

## **Cardiofaciocutaneous Syndrome**

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### SYNONYMS

CFC syndrome

Cardio-facio-cutaneous syndrome

### DEFINITION

Cardiofaciocutaneous (CFC) syndrome is a relatively rare genetic disorder first described by Reynolds et al. in 1986 based on the observation of eight unrelated patients with very similar facial appearance characterized by unusually sparse, brittle, curly hair, large head (macrocephaly), a prominent forehead, and abnormal narrowing of the sides of the forehead (bitemporal constriction); mental retardation; failure to thrive; congenital heart defect; short stature and ectodermal abnormalities.

DIFFERENTIAL DIAGNOSIS: Noonan syndrome, Costello syndrome

### SYMPTOMS AND SIGNS:

Most patients are initially referred because of feeding difficulties (poor suck), and failure to thrive; later on, because of psychomotor developmental delay and other clinical manifestations. In general CFC patients have an easygoing behavior, are cheerful and cooperative.

#### **Facial Appearance**

Affected individuals may have an unusually large head (macrocephaly); high forehead and abnormal narrowing of the sides of the forehead (bitemporal constriction), causing the head to appear "box-like" in shape. The ears are abnormally angulated towards the back of the head (posteriorly angulated). The nose is short, bulbous and with anteverted nostrils. There is also an underdevelopment (hypoplasia) of the ridges of the bone above the eyes (supraorbital ridges); widely spaced eyes (ocular hypertelorism); downslant of eyelid openings and ptosis (drooping of one or both upperlids).

#### **Skin, hair and nails**

According to the medical literature all patients have some kind of ectodermal abnormality either of skin, hair or nails.

Children with CFC syndrome usually have sparse, slow growing, curly scalp hair that is abnormally dry and brittle (friable). They also have absent or sparse eyebrows and eyelashes. In some cases the nails are fast growing.

Skin involvement ranges from dry skin to hyperkeratosis. The frequency in which skin abnormalities are found is: hyperkeratosis (37%), keratosis pilaris (33%), ichthyosis (31%), eczema (26%), hemangiomas (24%), hyperelastic skin (22%), hyperkeratosis of palms and soles (13%), *café-au-lait* spots (9%), generalized hyperpigmentation (5%) and *cutis marmorata* (2%).

#### **Heart**

Congenital heart defect is present in 77.8% of reported patients, particularly obstruction of the normal flow of blood from the lower right chamber (ventricle) of the heart to the lungs (valvar pulmonary stenosis, 37%) and/or an abnormal opening in the fibrous partition (septum) that divides the two upper chambers (atria) of the heart (atrial septal defects, 35%). Hypertrophic cardiomyopathy has also been reported and is present in 11% of the patients with cardiac involvement.

## **Mental retardation**

According to the medical literature, some 90% of children with CFC syndrome have mild to severe mental retardation, most having moderate retardation. Motor delays are reported in 81.5% and speech delay in 46.3%.

## **Additional abnormalities**

Short stature is present in 77.8% of reported patients and webbed neck in 50%. Abnormal shape of the thorax (*pectus carinatum*) has been described in 27.8% of the cases. Joint hyperextension has been noted in 22.2% of the patients. Hypotonia (reduced muscle tone), especially during the first years of life, has been reported in 27.8% of the cases. Seizures are noted in 14.8% of patients and apparent hydrocephalus in 9.3%. Enlargement of the liver (hepatomegaly) is present in 9.3% of cases and of the spleen (splenomegaly) in 14.8%. Undescended testes (cryptorchidism) are present in 43.5% of boys.

## **ETIOLOGY/EPIDEMIOLOGY**

Males and females are affected equally and patients are reported from all continents. The number of published patients is now close to 100, however many more unpublished cases are known. All patients diagnosed with CFC syndrome are sporadic cases born to non-consanguineous parents and with no history of genetic disease. They also have apparently normal chromosomes. There has been statistical evidence of increased paternal age, which suggests a new mutation of an autosomal dominant gene as the cause of the syndrome. Two chromosomal rearrangements have been described in CFC patients inherited in both from phenotypically normal mothers. To date there is no clue to the molecular defect responsible for the CFC syndrome.

## **DIAGNOSIS**

The diagnosis is purely clinical, based on the mentioned traits. None of them are pathognomonic or obligatory and it is their general pattern that makes the diagnosis.

Noonan and Costello syndromes must be distinguished. Noonan syndrome patients, in general, have a less severe mental impairment and ectodermal involvement and a slightly different facial appearance; some may present bleeding disorders. Some cases of Noonan syndrome can now be confirmed by molecular diagnosis, mutations having been found in the *PTPN11* gene [Tartaglia et al., 2001]. In the Costello syndrome, there is worse skin involvement with the presence of calluses on palms and soles, skin tags on the face, especially around the mouth and nose, periorificial papillomas; short Achilles tendons; scoliosis; radio-ulnar synostosis of the elbow, with ulnar deviation of the hands and a substantially increased risk of malignancy. Chromosomes are normal as a rule and most cases are sporadic. Some familial cases have been attributed to parental germinal mosaicism [Lurie, 1994].

## **TREATMENT**

Treatment is symptomatic. Gastrostomy has been an excellent solution for the kids with severe feeding problems. Cryptorchidism must be corrected surgically in the first years of life to avoid malignant transformation of the testes. Seizures, if present, must also be well controlled and the heart condition, which is the only life threatening complication, particularly the hypertrophic cardiomyopathy, must be under regular and careful cardiologic follow up.

The skin condition, in general, responds well to moisturizers and ointments applied regularly.

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