Iris coloboma, ptosis, hypertelorism, and mental retardation: Baraitser-Winter syndrome or Noonan syndrome?

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Abstract
Three children have been reported with a combination of iris coloboma, ptosis, hypertelorism, and growth and mental retardation with possible autosomal recessive inheritance. We report a single case whose clinical features encompass this syndrome and Noonan syndrome, and discuss the possible interpretations of this complex phenotype.

(J Med Genet 1993;30:425–6)

Delineation of new syndromes and differential diagnosis between partially overlapping syndromes remain the most exciting and delicate task of dysmorphologists. A child is presented here whose phenotype links two apparently different syndromes, the well known Noonan syndrome and the rare Baraitser-Winter syndrome.

Case report
This boy is the second child of non-consanguineous Caucasian parents. Birth weight was 3560 g. Several physical anomalies were detected during infancy (fig 1), including bilateral iridoretinal coloboma extending to the optic nerve on one side, hydroureters related to horseshoe kidney, and perceptive deafness (−60 dB) requiring a hearing aid. He grew regularly at about −3 SD for height until puberty. His psychomotor development was delayed; he walked at 18 months and spoke his first words at 3 years. He attended special school and was able to read and write with much difficulty. Seizures occurred from 12 years of age.

He was first seen for evaluation at the age of 17 years. He was 160 cm tall (−2 SD), weighed 50 kg, and had an OFC of 52 cm (−3 SD). He had striking dysmorphic features (fig 2) including a triangular shaped face, broad forehead, bitemporal constriction, hypertelorism (inner intercanthal distance 40 mm, outer intercanthal distance 104 mm), left lower quadrant coloboma, iris heterochromia, chubby cheeks, thick lips, high arched palate, low set, posteriorly rotated ears, and a very low posterior hairline. Mild webbing of the neck and pectus excavatum were present (thoracic circumference 77 cm, intermammary distance 19 cm). Spontaneous puberty occurred at 13 years. Cubitus valgus and naevi were not seen. ECG was normal. Echocardiography disclosed tricuspid insufficiency grade II, but no vascular stenosis and no myocardial hypertrophy. EEG showed an irritative pattern. CT scan was normal. Bilateral mild coxa valga was present. Karyotype was 46,XY. Fragile X mutation was excluded.

The family history was unremarkable. His parents and his older sister were healthy, mentally normal, and of normal stature. The parents’ fundi were normal. Two cousins and a sister of the father were purportedly moderately mentally retarded, but it was not possible to examine them. A brother of the father had severe mental retardation attributed to birth trauma. No-one had a Noonan phenotype in family photographs but the paternal grandmother and great grandmother were very short (probably below 150 cm).

Discussion
The initial diagnosis made for this patient was Noonan syndrome. This highly pleiotropic disease shows multiple anomalies, but, to the best of our knowledge, iris coloboma has only been reported once (unilateral iris coloboma with normal fundus) and heterochromia has never been reported. Noonan syndrome is known to be heterogeneous; Noonan-neurofibromatosis syndrome is now proved to be a phenotypic variant of NF1. Costello syndrome, King syndrome, and CGD syndrome are other ‘variants’ of Noonan syndrome.
awaiting a definite classification. The patient presented here shows many phenotypic features of Noonan syndrome, but because the typical cardiac defects are lacking, Duncan's scoring for Noonan syndrome is inconclusive: 74/146 (51%).

Several other syndromes are characterised by the triad hypertelorism-coloboma-ptosis. In frontofacionasal dysplasia, these signs are accompanied by median facial clefting.\(^3\) In Hanley syndrome, osteochondritis multiplex and camptodactyly are observed.\(^4\) In Zurich-Keve syndrome, ectodermal dysplasia and migratory ichthyosis are present.\(^5\) In the dominant Cotsirilos-Taylor syndrome,\(^6\) the triad is a part of a Rubinstein-Taybi-like syndrome. In Gardner-Morrison syndrome, genital and anorectal malformations and thrombocytopenia are present.\(^7\) Le Marec-Odent syndrome, occurring in double cousins, presents with a large, bulbous nose, cleft palate, microphthalmia, and arhinencephaly.\(^8\) All these diagnoses were easily discarded in our case.

Baraitser and Winter\(^9\) reported three children with a new syndrome of iris coloboma, ptosis, hypertelorism, broad and flat nasal bridge with epicantus inversus, mental retardation, and postnatal growth retardation. Two of them were sibs born of first cousin Asian parents, thus suggesting autosomal recessive inheritance. One of them had a short neck and low posterior hairline. They share with Noonan syndrome mental and growth retardation, hypertelorism, chubby cheeks, and pointed chin, although, according to the authors, the facial gestalt of the affected children was different. Our patient resembles case 1 of Baraitser and Winter.\(^9\)

Several mutually exclusive diagnoses should be considered for our patient: (1) a new syndrome with coloboma and Noonan-like phenotype, (2) Baraitser-Winter syndrome: our patient has a more severe expression of the disease, and broadens its clinical spectrum to include several new Noonan-like features, (3) Noonan syndrome and, independently, coloboma (the same explanation could be given for the Baraitser-Winter cases), (4) Noonan syndrome only. Coloboma would then be a new, uncommon, but pathogenetically related feature of it. On this hypothesis, Baraitser-Winter syndrome should perhaps only be viewed as another clinical variant of Noonan syndrome and lumped with it (possibly indicating lack of expression in a carrier parent or germinal mosaicism and coincidental consanguinity).

Although we personally favour the second hypothesis, the first hypothesis remains possible, and the third and fourth cannot be confidently rejected at the moment. New reports of patients with coloboma-hypertelorism-ptosis syndrome will be necessary to clarify this issue.

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doi: 10.1136/jmg.30.5.425

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