CASE REPORT

Disruption of the Photoreceptor Inner Segment–Outer Segment Junction in a 6-Year-Old Girl with Joubert Syndrome

Shimpei Baba^a, Eri Takeshita^a, Hiroko Yamazaki^b, Mikako Tarashima^c, and Masayuki Sasaki^a

^aDepartment of Child Neurology, National Center Hospital, National Center of Neurology and Psychiatry (NCNP), Kodaira, Tokyo, Japan;

^bDepartment of Ophthalmology, Kohnodai Hospital, National Center for Global Health and Medicine, Ichikawa, Chiba, Japan; ^cSakura-so Rehabilitation and Nursery Center for Disabled Children, Saitama, Saitama, Japan

ABSTRACT

Joubert syndrome (JS) is a spectrum of genetic disorders characterised by cerebellar and brain-stem malformation called “molar tooth sign”, resulting in hypotonia, developmental delay, and intellectual disability. Here we describe a young female JS patient with “salt-and-pepper” fundus and inner segment–outer segment junction (IS/OS line) discontinuity, with a lack of external limiting membrane. Ocular coherence tomography (OCT) detected blurred external retinal layers in the macula centre. Although JS patients often have retinal degeneration with varying severity, few investigators have utilised OCT in their investigations. Our findings will help clarify the precise mechanisms of retinal involvement in JS.

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Introduction

Joubert syndrome (JS), an inherited congenital cerebellar ataxia, is characterised by an unusual midbrain–hindbrain malformation referred to as “molar tooth sign” and occurs in approximately 1 in 80,000–100,000 live births.¹ JS features heterogeneous clinical and genetic backgrounds, and patients exhibit variable manifestations with possible involvement of other organs, such as the kidney, liver, and retina. The most common complication is retinal degeneration, which ranges in severity from Leber congenital amaurosis to slowly progressive retinopathies with partially preserved vision.² Several previous reports have described the features of JS patients using ophthalmic examinations, visual evoked potential (VEP), and electroretinography (ERG).^{3–5} However, only a few detailed reports have included the use of ocular coherence tomography (OCT). Here we report the case of a patient with JS, “salt-and-pepper” fundus, and characteristic findings in annual OCT studies.

Case presentation

The patient was a 6-year-old female born to unrelated healthy parents and with normal antenatal, perinatal, and family histories. Abnormal eye movement, delayed motor development, episodic tachypnoea, and truncal hypotonia were observed from early infancy. The patient began walking at the age of 2 years but exhibited an ataxic gait. She was referred to our hospital at the age of 4 years. Clinical neurological examinations detected cerebellar ataxia. The patient could smoothly pursue a slow-moving object but exhibited partial oculomotor apraxia with delayed saccade initiation. She had a normal intelligence level, and her intellectual quotient was 114 when measured by the Tanaka–Binet test. Brain magnetic resonance imaging revealed moderate cerebellar vermis hypoplasia and thickened and elongated superior cerebellar peduncles, with no superior cerebellar peduncle decussation (Figure 1).

The patient had never complained about visual disturbances. On ophthalmic examination, her

CONTACT Eri Takeshita, MD, PhD erit@ncnp.go.jp Department of Child Neurology, National Center Hospital, National Center of Neurology and Psychiatry, 4-1-1 Ogawahigashi-cho, Kodaira, Tokyo 187-8551, Japan.

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Figure 1. Magnetic resonance imaging findings in a patient with Joubert syndrome. (A, B) Sagittal T1-weighted images showing hypoplasia of the vermis (A, arrows), and secondary enlargement of the fourth ventricle and thickened, elongated superior cerebellar peduncles (B, arrow). (C, D) Axial T2-weighted images. A “molar tooth sign” was formed by the mildly elongated and thickened superior cerebellar peduncles (C, arrow) and deepened interpeduncular fossa (D, arrowhead). (E) Diffusion tensor imaging showing absence of decussation in the superior cerebellar peduncles (orange and purple lines).

visual acuities were $VD = 0.4$ ($1.0 \times +1.5$ D cyl $+1.75$ D Ax 80°) and $VS = 0.6$ ($1.0 \times +1.75$ D cyl $+1.75$ D Ax 90°), which were measured using Landolt ring chart. Slit-lamp examination and VEP results were normal. ERG was recorded with an LE-4000 system (TOMEY, Aichi, Japan), which revealed subnormal patterns with decreased amplitude in both dark- and light-adapted ERGs, suggesting impaired activity of the rod and cone cells (Figure 2). She also exhibited “salt-and-pepper” retinal pigmentation (Figure 3A and B) and an enlarged Mariotte blind spot in the Goldmann perimeter. OCT (RTVue-100; Optovue, Fremont, CA, USA) revealed thinning of the whole retina (Figure 3C) relative to that seen in normal children, as previously reported by Al-Haddad et al.⁶ Striking inner segment–outer segment (IS/OS) line discontinuity, lack of an external limiting membrane, and blurred external retinal layers were observed both in the centre of the macula and the marginal region (Figure 3D). In addition, abdominal ultrasound detected a kidney cyst, indicating the potential involvement of other organs. Based on these findings, the

patient was diagnosed with JS with oculorenal defects.

Over a 2-year follow-up period post diagnosis, the best-corrected visual acuity was maintained at 1.0 and OCT findings did not progress; however, a ring scotoma was confirmed in the Goldmann perimeter (Figure 4), suggesting the progressive nature of the patient’s retinal dystrophy.

Discussion

Improvements in OCT technology now allow for the delineation of retinal structures. The IS/OS line on OCT images is considered to represent a key hallmark of photoreceptor cell integrity, and this line is known to be disrupted in various diseases (e.g., retinitis pigmentosa).⁷ Based on OCT findings in our case, OCT was thought to be useful method for documenting retinal abnormalities in JS as well, even though its role in detecting progression of retinal dystrophy was undetermined. To our knowledge, this is the first reported case of IS/OS line discontinuity in a patient with JS. Our data are valuable because most JS patients have some degree of intellectual

Figure 2. The ISCEV standard electroretinogram. (A) Rod response. B-wave amplitude was severely diminished in both eyes. (B) Maximal response. Both A- and B-wave amplitudes were diminished in both eyes, especially in the right eye. The oscillatory potentials were also attenuated in the left eye, whereas barely identifiable in the right eye. (C) Cone response. Both A- and B-wave amplitudes were diminished in both eyes. (D) 30-Hz flicker. Amplitude of each response was attenuated.

Figure 3. Fundus photography and optical coherence tomography (OCT). (A, B) Fundus photography revealed "salt-and-pepper" retinal pigmentation. A and B show the macular centre of the left eye and peripheral region of the right eye, respectively. (C) Map of retinal thickness of the left eye. The green area lies within normal limits, whereas the blue area lies outside the normal limits. (D) OCT image of the right eye. The inner segment-outer segment line (IS/OS line) showed marked disruption in the centre of the macula and in the marginal region. IS/OS line disruption was worse in the paramacular region (arrows) than in the macular centre.

disability and are unable to remain still during OCT examinations.

The genetic basis of JS is complicated and only partly understood. Over 20 causative genes

have been reported to date, some of which are related to various ciliopathies that affect primary cilia,¹ immotile organelles that protrude from the cell surface. In many adult tissues, cilia act

Figure 4. Goldmann visual field testing. (A) Enlargement of the Mariotte blind spot was observed at the age of 4 years. (B) Ring scotoma was confirmed at the age of 6 years.

as a sensory system to detect extracellular signals and play roles in the regulation of tissue maintenance, polarity, or proliferation. In the retina, photoreceptors contain primary cilia known as connecting cilia, slender structures that connect the outer and inner segments.⁸ These connecting cilia are thought to be disturbed in JS patients, but thus far, few *in vivo* findings have been acquired to support this hypothesis. Our findings indicate a role of OCT in detecting celio-pathy, which may be the mechanism underlying the retinal dystrophy observed in JS.

Considering the severity of IS/OS line disruption on OCT, the visual acuities of the patient were considerably good. This discrepancy can be explained by the lesion distribution in the retina. As the severity of IS/OS line disruption was predominant in the paramacular region and mild in the macular centre, the visual acuity of the patient might have been preserved at 4 years of age and seemed not to progress over 2 years. Preserved visual field centre in the Goldmann perimeter coincided with this theory.

Only one previous report has used OCT to evaluate retinal involvement in JS patients. Makino et al. reported OCT images acquired from two brothers with JS. Despite OCT images being normal, the fundi of these particular patients exhibited only small colobomas and mild chorioretinal discoloration without the “salt-and-pepper” retinopathy observed in our current patient.⁹ Given the heterogeneity of JS, the underlying aetiology of fundus findings was assumed to differ between the cases described by Makino et al. and the present patient.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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