Questions

1. What is the pathognomonic sign of JS?
2. What are the clinical features of JS?
3. What are the renal manifestations typically seen in JS including the radiological and histological findings?
4. What features of this boy’s biopsy was unusual for JS?

Answers

Question 1

Joubert syndrome (JS) was first described by Dr Marie Joubert in 1968 in a family of four siblings, all of whom presented with cerebellar vermis agenesis, ataxia, oculomotor abnormalities and developmental delay. Subsequently, a neuroradiological mid-hindbrain malformation, known as the ‘molar tooth sign’ (MTS), was identified. This malformation is caused by hypoplasia of the cerebellar vermis with fourth ventricle deformity and a sagittal vermian cleft due to incomplete vermis fusion. Elongated and thickened superior cerebellar peduncles with a widened interpeduncular fossa are also present [1]. The absence of a normal vermis results in a midline cleft between the cerebellar hemispheres, resulting in the ‘bat wing’ sign on an magnetic resonance imaging (MRI) scan [2]. The term Joubert syndrome and related disorders (JSRD) was then established to describe a group of other conditions commonly sharing the MTS. The JSRD spectrum includes JS with retinal disease, JS with hepatic disease, JS with orofaciodigital disease and JS with renal disease. The MTS is widely thought to be pathognomonic of JSRD, although there is some disagreement in the literature [3, 4].

Question 2

The typical features of JS are hypotonia evolving into ataxia and developmental delay, usually associated with impaired intellectual function, and abnormal ocular movements [5]. Respiratory pattern abnormalities may occur in the first few months of life which typically manifest as apnoeic episodes or episodic hyperpnoea [6]. Oculomotor dyspraxia is one of the most characteristic neurological abnormalities and presents as an inability to fix and follow accompanied by compensatory head movements and, commonly, as positional nystagmus. Most children with JS have a degree of intellectual impairment although the severity of this can be very variable [7].

In addition to the typical neurological features, there are also renal, ocular, hepatic and skeletal abnormalities. The ocular issues result from retinal dystrophy and present with reduced visual acuity which can progress to retinal blindness [8]. Colobomas can also be present, normally affecting the posterior segment of the eye [9].

A small number of patients with JS develop liver disease, usually in the form of congenital hepatic fibrosis, due to problems in embryogenesis and resultant portal tract fibrosis [10]. An association between JS and polydactyly has been repeatedly observed, with a frequency of 8–16% [11], as well as mild to severe scoliosis (probably secondary to hypotonia) [12].

Question 3

The reported prevalence of renal disease in JSRD is approximately 23–30% [13, 14], and the condition presents as nephronophthisis (NPHP). Previously, patients with cystic dysplastic kidneys and the MTS had been designated as having a separate syndrome, known as Dekaban–Arima syndrome, but in fact on re-evaluation of these had histological findings in keeping with NPHP and, consequently, the existence of this syndrome is questionable [15].
NPHP patients typically present with polyuria and polydipsia, and NPHP ultimately leads to progressive renal failure, usually within the first three decades of life [16]. The predominant form of NPHP is juvenile, although a much rarer infantile form also exists. The typical features revealed by ultrasonography are normal or reduced kidney size [note that normal-sized kidneys in end-stage renal disease (ESRD) is unusual], loss of corticomedullary differentiation and small cysts at the corticomedullary junction [17]. On renal biopsy, structural tubulointerstitial abnormalities are seen including tubular atrophy, interstitial fibrosis and tubular basement membrane defects [18]. (Note that in infantile NPHP there can be enlarged kidneys on the ultrasound scan, and renal biopsy findings include cortical microcysts and normal tubular basement membrane.)

Question 4

In general, juvenile NPHP presents with biopsy findings of severe chronic tubulo-interstitial changes with secondary tubular dilatation but with minimal inflammation. Conversely, tubulointerstitial nephritis (TIN) usually shows marked interstitial inflammation with minimal chronic change. In this boy’s biopsy there was extensive lymphocytic infiltration of tubules and a dense interstitial inflammatory infiltrate of lymphocytes, presenting a histological picture of acute TIN rather than the expected picture of chronic change one would expect in NPHP.

Discussion

In this report we describe a missed diagnosis of JS in a 9-year-old boy. JS is rare, with an estimated incidence of between 1 in 80,000 to 1 in 100,000 live births globally [19], although the incidence is higher in areas of the world with higher rates of consanguinity [14]. It is important to consider it in any child presenting with hypotonia, pathological ocular movements (both nystagmus or oculomotor apraxia) and developmental delay. The diagnosis can be confirmed with a brain MRI to determine the presence of the MTS.

Once a diagnosis of JS is made, careful assessment of other organ involvement is the next step. Renal assessment must include renal function, urinalysis (looking specifically for concentrating defects) and ultrasonography examination. It is currently recommended that such screening tests occur annually [19]. If there is any suspicion of NPHP, renal biopsy or genetic testing can be performed for confirmation.

The ultrasound findings of normal sized kidneys and loss of corticomedullary differentiation in this case are fairly non-specific although they fit with underlying NPHP. The difficulty in this case was the unusual biopsy findings. Although subsequent retrospective review of the biopsy confirmed the diagnosis of JS, the histological findings point to an acute TIN. As such, this case is an atypical histological presentation of NPHP.

The NPHP of this patient was confirmed by genetic testing. JS is an autosomal recessive condition, and a number of mutations in genes encoding proteins of the primary cilium have been identified, hence the classification of JS and JSRD as ‘ciliopathies’ and the clinical manifestations of the disease. Note that there have been rare cases of X-linked recessive inheritance (OFD1 mutation as an interacting partner of the LCA5-encoded ciliary protein lebercilin) [20]. To date, at least 25 genes have been identified, although the number is rapidly expanding [21].

Approximately 25% of all NPHP cases involve a deletion in the NPHP1 (nephronophthisis 1) gene [16]. Conversely, only 10% of children with NPHP have extrarenal abnormalities (including the MTS and JS), and the prevalence of NPHP1 deletions in JS is rare, although reported variably in the literature [22]. It is recommended that all children presenting with features of NPHP should be screened for this deletion. If a molecular genetic diagnosis can be made, then a renal biopsy should not be necessary. The boy in the case reported here was homozygous for the common 290-kb deletion in NPHP1 (PCR analysis revealed a homozygous deletion of both exon 5 of the NPHP1 gene and DNA marker 187.41, but not for the control site on chromosome 2 q35, and therefore no further testing was undertaken). His parents have not been tested for carrier status due to resource availability. Of note, he has two unaffected half siblings.

NPHP1 encodes a protein called nephrocystin-1 that has been identified in the primary renal cilia as well as the cell adherens junctions [23]. Patients with deletions in NPHP1 appear to move towards end-stage kidney disease
earlier than those with mutations in other genes involved in JS, such as NPHP1-6, NEK8, RPGIP1L and AHI1, amongst others.

In conclusion, this report highlights the importance of keeping a wide differential diagnosis in mind when a patient presents with a complex phenotype involving multiple organ systems. Retrospective reviews of imaging studies previously reported to be normal can on occasion be useful in identifying signs of disease.