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Joubert Syndrome: When to Suspect a Ciliopathy in a Patient with Liver Failure and Syndromic Phenotype

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1. Abstract

Joubert Syndrome (JS) and related disorders (JSRD) are a group of rare and heterogeneous conditions that share as a hallmark the "molar tooth sign" (MTS), a complex midbrain-hindbrain malformation visible on brain imaging. Ten causative genes with different patterns of inheritance have been identified to date, all encoding for proteins of the primary cilium. This structure is fundamental for several organs as cerebellum, brainstem, retina, kidney and liver. For this reason, six JSRD clinical subgroups have been described according to the organ involvement. Hereby, we describe a patient in which the initial finding of congenital hepatic fibrosis has finally led to the diagnosis of JS with hepatic defects, with the identification of the variants c.675G>A (p.Trp225Ter) and c.2417_2419dup (p.Asn806dup) in TMEM67. Despite it can be hindered by the clinical heterogeneity and the rarity of this condition, an early diagnosis of JS can be fundamental to establish an appropriate follow-up of the patient and to assess the reproductive risk of the family members.

2. Introduction

Joubert Syndrome (JS) and related disorders (JSRD) are a group of heterogeneous conditions with a global incidence estimated between 1/80.000 and 1/100.000 live births. They all share as a hallmark the "molar tooth sign" (MTS), a complex midbrain-hindbrain malformation visible on brain imaging [1] that results from hypo-dysplasia of the cerebellar vermis, deep interpeduncular fossa and thickened superior cerebellar peduncles. This malformation is determined by mutations in one of the ten causative genes identified to date and can follow an autosomal recessive or X-linked recessive pattern of inheritance. All these genes encode for proteins of the primary cilium, thus allowing the inclusion of JSRD in the "ciliopathies" [2]. Primary cilia are known to play key roles in the development and functioning of cerebellum, brainstem, retina, kidney tubules and bile ducts [3]. For this reason, there is high variability among JSRD phenotypes, even though they share neurological features as hypotonia, ataxia, developmental delay and intellectual disability. Six different JSRD subgroups have been described according to the organ involvement: pure JS, JS with ocular defect (such as retinal dystrophy), JS with renal defect (such as nephronophthisis), JS with oculorenal defects, JS with orofaciodigital defects (such as polydactyly), JS with hepatic defects (such as congenital hepatic fibrosis, CHF) [1].

In the latter group, which is caused in 70% of cases by mutations in *TMEM67* [4], liver disease results from an embryonic malformation of the ductal plate, with cystic dilatation of the primitive biliary structures and fibrosis of the portal tracts [5]. The severity of the phenotype may range from serum AST and ALT elevation to early-onset hepato(spleno)megaly, cirrhosis and liver failure. This clinical heterogeneity, together with the inconstant liver involvement in JSRD, makes difficult to correlate liver failure with a ciliopathy. Hereby, we describe a case of a patient in which the

initial finding of congenital hepatic fibrosis has finally led to the diagnosis of Joubert syndrome.

3. Results

The proband was a 41 year old male with no familial history of neurological issues. His older sister was in good health, while his younger sister had died at 24 days due to congenital heart malformation of undetermined nature. The patient was born at term from normal pregnancy. The parents reported delayed psychomotor development with attainment of autonomous walking ability at 5 years of age and mild intellectual disability (no evaluation in a neuropsychological setting has been made). At the age of 19 the patient underwent renal transplantation due to nephronophthisis. Ten years later, he had three polypoid hamartomas removed from the gastric antrum and in the same year, due to drug resistant ascites caused by congenital hepatic fibrosis, he needed a Transjugular Intrahepatic Portosystemic Shunt (TIPS). Six years later, at the age of 35, the patient underwent angioplasty because of stenosis of the shunt and several episodes of acute-on-chronic hepatic encephalopathy were reported at the age of 39 and 40 years. At the age of 39 the patient had a tibio-tarsal fracture of the right foot due to severe osteoporosis (bone densitometry revealed a T-score of -4,6 both in the lumbar vertebrae and in the femur) and one year later he presented intestinal sub-obstruction followed by an episode of acute pancreatitis (a CT scan showed several cysts in the pancreas).

The patient first came to our attention at 41 years of age, when he was admitted to the Gastroenterology Department due to liver failure with severe ascites, foot oedema, itching and hepatic encephalopathy (MELD score: 18). The gastroscopy documented esophageal varices of grade F1 according to Esophageal Varices' Classification of the Japanese Research Society for Portal Hypertension [7]. On clinical examination, he presented right inguinal hernia, macroglossia and spaced teeth.

Given the liver failure and the assessment of multiple cysts in liver, pancreas and kidneys, we requested a molecular analysis through Next Generation Sequencing of a panel of genes associated with ciliopathies. Molecular analysis revealed the presence of the variants c.675G>A (p.Trp225Ter) and c.2417_2419dup (p.Asn806dup) in *TMEM67*. Segregation analysis in the proband's parents demonstrated the paternal origin of the variant c.675G>A (p.Trp225Ter) and the maternal origin of the variant c.2417_2419dup (p.Asn806dup).

The molecular diagnosis was reached after the patient's demise due to liver failure at 42 years of age.

4. Discussion

The diagnosis of ciliopathies is hindered by their low incidence and by the non-specificity of the clinical presentation, even for the classical forms. JS is often undiagnosed during childhood, especially if intellectual disability is the only clinical presentation. In these cases, it is common to find complications such as juvenile nephronophthisis during late adolescence or liver failure due to congenital liver fibrosis during adulthood [6].

The role of imaging can be fundamental to support clinicians. MRI of the brain is the gold standard to assess the presence of the MTS sign, but when MRI is not available or cannot be performed due to the patient's conditions, other signs of the ciliopathies can be detected through CT scan. Besides multiple pancreatic, hepatic and renal cysts, even the MTS sign can be visible on CT imaging. Finally, genetic testing is fundamental to establish the definitive diagnosis and to give the family members a correct reproductive risk.

Once the diagnosis is established, a strict surveillance of the target organs, especially liver and kidneys, is necessary for early detection and treatment of complications, given the current lack of a curative treatment.

5. Conclusion

JS and related disorders are very rare clinical conditions. A genetic diagnosis is crucial for the risk assessment in the proband's siblings and their offspring. Hereby, we emphasize the importance of early diagnosis because appropriate follow-up and supportive measures delay the onset of complications and improve patients' quality of live. The development of a curative treatment necessitates further research on this disease.

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