Original articles

Joubert’s syndrome with retinal dysplasia: neonatal tachypnoea as the clue to a genetic brain-eye malformation

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SUMMARY Five children with features of Joubert’s syndrome and Leber’s amaurosis are described. The presenting symptoms were panting tachypnoea in the newborn, prolonged apnoeic attacks in the neonatal period (in both of identical twins), global developmental delay, and failure to develop vision. Three children had multiple hemifacial spasms, such as have been seen in Joubert’s syndrome, and the same three had cystic dysplasia of the kidneys. Necropsy confirmed the retinal and renal pathology, together with agenesis of the vermis and brainstem dysgenesis in the identical twins. It is concluded that a gene for Leber’s amaurosis may commonly manifest itself as the specific hind brain malformation underlying Joubert’s syndrome.

In infants with respiratory irregularities (especially rapid panting), hemifacial spasms, or developmental delay, absence of the cerebellar vermis should be specifically sought by ultrasound and computed tomography, and the electroretinogram measured, whether or not impaired vision is clinically evident.

Joubert’s syndrome\(^1\)\(^-\)\(^15\) comprises episodic panting tachypnoea and jerky eye movements in the neonatal period with subsequent ataxia, dyscoequilibrium, and mental handicap accompanied by agenesis of the cerebellar vermis and brainstem malformation.\(^16\)

Leber’s amaurosis (congenital retinal blindness) is an autosomal recessive disorder characterised by visual impairment, normal optic fundus in infancy, and miniscule electroretinogram response; cerebral and renal malformations often exist.\(^17\) We describe five children with features of both disorders (proved at necropsy in two children) to alert paediatricians to specific cerebral imaging and retinal function studies in neonates with unexplained panting tachypnoea.

Case reports

Case one. A boy, the first child of healthy, unrelated Scottish parents (mother aged 34 years, father 27 years), was born at term by elective caesarean section, after an uneventful pregnancy. His birthweight was 2980 g and Apgar scores were 7 at one minute and 9 at five minutes. He was admitted to the paediatric department because of an abnormal respiratory pattern consisting of episodes of tachypnoea (200 per minute) of up to two minutes duration, alternating with apnoea (10 to 35 seconds), without colour change or alteration in heart rate. The baby’s head circumference was 34 cm, the facies was odd (small eyelid aperture, flat upturned nose), and the tongue protruded (Fig. 1). Jerky, rapid, irregular conjugate eye movements and general hypotonia were present. The tachypnoea was exacerbated when the baby was stimulated but diminished during sleep. Frequent hemifacial spasms associated with pallor, sweating, and prolonged apnoea (up to 40 seconds) were observed.

The following investigations were normal: full blood count, serum urea, electrolytes, liver function tests, thyroid studies, pyruvate, lactate, ammonia, pH, Pco\(_2\), bicarbonate, free fatty acids, chromosome studies, plasma and urinary amino acids, and urinary organic acids. Bacteriological and viral
cultures of blood, cerebrospinal fluid, and urine were negative. In addition, the electroencephalogram, brainstem auditory evoked responses, electrocardiogram, and skull and chest radiographs were normal. The respiratory pattern was attributed to ‘immaturity of the respiratory centres’ and the infant was discharged home at 3 weeks of age.

At 3 months of age the infant was visually inattentive and was referred to this hospital. The physical findings were as described at birth. Sleep stages were difficult to identify because of tachypnoea and abnormal eye movements, but tachypnoea and hemifacial spasms seemed to occur while awake and during rapid eye movement and non-rapid eye movement sleep, whereas prolonged apnoea occurred only during non-rapid eye movement sleep. Pupils were of normal size and reacted to light. Fundoscopy showed normal discs and maculae with some thinning of the retinal pigment layer and exposure of the underlying choroidal vessels.

Joubert’s syndrome was suspected and a computed tomogram showed an enlarged fourth ventricle extending higher than usual with a reduced density area extending posteriorly, confirming vermal agenesis (Fig. 2). The electroretinogram was unrecordable with skin electrodes: with corneal electrodes the following recordings were made: 5 μV mesopic b wave (normal 30 to 70 μV); a 5 μV 3 minute dark adapted scotopic b wave (normal 140 to 200 μV); a 6 μV 6 minute dark adapted scotopic b wave (normal 150 to 250 μV). Visual evoked responses were of small amplitude and delayed (200 ms seconds to P1). This gross attenuation of the

Fig. 1  Patient in case 1 aged 8 months showing characteristic tongue protrusion. He had a flat upturned nose and small eyelid apertures.

Fig. 2  Patient in case 1: serial computed tomograms of the posterior fossa showing an enlarged fourth ventricle with an area of low attenuation posteriorly consistent with vermal agenesis.
electroretinogram confirmed retinal dysplasia. Intravenous pyelogram showed multiple small cysts bilaterally.

At the time of writing the child is 3 years old and is hypotonic, sits unsupported, but is unable to crawl or speak. He has severe visual impairment, episodic hyperpnoea (although less strikingly), and hemifacial spasms. The electroretinographic findings are unchanged.

Cases 2 and 3. Cases 2 and 3, both boys, were monozygous twins (proved by zygosity testing) born to healthy unrelated Scottish parents aged 34 and 35 years. Two previous siblings had died of primary apnoea in the neonatal period. A boy born at term had tachypnoea (130 per minute) and apnoea; despite ventilation he died at 48 hours of age. Necropsy showed polycystic kidneys, pulmonary haemorrhage, and a dilated fourth ventricle. A second infant, a girl, failed to respond to resuscitation at birth. At necropsy polycystic kidneys, pulmonary haemorrhage, and a dilated fourth ventricle were found. The appearance of the cerebellar vermis was not documented in either infant. Chromosome studies were normal and viral titres were negative in both infants. Another sibling (a boy) is alive and healthy.

The twin pregnancy was uncomplicated until the onset of premature labour at 34 weeks’ gestation. Both twins were delivered by low cavity forceps. Clinical, biochemical, radiological, ultrasonic, electrophysiological, and necropsy findings were virtually identical in both and a single description follows.

Case 2
Apgar scores were 5, 9, and 10 at one, five, and 10 minutes respectively. Birthweight was 2320 g and head circumference 32-5 cm. Irregular, panting respirations, alternating ‘facial palsy’, dysmorphic facies, and enlarged right kidney were noted immediately. On day two apnoeic attacks with cyanosis and bradycardia lasting up to three minutes developed and apparently were terminated by bag and mask ventilation.

Electrolytes, glucose, haemoglobin, cerebrospinal fluid examination, and chest radiograph were normal and cultures of cerebrospinal fluid blood and urine were sterile. The abnormal breathing pattern was attributed to prematurity, and aminophylline suppositories were given without effect on the frequency or duration of apnoea. The infant was discharged home at age 4 weeks.

The infant was admitted to this hospital at age 9 weeks, after frequent prolonged apnoeic attacks. On examination, head circumference was 36-5 cm (50th centile) and fontanelles were wide. There was a small vascular malformation of the skin over the upper occiput. Jerky, irregular conjugate eye movements, protruding tongue, dysmorphic facies, alternating hemifacial spasms (Fig. 3), and tachypnoea (150 per minute) with apnoea up to three minutes duration, noticeable head lag, hypotonia, and bilateral syndactyly of the second and third toes were present.

A clinical diagnosis of Joubert’s syndrome was made and on transfontanelle ultrasound scanning of the posterior fossa, the normal pyramidal fourth ventricle was shown to be replaced by an oblong transsonic area above the cerebellum on both longitudinal and transverse scans, suggesting agenesis of the vermis of the cerebellum (Fig. 4).

As ultrasound findings in Joubert’s syndrome have not been described previously, computed tomography was performed. An enlarged fourth ventricle extending higher than usual, with an atrophic area in the region of the cerebellar vermis, supporting vermal agenesis was shown (Fig. 5). Polygraphic recordings showed tachypnoea and hemifacial spasms while awake and during rapid and non-rapid eye movement sleep, but apnoea occurred during non-rapid eye movement sleep only.

![Patient in case 2 aged 9 weeks showing right hemifacial spasm.](http://adc.bmj.com/first-published-as/10.1136/adc.59.8.709/)
Ultrasound examination of the kidneys and intravenous pyelogram showed cystic changes in the right kidney; the left kidney was not visualised.

At 12 weeks of age the infant was visually unresponsive. Fundoscopy showed slight accentuation of pigmentation in an equatorial distribution suggesting retinal aplasia of Leber's amaurosis. The electoretinogram, recorded with corneal electrodes, was grossly abnormal; a 10.5 μv mesopic b wave (normal 30 to 70 μv) and 10 μv 10 minute scotopic b wave (normal 150 to 250 μv) were recorded confirming Leber's amaurosis. Chromosomes, determined by Giemsa banding, were normal. The infant was discharged home at 4 months of age but died two weeks later after an episode of prolonged apnoea.

The main findings at necropsy examination were in the skull, brain, eyes, liver, and kidneys. There was a small circular midline defect (3 mm diameter) in the upper occiput containing meningeal tissue only. There was a small vascular malformation of the skin and subcutis overlying the occult meningocele. The base of the brain showed the unci to lie more closely together than normal, completely overhanging the mammillary bodies. The brain stem and the cranial nerves were normal externally, but on section the olives were unusually prominent. The cerebellum (90 g) had an unusual shape, being rounded when viewed from above. The cerebellar hemispheres were applied to each other with complete absence of the vermis and a midline cleft. Apart from agenesis of the vermis, the cerebellum was unremarkable.

The histological findings in the cervico-medullary junction, cerebellum, pons, thalamus, mid-brain, and cerebral hemisphere were unremarkable. In the medulla the olives showed a striking hyperplasia of neurones with roughly 30% more neurones by comparison with normal specimens. The tractus solitarius could not be identified in two levels of medulla and two levels of pons. In some situations in
which the tract might be expected to be seen, there were small collections of neurones which could not be readily classified as belonging to any other nuclear system.

The only macroscopic abnormality in the eyes was a fine pigmented disturbance in the mid-periphery of each eye, with a broad pale tongue radiating from the disc and macula. The anterior segments were unremarkable. There was a selective reduction in the number of nuclei in the mid-peripheral and posterior outer nuclear layer and in the mid-periphery there was an appreciable reduction in the melanosome content of short segments of the retinal pigmented epithelium. Thus, there was definite evidence of geographical tapetoretinal degeneration.

The liver (244 g) was slightly enlarged. The capsular and the cut surfaces showed a uniformly fine granular appearance but there was no cyst formation. There was a diffuse increase in the size of the portal tracts with an interconnecting network of bile ductules, some of which were dilated. The hepatocytes were unremarkable.

The kidneys were both abnormal. The left kidney (0.9 g) was a tiny dysplastic mass in the normal renal site associated with atresia of the upper half and hypoplasia of the lower half of the ureter. The right kidney (29 g) showed exaggerated fetal lobulation and several thin walled cysts (up to 3 mm diameter) projecting from the subcapsular surface, mainly at the poles. The cut surface showed disorganisation of the normal corticomedullary architecture. The pelvic-vascular system and the ureter were essentially normal. The left kidney showed severe dysplastic change with abnormal tubules, microcysts, and heterotopic cartilage, but no normal renal parenchyma. In the right kidney there was considerable glomerulotubular differentiation but widespread dysplastic change varying from mild to severe.

**Case 3**

After the death of his twin at home, this infant was readmitted to hospital. Profound hypotonia, no psychomotor development or visual responses, hemifacial spasms (Fig. 6), jerky eye movements, and episodic tachypnoea and apnoea were present until the baby’s death at 13 months of age during a prolonged apnoeic episode.

**Case 4.** A girl, the first child of healthy, unrelated Scottish parents (mother aged 22 years, father 34 years), was delivered by elective caesarean section for breech position after premature rupture of membranes, at 36 weeks’ gestation. Her birthweight was 2960 g and head circumference was 34 cm.

Apgar scores were 8 at one minute and 9 at five minutes. The infant was admitted to the neonatal unit because of tachypnoea (100 per minute), for which no cause was found. The tachypnoea diminished over the first week and the infant was discharged home.

At 6 months of age the infant was referred to hospital because of floppiness and suspected poor vision. Poor head control, mild hypotonia, brisk lower limb reflexes, tongue protrusion, absent visual following or fixation, and jerky eye movements were found. A diagnosis of non-specific global delay was made. The child smiled at age 4 months, reached out for objects at 14 months, and sat unsupported at 16 months.

At 18 months she was referred to this hospital. On examination there was constant tongue protrusion with episodic tachypnoea (80 to 100 per minute). The child sat unsupported but there was noticeable truncal ataxia and increased tone and reflexes in the lower limbs. Jerky ocular pursuit movements and
decreased visual acuity with normal optic fundi and pupil reactions were found. There was no speech or play.

The breathing pattern, ataxia, and eye movements suggested Joubert’s syndrome. Computed tomography was performed, showing dilatation of the fourth ventricle which communicated with a posterior cystic area between the cerebellar hemispheres (Fig. 7) consistent with agenesis of the cerebellar vermis. The electroretinogram showed considerably reduced values: mesopic b wave 6 μV (normal 30 to 70 μV); 5 minute scotopic b wave 16 μV (normal 150 to 250 μV). Ultrasonography of the kidneys showed no abnormality. Chromosomes, determined by Giemsa banding, were normal.

Case 5. A girl, the first child of healthy, unrelated Scottish parents aged 24 and 26 years, was born at term by normal delivery. She weighed 2660 g and her head circumference was 36 cm. She was admitted to the neonatal unit after episodic panting tachypnoea (120 per minute) which was exacerbated when she was stimulated. No cause was found for the tachypnoea which was less prominent after 4 weeks of age. There was a vascular malformation of the skin overlying the occiput.

At 3 months of age the infant was not following or fixing with the eyes and was referred to this hospital. Her respiratory pattern was normal, but she had hypotonia, head lag, jerky eye movements, tongue protrusion, and no visual fixation or following. Pupils were of normal size and reacted to light.

The optic fundi were normal. The electroretinogram was unrecordable. Computed tomography showed the fourth ventricle extending higher than usual with a low density area in the region of the cerebellar vermis. Intravenous pyelogram showed bilateral cystic kidneys. Chromosomes were normal.

All milestones were delayed. The child walked at 4½ years; at 7 years she is blind, hypotonic, and walks with broad based ataxic gait. There is no speech, constant tongue protrusion, and severe mental retardation. The electroretinogram is absent.

**Discussion**

In 1981 we speculated that the abnormal eye movements and poor visual attention in our patient in case 1 might have a peripheral rather than a central mechanism. The electroretinogram was sought and found to be grossly deficient (confirmed at follow up). A child previously coded as having Leber’s amaurosis was found to have a neonatal history and other findings typical of Joubert’s syndrome (case 5). At this time the Japanese report of the coincidence of Joubert’s syndrome and Leber’s amaurosis was received. We then alerted others in the field to this connection from which followed the observations of Aicardi et al. The clinical and pathological findings in the twins (cases 2 and 3) confirmed the association. The patient in case 4 was then referred to us for electroretino-
<table>
<thead>
<tr>
<th>Author</th>
<th>No of Cases</th>
<th>Sex</th>
<th>Family history</th>
<th>Vision</th>
<th>Electro-retinogram</th>
<th>Other features</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joubert et al⁵</td>
<td>5</td>
<td>4 M</td>
<td>+ (4 sibs)</td>
<td>N (2)</td>
<td>ND</td>
<td>Protruding tongue (2), microphaly (1), high arched palate (1), polydactyly (1), occipital meningoencephaloele (1), seizures (1), abnormal electroencephalogram (4)</td>
<td>2 Died aged &lt;3 years</td>
</tr>
<tr>
<td>Santolaya et al²</td>
<td>1</td>
<td>F</td>
<td>–</td>
<td>ND</td>
<td>ND</td>
<td>Protruding tongue, occipital meningocele, ptosis, seizures, abnormal electroencephalogram</td>
<td>Died aged 2 years</td>
</tr>
<tr>
<td>Bolshozauser et al³</td>
<td>3</td>
<td>2 M</td>
<td>+ (2 sibs)</td>
<td>N (1)</td>
<td>ND</td>
<td>Protruding tongue (2) epicanthc folds (1)</td>
<td>2 Died aged &lt;3 years</td>
</tr>
<tr>
<td>Calenger⁴</td>
<td>1</td>
<td>M</td>
<td>–</td>
<td>ND</td>
<td>ND</td>
<td>Not recorded</td>
<td>Died aged 16 days</td>
</tr>
<tr>
<td>Tomita et al⁶</td>
<td>1</td>
<td>M</td>
<td>–</td>
<td>Blind</td>
<td>NR</td>
<td>Occipital meningocele, abnormal ears, facial weakness, retinal aplasia</td>
<td>Alive</td>
</tr>
<tr>
<td>Dralle and Schmidt-Sommerfeld⁷</td>
<td>2</td>
<td>M</td>
<td>–</td>
<td>ND</td>
<td>ND</td>
<td>Dymorphic facies (2), occipital meningocele (2), polydactyly (1), protruding tongue (1), seizures (1), abnormal electroencephalogram (2)</td>
<td>1 Died aged &lt;3 years</td>
</tr>
<tr>
<td>Curatolo et al⁷</td>
<td>1</td>
<td>M</td>
<td>–</td>
<td>? Reduced at age 6 months</td>
<td>ND</td>
<td>Facial exostosis, procnathism, posterior sydcntyly, agenesis of the corpus callosus, abnormal electroencephalogram</td>
<td>Alive</td>
</tr>
<tr>
<td>Lindhout et al⁸</td>
<td>1</td>
<td>M</td>
<td>–</td>
<td>Reduced at age 6 months</td>
<td>ND</td>
<td>Protruding tongue, retinal colobomata</td>
<td>Alive</td>
</tr>
<tr>
<td>Burreoni et al⁹</td>
<td>1</td>
<td>F</td>
<td>–</td>
<td>N</td>
<td>ND</td>
<td>Protruding tongue, seizures, abnormal electroencephalogram</td>
<td>Alive</td>
</tr>
<tr>
<td>Aparicio-Meix and Pascaul Castroviejo⁰</td>
<td>3</td>
<td>M</td>
<td>ND</td>
<td>N</td>
<td>ND</td>
<td>Hemifacial spams, occipital encephaloele, abnormal electroencephalogram</td>
<td>Alive</td>
</tr>
<tr>
<td>Bolshozauser et al¹¹</td>
<td>1</td>
<td>F</td>
<td>+</td>
<td>N</td>
<td>ND</td>
<td>Facial weakness (2)</td>
<td>Alive</td>
</tr>
<tr>
<td>Egger et al¹³</td>
<td>1</td>
<td>M</td>
<td>–</td>
<td>N</td>
<td>ND</td>
<td>Nucus posterior fontanelle</td>
<td>Alive</td>
</tr>
<tr>
<td>Suzuki et al¹⁴</td>
<td>1</td>
<td>M</td>
<td>–</td>
<td>ND</td>
<td>ND</td>
<td>Occipital meningocele, abnormal electroencephalogram</td>
<td>Died aged &lt;1 year</td>
</tr>
<tr>
<td>Aicardi et al¹⁵</td>
<td>5</td>
<td>4 M</td>
<td>+ (5)</td>
<td>Reduced (5)</td>
<td>ND (2)</td>
<td>Dymorphic facies (3), occipital meningocele (1), ptosis (1), campylodactyly (2), retinal colobomata (2), retinal aplasia (3)</td>
<td>2 Died aged &lt;4 years</td>
</tr>
<tr>
<td>Present report</td>
<td>5</td>
<td>3 M</td>
<td>+ (2)</td>
<td>Poor (5)</td>
<td>R (4)</td>
<td>Protruding tongue (5), hemifacial spams (3), occipital meningocele (2), cystic kidneys (3), retinal aplasia (2)</td>
<td>2 Died aged &lt;13 months</td>
</tr>
</tbody>
</table>

N=normal; ND=not done; NR=no response; R=reduced response.
graphic investigation once the diagnosis of Joubert’s syndrome had been suspected.

The five cases reported here illustrate the variability in presentation of Joubert’s syndrome—panting tachypnoea at birth (case 1); prolonged apnoea attacks, tachypnoea, and hemifacial spasms in the neonatal period (cases 2 and 3); global developmental delay (case 4) and failure to develop vision (case 5). Although the clinical hallmark of the syndrome is neonatal episodic hyperpnoea resembling the panting of a dog, the significance of this was not recognised at birth in any of these patients. In addition, the abnormal respiratory pattern tends to wane with age, thus the importance of a detailed neonatal history in older children presenting with the features described.

The necropsy findings in two cases were comparable with published pathological reports of Joubert’s syndrome and Leber’s amaurosis.

The cases of Joubert’s syndrome reported to date are summarised in Table 1. All showed panting tachypnoea at birth and partial or total agenessis of the cerebellar vermis.

Conflicting reports have been published on the relation between the respiratory pattern and sleep stages, probably due to the difficulty in identification of sleep phases in these infants. It has been suggested that the respiratory irregularity may be attributable to anomalies of the solitary tract (tractus solitarius) and gracile nuclei seen at necropsy, as these are thought to be important as relay centres for a variety of chemical and sensory stimuli that affect ventilation.

Neuroradiological studies show an unusually shaped fourth ventricle and a midline defect in the posterior fossa compatible with vermal agenesis. There is considerable variation in the size and shape of the fourth ventricle and cisterna magna even within the same family. The use of ultrasonography in Joubert’s syndrome has not been reported previously.

Variable features described in Joubert’s syndrome include dysmorphic facies (eight cases), seizures (five cases), electroencephalographic abnormalities (13 cases), skeletal abnormalities (seven cases), and agenessis of the corpus callosum (one case). Hemifacial spasms, seen in three patients in this report, have only been described once previously, but we suspect that these spasms were responsible for the ‘facial palsy’ described in three further cases.

Malformation syndromes exhibiting some of the features of Joubert’s syndrome, but distinguishable clinically and pathologically, are shown in Table 2. Despite the findings of abnormal eye movements in most cases, detailed ophthalmological assessment has been reported in only seven. Four of the remainder were not following or fixating at 6 months of age, one died aged 18 days, in six no reference was made to vision, and in 10 it was said to be ‘normal’. The ocular abnormalities reported are retinal colobomata and Leber’s amaurosis. The latter association may have been underestimated in earlier reports where electroophthalmological studies were not performed. Clinical assessment of visual acuity is difficult in mentally retarded patients: in Leber’s amaurosis visual impairment may be mild and fundus appearance normal in infancy while the electoretinogram is grossly attenuated. The electoretinogram has been unrecordable or miniscule in nine of the 10 cases in which it has been measured (Table 1): the

### Table 2  Malformations having some features in common with Joubert’s syndrome

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Key features</th>
<th>Variable features</th>
<th>Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meckel’s syndrome</td>
<td>Occipital encephalocele</td>
<td>Cleft lip with or without cleft palate; microcephaly; anophthalmia; clcfi palate; cryptorchidism</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Polycystic kidneys</td>
<td>Polycystic kidneys</td>
<td>Polycystic fibrotic liver; anencephaly; occipital meningencephalocele; microcephaly; anophthalmia; clcfi palate; cryptorchidism</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Brain malformation</td>
<td>Brain malformation</td>
<td>Respiratory distress</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Polydactyly syndrome</td>
<td>Polydactyly</td>
<td>Respiratory distress</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Mohr’s syndrome</td>
<td>Lingual malformation</td>
<td>Respiratory distress</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Dandy-Walker syndrome</td>
<td>Hydrocephalus</td>
<td>Polydactyly; cleft palate; renal abnormalities; spinal dysplasia; agenessis of corpus callosum; cluster breathing</td>
<td>Usually sporadic with rare exception</td>
</tr>
<tr>
<td>Hard E syndrome</td>
<td>Encephalocele</td>
<td>Encephalocele</td>
<td>Autosomal recessive</td>
</tr>
</tbody>
</table>
exception was a child with polydactyly and lingual malformation who had certain resemblances to Mohr’s syndrome.

Although some workers have suggested that maturation of the response to light is not attained until the end of the first year, in our experience and that of others, the electroretinogram is easily recordable in infants with normal vision and is of sufficient amplitude, leaving no scope for confusion with Leber’s amaurosis.

The occurrence of neurological abnormalities and cystic kidneys with Leber’s amaurosis is well recognized. Neurological features include epilepsy, mental retardation, cerebral diplegia, diffuse cerebellar hypoplasia, and aplasia of the cerebellar vermis. The last association cannot be explained on embryological grounds: the lips of the rostral rhombencephalon fuse to form the vermis between 40 and 50 days’ gestation dating the teratogenic event in vermal agenesis to that period, whereas Leber’s amaurosis is thought to be a disorder of the late stages of growth and differentiation. This theory is supported by the finding that in Leber’s amaurosis all three nuclear layers and both plexiform layers are well developed and there is some differentiation of cones, suggesting that differentiation reaches at least 18 weeks before development is interrupted.

The occurrence of the association of Joubert’s syndrome and Leber’s amaurosis within a sibship affecting both sexes, its occurrence in a consanguineous mating and its concordance in monozygous twins (present report) suggests autosomal recessive inheritance and suggests that unless there is close genetic linkage both anomalies are due to a single gene defect.

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References


Joubert’s syndrome with retinal dysplasia


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