Acute lymphoblastic leukaemia in a patient with cardiofaciocutaneous syndrome

Cardiofaciocutaneous syndrome (CFC syndrome) is a multiple congenital abnormality syndrome associated with characteristic facial appearance, congenital heart defects, ectodermal anomalies, and growth failure. The most frequent cardiac anomalies are pulmonary stenosis and atrial septal defect. The facial characteristics are high forehead, hypoplasia of the supraorbital ridges, downward slanting palpebral fissures, depressed nasal bridge, and posteriorly angulated ears with prominent helices. The often woolly hair is sparse and friable. The skin shows hyperkeratosis that can be as severe as generalised ichthyosis. There is an assumption that Noonan syndrome (NS) and CFC syndrome are closely linked. However, in NS there is a link with malignancies, but in CFC syndrome no descriptions of cases with a malignancy have been published.

We report a 5 year old girl of unrelated, white parents (at birth paternal age was 47 years and maternal age was 29 years) with CFC syndrome, who presented with acute lymphoblastic leukaemia (ALL).

During the pregnancy there was polyhydramnios. Delivery at 40 weeks was uncomplicated and birth weight was 3500 g. At the age of 10 months the diagnosis of CFC syndrome was made based on dysmorphic features, cardiac anomalies, and skin abnormalities. Cardiac features included an axis in the left upper quadrant, with low voltages over the left precordial leads on ECG, mild pulmonary stenosis (an estimated gradient of 16 mm Hg), and an atrial septal defect on Doppler echocardiography. On repeated investigation at the age of 3½ years the pulmonary stenosis was no longer detectable but the atrial septal defect with left to right shunt was still noted. In addition, asymmetrical hypertrophy of the interventricular septum directed towards the left ventricular outflow tract was noted. Initially, at the age of 10 months, skin anomalies were confined to mild hyperkeratosis. Biopsy showed acrokeratosis verruciformis. At the age of 3 years, disseminated keratotic follicular changes had developed, compatible with keratosis pilaris.

Additional investigations included a skeletal survey, which showed no anomalies and a normal bone age, and a cerebral MRI scan at the age of 1 year, showing delayed and irregular myelination, widening of the subarachnoid space, and slightly enlarged ventricles. Ophthalmological investigations were normal.

On examination when ALL was diagnosed, weight was 23.5 kg (>98th centile), height was 110.5 cm (50th centile), and head circumference was 53 cm (90th centile). The following anomalies related to the CFC syndrome were present: a high and prominent forehead, woolly, sparse hair, moderately low set ears with prominent helices, pits in both helices, hypertelorism, absent eyebrows, epicanthic folds, mildly downward slanting palpebral fissures, depressed nasal bridge, broad mouth, shield thorax, mild joint laxity, and four café au lait spots (2 cm) on the trunk and right leg (fig 1). Her developmental age was estimated to be 1½ years. Anomalies related to the acute lymphoblastic leukaemia were hepato- and splenomegaly. Lymphoblasts were seen in the peripheral blood (8% of 1.4 × 10⁹/l leucocytes). Bone marrow aspirate showed 98% lymphoblasts positive for TdT, HLA-Dr, CD34, CD13, CD33, CD19, CD10, CD22, and CD79 and negative for cytoplasmic IgM and membrane IgM, -k, -λ, CD15, CD65, myeloperoxidase, and T cell markers. Cytogenetic analysis showed 45,46,XX,del(4)(p14), del(15)(p21p22),+10,t(12;21)(p13;22),+del(12)(p11;p12), del(13)(q13q24), del(16)(p19),del(17)(p10), del(22)(q11q13)(27) and 46,XX[13]. FISH studies were negative for BCR/ABL fusion and positive for TEL/AML1 fusion. Examination of cerebrospinal fluid showed no lymphoblasts.

Induction therapy consisted of vincristine, daunomycin, and E coli asparaginase; remission was achieved in five weeks. The very rapid loss of hair during the first two weeks of treatment was striking. For prophylaxis of a central nervous system relapse methotrexate was given. At present the patient is still on maintenance treatment, which is composed of vincristine, daunomycin, 6-mercaptopurine, and methotrexate.

In 1996 Krajewska-Walasek et al summarised the anomalies related to CFC. Common symptoms, also present in our patient, are polyhydramnios, psychomotor retardation, relative macrocephaly, cortical brain atrophy, abnormal hair, skin anomalies, cardiac defects, shield thorax, and joint laxity. Pulmonary stenosis, atrial septal defect, and hypertrophic cardiomyopathy are the most frequent cardiac defects reported in CFC. The leukaemia in the present patient was an ALL of common phenotype. Findings, including the TEL/AML1 fusion, which is noted in 20-30% of childhood ALL, indicate a favourable ultimate outcome. CFC cases are mostly sporadic, but autosomal dominant inheritance has been suggested, although the described family may also fit the diagnosis of...
NS. CFC syndrome has often been compared to NS, which follows an autosomal dominant pattern of inheritance and of these patients are sporadic cases. Linkage of NS with a locus on 12q24 has been reported in two families, but in most families no linkage with this locus could be established. The similarity of NS to CFC syndrome is especially clear in the facial dysmorphology, the nature of the cardiac defects, and decreased growth. In CFC syndrome additional findings are skin abnormalities, hypotrichosis, mental retardation, and eye anomalies. These similarities and differences are still a matter of debate; some think that NS and CFC syndrome are genetically different conditions, and others assume that NS and CFC syndrome are either allelic variants or constitute a contiguous gene syndrome. Recently, in a single family, it was suggested through linkage analysis that NS and CFC resulted from a variable expression of the same genetic defect.

Malignancies have not been previously reported in patients with CFC syndrome, but in NS there are reports of various types of malignancies, including rhabdomyosarcoma, malignant schwannoma, phaeochromocytoma, ganglioneuroma, and myelodysplasia. ALL is reported most frequently. An explanation for the discrepancy in the occurrence of malignancies in NS and CFC syndrome might be the small number of patients diagnosed with CFC syndrome, in contrast to the large number of NS patients. Also the low incidence of paediatric malignancies should be considered; in The Netherlands the figure is 13 per 100,000 in 0-14 year olds. As a result it remains uncertain whether the occurrence of leukaemia in the present case is truly another manifestation of the CFC syndrome or merely coincidence.

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