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The Clinical Landscape with Biochemical and Immunological Indicators of Prolidase Deficiency

Prolidaz Eksikliğinin Biyokimyasal ve İmmünolojik Göstergeleriyle Klinik Görünümü

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Abstract

This article examines Prolidase Deficiency (PD), an autosomal recessive disorder marked by diverse clinical symptoms and significant biochemical and immunological abnormalities. Originating from mutations in the peptidase D (PEPD) gene, PD disrupts the metabolism of proline-rich proteins, leading to a range of manifestations. Clinically, PD presents early with growth delays, recurrent infections, and autoimmune disorders, with neurological impacts including developmental delays and intellectual disabilities. Skin issues like chronic ulcers and eczema are common, and respiratory complications add to the disease's complexity. Gastrointestinal features and hematological conditions such as anemia and thrombocytopenia further complicate PD. Immunologically, PD is associated with hypergammaglobulinemia and systemic lupus erythematosus (SLE), highlighting the immune system's involvement. Biochemically, imidopeptiduria serves as a critical diagnostic marker. Diagnostics range from high-performance liquid chromatography to MALDI-TOF MS, while treatment strategies are diverse, reflecting the challenge of managing PD. This study emphasizes the need for a comprehensive approach to understand and manage the multifaceted nature of PD.

Keywords: Prolidase, PEPD gene, Hypergammaglobulinemia, Hypocomplementemia, Imidopeptiduria, Autosomal recessive.

Özet

Bu makale, çeşitli klinik semptomlar ve önemli biyokimyasal ve immünolojik anormalliklerle karakterize otozomal resesif bir hastalık olan Prolidaz Eksikliğini (PE) incelemektedir. Peptidaz D (PEPD) genindeki mutasyonlardan kaynaklanan PE, prolin açısından zengin proteinlerin metabolizmasını bozarak çeşitli belirti ve bulgulara yol açar. Klinik olarak PE, büyümede gecikme, tekrarlayan enfeksiyonlar ve otoimmün bozukluklarla birlikte, gelişimsel gecikmeler ve zihinsel engeller gibi nörolojik etkilerle erken dönemde ortaya çıkar. Kronik ülser ve egzama gibi cilt sorunları yaygındır ve solunum komplikasyonları hastalığın karmaşıklığını artırmaktadır. Gastrointestinal özellikler ve anemi ve trombositopeni gibi hematolojik durumlar PE'yi daha da karmaşık hale getirir. İmmünolojik olarak PE, bağışıklık sisteminin katılımını gösteren hipergammaglobulinemi ve sistemik lupus eritematozus ile ilişkilidir. Biyokimyasal olarak imidopeptidüri kritik bir tanısal belirteç görevi görür. Teşhis, yüksek performanslı sıvı kromatografisinden MALDI-TOF MS'ye kadar çeşitlilik gösterirken tedavi stratejileri de çeşitlidir ve PE yönetiminin zorluğunu yansıtır. Bu çalışma, PE'nin çok yönlü doğasını anlamak ve yönetmek için kapsamlı bir yaklaşıma olan ihtiyacı vurgulamaktadır.

Anahtar Kelimeler: Prolidaz, PEPD geni, Hipergammaglobulinemi, Hipokomplementemi, İmidopeptidüri, Otozomal resesif.

Introduction

Prolidase (E.C. 3.4.13.9), a key cytosolic peptidase, is critical for the catabolism of endogenous and dietary proteins, specifically by cleaving proline or hydroxyproline residues at the terminal stage of protein metabolism [1,2]. This enzyme is integral to the breakdown and recycling of collagen and proline-dense proteins [1–3]. Genetic defects in the peptidase D (PEPD) gene, responsible for prolidase synthesis, result in a rare autosomal recessive disorder known as prolidase deficiency (PD) [4–6]. Treatment of PD is intricate, requiring a comprehensive approach across various systems, and remains without a definitive cure [7]. PD's biochemical signature includes significant imidodipeptiduria, especially of x-proline and x-hydroxyproline, with these dipeptides also showing elevated levels in plasma, attributed to impaired prolidase function [8,9]. Confirming a PD diagnosis involves measuring cellular prolidase activity and identifying mutations in the PEPD gene [10]. The phenotypic variability observed among affected individuals, even within the same family, and the elusive genotype-phenotype correlation present ongoing research challenges [11,12]. This study aims to encapsulate the full spectrum of phenotypes documented in PD cases with confirmed molecular diagnoses, address the divergent clinical presentations, and explore the functional studies that may elucidate further aspects of this mysterious condition.

Initial Manifestations

Prolidase deficiency often first manifests as a variable combination of growth delays, organ enlargement, recurrent infections, skin lesions, autoimmune responses similar to systemic lupus erythematosus (SLE), elevated IgE levels, and blood cell deficiencies, including anemia and thrombocytopenia [12–14]. Symptoms typically arise in early childhood, usually before the age of two, although the age and severity of onset can vary even among family members [6,11]. Skin lesions, while common, are not always the initial indicator; rather, symptoms tend to emerge gradually from infancy to the third decade of life, with some experiencing a late onset of symptoms like leg ulcers in their thirties [4,6,12].

Neurological Symptoms

A significant proportion of individuals with prolidase deficiency, more than half, exhibit developmental delays or intellectual disabilities ranging from mild to severe [4,12,15–17]. However, reports indicate that some patients in different ages presented no developmental setbacks. Instances of developmental normalization, speech, and motor delays have also been documented [6,12,18]. Neurological diversity, even among siblings, points to additional influencing factors. Notably, other neurological symptoms include bilateral hearing loss, vision impairment, and seizures, particularly in a patient with PD-related SLE showing magnetic resonance imaging evidence of central nervous system involvement [14,19,20]. Imaging in other cases has revealed cerebral microthrombosis and slight brain atrophy [20,21].

Skin Findings

Prolidase deficiency encompasses various skin symptoms. Chronic ulcers are noted in most of the patients, typically manifesting in childhood and predominantly on the lower extremities. These ulcers may occur without obvious triggers and do not necessarily indicate PD if absent [4,22]. Additional symptoms include eczema, reported in most cases, often with associated rashes varying in appearance from erythematous to purpuric [22–25]. Telangiectasias were observed in majority of patients, frequently on the lower limbs [22,26–28].

Respiratory Complications

Respiratory issues, such as recurrent infections and pneumonia, affect the vast majority of PD patients, presenting a significant clinical challenge [4,17,22,25,29–31]. A 2016 study that examined 21 patients, has highlighted a high incidence of chronic lung disease and features like bronchiectasis and fibrosis on computed tomography scans, emphasizing the need for vigilant respiratory management in PD [32]. Complications like pulmonary fibrosis have been observed, with some patients showing progressive lung damage despite treatment [33,34]. These respiratory difficulties are a critical concern in PD management and patient

prognosis, though specific data on life expectancy impacts are yet to be detailed.

Gastrointestinal Features

In prolidase deficiency, splenomegaly is common, with some cases necessitating removal [12,19]. Over half of the patients exhibit liver enlargement, hepatosplenomegaly [35,36]. Gastrointestinal complications include gastric and colonic ulcers, even in very young patients, and conditions mimicking Crohn's disease with findings such as serpiginous ulcers and pseudopolyps [37,38]. These symptoms require careful gastrointestinal evaluation in PD management.

Hematological Complications

In PD, anemia is a prevalent condition, affecting 76% of patients, some of whom also have SLE [6]. This anemia can present as microcytic hypochromic due to iron deficiency or as hemolytic anemia confirmed by a positive Coombs test [6]. Additionally, more than half of the patients experience thrombocytopenia, further complicating their clinical management [12,23,25,30,36,39].

Immunologic Disorders

Immunological disorders observed include hypergammaglobulinemia with elevated IgE levels, systemic lupus erythematosus, and hypocomplementemia with reduced C3-C4 levels [17,40]. Hypergammaglobulinemia IgE was identified in more than half of the subjects [3,17,35,36,39], accompanied by heightened expressions of IL-23 and TNF-alpha [39].

SLE or SLE-like conditions were documented in some of the patients [13,40]. Around 10% of patients with complete deficiency exhibited SLE [41]. Some patients displayed antibodies against Sm antigens, the Ro-hYRNA complex, chromatin, or native DNA, while others developed either an incomplete form of lupus or full-blown SLE [41].

Hypocomplementemia was found in almost half of the group, with some of these cases also having SLE [19,40]. Normal levels of C1q were noted [41], but CH50 levels were not reported. Additionally, raised IgG levels and decreased neutrophil chemotaxis were also observed [17,19,22,40].

Imidopeptiduria

Imidopeptiduria as a biochemical marker

In PD, analysis of urinary amino acids showed significant excretion of imidodipeptides like proline-glycine or proline-hydroxyproline in all tested patients [4,7,8]. This massive excretion of imidodipeptides, negligible in healthy individuals, is a key biochemical marker for PD diagnosis. These dipeptides also accumulate in patients' fibroblasts and blood [4], with serum levels being lower than in urine.

Diagnostic methods for imidopeptiduria

Imidopeptiduria is often diagnosed using high-performance liquid chromatography (HPLC), identified by high ninhydrin-positive peaks [7]. These peaks are confirmed after hydrolyzing urine samples and reanalyzing for proline and hydroxyproline profiles. Other diagnostic methods include exchange chromatography, thin-layer chromatography, capillary electrophoresis, and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) [7,8]. Early detection is possible in newborns, even if asymptomatic. However, increased imidodipeptides excretion is also reported in conditions like increased bone turnover, multiple fractures, osteomalacia, and rickets [6,42].

Confirmatory Tests and Treatment Trials

The definitive diagnosis of PD involves measuring cellular enzymatic activity or genetic sequencing of PEPD [10–12,17].

A study investigating urinary proline-containing dipeptides found no direct correlation between these levels and supplementation with $MnCl_2$, vitamin C, and L-proline, although urinary dipeptide levels generally decreased during treatment [25]. Additionally, in an apheresis exchange trial conducted monthly for four months, urine tests in two patients showed reduced concentrations of imidodipeptides [23].

Other

In a study, researchers explored the correlation between prolidase enzyme activities in

varicose venous walls and seminal fluid with sperm parameters in patients suffering from grade 3 varicocele. The study uncovered a significant negative correlation between sperm counts and the activity of prolidase enzyme in varicose venous walls, alongside a positive correlation with the enzyme's activity in seminal fluid. However, no significant link was found with respect to sperm motility. These findings underscore the potential role of varicose venous wall prolidase enzyme activity in the progression of azoospermia and infertility among varicocele patients, offering new insights into the impact of this enzyme on male fertility [43].

Conclusion

This study highlights the complex nature of PD, characterized by a spectrum of clinical manifestations and significant biochemical and immunological markers. The variability in symptoms and the systemic impact of PD emphasize its multifaceted nature. The role of imidopeptiduria as a diagnostic marker is particularly notable. Despite advances in understanding PD, challenges remain in its management and treatment. This underscores the need for continued research to improve diagnostic precision and therapeutic approaches for PD.

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