Asymmetric crying facies associated with congenital hypoparathyroidism and 22q11 deletion

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Asymmetric crying facies is caused by congenital hypoplasia or agenesis of the depressor anguli oris muscle. Associations of this facial defect with major congenital anomalies have been reported, most commonly in the cardiovascular system and less frequently involving the genitourinary, musculoskeletal, cervicofacial, respiratory, and rarely, the endocrine system. CATCH 22 is a medical acronym for cardiac defects, abnormal facies, thymic hypoplasia, cleft palate and hypocalcemia and a variable deletion on chromosome 22q11. The deletion within chromosome region of 22q11 may occur in patients with dysmorphologic and cardiological syndromes: DiGeorge syndrome, velocardiofacial syndrome and conotruncal anomaly face syndrome. We report a newborn infant who had asymmetric crying facies associated with congenital hypoparathyroidism, severe neonatal hypocalcemia and tetralogy of Fallot. Genetic confirmation of chromosome 22q11 deletion was made.

Key words: asymmetric crying facies, hypoparathyroidism, hypocalcemia, tetralogy of Fallot, 22q11 deletion, newborn/infant.

Asymmetric crying facies (ACF) is caused by congenital hypoplasia or agenesis of the depressor anguli oris muscle (DAOM) on one side of the mouth. Patients with this anomaly usually present with a droop of one corner of the mouth on the intact side while crying or grimacing. Forehead wrinkling, eye closure and nasolabial fold depth remain intact and equal on both sides. Affected infants suck well without drooling from either corner of the mouth. These findings differentiate this disorder from facial nerve palsy. Diagnosis can be established by clinical picture and/or an electromyographic study.

The recognition of the importance of parathyroid hormone (PTH) deficiency presenting during the first weeks of life has grown with improved clinical laboratory techniques. Cytogenetic and molecular genetic diagnosis have provided the means to characterize several forms of congenital hypoparathyroidism.

We report this case to stress the importance of 22q11 deletion in various multisystem disorders.

Case Report
A seven-day-old male infant having cardiac murmur and convulsion was referred to our University Hospital. The baby was born at term by cesarean section weighing 3600 g. He was the first child of a healthy 22-year-old mother and a healthy 24-year-old father. There was no consanguinity between parents.

At admission to our pediatric emergency service, he had focal clonic seizures. The baby was irritable. The systolic ejection murmur was heard at the left sternal border. Total calcium and phosphorus concentrations were 5.5 mg/dl and 7.7 mg/dl, respectively. The level of intact PTH was inappropriately low, 0.01 pg/ml (normal range 6.8 pg/ml). X-ray examination of the chest revealed normal heart size, elevation of the cardiac apex, concavity in the region of the main pulmonary artery, diminished pulmonary vascularity and normal thymic shadow. Echocardiography established the diagnosis of tetralogy of Fallot. CD3 (66.0%-4250/mm³), CD4 (42.4% 2730/mm³), and CD8 (22.4%-1442/mm³)
T-cell counts were normal. Fluorescent in situ hybridization testing provided genetic confirmation of chromosome 22q11 deletion.

Other laboratory investigations including hemoglobin, hematocrit, acid-base values, glucose, electrolytes, urea, creatinine, SGOT, SGPT, magnesium, total protein, albumin and urine analysis were normal.

After initial treatment with intravenous infections of 8 ml of a 10% solution of calcium gluconate at the rate of 1 ml/min, we started 50,000 IU vitamin D2 and oral calcium gluconate (75 mg Ca/kg) divided into six feedings. With this therapy, the calcium concentration increased to 9.6 mg/dl and the phosphorus concentration. Decreased to 5.8 mg/dl.

After cessation of seizure activity, asymmetric crying facies was detected. The left corner of the mouth drew left and downward while the right moved little or not at all. Palpable thinning of the right lower lip near its left margin was noted (Figs. 1, 2). Electromyographic examination of the right depressor anguli oris muscle showed diminished motor unit activity.

Discussion

Congenital hypoplasia or absence of the AO is a minor congenital anomaly causing ACF. This anomaly is easily recognizable clinically in newborns when crying but becomes less obvious with increasing age as smiling and functions of the risorius and other facial muscles dominate the child’s facial expressions. It must be distinguished from facial palsies of traumatic and central origin. In 1969, Cayler reported an association between hypoplasia of the DAOM and congenital heart diseases and coined the term “cardiofacial syndrome”. The interesting aspect of this abnormality lies in the frequently associated abnormalities. Cardiac, urogenital, musculoskeletal, respiratory, cervicofacial and endocrine defects have been described in cases with ACF. Therefore it is suggested that ACF can be used as an index of other congenital malformations.

Hypoparathyroidism is a rare cause of hypocalcemia in the newborn period. Other biochemical findings include hyperphosphatemia, hypomagnesemia, and a normal or low alkaline
phosphatase. The diagnosis is confirmed by finding of low or absent immunoreactive PTH levels. This condition may be familial, with X-linked recessive, autosomal dominant, and recessive patterns of inheritance described. Hypoparathyroidism, thymic aplasia, congenital abnormalities of the heart and great vessels and other dysmorphic features may result from deletions within chromosome 22q11.

Microdeletion in chromosome 22q11 is one of the most frequent known intrachromosomal deletions, with an estimated incidence of 1:4,000-5,000. There is a wide variability in the clinical features, but most common are conotruncal cardiac anomalies present in about 75% of cases. Hypoparathyroidism is another typical finding well known since the first report of DiGeorge in 1965, and hypocalcemia has been reported in up to 60% of patients with monosomy 22q11. This deletion has been identified in velocardiofacial syndrome (VCFS) (cleft palate, learning disabilities, cardiac anomalies, craniofacial dysmorphic features), isolated congenital heart disease, isolated congenital hypoparathyroidism and asymmetric crying facies. The same deletion has been described with variability in phenotypic expression, even intrafamilial. It has been suggested that all these conditions should be included under the acronym “CATCH-22” (cardiac abnormality, abnormal facies, thymic hypoplasia, cleft palate and hypocalcemia). The basic embryologic fault in these disorders is a developmental field defect of the facial neural crest tissues, involving the third and fourth pharyngeal arches.

Alikaşifoğlu et al. studied 22q11 deletion in 32 patients with conotruncal cardiac anomalies. A 22q11 deletion was detected in two patients. One of the two 22q11 del (+) patients had unilateral facial nerve palsy. A large number of cases with chromosome 22q11 microdeletions who have an asymmetric crying facies have been reported.

These defects may be difficult to diagnose because many of them are mild or occult. In our patient we detected ACF associated with congenital hypoparathyroidism, severe neonatal hypocalcemia, tetralogy of Fallot and 22q11 deletion without apparent dysmorphic features. We were unable to find thymic hypoplasia or aplasia, and CD3, CD4 and CD8 T-cell counts were normal.

As the chromosome 22q11 microdeletion syndromes are multisystem disorders, making an early diagnosis is important from an anticipatory guidance perspective, and these individuals are at increased risk of requiring medical interventions. In addition, the microdeletion may be inherited as a dominant trait; therefore, careful examination of first-degree relatives is indicated. The incidence of chromosome 22q11 microdeletions, in individuals with apparently isolated asymmetric crying facies, is not precisely known. In the interim, in addition to the recommendations by Lahat and colleagues, careful dysmorphology assessments and consideration of investigations for chromosome 22q11 deletions are indicated in all newborns with asymmetric crying facies.

REFERENCES