

Case Report

Prolidase deficiency with hyperimmunoglobulin E: A case report

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Prolidase deficiency is a rare, inherited disorder characterized by ulceration of the skin, mental retardation, and massive urinary excretion of imidodipeptides. Most patients also have recurrent infections, an unusual facial appearance, and splenomegaly. We describe a girl presenting with chronic dermatitis, recurrent respiratory tract infections since her first months of life, and a coarse face with hypertelorism and ocular proptosis. The diagnosis of prolidase deficiency was made at 4.5 months of age. The immunologic study in this patient showed an extreme and progressive increase of total immunoglobulin E (IgE) in serum (reaching the value of 77,600 IU/l) and defective chemotactic function of the neutrophils. Treatment with a hyper-proteic diet supplemented with ascorbic acid, manganese chlorite, and topical proline resulted in reduction of the frequency and severity of the infections and significant improvement of the skin lesions. The authors discuss the immunologic alterations and the favorable evolution with treatment in this patient.

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Prolidase deficiency (Mckusick 170100) is an innate error of the metabolism of proline and hydroxyproline, which occurs with an incidence of 1–2 per 1,000,000 persons and depends upon having an autosomal-recessive transmission whose gene is located to chromosome 19. Prolidase enzyme (imidodipeptidase, peptidase D) cleaves imidodipeptides, which result essentially from degradation of collagen (1–3). In most patients the disease onset occurs during the first year of life, but it may remain dormant until adulthood (1).

Clinically, prolidase deficiency is characterized by chronic dermatitis, recurrent ulcers of the lower limbs, frequent infections (otitis, sinusitis, pneumonia, and skin infections), and mental retardation in 50% of the patients. A prominent forehead, ptosis, and ocular proptosis (in the most severe cases), splenomegaly, anemia, hypotonia, and abnormalities of posture, may also be present (1–4).

The diagnosis is based on the high levels of proline and hydroxyproline in urine and can be

confirmed by evaluation of the enzymatic activity in erythrocytes, leucocytes, lymphocytes, fibroblasts, and amniocytes (1,4).

Some immunologic changes may be present, including increased levels of serum immunoglobulins (immunoglobulin A [IgA], immunoglobulin G [IgG], and immunoglobulin M [IgM]), decreased levels of complement system factors (C1q, C3, and C4), and impaired chemotaxis of the neutrophils (5). Prior to the present study, no reports have been made of the level of total immunoglobulin E (IgE) in prolidase deficiency.

There is no effective treatment for prolidase deficiency. However, a hyper-proteic diet supplemented with ascorbic acid and manganese chlorite (cofactors for prolidase activity) has been associated with clinical improvement and reduction of the imidodipeptiduria. The application of proline and glycine onto affected areas has been associated with an improvement of the skin lesions (1,6–8).

This individual patient was described at the time of diagnosis from the metabolic viewpoint

(9). We emphasize the existence of an extremely high level of total IgE in this patient and discuss the possible link between prolidase deficiency and hyperimmunoglobulin E syndrome (HIES).

Clinical case

A.L.C.F is a 7-year-old white girl, the first child of healthy, related parents (first-degree cousins). Pregnancy and delivery were uneventful. Her birth weight was 3,250 g and her length was 49 cm. She had a coarse face with hypertelorism and ocular proptosis. There was no family history of atopy. The karyotype was normal.

She had an apparently normal skin after birth, but in the first month an erythematous rash (with scaling) progressively appeared, becoming exudative with crust formation.

Analytically, she presented with anemia (hemoglobin 8.7 g/dL), an eosinophil count of 520/mm³, and increased total IgE (1,800 IU/ml). The metabolic study showed heavy imidodipeptiduria: total proline in urine was 10,908 µmol/mmol creatinine; total hydroxyproline in urine was 2,622 µmol/mmol creatinine (normal: 176–759); and the proline/hydroxyproline ratio was 41 (normal: 128).

The diagnosis of prolidase deficiency was established at 4.5 months of age by evaluation of the enzymatic activity in cultured skin fibroblasts (8 nmol/min/mg of protein; normal, 151 ± 25).

During the first year of life the patient had recurrent, severe infections (purulent otitis, two episodes of pneumonia, and skin infections), resulting in frequent hospitalization.

At 2.5 years of age the patient started a hyperproteic diet supplemented with ascorbic acid (100 mg/daily) and manganese chlorite (2 mg/daily). A decrease in the frequency and severity of the infections was achieved, but the erythematous rash with scaling persisted.

At 4.5 years of age the patient began topical application of proline on affected areas. Significant improvement of the skin lesions was verified (Fig. 1), but the imidodipeptiduria with a high proline/hydroxyproline ratio persisted.

The immunologic evaluation showed an elevated serum concentration of IgA (5.59 g/l), IgG (21.7 g/l), IgG₂ (2.75 g/l), and IgG₄ (1.95 g/l). The IgM level was normal (1.58 g/l).

The total IgE serum concentration progressively increased, reaching 77,600 IU/ml (Fig. 2). The eosinophil count varied between 0/mm³ (3) and 1,200/mm³ (3). Specific IgE for *Dermatophagoides pteronissinus* was class 4, and for *Dermatophagoides farinae* and dog dander was class 3. The patient also presented with impaired



Fig. 1. Coarse face with hypertelorism and ocular proptosis.

chemotaxis of neutrophils (as judged by neutrophil chemotaxis testing under agarose for homologous serum activated with Zymosan A (from *Saccharomyces cerevisiae* (Sigma-Aldrich Química, S.A., Sintra, Portugal). Normal phagocytosis and complement activity was found.

According to Grimbacher's scoring system for clinical and laboratory findings in individuals with HIES, this patient had a score of 34 points (affected patients have a score of ≥ 15 points) (10).

She never presented with serious staphylococcal or candida infections and did not develop pulmonary sequelae of infection. At present, at 7 years of age, she has achieved a reasonable weight gain (10th centile) and height gain (50th centile), and an adequate psychomotor development (QG 90; Griffith scales).

Discussion

Prolidase deficiency is a rare, inherited disease with variable clinical expression and prognosis. Up to 30 cases have been reported in the literature (1–3).

Patients with prolidase deficiency present with chronic dermatitis and recurrent bacterial infections, among other features. Variable immunologic abnormalities have been reported, including high titres of serum IgA, IgG, and IgM, reduction of some factors of the complement system (C3,

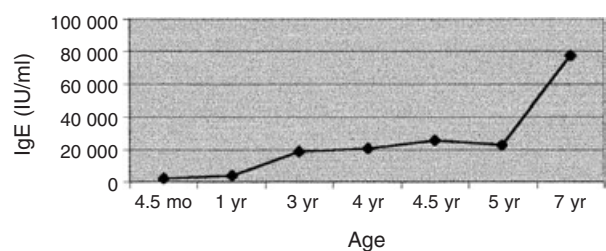


Fig. 2. Variation of total IgE levels with age.

C4, and C1q), and impaired chemotactic function of the neutrophils (1,5).

HIES is a rare primary immunodeficiency with marked variation in clinical symptoms and signs. Patients with HIES usually present with a coarse face, severe dermatitis with recurrent abscess formation, respiratory tract infections, and very high titres of serum IgE. Some also present with defective chemotaxis of the neutrophils (11,12).

The extremely high levels of total IgE detected in the patient described in this case report pose two diagnostic questions: can it be a feature related to prolidase deficiency, or is it a result of the association with HIES?

According to Grimbacher's scoring system for HIES, the child described in this case report can be considered as affected with HIES (10). However, the improvement of the skin lesions and the good evolution observed, without the occurrence of severe infections and abscess formation, are not suggestive of HIES.

HIES genetics is complex. This syndrome is expected to result from many independent mutations, indicating genetic heterogeneity. Some cases are consistent with a dominant inheritance with variable penetrance, but most cases are sporadic.

Grimbacher et al. scored 19 kindreds with multiple cases of HIES and genotyped the members with polymorphic markers in a candidate region on human chromosome 4. Linkage analysis confirmed the existence of a disease locus for HIES in the proximal 4q region; however, some families could not be linked to chromosome 4 (10).

The diagnosis of prolidase deficiency is well established in the child described in this case report. The locus of prolidase deficiency is mapped to the long arm of chromosome 19. Further genetic studies might elucidate an eventual linkage between HIES and prolidase deficiency in this patient.

There is no effective treatment for prolidase deficiency. The introduction of a diet supplemented with amino acids, ascorbic acid, and manga-

nese chlorite can lead to clinical improvement (1,2). Transfusions with erythrocytes, previously activated at 37°C with manganese chlorite, have been attempted, but with little success (1,2). Recently, a mixture of proline and glycine has been applied topically to the skin lesions, with good results (6–8). In the patient of this case report, a significant improvement was verified following topical application of proline and glycine to the skin lesions.

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