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Acrodermatitis enteropathica – a diagnostic challenge: case report of late-onset, genetically proven disease with normal zinc serum levels

Acrodermatitis enteropatica – wyzwanie diagnostyczne. Opis przypadku choroby o późnym początku, genetycznie potwierdzonej, przebiegającej z prawidłowym stężeniem cynku

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Abstract

Acrodermatitis enteropathica is a rare genetic metabolic disorder affecting the absorption of zinc ions in the digestive tract. The classic clinical manifestation of zinc deficiency, seen in about 20% of cases, is the triad of symptoms: acral and periorificial dermatitis, diarrhoea, and alopecia. This case report of a 16-month-old girl with an atypical course of acrodermatitis enteropathica posed a diagnostic challenge for clinicians. The first skin lesions appeared after infancy and initially presented as blisters; later, the patient developed a more severe clinical picture including erythematous plaques, paronychia, and alopecia. Zinc serum levels were within reference ranges. Genetic testing showed a pathogenic mutation characteristic of acrodermatitis enteropathica in the *SCL39A4* gene. Marked improvement in the healing of skin lesions was observed only after the initiation of oral zinc supplementation. Making a proper diagnosis in cases of metabolic disorders can significantly improve the patient's quality of life and prevent distant consequences, such as mental and physical retardation.

Keywords: acrodermatitis enteropathica, zinc, zinc deficiency, whole exome sequencing

Streszczenie

Acrodermatitis enteropathica jest rzadkim genetycznym zaburzeniem metabolicznym wpływającym na osłabione wchłanianie jonów cynku w przewodzie pokarmowym. Klasyczną manifestacją kliniczną niedoboru cynku, obserwowaną w około 20% przypadków, jest triada objawów: dystalne i okołoustne zapalenie skóry, biegunka i łysienie. Przedstawiono opis przypadku 16-miesięcznej dziewczynki z nietypowym przebiegiem *acrodermatitis enteropathica*, który stanowił wyzwanie diagnostyczne dla klinicystów kilku specjalności. Pierwsze zmiany skórne pojawiły się po okresie niemowlęcym i początkowo miały charakter pęcherzy, później rozwinął się obraz kliniczny obejmujący rumieniowe blaszki, zanokcicę i łysienie. Stężenie cynku w surowicy mieściło się w zakresie referencyjnym. Badanie genetyczne wykazało patogenną mutację charakterystyczną dla *acrodermatitis enteropathica* w genie *SCL39A4*. Zaobserwowano spektakularną poprawę gojących się zmian skórnych szybko po rozpoczęciu doustnej suplementacji cynku. Ustalenie poprawnego rozpoznania w przypadku zaburzeń metabolicznych może znacząco poprawić jakość życia pacjentów i zapobiec odległym konsekwencjom, takim jak upośledzenie umysłowe i fizyczne.

Słowa kluczowe: *acrodermatitis enteropathica*, cynk, niedobór cynku, sekwencjonowanie całego eksomu

BACKGROUND

Acrodermatitis enteropathica (AE) is a rare autosomal recessive disorder with a global incidence rate of 1–5:500,000 children, independent of gender and ethnicity[1]. The disease is characterised by a deficiency in the intestinal absorption of zinc, an essential trace element that plays a vital role in the proper functioning of various metabolic and biochemical pathways in the body[2]. It is caused by a partial or complete deficiency of the zinc ligand-binding protein, which is encoded by the *SLC39A4* gene on chromosome 8q24.3.2[1,3]. Classic clinical manifestations include periorificial and acral dermatitis, diarrhoea, and alopecia. The triad occurs only in 20% of cases[4]. The diagnosis of AE is based on specific clinical symptoms and low serum zinc levels[1,3,4]. Cases of inherited zinc deficiency can be fatal if left untreated[5]. The treatment of choice is life-long prompt zinc replacement with a dose of 3 mg/kg, which frequently leads to rapid clinical improvement within a few days[4]. In some cases, zinc deficiency can be acquired and secondary to abnormal intake or other chronic diseases[6]. In these cases, the clinical manifestations may be mild, and zinc supplementation can also be temporary, depending on the underlying cause[5]. Typically, the manifestation of inherited AE in infants is seen after weaning from breastfeeding or switching to formula or cow's milk, which contains a lower amount of exogenous zinc-iron transport proteins compared to breast milk[7]. Babies who are not breastfed tend to develop symptoms earlier – usually between the 4th and 10th weeks of life, when zinc stores from foetal life are depleted[5,7]. There is also a type of zinc deficiency in infants known as transient neonatal zinc deficiency, which can occur even in exclusively breastfed newborns due to low zinc concentrations in the mother's breast milk caused by maternal mutations in the *SLC30A2* gene[5,8].

The described case of AE is distinguished by unusual clinical features – an atypical onset, with the first symptoms appearing in the second year of life in a formula-fed baby, tense blisters for a prolonged period, and normal serum zinc levels. The final diagnosis was made using sophisticated genetic testing, specifically whole exome sequencing (WES).

CASE REPORT

A 16-month-old girl was admitted to the dermatology clinic with skin changes that appeared at the age of 14 months. The girl was born at term, without any complications, and developed normally. She is the first child of non-consanguineous parents with no history of skin diseases. She was never breastfed, and had been strictly formula-fed until the age of 6 months, after which solid foods were gradually introduced. At the age of 12 months, the formula was changed to a toddler-specific formula.

At the age of 13 months, she experienced an upper respiratory tract infection, which was treated with amoxicillin with clavulanic acid, with good results. One week after the

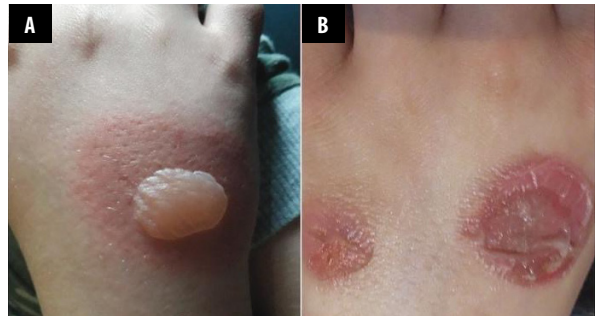

Fig. 1. Initial clinical features: **A.** *tense blisters on erythematous base suggesting EM;* **B.** *erosions resembling those observed in EB*

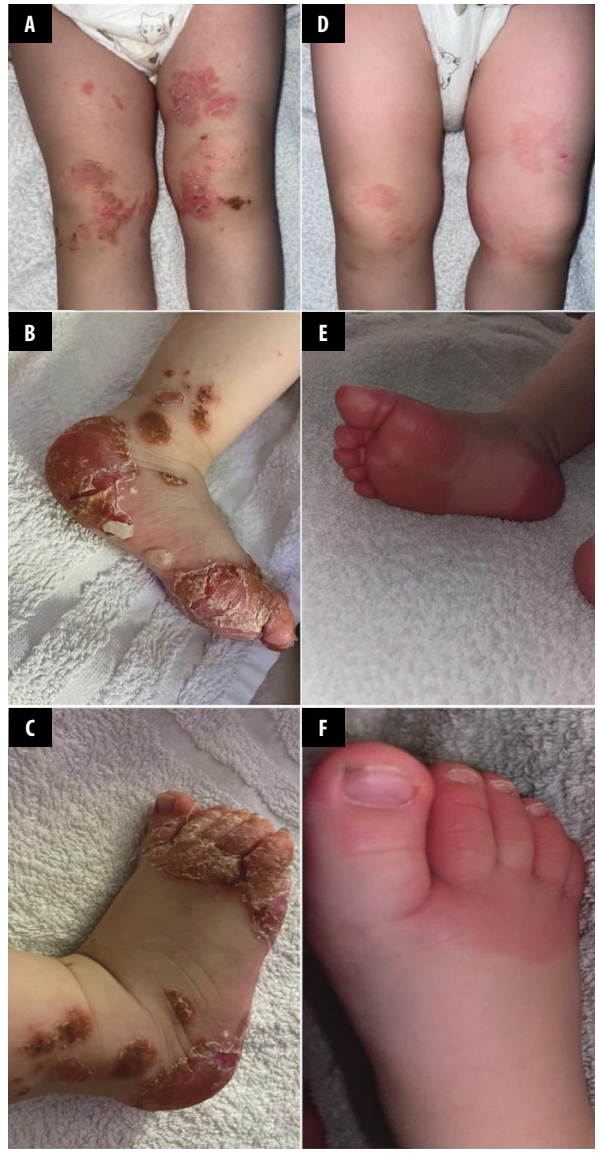

Fig. 2. Clinical features developed two months later: **A.** *symmetrical erythematous plaques with scaling and crusting at the periphery, located on traumatised areas (like in EBA);* **B, C.** *erythematous plaques covered by yellow crusts, resembling epidermolysis bullosa or epidermolytic ichthyosis;* **D, E, F**. *complete clinical remission after zinc supplementation*

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Fig. 3. Clinical appearance of scalp: **A.** *before developing the disorder;* **B.** *intense alopecia during the course of the disorder;* **C.** *trichoscopy of scalp – exclamation mark hairs and hair thinning*

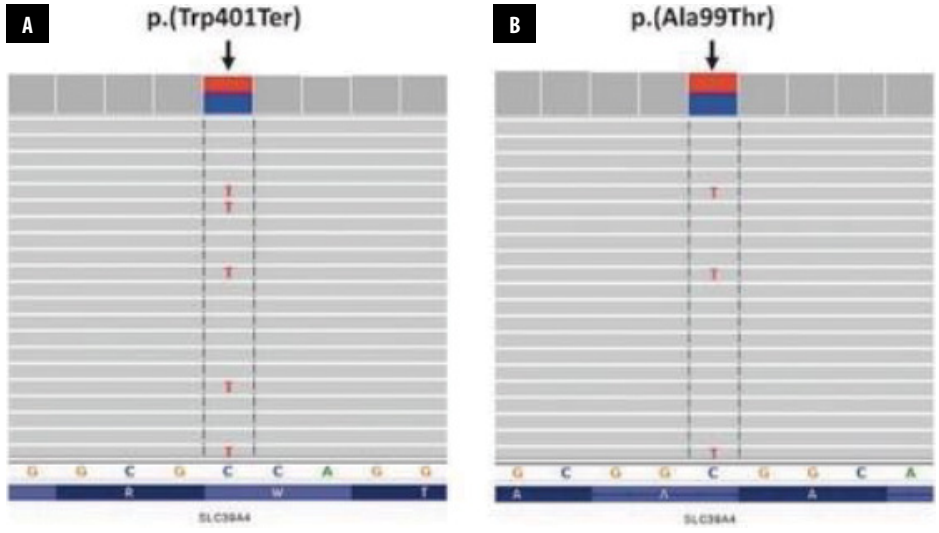

Fig. 4. WES results of the SLC39A4 *gene in proband sample:* **A.** *p.(Trp401Ter) variant;* **B.** *p.(Ala99Thr) variant*

initiation of antibiotic therapy, she developed perioral and diaper dermatitis, as well as a papular rash on her abdomen and legs. After a few days, painful blisters appeared on her feet and hands (Fig. 1 A, B), accompanied by paronychia, and the girl stopped walking. She also developed fungal stomatitis. One month after the appearance of the first skin changes, she experienced a 2-week episode of diarrhoea with 5–6 watery stools per day. Over the next three months, she was diagnosed with allergic dermatitis, drug-induced dermatitis, hand, food and mouth disease, and even epidermolysis bullosa (EB), and was treated topically with steroids, antibiotics, and antifungals, but without improvement. The child was nervous, weepy, anxious, and had no appetite.

During the physical examination, the girl was irritable and appeared to be in pain. Her weight and height were at the 50th percentile. She presented with symmetrical erythematous plaques involving the perioral and anogenital areas, as well as her legs, feet, and hands, with blisters on the soles (Fig. 2 A–C). She also had paronychia and non-scarring alopecia. Dermoscopy of the scalp revealed exclamation mark hairs and hair thinning (Fig. 3 A–C). Direct immunofluorescence (DIF) was negative. Routine tests including complete blood count, C-reactive protein, albumins, iron, cooper, and alkaline phosphatase (a zinc-dependent enzyme) were within reference ranges, including the zinc concentration – 7.94 µmol/L (normal range: 7.7–15.0). Given the normal but low serum zinc level, the diagnostic work-up was expanded to include genetic testing. The proband's DNA sample was isolated from peripheral blood using the NGS-based WES with the Human Core Exome Kit (Twist Bioscience, South San Francisco, CA, USA), according to the manufacturer's instructions.

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The enriched library was paired-end sequenced (2 × 100 bp) on NovaSeq 6000 (Illumina, San Diego, CA, USA) to a mean depth of 150× (GE10 99.6%, GE20 99.5%). Reads were aligned to the GRCh38 (hg38) reference genome. WES variant prioritization was performed as previously described[9].

The WES results revealed compound heterozygous variants in the *SLC39A4* in the proband [hg38 8:144414042-C>T, c.1203G>A NM_130849.4, p.(Trp401Ter) and hg38 8:144415989-C>T, c.295G>A, NM_130849.4, p.(Ala99Thr)] (Fig. 4 A, B). The p.(Trp401Ter) variant is nonsense, while the p.(Ala99Thr) variant is missense. According to the ClinVar database (https://www.ncbi.nlm.nih.gov/clinvar/), the p.(Trp401Ter) variant is predicted to be pathogenic. In turn, the p.(Ala99Thr) variant is classified in ClinVar as likely pathogenic, however its pathogenicity is predicted based on one submission. According to the gnomAD database (http://gnomad.broadinstitute.org/), the nonsense p.(Trp401Ter) variant has an allele frequency of 0.0000131, while the missense p.(Ala99Thr) variant has an allele frequency of 0.00000473.

On the basis of clinical presentation, low-normal serum zinc levels, and genetic findings, a diagnosis of AE was made. Oral replacement of zinc ions at a dose of 3 mg/kg/day in the form of zinc hydrogen aspartate led to prompt improvement in the patient's skin and general condition. After 2 months, the dosage of zinc supplementation was reduced to 1 mg/kg/day. The patient is now in clinical remission (Fig. 2 D–F) and developing normally.

DISCUSSION

This case presented a challenge for both paediatricians and dermatologists. For about 3 months, the patient's skin lesions were misdiagnosed by several doctors due to the atypical and evolving clinical features, as well as the patient's history. During the first admission to our dermatology clinic, the baby girl mainly presented with tense blisters forming a "string of pearls" configuration, located on traumatised areas (hands, knees, and feet) and on the face. As a result, genetic and autoimmune blistering disorders were initially taken into consideration[1]. The most common childhood disorders, such as linear IgA bullous dermatosis (LABD) and EB acquisita (EBA), were excluded using DIF. Furthermore, the most likely genetic disorders in infancy, i.e. EB or ichthyosis, were excluded based on the late onset of skin lesions, healthy skin at birth, and negative family history of hereditary skin diseases. However, it is important to note that some congenital blistering disorders may develop at a later age (e.g. progressive EB junctional – EBJ, dominant EB dystrophica – EBD).

Given the coincidence between the appearance of the first skin changes and the infection of upper respiratory tract treated with amoxicillin, erythema multiforme (EM) was initially considered[10]. Hair loss could also have suggested EM associated with infection. However, simple anti-inflammatory ointments did not improve the skin lesions within one month of therapy.

The clinical appearance evolved, with blisters beginning to heal, whereas red-brownish plaques covered by scaling appeared. Taking into account the clinical presentation and the chronology of new skin changes, the diagnosis of AE was most likely, but not obvious. AE usually starts with characteristic brown-reddish plaques, sometimes accompanied by blisters at the same time[1]. However, in this case, blisters preceded the characteristic AE lesions for a prolonged period. Moreover, in typical AE cases, skin changes in formula-fed babies occur in the first few weeks of life, whereas in breastfed babies, they typically appear after weaning[6,7]. It is unusual for breastfed infants to present with clinical features of zinc deficiency due to a mutation in the *SCL30A2* gene in the mother that results in low concentrations of zinc ions in breast milk[5,8]. The patient was formula-fed from the first day of life, but the initial skin changes appeared at the age of 14 months. The atypical disease onset suggests that a previous infection or antibiotic therapy caused the appearance of the phenotypic features of the disease. The mechanism that prevented the girl's genetic mutation from revealing itself for so long is unknown. In the literature, the aetiology of zinc deficiency is divided into four groups: insufficient intake (e.g. undernourishment), increased loss (e.g. disorders of the gastrointestinal or urinary tract), malabsorption (hereditary conditions like AE and cystic fibrosis, or acquired conditions such as gastrointestinal chronic inflammatory diseases like Crohn's disease and coeliac disease), increased requirement (e.g. in preterm infants)[6]. To determine whether the zinc deficiency was hereditary or acquired, we carried out genetic testing, which showed a mutation characteristic of AE in the *SLC39A4* gene. This protein has a similar structure to the zinc/iron-regulator transporter-like protein (ZIP) family. *SLC39A4* is located on the cell membrane and is essential for zinc uptake in the intestine. It is also believed to play a crucial role in zinc uptake in *Arabidopsis thaliana*, a model organism in genetics[11]. The variants studied in the *SLC39A4* gene were previously linked to AE[12]. The p.(Trp401Ter) variant was found in compound heterozygosity in Austrian patient in exon 7 of 12. The variant negatively affects the zinc-binding site and the last five transmembrane protein domains[12]. The p.(Ala99Thr) variant was identified in compound heterozygosity in an 11-month old boy and later in his newborn brother[13]. The studied variant was found in exon 2 localised in the hydrophobic core[14]. According to the PolyPhen-2 and SIFT prediction programmes, p.(Ala99Thr) possibly affects the zinc transporter protein[13].

In the literature, in most cases of AE, laboratory tests measuring plasma zinc levels typically show zinc concentrations below the lower limit[1]. However, zinc levels in serum or plasma have only limited value as biomarkers of zinc deficiency because they account for only 0.1% of zinc in the body[5]. Low zinc levels can also be observed in acute-phase reactions or hypoalbuminaemia in patients without zinc deficiency[2]. On the other hand, in some patients with the typical clinical presentation of AE (improved by a good response to zinc replacement), lab tests show normal zinc

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levels[2]. Therefore, the diagnostic path should be extended to include zinc-dependent enzymes like alkaline phosphatase, which is frequently decreased in patients with zinc deficiency[1]. In the current case, the alkaline phosphatase level was within the normal range. The laboratory test results for the presented patient showed a serum zinc level within the normal range, but close to the lower limit of norm. Interestingly, normal zinc levels in patients with AE can be observed in 30% of cases and do not rule out the diagnosis of AE[2]. Since zinc deficiency may lead to physical and mental retardation in infancy and also immunodeficiency[15], a WES genetic test has to be performed for a prompt diagnosis.

The main diagnostic clue in this case of AE was the rapid and significant response to zinc supplementation, involving the healing of the patient's skin lesions within a few days, improvement in her ability to walk, restored appetite, and subsequent hair regrowth. The girl remains under observation while taking a maintenance dose of zinc ions.

CONCLUSIONS

The purpose of presenting this case report is to emphasise that a rare disease like AE may have an unusual course. The case of the patient described here was extremely challenging in terms of diagnostics because of atypical initial clinical picture, onset after infancy, and normal serum zinc levels during the entire course, which can unfortunately be misleading. The final diagnosis in atypical cases, such as the one described in this publication, could only be made through genetic testing like WES. Making the correct diagnosis is important for the patients' long-term well-being. Lifelong supplementation of zinc ions can significantly improve the quality of life and prevent distant physical and mental impairment. While awaiting final results, ad hoc zinc substitution is a beneficial and low-risk treatment option.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the content of this publication and/or claim authorship rights to this publication.

Author contribution

Original concept of study: MSR, KW. Collection, recording and/or compilation of data: MSR, BW, EHP, KR, AW, RP, KW. Analysis and interpretation of data: MSR, BW, EHP, CK, KR, AW, RP. Writing of manuscript: MSR, RP, KW. Critical review of manuscript: CK, KW. Final approval of manuscript: KW.

Ethics approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki.

Consent for publication

Informed and written consent form was obtained from the patient's parents.

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