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CASE REPORT

Early Postnatal Genetic Diagnosis for Joubert Syndrome Type 14

Nadine Anne De Battista, Valerie Said Conti, Ryan Farrugia

Background

Joubert syndrome is an autosomal recessive condition characterised by a midbrain-hindbrain malformation giving rise to the characteristic "molar tooth sign" on MRI. Common signs and symptoms include neonatal breathing dysregulation, hypotonia and developmental delay. A spectrum of conditions referred to as Joubert syndrome and Related Disorders (JSRD) have also been described, referring to the presence of multiorgan involvement in addition to the neurological signs and symptoms characterising "pure Joubert".

Case Presentation

We report a case of JS type 14 (homozygous pathogenic variant in TMEM237) in a male neonate referred antenatally with a brain malformation and bilateral cystic kidneys on ultrasound and MRI, raising the suspicion of a ciliopathy. Clinical features at birth included hypotonia, hydrocephalus, ocular colobomas and breathing difficulties which required mechanical ventilation.

Conclusion

Antenatal suspicion followed by confirmation of JS in the immediate postnatal period, has enabled early timely intervention by a multidisciplinary team, thus optimising parental counselling, developmental outcomes, and monitoring for potential future complications.

Nadine Anne De Battista MD, MRCPCH
Department of Child and Adolescent Health
Mater Dei Hospital,
Msida, Malta

Valerie Said Conti, MD, DCH, FRCPCH
Department of Child and Adolescent Health
Mater Dei Hospital,
Msida, Malta

Ryan Farrugia, MD, MSc, MRCPCH
Department of Child and Adolescent Health
Mater Dei Hospital,
Msida, Malta

INTRODUCTION

Joubert Syndrome (JS) results from complex midbrain-hindbrain malformation involving underdevelopment or complete absence of the cerebellar vermis, its hallmark being the characteristic diagnostic "molar tooth sign" on magnetic resonance imaging (MRI).[1] It is mostly inherited in an autosomal recessive manner, though various other patterns of inheritance have also been described.[2]

Presenting signs and symptoms vary, but commonly include neonatal breathing dysregulation and hypotonia, developing into early childhood coordination disorders and oculomotor apraxia. Developmental skills particularly motor and language, tend to be delayed. Distinctive facial features might also be observed such as ptosis, low-set ears, and a broad forehead.[3]

Joubert syndrome related disorders (JSRD) refers to the spectrum of conditions characterised by the presence of multiorgan involvement in addition to the neurological symptoms described above. Over 30 different types have been described to date, with involvement of ocular, renal, hepatic, skeletal and orofaciodigital systems. JSRD are part of the expanding group of ciliopathies, thought to result from gene mutations leading to malfunctioning primary cilia, thus disrupting crucial cell signalling pathways during development. Mutations known to cause JS are found in 60-90% of children with this condition, the remainder of which are still pending a precise genetic diagnosis.[3-4]

A case of JS type 14 is hereunder presented; caused by homozygous or compound heterozygous mutations in the TMEM237 gene on chromosome 2q33. Additional findings which may characterise this type include the presence of renal cysts, eye abnormalities and postaxial polydactyl.[5]

CASE PRESENTATION

A male neonate with an antenatal history of schizencephaly, hydrocephalus and cystic kidneys was delivered at 38^{+6} weeks gestation via emergency caesarean section for foetal distress. He was immediately noted to develop tachypnoea with episodes of prolonged apnoeas, requiring early intubation and mechanical ventilation.

Ultrasound and MRI brain confirmed extensive schizencephaly with dilatation of the lateral and 4th ventricles. He required insertion of a ventriculoperitoneal shunt on day 16 because of increasing apnoeas. Repeat MRI scans showed a persistent infratentorial cyst, with gradual enlargement and extension above the posterior fossa, requiring repeated shunt revisions leading to a reduction in the size of the posterior fossa cyst and improvement in drainage and clinical condition. He required minimal oxygen and despite persistent self-resolving episodes of apnoeas, he was weaned off completely from respiratory support by day 53 of life.

Maximal serum creatinine perinatally was 90umol/l which dropped to 30umol/l by 3 months of age and has been stable since. He was discharged from hospital at 4 months of age with extensive developmental delay, poor head control and axial hypotonia.

Investigations

The presence of a brain malformation and renal cysts on his antenatal scans led to the early suspicion of a ciliopathy, and he was referred to the multidisciplinary team allowing early postnatal intervention with a full workup, to confirm the diagnosis and to actively look for other possible associated anomalies.

Initial MRI showed a Dandy-Walker malformation with enlargement of the posterior fossa and a wide communication between the fourth ventricle and the posterior subarachnoid. Dysgenesis of the cerebellar vermis with only a tiny superior component was observed. Absence of the septum pellucidum, dysgenesis of the corpus callosum with a resultant dorsal cyst (initially thought to be schizencephaly), atresia of the cerebral aqueduct and an enlarged right lateral ventricle in keeping with colpoencephaly were also reported.

EEG (electroencephalogram) and cerebral function monitoring excluded seizures as a cause of the child's apnoeas. An echocardiogram was normal.

Postnatal renal US and MRI confirmed bilateral cystic dysplastic kidneys, measuring 8cm with abnormal morphology and echogenic central parenchyma with scattered predominantly peripheral cysts of varying size in keeping with bilateral cystic cortical dysplasia. Imaging appearances on MRI were suggestive of nephronophthisis.

Ophthalmic review showed bilateral optic disc colobomas.

Karyotype was confirmed to be male. By 6 weeks of age exome sequencing confirmed a homozygous pathogenic variant in the TMEM237 gene, suggestive of JS type 14. Parental carrier testing was also performed.

Differential Diagnosis

Various pathogenic variants in genes that cause JSRD, have been identified in other syndromes with overlapping clinical findings, (Table 1).

Treatment

Treatment for JS is mainly supportive. Respiratory support is commonly required during the neonatal period. Insertion of a ventriculoperitoneal shunt with two subsequent revisions was required for this child, in view of progressively worsening hydrocephalus

Table 1 *Table describing syndromes with pathogenic genetic variants and clinical findings overlapping with JSRD*

Syndrome/Condition	Features
Goldstron syndrome	Polycystic kidneys, Dandy-Walter +/- hepatic fibrosis
Bardet-Biedl syndrome	Retinal dystrophy, renal disease, polydactyly, genital malformation, hypogonadism
Leber congenital amaurosis	Retinal dystrophy, global development delay and neonatal apnoeas
Meckel syndrome	Cystic renal disease, posterior fossa abnormalities, hepatic fibrosis
Hydrolethalus syndrome	Midline brain anomalies, polydactyly, micrognathia
Acrocallosal syndrome	Corpus callosum agenesis, posterior fossa anomalies, hypertelorism, polydactyly

secondary to inadequate drainage of the ventricular systems. Physiotherapy and occupational therapy input were sought early, and he was referred to the local Child Development and Assessment Unit to help improve developmental outcomes and guide educational needs and social support. His parents were trained in basic life support, and domiciliary oxygen and an apnoea monitor were provided for emergency use. Parental carrier testing and genetic counselling was carried out by the genetics team.

DISCUSSION

Pathophysiology And Genetics

More than 200 cases of JSRD have been published since originally described, with mutations in over 30 genes including AHI1, NPHP2 and CEP290, all of which result in malfunctioning primary cilia. The presence of these crucial cell signalling proteins across multiple organ systems, explains the multiorgan involvement in JSRD. Currently, a molecular genetic diagnosis can be established in 60-90% of cases, enabling family counselling and prenatal diagnosis should a specific mutation be found.[4]

Clinical Features And Diagnosis

Heterogenous clinical presentation and lack of awareness explain the wide range of age at diagnosis reported, with an average age of 33 months being reported in one study by Maria et al., and a mean of 6.67 ± 8.10 years in a study by Nuovo et al.[6-7] Prenatal accurate diagnosis using only imaging is very difficult, with genetic testing being required. Diagnostic criteria continue to evolve but are mainly based on the presence of a "molar tooth sign" (combined presence of a deep posterior interpeduncular fossa, prominent superior cerebellar peduncle and vermian hypoplasia) on MRI, in combination with developmental delay, hypotonia and late-onset ataxia.[4]

Developmental delay usually spans across multiple areas but interestingly, developmental outcome is independent of the severity of the intracranial malformations diagnosed on MRI.[8] Moreover, despite breathing dysregulation being considered a classical sign of JS, it is not a consistent feature, reported as being present in 44% to 71% of children.[9]

Treatment And Outcomes

Gene therapy is only available in a research setting. The outcome ranges from mortality in childhood to surviving patients with mild to severe developmental delay.[8] Therefore, recognising JS and related disorders early on in life, remains a key factor in improving developmental outcomes, whilst also allowing for appropriate timely parental counselling.

CONCLUSION

JS is an autosomal recessive ciliopathy, resulting in complex midbrain-hindbrain malformation giving rise to the characteristic "molar tooth" sign on MRI. Signs and symptoms include neonatal hypotonia, breathing dysregulation, developmental delay, and ataxia. Multiorgan involvement characterises JSRD. Treatment is mainly supportive. Heterogeneity in presentation and outcomes, makes early recognition desirable to allow for counselling and early intervention by multidisciplinary teams.

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