

# Cardiofaciocutaneous Syndrome With Occipital Encephalocele

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## Abstract

Cardiofaciocutaneous (CFC) syndrome is a rare multiple congenital anomalies/mental retardation (MCA/MR) syndrome characterized by growth failure, distinctive facial appearance, ectodermal abnormalities, and congenital heart defects<sup>1</sup>. Around 100 cases have been reported in literature to date. We describe here a child with features of cardiofaciocutaneous syndrome. Parental consanguinity and occipital encephalocele was present in our case; this has hitherto not been described in literature.

## INTRODUCTION

Cardiofaciocutaneous syndrome (OMIM 115150) is a rare genetic syndrome. Reynolds et al in 1986 first described this syndrome on 8 unrelated patients<sup>1</sup>. The common features in this disorder include large head, bitemporal constriction, anti-mongoloid slant of palpebral fissures, large and low-set ears, skin keratosis, congenital heart defects and psychomotor retardation. These features may be noticed at birth or may appear as the child grows. No sex predilection has been noted. The cases are sporadic and do not follow any definite pattern of inheritance. Diagnosis is based on clinical phenotype and no specific diagnostic tests are available.

## CASE REPORT

A.M., a 3 year old male child residing on an island near Sandakan, East Malaysia and belonging to the kegayan race was brought to our clinic with history of delayed milestones. The child was born at full term by an uneventful home delivery. Third degree parental consanguinity was present. The father was 40 years at the time of birth. The child started rolling over at 1 year, started sitting at 2 years, and standing at 3 years and on presentation could walk only with support and could not run. He could feed himself and his speech was predominantly in monosyllables. He could obey simple commands and respond to "No". He could verbalize his toilet demands. His appetite was normal and he had no feeding problems. There was no history of convulsions, hearing or visual disturbances. No abnormal movements were noticed. There were no bowel or bladder complaints and past history was not contributory. There was no family history of similar complaints. The child was last in birth

order and the elder 4 siblings and parents were normal.

On examination, vital parameters were stable. He weighed 11.5 kg and his length was 87 cm (both <3<sup>rd</sup> percentile, National Centre for Health Statistics growth chart). He had macrocephaly with a head circumference of 56 cm. His forehead was prominent; he had hypertelorism, bilateral temporal constriction, anti-mongoloid slant of eyes, short upturned nose and low set, large ears. Eyebrows and eyelashes were scanty and hairs were scarce, dry, curly and brittle (Fig. 1).

**Figure 1**

Figure 1: 3 year old child with cardiofaciocutaneous syndrome



Skull examination revealed a small occipital encephalocele (Fig. 2).

**Figure 2**

Figure 2: Defect in skull in occipital area underlying encephalocele



The child had dry skin with hyperkeratosis. These were more marked in the axilla, sacral area, perianal region and lower limbs. The external genitalia were normal. The child had a developmental quotient of 33-40%. Hearing was normal. He had no squint, refractive error or nystagmus. Fundus examination was normal. He had an ejection systolic murmur best heard in pulmonary area. Respiratory and alimentary system examinations were normal. A chest radiograph and ECG were normal. Echocardiography revealed mild valvular pulmonary stenosis. Chromosomal analysis was apparently normal. CTscan brain was reported as showing mild bilateral brain atrophy. Bone age was estimated to be 1 year.

The child's condition was discussed with the mother and interventions were made to enhance physical and psychological development. Dietetic advice was given and child was put on regular follow-up clinic visits.

### **DISCUSSION**

Cardiofaciocutaneous syndrome is an extremely rare genetic disorder. The manifestations include congenital heart defects, characteristic facial features, ectodermal abnormalities, and growth retardation. Patients with this

disorder have a high forehead, bitemporal constriction, hypoplasia of supraorbital ridges, anti-mongoloid slant, depressed nasal bridge, posteriorly angulated ears with prominent helices. Hair is sparse and friable. Skin usually shows patchy hyperkeratosis or generalized ichthyosis<sup>1,2,3,4,5</sup>. All these features were present in our child. In addition, he also had an occipital encephalocele. This has to date not been reported in any of the CFC cases in literature.

The most common heart defects associated with CFC syndrome are pulmonary stenosis, atrial septal defect or hypertrophic cardiomyopathy<sup>6</sup>. Our child had mild valvular pulmonary stenosis.

Skin abnormalities are seen in all cases of CFC syndrome. These vary from dry skin to hyperkeratosis. Eczema and generalized pigmentation have been reported and nails are thin and opalescent. There may be finger tip pads and hair is usually thin and sparse<sup>5,7</sup>. Our child had hyperkeratotic areas, hair was thin and sparse, nails were thin and opaque, but there was no pigmentation and no finger tip pads. CFC syndromes with no hyperkeratosis have also been reported<sup>7,8</sup>. Rarely, hemangiomas, café-au-lait spots, hyperelasticity and cutis marmorata have been described with CFC syndrome<sup>5,9</sup>.

Mental retardation is usually seen in CFC syndrome. However, Monoukian et al in 1996 described a 25 year old female with features of CFC syndrome but with normal intelligence<sup>10</sup>. Our child suffered from moderate to severe developmental delay.

Grebe and Clericuzio in 2000 described stringent clinical diagnostic criteria for CFC syndrome. These included macrocephaly, characteristic facial appearance, growth failure, heart defects, sparse, curly hair, neurologic impairment/developmental delay, gastrointestinal dysfunction, ocular abnormalities/dysfunction, history of polyhydramnios and hyperkeratotic skin lesions<sup>4</sup>. In our child, a history of polyhydramnios could not be elicited because it was a home delivery. Ocular and gastrointestinal dysfunctions were absent. Occipital encephalocele was an added feature, not seen in previously reported cases.

CFC syndrome is considered to be sporadic due to de novo mutations<sup>5</sup>. Parental consanguinity, noted in our case, has not been reported in any of the previous cases. In 1991, Fryer et al pointed out the phenotypic overlap between CFC and Noonan syndrome. But cytogenetic studies revealed that these two are distinct and that missense mutations of

PTPN11 gene seen in Noonan syndrome do not occur in CFC syndrome. Hence diagnosis of CFC syndrome is purely clinical and no specific diagnostic laboratory tests are available<sup>11,12,13</sup>. Chromosomal analysis in our child was also noted to be normal. Rauen et al in early 2000 reported 2 cases of CFC syndrome with interstitial deletion at 12q21.2q22, proximal to the critical region for Noonan syndrome<sup>14,15</sup>. This was however refuted by a study conducted by Kavamura MI et al<sup>16</sup>. A recent analysis revealed that CFC syndrome could possibly be due to acquired mutations in genes encoding components of the mitogen-activated protein kinase (MAPK) signaling pathway<sup>17</sup>. In our case, such detailed cytogenetic analysis could unfortunately not be performed.

Advanced paternal age seen in our case has also been reported in previous studies<sup>18,19</sup>.

Rare features found to be associated with CFC syndrome include ptosis, short neck, webbed neck, submucous cleft palate, feeding difficulties, congenital muscular hypotonia, joint hyperextension, pectus carinatum, scoliosis, microcephaly, seizures, hepatomegaly, splenomegaly, cytotrichidism and acute lymphoblastic leukemia<sup>3,5,10,20</sup>.

CTscan of the brain in CFC syndrome usually shows mild hydrocephalus, cortical atrophy, hypoplasia of frontal lobes and/or brain stem atrophy<sup>5</sup>. In our case, the child had bilateral brain atrophy. Skin biopsy can be carried out to evaluate type of skin involvement but it lacks high diagnostic value<sup>6</sup>.

Children with this disorder require symptomatic treatment. A multidisciplinary approach is needed with involvement of occupational therapist and speech therapist. Surgery may be indicated for severe symptomatic heart lesions. Those with severe feeding difficulties may benefit from feeding tubes or gastrostomy. Skin hygiene should be maintained<sup>6</sup>.

Prognosis of CFC syndrome is fair. Children with this syndrome usually lead a normal life span. The risk of recurrence of CFC syndrome is 1-3 % in siblings. But this risk increases to 50% in offspring of affected individuals. Prenatal diagnosis is yet not possible<sup>6</sup>.

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