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SHORT COMMUNICATION

Identification of a Novel Mutation in the *SLC39A4* Gene in a Case of Acrodermatitis Enteropathica

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Acrodermatitis enteropathica is an autosomal recessive disorder with hypozincaemia due to impaired intestinal absorption of zinc. It is the result of a mutation in the *SLC39A4* gene encoding the zinc transporter protein ZIP4. The symptoms develop shortly after weaning. Dermatological signs include highly exudative periorificial and acral lesions. The lesions are typically accompanied by alopecia, diarrhoea and impaired development.

We report here a case of an infant with typical dermatological signs of zinc deficiency. Zinc substitution resulted in rapid resolution of the symptoms. Genetic analysis revealed compound heterozygosity of a novel mutation c.1130_1140dup (p.Thr381Serfs*4) in the *SLC39A4* gene, inducing a premature stop codon at position 384, and the well-known mutation c.1120G>A (p.Gly374Arg).

CASE REPORT

An 8-month-old female breastfed infant developed erythema and papules in occipital, perioral, periocular, buccal and genital areas 3 weeks after weaning. Within a few days the lesions became more livid and crusty (Fig. 1, *top*), followed by blisters, abnormalities of the fingernails and diarrhoea.

Zinc substitution resulted in rapid resolution of the symptoms (Fig. 1, *bottom*). Genomic DNA from the patient was sequenced by a high-throughput method targeting the entire untranslated, intronic and exonic regions of *SLC39A4*, based on an enrichment by SureSelect technology (Agilent) and a reading by a Genome Analyzer IIx sequencer (Illumina), with a mean sequencing read depth of 227X. The variants identified were validated by double-stranded sequencing with Big Dye Terminator on ABI PRISM 3130XL. We identified 2 compound heterozygous mutations in exon 6 of the child's *SLC39A4* gene: c.1120G>A (p.Gly374Arg), inherited from the father, and c.1130_1140dup (p.Thr381Serfs*4), inherited from the mother.

DISCUSSION

Acrodermatitis enteropathica is a rare autosomal-recessive inherited disorder. It is caused by a bi-allelic mutation in the *SCL39A4* gene on human chromosomal region 8q24.3 encoding the zinc transporter protein ZIP4 (1, 2). Our patient exhibited the characteristic early dermatological symptom of the disease, which is a highly exudative periorificial and acral dermatitis. Usually, acrodermatitis enteropathica mutations become phenotypically manifest shortly after weaning, which was the case in our patient. The delayed occurrence of the symptoms in breastfed babies is explained by the higher bioavailability of zinc in human than in bovine milk. The usual decrease in zinc serum levels was not sought in our patient, but she presented with characteristic diarrhoea, which justified zinc substitution (3–5 mg zinc per kg body weight) resulting in rapid resolution of all symptoms (3, 4). By contrast, if supplementation is delayed, acrodermatitis is also typically accompanied by alopecia, and failure to

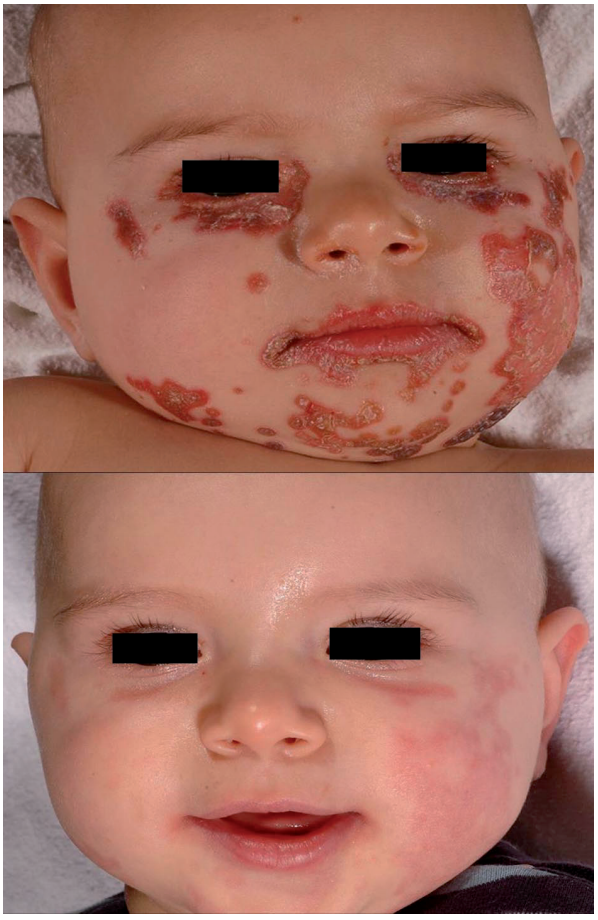

Fig. 1. The skin of the 8-month-old child before (*top*) and 3 weeks after (*bottom*) treatment.

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thrive. If untreated, acrodermatitis enteropathica is often lethal (3).

The intestinal zinc transporter ZIP4, encoded by *SLC39A4*, is the main actor of zinc homeostasis. Its mutations, observed in acrodermatitis enteropathica, lead to a changed protein processing, protein expression or a diminished transporting activity (3). Approximately 30 different acrodermatitis enteropathica mutations have been shown to affect the extracellular zinc-binding domain or 1 of the 8 transmembrane domains (5). In the case reported here both the already known p. c.1120G>A (p.Gly374Arg) and the newly identified c.1130_1140dup (p.Thr381Serfs*4) mutation affect the second transmembrane domain (6). The p.Gly374Arg mutation causes decreased cell surface expression of the ZIP4 protein, probably due to a failure in protein folding by an impaired N-glycosylation (7), whereas the p.Thr381Serfs*4 mutation induces premature truncation of ZIP4.

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No ethics approval was required, as analysis was necessary for diagnostic reasons to determine the lifelong necessity for zinc substitution.

The authors declare no conflicts of interest.

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