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Giant Choledochal Cyst in a Child With Spinocerebellar Ataxia: A Potential Molecular Link Through Aberrant Cytosolic Calcium Signaling

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To the Editor,

Spinocerebellar ataxias (SCAs) are a group of progressive neurodegenerative disorders that primarily manifest as adult-onset cerebellar ataxia. To date, approximately 30 subtypes have been identified (Klockgether et al. 2019). Two of these, that is, SCA15 and 29, share a single causative gene, that is, *ITPR1*: haploinsufficiency in *ITPR1* causes an adult-onset progressive form, that is, SCA15, whereas presumed gain-of-function variants cause an infantile-onset non-progressive form, that is, SCA29 (van de Leemput et al. 2007; Casey et al. 2017).

A choledochal cyst results from a developmental malformation of the biliary tree. Affected individuals present with cholestasis during infancy (Ciccioli et al. 2025). Early recognition and timely surgical intervention are necessary, particularly due to its carcinogenic potential (Aydin Mericoz et al. 2021). Choledochal cysts can occur in isolation or in the setting of pre-existing genetic disorders. Their postulated mechanisms include interactions of various molecular signaling cascades and chemokines (Banales et al. 2019).

As for a combined phenotype of a choledochal cyst and cerebellar ataxia, a recent trio-based exome study of 31 patients with choledochal cysts reported one subject with a de novo frameshift variant in *PPP2R2B* who had "spinocerebellar ataxia" (Wong et al. 2016). The molecular link between cerebellar ataxia and choledochal cysts remains to be explored.

The proband was born via normal spontaneous vaginal delivery at 39 weeks of gestation. He had a birth weight of 3132 g (−0.18 SD), a length of 49.5 cm (+0.14 SD), and a head circumference of 31.5 cm (−1.38 SD). A fetal ultrasound examination at 26 weeks of gestation identified a cyst between the liver and the bladder. At birth, he was diagnosed with choledochal cyst type Ia (Figure 1A). The cyst measured 4 cm in diameter. He underwent gallbladder drainage at 1 month of age, followed by complete resection of the extrahepatic bile duct and hepaticojejunostomy at 3 months of age.

Around that time, the patient exhibited abnormal eye movements characterized by rapid rightward and upward eye deviations with no visual pursuit. A magnetic resonance imaging of the head demonstrated no abnormalities. His subsequent psychomotor development was delayed; he gained head control at 8 months and could sit unsupported at 1 year and 3 months of age. By 2 years of age, he was unable to walk independently or speak meaningful words.

Abbreviation: SCA, spinocerebellar ataxia.

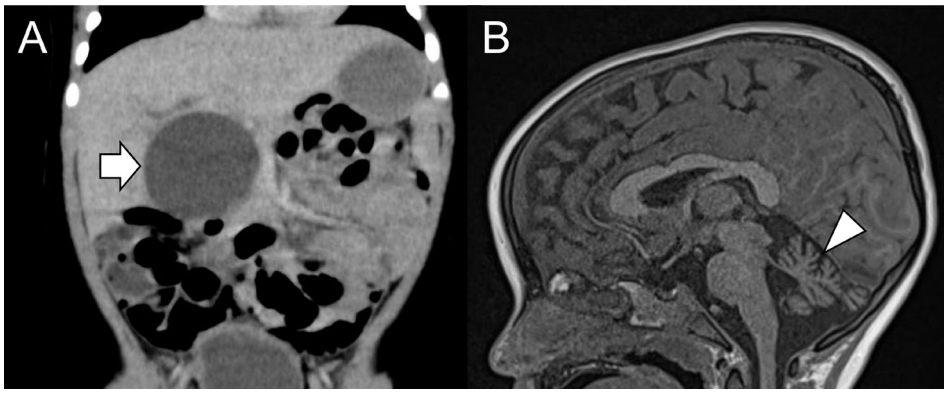

FIGURE 1 | Radiographic features in the abdomen and brain. (A) A coronal image of abdominal magnetic resonance imaging at 3 months of age showed a dilated bile duct (an arrow). (B) A sagittal image of cerebral magnetic resonance imaging at 3 years and 8 months of age showed cerebellar atrophy (an arrowhead).

At the time of referral to us at the age of 2 years and 3 months, his height was 85.3 cm (−0.9 SD), his weight was 12.1 kg (−0.2 SD), and his head circumference was 50.0 cm (+0.7 SD). There was no deformity or characteristic facial features. A neurological examination revealed muscle hypotonia and truncal ataxia. There were no abnormalities in ocular movements or deep tendon reflexes. The Analytic Testing for Development in Infancy and Childhood showed moderate developmental delay with a developmental quotient of 36 (35 in locomotor activity, 28 in manual activity, 24 in basic habits, 48 in interpersonal relationships, 39 in receptive language, and 44 in expressive language). A magnetic resonance imaging of the head at 2 years and 4 months of age showed cerebellar atrophy. The auditory brainstem response was normal.

Repeated brain magnetic resonance imaging at 3 years and 8 months showed a progression of cerebellar atrophy (Figure 1B). At the age of 4 years and 10 months, he had a febrile seizure lasting approximately 30 min that required emergent transport to the hospital. There were no further recurrences of seizures since then. By 5 years and 7 months of age, he could stand, but his gait was unsteady, and he could walk only a few steps with truncal ataxia. His language ability was limited to expressing a few two-word sentences.

Chromosome analyses using G-banding and array comparative genomic hybridization revealed no abnormalities. After obtaining written consent from his parents, a trio-based whole genome analysis was performed. The research protocol was approved by the Research Ethics Board of the National Center for Child Health and Development (Approval number 2020-326). The trio-based analysis showed a de novo heterozygous variant (c.805C>T p.(Arg269Trp)) in *ITPR1* (NM_001378452.1), that is, chr3:g.4645678C>T (GRCh38). This variant had a CADD score of 27.1 (phred) where scores above 20 are considered deleterious and was reported as "Pathogenic/Likely pathogenic" in the ClinVar database (Variation ID: 265201). According to the guidelines for the interpretation of sequence variants by the American College of Medical Genetics and Genomics, this variant is considered "pathogenic" (PS1, PS2, PM2, and PP3). Sanger sequencing confirmed the results. No reported variants for choledochal cysts were identified (Wong et al. 2016).

From a molecular standpoint, cytosolic calcium signaling plays a critical role in the development of the brain and bile duct. The causative gene for SCA29, that is, *ITPR1*, encodes inositol-1,4,5-trisphosphate receptor type 1 (IP3R1), which is involved in intracellular calcium signaling in cerebellar Purkinje cells (Matsumoto and Nagata 1999). Interestingly, the expression of inositol 1,4,5-trisphosphate receptors is selectively lost in the biliary epithelium of a rat model of cholestasis and in surgical specimens of various human cholestatic disorders (Shibao et al. 2003). Furthermore, the proper distribution of these receptors is necessary for the cellular organization of cholangiocytes (Hirata et al. 2002). Taken together, these findings suggest that choledochal cysts represent a neomorphic phenotype caused by alterations in inositol 1,4,5-trisphosphate signaling.

The present observation is similar to an existing subgroup of SCA that is prone to hepatobiliary complications. Biallelic variants in *SCYL1*, which regulates the integrity of Golgi transport, cause SCA21 and CALFAN syndrome (Lenz et al. 2018). The latter is an acronym that stands for low γ-glutamyl-transferase *c*holestasis, *a*cute *l*iver *f*ailure, *a*nd *n*eurodegeneration. Patients present with cerebellar ataxia and atrophy, as well as infantile-onset cholestasis and acute liver failure (Schmidt et al. 2015). In addition to SCA21, SCA29, and perhaps also SCA15, may need to be added to the list of SCA subtypes that require abdominal screening to search for hepatobiliary complications using liver function tests and/or ultrasonography.

A boy with spinocerebellar ataxia and a giant choledochal cyst was found to have a de novo heterozygous variant in *ITPR1*, which encodes the inositol-1,4,5-trisphosphate receptor type 1. The combined phenotype appeared to represent a shared pathogenesis affecting cytosolic calcium signaling, rather than a chance association. Further accumulation of the detailed hepatobiliary phenotypes in this group of SCAs is warranted.

Author Contributions

Hiromi Sumitomo: writing – original draft, data curation. **Tomoyuki Akiyama:** writing – review and editing, data curation. **Tadashi Kaname:** writing – review and editing, investigation, formal analysis. **Toshiki Takenouchi:** writing – review and editing, supervision, project administration, conceptualization.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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