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Case Report

Suspicious ultrasound markers of joubert syndrome can lead to early prenatal diagnosis

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ABSTRACT

Joubert syndrome is a rare autosomal recessive inherited disease associated with many signs and symptoms. Joubert syndrome (JS) was first discovered by Marie Joubert in 1969. Joubert's syndrome presents as low muscle tone (hypotonia), have difficulty coordinating movements (ataxia), have episodes of fast or slow breathing and abnormal eye movement (ocular motor apraxia). Developmental delay and intellectual disability generally accompany. Additional findings can include retinal dystrophy, renal disease, ocular colobomas, occipital encephalocele, hepatic fibrosis, polydactyly, oral hamartomas, and endocrine abnormalities. Both intra- and interfamilial variation are seen. The main aim should be to diagnose these cases antenatally. Number of ultrasound features have been described which are indicator of possibility of Joubert's syndrome. The confirmatory diagnosis then can be done by MRI. We describe a case of suspicious JS prenatally who had previous baby diagnosed as JS after termination at 20 weeks. We also discuss the antenatal diagnostic management of pregnancies who have a previous history or at high risk of Joubert's syndrome.

1. Introduction

Joubert Syndrome is a rare autosomal disease associated with many signs and symptoms. Its an inherited disease in autosomal recessive mode. Marie Joubert was the first one to talk about Joubert Syndrome (herein after referred to as JS) in 1969.[1]

Joubert Syndrome and all related disorders involve delay in development of child or infant and numerous congenital anomalies. The most prominent feature is "Molar Tooth Sign" which is visible via MRI, which is a complex mid-brain and hind-brain malformation where cerebellar vermis and brainstem are maldeveloped. Most infants with JS show hypotonia (low muscle tone), ataxia (have difficulty coordinating movements), ocular motor apraxia (episodes of fast or slow breathing and abnormal eye movement). Developmental delay and intellectual disability generally can also present themselves later. Additional findings can include dystrophy of retina, renal disease, encephalocele, liver fibrosis, polydactyly, oral hamartomas, and endocrine abnormalities. Familial variations (intra and inter) are seen. Early (less than 20 weeks) prenatal diagnosis is difficult & rare. MRI is usually the choice of modality for diagnosis.

We describe a case of suspected JS prenatally, who had earlier terminated at 20 weeks due to anomalies in brain, which were later diagnosed as JS. We discuss the differential diagnosis on ultrasound. The aetiology of JS, the diagnostic options, symptoms presented and how to diagnose has been discussed in this case report.

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2. Case Presentation

A 23-yrs old third gravida came to OPD with consanguineous marriage. She had two previous pregnancy losses – first was a miscarriage at 45 days and second was a termination at 20 weeks after anomaly scan. In the second pregnancy, anomaly scan showed ventriculomegaly and cerebellar hypoplasia and double superior vena cava. Pregnancy was terminated. After counselling foetus was sent for autopsy, which showed diffused cerebellar and vermian hypoplasia, bilateral gross ventriculomegaly and double superior vena cava – thereby confirming JS.

In current pregnancy, NT scan and double marker were identified as low risk. However, given the previous history, as a precautionary measure she was recommended to undergo an anomaly scan at 17 weeks to rule out any anomalies. The brain scan revealed dilated lateral ventricles, prominent superior cerebellar peduncles, rudimentary CSP, underdeveloped posterior fossa, cerebral mantle appeared thin and tiny blake pouch cyst.(Figure 1)

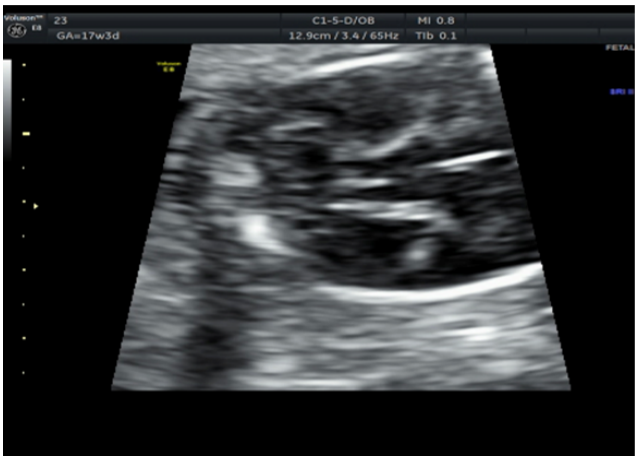

Fig. 1: Brains scan at 17 weeks

The findings were not classical for JS and it was too early for the anomalies to be seen on ultrasound. Option of amniocentesis was discussed, and patient was offered MRI at 22-24 weeks, but she was not keen to continue the investigation and opted for termination. She underwent medical termination with Mifepristone and Misoprostol and aborted the foetus after 10 hours. She did not consent for autopsy however baby tissues were sent for sequencing and for both parents karyotyping was sent for geneticist's opinion.

3. Discussion

The three most prominent features in JS are cerebellar vermis hypoplasia, hyperventilation which can be interrupted and defect in the control of voluntary, purposeful eye movement (oculomotor apraxia). JS comes under the disorder caused by Ciliopathy. 'Ciliopathy' is a group of abnormality defined by defective ciliary function. Primary cilia are important in performing main tasks in developmental processes. They help in embryonic development by acting as sensory units. They help to capture and send signals from the surroundings. Ciliopathy includes JB and related disorders. The incidence of JS and related disorder JSRD is thought to approximately 1:100,000. JS affects many parts of the body and can present differently in different individuals even among same family. It shows considerable heterogenicity in presentation and molecular basis.

JSRD is classified into six phenotype subgroups:

1. Pure JS;
2. JS with ocular defect
3. JS with renal defect
4. JS with oculorenal defects
5. JS with hepatic defect and
6. JS with orofaciodigital defects.

Antenatal diagnosis of JS should be tried when couple gives positive family history. If mid brain findings show abnormality, one sees polydactyly or kidney abnormalities, One should keep JS in mind. The most prominent sign in all form of JS is Molar Tooth sign. It has combination of following features – the superior cerebellar fibre tracts fail to decussate normally which in turn leads to peduncles getting enlarged specially in horizontal direction. The absence of these fibres crossing each other decreases the AP diameter of midbrain. Therefore, interpeduncular cistern deepens. The Vermian hypoplasia is seen as well. These findings combined give a 'Molar Tooth sign" on CT and MRI axial images. The Fourth ventricle may appear Bat wing or umbrella shaped as a result of deep cleft which appears in superior vermis. Other features apparent can be abnormality of vermis (foliar pattern) and length of Ponto mesencephalic junction increases in cranial to caudal direction.

Quarello et al. emphasised on abnormal appearance of fourth ventricle in JS. The fourth ventricle becomes bigger and since the cerebellar fibres are not decussating normally the shape of its floor changes. It points anteriorly.[2]

In addition to the MTS and Vermis Hypoplasia, JS can present other abnormalities like hypoplasia of mesencephalon, cysts of white matter, dysgenesis of corpus callosum, polymicrogyria, oedema of cerebrum etc. Hydrocephalus can also be seen.[3]

Other prenatal sonographic findings are not specific and can be in form of increased Nuchal translucency, agenesis of cerebellar vermis, encephalocele, enlarged ventricles, cysts in kidneys, cleft lip or palate. Polydactyly and abnormalities of tongue can also be present. Whenever Increased NT is seen, ask for family history and look for polydactyly.[4] These subtle findings can help diagnose JS early. However, hypoplasia of Vermis is difficult to diagnose before 18 weeks.

4. Conclusion

Past history information gathering should include questions about such symptoms during initial visit. If there is confirmation of family history, early anomaly scan (16 weeks) should be done. Alternatively serial ultrasounds should be advised for continued monitoring of ventriculomegaly and fetal growth. The structures to be examined are the posterior fossa, cisterna magna measurement, evaluation for encephalocele, polydactyly and kidney abnormalities. At 20 weeks again re-examination of these structure and vermis measurement should be done. At 22-23 weeks MRI should be done.[5]

Depending on the gestational age and suspicion of JS, couples should be counselled with all options including termination. If termination is advised, autopsy should necessarily be done for confirmation of diagnosis

Its difficult to diagnose JS antenatally. However, positive family history or signs on ultrasound as described earlier should raise the suspicion of JS which can be confirmed by MRI later. All efforts should be put in to diagnose JS antenatally.

5. Source of Funding

None.

6. Conflict of Interest

None.

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