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New Syndrome of Congenital Circumferential Skin Folds Associated with Multiple Congenital Anomalies

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Abstract

Congenital circumferential skin folds can be found in individuals with no additional defects, as well as in patients with multiple congenital anomalies and developmental abnormalities. Current data point to etiological heterogeneity of syndromic cases. We describe a 7-month-old girl with a novel combination of symmetrical congenital circumferential skin folds, dysmorphic features, and multiple congenital abnormalities. Examination of the patient revealed symmetrical congenital circumferential skin folds and dysmorphic features, as well as multiple congenital anomalies including nasal pyriform aperture stenosis, ventricular septal defect, absent spleen, camptodactyly, and severe psychomotor retardation. Skin biopsy demonstrated subcutaneous fat extending into the superficial and deep reticular dermis. Sequencing of the *CDON*, *SHH*, *ZIC2*, *SIX3*, and *TGIF* genes (associated with holoprosencephaly) did not disclose pathogenic alterations. Extensive review of previously described cases of syndromic congenital circumferential skin folds did not reveal a similar combination of clinical and histopathological findings.

The terms "circumferential skin folds" and "circumferential skin creases" are used interchangeably in the medical literature. Circumferential skin folds differ from skin folds observed in cutis laxa–related syndromes because they involve subcutaneous tissue in addition to the skin. Current data point to etiological heterogeneity of syndromic cases involving congenital circumferential skin folds (CCSF). Generalized folding of redundant

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skin was first reported in an otherwise normal girl with underlying diffuse lipomatous hypertrophy on skin biopsy (1). The descriptive name “Michelin tire baby syndrome” was coined because of the physical resemblance of these patients to the mascot of a French tire manufacturer (MIM156610), but this term is pejorative, and we suggest replacing it with “congenital circumferential skin folds” (CCSF). CCSF can be observed in individuals with no additional defects, as well as in patients with multiple congenital anomalies and developmental abnormalities (2–8). An autosomal-dominant mode of inheritance has been documented in several families with nonsyndromic CCSF (9–11).

Congenital nasal pyriform aperture stenosis (CNPAS) is a rare cause of nasal obstruction. It is caused by a bony overgrowth of the median nasal process of the maxilla. The disorder is considered, at least in some patients, to be a mild form of holoprosencephaly (HPE) (12). CNPAS occurs as an isolated condition or in association with other midline defects. The spectrum of HPE varies from alobar, semilobar, or lobar holoprosencephaly; hypertelorism; midface hypoplasia; nasal anomalies; and midline facial clefting to its microforms, such as microcephaly, pyriform aperture stenosis, and solitary single maxillary incisor or supernumerary mesiodens. HPE is classified into syndromic and nonsyndromic forms. The etiology of HPE is highly heterogeneous and includes a large number of genes and environmental factors (13–15).

We report on clinical, histopathologic, and genetic findings in a patient with a previously undescribed combination of CCSF, dysmorphic features, and multiple congenital abnormalities. We review clinical and genetic findings of previously reported syndromic CCSF cases.

MATERIALS AND METHODS

Sequencing of *SHH*, *ZIC2*, *SIX3*, and *TGIF* was performed using bidirectional dideoxynucleotide sequencing using methods previously described (17–20). Sequencing of the *CDON* gene was performed with primer sets designed using the PRIMER3 program (http://frodo.wi.mit.edu/primer3/). All exons, including exon–intron junctions, were amplified from genomic DNA with primers designed from the genomic sequences available from the University of California at Santa Cruz (UCSC) Genome Browser database. Both strands of the polymerase products were sequenced using BigDye Terminators (Applied Biosystems, Foster City, CA) on a 3130xl Genetic Analyzer sequencer (Applied Biosystems). Sequence chromatograms were analyzed using sequencing analysis software version 5.2 (Applied Biosystems). Finally, the sequence was compared with the wild-type sequence obtained from the UCSC genome browser using SEQUENCHER software version 4.1.4 (Applied Biosystems). Sequencing of the *PORCN* gene was performed as previously described (21).

RESULTS

Case History

This 7-month-old girl was born to healthy nonconsan-guineous parents. The mother, aged 34, is of Libyan–Bulgarian Jewish origin, and the father, aged 35, is of Kurdish Jewish

origin. No similar birth defects or illnesses were reported in the family. The parents have two other children, who are healthy. The pregnancy was uneventful and maternal estriol values were normal. On fetal ultrasound, a ventricular septal defect and caudothalamic pseudocyst were detected. The child was born at 41 weeks gestation. Her birth weight was 3,140 g (−1 SD), length 49 cm (−0.5 SD), and head circumference 34.5 cm (1.6 SD). At birth, she was noticed to be dysmorphic and had CCSF and multiple congenital anomalies (Fig. 1, Table 1). On the first day of life, she failed to breathe spontaneously and was artificially ventilated. She had several episodes of hypoglycemia. At the age of 2 months she underwent functional endoscopic sinus surgery for correction of CNPAS. She was severely developmentally retarded. Neurological examination shortly after birth revealed the absence of spontaneous movements, hypotonia, absent Moro reflex and sucking reflex, poor gag reflex, and jitteriness. She was unable to swallow and was fed by feeding tube.

Laboratory Evaluation

Metabolic studies, including glucose, urea, creatinine, serum amino acids, creatine kinase, blood lactate and pyruvate, ammonia, urinary organic acids, and very long chain fatty acids, were normal. Liver enzymes were normal. Thyroid function, growth hormone, cortisol, insulin, total cholesterol, urine steroid profile, and adrenocorticotrophic hormone test were also all normal. Transferrin analysis, to exclude a congenital disorder of glycosylation, was negative, as was the TORCH screen. Examination of brainstem auditory-evoked potentials and eye examination including fundoscopy were normal. Repeated chest radiographs demonstrated interstitial diffuse lung infiltrates, and a ventricular septal defect was found on echocardiography. Abdominal ultrasound showed a central liver, absent spleen, and normal kidneys. Spleen and liver single photon emission computed tomography demonstrated no evidence of splenic tissue. A head computed tomography scan revealed nasal anterior pyriform aperture stenosis. Magnetic resonance imaging of the brain at 7 months revealed mild delay in myelination compatible with 6 months of age and mild ventricular and extraventricular dilatation of cerebrospinal fluid spaces compatible with extraventricular obstructive hydrocephalus. Skeletal radiographs and electroencephalogram were normal.

The karyotype was normal female. Microarray analysis (Signature Genomic Laboratories, Spokane, WA, USA) using a 105K oligonucleotide array detected no abnormalities in the DNA of this patient. Sequencing of the *CDON* gene, which causes a microform of holoprosencephaly in homozygous knockout mice (22), and sequencing of the four most common genes associated with HPE (*SHH*, *ZIC2*, *SIX3*, and *TGIF*) did not indicate pathogenic alterations.

Skin biopsy (Fig. 2) demonstrated hypertrophic subcutaneous fat replacing the superficial and deep reticular dermis, occasionally adjacent to the epidermis. Adipocytes were also observed around adnexal structures. Dermal smooth muscle was not present. Masson Trichrome and Weigert's elastica stains showed a normal distribution and amount of dermal collagen and elastic fibers. Based on the histopathologic findings and the clinical picture, the diagnosis of diffuse nevus lipomatosus as the underlying lesion in the patient's CCSF was made. Electron microscopy was performed on a glutaraldehyde- fixed biopsy specimen; ultrastructural abnormalities were not found in the connective fibers.

DISCUSSION

We describe a patient with a previously unreported combination of CCSF, dysmorphic features, and multiple congenital anomalies including pyriform aperture stenosis, ventricular septal defect, absent spleen, camptodactyly, and severe psychomotor retardation. A skin biopsy demonstrated nevus lipomatosus with thin dermis, which has rarely been reported in association with CCSF (1,23). The most frequent histological finding in nonsyndromic cases is smooth muscle hamartomatosis (24–28). Some patients show associated hirsutism (23,29), retinopathy (4), and neuroblastoma (10). Congenital lipomatosis as the cause of CCSF has also been reported. Fragmented elastic fibers in addition to smooth muscle hamartoma with decreased deposition of elastin were observed in one study (29). Skin folds may appear as a result of excessive proliferation of subcutaneous tissue, differentiating as smooth muscle or fat cells. The appearance of the skin folds in this patient worsened with time, whereas in the previously described cases, they appeared to become much less pronounced as the child grew (16). It is possible that the mechanism causing worsening of the skin folds is related to excessive proliferation of fat cells with time. Alternatively, hypoplasia of the dermis causing abnormal fat distribution might explain the subcutaneous fat extending into the superficial and deep reticular dermis.

The only syndrome known to be associated with thin dermis is focal dermal hypoplasia, or Goltz syndrome (MIM #305600). Our patient does not show typical features of this syndrome, such as osteopathia striata, coloboma, or lobster claw deformity. In addition, CCSF have not been described in this syndrome. Mutation analysis failed to reveal pathogenic mutations in the *PORCN* gene, which is associated with this syndrome (21).

The association between holoprosencephaly microforms and situs inversus has been described previously (30), indicating that the same genemay be responsible for heterotaxy and midline defects. None of the reported patients with such an association have circumferential skin folds.

Several cases of individuals with syndromic CCSF described share similar dysmorphic and clinical features that differ from the features of our patient (Table 2). Consistent malformations in these patients include CCSF, epicanthal folds, eye abnormalities, cleft palate, hearing loss, and genital abnormalities. The clinical picture in all these patients seems to be compatible with hearing impairment, undescended testes, circumferential skin creases, and mental handicap (HITCH syndrome). The parents of the siblings reported by Tinsa et al (8) and Kharfi et al (7) are first cousins, suggesting that autosomal recessive inheritance in HITCH syndrome is likely. We question whether the sibling pair that Tinsa et al (8) described is the same as that Kharfi et al (7) described because of the overlapping clinical details, including identical birth weight, family history, and clinical features. In both cases, the proband's sister, who also had CCSF, died at the age of 2 months.

The genetic basis of syndromic and nonsyndromic cases of CCSF is unknown. In several patients, chromosomal abnormalities have been described (Table 3): partial deletion of chromosome 11, inversion of chromosome 7, and diploidy or triploidy mosaicism. Two patients with CCSF and clefting of the mouth show apparently balanced chromosome 7

inversions with a breakpoint at 7q31.1 and 7q31.2. This might be a coincidental finding, but the presence of a mutation on the second allele or a small unbalanced inversion in the proband (with a balanced inversion in unaffected family members) cannot be excluded. No genes causing Mendelian forms of CCSF disorder have been identified.

In conclusion, CCSF represents a distinct clinical entity, with variable underlying etiologies and manifestations including nonsyndromic and syndromic forms. The most frequent syndromic form is HITCH syndrome. The patient described in this report shows novel phenotypic features of syndromic CCSF.

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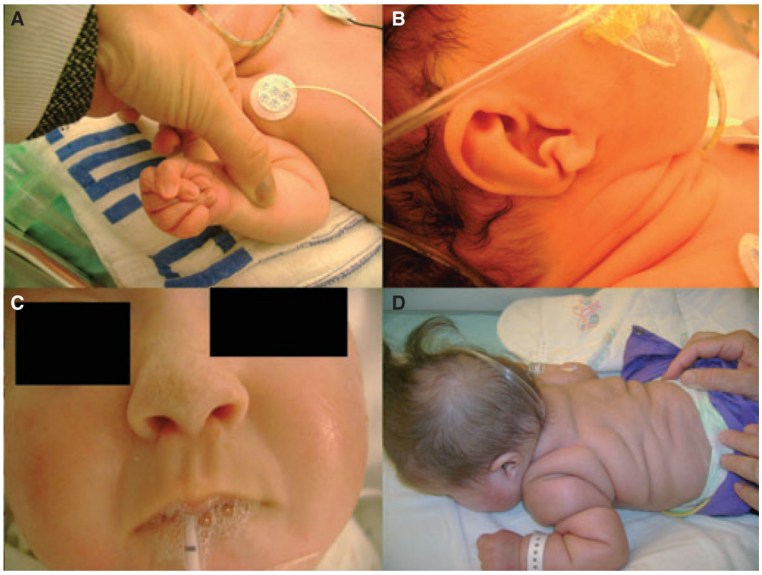

Figure 1.

Clinical features of the patient. Clenched hands (**A**); ear abnormalities including deep bilateral earlobe crease, hypertrophic antitragus and attached earlobe (**B**); prominent philtrum with a central ridge (**C**); congenital circumferential skin folds (**D**).

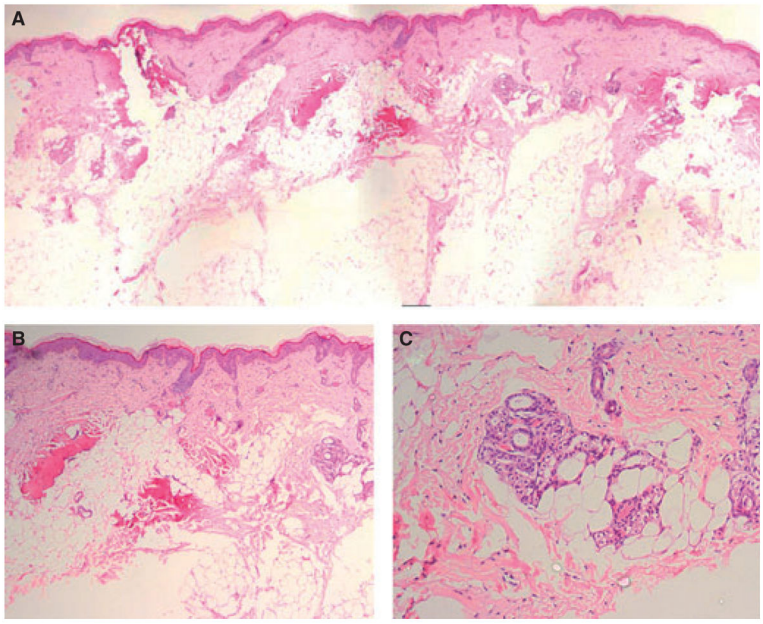

Figure 2.

A skin biopsy demonstrated subcutaneous fat extending into the superficial and deep reticular dermis, occasionally adjacent to the epidermis (**A**,**B**, H&E, 50–200×). Adipocytes were also observed around adnexal structures such as sweat glands (**C**, H&E, ×400).

TABLE 1

Phenotypic Features of Our Patient

Organ system	Clinical findings
Head	Very large anterior and posterior fontanelles with widely open metopic suture, sparse frontolateral hair
Ears	Low-set ears, bilateral deep earlobe crease, hypertrophic antitragus, attached earlobes
Eyes	Downslanting palpebral fissures, midfacial hypoplasia with mild proptosis
Philtrum	Prominent philtrum with central ridge
Mouth	Broad alveolar ridges
Chest	Small nipples
Limbs	Bilateral III–V finger camptodactyly, long and thin fingers, II–IV toe camptodactyly, prominent heels
Genitalia	Indentation on clitoris, perianal groove, anterior placement of anus
Skin	Symmetric congenital circumferential skin folds of upper and lower limbs and back

TABLE 2

Reported Cases of HITCH Syndrome

Reference	2 (the same patient described in 1—case 1)	5	6	8 **
Age	4.5 yrs	2 yrs 5 mos	3 yrs	9 yrs*
Sex	Male	Male	Male	Male
Short stature	+ (less than −4SD)	− (−1.8SD)	− (−1.6 SD)	+ (−3 SD)
Microcephaly	− (−1.8SD)	+ (−3 SD)	− (−1.6 SD)	+ (−6.5 SD)
Dysmorphic features	High forehead, elongated face, bitemporal sparse hair, broad eyebrows, blepharophimosis, telecanthus, broad nasal bridge, puffy cheeks, microstomia, enamel hypoplasia, micrognathia, microtia, posteriorly angulated ears, aberrant teeth	Epicanthal folds, small, low-set posteriorly angulated ears with thick overfolded helices, microstomia	High forehead, bitemporal sparseness of hair, mild epicanthal folds, micrognathia	Elongated face, hypertelorism, bilateral epicanthal folds, upslanting palpebral fissures, wide nasal bridge, low-set posteriorly rotated ears, overfolded thick helices, aberrant teeth, decay of several teeth
Skin	CCSF on upper and lower limbs, loose skin	CCSF on arms, legs and digits	CCSF, multiple café au lait spots	CCSF on upper and lower limbs
Eye abnormalities	Microphthalmia, microcornea, severe optic nerve hypoplasia	Microphthalmia, microcornea	−	Microphthalmia
Cleft palate	+	+	−	+
Pectus excavatum	+	+ hypoplastic nipples, positioned high in the chest	−	+ widely spaced nipples
Scoliosis	+	−	−	−
Limbs	Long fingers, overlapping toes	−	−	II–III toe syndactyly, metatarsus abductus
Genital abnormalities	Hypoplastic scrotum	−	Undescended testes, hypoplastic scrotum	Ureterocele, hypospadias
Hernias	Inguinal and umbilical	−	−	−
Hearing loss	+	−	+	+
Developmental delay/mental retardation	Severe mental retardation	Moderate to severe psychomotor delay	Mental retardation	Severe mental retardation
Roentgenologic findings	Computed tomography: dilated lateral ventricles; echocardiography: tricuspid regurgitation	−	Brain ventricular dilatation	Radiographs: diffuse osteopenia; brain magnetic resonance imaging: hypoplastic vermis, hypoplastic corpus callosum, dilatation of ventricles
Histological findings	NA	NA	Collagen bundles thickened and closely packed in the deep dermis	Normal (right tight)

*Sister of this patient with congenital circumferential skin folds died at the age of 2 months.

**The same sibling pair possibly described in reference 7.

TABLE 3

Reported Cases of Congenital Circumferential Skin Folds with Chromosomal Abnormalities

Reference	Clinical features	Histological features	Karyotype
23,31	Low-set ears with abnormal helices, microcephaly, esotropia, rocker-bottom feet, severe mental retardation	Nevus lipomatosus	46XXdel(11)q21q23
2 (patient 2)	Macrostomia with horizontal clefting, hypertrichosis, inguinal hernias, seizures, mental retardation	NA	46,XY, inv(7)(q31.2;q32.1)mat
26	Dysmorphism, submucous cleft palate, clefting of the mouth, genital and dental anomalies, hirsutism, seizures moderate mental retardation	Smooth-muscle hamartoma	(46,XY,inv(7)(q22q31.3)mat
32	Grade IV hypospadias, discontinuous nevus flammeus, hyperpigmented area, asymmetry of lower limbs, tapering fingers, preauricular pit, atrial septal defect type II IQ of 83	NA (ultrasound: diffuse hypertrophy of connective tissue)	Blood: normal karyotype Fibroblast culture: 69,XXY Interphase fluorescence in situ hybridization on buccal mucosa XXY/XY

NA, not available.