Case Report

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Surgery Section

A Case of Infantile Achalasia in Alacrima–Achalasia–Mental Retardation Syndrome: A Rare and Complex Association

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ABSTRACT

Alacrima-Achalasia-Mental Retardation (AAMR) syndrome, also known as GDP-Mannose Pyrophosphorylase A (GMPPA)-Congenital Disorder of Glycosylation (GMPPA-CDG), is a rare autosomal recessive condition characterised by alacrima, achalasia, and intellectual disability. Due to its rarity and the variable clinical presentation, diagnosis is often delayed. Hereby, the authors present a case of one-year-old female with progressive feeding difficulties, global developmental delay, and failure to thrive. Evaluation revealed absence of tear production, with radiologic and endoscopic confirmation of achalasia. Genetic testing identified a homozygous pathogenic variant in the GMPPA gene, confirming GMPPA-CDG. Despite an unremarkable perinatal and family history, the clinical triad was evident. Surgical management with Heller myotomy and Dor fundoplication led to significant symptomatic relief and catch-up growth. The present case highlights the importance of early syndromic recognition and genetic confirmation in children with feeding and developmental concerns. Timely surgical and multidisciplinary interventions can improve outcomes in rare neurogastroenterological disorders like GMPPA-CDG.

Keywords: Congenital disorder of glycosylation, Developmental delay, Paediatric achalasia

CASE REPORT

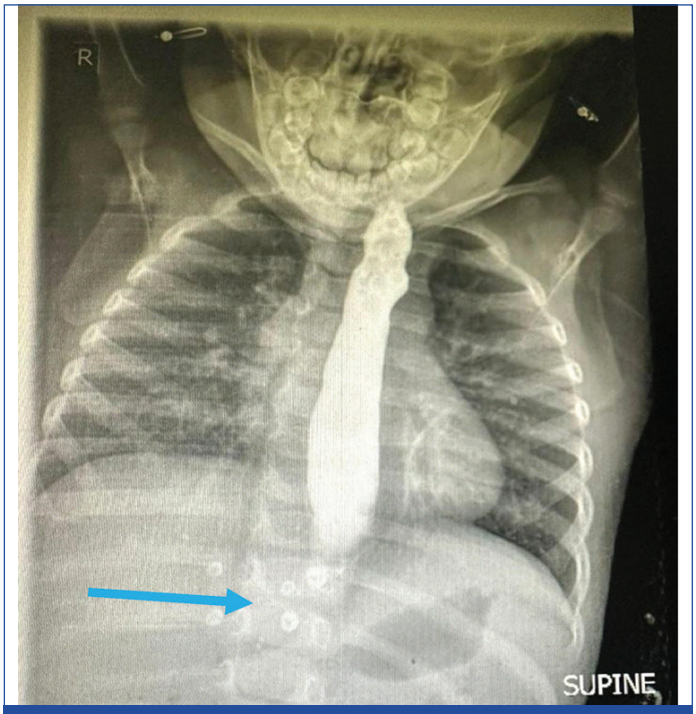
A one-year-old female child presented to tertiary care centre with progressive feeding difficulties and failure to thrive since the age of four months. Parents also reported delayed gross motor and language milestones, with a noticeable worsening of symptoms over the preceding month. The child was born at 39 weeks of gestation via elective lower-segment cesarean section due to a nuchal cord. Appearance, Pulse, Grimace response, Activity, and Respiration (APGAR) scores were 8 and 9 at 1 and 5 minutes, respectively, with a birth weight of 1.8 kg. The neonatal period was uneventful, with no requirement for Neonatal Intensive Care Unit (NICU) care. However, global developmental delay became apparent in early infancy. There was no history of seizures, developmental regression, or plateauing of skills.

On examination, the child was alert but severely undernourished. Vital signs were within normal limits: temperature 98.2°F, heart rate 98 bpm, respiratory rate 27/min, and blood pressure 100/70 mmHg. No pallor, icterus, lymphadenopathy, or pedal oedema was observed. Systemic examination revealed no abnormalities.

Complete blood count: haemoglobin 11 g/dL, total leukocyte count 18,500/mm^3, platelet count within normal limits. Serum electrolytes: sodium 139 mmol/L, potassium 4.6 mmol/L, chloride 100 mmol/L. Cardiac evaluation: Electrocardiogram (ECG) and 2D echocardiography findings were normal.

Upper Gatrointestinal (GI) endoscopy showed a markedly dilated oesophagus with mucus retention. The gastroesophageal junction was located 18 cm from the incisors. No evidence of varices, strictures, or mucosal pathology was noted. Barium swallow demonstrated a grossly dilated oesophagus with delayed contrast clearance, consistent with infantile achalasia [Table/Fig-1].

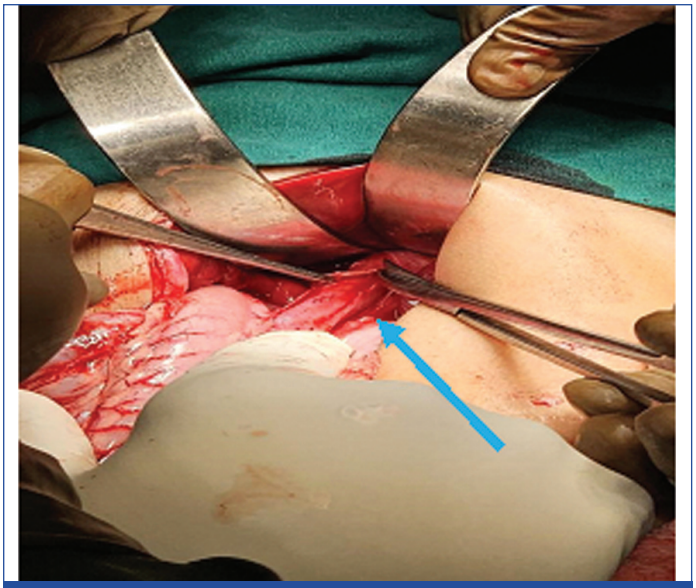
Whole-exome sequencing revealed a homozygous pathogenic missense variant in the GMPPA gene, confirming the diagnosis of AAMR syndrome an autosomal recessive neurodevelopmental disorder. Karyotyping was normal, and there was no family history



[Table/Fig-1]: Barium swallow radiograph demonstrating classic 'bird-beak' appearance in achalasia.

suggestive of genetic or neurological diseases. A diagnosis of infantile achalasia in the context of AAMR syndrome was established, based on clinical features, radiologic imaging, and genetic confirmation.

Initial management included oral nifedipine to temporarily lower the Lower Oesophageal Sphincter (LES) tone and provide symptomatic relief. Definitive surgical intervention was performed via an open Heller myotomy with Dor fundoplication under general anaesthesia. Intraoperative findings included exposure of the lower oesophageal sphincter region after myotomy, with



[Table/Fig-2]: Intraoperative view of open Heller's cardiomyotomy with partial (Dor) fundoplication (Blue arrow).

division of the crura of the diaphragm to facilitate mobilisation of the fundus for the partial (Dor) fundoplication [Table/Fig-2]. A 6-7 cm longitudinal myotomy was carried out on the anterior oesophageal wall, sparing the mucosa. The procedure was completed uneventfully.

The child had an uneventful postoperative recovery. At both 7-day and 1-month follow-up visits, she showed significant improvement in feeding behaviour and weight gain. Caregivers reported complete resolution of dysphagia, regurgitation, and vomiting. Long-term follow-up was advised to monitor nutritional status, neurodevelopmental progress, and recurrence risk.

DISCUSSION

Achalasia is a rare oesophageal motility disorder marked by absent peristalsis and impaired relaxation of the LES, typically resulting from degeneration of inhibitory neurons within the myenteric (Auerbach's) plexus [1,2]. Clinically, it presents with progressive dysphagia, vomiting, and weight loss. In infants and young children, symptoms often mimic Gastro-Oesophageal Reflux Disease (GERD), leading to delays in diagnosis. Such delays may result in serious complications, including failure to thrive, recurrent aspiration pneumonia, and repeated hospitalisations [1].

The estimated incidence of achalasia is 2.92 per 100,000 individuals in adults [2] and approximately 0.11 per 100,000 children annually, with fewer than 5% of cases diagnosed before the age of 16 [3]. Infantile achalasia is exceptionally rare, with its true incidence unknown and largely confined to isolated case reports. While most cases are idiopathic, achalasia may also occur in association with syndromic conditions such as Allgrove syndrome (alacrima, achalasia, and Adrenocorticotropic Hormone (ACTH)-resistant adrenal insufficiency), trisomy 21, congenital central hypoventilation syndrome, eosinophilic oesophagitis, and Chagas disease [3]. A less frequently reported association is GMPPA-Congenital Disorder of Glycosylation (GMPPA-CDG), also known as AAMR syndrome, characterised by alacrima, achalasia, and intellectual disability, caused by biallelic loss-of-function variants in the GMPPA gene. Unlike Allgrove syndrome, GMPPA-CDG is not associated with adrenal insufficiency, making this an essential distinguishing feature [1].

The pathophysiology involves degeneration or dysfunction of inhibitory neurons within the myenteric (Auerbach's) plexus, especially those synthesising nitric oxide [4]. This neuronal impairment results in loss of oesophageal peristalsis and failure of LES relaxation, causing oesophageal dilation and food stasis [5]. Although the exact mechanism in infants remains unclear, congenital neuronal aplasia or progressive neurodegeneration has been proposed. Emerging studies support a combined neurogenic and myogenic aetiology. In syndromic presentations, such as AAMR, the presence of gastrointestinal and neurodevelopmental abnormalities endorses the hypothesis of neurocristopathy, suggesting a common defect in neural crest or enteric nervous system development [1,3].

Genetic syndromes associated with achalasia: infantile achalasia can be a feature of several genetic syndromes. The most widely recognised is Allgrove syndrome (AAA syndrome), characterised by achalasia, alacrima, and adrenal insufficiency, typically diagnosed by identifying pathogenic variants in the AAAS gene [1]. However, in patients presenting with achalasia and alacrima without adrenal dysfunction, alternative diagnoses should be considered. These include GMPPA-CDG (formerly AAMR syndrome), Trafficking Protein Particle Complex Subunit 11 (TRAPPC11)-related disorders, and other emerging syndromic associations [6,7].

The AAMR syndrome, now classified as GMPPA-CDG, is an autosomal recessive disorder caused by biallelic mutations in GMPPA, which encodes GMPPA. In our patient, whole-exome sequencing revealed a homozygous pathogenic missense variant in GMPPA, with a normal karyotype [1]. The core clinical features of AAMR include alacrima, achalasia, and global developmental delay or intellectual disability. Unlike Allgrove (AAAS) syndrome, AAMR is not associated with adrenal insufficiency, offering a critical point of differentiation. Other variable features may include hypotonia, seizures, and subtle dysmorphic traits [3,8]. Koehler K et al., demonstrated that GMPPA deficiency leads to elevated GDP-mannose levels, possibly disrupting glycosylation by affecting GMPPB function [6]. A mannose-restricted diet has been proposed as a therapeutic approach, although its clinical efficacy remains under investigation. The present patient exhibited the classic triad of AAMR—alacrima, achalasia, and developmental delay without adrenal involvement or notable dysmorphic features [1].

Historically, the first case of infantile achalasia was reported in 1953 in a six-month-old who underwent successful surgery at nine months [4]. Geiculescu I et al., (2022) described an eight-month-old who was initially misdiagnosed with GERD and later treated with Heller's myotomy [1]. Shettihalli N et al., (2010) also reported successful surgical management in a preterm neonate [5]. The present report adds to the growing body of evidence on syndromic achalasia, emphasising the importance of genetic testing in atypical presentations and advocating for multidisciplinary care in rare disorders such as AAMR.

CONCLUSION(S)

The present report highlights a rare presentation of AAMR syndrome in a one-year-old female with progressive feeding difficulties, global developmental delay, and failure to thrive. The present case emphasises the critical role of early syndromic recognition, timely genetic diagnosis, and multidisciplinary care in improving outcomes in rare neurogastroenterological disorders such as GMPPA-CDG.

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