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Case Report

Genetics Section

A Case Report of Cantu Syndrome Highlighting the Importance of Genetic Sequencing in Addition to Radiological Testing

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ABSTRACT

An infant initially suspected to have glutaric aciduria was later diagnosed with Cantu syndrome and found to be a carrier of Congenital Disorder of Glycosylation Type 1j. This case involved a five-month-old male infant with Atrial Septal Defect (ASD) and Patent Ductus Arteriosus (PDA) who was under treatment and admitted with a history of recurrent respiratory tract infections, developmental delay, and dysmorphic facies. A metabolic workup was performed. Computed Tomography (CT) brain showed features suggestive of glutaric aciduria; however, MRI brain revealed tortuosity of the cerebral vessels, which was inconsistent with that diagnosis. Hence, Whole Exome Sequencing (WES) was performed. The WES revealed a pathogenic variant in the ABCC9 gene, which is pathognomonic of Cantu syndrome. It also showed a pathogenic variant in the DPAGT1 gene, diagnostic of Congenital Disorder of Glycosylation Type 1j. This is the first reported case in which both mutations were identified in the same patient. WES was subsequently performed for the parents, and the infant's father was found to have heterozygous pathogenic variants in both genes identified in the proband. This study emphasises the importance of genetic sequencing in establishing an early and accurate diagnosis, thereby enabling disease-specific novel treatment approaches and long-term follow-up.

Keywords: Genetics, Rare disease, Whole exome sequencing

CASE REPORT

A five-month-old male infant, the second child born to non-consanguineous parents, was admitted with respiratory distress. The baby was delivered by emergency Lower Segment Caesarean Section (LSCS) due to foetal distress and premature rupture of membranes, as a moderate preterm infant weighing 2.1 kg, with a birth length of 42 cm and a head circumference of 30 cm—appropriate for gestational age—to a hypothyroid mother at 33 weeks of gestation.

Postnatally, the baby was admitted to the Neonatal Intensive Care Unit (NICU) and treated for apnea of prematurity and neonatal jaundice. C-reactive protein was negative, and blood culture was sterile. At three months of age, the infant was admitted and treated for bronchiolitis. Echocardiography revealed ASD and PDA, and the infant was started on anti-failure medications. Direct laryngoscopy confirmed a diagnosis of laryngomalacia. The infant was hospitalised again the following month for another respiratory illness. The mother reported a history of the death of their first child on day one of life due to an unspecified cardiac problem. The medical records were unavailable, and no genetic testing had been performed for the deceased sibling. At the time of the current admission, the infant was noted to have motor developmental delay. He had not yet attained head control, although a social smile was present. The infant was on formula feeds with appropriate dilution.

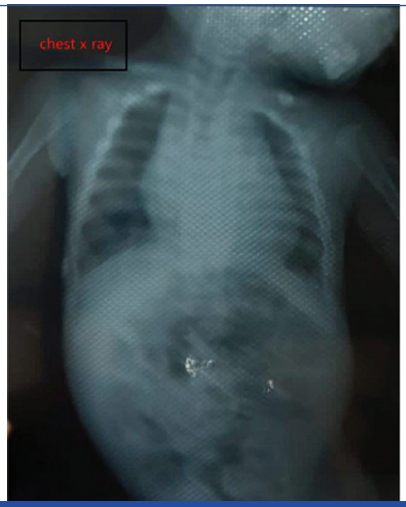
On physical examination, the infant had coarse facial features with thick scalp hair, a prominent forehead, a broad nasal bridge, and low-set ears. Examination of the oral cavity revealed a high-arched palate. An umbilical hernia was noted. A strawberry hemangioma was present in the right inguinal region. Examination of the genitalia showed bilateral hydrocele and phimosis. The audiological screening was normal.

On auscultation of the lungs, bilateral wheeze was heard. Cardiac auscultation revealed an ejection systolic murmur at the left sternal border, in addition to normal first and second heart sounds. Mild hypotonia was noted in all four limbs.

On ophthalmologic screening, the infant was unable to fix or follow light, although fundus examination was normal. Follow-up was advised. Basic investigations related to the current respiratory illness were performed, and treatment was initiated with oxygen support, antibiotics, and nebulisation.

In view of the coarse facies and developmental delay, an Inborn Error of Metabolism (IEM) was suspected, and a metabolic workup was ordered.

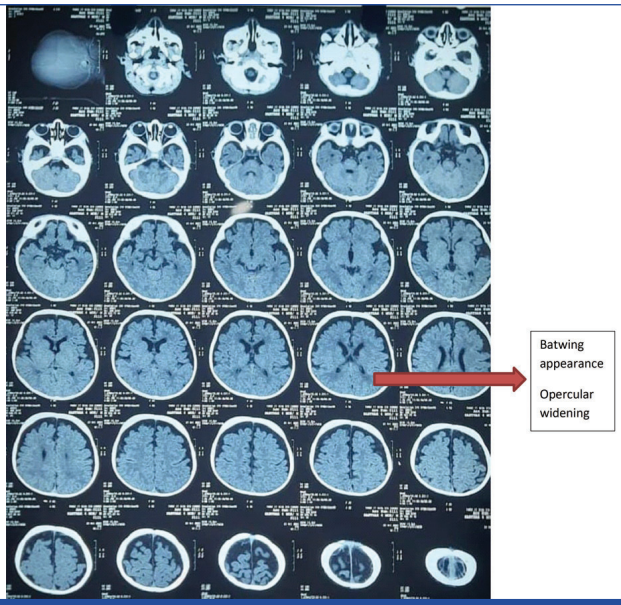
A skeletal survey showed bone age corresponding to chronological age. Chest X-ray revealed cardiomegaly [Table/Fig-1]. Based on the history, clinical features, and external morphological appearance [Table/Fig-2], a provisional diagnosis of IEM or genetic syndrome was considered.



[Table/Fig-1]: Chest X-ray showing cardiomegaly.

[Table/Fig-2]: Clinical picture and external morphological appearance.

CT brain findings were consistent with glutaric aciduria type 1, showing expansion of the cerebrospinal fluid spaces of the temporal lobes and widened Sylvian fissures, giving a classical "bat-wing" appearance [Table/Fig-3] [1]. The radiological findings are summarised in [Table/Fig-4].

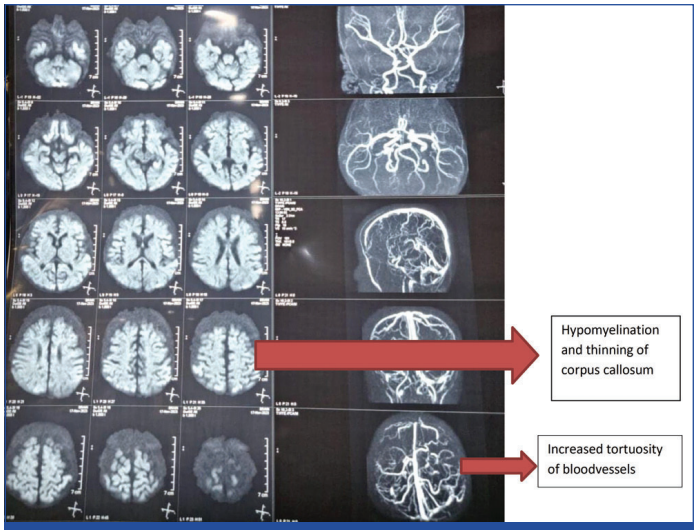


[Table/Fig-3]: CT brain.

Investigations	Findings
Chest X-ray	Increased bronchovascular markings Cardiomegaly
Skeletal survey	Normal for age
ECHO	Small ASD 2.8 mm Restrictive PDA 2.1 mm
CT brain	Bat wing appearance Bilateral frontal and temporal cerebrospinal fluid spaces appears prominent Bilateral opercular widening
MRI brain	Hypomyelination with thinning of corpus callosum Hypomyelination of whitematter in bilateral cerebral hemispheres Cerebral vessels appears tortuous for age
Magnetic resonance spectroscopy	Normal

[Table/Fig-4]: Radiological investigations.

However, MRI brain showed increased tortuosity of the middle cerebral arteries and vertebral arteries, which did not support the diagnosis of glutaric aciduria [Table/Fig-5]. The metabolic screening (tandem mass spectrometry) was also negative for glutaric aciduria [Table/Fig-6].



[Table/Fig-5]: MRI brain.

Parameters	Values
Serum lactate	55 mmol/l
Serum ammonia	50 microgram/dL
Urine Ph	6.2
Venous blood gas analysis	Normal
Ph	7.416
Sodium / potassium / chloride / bicarbonate	140/3.8/115/26 mmol/l
Tandem mass spectrometry	Negative
Urine organic acid analysis	Normal
Amino acid estimation by LC- MS	Normal

[Table/Fig-6]: Metabolic work-up.

Considering the low excretor phenotype of glutaric aciduria type 1 [2], Whole Exome Sequencing (WES) was performed, specifically evaluating the GCDH gene. The much-anticipated WES report was remarkable. It revealed a pathogenic mutation in the ABCC9 gene, transcript NM_005691.4, Exon 29, a missense variant c.3347G>A (p.Arg1116His) (Depth–76X) in a heterozygous state, classified as a pathogenic variant associated with ABCC9 gene–related disorders, inherited in an autosomal dominant manner, and pathognomonic of Cantu syndrome (CS, OMIM 239850) [3]. Additionally, a pathogenic variant in the DPAGT1 gene, transcript NM_001382.4, Exon 1, c.85A>T, was detected in a heterozygous state, inherited in an autosomal recessive manner.

Reverse phenotyping was carried out for the ABCC9 gene mutation in this infant, and a geneticist's opinion was obtained. The facial features were consistent with Cantu syndrome [4]. Cardiomegaly noted on chest X-ray and the presence of PDA (clinically and on echocardiography) supported the diagnosis [5]. Radiological opinion confirmed that the cerebral blood vessels were tortuous for age [6], which is a characteristic feature of Cantu syndrome.

Treatment and follow-up: The infant was treated with oral furosemide at a dose of 1 mg/kg/day for cardiac failure. Regular follow-up was advised with periodic echocardiography and skeletal surveys. During the post-discharge follow-up after one month, the infant had still not attained head control. Samples from both parents were sent for Whole Exome Sequencing (WES). The father of the proband was found to carry the same mutations: ABCC9 gene (NM_005691.4, Exon 29, c.3347G>A, p.Arg1116His) (20X/135X), heterozygous pathogenic variant, consistent with an ABCC9 gene–related disorder. DPAGT1 gene (c.85A>T, p.Ile29Phe) (71X/160X), heterozygous pathogenic variant, inherited in an autosomal recessive manner.

Both the father and the proband also had a pathogenic variant in the HBB gene, c.20A>T (p.Glu7Val). The mother tested negative for all three variants; however, she was found to have a pathogenic

variant in the HBB gene, (NM_000518.5, Exon 3, c.364G>C, p.Glu122Gln) (71X/165X), present in the heterozygous state in the proband. Another HBB gene variant, c.20A>T (p.Glu7Val), was inherited from the father. Thus, WES findings confirmed that the infant inherited the ABCC9 mutation from his father, showing significant variable expressivity compared to the paternal phenotype. Genetic counselling was provided to the parents regarding the risk of recurrence of Cantu syndrome in future pregnancies.

DISCUSSION

Cantu syndrome is primarily caused by mutations in the ABCC9 gene. To date, approximately 150 cases have been reported worldwide [7]. The ABCC9 protein encodes the sulfonylurea receptor, which is expressed in cardiac, skeletal, and smooth muscle tissues [8]. Cantu syndrome is also known as hypertrichotic osteochondrodysplasia.

In this report, we provide a comparative analysis of our patient with a few previously reported cases of Cantu syndrome, as summarised in [Table/Fig-7] [9,10]. Patients with Cantu syndrome generally have a near-normal life expectancy, though long-term follow-up is recommended to monitor for cardiac and skeletal complications [11].

Clinical features	CS, OMIM 239850	Present case
Inheritance	Autosomal dominant	Present
Birth weight	More than 90th percentile	Absent
Head	Macrocephaly	Absent
Face	Coarse facies	Present
Eyes	Prominent forehead	Present
	Long philtrum	Absent
	Epicanthal folds	Absent
	Long curly eyelashes	Present
Mouth	Thick lips	Present
	Gingival hypertrophy	Absent
Neck	Short neck	Absent
Cardiovascular	Cardiomegaly PDA	Present
	Pericardial effusion Congenital left ventricular hypertrophy Bicuspid aortic valve	Absent
Chest	Narrow thorax and shoulders Widened ribs	Absent
Abdomen	Umbilical hernia	Present
Skeletal	Delayed bone age Osteoporosis Widened posterior fossa Enlarged sella Platyspondyly	Absent at presentation
Central nervous system	Developmental delay	Present
Diagnosis		
Molecular basis	Mutation in ATP binding cassette subfamily C membrane 9 gene	Present
Treatment		
Glibenclamide	Clinical improvement [9]	Planned to start
PDA surgery/device closure	Clinical improvement [10]	Planned in future
Management of scoliosis via bracing	Improvement noted	Planned in future
Life expectancy	Near normal	On follow-up

[Table/Fig-7]: Comparative analysis of clinical features of cantu syndrome of the present case with previously reported cases [9,10].

A mutation in the DPAGT1 gene is associated with Congenital Disorder of Glycosylation Type 1j (CDG-1j), which is characterised by dysmorphic facies, developmental delay, hypotonia, refractory epilepsy, and intellectual disability [12]. This mutation can lead to muscle weakness, with symptoms that may become evident as the child grows older [13]. In severe cases, this mutation can result in intrauterine death. To date, only 26 cases with this mutation have been reported in the literature, excluding the present case [14]. IQ assessment is recommended when the child reaches five years of age to evaluate the extent of cognitive development.

CONCLUSION(S)

This study reports a rare case of Cantu syndrome co-occurring with a DPAGT1 gene mutation, underscoring the importance of Next-Generation Sequencing (NGS) in modern clinical practice. It highlights the fact that rare ("orphan") diseases, which can only be diagnosed through Whole Exome Sequencing (WES), may otherwise be missed if genetic testing is not performed.

Genetic testing of the parents further aids in identifying the mode of inheritance and assessing the risk of recurrence in future pregnancies.

Acknowledgement

Informed consent was obtained from the infant's father regarding publication. We sincerely thank the patient's parents for their cooperation and consent to publish this case report.

Data Sharing Statement: All relevant data supporting the findings of this study are included within this manuscript.

Ethics Approval: As per our institutional protocol, ethical approval is required for publication of case reports. This case was approved by the Institutional Ethics Committee of Government Medical College, Omandurar Government Estate (Registration Number: ECR/1492/INST/TN/2021) with approval number P-07/06/2024.

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