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New Syndrome: A Novel Multiple Congenital Anomaly-Mental Retardation Syndrome with Pierre Robin Sequence and Cerebellar Hypoplasia in Two Sisters

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Abstract

We report on the similar phenotypes and clinical course of two sisters. Both patients had an enlarged cisterna magna suggestive of cerebellar hypoplasia, agenesis/hypoplasia of the corpus callosum, Pierre Robin sequence requiring tracheostomy, camptodactyly, microphthalmia, colobomas, seizures, a distinctive facial appearance, global developmental delay and mental retardation. We propose that the distinct pattern in these sisters constitutes a previously undescribed syndrome of likely autosomal recessive inheritance.

Keywords

new syndrome; congenital anomaly; Pierre Robin sequence; cerebellar hypoplasia; camptodactyly

INTRODUCTION

We report on two sisters with similar phenotypes that overlap Ritscher-Schinzel syndrome (cranio-cerebello-cardiac syndrome) and Toriello-Carey syndrome. The distinct pattern of malformations suggests a provisionally unique syndrome inherited in an autosomal recessive pattern.

CLINICAL REPORTS

Family History

The parents of the 2 sisters described below are healthy without medical problems. The parents are nonconsanguineous and have an unaffected daughter. Maternal history was significant for a spontaneous abortion at approximately 8 weeks gestation.

Patient 1

Precipitous vaginal delivery at home occurred at 37 weeks of gestation. No maternal teratogenic exposures were reported. She was admitted to the neonatal intensive care unit for respiratory distress and found to have multiple anomalies including Pierre Robin sequence with cleft palate, a 2-vessel cord, and abnormal findings on brain magnetic resonance imaging (hypoplasia of the corpus callosum, enlarged posterior fossa, and abnormal cerebellum with normal myelination). Birth weight was 2830 gm (25th centile), length was

50 cm (50th centile), and head circumference was 33 cm (10th centile). She presented with hypoglycemia and hyperbilirubinemia that quickly resolved. Supplemental oxygen was required. Severe gastroesophageal reflux was documented. She was discharged to home at 6 weeks.

At 3 months, her weight was 4.98 kg (25th centile) and her head circumference was 37.5 cm (10th centile). Findings on physical exam (Fig. 1) included brachycephaly with metopic prominence, microphthalmia, down-slanting palpebral fissures, anteverted nares, prominent appearance of the nasal tip with hypoplastic nasal alae, low-set and posteriorly angled ears, narrow ear canals, small mouth with down-turned corners, Pierre Robin sequence, camptodactyly of the fingers with the index fingers overriding the third fingers, hypoplastic flexion creases, congenital hip dysplasia, and lateral deviation of the second toes.

At 21 months her length was 81.5 cm (25th centile), her weight was 10.8 kg (25th centile), and her head circumference was 44.5 cm (<2nd centile). Her head circumference slowly went from the 25th centile at one month of age to the 2nd centile at approximately 8 months of age. She had profound developmental delay (non-regressive). A gastrostomy tube was required due to her feeding difficulties. Ophthalmologic evaluation showed a partial thickness coloboma of the iris inferiorly in the left eye. Other problems included contractures (elbows, wrists, knees and ankles), neuromuscular scoliosis, constipation, history of urinary tract infections, pneumonia requiring hospitalization, and intractable seizures. An echocardiogram showed the left superior vena cava draining to the coronary sinus.

Magnetic resonance imaging (MRI), performed at 2 and 3 years, showed an enlarged cisterna magna, hypoplasia of the anterior corpus callosum, and cerebellar hypoplasia. The cerebellar vermis was intact. In addition, there was some mild volume loss of her cerebral hemispheres (Fig. 2).

She was evaluated at 4 years and 8 months of age in the genetics clinic (Fig. 3). Her length was 103.5 cm (25th centile), her weight was 17.9 kg (50th centile), and her head circumference was 49 cm (25th centile). She was still significantly developmentally delayed (no speech or ambulation) with mental retardation. She had persistent intractable seizures characterized by sudden marked reduction in breathing, gasping respirations, unresponsiveness with the development of small amplitude twitching of the limbs. An electroencephalogram showed diffuse generalized slowing with multifocal epileptiform discharges, much more prevalent on the left side. She was noted to have worsening visual acuity thought to be central in origin, horizontal gaze paresis, and myopia. Ophthalmologic evaluation under anesthesia showed the partial thickness iris coloboma in the left eye, mild nuclear lens opacities in both eyes, and tilted appearing optic nerves. She was diagnosed with central hypoventilation and a tracheostomy had been performed due to respiratory compromise from the Pierre Robin sequence. Frequent urinary tract infections led to imaging studies that showed normal kidney structure and no vesicoureteral reflux, although pooling of urine in the vagina was noted. Her parents reported a high pain threshold. The contractures of her elbows, wrists, knees and ankles had worsened.

High resolution banded chromosomes at the 525-band level were normal (46,XX). Array comparative genomic hybridization using patient DNA and a 1 Mb human BAC array chip (Spectral Genomics™, Houston, TX) did not identify an imbalance.

Patient 2

This sib had a prenatal ultrasound at 21-weeks gestation that showed abnormal posturing of her hands, mild hydrocephalus with probable agenesis of the corpus callosum, micrognathia,

and a two-vessel cord. Prenatal vitamins were taken throughout pregnancy. Occasional use of alcohol and tobacco during the first month of pregnancy was reported.

Spontaneous vaginal delivery occurred at 38 weeks gestation. Pierre Robin sequence with cleft palate was noted at birth, and she was intubated, eventually requiring tracheostomy. Seizure activity was noted shortly after birth and an electroencephalogram showed some asymmetry in the amplitude, more prominent on the left. Her birth weight was 3120 grams (50th centile), birth length was 52 cm (90th centile), and birth head circumference was 34.5 cm (90th centile). MRI showed findings similar to her sister (corpus callosum dysgenesis, and cerebellar hypoplasia with an intact vermis) (Fig. 4).

Findings on physical exam (Fig. 5) included a metopic prominence, shallow orbits, microphthalmia, bilateral optic nerve colobomas, down-slanting palpebral fissures, anteverted nares, prominent appearance of the nasal tip with hypoplastic nasal alae, lowset and posteriorly angled ears, stenotic ear canals, small mouth with down-turned corners, Pierre Robin sequence (requiring tracheostomy), camptodactyly of the fingers with the index fingers overriding the third fingers, hypoplastic flexion creases, mild hypoplasia of superior labia majora, and lateral deviation of the second toes. An echocardiogram showed an atrioseptal defect and a left superior vena cava draining to a dilated coronary sinus. Results of high resolution banded chromosomes at the 550 band-level were normal (46,XX) and fluorescence in-situ hybridization with probes from all subtelomeric chromosomal regions and the 22q11 region were normal.

She was again evaluated at 6 months of age. Her height was 63.7 cm (25th centile), her weight was 6.2 kg (10th centile) and her head circumference was 39 cm (<2nd centile). She was developmentally delayed and did not roll over or sit. She was diagnosed with gastroesophageal reflux with aspiration and required nasogastric feeds. A gastrostomy tube and fundoplication were planned. She had persistent seizures with generalized convulsive movements. She also had a history of bronchiolitis requiring intubation, and pneumonia requiring hospitalization since her last evaluation.

DISCUSSION

The two patients described in this report have strikingly similar phenotypes (Table I). The occurrence of such similar phenotypes in two sisters (born to unaffected parents) suggests an autosomal recessive pattern of inheritance, although parental gonadal mosaicism cannot be excluded.

Differential diagnoses for the two siblings were considered. Features of the brain abnormalities in our patients fit into the constellation of cerebellar region abnormalities encompassing a continuum of defects often described as the Dandy-Walker malformation, Dandy-Walker variant, or a simple enlarged cisterna magna [Barkovich et al., 1989; Chitayat et al., 1994; Patel and Barkovich, 2002]. The Dandy-Walker malformation has been associated with many underlying diagnoses, and Chitayat et al. tabulated over 100 conditions associated with a Dandy-Walker malformation [1994]. A specific single gene disorder or multiple malformation syndrome with the same spectrum of findings described in our two patients was not readily recognized, but many of the clinical features of our two patients are similar to some of the findings of patients with Ritscher-Schinzel syndrome and Toriello-Carey syndrome.

Ritscher-Schinzel syndrome was first described in 1987 in a report of two sisters with a Dandy-Walker (like) malformation, atrio-ventricular septal defect and a similar pattern of craniofacial anomalies [Ritscher et al., 1987]. In 1989, another case was reported and described as 3C dysplasia (noting a triad of cranio-cerebello-cardiac abnormalities) [Verloes

et al., 1989]. In 2001, Leonardi et al. reviewed all previously reported cases of Ritscher-Schinzel or 3C syndrome and described 4 new cases (a total of 28 cases), and attempted to define minimum diagnostic criteria. They proposed that a patient with Ritscher-Schinzel syndrome must minimally manifest the following: 1. Congenital heart malformation(s) other than a patent ductus arteriosus alone; 2. Dandy-Walker malformation, cerebellar vermis hypoplasia, or enlarged cisterna magna; 3. Cleft palate, ocular coloboma, or four of the following: prominent occiput, prominent forehead, hypertelorism, micrognathia, down-slanting palpebral fissures, and depressed nasal bridge [Leonardi et al., 2001]. Leonardi et al. [2001] further clarified that the diagnosis could be made with just two systems affected if there is a sibling with Ritscher-Schinzel syndrome, recognizing that phenotypic variability may exist. This is supported by the report of two siblings by Marles et al. [1995] in which one sibling had a normal head sonogram while the other had a Dandy-Walker malformation (both with heart malformations and colobomas).

One of our patients had a heart malformation (an atrioseptal defect with a left superior vena cava draining to a dilated coronary sinus), but the older affected sister only had a left superior vena cava draining to the coronary sinus. Cardiac malformations are a relatively consistent finding in the Ritscher-Schinzel syndrome. Our two patients may represent phenotypic variability of Ritscher-Schinzel syndrome, but the other clinical findings are beyond those observed in Ritscher-Schinzel syndrome.

Toriello and Carey [1988] described an autosomal recessive disorder with agenesis of the corpus callosum, telecanthus, short palpebral fissures, a small nose with anteverted nares, Pierre Robin sequence, laryngeal anomalies, cardiac defects, brachydactyly and hypotonia. Barisic et al. [2003] reviewed the 16 reported cases at that time in addition to two new cases. Their review reported that 17/18 had a cardiac defect and 10/13 had x-ray skeletal defects. Most of the major anomalies seen in Toriello-Carey syndrome are midline defects [Chinen et al., 1999] with some reports of anal, genitourinary and laryngeal anomalies (not seen in the herein reported sibs) [Jespers et al., 1993; Aftimos and McGanghran, 2001]. Our patients lack some of the constellation of features seen in Toriello-Carey syndrome including the lack of laryngeal anomalies, gastrointestinal anomalies, and characteristic facial appearance [Toriello et al., 2004].

Joubert syndrome includes cerebellar vermis hypoplasia and patients can have cleft lip or palate in addition to hypotonia, abnormal breathing, and/or abnormal eye movements [Kosaki et al., 1997; Leonardi et al., 2001], but the herein described siblings lack the abnormal eye movements, ataxic movements, or hyperpnea of Joubert syndrome. In addition, our sibs do not have the hypoplasia of the vermis as observed in Joubert syndrome.

Holder-Espinasse et al. reviewed 117 patients with Pierre Robin sequence and 48% were classified as isolated, 35% were classified as syndromic (65% of syndromic cases due to Stickler syndrome, deletion 22q11.2 spectrum, Treacher Collins syndrome and teratogenic syndromes), and 17% were classified as having other associated anomalies [2001]. The fact that 17% of the patients reviewed with Pierre Robin sequence had another associated anomaly without a recognizable syndrome [Holder-Espinasse et al., 2001] suggests that there are many other undelineated syndromes or syndromes that are not readily recognizable in association with Pierre Robin sequence.

The sisters presented in this report have some similarities to the Ritscher-Schinzel syndrome and the Toriello-Carey syndrome. Perhaps the additional findings in our patients represent a larger contiguous gene deletion. We propose, however, that the distinct similarity and pattern in these siblings suggest a previously undescribed syndrome of autosomal recessive inheritance.

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Fig. 1.
Patient 1 at 3 months of age.

Fig. 2. Magnetic Resonance Imaging of Patient 1. Images showed an enlarged cisterna magna, cerebellar hypoplasia with an intact cerebellar vermis, and hypoplasia of the anterior corpus callosum. (**A:** At 2 years. **B:** At 3 years.)

Fig. 3.
Patient 1 at 4.5 years of age. **A:** Lateral view of face. **B:** Frontal view. **C:** View of hand.

Fig. 4. Magnetic Resonance Imaging of Patient 2 during neonatal hospitalization showed cerebellar hypoplasia and corpus callosum dysgenesis.

Fig. 5.
Patient 2 during neonatal hospitalization **A:** Frontal view of face. **B:** Anterior view of foot.
C: View of hand.

Table I**Clinical Findings in Two Sisters**

Findings	Patient 1	Patient 2
Craniofacial		
Coloboma	iris	optic nerve
Microphthalmia	+	+
Down-slanted palpebral fissures	+	+
Low-set and posteriorly angled ears	+	+
Anteverted nares	+	+
Hypoplastic nasal alae	+	+
Small mouth	+	+
Down-turned corners of the mouth	+	+
Pierre Robin sequence with cleft palate	+	+
CNS		
Seizures	+	+
Hypoplasia of anterior corpus callosum	+	+
Enlarged cisterna magna	+	+
Cerebellar hypoplasia	+	+
Other		
Atrioseptal defect	-	+
LSVC draining to coronary sinus	+	+
2-vessel cord	+	+
Camptodactyly	+	+
Congenital hip dysplasia	+	-
Scoliosis	+	-
Developmental delay	+	+
Mental retardation	+	unknown *

left superior vena cava (LSVC); + = present; - = absent;

* too young