Neurologic and Gastrointestinal Dysfunction in Cardio-facio-cutaneous Syndrome: Identification of a Severe Phenotype

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Controversy exists over the distinction between cardio-facio-cutaneous (CFC) syndrome and Noonan syndrome (NS). Several authors have suggested that they are different phenotypes of the same condition. We present the cases of two patients with CFC syndrome to show that it is a distinct condition with a unique combination of findings and a more complex natural history. These patients, both girls, were born with signs of fetal edema following pregnancies complicated by polyhydramnios. Each has short stature with relative macrocephaly; fuzzy, sparse hair; and the typical craniofacial features, including a square forehead. Both have heart abnormalities, failure to thrive, and severe feeding problems requiring gastrostomy. They are markedly hypotonic and developmentally delayed. They show signs of frequent eyelid fluttering and have oral aversion, tactile hypersensitivity, and sensory integration abnormalities. Keratosis pilaris, the characteristic skin symptom, is also present in both patients. In a review we identified 56 cases of CFC syndrome. We scored these cases by 10 clinical criteria and identified a subset with a specific, severe phenotype distinct from that of NS. The serious neurologic and gastrointestinal complications, in addition to the skin abnormalities and characteristic facies in this group, clearly separate these patients from the mildly affected ones, most of whom appear to have NS or another syndrome. We discuss the differences between the severe CFC phenotype and those of overlapping conditions. We set forth stringent diagnostic criteria for CFC syndrome, the initial step toward identifying a molecular basis for this condition. Am. J. Med. Genet. 95:135–143, 2000. © 2000 Wiley-Liss, Inc.

KEY WORDS: macrocephaly; keratosis pilaris; eyelid fluttering; gastrointestinal; polyhydramnios; hypotonia

INTRODUCTION

Clinical geneticists play a crucial role in syndrome delineation and definition. Data gathered in such studies provide the foundation leading to insights into pathogenesis and cause. To approach an identification of the molecular basis of cardio-facio-cutaneous (CFC) syndrome, we identified an extreme phenotype and set forth stringent diagnostic criteria. CFC syndrome was first reported by Reynolds et al. [1986] in eight patients with the following signs and symptoms: a characteristic facial appearance; ectodermal abnormalities; growth failure; developmental disability or mental retardation; growth retardation (height/weight < 3%); relative macrocephaly; thin and sparse hair; skin lesions, usually keratosis pilaris; eye abnormalities, including ptosis, strabismus, and nystagmus; webbing of the neck; congenital heart defects, including pulmonic stenosis and atrial septal defect; splenomegaly; cutaneous vascular malformations; and hernias.

The craniofacial anomalies of CFC syndrome include a high cranial vault with bitemporal narrowing; hypoplasia of the supraorbital ridges with downward-slanting palpebral fissures, epicanthal folds, and ptosis; depressed nasal bridge with anteverted nares; posteriorly angulated auricles with hypertrophy of helices; high, arched palate; and sparse, curly hair.

We were prompted to review CFC syndrome after evaluating two patients with apparent CFC syndrome who showed signs of severe impairment but with several features not reported previously.
MATERIALS AND METHODS

Patient 1

Patient 1 is a girl born at 33 weeks of gestation to a 24-year-old primagravida mother who experienced polyhydramnios requiring several reduction amniocenteses; ultrasonography showed a cystic hygroma. The chromosomes were 46,XX. The infant’s birth weight was 1,945 g, her length was 42 cm, and her head circumference (OFC) was 29.5 cm, all between the 10th and 50th percentiles for gestational age. An echocardiogram showed two small atrial septal defects, and renal ultrasonography showed a dilated collecting system.

On examination, the infant had sparse eyebrows; slightly downward-slanting palpebral fissures with inferior epicanthal folds; an apparently low-set, abnormally modeled, upturned nose; a short neck with excess skin; and a shield chest with widely spaced, hypoplastic nipples (Fig. 1A,B). She had severe feeding problems, with poor suck, and gastroesophageal reflux, which caused failure to thrive. Fundoplication and gastrostomy were performed when the infant was 11 months of age. She then developed marked oral aversion. She later required a tracheostomy for laryngotracheomalacia. Cardiology follow-up at 4½ months found hypertrophic cardiomyopathy. An ophthalmology evaluation showed nystagmus, with cortical visual impairment and structurally normal eyes. Chromosomes at the 500-band resolution were 46,XX.

Magnetic resonance imaging confirmed plagiocephaly, with right occipital flattening; absence of the corpus callosum, increased ventricular size, and decreased cortical volume. A cranial magnetic resonance venogram, undertaken because of unusual cephalic venous engorgement, showed a focal area of stenosis in the midportion of the left internal jugular vein. The infant was severely developmentally delayed, with marked hypotonia and no language. By 13½ months of age she could not sit and could roll over only halfway.

On physical examination at age 3 years, her height was 34 inches, (< 3rd percentile), and her weight was 27 pounds, 6 ounces (10–25th percentile). She had a box-shaped forehead, with bitemporal constriction; hypertelorism with downward-slanting palpebral fissures; bilateral ptosis; hypoplastic supraorbital ridges; and posteriorly angulated ears with thick helices. The nose had a rounded tip with anteverted nares. The pal-
ate was high and arched and the neck broad and webbed, with a tracheostomy (Fig. 2A,B). Her chest had a pectus carinatum deformity, with widely spaced, hypoplastic nipples. Cardiac auscultation showed a grade II/VI murmur. Her hair was very sparse, thin, and curly. Her skin was hyperkeratotic, with small erythematous papules on the face and limbs (Fig. 2B). She was hypotonic with horizontal nystagmus, and she had unusual recurrent episodes of eyelid fluttering brought on by minimal stimulus. She had severe oral aversion and tactile hypersensitivity. She could sit independently but did not stand. She had just started to clap her hands to music and had a one-word vocabulary.

At the age of 4 1⁄2 years (Fig. 3A,B), her height was 90 cm (< 3rd percentile), her weight was 15.2 kg (10–25th percentiles), and her OFC was 49.5 cm (25–50th percentiles). She tolerated a Passey-Muir valve over the tracheostomy, allowing for vocalization, and her tactile hypersensitivity had decreased significantly. She could stand with assistance, but she was not yet toilet trained. The hypertrophic cardiomyopathy was stable with no outflow tract obstruction, but kyphosis with a gibbus had developed. Renal function was normal.

Patient 2

Patient 2 was born at 35 weeks' gestation to a 29-year-old gravida 3, para 2 mother, following a pregnancy complicated by severe polyhydramnios requiring several therapeutic amniocenteses; the mother experienced preterm labor. The infant was large for gestational age, with severe congenital edema and macrocephaly. Her birth weight was 3,555 g (> 90th percentile), her length was 48.5 cm (90th percentile), and her OFC was 36 cm (> 90th percentile).

At 5 days of age she had facial edema, a squareshaped forehead, posteriorly angulated ears, sparse eyebrows, ocular hypertelorism, slightly narrow palpebral fissures, prominent glabellar and nasal bridge hemangiomas, excess nuchal skin, and decreased axial tone (Fig. 4A,B). She failed to thrive and had gastrointestinal reflux, necessitating gastrostomy tube placement at 5 months of age. Severe oral aversion developed, and a first-degree laryngeal cleft was diagnosed. The infant had profound congenital hypotonia, global developmental delay, and optic nerve hypoplasia with severe visual impairment (20/300 vision). Renal ultrasonography showed left hydronephrosis, an echocardiogram showed abnormal mitral and tricuspid valves,
and brain magnetic resonance imaging showed diffuse cerebral atrophy. A dermatology evaluation indicated generalized keratosis pilaris.

At age 4 1/2 years of age, her height was 95 cm (< 2nd percentile), her weight was 31.5 pounds (5th percentile), and her OFC was 50.5 cm (50th percentile). She had a square forehead, with right occipital flattening; sparse, fuzzy hair; and mild hypertelorism (Fig. 5A,B). In addition, she had a prominent left hemithorax, grade 3/6 systolic ejection murmur, and a protuberant abdomen with a gastrostomy tube. Her skin evidenced hyperkeratosis pilaris (Fig. 6), and she had a reddened face. Neurologic findings included mild hypotonia, poor oral motor coordination, the same unusual eyelid fluttering noted in patient 1, and global developmental delay. She could pull to a sitting position and achieve a four-point stance. She cooed and laughed but did not speak words. In both cases the family histories were unremarkable.

We reviewed 56 cases from the literature [Neri et al., 1987; Reynolds et al., 1986; Chrzanoska et al., 1989; Graham et al., 1989; Mucklow, 1989; Sorge et al., 1989; Gross-Tsur et al., 1990; Bottani et al., 1991; Corsello et al., 1991; Fryer et al., 1991; Matsuda et al., 1991; Fryns et al., 1992; Ghezzi et al., 1992; Kajii et al., 1992; Somer et al., 1992; Turnpenny et al., 1992; Borradori et al., 1993; Lopez-Rangel et al., 1993; Raymond and Holmes, 1993; Young et al., 1993; Ward et al., 1994; Krajewska-Walasek et al., 1996; Lecca et al., 1996; Leichtman, 1996; Manoukian et al., 1996; McDaniel et al., 1997; Sabatino et al., 1997], which had been diagnosed as CFC. We scored each case, using 10 major clinical findings of the syndrome and giving one point for each finding. We employed original major signs of relative macrocephaly; characteristic facial features; growth retardation; cardiac defect; sparse, curly hair; and neurologic impairment/DD [Reynolds et al., 1986]. We included the skin changes only when they were identified as hyperkeratotic. To these original eight criteria, we added gastrointestinal dysfunction, ocular abnormalities/dysfunction, and a history of polyhydramnios (Table I).

**RESULTS**

Our review yielded the results in Table II. Twelve of 56 cases had a score of ≥ 7 points, associated with a severe CFC phenotype. Seven had a score of 5–6 points, with an intermediate phenotype. These cases, in particular, illustrate the overlap between CFC and

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Fig. 3. **A**: Frontal view of patient 1 at age 4 1/2. **B**: Lateral view of patient 1 at age 4 1/2.
Fig. 4. A: Frontal view of patient 2 at age 5 days. B: Lateral view of patient 2 at age 5 days. Note the excess nuchal skin.
Noonan syndromes. Finally, 38 cases, over half of the total, had a variable and generally much milder CFC phenotype, which was often more reminiscent of either Noonan syndrome or another multiple malformation syndrome.

**DISCUSSION**

The differential diagnosis of CFC syndrome includes Noonan, Costello, and several other malformation syndromes. Controversy exists concerning whether CFC and Noonan syndromes are distinct conditions or different phenotypes of the same condition [Fryer et al., 1991; Neri et al., 1991; Leichtman, 1996; Lorenzetti and Fryns, 1996; Neri and Zollino, 1996]. We noted considerable variability in phenotype among the published cases of CFC syndrome, from those with extremely mild manifestations to those associated with extensive medical problems.

The clinical overlap of CFC and Noonan syndromes has been discussed at length by several authors, most notably by Neri et al. [1991] and later by Wieczorek et al. [1997]. Both of these articles include detailed comparisons of the incidence of specific clinical findings in each syndrome; in the article by Wieczorek et al., Costello syndrome is delineated as well. The conclusion of both articles is that even though CFC and Noonan syndromes share several manifestations, most notably cardiac defects, similar craniofacial findings, and growth retardation, there are differences between the two conditions, and they should be regarded as separate conditions. We agree with this conclusion, because our stricter diagnostic criteria have allowed us to identify a severe CFC phenotype that has little clinical overlap with that of Noonan syndrome.

There exist parallels to our work in the study of the diagnostic criteria and natural history of Sotos syndrome published by Cole and Hughes [1993]. In this report the authors state that the lack of specificity of diagnostic criteria for Sotos syndrome is the central issue. There are many children who appear abnormal, with macrosomic, hypotonic, features, not all of whom have Sotos syndrome. Before the more specific diagnostic criteria put forth in this study, Sotos syndrome was overdiagnosed. Likewise, in the case of CFC syndrome, all the signs are nonspecific, including failure to thrive, developmental delay, and cardiac defects. Several manifestations may be due to the effects of fetal edema and are therefore also nonspecific and overlap with
those of Noonan syndrome. Only by using more stringent diagnostic criteria have we been able to identify the severe phenotype of CFC syndrome described here.

A comparison of CFC and Noonan syndromes using our diagnostic criteria shows striking differences. A history of polyhydramnios was seen only in the severe CFC cases (10/14), and in our patients this condition was severe enough to require reduction amniocentesis. Polyhydramnios is not typical in Noonan syndrome, though one review article by Sharland et al. [1992] documented it in 33% of their patients. This figure has not been confirmed in other Noonan studies [Allanson et al., 1985; Mendez and Opitz, 1985; Allanson, 1989]. Relative or absolute macrocephaly is also a key feature seen only in CFC syndrome (14/14 severe phenotype cases).

Ocular and auricular abnormalities are features of both conditions, and there is a somewhat similar facial appearance. Patients with CFC syndrome tend to have a more boxy and taller forehead with bitemporal constriction, which is not typical of Noonan syndrome. The evolving phenotype of Noonan syndrome has been well documented in a study by Allanson et al. [1985] and includes several characteristics not seen in CFC syndrome. In both conditions the eyes are described as hyperteloric with downward-slanting palpebral fissures and, occasionally, eyelid ptosis. In Noonan syndrome the lids often are described as thick and hooded, whereas in CFC syndrome the orbits have a more shallow appearance. The facial structure in Noonan syndrome is characterized as triangular later in childhood, with lengthening of the chin, which is not characteristic of CFC syndrome. There have been no long-term follow-up reports on adult patients with CFC syndrome, to allow for description of the changing phenotype with age. We agree with the comments of several authors that the facial phenotype is not the distinguishing characteristic of CFC syndrome and may be the “congenital lymphedema face,” that is, the common phenotypic end point of prenatal-onset lymphedema, as described by Opitz [1986].

In both conditions there are heart malformations, but valvular pulmonic stenosis is the hallmark of Noonan syndrome. In CFC syndrome several cardiac anomalies have been reported, including valvular pulmonic stenosis and septal defects. Our series of severely affected patients had a wide variety of heart abnormalities, listed in Table III. The similar heart defects in both conditions may be the result of altered blood flow due to lymphatic obstruction, as proposed by Witt et al. [1987].

Severe feeding problems with gastroesophageal reflux, vomiting, and oral aversion, often necessitating gastrostomy tube placement, are typical only in CFC syndrome. While failure to thrive is common in infancy in patients with Noonan syndrome, it is not characterized by severe feeding problems. The gastrointestinal dysfunction in CFC syndrome was noted in an article by McDaniel and Fujimoto [1997], who reported the case of a patient with CFC syndrome and intestinal malrotation. They found digestive problems in 26 of 57 reported patients with CFC. The most common finding was feeding difficulty, found in 15 patients. In our series of patients with the severe phenotype, seven of 14 patients had feeding problems with vomiting, and failure to thrive was seen in all 14. While short stature is seen in 50% of Noonan syndrome patients, it typically is associated with normal weight measurements, especially in childhood and later years. CFC syndrome patients have failure to thrive beginning in infancy, with height and weight measurements below the fifth percentile.

Ectodermal abnormalities are present in both conditions, but they, too, differ in type. Both conditions manifest curly hair, but it is typically thin and sparse

<table>
<thead>
<tr>
<th>TABLE 1. Diagnostic Criteria for Cardio-facio-cutaneous Syndrome—Severe Phenotype</th>
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<tr>
<td>Macrocephaly</td>
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<tr>
<td>Characteristic facial features</td>
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<tr>
<td>Growth retardation</td>
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<tr>
<td>Cardiac defect</td>
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<tr>
<td>Sparse, curly hair</td>
</tr>
<tr>
<td>Neurologic impairment/developmental delay</td>
</tr>
<tr>
<td>Gastrointestinal dysfunction</td>
</tr>
<tr>
<td>Ocular abnormalities/dysfunction</td>
</tr>
<tr>
<td>History of polyhydramnios</td>
</tr>
<tr>
<td>Hyperkeratotic skin lesions</td>
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Fig. 6. Hyperkeratotic skin lesions on the knee of patient 2.
in CFC and thick and woolly in Noonan syndrome. In Noonan syndrome café-au-lait spots and nevi are common, whereas hyperkeratotic lesions are classic in CFC. Some patients with CFC syndrome reportedly have had cutis laxa and dark skin pigmentation, which are characteristic of Costello syndrome. The typical finding in CFC syndrome is keratosis pilaris, a severe condition involving extensive areas of the body. A condition called keratosis pilaris atrophicans facei (or ularythema oophyrogenes, a congenital form of follicular keratosis), affecting only the cheeks and eyebrows, has been reported in association with woolly hair both with and without Noonan syndrome. One study found this association in 14% of Noonan syndrome patients, which serves as further evidence of the clinical overlap of these two conditions.

The degree of neurologic impairment in CFC syndrome is one of the most significant findings that distinguishes it from Noonan syndrome. The neurologic impairment in CFC syndrome is typically severe, with profound hypotonia, and generally mild in Noonan syndrome. Mental retardation is seen in approximately 25% of Noonan syndrome patients and is usually mild, whereas most patients with the severe CFC phenotype have significant global developmental delay and/or mental retardation. Structural central nervous system changes also may be a common cause of neurologic problems in CFC syndrome, as illustrated by the abnormal findings in 10 of 14 patients with severe disease symptoms in our series. Nine patients exhibited cerebral atrophy with enlarged ventricles, and our patient 1 also had an absent corpus callosum. No cranial imaging was performed in the other four patients.

Central nervous system malformations, in fact, may be underreported in CFC syndrome, as noted by Wiecezorek et al. [1997]. In their review, no computed tomography scan was undertaken in 33 of 55 reported CFC patients. Of those who underwent imaging, 21 had "hydrocephalus," and five had structural abnormalities of the brain. Eye abnormalities were also common in the patients with a severe phenotype (8/14); they included optic nerve pallor in five, nystagmus in five, and refractive problems in five. Eyelid fluttering similar to blepharospasm has been reported only in CFC syndrome (2/14) and appears to be a unique finding in this condition.

Finally, Noonan syndrome is frequently autosomal dominant, with one gene locus localized on chromosome 12q. In contrast, all the severe cases of CFC syndrome have been sporadic, suggesting a new dominant mutation. Autosomal recessive inheritance is less likely, given the lack of familial occurrence or parental consanguinity. In light of the phenotypic overlap with Noonan syndrome, the two conditions may represent a contiguous gene syndrome. The combination of neurologic and ectodermal abnormalities suggests a defect in fatty acid metabolism. Once the gene for Noonan syndrome is isolated, it will be important to include CFC patients in the mutation screening. As has been found in several other conditions, it may be that Noonan syndrome patients carry a frameshift or nonsense mutation, leading to a truncated protein product, while CFC syndrome patients carry a missense mutation.

We draw several conclusions about CFC and Noonan syndromes from this review of the medical literature. Although phenotypic overlap between CFC and

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### TABLE III. Cardiac Findings in the Patients With Severe Cardio-facio-cutaneous Syndrome

<table>
<thead>
<tr>
<th>Abnormalities</th>
<th>No. of patients</th>
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</thead>
<tbody>
<tr>
<td>Pulmonic stenosis (vavular and subvalvular)</td>
<td>7</td>
</tr>
<tr>
<td>Peripheral pulmonic stenosis</td>
<td>1</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>1</td>
</tr>
<tr>
<td>Ventricular septal defects</td>
<td>2</td>
</tr>
<tr>
<td>Atrial septal defect</td>
<td>2</td>
</tr>
<tr>
<td>Thickened valves</td>
<td>1</td>
</tr>
<tr>
<td>Aortic</td>
<td>1</td>
</tr>
<tr>
<td>Mitral</td>
<td>1</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>2</td>
</tr>
<tr>
<td>Right atrial hypertrophy</td>
<td>1</td>
</tr>
<tr>
<td>Asymmetric septal hypertrophy</td>
<td>1</td>
</tr>
<tr>
<td>Right bundle-branch block</td>
<td>1</td>
</tr>
</tbody>
</table>
Noonan syndromes exist, there are clearly differences in their clinical manifestations. The facial anomalies in these two conditions are similar, perhaps representing the effects of fetal edema, and do not aid in differentiating between them. The reported CFC patients include a subset with severe neurologic impairment and gastrointestinal dysfunction; the two patients in our report are part of that subset. In addition, a history of polyhydramnios, relative macrocephaly, sparse hair, and keratosis pilaris is typical. We also have identified a unique eye-fluttering behavior in our two patients, which may be analogous to the distinctive hyperpnea in Joubert syndrome and may aid in the diagnosis of additional patients with CFC. For the two patients whose cases are reported here, correct diagnosis has been important in allowing aggressive management of gastrointestinal dysmotility. We anticipate that there are many individuals with gastrointestinal and neurologic features who remain undiagnosed because the syndrome historically has emphasized the cardiac, facial, and cutaneous findings.

This review delineates a core phenotype for CFC syndrome that should allow for more focused investigation of the source of this disorder. The severe phenotype of CFC syndrome, as described here, should be the basis for developing strict diagnostic criteria until a molecular basis for this condition is identified. Once the basic defect is known, then milder cases can be studied and the phenotype expanded.

REFERENCES


