CASE REPORT

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A 30 months old girl affecting from Joubert syndrome presenting with severe developmental delay and renal nephronophtasis

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Abstract

Joubert syndrome is a rare autosomal recessive disorder impairing ciliary function leading to a variety of manifestations in different organ systems including central nervous system, eyes, liver, kidney and skeleton. It presents with hypotonia, neonatal abnormal respiratory patterns and abnormal eye movements such as nystagmus and oculomotor apraxia. The condition is either pure or associated with other disorders (JSRD). Hereby, we report a case of a 30 month old girl with Joubert syndrome and renal nephronophtasis who first was found to have abnormally large echogenic kidneys prenatally and later in 6th month having a Joubert syndrome related disorder was established.

Keywords: Nephronophtasis, Joubert syndrome, Joubert syndrome related disorders.

INTRODUCTION

Joubert syndrome is a rare autosomal recessive disorder affecting primarily ciliary development in different organs from central nervous system to eyes, kidneys, liver and skeleton [1]. This condition is characterized with abnormal respiratory patterns of tachypnea fallowed by apnea especially during early infancy, hypotonia, developmental delay, mental retardation, abnormal eye movements (nystagmus and oculomotor apraxia), abnormal facial features and in late infancy features of cerebellar malfunction such as ataxia and speech difficulties [2]. Joubert syndrome related disorders (JSRD) entails the main features of pure Joubert syndrome besides showing manifestations of involvement of other organs giving them their special syndromic or mnemonic names [3]. Hereby we describe a case of JSRD with all the criterion for Joubert syndrome plus kidney involvement. This case report is to stress further the importance of diagnosing special syndromes correlated with cystic kidney disease to assign their associated mutations which can guide family planning consultation.

CASE REPORT

A 30-month-old girl presents to our subspecialty ward of nephrology at Children Medical Center in Tehran and hospitalized due to recurrent resistant urinary tract infections. She has been recently treated repeatedly for recurrent urinary tract infection in her home town. She was first diagnosed to have large cystic kidneys prenatally at about 16th week of gestational age. She was born through a normal vaginal delivery with no history of asphyxia. Her parents were first cousins and she was their first and the only child. According to her parent's description she was very flaccid with a slight ptosis in her right eye with abnormal eye movements without any difficulty in breathing. Her past medical history was insignificant other than having recurrent urinary infections. She did not meet the growth and developmental milestones as she was unable to sit without support and did not have head control before attending occupational therapy sessions. On examination, her blood pressure was normal, she was tachypenic with a respiratory rate of 55 per minutes. She looked macro cephalic and had facial

features of frontal bossing, wide nasal bridge, deep set eyes with bilateral ptosis (more prominent in the right side, perpendicular nystagmus and accidental gaze deviations (Figure 2). She was unable to fix an fallow moving objects consistently during examination. She was sitting on her own with a mild truncal ataxia. The upper and lower limbs showed features of extensor-flexor stimulus disproportion as claw hand and talipes equinus. Deep tendon reflexes were augmented. Both kidneys were palpable and large extending to lower quadrants with a firm consistency.

We consulted neurologists because of developmental delay and they suggested a brain MRI exam which revealed thickening and parallel appearance of superior cerebellar peduncles associated with distortion and enlargement of fourth ventricle and vermi and hypoplasia with molar tooth appearance brain stem suggestive of Joubert syndrome (Figure 1). Figure 1: Brain MRI White and gray matter was normal in signal intensity. The exam was otherwise normal. Further molecular genetic testing confirmed the diagnosis. The proband was found to carry homozygote variants of INPP5E, APOC3 and PADI3 genes on Sanger sequencing. Further investigation of the parents to find the same mutations spotted her mother as heterozygote (carrier) for a likely pathogenic variant defined as c.1132c>T (p.R378C) in exone 4 of INPP%E gene (NM_019892). (Figure 2) Sonographic studies showed renal hyperechogenicity, poor corticomedulary differentiation and corticomedullary cysts; findings compatible with nephronophtisis. Urodynamic studies (UDS) was conducted which showed pressure in voiding and high residue. With a serum creatinine level of 1.4 and an estimated glomerular filtration rate (eGFR) of 30 she falls in stage 3 CKD categories. Voiding cystouretrography study appeared normal (figure 3). She was discharged with prophylactic cephalexin and educating her parents for clean intermittent catheterization (CIC).FIGURE 3.

Figure 1: Brain MRI demonstrating Vermian aplasia and molar tooth malformation of cerebellar peduncles

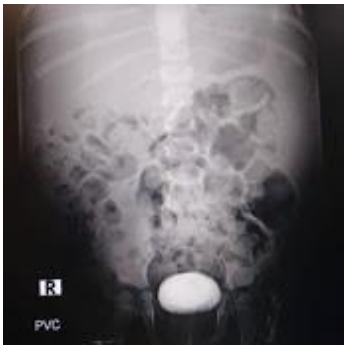

Figure 2: VCUG demonstrating normal findings

Figure 3: Characteristic appearance of the child with Jobert syndrome

Table 1: Candidate homozygote variants

Gene	Variation	Type	dbSNP ID & MAF	Clin Var Database	In silico Prediction	ACMG classification	Disorder & OMIM
INPP5E	NM_019892 Exon4 c.C1132T p.R378C	SNV (Homo)	rs121918130 (0.0000439)	pathogenic	Damaging	Likely Pathogenic	Joubert syndrome 1(AR)
APOC3	NM_000040 Exon2 c.C55T p.R19	Stopegain (Hetero)	rs76353203 (0.0007)	Pathogenic	damaging	VUS	APO_LP 3 deficiency
PADI3	NM_016233 Exon3 c.T335A P.L112H	SNV (Hetero)	rs142129409 (0.0003)	pathogenic	damaging	VUS	Uncombable hairsyndrome (AR)

DISCUSSION

With a prevalence of less than 1/100,000 live births, JS manifests as hypotonia, respiratory problems during neonatal period, developmental delay and abnormal eye movements [4]. Because of unspecific varied manifestations of the disease, it is usually undiagnosed until late infancy where the patient is assessed for developmental delay and examined by magnetic resonance imaging. The mean age at which the diagnosis is confirmed is 33 months [5]. This baby was first diagnosed of having JS at her 30 months when she was referred to our hospital for developmental delay and recurrent urinary tract infections. Brain MRI showed molar tooth configuration of cerebellar peduncles compatible with JS. The molar tooth appearance of midbrain-hindbrain on MRI caused by abnormally oriented and thickened cerebellar peduncles is pathognomonic finding for JS [4]. JSRD are subdivided into six categories: pure JS, JS with ocular anomalies, JS with occulorenal defects, JS with hepatic defects, JS with renal disorders, JS with orofaciodigital defects [4]. Our patient had all the main features of Joubert syndrome besides nephronophtisis. With new

molecular genetic tests, all these divers' group of so-called JS related disorders go under single physiopathological diagnosis of ciliopathies [3]. It has been hypothesized that some mutations cause the primary cilium/basal body apparatus to function defectively causing the complex phenotype of this syndrome [5]. Our genetic testing revealed some possible culprit genes in both proband and her mother. Her father was wild-type homozygote (not carrier) for a likely pathogenic variant defined as c.1132c>T (p.R378C) in exon 4 of INPP5E gene (NM_019892); indicating that the proband has got one allele from her mother and the other half through a possible de novo mutation. Genetic testing is crucial in these conditions to rule out de novo mutations and give a precise consultation on family planning and antenatal diagnosis. It may also help in determining prognosis and outcome of the disease as some mutations like homozygous deletion of the NPHP1 gene have been implicated in progressive renal disease [5]. Mutations in the AHI1 gene manifest as retinal dystrophy, polymicrogyria or later onset nephronophtisis [6]. As some complications may develop later, it is suggested that all patients be fallowed with annual eye examinations or periodic renal and hepatic function screening tests [6].

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Conflict of Interest

We declare that we have no conflict of interest.

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