Japanese Journal of Gastroenterology and Hepatology

Short Communication

ISSN: 2435-1210 | Volume 10

Twenty Years Follow-Up of Acrocallosal Patients Revealing New Clinical Features

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Received: 16 Dec 2024
Accepted: 31 Dec 2024
Published: 06 Jan 2025
J Short Name: JJGH

Citation:

Chong Ae Kim. Twenty Years Follow-Up of Acrocallosal Patients Revealing New Clinical Features.
J Gastro Hepato. 2025; V10(14): 1-3

1. Short Communication

Acrocallosal Syndrome (ACS) is a monogenic, autosomal recessive condition, with intellectual disability, dysmorphic facial features, central nervous system abnormalities and distal limb malformations. It is caused by pathogenic biallelic variants on the kinesin family member 7 gene, which encodes a cilia-associated protein that is part of the kinesin family regulating GLI transcription factors that controls the hedgehog signaling pathway. The gene product also functions as a stabilizer of cell microtubules, and for that reason, ACS can be considered a ciliopathy [1]. Since its first description in 1980 [2], multiple cases have been reported in the literature. However, it was only with the advent and accessibility of sequencing technologies that point mutations in the *KIF7* as a candidate gene for ACS were identified [1]. Despite advances in understanding the disease mechanism and its clinical presentation, long-term clinical data remain scarce. Here, we describe two unrelated probands followed for over 20 years in a tertiary genetics clinic in Brazil. Patient 1 is a Brazilian male proband referred to our team by the maternity ward where he was born with limb malformations and suspected hydrocephalus. He is the second child of a healthy and non-consanguineous couple that had three previous spontaneous abortions (without further investigation) and already had one healthy male child. At conception, his mother was 32 years old, and his father was 34 years old. Patient 1 was delivered at term following an uneventful pregnancy, with normal birth length and weight (percentiles 22 and 33, respectively) and a head circumference of 36 cm (percentile 92). His APGAR score at one minute was 3, improving to 7 after appropriate intervention, and he was transferred to the neonatal intensive care unit (NICU). During his first week of life, he experienced asymptomatic hypoglycemia and transient jaundice but was otherwise stable and discharged after 2 weeks. At his first genetic evaluation, at 3 months, facial dysmorphisms were noted, including ocular hypertelorism, down-slanting palpebral fissures, and macrocrania. He also exhibited duplication of the right hallux, bilateral cutaneous syndactyly of the second and third toes, and bilateral cryptorchidism. Imaging studies, including brain MRI, echocardiogram, and skeletal X-ray, revealed agenesis of the corpus callosum, hypoplasia of the cerebellar vermis, a small ventricular septal defect, dextrocardia, and duplication of the right toe phalanges. Ophthalmologic evaluation revealed optic nerve hypoplasia, nystagmus, and lagophthalmos. Banding G karyotype was normal. ACS was suspected, but molecular confirmation was not possible at the time. The diagnosis was finally confirmed in adolescence through whole exome sequencing, which identified a homozygous pathogenic frameshift variant in the *KIF7* gene: (NM_198525.3):c.2896_2897del:p.(Ala966Profs*81). During a 20 year follow up, Patient 1 evolved with global developmental delay and severe intellectual disability. He was never able to walk or speak. At age 6, he was diagnosed with epilepsy but his seizures were well controlled with Levetiracetam. He

remained seizure-free and medication-free between ages 16 and 20 but had a seizure recurrence during his recovery time after he was submitted to a scoliosis corrective surgery. The same anticonvulsivant drug was reintroduced with a good clinical response. He was submitted to a corrective surgery of bilateral lagophthalmos, without any complications. No surgery was required for his cardiac condition. Regarding his growth, Patient 1 has postnatal short stature (-2.7 SD) and macrocrania (final head circumference of 58.5 cm, z +2.4 SD). Growth hormone therapy was discussed but not initiated. Interestingly, he presented severe gastroesophageal reflux disease (GERD) with persistent vomiting, regurgitation, and choking led him to three aspiration pneumonia episodes in infancy. He received Domperidone and Ranitidine and his symptoms improved by age 11, with resolution of choking episodes but persistence of difficulty in swallowing solid food. Still now, at the age of 20 years old, his diet is restricted to liquid and pasty foods. This patient is still followed with annual consultations and he is now 20 years old, he measures 153 cm (-3.3 SD) and weighs 52 kg (-2 SD). He maintains his head circumference of 58.5cm. Patient 2 is a Brazilian female proband born to a consanguineous couple (second cousins once removed). Her mother was 45 years old at conception and her father was 51. She has one older, healthy sister. She was born at term with meconium release during labor and was immediately transferred to the NICU. Her birth weight and length were at the 50th percentile, but no information regarding her head circumference was available. She was discharged home after 15 days. Her first genetic consultation was at age of 3, and she was referred by the gastropediatrics team due to agenesis of the corpus callosum and suspected hydrocephalus. Again, dysmorphic features were noted, including ocular hypertelorism, a broad forehead, and a broad nasal bridge. She also exhibited bilateral cutaneous syndactyly of second and third toes and a history of recurrent otitis media and global developmental delay. Skeletal survey was requested and the images revealed an unusual sternal cleft. Brain imaging confirmed agenesis of the corpus callosum. Cardiac and ophthalmologic evaluations and blood karyotype were normal.

Again, ACS was suspected, but molecular confirmation could only be achieved in adolescence through whole exome sequencing, identifying the same homozygous pathogenic frameshift variant in *KIF7*: (NM_198525.3):c.2896_2897del:p.(Ala966Profs*81). Her clinical course for the past 24 years includes global developmental delay with no acquisition of walking or speech and severe intellectual disability. She also has short stature (-4.3 SD), but head circumference remained within normal range. She has a diagnosis of neurogenic bladder with stable kidney function under nephrology care. Patient 2 also presents spinal scoliosis but no surgery was indicated. Interestingly, severe GERD with dysphagia was present since birth, manifesting as choking, regurgitation, and persistent hiccups, leading to five aspiration pneumonias in early childhood. GERD was confirmed through esophagogastric contrast radiography, though upper gastrointestinal endoscopy and swallowing studies were normal. Bromopride treatment was initiated, and GERD symptoms improved over time, with dysphagia eventually restricted to liquids. She was followed annually and is now 24 years old, 135.1 cm and (-4.3 SD) and 52 kg (-0.79 SD).

2. Discussion

Two cases described expand the clinical spectrum of ACS by emphasizing the role of GERD and dysphagia as significant early manifestations of the condition. Both patients presented with severe symptoms in infancy, including regurgitation, choking, and recurrent aspiration pneumonias, consistent with microaspiration secondary to GERD. Importantly, symptoms improved over time in both patients. By adolescence, GERD was well controlled, and dysphagia was limited to liquids in Patient 2, while Patient 1 remained restricted to pasty and liquid diets. These findings suggest a potential natural history of gastrointestinal symptoms in ACS, where severity decreases with age. The presence of GERD and dysphagia in ACS may be linked to neuromuscular dysfunction or impaired cilia function, which could affect esophageal motility and swallowing mechanisms. Early identification and management of these symptoms, including pharmacological treatment, nutritional support, and speech therapy, are critical to preventing aspiration-related complications (Table 1). The variant identified in both patients is a frameshift mutation leading to a premature stop codon, predicted to result in nonsense-mediated decay of the transcript. This variant has been previously reported in both homozygous and compound heterozygous states [3], with five entries in ClinVar, including one from another Brazilian patient.

	Clinical Findings					
Proband	CNS	Extremeties	Developmental milestones	Gastrointestinal	Facial dysmorphisms	Eyes
Patient 1	Absent corpus callosum Vermis hypoplasia	Duplicated hallux 2-3 toes syndactyly	Global delay Severe mental disability	Gastroesophageal reflux with maintained restriction to solid aliments	Ocular hypertelorism Downstanted palpebral fissures Macrocrania	Optic nerve hypoplasia, lagophtalmos and nystagmus
Patient 2	Absent corpus callosum Hydrocephalus	2-3 toes syndactyly	Global delay Severe mental disability	Severe gastroesophageal reflux with preogressive improvement os symptoms	Ocular hypertelorism Broad forehead Broad nasal bridge	No findings

	Clinical Findings					
Proband	Genitourinary	Seizures	Heart	Height	Skeletal	Family history
Patient 1	Cryptorchirdism	Well controled seizures	IVC and dextrocardia	Short stature (- 2.7 SD)	Duplicated hallux	Consanguinity
Patient 2	Neurogenic bladder	No seizures	No findings	Short stature (- 4.3 SD)	Sternal cleft	No reported consanguinity

Table 1: Clinical findings in two patients diagnosed with Acrocallosal Syndrome.

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