Revista de Ciencias Médicas de Pinar del Río

ISSN: 1561-3194 **RNPS:** 1877
Rev Ciencias Médicas. 2025; 29(S2): e7043

REVIEW ARTICLE

Multidisciplinary approach to the management of Proteus syndrome: literature review on its congenital and multisystemic manifestations

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Received: December 30, 2025
Accepted: December 31, 2025
Published: December 31, 2025

Citar como: Herrera-Panchi MP, Baño-Yanchapanta AC, Pilamala-Camino AN, Mejía-Flores NV. Enfoque multidisciplinario en el manejo del síndrome de Proteus: revisión bibliográfica sobre sus manifestaciones congénitas y multisistémicas. Rev Ciencias Médicas [Internet]. 2025 [citado: fecha de acceso]; 29(S2): e7043. Disponible en: http://revcmpinar.sld.cu/index.php/publicaciones/article/view/7043

ABSTRACT

Introduction: Proteus syndrome is an extremely rare congenital disease characterized by excessive and heterogeneous tissue growth, posing a clinical and therapeutic challenge for healthcare teams.
Objective: to analyze the available scientific evidence in order to describe the clinical manifestations, diagnosis, and multidisciplinary management strategies of Proteus syndrome.
Methods: a systematic review of the scientific literature was conducted across various databases. The search was performed using an algorithm with keywords and Boolean operators, allowing the identification of relevant sources. Selected studies, after applying inclusion and exclusion criteria, were critically analyzed considering timeliness, methodological quality, and thematic relevance, and integrated into the final synthesis of the review.
Development: the findings highlight the clinical heterogeneity of the syndrome, with cutaneous, osseous, vascular, and neurological involvement. The somatic mutation in the AKT1 gene explains tissue overgrowth and opens therapeutic perspectives targeting the PI3K/AKT/mTOR pathway. Nursing plays an essential role in early detection, education, and emotional support, within teams that include geneticists, surgeons, physiotherapists, and psychologists. The need for standardized protocols and international cooperation to improve diagnosis and treatment is emphasized.
Conclusions: a multidisciplinary approach is indispensable to optimize the management of Proteus syndrome. Nursing is consolidated as a central axis in comprehensive care, while genetic advances offer new therapeutic possibilities. The rarity of the disease demands global collaboration and ongoing research to strengthen diagnostic and therapeutic strategies.

Keywords: Congenital Abnormalities; Genetic Diseases, Inborn; Rare Diseases; Proteus Syndrome.

ISSN: 1561-3194 **RNPS:** 1877
Rev Ciencias Médicas. 2025; 29(S2): e7043

INTRODUCTION

Proteus syndrome is an extremely rare congenital disorder characterized by excessive overgrowth of tissues and organs, with multisystemic manifestations including skeletal malformations, skin and adipose tissue overgrowth, vascular anomalies, and benign tumors. First described in 1979 by Cohen and Hayden, this condition results from a somatic mutation in the *AKT1* gene, which regulates the PI3K/AKT/mTOR signaling pathway, affecting cellular growth and tissue development.[1] It presents with a wide variety of symptoms, all characterized by focal macrodactyly, partial gigantism of hands/feet, characteristic cerebriform dermatoglyphs on palms and soles, hemihypertrophy, subcutaneous tumors (lymphangiomas and lipomas), pigmented nevi, and focal megalencephaly, among others. The syndrome is also pleomorphic over time.[2]

Proteus syndrome exhibits a broad and variable clinical spectrum, complicating early diagnosis and optimal management. This disorder is characterized by hypercellularity and heterogeneity of affected tissues, which can lead to severe complications such as pulmonary embolisms and high surgical risks due to asymmetric overgrowth of different body parts.[3]

Comprehensive management of Proteus syndrome requires close collaboration among multiple medical specialties, including plastic surgery, orthopedics, dermatology, and medical genetics. Corrective and reconstructive surgery plays a crucial role in improving patients' quality of life by addressing significant bone and skin deformities that may limit mobility and cause chronic pain.[4]

Nursing plays a fundamental role in the care of patients with Proteus syndrome, providing comprehensive support ranging from postoperative wound management to patient and family education about the disease and its long-term management. Nursing care focuses on continuous monitoring of vital signs, administration of specific therapies, and emotional support for both the patient and caregivers.[5]

Genetically, Proteus syndrome is primarily associated with somatic mutations in the *AKT1* gene, affecting the PI3K/AKT/mTOR signaling pathway. This pathway is crucial in regulating cellular growth and tissue differentiation, explaining the excessive growth patterns observed in affected patients.[6] Recent research has highlighted the role of therapies targeting the PI3K/AKT/mTOR pathway as potential treatment options for Proteus syndrome, showing promising advances in reducing tissue overgrowth and improving quality of life. However, challenges remain regarding therapy accessibility and management of secondary complications.[7]

Clinically, the diagnosis of Proteus syndrome is based on established clinical criteria, including progressive asymmetric overgrowth and specific anomalies in affected organs and tissues. Molecular genetic confirmation via sequencing is crucial to differentiate the syndrome from other conditions with similar clinical overlap, such as CLOVES syndrome.[8]

Multidisciplinary management of Proteus syndrome requires a holistic approach that addresses not only medical and surgical aspects but also psychological and social dimensions for the patient and their family. Integration of physical and occupational therapies is essential to optimize function and quality of life throughout the patient's lifespan.[9]

ISSN: 1561-3194 **RNPS:** 1877
Rev Ciencias Médicas. 2025; 29(S2): e7043

Currently, research on Proteus syndrome is at a critical stage. Despite advances in understanding this rare congenital disorder, there is still no consensus on etiology, diagnosis, or treatment options. Available scientific literature is fragmented and limited, hindering the development of comprehensive care strategies. Additionally, the multisystemic manifestations of Proteus syndrome are highly variable and complex, complicating clinical diagnosis and management. Given these considerations, this review was conducted to analyze available scientific evidence to describe the clinical manifestations, diagnosis, and multidisciplinary management strategies of Proteus syndrome.

METHODS

This study was designed as a systematic bibliographic review to synthesize available scientific evidence on Proteus syndrome and its multidisciplinary management. The search period spanned from January 2019 to July 2024 to include recent and relevant literature.

Information sources included PubMed, SciELO, Dialnet, Redalyc, Google Scholar, and ScienceDirect, supplemented with secondary references from bibliographies of relevant articles. Grey literature was excluded due to limited availability of peer-reviewed, full-text documents. The search strategy used keywords and Boolean operators, including terms such as "Proteus syndrome" AND "multisystemic manifestations" OR "comprehensive approach" OR "nursing." Publications in Spanish, English, and Portuguese were considered to ensure broad coverage.

Inclusion criteria were: articles published between 2019 and 2024, case reports, systematic or narrative reviews, and clinical reports directly related to Proteus syndrome. Duplicates, articles without full text, publications outside the defined timeframe, and irrelevant documents were excluded.

The selection process occurred in two phases: first, title and abstract screening to exclude non-relevant records; second, full-text review of eligible articles. Initially, 230 records were identified; 60 duplicates and 123 non-compliant records were removed. Finally, 20 articles were included in the synthesis. The procedure was represented using a PRISMA flow diagram (Figure 1), illustrating identification, screening, eligibility, and inclusion stages.

Data extraction was performed systematically, collecting key variables such as author, publication year, study design, number of cases or sample size, main findings, and journal of publication. Analysis was qualitative, grouping results into thematic categories: clinical manifestations, diagnosis, multidisciplinary management, and nursing role. No meta-analysis was performed due to design and outcome heterogeneity.

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Rev Ciencias Médicas. 2025; 29(S2): e7043

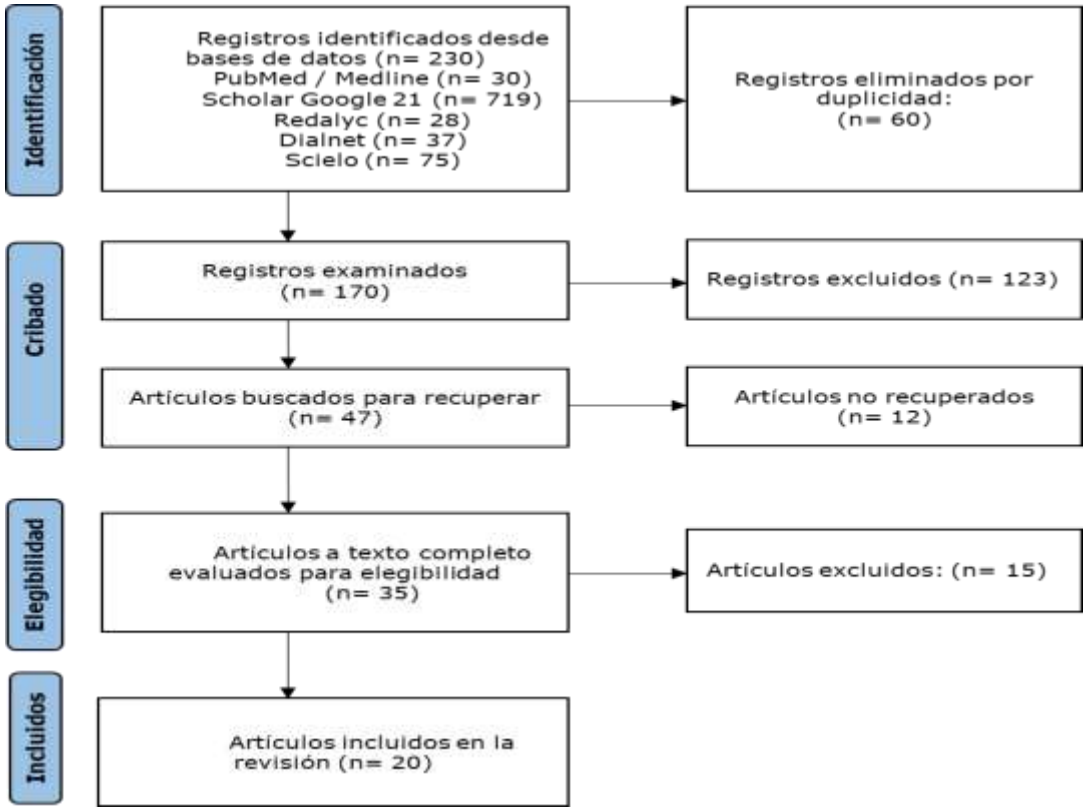

Figure 1. PRISMA-based selection process.

DEVELOPMENT

Analysis of the scientific literature revealed several relevant aspects regarding Proteus syndrome and its comprehensive nursing approach for this congenital condition with multisystemic manifestations. Table 1 presents findings from various reported case studies. These clinical cases highlight the heterogeneity of Proteus syndrome manifestations, which can affect the skin, bones, vascular system, and nervous system, among others. Reports emphasize the importance of a multidisciplinary approach from early disease stages, involving specialists such as geneticists, to achieve early diagnosis and appropriate comprehensive management planning.

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Table 1. Findings and evidence from evaluated scientific articles.

Source	Year	Description
Yabar R et. al.,[10]	2019	Two Proteus syndrome cases referred to Genetics: one for craniofacial dysmorphism, the other with suspected diagnosis. Both required multidisciplinary evaluation and management.
Peña J et. al.,[11]	2021	21-year-old patient treated with growth hormone inhibitors and managed by a multidisciplinary team. Mother and daughter were discharged without apparent complications.
Santana Hernández EE et. al.,[12]	2019	8-year-old patient developed gluteal and left thigh muscle hyperplasia with dorsal subcutaneous and adipose tissue increase at age 2. At age 3, distal phalanx amputation of the right second toe was required due to cortical hypertrophy preventing proper foot fitting.
Portuondo E et al.,[13]	2019	10-month-old female infant, born to an adolescent mother with fetal exposure to tobacco, marijuana, and alcohol, presented with macrocephaly and right-sided facial hemihypertrophy. Met clinical criteria for Proteus syndrome and responded favorably to spasm control.
Morales M et al.,[14]	2019	Patient with excessive, progressive, and deforming overgrowth exclusively in the right foot. These features align with the three general diagnostic criteria for Proteus syndrome: mosaic distribution, sporadic occurrence, and progressive course.
Carvajal D et al.,[15]	2019	Dermatological evaluation is essential for early recognition of Proteus syndrome. Vascular malformations and adipose tissue dysregulation should raise suspicion, enabling early referral for multidisciplinary management of extracutaneous complications.
Meléndez P et al.,[16]	2023	Turner's diagnostic criteria for Proteus syndrome require 3 major criteria—mosaic distribution, sporadic occurrence, progressive course—and 5 specific criteria: disproportionate lower limb overgrowth, epidermal nevi on neck/abdomen/back, lipomas, venous malformations, and characteristic facial phenotype.
Bertanha Met et al.,[17]	2019	Proteus syndrome deformities present with wide clinical variability and can severely impact patient self-esteem. Treatment must be palliative and multidisciplinary. Amputations can yield good outcomes by enabling physical rehabilitation with prostheses, facilitating social reintegration and nutritional recovery.
Guerrero S et al.,[18]	2019	Proteus syndrome is an orphan disease with limited understanding of its pathophysiology, genetic variability, and management. Less aggressive reconstructive surgeries can be proposed across severity levels. In this case, goals included improving energy expenditure, gait pattern, and enabling conventional footwear use.

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Maluf I et al.,[19]		Management requires a multidisciplinary team. Key manifestations must be screened. Follow-up must be prolonged due to the syndrome's polymorphic nature. Psychosocial and educational support is essential. Surgeries involve excision of extensive, highly vascularized tumors.

The heterogeneous clinical manifestations of Proteus syndrome affect multiple body systems—including skin, bones, vascular, and neurological systems. These cases demonstrate the value of a multidisciplinary approach from early disease stages. As reviewed studies show, genetic referral enabled early diagnosis and comprehensive management planning. Additionally, the syndrome's complexity in scenarios such as pregnancy underscores the need for multidisciplinary supervision to ensure positive outcomes.

Epidemiologically, Proteus syndrome affects an extremely small proportion of the global population, with fewer than 200 documented cases to date. This rarity highlights the importance of international collaboration and knowledge exchange among specialized centers to improve early diagnosis and effective management of this complex disease.[9]

Proteus syndrome is an extremely rare congenital disorder characterized by excessive and heterogeneous overgrowth of various tissues and organs, resulting in a broad spectrum of clinical manifestations. As evidenced in this literature review, this condition represents a true challenge for healthcare teams in both diagnosis and therapeutic management.[14]

A key aspect is the multisystemic nature of Proteus syndrome, involving cutaneous, skeletal, vascular, and neurological alterations, among others.[10] This clinical complexity hinders early recognition—critical for timely intervention and prevention of severe complications.[18] Clinical suspicion based on established criteria is the crucial first step to refer patients to specialized centers and confirm diagnosis through genetic testing.

A study by Portuondo found coexistence of Proteus syndrome and West syndrome in an infant, indicating possible neurological comorbidities.[13] In this context, nursing professionals—who are on the front lines of care—must be trained to recognize characteristic signs and symptoms of Proteus syndrome.[15] As highlighted in reviewed studies, nursing plays a fundamental role in comprehensive patient care, providing specific interventions, therapeutic education, and emotional support to both patients and families.[17]

The syndrome can affect tissues derived from any of the three germ layers. The random or mosaic distribution of its manifestations throughout the body is the hallmark of this disorder.[16]

Furthermore, close collaboration among various medical specialists—plastic surgery, orthopedics, dermatology, genetics, among others—is essential to effectively address the multiple complications Proteus syndrome patients may present.[12] As evidenced in reported cases, this multidisciplinary approach optimizes clinical outcomes and improves patients' quality of life.[11] Finally, as various studies indicate, integration of physical and occupational therapies, along with emotional support and education, is fundamental to optimize function and quality of life throughout the patient's lifespan.[19]

ISSN: 1561-3194 **RNPS:** 1877
Rev Ciencias Médicas. 2025; 29(S2): e7043

Although this review provides valuable information on clinical manifestations and multidisciplinary management, current Proteus syndrome research has several limitations. First, the disease's rarity means available data come from a limited number of cases, potentially affecting generalizability. Additionally, clinical presentation variability and lack of consensus on some diagnostic criteria may hinder study comparability. These limitations underscore the need for further research involving larger patient cohorts and more exhaustive exploration of the disease's diverse manifestations and respective therapeutic solutions.

CONCLUSIONS

Proteus syndrome is a rare and complex disease requiring a multidisciplinary approach to address its diverse clinical manifestations. Nursing plays an essential role in early detection, comprehensive management, and emotional support for patients and families, while genetic advances and therapies targeting the PI3K/AKT/mTOR pathway offer new treatment perspectives. Early, genetically confirmed diagnosis—combined with collaboration among reconstructive surgery, physiotherapy, psychology, and genetics specialists—is key to optimizing care. However, challenges in accessibility and applicability of these innovations persist, highlighting the need for standardized protocols, international cooperation, and ongoing research. In this context, a holistic approach integrating medical, psychological, and social dimensions is indispensable to improve the quality of life of those affected by this condition.

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