Joubert syndrome: long-term follow-up

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Twenty-nine patients (16 males, 13 females) with Joubert syndrome were identified from ophthalmology, neurology, and genetic databases covering a 15-year period at Great Ormond Street Hospital, London. Criteria for diagnosis included absent or markedly hypoplastic cerebellar vermis, abnormal eye movements, and developmental delay. Five patients had died. Scans and notes were available for 22 patients, and 18 cases were clinically reviewed. The median age was 10 years 10 months (range 3 mo to 19 y), with one new patient seen at 3 mo of age. Cerebellar vermis hypoplasia/aplasia with the ‘molar tooth sign’ in the axial plane was present in 22 of 22 patients, coloboma in 6 of 22, and polydactyly in 6 of 22. In the 18 clinically reviewed, apnoea occurred in 13 patients. Five had renal problems with cysts and 4 of 5 had abnormal electroretinograms (ERGs). Visual electrophysiology was abnormal in 14 of 18 patients, and in 6 there was evidence of deterioration in the ERG. Blood investigations of organic acids, phytic acid, very-long-chain fatty acid, and transferrin were normal in 12 patients tested. Developmental assessment showed that 6 of 15 patients aged more than 5 years were at mainstream school, and 12 of 18 had started walking between 22 months and 10 years. Speech difficulties and behavioural problems were prominent.

Joubert syndrome is an autosomal recessive disorder named after Marie Joubert (Joubert et al. 1969), who, with her coworkers, characterized four patients with episodic tachypnoea and apnoea, abnormal eye movements, developmental delay, ataxia, and absence of the cerebellar vermis. Dekaban (1969) described two siblings with the same clinical findings who also had a retinal dystrophy: this has been described as a congenital retinal dystrophy (Aicardi et al. 1983). Boltshauser and Isler (1977) proposed that the condition, with or without retinal dystrophy, should be referred to as Joubert syndrome, but others have suggested the term ‘Debeker syndrome’ for the subgroup with retinal dystrophy (Sarava and Baraïter 1992). Boltshauser et al. (1995) reviewed a series of 12 patients and identified a subgroup of patients within Joubert syndrome with both renal involvement and a retinal dystrophy. Others have subsequently reviewed the diagnostic criteria for Joubert syndrome (Maria et al. 1999, Merritt 2003). The classical neuroimaging finding is of cerebellar vermis abnormalities with the following features: minimal connection between both cerebellar hemispheres; umbrella-shaped fourth ventricle; and stretched superior cerebellar peduncles and deep interpeduncular fossa leading to the ‘molar tooth sign’ of the mesencephalon, which is a description of the appearance seen on cross-sectional images taken in the axial plane (Maria et al. 1999, McGraw 2003).

Since its first description, a range of other clinical findings have been described in association with Joubert syndrome including occipital meningoencephalocele (Joubert et al. 1969, Houdou et al. 1986), dysmorphic faces (Wilson and Waber 1992), duodenal atresia (Lambert et al. 1989), facial palsy (Joubert et al. 1969, Boltshauser et al. 1981), cystic kidneys (King et al. 1984), congenital hepatic fibrosis (Lewis et al. 1994), polydactyly (Egger et al. 1982, Kher et al. 1994), tongue tumours (Egger et al. 1982), and ocular fibrosis (Appleton et al. 1989, Jacobsen et al. 1992). Ocular findings have included chorioretinal coloboma (Lindhout et al. 1980, Laverda et al. 1984, Beemer and Gooskens 1985, Kher et al. 1994), ptosis (Harman-Van Bijkevorsel et al. 1983, Houdou et al. 1986), saccade initiation failure (ocular motor apraxia; Moore and Taylor 1984, Lambert et al. 1989, Harris et al. 1996), nystagmus (Joubert et al. 1969, Lambert et al. 1989), and strabismus (Moore and Taylor 1984). Biochemical abnormalities have also been described: histidinaemia (Appleton et al. 1989) and Gaucher type 1 (van Royen-Kerkhof et al. 1998). Little is known about the long-term outcome of Joubert syndrome. Some authors suggest that nearly all living children with this disorder have severe disabilities (Boltshauser et al. 1977, Curatolo et al. 1980, Aicardi et al. 1983, Gitten et al. 1998) and that both cognitive and motor functions will deteriorate with time (Cantani et al. 1990). Others have indicated a much better outcome (Zeigler et al. 1990). In the present study we recalled and reviewed all patients diagnosed as having Joubert syndrome over the past 15 years at the Great Ormond Street Hospital for Children, London, to establish the clinical outcome, assess any evidence of progression, and look for evidence of biochemical abnormalities.

Methods

The study was performed at Great Ormond Street Hospital for Children. Ethical approval was obtained from the hospital’s ethics committee, and informed consent was obtained from the parents of each patient. Patients with a diagnosis of Joubert syndrome were located from the ophthalmology,
neurology, and genetic departments’ databases. Diagnosis depended upon the presence of abnormal neonatal breathing, abnormal eye movements, developmental delay, and an abnormal cerebellar vermis. The case notes, blood results, renal tract investigations, and computerized tomography (CT) or magnetic resonance imaging (MRI) scans were reviewed and arrangements were made to recall the patients. Those examinations that had previously been inadequate or overlooked were repeated at recall.

Each recalled patient underwent a renal ultrasound, a neuro-ophthalmological review, formal eye movement recordings, electroretinograms (ERGs), visual evoked potentials (VEPs), and an eye examination that included visual acuity assessment, slit lamp microscopy of the anterior segment, cycloplegic refraction, and fundoscopy. Biochemical studies were also performed with consent. These included liver function tests, urea and electrolytes, very-long-chain fatty acids, pipecolic acid, and histidine.

**VISUAL ELECTROPHYSIOLOGY**

Mixed rod–cone ERGs were recorded from skin electrodes positioned close to the lower eyelid margin or from DTL fibre electrodes (Dawson et al. 1979) depending on patient cooperation. A photic stimulator (GrassPS22; 3/sec, setting 4, peak intensity 4.75 × 106 lumens) provided flash stimulation under scotopic conditions (see Kriss and Thompson 1997 for details of the protocol). Responses were averaged with a Sensor ER94 (Medelec, Oxford, UK). Flash VEPs were recorded at the same time as ERGs. Pattern reversal stimulation was attempted for each patient. A range of black and white checkerboard stimuli (subtending 400′, 100′, 50′ and 25′ check size) were counterphased 3/sec on a monitor subtending 28′ × 21′. The VEPs were recorded from electrodes positioned at the inion and 3.5cm above it (Oz, International 10–20 system; Jasper 1958). An electrode at F3 (International 10–20 system) served as the common reference.

**EYE MOVEMENT RECORDING**

Horizontal eye movements were recorded with direct-current electro-oculography. Silver–silver chloride electrodes were attached with tape at the outer canthus of each eye, with a reference electrode at the mid-forehead. Video monitoring of the patient was performed throughout the recording session. Infrared monitoring was used when testing the vestibulo-ocular reflex in absolute darkness.

Optokinetic nystagmus was elicited by rotating a brightly coloured and patterned full-field curtain around the patient. Leftward and rightward optokinetic nystagmus at speeds of 25 and 50′/sec were recorded. Rotating the patient on the Barany chair (motorized rotating chair) while in complete darkness tested vestibulo-ocular reflex. The chair was accelerated at 18′/sec to a speed of 80′/sec and this speed was maintained for 40 seconds before decelerating at 18′/sec to rest. After a further 40 seconds the chair was rotated in the opposite direction. For a full description of protocol see Jacobs et al. (1992) and Harris et al. (1992).

**Results**

Twenty-nine patients (16 males, 13 females) were identified as having Joubert syndrome as their final diagnosis. This included four pairs of siblings. Eleven patients were unavailable for review: five (18%) patients had died (two from respiratory failure [age under 1 year], two from renal failure, and one from aspiration pneumonia secondary to a cleft palate under 1 year); one was in renal failure having dialysis after a failed transplant; two patients (siblings) had migrated; two other siblings had been adopted with no trace; and a further one unrelated patient declined re-attending the department. Details were used when available and relevant to the study.

Therefore, eighteen patients (11 males, 7 females) were reviewed in this study. Median age was 10 years 10 months (range 3mo to 21y) with a median of 8 years 5 months’ (range 3mo to 19y) follow-up (one patient was seen as a new case at 3 months old). Four pregnancies were reported as abnormal: in two of them the pregnancy had been complicated with polyhydramnios (one with duodenal atresia, one with rhesus disease), one was born with meconium staining of the liquor, and one was induced because there was a leak of amniotic fluid.

**NEURORADIOLOGY**

MRI and/or CT were reviewed in 22 patients. Cerebellar vermis aplasia/hypoplasia was present in 22 of 22 patients. The vermis was aplastic in eight and hypoplastic in 14 patients, affecting mainly the postero-inferior part. In all these cases the midbrain and superior cerebellar peduncles displayed the ‘molar tooth appearance’.

Associated features were noted on the MRI/CT scans of five patients. These were brainstem hypoplasia in two, occipital meningocele in one, corpus callosum dysgenesis in one, moderate dilatation of the ventricular system in one, and non-specific high signal lesions in the white matter in a patient who also had seizures.

**CLINICAL AND BIOCHEMICAL ASSOCIATIONS**

Associated systemic features in 22 patients were as follows: bilateral tight Achilles tendons (n = 2); pyloric stenosis (n = 1); thoracic scoliosis (n = 2); general joint laxity (n = 3); haeman-gioma (n = 3); duodenal atresia (n = 1); keratoconus (n = 1); partial third nerve palsy (n = 1).

One sibling had a tracheo-oesophageal fistula and another sibling had anophthalmos.

EEG was recorded in 10 patients and was abnormal in five: two of five had seizures; two of five had sharp discharges over focal areas but no recognizable epilepsy (one with right-sided occipital seizures and one with sharp discharges over right frontal lobe); the fifth had infrequent paroxysmal features of a multifocal distribution consistent with the MRI of multifocal white matter intensities.

Apnoeic episodes occurred in 13 of 18 patients, and in 10 of them they were a transient phenomenon lasting up to 3 months. One patient spent several weeks in the paediatric intensive care unit because of severe tachypnoeic episodes; another required oxygen at home; and a third patient had apnoeic episodes until 18 months of age.

Chorioretinal coloboma were seen in six of 22 patients. Postaxial polydactyly was present in six of 22: both were present in only three patients.

Five patients had renal cysts, and four of these also had an abnormal ERG. The fifth patient with ultrasound evidence of multiple renal cysts had normal ERGs but was only 2 years old. The other 13 patients were normal in this respect.

Organic acids, phytic acids, very-long-chain fatty acids and amino acids were normal in 12 patients tested. Plasma transferin isoelectric processing had been performed in 10 patients; it...
was performed as part of tests to exclude other diagnoses, and this was also normal. Routine karyotype was normal in 10 patients tested. Muscle biopsy was performed on two patients and was normal.

**DEVELOPMENTAL FINDINGS**
Discussion with the parents and note letter review revealed that general hypotonia was an early observation in all 18 patients. All patients also demonstrated some degree of motor and developmental delay, although this varied from mild to very severe. Twelve of 18 patients had walked unaided with a broad-based gait between 22 months and 10 years (one with orthosis, reason unclear). The corresponding times for sitting unaided and standing were delayed.

No formal speech assessment or IQ assessment was performed during the study. However, all children were attending or had attended speech therapy. Of those 15 children over 5 years old, 11 had developed intelligible speech and six were attending mainstream school. Even in those six children, speech remained a problem with difficulty in pronouncing words such that, in many cases, the parents could understand but newcomers had difficulty. Five had mild disability although they had achieved toilet training and self-feeding. Four had severe disability, with failure to develop even these basic skills.

In eight of 15 cases, parents volunteered the occurrence of severe temper tantrums and confirmed a large differential between comprehension and verbal ability.

**EYE MOVEMENT FINDINGS**
Saccade initiation failure (ocular motor apraxia) was evident in 14 of 18 patients; there was a variable failure of quick phases during induced optokinetic nystagmus or vestibular nystagmus, causing the eyes to deviate to the mechanical limit of gaze (i.e. locking up). In 13 patients the locking up was intermittent, but in one it was total with no saccades observed. Of these, eight exhibited head thrusting as a compensatory behaviour to shift the direction of gaze, and a further three patients showed synkinetic blinks where previously head thrusting had been recorded.

Five patients were associated with torsional nystagmus, three with horizontal pendular nystagmus, and two with upbeat nystagmus. One patient exhibited skew deviation and three had alternating gaze deviations, which were reminiscent of ping-pong gaze in one but were noticeably aperiodic in the other two.

There was one patient with a convergent squint, five with divergent squints, and five with alternating vertical squints.

**VISUAL ELECTROPHYSIOLOGY**
A normal flash with a well-preserved pattern VEP to small and medium-sized checks (subtending 25' to 100'), suggesting good acuity levels, with a normal ERG, was found in four of 18 patients. However, in one of these patients the ERG was reduced in amplitude although still within the normal range. These findings were stable over the follow-up period (mean 6 years).

Retinal responses were markedly abnormal in the remaining 14 of 18 patients, with the flash ERGs being significantly attenuated and degraded. In 10 of these 14 patients, flash and pattern reversal VEPs could be elicited, but in the remaining four only attenuated flash VEPs were evident, indicating that vision was at a rudimentary level only. In six patients there was evidence of deterioration according to the ERG recordings over the follow-up period.

**OCULAR EXAMINATION**
Anterior segment examinations were normal in all the 18 patients clinically reviewed. Fundal examination in those patients with an abnormal ERG revealed retinal pigment epithelium mottling in 14 patients. In four of these patients with abnormal ERG and only a very attenuated flash VEP, there was marked motting of the retinal pigment epithelium, especially at the macular area. In the remaining four of 18 patients with normal visual electrophysiology (VEPs and ERGs) the fundal examinations were normal.

Table I summarizes the visual acuities in the 18 patients, and their relationship with retinal involvement. It can be seen that poor levels of acuity (less than 6/24) are associated with retinal involvement. Interestingly, two patients with moderate levels of vision (6/12 to 6/18) had no retinal involvement and the reduced vision seems most likely to have been due to nystagmus.

**Discussion**
The diagnosis of Joubert syndrome as opposed to other similar clinical conditions is difficult because of the current absence of a specific test or genetic marker (Blair et al. 2002). Several syndromes that have been considered distinct from Joubert syndrome have occasionally been grouped clinically with it, including cerebello-oculo-rex syndromes (Satran et al. 1999). In the present study every effort was made to include only those patients that the departments of neurology, ophthalmology, and genetics all agreed have Joubert syndrome. The criteria used were the presence of developmental delay, abnormal ocular movements, and the presence of marked cerebellar vermis abnormalities leading to the presence of the ‘molar tooth sign’ (Maria et al. 1999, McGraw 2005).

In four inherited syndromes, Dandy–Walker malformation, cerebellar vermis hypoplasia–oligophrenia–ataxia–coloboma and hepatic fibrosis syndrome (COACH), carbohydrate-deficient glycoprotein syndrome (CDG), and Joubert syndrome, the finding of cerebellar vermis hypoplasia or aplasia with multiple other ocular and systemic findings usually provides the basis for differential diagnosis (see Table II). Others have looked at the similarity between CHARGE (coloboma of the eye, heart defect, atresia of the choana, retarded growth and development, genital hypoplasia, and ear anomalies or deafness) and Joubert syndrome (Menenzes and Coker 1990).

Di Rocco (1993) suggests that Joubert syndrome with retinal dystrophy and renal cysts might represent CDG, and CDG must be considered in any patient with cerebellar dysplasia.

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**Table I: Visual acuity (Snellen) and associated retinal involvement (n=18)**

<table>
<thead>
<tr>
<th>Visual acuity</th>
<th>No retinal involvement</th>
<th>Retinal involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>6/6 to 6/9</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>6/12 to 6/18</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>6/24 to 6/60</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>&lt;6/60</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Total, n</td>
<td>4</td>
<td>14</td>
</tr>
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and renal or liver cysts. It can be excluded by performing isoelectric focusing of plasma transferrin, which is carbohydrate deficient in affected patients. Orofacial digital syndrome also needs to be considered as potentially overlapping with Joubert syndrome; Smith and Gardner-Medwin (1993) describe a brother and a sister with learning disability, abnormalities of the cerebellar, characteristic metronome eye movements, lingual hamartomas, and postaxial polydactyly.

Cerebellar vermian dysgenesis is a cardinal feature in Joubert syndrome; all of the patients in our study exhibited this sign, with the presence of the ‘molar tooth sign’ in the axial plane. The association of Joubert syndrome with more profound hypoplasia postero-inferiorly was confirmed. A review of all the scans for other problems did not lead to any constant or common other associations. The hypoplastic cerebellar vermis could explain only motor problems and not any associated learning disability. Even a review of the cerebral cortex on those MRIs performed recently revealed no abnormality.

**DEVELOPMENTAL FINDINGS**

Many of the reports so far have tended to indicate a poor developmental prognosis for these patients. It was thought that all living children with the disorder have severe disabilities (Bolshauzer et al. 1977, Curatolo et al. 1980, Acari et al. 1983, Calleja-Perez et al. 1998). Severe learning disabilities are generally accepted as an integral part of Joubert syndrome (Gitten et al. 1998). However, there are reports on older patients with Joubert syndrome that have drawn attention to the possibly better than expected outcome. Casaer et al. (1985) described a patient who had possibly isolated agenesis of the vermis but did have features of Joubert syndrome (transient early breathing abnormalities, irregular jerky eye movements). Zeigler et al. (1990) reported on one child aged 8 years with Joubert syndrome: although severe learning disability was evident until about the age of 5 years, unexpected and exceptional capabilities were evident at a later follow-up.

In this study we followed up a group of these children and conclude that severe learning disability is not an absolute feature of the syndrome. Six of 15 children in our study were older than 5 years and were attending mainstream school with varying amounts of help. The eye movement abnormalities together with severe motor disorder can give an early false impression of the severity of intellectual disability. Gitten et al. (1998) have reported that the degree of developmental delay and the severity of central nervous system malformations seem to be independent. The severe motor difficulties that are experienced in this syndrome, together with the eye movement problems and speech difficulties, create a barrier to effective communication so that early intellectual and emotional development are hard to assess. Failure to recognize this can lead to affected children being labelled as having a disability. Steinlin et al. (1997) reported 19 children with Joubert syndrome with variable motor and cognitive development. Our study supports this observation. In all of our patients there was a differential delay, with motor development being most affected and comprehension abilities almost uniformly being reported as ahead of other abilities.

In eight patients with good comprehension skills yet poor vocalization, the parents reported prominent temper tantrums. It has been suggested that this might be due to difficulty in vocalization. Twelve patients were undergoing speech therapy. There is a strong relationship between articulatory deficits and saccade initiation failure (Harris et al. 1996, Jan et al. 1998), and this might be attributable to vermis malformation (see Harris et al. 1998).

**OCULAR FINDINGS**

Joubert syndrome is often associated with retinal problems,
which were originally described by Dekaban (1969) and were not reported by Joubert et al. (1969) in their cases, leading to a suggestion that two different names be used depending on the presence of a retinal dystrophy. Although our protocol is to record VEP and ERG simultaneously, previous studies of Joubert syndrome have recorded ERGs alone and Joubert syndrome has been associated with very attenuated or undetectable rod-mediated ERGs previously classified as a variant of Leber’s amaurosis (Tomita et al. 1979, King et al. 1984, Moore and Taylor 1984).

Our findings support the reports in the literature that retinal abnormalities occur in a sub-group of patients carrying the diagnosis of Joubert syndrome (Bolshhauser and Isler 1977, Saraiva and Baraitser 1992, Bolshhauser et al. 1995). Visual electrophysiology had been performed in 18 patients and was found to be abnormal in 14 of them. Among the four normal recordings were those from the youngest patients in our study, and one of them had evidence of deterioration although still in the normal range. We found evidence of progressive retinal damage in six other patients with longer follow-up. Failure to detect any deterioration in other patients’ ERGs might have several explanations. The original recording showed that function might have been so severely affected as to be almost not recordable so that small changes made very little difference, or there was inadequate follow-up on some patients. In four of 14 patients with abnormal ERGs, the ERG and VEP could not be detected from background activity and the patients effectively had total visual impairment. Examination of the fundi of these patients revealed mottling of the retinal pigment epithelium, especially at the macula area.

Saraiva and Baraitser (1992) concluded that retinal dystrophy runs in families and is never absent when renal cysts are present. The renal cysts are multiple, small, and cortical, and affected kidneys also have interstitial chronic inflammation and fibrosis. We found renal abnormalities in five patients, all of whom had undergone visual electrophysiology; in four of them this was abnormal. However, there was one patient with a prominent cyst on renal ultrasound who had normal electrophysiology. This exceptional patient was 2 years old and only a single recording had been made, so it is possible that a retinal abnormality might develop later. Unfortunately review was not possible.

EYE MOVEMENTS

A range of eye movement abnormalities were present, the most common being saccade initiation failure, which was seen in 15 of 18 patients reviewed.

It is not possible to relate the eye movement abnormalities to precise anatomical sites owing to the widespread malformations in Joubert syndrome. A recent post-mortem study of Joubert syndrome (Yachnis and Rorke 1999) revealed not only vermis aplasia but also malformations of the dentate nuclei and atrophy of the cerebellar cortex. There were multiple medullary malformations including hypoplastic inferior olives, thinning of the reticular formation neurons, displaced segmental nuclei (including vestibular nuclei), and a malformed cervicomedullar area involving the posterior median sulcus, fasciculi gracilis and cuneatus, and solitary nucleus.

Saccade initiation failure has been associated with a wide range of congenital and acquired conditions (see Cassidy et al. 2000). However, there is a strong association of saccade initiation failure with vermiain malformations (Eda et al. 1984, Shawkat et al. 1995, Harris et al. 1998, Jan et al. 1998), or acquired vermian lesions including tumours and neurodegenerative condition (Cassidy et al. 2000). In the Cassidy study all had cerebellar vermis hypoplasia (eight had absent vermis and 14 had hypoplastic vermis predominantly affecting the posterior-inferior part). Although vermis hypoplasia seems the most likely cause of saccade initiation failure in Joubert syndrome, the mechanism is unclear because primary vermis seems to be more involved with saccade accuracy than timing (discussed by Harris et al. 1998).

Nystagmus was seen in 10 of 18 patients. The nystagmus was torsional in five of them and could not be measured by our equipment. In four it was horizontal pendular and in one it was upbeat. These varieties of nystagmus were not typical of congenital sensory nystagmus even in those with an associated retinal dystrophy, and we attribute the nystagmus to a neurological cause (Casteels et al. 1992) probably resulting from brainstem malformation.

A peculiar observation in three children was periodic horizontal alternating gaze shifts, in which the eyes would swing conjugately between extreme horizontal gaze position over about 5 to 15 seconds. We have not seen this phenomenon associated with any other condition. It bears some resemblance to periodic alternating esotropia (but without the esotropia) described by Hamed and Silbiger (1992) in a patient with hypoplasia of the vermis and brainstem. One possibility is that the deviations reflect periodic alternating nystagmus without quick phases (owing to saccade initiation failure; Harris 1997).

Conclusion

Retinal dystrophy is strongly associated with renal abnormalities. The retinal dystrophy in Joubert syndrome might be progressive. Not all children affected have severe disabilities. Saccade initiation failure is not invariant.

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Tony Kriss died while this project was under way. His contributions to paediatric visual electrophysiology and to the development of visual science will live on, as will our memories of his kind and goodhumoured approach to life and his collegiality. He will be missed but never forgotten, and we dedicate this article to him.