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Feature Article

Noonan syndrome and its related disorders

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Abstract The diagnosis of Noonan syndrome still rests on its clinical features. There are several syndromes to consider in the diagnosis of Noonan syndrome. These include cardio-facial-cutaneous syndrome, LEOPARD syndrome, neurofibromatosis–Noonan syndrome and Costello syndrome. The facial appearance and part of the clinical features of these syndromes are very similar to Noonan syndrome. Molecular research likely will elucidate whether these syndromes are variations of Noonan syndrome or etiologically different disorders.

Key words: cardio-facial-cutaneous syndrome, Costello syndrome, LEOPARD syndrome, neurofibromatosis–Noonan syndrome, Noonan syndrome.

Introduction

Noonan syndrome is a well known autosomal dominant disorder characterized by a peculiar facies with hypertelorism, ptosis, down slanting palpebral fissure, low set posteriorly rotated ears and short neck, a congenital heart defect including pulmonary stenosis or hypertrophic cardiomyopathy, short stature, a pectus deformity and cryptorchidism in males. The incidence of Noonan syndrome is estimated to be between 1:1000 and 1:5000. Approximately half of all cases are familial and the gene locus of this syndrome was recently assigned to 12q22-qter.[1] The diagnosis of Noonan syndrome, however, still rests on its clinical features. In this article, I would like to introduce four syndromes for the differential diagnosis of Noonan syndrome. These four syndromes have Noonan-syndrome-like facies and some characteristics similar to Noonan syndrome.

Cardio-facial-cutaneous syndrome

The facial appearance of cardio-facial-cutaneous (CFC)[2] syndrome includes high forehead, relative megalencephaly, bitemporal constriction, hypoplasia of supraorbital ridges, curly and sparse hair, downward slant of the palpebral fissures, depressed nasal bridge and posteriorly angulated ears with prominent helices. These characteristic facies are very similar to those of Noonan syndrome. Skin changes vary from patchy hyperkeratosis to generalized ichthyosis and hemangiomatosis (Fig. 1). The most common cardiac defects are pulmonary valve stenosis and atrial septal defects. The patients are usually affected with mild to severe mental retardation. If Noonan syndrome is suspected and skin changes are also seen, then this diagnosis should also be considered.

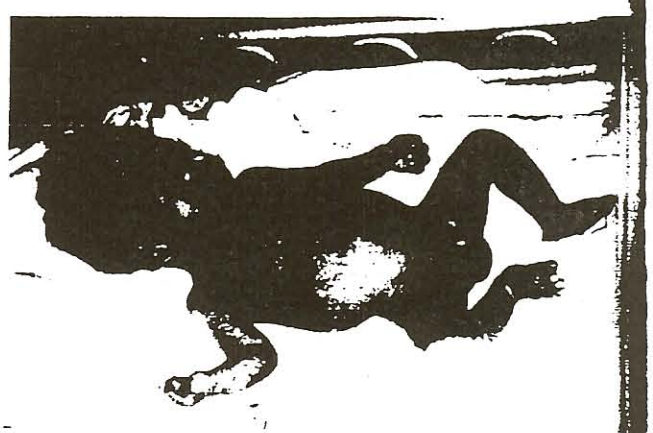

Fig. 1 An infant with cardio-facial-cutaneous syndrome. Note hemangioma on the right hand and hyperkeratosis on the lower extremities.

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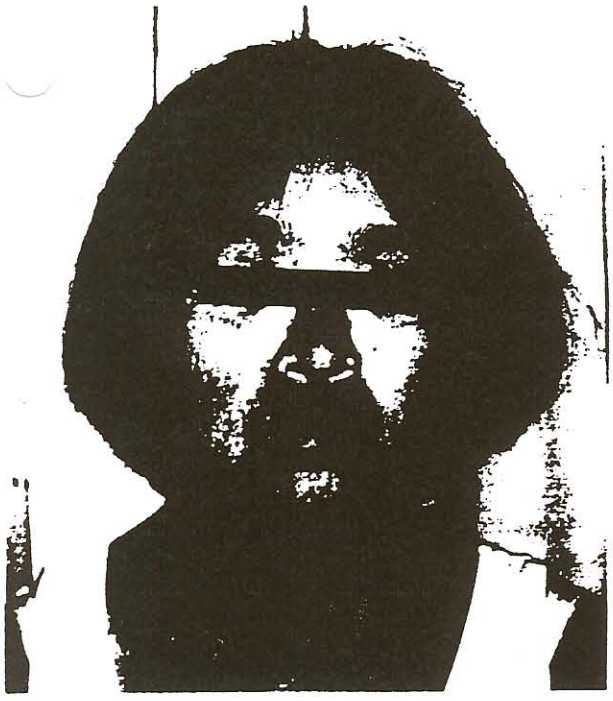

Fig. 2 A 15 year old girl with LEOPARD syndrome.

LEOPARD syndrome

LEOPARD is the acronym denoting Lentigines, EKG abnormalities, Ocular hypertelorism, Pulmonic stenosis, Abnormalities of genitalia, Retardation of growth and Deafness.[1] Multiple lentigines are 2–8 mm in diameter and scattered over the face, scalp, neck, trunk, genitalia, upper limbs, palms and soles (Fig. 2). They are more sparse below the knees and the mucous membranes are spared. The lentigines may present at birth or during childhood and increase in number and darken with age. Biopsy of the lentigines reveals intracellular giant pigment granules similar to those found in neurofibromatosis. EKG abnormalities indicate axis deviations, unilateral or bilateral hypertrophy, and conduction abnormalities. Facial characteristics including ocular hypertelorism are somewhat similar to those of Noonan syndrome. Other

Fig. 3a, b An infant with neurofibromatosis–Noonan syndrome.

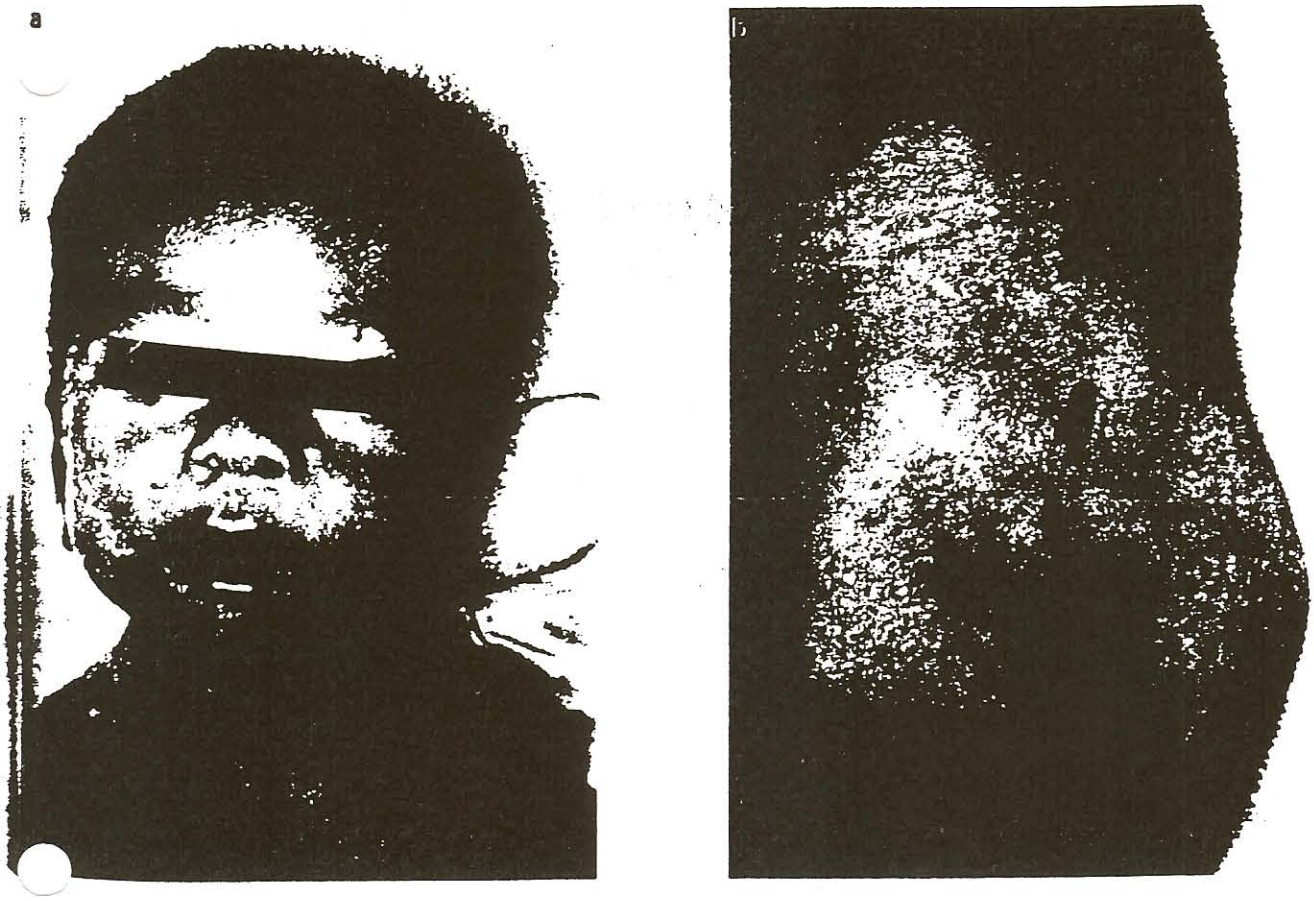

Fig. 4 An infant with Costello syndrome.

findings include pulmonary stenosis, obstructive cardiomyopathy, cryptorchidism, growth failure, sensorineural hearing loss and mild mental retardation. Other less common findings are ocular ptosis, delayed puberty and skeletal abnormalities such as kyphoscoliosis, pectus carinatum or excavatum.

Neurofibromatosis–Noonan syndrome[4]

It is unclear if neurofibromatosis–Noonan syndrome is etiologically the same as, or different from, Noonan syndrome. Neurofibromatosis type 1 (NF1) is characterized by cafe au lait patches, benign neurofibroma and susceptibility to cancer; and recently the gene responsible for NF1 was cloned. Some patients with Noonan syndrome are affected with cafe-au-lait spots and neurofibroma (Fig. 3). It is suggested that the gene locus of Noonan syndrome and that of NF1 are close to each other and some patients have a deletion including both loci and suffer from both disorders. However, the linkage between Noonan syndrome and NF1 has not been proved.

Costello syndrome

Costello syndrome[5] is a recently identified multiple congenital anomaly and mental retardation (MCA/MR) syndrome. The clinical features include macrocephaly, sparse and curly hair, epicanthus, depressed nasal bridge, short and wide nose, nasal papillomata, thick lips, short neck, dark, loose skin of the hands and feet, and tight Achilles tendons[6] (Fig. 4). The facial appearance is very similar to that of Noonan syndrome. Mental retardation in Costello syndrome is usually moderate to severe. This syndrome should be considered in Noonan syndrome patients with severe mental retardation, sparse and curly hair and loose skin of the hands and feet.

Conclusion

Noonan syndrome has a very wide spectrum of symptoms. The different diagnosis may be made by 'a splitter' or 'a lumper'. One of the gene loci of Noonan syndrome was recently assigned to 12q22-qter. Molecular research likely will elucidate whether these four syndromes are variations of Noonan syndrome or etiologically different disorders.

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