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Pontine Tegmental Cap Dysplasia With a 2q13 Microdeletion Involving the NPHP1 Gene: Insights Into Malformations of the Mid-Hindbrain

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The case of a young man with multiple brain and somatic anomalies that presented diagnostic difficulties, is discussed in this report. A majority of his features were suggestive of Joubert syndrome—although it was felt that he did not fully meet diagnostic criteria. The subsequent evaluations included a magnetic resonance image of the brain, that was found to be consistent with pontine tegmental cap dysplasia. Chromosomal microarray studies showed a 2q13 deletion. A gene associated with Joubert syndrome, NPHP1, is within this region. This case highlights several important aspects of the diagnosis and nosology of malformations of the mid-hind brain.
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Pontine tegmental cap dysplasia (PTCD) is a very recently described condition, having been first reported in 4 patients by Barth et al[1] in 2007. To date, there have been only 14 cases described.[1-3] The key neuroimaging features of PTCD include hypoplasia of the cerebellar vermis, subtotal absence of the middle cerebellar peduncles, flattening of the ventral pons, a vaulted pontine tegmentum, absent inferior olivary prominence, and a deeper than normal interpeduncular fossa (the "molar tooth sign"). These patients have been reported to have a variety of neurologic abnormalities, including hearing impairment in most if not all patients, facial palsies, bilateral trigeminal nerve dysfunction, oculomotor apraxia, ataxia, impaired swallowing, horizontal gaze palsy, seizures, and central ventilation abnormalities. Commonly reported somatic abnormalities include vertebral anomalies and craniofacial dysmorphisms. These findings are summarized in Table 1.

PTCD belongs to a group of related conditions that share in common malformations of the midbrain hindbrain.[4] A hierarchal scheme has been devised in the classification of these disorders. Under this general category are those conditions that involve changes of both mid- and hindbrain. Under this category are those conditions that share in common the molar tooth sign (MTS).[5] Conditions described in this group include the following syndromes: Joubert, Senior-Loken, COACH, Dekaban-Arima, oro-facial-digital type VI, and encephalocoele with renal cysts. PTCD is now the newest member of this collective.

To date, no known etiology for PTCD has been identified. Laboratory investigations of the reported patients have shown normal karyotypes, detailed metabolic testing, single locus 22q11 fluorescent in situ hybridization (FISH), subtelomeric FISH panel studies, and NTN-1 and DCC gene testing.[1,3] Mildly elevated liver transaminases and serum CK levels have been the only reported laboratory abnormalities. Before our patient, none of the reported patients have had comparative genomic hybridization (CGH) studies.[3]

We report a 16-year-old male with the classic neuroimaging and physical features of PTCD. Array CGH studies showed a very small (96 kb) 2q13 deletion. This represents the 15th case report of a patient with PTCD and the first case of a molecular genetic abnormality as the identified cause of the condition. The deleted region encompasses the NPHP1 gene, a gene reported in association with Joubert syndrome. Thus, this case provides several important insights into the etiology of those conditions associated with the MTS.

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Table 1 Features of Pontine Tegmental Cap Dysplasia, Joubert Syndrome, and the Reported Patient

	Pontine Tegmental Cap Dysplasia	Joubert Syndrome	Joubert Syndrome Type 4	Patient
Head and neck				
Head		Macrocephaly		Relative macrocephaly
Face		Prominent forehead		
		High, rounded eyebrows		
		Hemifacial spasms		
Ears	Hearing loss or deafness in most patients	Low-set ears		Intermittently failed hearing screens
		"Tilted" ears		
Eyes	Oculomotor apraxia in 2 patients	Abnormal, jerky eye movements	Abnormal eye movements	Right esotropia as an infant, now with exotropia
	Nystagmus in 1 patient	Impaired smooth pursuit		
		Impaired saccades	Oculomotor apraxia	
		Oculomotor apraxia	Nystagmus	Amblyopia
		Coloboma of optic nerve	Hypometric Saccades	Anisometropia
		Chorioretinal coloboma		Myopic astigmatism
		Retinal dysplasia (less common)		Nystagmus
		Retinal dystrophy (less common)		
		Epicanthal folds		
		Ptosis		
Nose		Upturned nose		
		Anteverted nostrils		
Mouth		Triangular-shaped open mouth		
		Protruding tongue		
		Rhythmic tongue movements		
		Soft-tissue tumors of the tongue (less common)		
Swallowing/ feeding	Impaired swallowing in 8 patients			
	5 patients required at least temporary use of a nasogastric or gastrostomy tube			
Respiratory		Neonatal breathing dysregulation		
		Hyperpnea, episodic		
		Tachypnea, episodic		
		Central apnea		
Cardiovascular	Mild atrial septal defect in 2			Variant right subclavian artery
Gastrointestinal/ abdomen				Constipation gastroesophageal reflux
Liver		Hepatic fibrosis (less common)		
Genitourinary				
Kidneys		Renal cysts (less common)	Nephronophthisis tubulointerstitial medullary cystic kidney disease	Partial duplication of left kidney
			Renal Failure	
Musculoskeletal				
Hands		Polydactyly, postaxial (less common) missing digital phalanges (less common)		
Feet/legs		Polydactyly, postaxial (less common)		External rotation of right leg
				Deformity of right 3rd toe
Musculature				Right inguinal hernia
Other	Vertebral anomalies in 5			Multiple vertebral and rib anomalies, including hemivertebrae, fused vertebrae, and associated rib anomalies
				Neuromuscular and congenital scoliosis pectus excavatum

Table 1 (continued)

	Pontine Tegmental Cap Dysplasia	Joubert Syndrome	Joubert Syndrome Type 4	Patient
Neurologic				
Central nervous system	Ataxia in 5 Head titubation in 2 Abnormal movements in 1 and no purposeful movements in 1 Seizures in 2 IQ ranged from normal to severe mental retardation	Delayed psychomotor development Mental retardation Ataxia Hypotonia Occipital meningocele (less common) Occipital myelomeningocele (less common) Hypoplasia of brainstem Malformation of brainstem structures MTS on MRI Cerebellar vermis hypoplasia Dysgenesis or agenesis of the cerebellar vermis Deep posterior inderpeduncular fossa Thick and elongated superior cerebellar peduncles	Hypotonia, mild Head "tilt" in infancy Gross motor delay, mild Cognitive impairment, mild Ataxia Impaired balance MTS on MRI Cerebellar vermis hypoplasia Long, thickened cerebellar peduncles	Seizure disorder Developmental delay Hypotonia Head titubation as an infant Hypoplasia of the inferior cerebellum, including the deep white matter, vermis, and middle peduncles MTS on MRI Tethered spinal cord at the level of L4 Ataxia Pontine tegmental cap dysplasia
Behavioral/ psychiatric manifestations	Decreased pain response in 1	Hyperactivity aggressiveness self-mutilation		Bruxism history of "digging" in eyes history of self-abusive behaviors during seizure episodes decreased sensitivity to pain history of oral sensitivity
Miscellaneous		Variable phenotype with genetic heterogeneity	Phenotypically mild from of Joubert syndrome genetic heterogeneity allelic disorder to juvenile nephronophthisis-1	
Molecular basis	Normal karyotype in 8 (2 did not have karyotype listed)	Mutation in the INPP5E gene on chromosome 9q34.3	Deletion in the nephrocystin gene (NPHP1)	99.6-kb deletion at 2q13, including target gene NPHP1

Case Report

Pregnancy and Delivery

This young man was born at 39 weeks via a cesarean section because of the breech position. The pregnancy was complicated only by maternal tobacco use. His family history was significant for a maternal second cousin with spina bifida, a paternal aunt with cystic fibrosis, and a paternal cousin with seizures but who is otherwise developmentally normal.

Growth

He has always been small for his age. He weighed 5 lb 7.5 oz and was 17.5-in long at birth. On physical examination at 16 years of age, his weight and height were both well below the third percentile, with his weight being 4.12 standard deviations below the mean and his height 5.12 standard deviations below the mean. His body mass index was in the 53rd percentile. He had a relative macrocephaly with a head circumference that was between the 25th and 50th percentiles. The patient has been described as exhibiting dysmorphic facial features since infancy with the following findings noted during various physical examinations: cranial frontal bossing and parietal prominence, flattened nasal bridge, large tongue that was frequently protruding from the mouth during infancy, tendency to have an open-mouth appearance, pectus excavatum and broad chest, deformity of the right third toe, external rotation of the right leg, high arched and narrow palate, and prominent ears (Fig 1).

Medical History

As an infant, the patient had gastroesophageal reflux and failure to thrive. He had a Nissen fundoplication and placement of a gastrostomy tube at the age of 1 year 3 months. The gastrostomy tube remains in place but is currently used only when he needs supplemental nutrition when he is sick.

The patient was noted to have a variant right subclavian artery off a left aortic arch on an abdominal imaging study. A subsequent echocardiogram revealed normal intracardiac

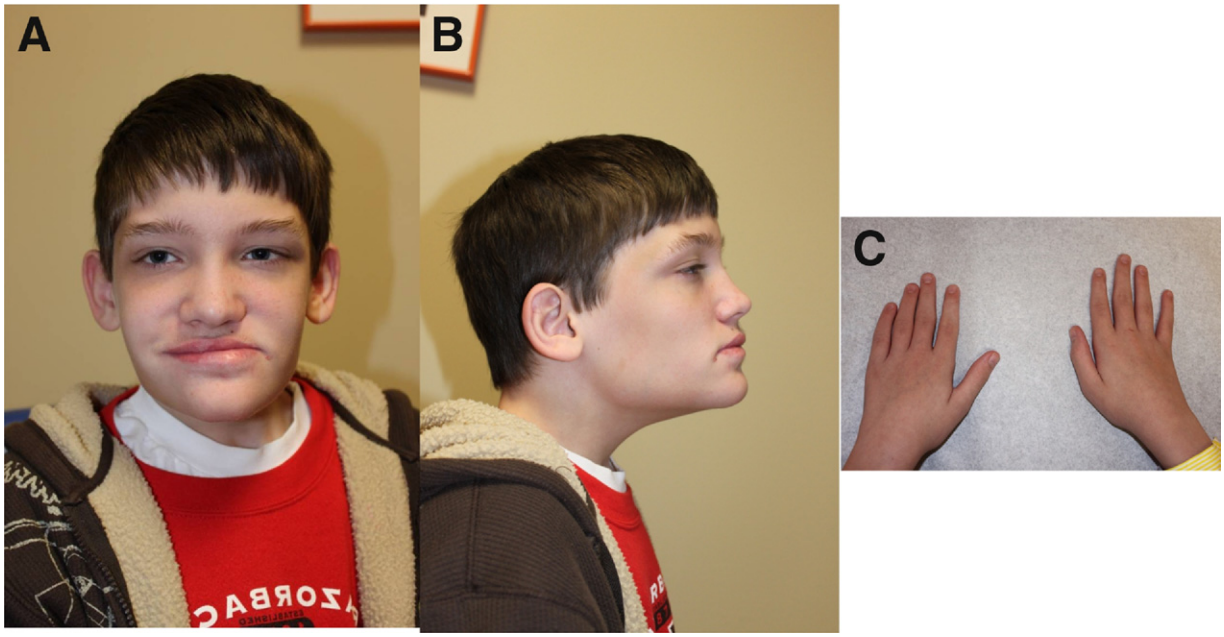

Figure 1 (A) (B) Frontal and lateral facial views and (c) hands of the reported patient. (Used with permission). (Color version of figure is available online.)

anatomy. He underwent the repair of a right inguinal hernia at the age of 3 months. Spinal x-rays have shown multiple vertebral segmentation anomalies, including multiple fused vertebrae and hemivertebrae with associated rib anomalies. X-rays have also revealed hypoplasia of the sacrum. The patient was found to have a low-lying conus at the L4-L5 level with a small syrinx extending from L1 through L3. He had detethering of his spinal cord at the age of 21 months. The patient had a retethering of the spinal cord, possibly because of significant scoliosis, and had a second detethering of the cord performed at 14 years of age. He has had both congenital and neuromuscular scoliosis and underwent posterior spinal fusion at 15 years of age. He has experienced numerous bouts of pneumonia.

Neurologic Assessments

The patient has been seen on multiple occasions over the years by pediatric neurologists. He has been described as having a variety of different neurologic signs and symptoms. He has had significant developmental delay of both motor skills and speech and has been noted to be hypotonic since infancy. He has been consistently noted to have both limb and especially truncal ataxia. He currently ambulates most of the time with the assistance of a reverse walker. As an infant, he had head titubation that resolved as he got older. Other findings early in childhood were brisk deep tendon reflexes, up-going toes, and intermittent spells of hyperpnea. He is reported to look with an upgaze. Abnormalities of the function of cranial nerves V and VII have been suggested. He has a seizure disorder with previous electroencephalograms showing multiple epileptiform discharges from a variety of foci, which is compatible with a diffuse encephalopathy. His most recent electroencephalogram was normal, but it was performed in the awake state only. He is described as having a flat affect although the parents did report occasional smiles. Self-injurious behaviors such as digging at his eyes and biting his lips and tongue have been frequently observed.

Neurosensory

He is followed in the ophthalmology clinic for amblyopia, anisometropia, and myopic astigmatism. As an infant, he was found to have right esotropia. However, more recent examinations have shown exotropia. He also has intermittment pendular nystagmus. He wears glasses. He has intermittently failed hearing screenings.

Evaluation

The patient had been seen several times by clinical genetics, but no specific diagnosis had been determined. Investigation into the etiology of his problems by both genetics and child neurology was significant for many normal tests including prometaphase karyotype, chromosome 15 methylation, sweat test, carnitine/acyl-carnitine studies, fatty acid (short and long chain) studies, leukocyte enzymes, transferrin isoelectric focusing, organic acid and amino acid assessment, and purine/pyrimidine studies.

Magnetic resonance imaging performed during the first year of life showed findings reported as "consistent with Joubert syndrome" (mainly because of the presence of an MTS). However, it was believed that he did not meet full criteria for a diagnosis of Joubert syndrome. This diagnosis was periodically revisited over the years he was followed. Repeat magnetic resonance imaging performed at 15 years of age was interpreted as being compatible with pontine tegmental cap dysplasia (Figs 2 and 3).

An Agilent (Agilent Technologies, Inc., Santa Ciara, CA, USA) human genome CGH 44K oligoarray chip revealed a

copy number change (CNC) characterized as a 96.6-kb deletion at 2q13 (linear location 110,219,766-110,316, 416 bp-hg18) involving the target gene NPHP1.

Discussion

The patient reported here is an example of a frequently occurring presentation, the child with multiple congenital anomalies without a unifying diagnosis. In particular, this case highlights the commonly encountered problem of a case in which the person fits many of the features of a known condition but is not classic for the condition (ie, does not meet diagnostic criteria). In this case, many of the features of Joubert syndrome were noted (Table 1). Over the course of over a decade, this diagnosis was entertained multiple times, but consensus could never be reached.

Two recent advances served to clarify the issues for this patient. First, in 2007, Barth et al[1] reported pontine tegmental cap dysplasia as a newly described entity. Thus, although this patient's magnetic resonance imaging changes were indeed congenital; there was no corresponding medical literature to neatly place his findings into a specific category before the Barth publication. With this description, a diagnosis could finally be made with certainty for this youth. This alone is tremendously helpful information for this family.

Second, the magnitude of the effect of the advent of array CGH as a diagnostic tool cannot be understated. For this patient, and countless others, the identification of a CNC on advanced microarray platforms has proven to be the long-sought answer for which families are looking. The CNC in this patient is quite small (96 kb). In fact, the official interpretation of his microarray study was a CNC of "unknown significance." This type of report is frustratingly common and provides a great deal of angst and uncertainty for both the patient and the physician. Oftentimes, this is as close as one can get in clarifying the situation. The significance of small duplications of deletions oftentimes simply cannot be firmly established given current technology and understanding. In this case, however, we were able to provide the family with more solid information. Looking into the morbid gene map for the deleted region revealed only 2 known functioning genes. One of these happens to be the NPHP1 gene, which is a gene reported to be the cause of Joubert syndrome in 1% to 2% of the cases.[6] This information then allows for the confident assignment of causation in this case with the CNC as the etiology of this young man's constellation of problems. There can be little doubt that the deletion of the NPHP1 gene is causally related to his medical issues.

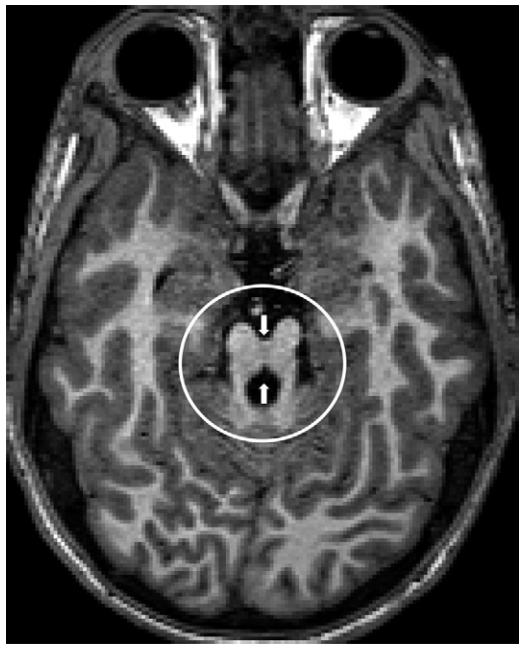

Figure 3 High resolution axial T1 weighted image at the junction of the midbrain and pons demonstrates thinning of both dorsal and ventral surfaces of the brainstem (arrows) imparting a "molar tooth" appearance (circle).

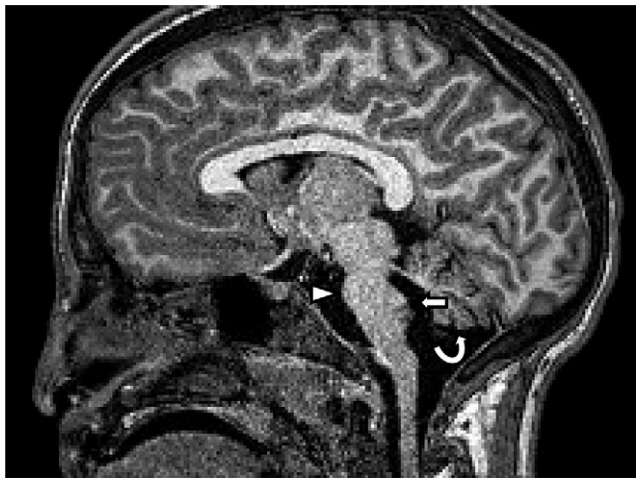

Figure 2 High resolution sagittal T1 weighted image through the midline of the brain, demonstrates hypoplasia of the belly of pons (arrow head) with dorsal pontine contour abnormality (arrow) protruding into the fourth ventricle. Also noted is inferior vermian hypoplasia (curved arrow). These constellation of imaging findings are typical for pontine tegmental cap dysplasia.

Finally, this discovery provides insight into the genetics of these conditions. Joubert syndrome is an autosomal recessive condition. Because this young man was phenotypically believed to be close to Joubert syndrome, a reasonable interpretation for the family would be that it was clearly possible and, in fact, likely that his condition was inherited as an autosomal recessive trait. With the new information from the CGH studies, it is now known that, in fact, this is not a recessive trait in him but rather dominant expression caused by haploinsufficiency. Currently, we are trying to coordinate parental studies. The information obtained from these tests will then allow for definitive recurrence risk counseling for the family.

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