adult onset ALD. The only neurological sign was deviant behaviors as frontal lobe symptoms; despite a diffuse high signal intensity was detected in the deep white matter in the MRI examination. Psychiatric symptomatology is presented and may be one of the earliest manifestations of ALD. Psychiatrists as well as and physicians may encounter ALD.

Keywords

Adrenoleukodystrophy, Very Long Fatty Acid, Frontal Lobe Symptoms

1. Introduction

Adrenoleukodystrophy (ALD) is a rare inherited metabolic disease. A mutation in the gene, ATP Binding Cassette subfamily D1 (ABCD1) gene, which encodes an ATP-binding cassette (ABC) transporter located in the

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long arm of an X-chromosome (Xq28), invariably leads to accumulation of saturated very long chain fatty acid (VLCFA), defined as those having more than 22 carbon chains: C ≥ 22. Accumulation of VLCFA causes adrenal insufficiency and demyelination of the central nervous system [1]. Its prevalence is currently estimated at 1:21,000 in the United States [2], 1:30,000 to 50,000 in males in Japan [3]. ALD is an X-linked disorder, although there are *de novo* mutations in 3% - 10% of ALD patients. Mothers of male patients are not necessarily carriers.

A variety of treatments have been used in cerebral ALD, e.g., Lorenzo's oil, low-fat diet, statins, immunosuppression, antioxidant agents, but they are not very effective. Despite significant mortality risk, bone marrow transplantation remains the only therapeutic intervention that can arrest the progression of cerebral demyelination in ALD [4].

The ALD can occur over a wide age spectrum with considerable clinical heterogeneity. Child cerebral ALD (under 10 years old): This form is the most progresssive pattern and the most frequent (30% - 35%), and often has a fatal course during the first decade of life due to the extensive demyelination of the cerebral hemispheres. Adolescent cerebral ALD (11 - 21 years old): This form presents in 4% - 9% of all ALD. It initially causes a decline in school performance. These early clinical symptoms are often misdiagnosed as ADHD and can delay the diagnosis of ALD. Adult cerebral ALD (over 22 years old): Adult cerebral disease presenting with adult-onset dementia is the least frequently observed. Adrenomyeloneuropathy (AMN): This form represents 25% of cases, and features of AMN usually appear in the third to fourth decade. These patients have significant neurological morbidities, predominantly involving the spinal cord, but including the risk of rapidly progressive cerebral disease. Addison-only: Adrenal insufficiency is the only sign of ALD in approximately 10% of affected individuals. This form presents in males between two years of age and adulthood. Women with ALD: The less frequently described forms include those observed in heterozygous women [5] [6].

We reported a 34-year-old man, who acted of theft, peep and obscenity, were with adult onset cerebral ALD. An elevated plasma VLCFA and a point mutation in the ABCD1 gene confirmed the diagnosis of ALD. The only neurological sign was deviant behaviors as frontal lobe symptoms; despite a diffuse high signal intensity was detected in the deep white matter in the MRI examination. Psychiatric symptomatology is presented and may be one of the earliest manifestations of ALD. Psychiatrists as well as physicians may encounter ALD. In the present case, the family history was the key to information to a correct diagnosis.

2. The Case

The patient was a 34-year-old, right-handed Japanese male who had one sister. He was born at full term weighing 3600 g. His level of functioning in society was normal. There were no particular findings in his past history.

He had acted willfully since the age of 29. At 34 years old, he stole, peeped, and uttered obscenities. His parents were concerned about him, and he saw a neurologist. MRI of the brain was shown extensive white matter changes. Notch 3 (CADASIL: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) genetic analysis was performed, but the condition was not detected. Therefore, he was seen at our institute.

His height and weight were 1.78 m and 65.9 kg (BMI: 22.3). Main findings in the systemic examination were pulse 62 bpm, blood pressure: 108/70 mmHg. Physical examination revealed darkening of the skin, with generalized oval brown hyperpigmentation especially on the face and oral mucosa. Thin and scanty scalp hair was specific in this case. The abnormalities of cranial nerves, motor and sensory, reflection, coordination, apraxia, and autonomic nerve function in neurological examination were not found.

Physiological and intelligence examinations were as follows: Auditory brain-stem response (ABR): V wave was delayed more than +3SD. Revised Hasegawa Dementia scale score was 28 (/30). Wechsler Adult Intelligence scale was total IQ 63. These physiological and intelligence examinations revealed pathology of brain function.

Results of laboratory data were as follows: LH: 5.5 mIU/mL (0.79 - 5.72), FSH: 8.6 mIU/mL (2.00 - 8.30), E2 10 pg/mL (15 - 35), DHEAS :63 g/dL (106 - 464), PRL: 6.9 ng/mL (4.29 - 13.69), GH: 0.1 ng/mL (<2.47), IGF1:162 ng/mL (−0.4 SD), renin: 1.5 mg/ml/h (0.3 - 2.9), Ald: 89 pg/mL (30 - 159), TSH: 2.70 μU/mL (0.5 - 3.0), FT3: 2.7 pg/mL (2.1 - 3.8), FT4: 1.2 ng/dL (0.8 - 1.5), ACTH: 137 pg/ml (7.2 - 63.3), Cortisol: 13 μg/dL (6.2 - 19.4). Plasma ACTH was increased and adrenal and testicular dysfunction was detected. Cerebrospinal fluid data was as follows; an initial pressure: 80 mm H_2O, cell count: 1/μL, Glucose: 63 mg/dL, Protein: 35

mg/dl, Myelin Basic Protein ≥40.0 pg/dL, IgG index: 0.51 (<0.73).

Head MRI showed severe atrophic changes in both frontal lobes. There were diffuse high intensity areas in the cerebral white matter (**Figure 1**). White matter lesions were marked in the periventricular zone. High signals were detected from the deep white matter of the U-fiber area in the frontal lobe. The gray matter was thinning. Brainstem atrophy was not clear.

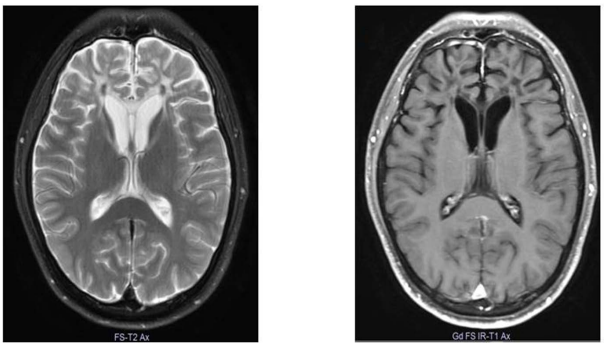
^{1}H-MR spectroscopy (H-MRS) of the white matter in the frontal lobes revealed an extreme decrease of N-acetylaspartate (NAA). An increase in the choline (Cho)/creatinine (Cr) ratio was also found (**Figure 2**). There was severe brain hypoperfusion in the cerebrum on single photon emission CT (SPECT) with 99mTc-ECD (**Figure 3**). The plasma VLCFA levels were elevated: C24:0/C22:0 = 1.437(0.628-0.977), C25:0/C22:0 = 0.056 (0.012-0.023), C26:0/C22:0 = 0.026 (0.003-0.006). The patient had been found the missense mutation c.1619T > C: p.Phe540Ser on the ABCD1 gene. A diagnosis of adult-onset ALD was determined.

One year later, there was no worsening of physical and neurological examinations. The symptoms of wandering aimlessly along the corridor were shown as stereotyped behavior and his eating habit was deviated. His state became abulic, affective, flattened and indifferent to his surroundings.

3. Discussion

1) The Plasma VLCFA Examination

His uncle was diagnosed with adrenomyelopathy (AMN) and died of hepatic cancer at the age of 59. He was



(a) (b)

Figure 1. Head MRI of T2WI mage (a): There were atrophic changes in both frontal lobes. White matter lesions were marked in the periventricular zone. High signals were detected from the deep white matter of the U-fiber area in the frontal lobe. The gray matter was thinning. Head MRI Gd contrast image (b): No contrast was seen.

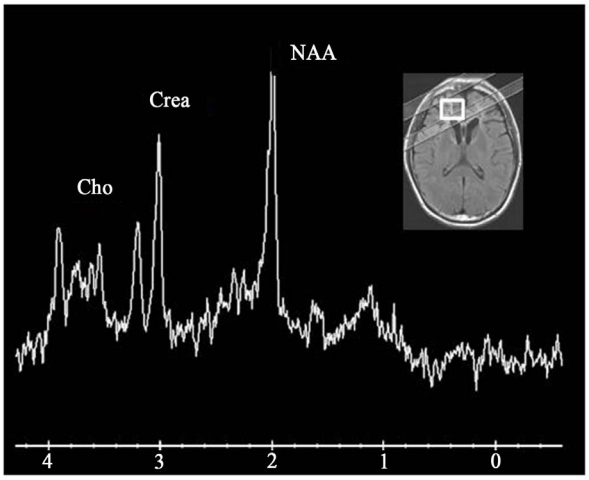


Figure 2. H-MR spectroscopy (MRS): The white matter in the frontal lobes revealed extreme decrease of N-acetyl aspartate (NAA). An increase in the choline (Cho)/creatinine (Cr) ratio was also found.

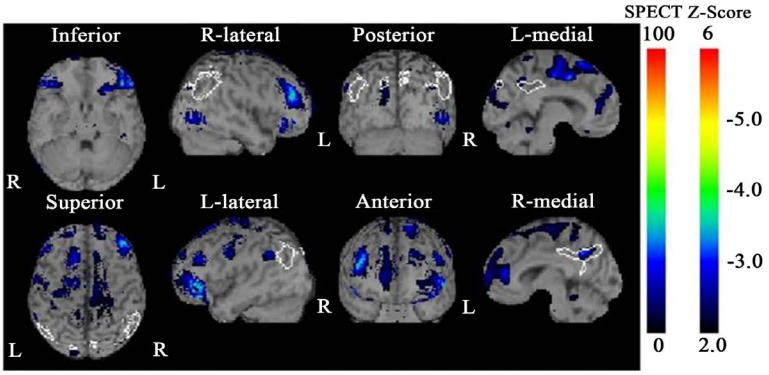


Figure 3. ECD-spectroscopy (eZIS): There was mild brain hypoperfusion in the cerebrum.

diagnosed with Krabbe disease, initially due to tightness of the lower limbs appearing at the age of 40. After three years of progressing symptoms, he was reevaluated. His plasma levels of VLCFA were measured. He was diagnosed with ALD by demonstration of elevated VLCFA, which started in the pure form of AMN, but included progressive cerebral disease. Molecular analysis was not performed. It was necessary to consider whether there was an advantage in diagnosing ALD in this case.

2) Molecular Genetic Studies of This Case

Targeted mutation analysis is the most effective means for carrier detection, and genetic counseling is needed. X-ALD is caused by mutation of the ABCD1 gene located on the X-chromosome. So far, 600 different mutations have been identified. Detailed ABCD1 mutational analysis has been carried out in 35 unrelated ALD individuals, and all had X-q28 ALD gene mutations [7] [8]. Six percent had large deletions, and 17% had an AG deletion in exon 5; the remainder had private mutations that were specific for each kindred, of which 55% had missense mutations and 30% had frame-shift mutations; nonsense mutations occurred in 8% and splice defects in 4%. No correlation between the nature of the mutation and the phenotype has been detected [9]. Whether to perform the genetic study was decided at a Genetics Department Conference. The patient and his parents desired the genetic study. The missense mutation was detected.

3) Molecular Genetic Studies of Relatives

ALD is an X-linked recessive disorder. Therefore, first-degree relatives of affected individuals will either be normal or inherit the gene defect. Genetic counseling is needed by the parents of the proband. This allows early diagnosis and testing of other family members. Inheritance by boys from female carriers is the most common, but *de novo* mutation or inheritance by daughters sired by men with AMN before the onset or adult cerebral type may be considered.

Evaluating the risk of presymptomatic affected individuals in the family is also important when the proband is diagnosed. Early diagnosis of the childhood cerebral type (particularly fast progression of the disease) is directed toward more reliable bone marrow transplantation. Prudent actions such as genetic counseling are required only when disease type is significantly different, is not without treatment even when the family is also available. The decision at the Genetics Department Conference was to leave providing information to the sister (32 years old, married) to the discretion of the parents. The mother underwent genetic analysis herself. The female sibling of the proband has a probability of being a carrier that is 50% of her parents.

4) Clinical Management

Bone marrow transplantation is now being used for ALD patients who have not yet demonstrated clinical symptoms but who have evidence of demyelination on MRI. The purpose is to provide the patient with healthy cells that have the ability to degrade VLCFA. The Loes score is used to determine adoption or not. That is detailed scoring system (0 - 34 points) developed by Dr. Loes which aids in determining the extent of myelin injury in the brain (e.g., very early stage = MRI score 1 - 3; early stage = MRI score 4 - 8; late stage = MRI score 9 - 13; very late stage = MRI score greater than 13) [9]. His total score was 9 (/34). This phenotype is adult cerebral ALD (**Table 1**). He had demonstrated clinical symptoms for more than 5 years and a wide white matter change on MRI. Bone marrow transplantation was not appropriate in this case.

The patients' plasma levels of ACTH were increased and adrenal and testicular dysfunction was detected. It is important to administer corticosteroid to keep the patient alive longer without affecting recovery of the neuronal damage. A regimen of hydrocortisone 10 mg was initiated.

Table 1. Loes score: Detailed scoring system developed by Dr. Loes aids in determining the extent of myelin injury in the brain: very early stage = score 1 - 3; early stage = score 4 - 8; late stage = score 9 - 13; very late stage = score greater than 13. In this case, the total score was 9.

Parietal occipital white matter: + 1 (atrophy of parietal lobe)
Anterior temporal white matter: + 0
Frontal white matter: periventricular, central, subcortical, atrophy + 4
Corpus callosum: Genu white matter change and atrophy + 2
Visual pathway: 0
Auditory pathway: 0
Pyramidal system: internal capsule white matter change + 1
Cerebellum: 0
Basal ganglia: 0
Anterior thalamus: 0
Global atrophy: mild + 1
Total 9 (/34) (Phenotype is adult cerebral ALD)

5) Phenotypes of ALD

The same gene abnormality within a family can produce a wide range of clinical phenotypes. In this case, the uncle was diagnosed with AMN, which was a different diagnosis from that of this case. The eventual phenotype of ALD in an individual will most likely be determined by the combination of several epigenetic and environmental modifiers, most of which have not been identified. Much research is currently focused on identifying these modifiers to better predict clinical outcome in individual patients [10].

In adult cerebral ALD, 80% of patients the initial demyelinating lesion is localized in the parieto-occipital region and the splenium of the corpus callosum. However, in about 20% of males with ALD, the white matter changes occur predominantly in the genu of corpus callosum and frontal lobes, or involve the pyramidal tracts with extension in the white matter of the centrum semiovale. This case exhibited this frontal dominant type.

6) ALD and Psychiatric Symptoms

Psychiatric symptomatology is present in many of the adult-onset cases reported in the literature and may be one of the earliest manifestations of the disease [11]. Metabolic diseases such as ALD are probably under recognized as a cause of psychiatric illness. Increased awareness of these disorders will lead to accurate diagnosis, appropriate treatment selection, and genetic counseling [12].

4. Conclusion

We reported the diagnosis of a 34-year-old man, with adult onset cerebral ALD. Psychiatric symptomatology is presented and may be one of the earliest manifestations of ALD. Consequently psychiatrists as well as physicians may encounter X-ALD.

Conflict of Interest

None declared.

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