# A rare cause of syndromic hypotrichosis: Nicolaides-Baraitser syndrome

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Nicolaides-Baraitser syndrome (NBS) is a recognizable pattern of human malformations so far reported only in 5 patients. This condition is chiefly characterized by congenital hypotrichosis, peculiar facial gestalt, short metacarpals, interphalangeal swelling, and growth and mental retardation. Although skin manifestations represent a prominent NBS feature, no particular attention has been paid to this condition in the dermatologic literature. Here, we report on the sixth patient with NBS, who requested dermatologic evaluation because of congenital sparse scalp hair. An integrated approach that involved the dermatologist, clinical geneticist, and radiologist was crucial for diagnostic definition. Literature review was carried out to better define the NBS clinical spectrum and to perform an in-depth differential diagnosis with other malformation syndromes presenting with congenital hypotrichosis. (J Am Acad Dermatol 2008;59:S92-8.)

In 1993, Nicolaides and Baraitser[1] described a 16-year-old girl presenting with hypotrichosis, unusual facial appearance, characteristic hand anomalies, and growth and mental retardation. Based on the observed distinctive phenotype, the authors proposed that this concurrence of rare features might represent a discrete clinical entity. Accordingly, this condition was subsequently reported, using the appellation of Nicolaides-Baraitser syndrome (NBS) in 4 additional patients.[2-4] Although congenital hypotrichosis represents one of the NBS key features, pertinent articles were published exclusively in journals focused on clinical genetics and dysmorphology. Therefore, dermatologists may be completely unaware of this condition that might be encountered.

Here, we report a 9-year-old girl showing a constellation of findings well fitting NBS. To our knowledge, she represents the sixth case of this extremely rare malformation syndrome. Through a comparative analysis of the current and previously published cases, we refine the NBS phenotype and orientate an in-depth differential diagnosis with other malformation syndromes presenting with congenital hypotrichosis.

## CASE REPORT

The proband came to us with congenital hypotrichosis and additional dysmorphic features, which required evaluation by a clinical geneticist. She was a 8 and 7/12-year–old girl, first child of nonconsanguineous parents. The patient was born when the mother was age 32 years and the father was age 29 years. Her father and younger brother were healthy, whereas the mother presented at birth with "collodion baby," which subsequently evolved in nonbullous ichthyosiform erythroderma. The diagnosis of autosomal recessive congenital ichthyosis was confirmed by the identification of compound heterozygous mutations in the transgluminase 1 gene. Family history was otherwise negative. The mother stopped retinoids intake 3 years before conception and, during pregnancy, was not exposed to any teratogen. Serologic screening for cytomegalovirus, toxoplasmosis, and rubella revealed negative findings. Maternal glucose serum levels were always within normal limits and body mass index was below 29. Fetal ultrasound scan at 32 gestational weeks demonstrated mild intrauterine growth retardation without additional fetal and placental anomalies. Amniocentesis revealed a normal female karyotype.

The patient was born at term (40 weeks) by normal delivery. Birth weight was 2060 g (<0.4th

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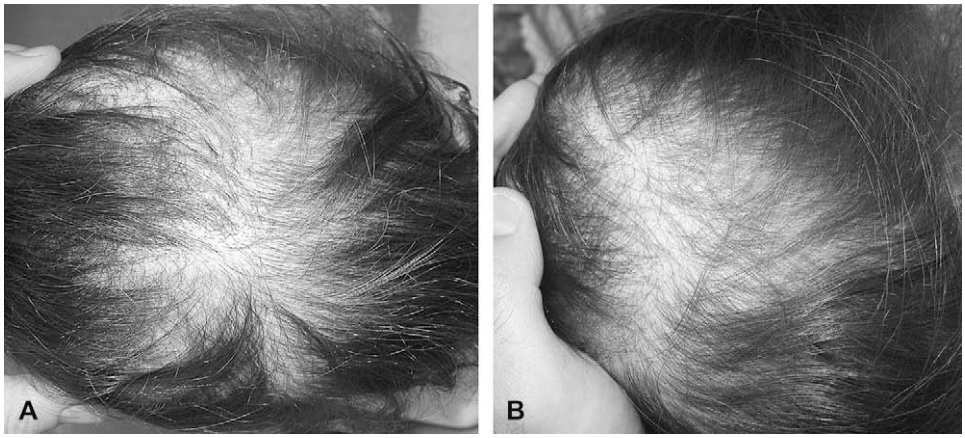


**Fig 1.** Sparse scalp hair on the vertex (**A**) and parieto-occipital region (**B**).

centile), length 46 cm (second centile), head circumference 33 cm (ninth centile), and Apgar score 8[1] and 9.[5] Because of the low birth weight, she was bottle fed for 10 days and gained weight without complications. Shortly after birth, small ostium secundum atrial septal defect and mild stenosis of the left pulmonary artery without significant hemodynamic consequence were noted and resolved spontaneously in a couple of months. The proband's mother noticed sparse scalp hair since a few weeks after birth. Patient's early development was within normal limits, as she obtained independent sitting at 6 months, walked at 17 months, and said first words at 19 months. However, although a true regression was not noticed, her subsequent progress was very slow. Dentition was normal.

At the time of examination, her weight was 20 kg (0.4th-2nd centile), height 121 cm (second centile), and head circumference 49.5 cm (0.4th centile). She had severe mental retardation (IQ < 35) with major difficulties in both verbalization and comprehension of verbal orders. For this reason, she required special school support. Her motor development was acceptable, as she was self-sufficient in indoor and outdoor walking and had good fine coordination and manipulative skills. However, she displayed clumsy running. On physical examination, hypotrichosis with hair of normal length, growth pattern, and texture was observed (Fig 1). Subcutaneous adipose tissue was scarcely represented and prominent umbilical stomp was also evident (Fig 2, *A*). Dysmorphologic examination revealed a constellation of facial anomalies including an inverted triangular shape, low front hairline, mild facial hirsutism, deep-set eyes, pointed nasal tip, thin nasal bridge, broad nares, relatively smooth philtrum, high-arched palate, and thick lower lip, although a true coarsening was not evident (Fig 2, *B*). In addition, the extremities revealed a peculiar aspect, consisting of "drumstick" fingers with prominent interphalangeal joints (Fig 2, *C*) and bilateral sandal gap. There was hyperlaxity of fingers contrasting with relatively limited motion of the large joints.

Microscopic examination of the hair under direct and polarized light did not reveal any anomaly. A complete metabolic screening, including serum amino and organic acids, lactate, ceruplasmin, copper, and zinc levels; biotinidase activity; transferrin eletrophoresis; and urine organic acid levels, revealed negative findings. Celiac disease and thyroid dysfunction were also excluded. Peripheral lymphocyte karyotype was 46,XX. Hand radiograph demonstrated bone age grossly concordant with chronologic age (Greulich and Pyle's standards[6]), bilateral ivory epyphysis of the fifth finger distal phalanx, and brachydactyly predominantly affecting the metacarpals (Fig 2, *D*). Metacarpophalangeal length measurement and profile pattern analysis demonstrated generalized long bone shortening particularly evident on the ulnar side (data not shown). Spine radiograph, brain magnetic resonance imaging, and kidney ultrasound all revealed negative findings. Audiologic and ophthalmologic surveys yielded normal results except for mild myopia.

## DISCUSSION

In our patient, permutation of growth retardation, developmental delay, peculiar facial appearance, congenital hypotrichosis, interphalangeal swelling, and short metacarpal bones is diagnostic for NBS. Characteristics of the current and the 5 previously described patients are summarized in Table I. Based on these data, a distinguishable pattern of dysmorphogenetic features for NBS emerges. Congenital hypotrichosis, moderate to severe mental retardation, and growth retardation often with prenatal

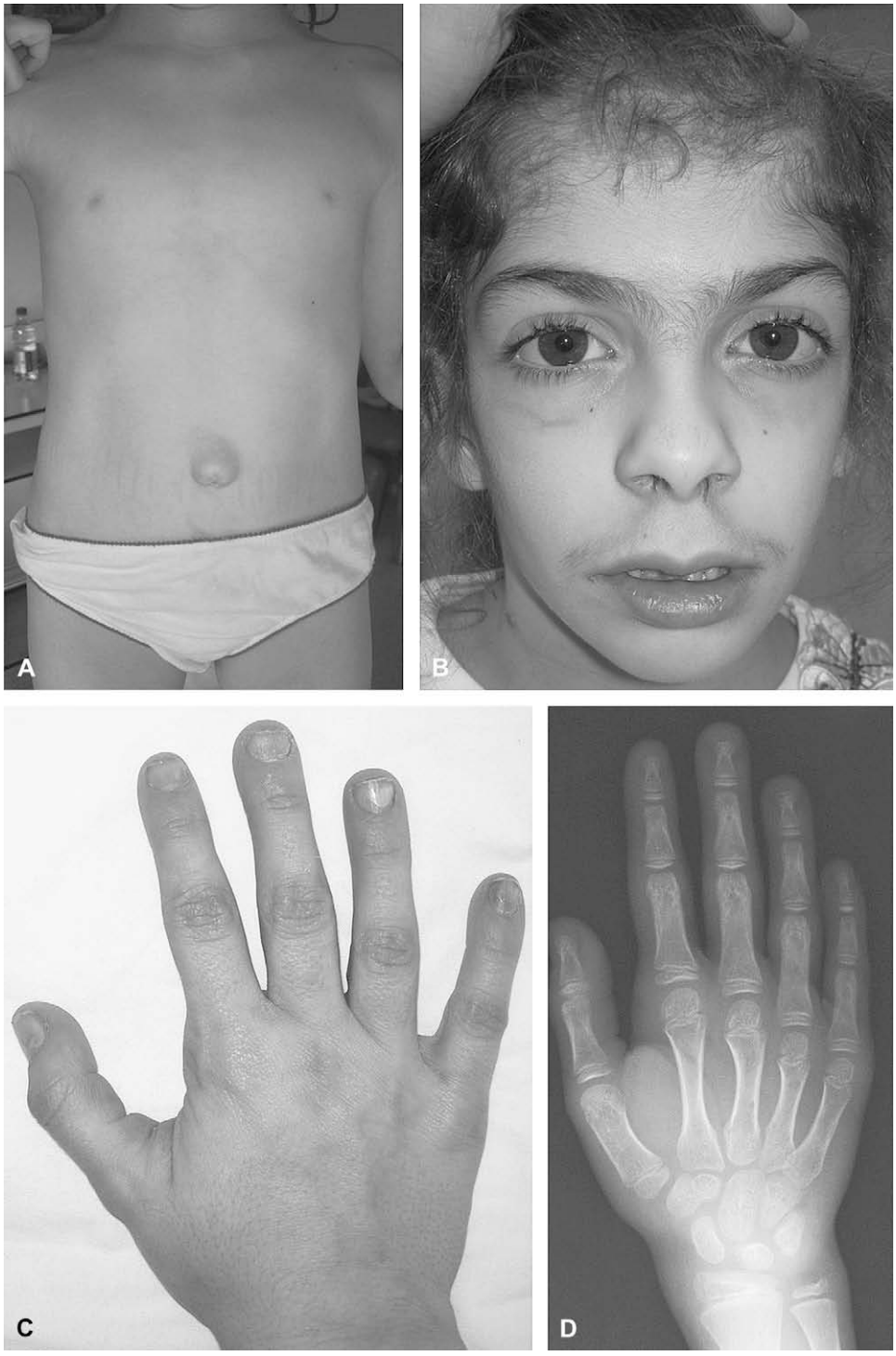


**Fig 2.** Deficient adipose tissue leading to lipoatrophic appearance; note prominent umbilical stomp (**A**). Peculiar facial gestalt consisting in triangular face, low front hairline with frontal hirsutism and mild synophrys, deep-set eyes, thin nasal bridge, broad nares, moderately flat philtrum, and prominent lower lip (**B**). Drumstick fingers with prominent interphalangeal joints (**C**). Hand radiograph (performed at age 8 and 7/12 years) showing bone age grossly concordant with chronologic age, bilateral ivory epiphysis of distal phalanx V, hypertrophic ungual tufts, generalized brachydactyly with particularly shortened metacarpals (**D**).

**Table I.** Characteristics of patients with Nicolaides-Baraitser syndrome

| Characteristic | Nicolaides and Baraitser[1] (1993) | Krajewska-Walasek et al[2] (1996) | Witters and Fryns[4] (2003) | Morin et al[3] (2003) | | Current patient | Total |
|---|---|---|---|---|---|---|---|
| | | | | Patient 1 | Patient 2 | | |
| Age at last examination, y | 16 | 19 | >18 | 6 | 22 | 9 | |
| Sex | F | M | F | F | F | F | |
| Maternal/paternal age, y | 23/39 | 22/26 | na/na | 25/26 | 25/na | 32/29 | |
| Consanguineous parents | − | − | − | − | − | − | 0/6 |
| IUGR/low birth weight | + | + | + | + | − | + | 5/6 |
| Postnatal growth retardation | + | + | + (Weight only) | + | + | + (Weight only) | 6/6 |
| Microcephaly | + | + | − | + | + | + | 5/6 |
| DD/MR | + (Severe) | + (Moderate-severe) | + (Moderate) | + (Severe) | + (Severe) | + (Severe) | 6/6 |
| Seizures | + | − | − | + | + | − | 3/6 |
| Hypotrichosis | + | + | + | + | + | + | 6/6 |
| Deficient adipose tissue | + | − | + | + | + | + | 5/6 |
| Prominent umbilical stomp | − | + | − | − | − | + | 2/6 |
| Facial dysmorphism | | | | | | | |
| Triangular face | + | + (Mild) | + | + | + | + | 6/6 |
| Deep-set eyes | + | + | + | + | + | + | 6/6 |
| Prominent ears | − | + | − | + | + | + | 4/6 |
| Posteriorly rotated ears | − | + | − | − | − | − | 1/6 |
| Pointed tip of nose | + | + | + | + | − | + | 5/6 |
| Thin nasal bridge | + | + | + | + | na | + | 5/5 |
| Broad nares | + | + | + | − | − | + | 4/6 |
| Long/flat philtrum | + | + | − | − | − | + | 3/6 |
| Thick lips (especially lower) | + | + | + | + | + | + | 6/6 |
| High-arched palate | + | + | + | − | − | + | 4/6 |
| Wide spaced teeth | − | + | − | + | − | − | 2/6 |
| Coarsening | + | − | + | + | + | − | 4/6 |
| Hand/foot anomalies | | | | | | | |
| Drumstick fingers | + | + | na | + | − | + | 4/5 |
| Interphalangeal swelling | + | + | + | + | + | + | 6/6 |
| Brachyphalangia | − | + | na | + | + | + | 4/5 |
| Cone-shaped epiphysis | + | − | na | + | − | − | 2/5 |
| Short metacarpals | + | + | na | + | + | + | 5/5 |
| Sandal gap | − | + | − | − | − | + | 2/6 |
| Scoliosis | − | − | + | + | + | − | 3/6 |
| Other features | Vesicoureteric reflux | Recurrent infections; cryptorchidism | − | Clubfoot; mild cerebral atrophy | Large joint contractures | − | 4/6 |

*DD/MR*, Developmental delay/mental retardation; *F*, female; *IUGR*, intrauterine growth retardation; *M*, male; *na*, not available.

**Table II.** Differential diagnosis of Nicolaides-Baraitser syndrome

| Feature | Nicolaides-Baraitser syndrome | Coffin-Siris syndrome | Tricho-rhino-phalangeal syndrome | Trichothiodystrophy | Cardio-facio-cutaneous syndrome |
|---|---|---|---|---|---|
| Growth retardation (prenatal and/or postnatal) | + | + | +/− (Type I); + (type II) | + | + |
| DD/MR | + | + | +/− (Type I); + (type II) | + | + |
| Facial dysmorphism | Triangular face, deep-set eyes, thin nasal bridge, prominent lower lip | Coarse face with broad nose, macrostomia and prominent lips | Bulbous and pear-shaped nose with notched alae nasi | Thin-beaked nose, protruding ears, receding chin | Coarse face, tall forehead, hypertelorism, down-slanting palpebral fissures |
| Cutaneous abnormalities | + | + | + | + | + |
| Sparse hair | + | + | + | + | + |
| Morphologic hair abnormalities | − | − | − | Brittle hair, trichoschisis, tiger-tail pattern | Brittle and curly hair |
| Follicular hyperkeratosis | − | − | − | + | + |
| Thick eyebrows | − | + | +/− | − | − |
| Hirsutism | +/− | + | − | − | − |
| Ichthyosis | − | − | − | + | +/− |
| Nail dystrophy | − | + (Fifth digit) | +/− | + | +/− |
| Deficient adipose tissue | + | − | − | − | − |
| Loose/redundant skin | − | − | + (Type II) | − | +/− |
| Hand abnormalities | + | + | + | − | − |
| IPJ swelling | + | − | − | − | − |
| IPJ lateral deviation | − | − | + | − | − |
| Brachydactyly | +/− | + (Fifth finger) | + | − | − |
| Short metacarpals | + | − | + | − | − |
| Cone-shaped epiphyses | +/− | − | + | − | − |
| Other key features | Seizures | Feeding difficulties; heart abnormalities; joint laxity; recurrent infections | Perthes-like anomaly; multiple exostoses (type II) | Photosensitivity; recurrent infections | Feeding difficulties; heart abnormalities*; seizures |
| Inheritance(s) | Sporadic | AR; AD (?) | AD (type I); contiguous gene syndrome (type II) | AR | AD |
| Gene(s) | Unknown | Unknown | TRPS1 | ERCC2, ERCC3, GTF2H5, TTDN1 | BRAF, KRAS, MEK1, MEK2 |

*AD*, Autosomal dominant; *AR*, autosomal recessive; *BRAF*, v-raf murine sarcoma viral oncogene homolog B1 (gene); *DD/MR*, developmental delay/mental retardation; *ERCC*, excision-repair, complementing defective, in Chinese hamster (gene); *GTF2H5*, general transcription factor IIH, peptide 5 (gene); *IPJ*, interphalangeal joint; *KRAS*, v-ki-ras2 kirsten rat sarcoma viral oncogene homolog (gene); *MEK*, MAPK/ERK kinase; *TRPS1*, tricho-rhino-phalangeal syndrome 1 (gene); *TTDN1*, trichothiodystrophy nonphotosensitive 1 (gene); +, common feature; **+/−**, occasional feature; −, never-reported feature.

*Pulmonary valve stenosis, atrial septal defect, and hypertrophic cardiomyopathy are the most common findings.

onset and resulting in deficient adipose tissue represent a constant triad. In particular, early development milestones seem to be reached within normal limits but subsequent progression is significantly delayed. Seizures, which were originally reported as a prominent feature,[1] are observed only in 50% of patients. Facial gestalt is striking and always characterized by an inverted triangular shape, deep-set eyes, thin nasal bridge, and thick lower lip. Pointed nasal tip and broad nares are quite common additional features. Coarsening seems progressive and may be unnoticed in some cases,[2] including the current one. Finally, hand anomalies, mainly including drumstick fingers, interphalangeal swelling, and stubby metacarpals, lead to a distinctive picture (Fig 2, *C* in this article and Fig 2 in Krajewska-Walasek et al[2]). Phalangeal shortening and progressive length alteration along the antero-to-posterior gradient, observed in our case, represent instead a previously unreported finding. However, we are not able to confirm this impression by metacarpophalangeal profile pattern analysis in other published cases because of the relatively low quality of available article copies.

In dysmorphology, the association of hypotrichosis, and growth and mental retardation, is not uncommon, as it may occur in at least 62 distinct conditions listed in the London Dysmorphology Database.[5] However, in most of them, the concurrence of sparse hair, and developmental and growth delay, in the same individual is exceptional and the constellation of additional findings makes straightforward the differential diagnosis. Therefore, only a limited number of these conditions may come to the attention of the dermatologist before a precise diagnosis has been made. In this setting, differential diagnosis of NBS mainly includes Coffin-Siris, tricho-rhino-phalangeal, and cardio-facio-cutaneous syndromes, and trichothiodystrophy (Table II).[7-10] An accurate evaluation of the clinical history, and of the facial, heart, and hand anomalies, drives the clinician toward the most probable diagnosis. However, examination of the skin and adnexa (especially, hair and nails) is of utmost importance to confirm the initial suspicion (Table II). In our patient, the concurrence of hypotrichosis and (mild) facial hirsutism mainly requests differentiation from Coffin-Siris syndrome. However, the characteristic pattern of hand anomalies, different overall facial appearance, and absence of hypotonia; feeding difficulties; and recurrent infections are not compatible with this condition.

Three additional genetic conditions, namely Menkes disease, and biotinidase and holocarboxylase synthetase deficiency, may present with hypotrichosis, and developmental and growth retardation.[11,12] These disorders usually display early and severe neurologic deterioration that poses little doubt about the hypothesis of an inborn metabolic disorder. However, in patients with partial biotinidase/holocarboxylase synthetase deficiency or with mild Menkes disease the diagnosis is usually delayed and, thus, NBS should be considered. Also in these cases, in addition to metabolic screening (ie, serum biotinidase activity, copper and ceruplasmin levels, and urine organic acid levels), skin examination can disclose specific clues, such as cutis laxa, hypopigmentation, and hair structural anomalies for Menkes disease, and eczematoid and xerotic lesions for biotinidase/holocarboxylase synthetase deficiency. Finally, in 1980, Dennis and Cohen[13] described two siblings presenting with features reminiscent of NBS but lacking microcephaly, characteristic hand anomalies, and growth retardation. In addition, an exhaustive metabolic screening was not carried out in these patients. Therefore, a syndromic classification of this family remains inconclusive.

NBS has been described so far in a total of 6 patients, all sporadic and born to unrelated parents. Five are female and one is male, but no differential disease expression between sexes is noted (Table I). At the moment, the origin of this condition remains unknown. The absence of consanguineous parents and advanced mean parental age at conception does not convincingly support both autosomal recessive and de novo dominant mutations. The skewed sex ratio suggests an X-linked dominant mutation; however, a contiguous gene syndrome or a still-unidentified environmental factor could be alternative hypotheses. Additional reports and molecular studies are needed to solve this issue.

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