Case Reports in Ophthalmology

Case Rep Ophthalmol 2018;9:102–107

DOI: 10.1159/000485964
Published online: February 1, 2018

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Case Report

A Case of Fundus Oculi Albinoticus Diagnosed as Angelman Syndrome by Genetic Testing

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Keywords
Angelman syndrome · Fundus oculi albinoticus · Optic atrophy · Congenital anomaly · Chromosome 15

Abstract
Purpose: To report a case of fundus oculi albinoticus diagnosed as Angelman syndrome (AS) via genetic testing. ***Case Report:*** This study reports on a 4-year-old boy. Since he had been having respiratory disturbance since birth, he underwent a complete physical examination to investigate the cause. The results indicated that he had various brain congenital abnormalities, such as a thin corpus callosum, as well as hydronephrosis, an atrial septal defect, and skin similar to patients with fundus oculi albinoticus. Examination revealed bilateral fundus oculi albinoticus, mild iridic hypopigmentation, optic atrophy, and poor visual tracking. Genetic testing revealed a deletion in the Prader-Willi syndrome/AS region on chromosome 15, and together with the results of methylation analysis, his condition was diagnosed as AS. Follow-up examinations revealed no change in the fundus oculi albinoticus and optic atrophy, nor did they indicate poor visual tracking. ***Conclusions:*** When fundus oculi albinoticus and optic atrophy are observed in patients with multiple malformations, AS should be considered as a differential diagnosis.

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Introduction

Angelman syndrome (AS) is a complex teratogenic disorder characterized by severe developmental anomalies, convulsions, lateral curvature, easily induced laughing seizures, ataxic gait, and sleep disorder, etc. [1, 2]. AS is caused by a gene dysfunction on chromosome 15, genetically derived from the person's mother, and it is regarded as a dysfunction resulting from the deletion or the mutation of the *UBE3A* gene copy [3]. The ophthalmic findings related to AS reportedly include fundus oculi albinoticus, poor visual tracking, eye movement abnormality, hyperopia, nystagmus, congestion failure, and aniridia, etc. [4–13].

Here, we report a case of fundus oculi albinoticus diagnosed as AS via genetic examination.

Case Report

This study reports on a 4-year-old boy who was born by vaginal delivery on August 7, 2013 (gestational age: 39 weeks; birth weight: 3,354 g; Apgar score: 3/10). Since he had been having respiratory disturbance since birth, oxygen therapy was administered. In addition, he had a swallowing disorder, etc. He underwent a complete physical examination after his admission to the Neonatal Intensive Care Unit at Osaka Medical College Hospital, Takatsuki-City, Japan, to investigate the causes of his condition. In regard to brain abnormalities, magnetic resonance imaging (MRI) of the boy's head revealed a thin corpus callosum, fissile brain disease, and polymicrogyria (Fig. 1a). Examination by MR urography revealed prominent ureteral dilation and hydronephrosis, and stenosis was observed at both the left and right ureteral inlets (Fig. 1b). In addition, atrial septal defects and milky skin were observed. Dandy-Walker syndrome was considered as a distinguishing malformation syndrome from the brain MRI findings, yet no definitive diagnosis was made. Thus, he was referred to the Department of Medical Genetics at Osaka Women's and Children's Hospital, Izumi-City, Japan. Upon examination, genetic testing results indicated a deletion of the Prader-Willi syndrome/AS (PWS/AS) areas. In combination with the results of methylation analysis, the diagnosis of AS was ultimately reached.

At 1 month after birth, the boy was referred to the Department of Ophthalmology, Osaka Medical College. Upon examination, no pupillary discrepancies in either eye and no obvious relative afferent pupillary defects were observed; however, the direct light reflection almost disappeared, and no visual response was observed. In regard to anterior ocular segment findings, the cornea was clear but slight hypopigmentation was observed in the iris (Fig. 2a, b). No abnormalities were found in the crystalline lens. In regard to fundus examination findings, hypopigmentation of the retinal pigment epithelium and the choroid and optic atrophy were observed in both eyes (Fig. 3a, b). Although he had been followed up periodically, no significant ophthalmic changes were detected in both optic atrophy and fundus oculi albinoticus with the development of his eyeballs. Now at 4 years old, both eyes have no light reflex and no visual responses, such as visual tracking.

Discussion

AS is a complex disease characterized by disorders, such as severe mental retardation, epilepsy, ataxic dyskinesia, and easily stimulated laughter [1, 2], and it reportedly occurs at a

frequency of 1 in every 15,000 births [2]. It is caused by the loss of function of the imprinted gene *UBE3A*, located on chromosome 15 q11–q13, most cases reportedly being due to a mutation [3], and the risk of recurrence in the next generation is considered to be extremely low. PWS also occurs due to a similar deletion on chromosome 15, but the deletion on the chromosome in PWS cases is derived from the father, while the deletion on the chromosome in AS cases is derived from the mother, so it is a different disease [3].

In AS cases, the clinical findings include the facial expression, referred to as "happy puppet" (i.e., smiling puppet), severe delay in mental development with no ability to speak, a small head, the action of hitting both hands, muscle tension decrease, seizure attacks, and/or laughing attacks (i.e., laughing for no reason) [2]. In cases of chromosomal deletion, white skin, mandibular protrusion, popping out of the tongue, a head that is flat at the back, and sleep disturbance, etc., may be observed.

Genetic testing is essential for the diagnosis of AS. The chromosome fluorescent in situ hybridization method using a DNA probe is useful for detecting chromosomal deletion, which occurs in 70% of all AS patients. Since this deletion cannot be detected by ordinary chromosome analysis, the combined use of methylation testing is considered useful. In light of the diagnostic criteria reported by Williams et al. [14], electroencephalogram examination is also considered effective for the diagnosis of AS.

In regard to the ophthalmic complications associated with AS, fundus oculi albinoticus, poor visual tracking, abnormal eye movements, hyperopia, nystagmus, congestion failure, and aniridia, etc., have been reported [4–13]. Michieletto et al. [4] examined such complications in 34 AS patients and found a refractive error in 97% of their patients, strabismus in 75%, and depigmentation in 53%. In their study on AS patients, Dickinson et al. [5] reported low pigmentation of the choroid and iris in 70% of their patients and optic atrophy in over 40%. Optical coherence tomography imaging appeared to be a useful examination to detect the morphological abnormalities, such as disc cupping, decreased retinal thickness, and abnormal macular contour. However, the patient in this study was bedridden, thus making optical coherence tomography imaging difficult to perform.

Even though the iris pigment in our patient was somewhat light, based on the fact that fundus examination clearly revealed fundus oculi albinoticus and that optic atrophy and poor visual tracking had also been observed, the findings in this case are consistent with those of previous reports on the ophthalmic findings in AS patients. However, our case differs from those of previous reports due to the merger of numerous brain congenital malformations, such as a thin corpus callosum, fissile brain disease, and polymicrogyria. The relationship between these abnormalities and AS is unknown, and it is highly possible that other genetic abnormalities may be involved. However, there have been reports on cases with genetic abnormality in the PWS/AS area, where the thin corpus callosum was merged [15], so this case could be related in some way.

In conclusion, the findings in this case of optic atrophy, hypopigmentation of the fundus and iris, and poor visual tracking suggest a poor prognosis of visual function. Our experience with this case has led us to believe that in patients in whom fundus oculi albinoticus and optic atrophy are observed together with multiple malformations, it is necessary to consider AS as a differential diagnosis.

Acknowledgements

The authors wish to thank John Bush for editing the manuscript.

Statement of Ethics

This case study was approved by the Ethics Committee of Osaka Medical College.

Disclosure Statement

There are no conflicts of interest to report for all authors.

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DOI: 10.1159/000485964

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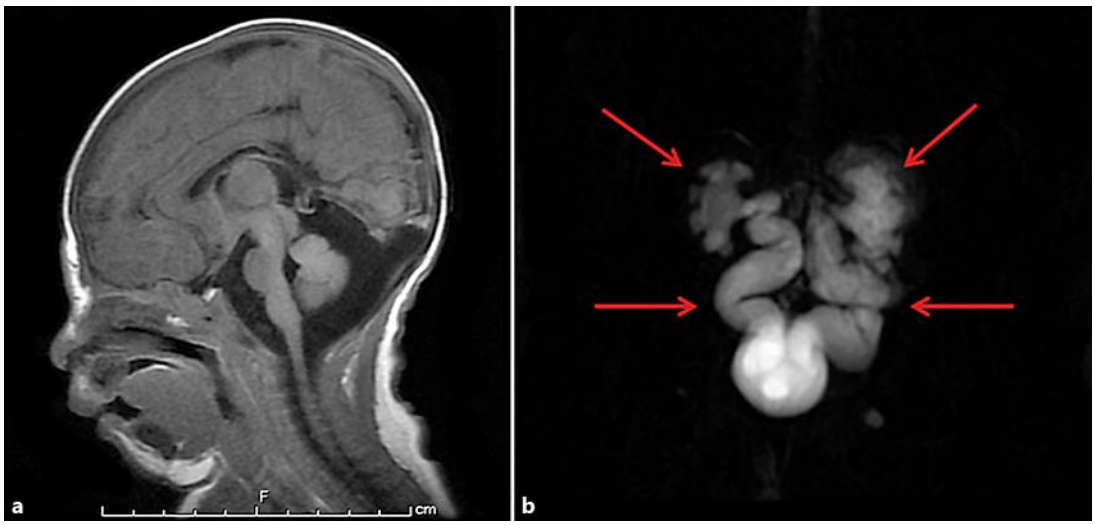

Fig. 1. Magnetic resonance image (MRI) of the patient's head and MR urography. **a** MRI of the head revealed a thin corpus callosum, fissile brain disease, and polymicrogyria. **b** MR urography revealed hydronephrosis.

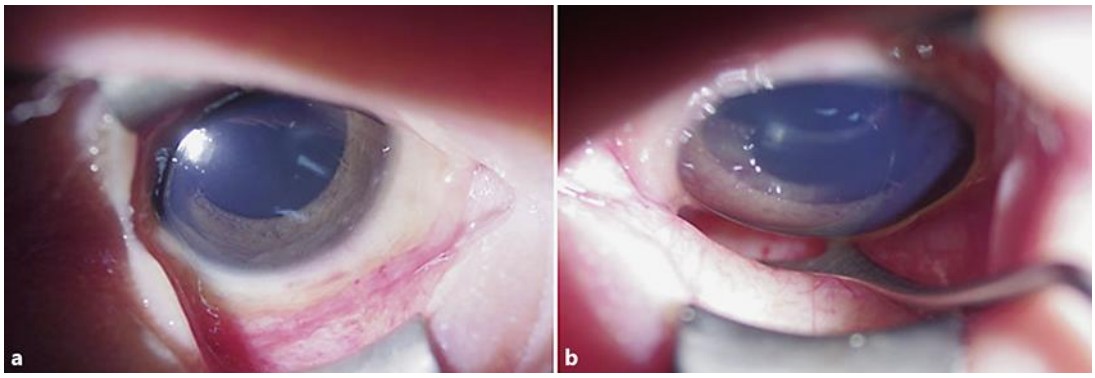

Fig. 2. Anterior segment photograph obtained 1 month after birth (**a** right eye, **b** left eye). Slight hypopigmentation was observed in the iris in both eyes.

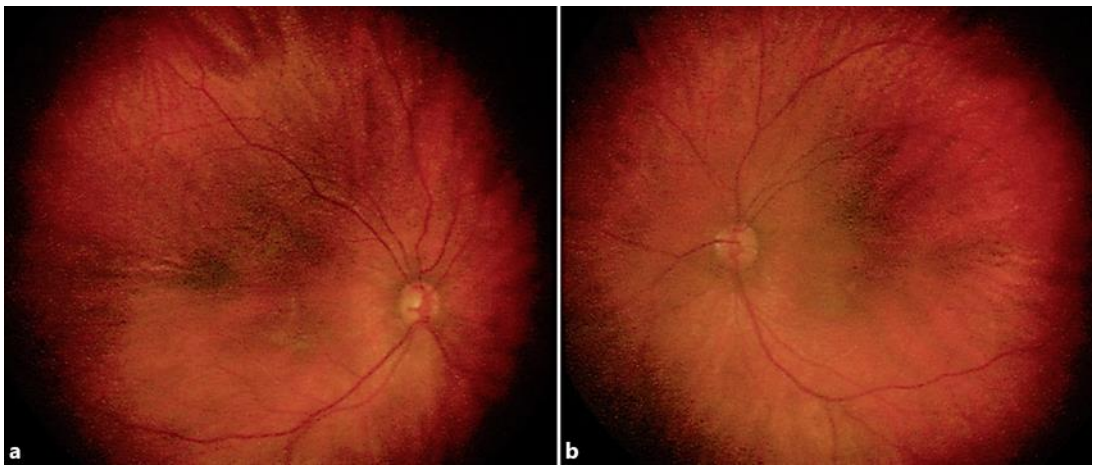

Fig. 3. Fundus photograph obtained 1 month after birth (**a** right eye, **b** left eye). Hypopigmentation of the retinal pigment epithelium and the choroid and optic atrophy were observed in both eyes.