

SHORT COMMUNICATION

Large Deletions in the *NSDHL* Gene in Two Patients with CHILD Syndrome

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CHILD syndrome (congenital hemidysplasia with ichthyosiform naevus and limb defects) is a rare X-linked dominant disorder characterized by congenital hemidysplasia, a strictly lateralized ichthyosiform naevus and ipsilateral limb defects including limb hypoplasia or complete amelia. It may be accompanied by punctate cartilage calcification, joint contractures, scoliosis, neurosensory hearing loss and organ malformations. Mild contralateral anomalies may also be present. The disorder is caused by mutations in the *NSDHL* gene encoding a member of the enzyme complex that removes the C-4 methyl group from lanosterol in cholesterol biosynthesis. Different mutations, including missense mutations, nonsense mutations, deletions, insertions and splice site mutations, have been identified (1). We describe here 2 sporadic cases of Chinese girls with CHILD syndrome.

CASE REPORTS

Patient 1 was a 4-month-old girl who was born with an inflammatory ichthyosiform naevus on the right side of her body with malformation and absence of toes of the ipsilateral foot (Fig. 1). X-rays showed absence of the third and fourth phalangeal bones of her right foot. A biopsy obtained from lesional skin showed hyperkeratosis, parakeratosis, acanthosis and perivascular lymphocytic infiltrate.

Patient 2 was a 4-year-old girl who was born with an inflammatory epidermal naevus on the right side of her body and ipsilateral defects of fingers and toes (Fig. 2 A, E). The naevus aggravated intermittently, and she had defective teeth. X-rays showed hypoplasia of her right fourth distal phalanx and right metatarsal and digital bones (Fig. 2F). Her right femur was 0.8 cm longer than the left.

Initially, we did not detect a mutation in the *NSDHL* gene using PCR followed by DNA sequencing. Subsequently, we performed real-time quantitative PCR (qPCR) using SYBR-Green according to the methods described by Borozdin et al. (2) using 6 amplicons in exon 2, 4, 5, 6, 7 and 8 of the *NSDHL*

gene. The result indicated a heterozygous deletion including exon 4–7 of the *NSDHL* gene in patient 1 and a deletion including exon 5–8 in patient 2.

DISCUSSION

Although missense and nonsense mutations were more common, large exon deletions have been identified in some patients, such as a deletion encompassing the complete *NSDHL* gene, a deletion including exon 6–8, and a microdeletion encompassing promoter/enhancer region and exon 1 of the *NSDHL* gene (3–5). Our findings expand the spectrum of mutations in *NSDHL* in CHILD syndrome, and indicate that large exon deletions may be not rare. As CHILD syndrome was rarely correctly diagnosed and reported in China, molecular genetic analysis could help us to make the right diagnosis, and distinguish from other similar disorders with skin and limb abnormalities originating from impaired cholesterol synthesis, such as X-linked dominant chondrodysplasia punctata (CDPX2) (1).

A recent study reported surgical treatment using dermabrasion and skin grafting from the contralateral unaffected skin that yielded satisfactory results (6), and on the basis of the putative pathogenesis that both deficiency of cholesterol and accumulation of toxic metabolic intermediates, topical application of 2% cholesterol and 2% lovastatin could reduce inflammation, skin thickening, scaling and lead to complete reversion of CHILD naevus (7). Similar results were obtained with an ointment containing simvastatin and cholesterol (8). Oral and topical ketoconazole, which decreased the accumulation of toxic pathway metabolites and possibly the endogenous elevated levels of retinoic acid, resulted



Fig. 1. (A, B) CHILD naevus and absence of ipsilateral toes. Note the linear area of uninvolved skin on the right leg.



Fig. 2. (A, B) CHILD naevus with absence or malformation of ipsilateral fingers and toes. (C) Hypoplasia of the right metatarsal and digital bones.

in an effective treatment of the naevus (8). As some ichthyosis-related disorders showed good responses to acitretin, we treated our patients with systemic acitretin (0.5 mg/kg/day). Three months later the inflammatory reaction of the lesions was alleviated slightly but the naevus still grew intermittently.

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