

Novel variant CPLANE 1: c.5051C>A (p.Ser1684Ter) in an Indian neonate with Joubert syndrome

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SUMMARY

Joubert syndrome (JS) is a rare ciliopathy that presents with the triad of hypotonia, developmental delay and molar tooth sign (MTS) in brain MRI. Next-generation sequencing has identified about 35 genes which are known to cause JS of which CPLANE 1 mutation is found in 8%–10% of cases. We report a case of JS in an Indian neonate who presented with hypotonia, dysmorphic facies, polydactyly, syndactyly and occipital encephalocele. MRI of the brain revealed MTS, and compound heterozygous mutations in CPLANE 1 gene were detected by clinical exome sequencing, one of them a novel variant CPLANE 1: c.5051C>A (p.Ser1684Ter) in exon 26, which was inherited from the parents.

BACKGROUND

Joubert syndrome (JS) is a rare disorder of ciliary dysfunction and is commonly inherited as autosomal recessive disorder. The triad of molar tooth sign (MTS), delayed development and hypotonia is the common phenotypical association in JS.¹ JS-related disorders (JSRDs) can have varied associations of which oro-facial-digital (OFD) manifestation is one of them.² It can present with dysmorphic facies, polydactyly along with irregular breathing pattern during neonatal period and later with ataxia and abnormal eye movements during infancy.² Associated mutations in 35 genes are identified to date in JS. Mutations in CPLANE 1 gene are observed in ~10% of cases.³ We report a case of JSRD with OFD manifestations and on evaluation was detected to have a novel variant in CPLANE 1 gene.

CASE REPORT

A male neonate born out of non-consanguineous marriage, delivered at term, with unremarkable antenatal and natal history, presented at 4 hours of life with soft swelling of 3×2 cm over occipital region. The swelling was transilluminant, typical of occipital encephalocele. Family history was unremarkable. This baby had birth weight 2410 g, length 47 cm and head circumference 32 cm. Examination revealed facial dysmorphism in the form of hypertelorism, bilateral ptosis, high-arched palate, low-set ears, wide open mouth and bow-shaped upper lip ([figure 1](#)). Postaxial polydactyly in the left hand ([figure 2](#)) and syndactyly of middle and ring fingers in the right hand were also noted ([figure 3](#)). In addition, the baby had widely spaced nipples. He had hypotonia of both upper and lower limbs. Signs of meningeal irritation were absent. The admission complete blood count (haemoglobin 167.5 g/L, total leucocyte count 11.41 × 10⁹/L, platelet count 276 × 10⁹/L), liver function tests (total bilirubin 2.3 mg/dL, direct bilirubin 0.4 mg/dL,

aspartate transaminase 32 U/L, alanine transaminase 28 U/L) and renal function tests (creatinine 0.23 mg/dL) were normal. Infantogram was normal. Endocrine evaluation on day 3 revealed normal thyroid function test (free thyroxine 1.3 ng/dL and thyroid-stimulating hormone 1.5 µIU/mL).

The baby underwent excision and dural patch repair of encephalocele on day 4 of life. In the post-operative period, he required invasive ventilation for 2 days followed by continuous positive airway pressure (CPAP) by bubble CPAP (bCPAP) for 2 days. He was transitioned to heated humidified high-frequency nasal cannula on day 9 of life. However, he developed episodes of apnoea with desaturation; hence, respiratory support was again upscaled to bCPAP. Arterial blood gas revealed mild metabolic acidosis and chest X-ray was normal. There was a gradual increase in cerebrospinal fluid (CSF) leakage from the operated site in the form of increased number of soaked gauze pieces/day. Antibiotics were upgraded from cefotaxime and amikacin to meropenem and vancomycin for clinical suspicion of sepsis. Sepsis screen was negative, CSF evaluation normal, and blood and CSF cultures were sterile.

MRI of the brain on day 10 revealed vermis hypoplasia, opposed bilateral cerebellar hemispheres, elongated bilateral superior cerebellar peduncles with prominent ventriculomegaly, giving the typical 'molar tooth' appearance along with agenesis of corpus callosum. Echocardiography revealed patent foramen ovale and ultrasound of the abdomen was normal. Otoacoustic emission was reported as referred bilaterally. Based on facial features, polydactyly and MTS, JS was suspected. Blood sample was sent for clinical exome sequencing to LifeCell diagnostics, an ISO 15189:2012 and National Accreditation Board for Testing and Calibration Laboratories (NABL)-certified laboratory. It revealed compound heterozygous mutation in Chromosome 5p13.2 at two locations, CPLANE 1: c.7477C>T (p.Arg2493Ter) in exon 36 and CPLANE 1: c.5051C>A (p.Ser1684Ter) in exon 26 confirming the diagnosis of JS. His parents were found compound heterozygous carrier for each variant.

Due to increasing soakage from surgical site, dural patch repair was done on day 15; G patch was sutured over boundaries followed by pressure dressing. Since imaging was not suggestive of hydrocephalus, we initially did not do a ventriculoperitoneal (VP) shunt. Persistent CSF soakage led to a suspicion of raised intracranial pressure as the cause; hence, a right-sided VP shunt was done on day 30 of life. There was no further soakage observed in the postoperative period. Apnoea was under control with caffeine and he did not have any further episodes of apnoea after VP shunt. The baby was discharged on day 35 of life on caffeine



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Figure 1 Index case having facial dysmorphism in the form of hypertelorism, bilateral ptosis, low-set ears, wide open mouth and bow-shaped upper lip.

for risks of apnoea in JS along with pressure dressing and with a weight of 2400g.

OUTCOME AND FOLLOW-UP

Telephonic follow-up on day 45 of life revealed that the baby had died after an episode of severe apnoea.

DISCUSSION

JS is detected in 1:80 000–1:100 000 live births and is associated with characteristic clinical and radiological findings.⁴ JS is typically associated with three primary findings of MTS in MRI of the brain, hypotonia with later development of ataxia and developmental delays/intellectual disabilities in infancy.¹ The index case had hypotonia on admission and MRI of the brain revealed the characteristic MTS, a typical finding in axial view of MRI of the brain at level of midbrain and pons due to hypoplasia of cerebellar vermis.

There is extensive phenotypical heterogeneity in JS. JS presenting with only neurological manifestation is known as pure JS. Respiratory system involvement manifesting as hyperventilation and abnormal facies is also well-known. Additional findings of ocular manifestation like colobomas, retinal dystrophy, renal disease, hepatic fibrosis (or COACH syndrome), occipital encephalocele, limb anomalies, endocrine abnormalities, etc lead to a spectrum of disorders known as JSRDs.^{2,3} Among the various JSRDs, JS with OFD features (JS-OFD) is a common subtype. Syndactyly between middle and ring fingers, preaxial polydactyly in hand and postaxial polydactyly in feet are the commonly associated limb abnormalities.² Our case had postaxial polydactyly in the left hand and syndactyly of middle and ring fingers in the right hand. High-arched eyebrows,



Figure 2 Postaxial polydactyly in the left hand.



Figure 3 Syndactyly between middle and ring fingers in the right hand.

ptosis and low-set ears observed in this baby were non-specific facial features which are also found occasionally in JS.⁵ These limb anomalies along with facial features were suggestive of JS-OFD. Endocrine abnormalities like growth hormone and thyroid hormone deficiency are known, but are not specific to any subtype of JS.⁶ In 6%–20% of cases, there is an associated lateral ventricular enlargement due to atrophy of brain and corpus callosum agenesis.⁷ Occipital encephalocele, ventriculomegaly and meningocele without classic features of Dandy-Walker syndrome requiring VP shunting are also known and were also observed in our case.⁸

JS is a disorder of the primary cilium and has overlapping clinical features and implicated causative genes with other ciliopathies. Acrocallosal syndrome, Bardet-Biedl syndrome, basal cell nevus syndrome, COACH syndrome, isolated nephronophthisis, Jeune asphyxiating thoracic dystrophy, Leber congenital amaurosis, Meckel syndrome, MORM syndrome and OFD syndrome are some common ciliopathies, which have overlapping clinical manifestations and genetic causation.⁹ This is most probably due to differential expression of similar spectrum of diseases.¹⁰ Neurological manifestations, ocular involvement, hepatic manifestations, renal disease, skeleton abnormalities, cardiac malformations and facial dysmorphisms are present in various permutations and combinations in all these ciliopathies.¹⁰

There is also an extensive genetic heterogeneity in JS. There are 35 known genes associated with JS.³ Most of them are inherited as autosomal recessive and one pathogenic variant in OFD1 as X linked inheritance. AHI 1, CC2D2A, CEP 290, CPLANE 1 and TMEM 67 are the five most common genes associated with JS.¹⁰ Eight per cent to 14% of cases of JS occur due to compound heterozygous mutation in the CPLANE 1 gene (*C5orf42*) on chromosome 5p13 and is labelled as JS-17, a JSRD.² The pathogenic variants are detected in 100% of these cases by sequence analysis and not by gene-targeted deletion/duplication analysis. Clinical exome sequencing of our case revealed compound heterozygous mutation in Chromosome 5p13.2 at two locations, CPLANE 1: c.7477C>T (p.Arg2493Ter) in exon 36 and CPLANE 1: c.5051C>A (p.Ser1684Ter) in exon 26.

CPLANE 1: c.7477C>T (p.Arg2493Ter) variant is observed in 0.0137% alleles from individuals of South Asian background and it causes loss-of-protein function by truncating the protein structure. This variant had prior pathogenic classification, indicating that this is a critical region required for the protein function and has been reported by Srouf *et al.*¹¹ CPLANE 1: c.5051C>A (p.Ser1684Ter) variant is novel and has not been reported previously as a benign or pathogenic variant to date. It is predicted that the protein truncation caused by this variant will lead to loss-of-normal protein function. This variant is a stop-gain variant in an exon of CPLANE 1 upstream of where nonsense-mediated decay is predicted to occur. There are further 69 downstream pathogenic variants with loss of function, the furthest variant being 1449 residues downstream from it. For these reasons, this variant is likely pathogenic for JS. To the best of our knowledge, this is the first case where the CPLANE 1: c.5051C>A (p.Ser1684Ter) variant is reported in JS.

OFD syndrome type VI (OFD VI) is a phenotypical subtype of JS and is a close differential with overlapping features. It is commonly associated with lingual hamartoma, oral frenulum, polydactyly, cleft lip or palate and has mutations in various genes including in CPLANE 1 gene.¹² Distinctive feature of OFD VI is central or mesaxial polydactyly which was absent in our case, thus clinching the phenotypical and genotypical association of JS-17.

Children with JS have an increased risk of central and obstructive apnoea.¹³ Apnoea can be a presenting symptom in cases of JS without hydrocephalus. Caffeine therapy is commonly used for prevention and treatment of apnoea of prematurity. This baby, though born at term gestation, was given caffeine therapy for control of apnoea. He responded well to it and post-VP shunt did not have any episodes of apnoea during hospital stay. Unfortunately, he succumbed to an episode of severe apnoea at home, even after starting on respiratory stimulant therapy with caffeine. Only a few reports suggest use of caffeine as respiratory stimulant in JS; further research to establish the role of caffeine therapy in management of apnoea in cases of JS must be explored.¹⁴ Continued home monitoring including polysomnography has a role, however was not feasible in our case due to financial constraints. This highlights the challenges of managing a

case of JS in low/middle-income countries. After bereavement counselling, the parents were also counselled regarding the feasibility of prenatal diagnosis and further carrier diagnosis, the implications of the genetic test and risks for future pregnancy.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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Learning points

- ▶ CPLANE 1: c.5051C>A (p.Ser1684Ter) variant is a likely pathogenic variant of Joubert syndrome (JS).
- ▶ Encephalocele without classic features of Dandy-Walker syndrome may require ventriculoperitoneal shunt in cases of JS due to raised intracranial pressure.
- ▶ Genetic testing of JS helps in better counselling of family.

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