Adrenoleukodystrophy with Frontal Lobe Involvement and Attention Deficit Hyperactivity Disorder-like Symptoms

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Abstract

We report a 11 year-old boy with adrenoleukodystrophy (ALD), who gradually became inattentive and hyperactive after ten years of age. His parents consulted with school counselor and were told that he might have attention deficit hyperactivity disorder (ADHD). We noticed his deterioration in intelligence and behavior and his cranial magnetic resonance imaging revealed bilateral abnormal intensity areas predominantly in the left frontal lobe to the basal ganglia, which surroundings was enhanced by Gd-DTPA suggesting demyelination. Statistical parametric mapping (SPM) using IMP single photon emission tomography showed decreased cerebral blood flow in the left frontal cortex, cerebellum, and brain stem. Abnormal levels of plasma very-long-chain fatty acids and genetic testing confirmed the diagnosis of ALD. His behavioral problems transiently improved with methylphenidate treatment, however he died in spite of bone marrow transplantation. This report emphasize that the importance of early medical evaluation when ADHD-like symptoms became prominent in a child who never had such problems before. Recognition of ADHD in the field of education enhanced after the recent promotion of special needs education. Necessity of medical evaluation in such a child to school teachers, nurses, counselors should be emphasized, so as not to be left undiagnosed and untreated.

Keywords: Symptoms; Frontal lobe; Pregnancy

Abbreviations:

ALD: Adrenoleukodystrophy; ADHD: Attention Deficit Hyperactivity Disorder; MRI: Magnetic Resonance Imaging

Introduction

Adrenoleukodystrophy (ALD) is a rare X-linked disorder that is characterized by progressive demyelination and adrenal insufficiency, and excessive accumulation of saturated long-chain fatty acids. Symptoms usually include progressive neurological symptoms such as cortical blindness, deafness, and dementia. Typical childhood ALD is rapidly progressive and ending in death in 2 to 4 years. In 1983, Marler and Moser have reported 2 “variant” ALD boys presented with frontal lobe syndrome with involvement of frontal lobes demonstrated by computed tomography [1]. There have been several reports on variant ALD in the literature [1-7], however description on symptoms in association with neuroimaging findings are still lacking. Moser et al. emphasized that ALD was often misdiagnosed as attention deficit hyperactivity disorder (ADHD) in boys [8]. We report a 11-year-old boy with variant ALD who presented with ADHD-like behavioral problems and rare neuroimaging findings.

Case Report

A 11-year old boy was referred to our hospital because his parents complained of their son’s difficulties in sustaining attention and behavioral problems, which gradually became prominent about 1 year ago. He was born at 40 weeks of gestation with a birth weight of 3,514 g. The pregnancy, labor, and delivery were uneventful. He was the second child of healthy unrelated parents. His mother's 2 brothers died at the age of 8 and 10, respectively with unknown cause of death. He had operation of nephrectomy of the right side because of reflux and hydronephrosis at the age of 2. His psychomotor development was normal and no behavioral problems were noted by teachers until the 3rd grade of elementary school. He was introverted and had interest in dinosaurus and card game, however his school performance was good. When he was in the 4th grade, he gradually became unable to concentrate on his tasks in the classroom. He began to hate taking notes and his writing became bad. He seemed unable to concentrate his homework and forget to bring things to school. He liked to chew his pencils and other objects. He was not aggressive and not oppositional. He did not leave his seat but his things to school. He liked to chew his pencils and other objects. He was not aggressive and not oppositional. He did not leave his seat but his school performance became worse in the 4th grade. His parents consulted the school counselor on his behavioral problems at school and at home, and they were told that he might have ADHD. The school counselor advised parents psychosocial management for children with ADHD. In the 5th grade, he began to leave his seat and abnormal impulsive behaviors such as getting into pond in the school, swimming in the river when he was getting home from school, and crossing with red signal became prominent. He became childish and liked to be hold by his lady teacher. He was referred to our hospital by an another clinical psychologist suspected having underlying pervasive developmental disorder.
Physical examination revealed no abnormalities. There were no signs of adrenal insufficiency. During neurological examination, he had poor eye contact with an examiner and he did not respond to questions adequately. He had short attention span and looked childish in his behavior. Cranial nerves were normal. He was clumsy but had no definite cerebellar signs. Reflexes were normal. The test of variables of attention (T.O.V.A.), which is a continuous performance test, indicated difficulty in sustaining attention in a highly stimulating high frequency response activity. Cranial computed tomography (CT) revealed bilateral asymmetrical low density areas predominantly in the left frontal lobe. The cranial magnetic resonance imaging (MRI) showed abnormal intensity areas (low in T1 weight image and high in T2 and FLAIR) in the white matter of the left frontal lobe extending to anterior limb of the internal capsule, thalamus, and to cerebral peduncle (Figure 1). Similar but smaller lesion in the internal capsule and cerebral peduncle in the right side were noticed. Enhancement at the periphery of the lesions was observed after injection of Gd-DTPA, suggesting demyelinated lesion (Figure 1). Statistical parametric mapping (SPM) using IMP single photon emission tomography [8] showed decreased cerebral blood flow in the left frontal cortex, cerebellum, and brain stem. The electroencephalogram revealed a slight increase in the slow-wave activity but no paroxysmal or periodic synchronous discharges were found. Auditory brain stem evoked potential, motor and sensory nerve conduction velocities were normal. Flash visual evoked potential revealed asymmetry in the left side. Routine laboratory studies were normal. Diurnal cortisol levels were normal. Plasma C26 fatty acid levels were significantly elevated C26/C22 = 0.068 (reference value < 0.033). Serum arylsulfatase was normal. The cell count, glucose, protein in the cerebrospinal fluid were normal, however myelin basic protein was slightly elevated: 154 pg/ml (reference value <102). The diagnosis of ALD was confirmed by the ALD gene testing.

Figure 1: Brain MR images at the age of 11 (A-D) and 3 months later (E,F). A: T1-weighted image (T1WI) showed low intensity lesions in the white matter of the left frontal lobe extending to the anterior limb of the internal capsule, the striatum, and the thalamus. B: T2-weighted image (T2WI) revealed more extensive lesion compared to T1WI Similar but smaller lesion in the internal capsule in the right side were noticed.C: FLAIR image reveals left side periventricular high intensity lesion. D: Enhancement at the periphery of the lesions was observed after injection of Gadriumum-DTPA (T1WI). E: Extension of the white matter lesion was noted 3 months after the initial MRI (T2WI). F: FLAIR image also demonstrated periventricular inhomogeneous high intensity lesions bilaterally.

Wechsler intelligence scale for children version III full scale intelligence quotient (IQ) was 74; Verbal IQ: 70, Performance IQ: 83. His total ADHD rating scale (DuPaul) [9,10] evaluated by his teacher was 47 (inattention:25, hyperactivity/impulsivity: 22), which was extremely high. To improve his ADHD-like symptoms, 10 mg methylphenidate was given in the morning with an informed consent from his parents. The total ADHD score by his teacher decreased to 37 (inattention: 15, hyperactivity/impulsivity: 22) in 4 weeks and the teacher noticed that he could again stay in the classroom and take notes for 2 months. However, his neurological symptoms and MRI lesions gradually progressed and he developed right sided incomplete hemiparesis one month later. He had successful bone marrow transplantation from his elder sister, however he died of fulminant adenovirus infection 2 months after bone marrow transplantation.

Discussion

Most cases of the typical ALD shows occipital involvement as a presenting feature. The unusual rostralcaudal progression has been reported scarcely in the English and Japanese literature [1-5]. Marler and Moser have reported a variant of childhood ALD affected two male cousins with characteristic features including a progressive frontal lobe syndrome (altered gait and behavior), bilateral frontal lobe CT hypodensity, slower progression, and spared vision [1]. Arari reported a 20-year-old patient who first developed the changes in character and behavior at the age of 9 [4]. He reviewed 8 pediatric cases in the literature presented with frontal lobe symptoms such as psychiatric, behavioral, and learning problems. Their onset of age was generally older compared to typical ALD; half of them started after 10 years of age (range: 7-14). The spared vision, less prominent neurological signs, slower progression were the characteristics of these 8 cases. Our patient also had these characteristics, however few previous reports have described the details of hyperactivity/inattention problems and their relationships with neuroimaging findings. Recent imaging studies revealed that dysfunction of the fronto-striatal neuronal networks were associated with ADHD. It is speculated that frontal lobes, caudate nucleus, thalamus, nucleus accumbens, and cerebellum are responsible lesions for ADHD. Castellote have reported a 9-year-old male patient who presented with 12-month history of prolonged learning and behavioral problems, short attention span, hyperkinetic motor movements, and emotional disorders [6]. The symptoms and MR imaging of the case was very similar to our case with involvement of the bilateral frontal white matter and both anterior limbs of the internal capsule. The ADHD-like symptoms in our case especially inattention and inhibition control were transiently improved by methylphenidate suggesting that involvement of postsynaptic dopaminergic dysfunction in the pathophisiology of this patient. Siva llango and Nambi recently reported an Indian 7-year-old boy with X-linked ALD presenting as ADHD [12]. MRI revealed symmetrical T2-hypertense white matter changes mainly in the anterior periventricular area. He was started on methylphenidate with a max. dose of 10 mg, but was replaced with risperidone for his disruptive behavior. The reason why our patient responded to methylphenidate in contrast to the Indian boy might come from the difference of lesions of white matter changes; frontal vs occipital lesion. Koeda conducted the questionnaire survey to 951 Japanese child neurologists on medical condition mimicking ADHD or misdiagnosed as ADHD [13]. The most frequent disorder mimicking ADHD was epilepsy, and less...
frequently slowly progressive brain tumor and ALD. ALD should be considered as a differential diagnosis of ADHD.

This report emphasize that the importance of early medical evaluation when ADHD-like symptoms became prominent in a child who never had such problems before. Recognition of ADHD in the field of education enhanced after the recent promotion of special needs education. Necessity of medical evaluation in such a child to school teachers, nurses, counselors should be emphasized, so as not to be left undiagnosed and untreated.

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