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Original article

Auditory agnosia as a clinical symptom of childhood adrenoleukodystrophy

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Abstract

Objective: To investigate detailed auditory features in patients with auditory impairment as the first clinical symptoms of childhood adrenoleukodystrophy (CSALD).

Subjects and methods: Three patients who had hearing difficulty as the first clinical signs and/or symptoms of ALD. Precise examination of the clinical characteristics of hearing and auditory function was performed, including assessments of pure tone audiometry, verbal sound discrimination, otoacoustic emission (OAE), and auditory brainstem response (ABR), as well as an environmental sound discrimination test, a sound lateralization test, and a dichotic listening test (DLT). The auditory pathway was evaluated by MRI in each patient.

Results: Poor response to calling was detected in all patients. Two patients were not aware of their hearing difficulty, and had been diagnosed with normal hearing by otolaryngologists at first. Pure-tone audiometry disclosed normal hearing in all patients. All patients showed a normal wave V ABR threshold. Three patients showed obvious difficulty in discriminating verbal sounds, environmental sounds, and sound lateralization and strong left-ear suppression in a dichotic listening test. However, once they discriminated verbal sounds, they correctly understood the meaning. Two patients showed elongation of the I–V and III–V interwave intervals in ABR, but one showed no abnormality. MRIs of these three patients revealed signal changes in auditory radiation including in other subcortical areas.

Conclusion: The hearing features of these subjects were diagnosed as auditory agnosia and not aphasia. It should be emphasized that when patients are suspected to have hearing impairment but have no abnormalities in pure tone audiometry and/or ABR, this should not be diagnosed immediately as psychogenic response or pathomimesis, but auditory agnosia must also be considered.

Keywords: Adrenoleukodystrophy (ALD); Auditory agnosia; Speech discrimination

1. Introduction

X-linked adrenoleukodystrophy (ALD) is a severe neurodegenerative disease involving progressive demyelination of the central nervous system, adrenal dysfunction, and accumulation of saturated very long chain

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fatty acids (VLCFA) in various tissues and body fluids. It is caused by a defect in the *ABCD1* gene at Xq28, which encodes a peroxisomal membrane protein [1]. There are several phenotypes, and childhood ALD (CALD) may often initially present with abnormal vision during the first to third grade of elementary school, and intellectual and/or behavioral change around 10 years old. Hearing impairment is also reported as the initial symptom of ALD [2–4], but the details of the auditory features have not been described, possibly due to the rapid progression of the disease leading to total disability or death [2,5,6].

One candidate cause of hearing impairment in CALD is white matter lesions in the auditory pathway. It is often difficult to definitively diagnose this hearing impairment, and it can be easily misdiagnosed as psychogenic response or pathomimesis.

Hematopoietic stem cell transplantation (HSCT) at an early stage of the disease is considered to be the only effective treatment for CALD [5,7,8]. Order-made gene therapy could be the treatment of choice in the near future [9]. Thus, it is very important to diagnose CALD correctly as early as possible.

We experienced 50 ALD patients who were referred to our outpatient clinic for further evaluation of their cognitive state before and after HSCT from 2001 to 2013. Among these patients, we observed three patients with hearing impairment as the first clinical feature. We studied the precise auditory and cognitive function in these three patients, and in this report we discuss the importance of the evaluation of auditory function in CALD.

2. Case histories

Brief clinical summaries of the three patients are shown in Table 1.

2.1. Patient 1

The patient was a 13-year-old Japanese boy. He showed poor response to being called. Repeated pure tone hearing tests at school showed normal results. However, conversation with him had become progressively harder, and he was not able to talk on the phone. He did not complain of his hearing difficulty. Other than his hearing problem, he was completely normal. Thus he was referred to a hospital at 13 years and 4 months of age. There he was diagnosed as CALD on the basis of brain MRI lesions (Fig. 1A), elevated plasma VLCFA, and mutation of the *ABCD1* gene. His adrenal function was normal. He was referred to us for further neuropsychological and neurophysiological evaluation of his condition.

His physical examination disclosed normal results. He could only answer very simple questions such as questions asking his name or his age. His corrected visual acuity was 0.1 in the left and 0.6 in the right. He had left homonymous quadrantanopia.

His pupils were dilated and reacted to light sluggishly. There were no pyramidal, cerebellar, nor sensorineural signs. Transport impairment of tactile and positional information was present.

2.2. Patient 2

The patient was an 11-year-old Japanese boy. At 10 years and 11 months of age, he began to complain of difficulty with hearing other people's talk. He missed instructions and was often believed to be absent-minded. His teacher found that he often did not react to being called, looked at his textbook upside down, wore his gym suits backwards and wrote confused, incorrect letters. One year later, he visited a psychiatric clinic and then a pediatric clinic. His brain MRI showed characteristic signal changes (Fig. 1B); thus, he was referred to a hospital and diagnosed as CALD on the basis of an elevated VLCFA level and mutation of the *ABCD1* gene. His auditory brainstem response (ABR) was normal. He had no vision complaints. However, left homonymous hemianopia was disclosed. He also had partial adrenal insufficiency. Gradually, he became short-tempered. At 11 years and 5 months of age, he was referred to our hospital for detailed evaluation.

His physical examinations showed normal results with no pigmentation of the skin. He was able to have short, simple conversations. The cranial nerves were normal. His deep tendon reflexes were exaggerated at the lower extremities, though his muscle tonus was normal. His reactions to tactile and painful stimuli were unstable. His position and vibratory senses were impaired in the left lower limb.

2.3. Patient 3

The patient was a 10-year-old Japanese boy. He showed no abnormal signs until he was 9 years and 11 months of age. He then began to respond less and less when he was talked to. His actions became slow and stagnated, and he spent less and less time with friends. His school performance declined. Five months later, an otolaryngologist diagnosed his hearing as normal. But his response to being called became worse and he often asked for statements to be repeated. Thus, he was referred to a pediatrician at the age of 10 years and 6 months. There he was diagnosed as CALD on the basis of the presence of intellectual deterioration, brain lesions on his MRI (Fig. 1C), and an increased VLCFA level. His adrenal function was normal. At 10 years and 9 months of age, he was referred to us for further evaluation.

His physical examinations were normal. He showed emotional incontinence and marked separation anxiety.