CHILD Syndrome in 3 Generations

The Importance of Mild or Minimal Skin Lesions

Mario Bittar, MD; Rudolf Happle, MD; Karl-Heinz Grzeschik, PhD; Leonora Leveleki, PhD; Michael Hertl, MD; Dorothea Bornholdt; Arne König, MD

Background: CHILD syndrome (congenital hemidysplasia with ichthyosiform nevus and limb defects, Online Mendelian Inheritance in Man 308050) is an X-linked dominant trait with lethality for male embryos. The disorder is caused by mutations in NSDHL (Online Mendelian Inheritance in Man 300275), a gene playing an important role in the cholesterol biosynthetic pathway. Most reports deal with sporadic cases, and only 5 cases of mother-to-daughter transmission have been documented. We present here a family with mild features of CHILD syndrome in 3 generations. Molecular analysis was used to confirm the diagnosis.

Observations: We studied 14 members of a family with CHILD syndrome. The 23-year-old proposita, her mother, 2 aunts, and her grandmother presented with mild or minimal skin lesions that had been present since infancy. Analysis of the NSDHL gene showed missense mutation c.370G→A in these 5 patients. This mutation was absent in the 9 clinically unaffected family members tested.

Conclusions: In this family, we recognized CHILD syndrome with mild or minimal features in 3 generations because we were able to verify our clinical diagnosis by means of molecular analysis. We assume that many cases that so far have been considered sporadic may in fact be familial when a meticulous physical examination of female family members is combined with molecular testing.

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The term CHILD syndrome is an acronym that denotes congenital hemidysplasia with ichthyosiform nevus and limb defects.1,2 It is an X-linked dominant trait with lethality for male embryos (Online Mendelian Inheritance in Man 308050). The underlying mutations of the NSDHL gene (NAD[P]H steroid dehydrogenase–like protein) at Xq28 (Online Mendelian Inheritance in Man 300275) involve the cholesterol biosynthetic pathway.3 Characteristic clinical features are a peculiar inflammatory skin disorder called CHILD nevus,4 which has a unique lateralization pattern5 with strict midline demarcation and ptychotropism (affinity to body folds).2 Associated ipsilateral extracutaneous defects in the form of hypoplasia or aplasia may involve the limbs and other skeletal structures, as well as the viscera, such as lung, heart,6 and kidney.1

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About 60 cases have been reported so far. Most authors described sporadic cases demonstrating typical clinical features, with some atypical manifestations. Only 5 cases of mother-to-daughter transmission were documented.7-11 We present here a family with mildly affected members in 3 generations. We emphasize the importance of molecular analysis to confirm the diagnosis in cases with atypical or minimal involvement.

A pedigree of this family is shown in Figure 1.

CASE 1

The 23-year-old proposita presented with inflammatory skin lesions involving several areas on the left side of her body. The cutaneous changes had been noted first at the age of 1 year. The findings from the physical examination showed lesions of CHILD nevus in the vulvar region with lateralization, ptychotropism, and hypertrophy of the ipsilateral labium majus (Figure 2). Both hands had multiple periangual hyperkeratoses with fissuring, with onychodystrophy of the left index finger (Figure 3). On both fifth toes, linear hyperkeratoses with brownish scaling were noted. Both big toes showed onychodystrophy. Moreover, the patient had bilateral plantar hyperkeratotic plaques with fissuring. The left side of her body, including the face, hands, and feet, was...
somewhat smaller than the right side. The short left leg resulted in mild scoliosis.

CASE 2

The 47-year-old mother of the proposita also had 1 healthy son. She had had 2 miscarriages. She had recognized a linear erythematous lesion with scaling on her right middle finger approximately 30 years previously. The lesion had shown some waxing and waning. At physical examination, dystrophy of the corresponding nail was noted (Figure 4). No other abnormalities were found.

CASE 3

The 53-year-old aunt of the proposita had a healthy daughter. The aunt had had 1 miscarriage. She had aplasia of the distal phalanx of the left fifth toe with pronounced onychodystrophy. No other abnormality was noted.

CASE 4

The 62-year-old aunt of the proposita had asymptomatic longitudinal onychodystrophy of her left index finger present since childhood. She had 1 healthy son and 2 healthy daughters. No other pathological features were noted.

CASE 5

The 82-year-old grandmother of the proposita was not available for physical examination, but the family reported that since childhood she had had a linear hyperkeratotic lesion of her left fifth toe, similar to the lesions in her granddaughter (case 1).

RESULTS

After having obtained informed consent, we took blood samples for DNA analysis from the 5 described individual...
als and from 9 clinically unaffected family members as shown in Figure 1. The molecular findings obtained in case 1 have been published previously in a mutation report. Initial single-strand conformation analysis in case 1 did not show any NSDHL mutation, but DNA sequence analysis showed missense mutation c.370G→A in exon 4, which was confirmed by means of amplification refractory mutation system testing (Figure 5). This mutation that represents an amino acid change from glycine to serine, G124S, was likewise present in the 4 other cases as described. No NSDHL mutation was found in the 9 clinically unaffected family members tested. Moreover, the G124S mutation was undetectable in 100 healthy control subjects.

**COMMENT**

In this family, CHILD syndrome was diagnosed in 3 generations. Remarkably, 4 of the 5 affected women had such mild involvement that a definite diagnosis would have been impossible without molecular confirmation. For example, a small linear inflammatory lesion with some onychodystrophy of 1 finger was noted in case 2. From a clinician’s point of view, this sign would not have been sufficient to establish a definite diagnosis of CHILD syndrome. Hence, we are now able to expand the clinical spectrum of CHILD syndrome by including cases of atypical or minimal involvement.

The clinical diagnosis as established in the proposita enabled us to recognize 4 other family members with CHILD syndrome by means of a combined clinical and molecular examination. The mild manifestations in these 4 additional cases may be explained by extreme lyonization occurring at random.

Genetically induced skewing of X inactivation is another possible explanation. Studies of sister-sister correlation in healthy families have shown that preferential inactivation of a given X chromosome may be determined genetically by a locus on the long arm (Xq25-q26) and by a locus in the region of the X-inactivation center. Moreover, analysis of X-inactivation profiles in monozygotic vs dizygotic healthy twin pairs have likewise revealed a strong genetic component to nonrandom X inactivation. These studies allow the hypothesis that a genetic factor controlled by the X chromosome carrying the NSDHL mutation may have led to preferential inactivation of this X chromosome, which led to a mild phenotype in various female gene carriers in this family.

A third, albeit rather hypothetical, explanation would be a particular genotype-phenotype correlation. The missense mutation G124S as described in this family has not yet been described in any other case. Accordingly, one might hypothesize that this mutation generally is associated with a mild phenotype as observed in several members of this family. So far, however, the amount of molecular data obtained in patients with CHILD syndrome does not allow us to draw any conclusion regarding a genotype-phenotype correlation. On the contrary, the cohort examined by our group provides evidence that a genotype-phenotype correlation is unlikely in CHILD syndrome because we were able to demonstrate that, considering phenotypic involvement, point mutations are as fatal as partial or even complete deletion of the NSDHL gene.
gene. For the time being, we propose that the phenotypic variety in female carriers of NSDHL defects is caused by the more or less random effect of X inactivation rather than by specific effects of a given type of mutation.

Remarkably, carriers with mild or minimal involvement have been described in families with 1 severely affected member—for example, the mother of a girl with full-blown CHILD syndrome had some minor linear lesions on her hand.8 In another family, the sister of a severely affected patient had bilateral minor lesions of CHILD nevus mainly on her fingers and toes without any associated extracutaneous defect.7 These examples, as well as the present family, show clearly that an NSDHL mutation may lead to a multisystem birth defect in the form of classic CHILD syndrome or to mild involvement that can be overlooked easily. Therefore, a thorough examination of female family members, especially of the mother, is mandatory before establishing a diagnosis of sporadic CHILD syndrome.

For the practical purpose of genetic counseling, a combined clinical and molecular examination will help in recognizing individuals with only mild or minimal features of CHILD syndrome. Hence, cases that have so far been considered sporadic may be revisited in the light of present knowledge. Apart from cases with minimal involvement, it is likewise important to remember that cases with atypical manifestations such as bilateral, almost symmetrical distribution of CHILD nevus have been confirmed at the molecular level.14 These examples impressively demonstrate the broad range of clinical manifestations of CHILD syndrome.

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Correspondence: Mario Bittar, MD, Department of Dermatology, National University of Cuyo, Jujuy 134 Apt 1, M5500DDD, Mendoza, Argentina (mariobittar@web.de).
Author Contributions: Study concept and design: Bittar, Happle, and König. Acquisition of data: Bittar, Leveleki, and Bornholdt. Analysis and interpretation of data: Bittar, Happle, Grzeschik, Leveleki, Bornholdt, and König. Drafting of the manuscript: Bittar and Happle. Critical revision of the manuscript for important intellectual content: Happle, Grzeschik, Hertl, and König. Obtained funding: Happle, Grzeschik and König. Administrative, technical, and material support: Happle, Grzeschik, Hertl, and König. Study supervision: Happle, Grzeschik, and König. Financial Disclosure: None.

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