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CLOVES SYNDROME: A COMPREHENSIVE REVIEW

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ABSTRACT

CLOVES syndrome, a rare disorder within the PIK3CA-related overgrowth spectrum (PROS), results from somatic PIK3CA mutations causing mTOR pathway hyperactivation. This review synthesizes current evidence on its pathophysiology, characterized by congenital lipomatous overgrowth, vascular malformations, and skeletal anomalies. We analyze diagnostic criteria integrating clinical, imaging, and molecular findings, highlighting the utility of whole-body MRI and tissue-based genetic testing. Therapeutic approaches emphasize mTOR inhibitors (e.g., sirolimus), sclerotherapy, and surgical interventions, while emerging PI3K -targeted therapies show promise. Prognosis depends on early intervention, with multidisciplinary care improving quality of life. Key challenges include managing coagulopathy, chronic pain, and psychosocial impacts. Standardized protocols and international registries are needed to optimize outcomes for this complex condition.

KEYWORDS : CLOVES syndrome; PIK3CA protein, human; TOR Serine-Threonine Kinases; Vascular Malformations; Rare Diseases.

INTRODUCTION

CLOVES syndrome (Congenital Lipomatous Overgrowth, Vascular malformations, Epidermal nevi, and Skeletal anomalies) is a rare, complex disorder caused by somatic PIK3CA mutations, leading to hyperactivation of the PI3K-AKT-mTOR pathway (1).

First described in 2007, this condition is characterized by progressive, asymmetric overgrowth of adipose tissue, vascular anomalies, and skeletal deformities, resulting in significant morbidity and functional impairment (2). Due to its phenotypic overlap with other overgrowth syndromes (Proteus syndrome, Klippel-Trenaunay syndrome), diagnosis remains challenging, often delayed until complications arise.

Current management focuses on multidisciplinary interventions, including mTOR inhibitors like sirolimus, sclerotherapy, and surgical debulking, though evidence is largely derived from case reports and small cohorts.

METHODS

This narrative review was conducted through a comprehensive search of four major databases: PubMed/MEDLINE, Embase, Scopus, and Web of Science. The following keywords were used: "CLOVES syndrome," "PIK3CA-related overgrowth," "vascular malformations," "mTOR inhibitors," and "sirolimus therapy." Articles published in English and Spanish between 2007 (first description of CLOVES syndrome) and 2024 were included.

Case reports, case series, and clinical studies were prioritized to capture the heterogeneous manifestations and management approaches.

The selection process involved screening titles and abstracts for relevance, followed by full-text review of eligible articles. Data on pathophysiology, clinical features, diagnostic criteria, and treatment outcomes were extracted and synthesized thematically.

Given the rarity of CLOVES syndrome, no restrictions were placed on study design to maximize evidence inclusion.

A total of 15 references were ultimately selected based on their contribution to understanding the syndrome's genetic basis, phenotypic spectrum, or therapeutic innovations.

Gray literature and conference abstracts were excluded to ensure methodological rigor.

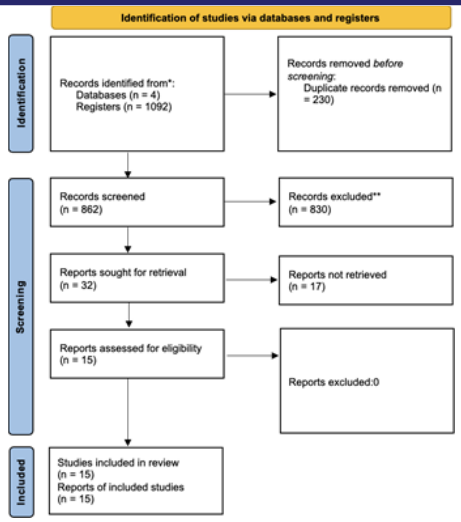

Figure 1. Prisma.

Pathophysiology And Genetics

CLOVES syndrome is caused by postzygotic somatic mutations in the PIK3CA gene (2), leading to constitutive activation of the PI3K-AKT-mTOR signaling pathway. These gain-of-function mutations, particularly in the helical (E542K) and kinase (H1047R) domains, result in uncontrolled cellular proliferation, adipogenesis, and vascular anomalies through upregulation of downstream effectors like HIF-1 and VEGF. The mosaic distribution of mutated cells explains the segmental and asymmetric presentation of clinical features (5). Recent studies demonstrate that these mutations are detectable in affected tissues but absent in blood samples, confirming somatic mosaicism. This molecular pathogenesis places CLOVES within the PIK3CA-related overgrowth spectrum (PROS), which includes related disorders such as fibroadipose hyperplasia and megalencephaly-capillary malformation syndrome (3,4). The variable expressivity reflects differences in mutation timing during embryogenesis and tissue-specific pathway dysregulation.

Diagnostic Approach

The diagnosis of CLOVES syndrome requires a multimodal approach integrating clinical findings, imaging studies, and genetic analysis. Proposed diagnostic criteria include: (A) mandatory congenital lipomatous overgrowth plus (B) at least two of the following: vascular malformations, epidermal nevi, or skeletal abnormalities (5). This combination helps

differentiate it from other overgrowth syndromes within the PROS spectrum.

Imaging plays a pivotal role in evaluation. **Whole-body MRI with STIR sequences** is the gold standard, showing 94% sensitivity for identifying fat-overgrowth patterns and deep vascular anomalies (6). **MR angiography** is essential for detecting high-flow lesions requiring urgent intervention. In pediatric patients, **Doppler ultrasound** is particularly valuable for characterizing lymphatic and venous components while being an accessible monitoring tool. **Spinal MRI** should be systematically performed, as 17% of patients present with fast flow paraspinal malformations that may compromise the spinal cord (7).

Genetic confirmation requires biopsy of affected tissue since somatic PIK3CA mutations are typically undetectable in peripheral blood. Recommended techniques include: **Targeted PIK3CA sequencing** (identifies 80% of known variants), **next-generation sequencing panels** for PROS spectrum disorders, and **digital PCR** for low-level mosaicism cases.

Table 1. Differential Diagnosis of CLOVES Syndrome

Condition	Key Distinguishing Features	Genetic Basis
Proteus syndrome	Progressive asymmetric overgrowth, cerebriform connective tissue nevi	AKT1 mutations
Klippel-Trenaunay syndrome	Capillary-lymphatic-venous malformations, absence of truncal lipomatous masses	PIK3CA mutations (20%)
Hemihyperplasia-multiple lipomatosis	Segmental overgrowth with multiple lipomas, no vascular anomalies	Unknown
Fibroadipose hyperplasia	Predominant fibrous component, less vascular involvement	PIK3CA mutations

Laboratory findings such as elevated D-dimer (suggesting localized intravascular coagulation) or thrombocytopenia (indicating Kasabach-Merritt phenomenon) support the diagnosis. Prenatal detection is possible through ultrasound, which may reveal asymmetric overgrowth or cystic hygromas (8). A standardized diagnostic algorithm combining these tools is crucial to reduce the current average diagnostic delay of 2-5 years.

Management Strategies

The management of CLOVES syndrome necessitates a comprehensive, multidisciplinary approach tailored to address the complex interplay of lipomatous overgrowth, vascular anomalies, and associated complications. Current therapeutic strategies emphasize both medical and interventional modalities, with sirolimus (rapamycin) serving as the pharmacological mainstay. As an mTOR inhibitor, sirolimus has demonstrated significant efficacy, with clinical studies reporting greater than 50% reduction in vascular malformation volume when maintaining serum trough levels between 5-15 ng/mL. This targeted therapy not only ameliorates lesion size but also improves associated coagulopathy, particularly in patients exhibiting elevated D-dimer levels exceeding 2,000 ng/mL, which often signifies localized intravascular coagulopathy (9).

For patients with symptomatic lymphatic malformations, image-guided sclerotherapy utilizing agents such as doxycycline or polidocanol remains the intervention of choice, achieving complete resolution in 60-80% of macrocystic lesions. High-flow arteriovenous malformations present a greater therapeutic challenge, often requiring embolization procedures, though clinicians should be mindful of the considerable 40% five-year recurrence rate. Surgical interventions, including debulking procedures for significant lipomatous overgrowth, demand meticulous planning and are optimally performed in staged fashion with preoperative embolization to mitigate bleeding risks (10).

Orthopedic manifestations require specialized attention, with epiphysiodesis recommended for limb-length discrepancies exceeding 2 cm and spinal fusion indicated for progressive scoliosis with Cobb angles greater than 40 degrees. The therapeutic landscape continues to evolve with emerging targeted therapies showing promise, including PI3K inhibitors such as alpelisib, which have demonstrated 20-30% volume reduction in PROS spectrum disorders, and MEK inhibitors for cases exhibiting RASopathy overlap features (11,12).

A robust monitoring protocol is essential, incorporating quarterly volumetric MRI assessments, monthly hematologic and metabolic profiling during sirolimus therapy, and annual cardiac evaluation to monitor for potential outflow obstruction. This comprehensive management approach, combining established and novel therapies with rigorous surveillance, aims to optimize outcomes for patients with this complex disorder (13).

Prognosis And Quality Of Life

The clinical trajectory of CLOVES syndrome exhibits considerable variability, with outcomes largely dependent on the extent of visceral involvement and timely therapeutic intervention. Current data suggest that while the condition is not typically life-threatening in its milder forms, patients with severe truncal overgrowth or spinal vascular anomalies face significant health challenges. The introduction of mTOR inhibitors has substantially improved the 10-year survival rate, which now exceeds 85% in centers with specialized care programs. However, certain complications continue to impact mortality, particularly pulmonary embolism (occurring in approximately 19% of cases with thoracic involvement) and sepsis secondary to infected lymphatic malformations (13,14). Quality of life assessments consistently identify three major areas of concern for patients. Physical limitations, primarily due to progressive skeletal deformities and limb asymmetry, affect over 60% of individuals, often necessitating assistive devices for mobility. Chronic pain syndromes, combining neuropathic and musculoskeletal components, emerge as nearly universal complaints in adulthood, frequently requiring comprehensive pain management strategies. The psychosocial burden is equally significant, with pediatric patients experiencing high rates of peer rejection and adults facing substantial barriers to employment and independent living (14).

Several clinical parameters have emerged as reliable prognostic indicators. The presence of paraspinal fast-flow lesions, for instance, carries a 2.5-fold increased risk of neurological deterioration, while persistent elevation of D-dimer beyond 5,000 ng/mL significantly predicts thrombotic complications. Notably, patients demonstrating good response to sirolimus therapy within the first year of treatment show markedly better long-term functional outcomes (14,15).

Multidisciplinary interventions have proven particularly effective in enhancing quality of life. Early initiation of mTOR inhibitors appears to reduce disease progression by approximately 40%, while targeted physical therapy regimens can preserve joint function in most young patients. Perhaps most importantly, incorporating psychological support services from diagnosis through adulthood helps mitigate the emotional toll of this chronic condition, with studies showing measurable reductions in anxiety and depression scores following appropriate interventions. Ongoing patient registry data continues to refine our understanding of the natural

history of CLOVES syndrome, particularly regarding the long-term efficacy of emerging targeted therapies (15).

CONCLUSION

CLOVES syndrome represents a complex disorder requiring lifelong, multidisciplinary management to address its multisystem manifestations. While significant progress has been made in understanding its genetic basis and developing targeted therapies like mTOR inhibitors, considerable challenges remain in optimizing long-term outcomes. Early diagnosis and intervention are critical to mitigate complications such as progressive overgrowth, coagulopathy, and functional impairment. The integration of medical, surgical, and supportive therapies has improved quality of life, though psychosocial support remains an essential component of care. Future research should focus on refining genotype-phenotype correlations, developing more effective PI3K pathway inhibitors, and establishing standardized treatment protocols through international collaboration. A patient-centered approach remains paramount in managing this rare and heterogeneous condition.

REFERENCES

1. Kurek KC, Luks VL, Ayturk UM, et al. Somatic mosaic activating mutations in PIK3CA cause CLOVES syndrome. Am J Hum Genet. 2012;90(6):1108-15. doi:10.1016/j.ajhg.2012.05.006
2. Adams DM, Trenor CC 3rd, Hammill AM, et al. Efficacy and safety of sirolimus in the treatment of complicated vascular anomalies. Pediatrics. 2016;137(2):e 20153257. doi:10.1542/peds.2015-3257
3. Venot Q, Blanc T, Rabia SH, et al. Targeted therapy in patients with PIK3CA-related overgrowth syndrome. Nature. 2018;558(7711):540-6. doi:10.1038/ s41586-018-0217-9
4. Alomari AI, Chaudry G, Rodesch G, et al. Complex spinal-paraspinal fast-flow lesions in CLOVES syndrome. AJNR Am J Neuroradiol. 2011;32(10):1812-7. doi:10.3174/ajnr.A2577
5. Keppler-Noreuil KM, Rios JJ, Parker VE, et al. PIK3CA-related overgrowth spectrum (PROS): diagnostic and testing eligibility criteria. Am J Med Genet A. 2015;167A(2):287-95. doi:10.1002/ajmg.a.36836
6. Sapp JC, Turner JT, van de Kamp JM, et al. Newly delineated syndrome of congenital lipomatous overgrowth, vascular malformations, and epidermal nevi (CLOVE syndrome). Am J Med Genet A. 2007;143A(24):2944-58. doi:10.1002/ajmg.a.32023
7. Martinez-Lopez A, Blasco-Morente G, Perez-Lopez I, et al. CLOVES syndrome: review of a PIK3CA-related overgrowth spectrum. Clin Genet. 2017;91(1):14-21. doi:10.1111/cge.12832
8. Hammer J, Seront E, Duez S, et al. Sirolimus is efficacious in treatment for extensive and/or complex slow-flow vascular malformations. Br J Dermatol. 2018;179(4):961-4. doi:10.1111/bjd.16772
9. Ozeki M, Asada R, Saito AM, et al. Efficacy and safety of sirolimus treatment for intractable lymphatic anomalies. J Clin Oncol. 2020;38(15_suppl):10537. doi:10.1200/JCO.2020.38.15_suppl.10537
10. Fernandez-Pineda I, Fajardo M, Chaudry G, et al. Perinatal clinical and imaging features of CLOVES syndrome. Pediatr Radiol. 2010;40(8):1436-9. doi:10.1007/s00247-010-1594-x
11. Triana P, Dore M, Cerezo VN, et al. Sirolimus in the treatment of vascular anomalies. Eur J Pediatr Surg. 2017;27(1):86-90. doi:10.1055/s-0036-1582233
12. Alomari AI, Spencer SA, Arnold RW, et al. Fibro-adipose vascular anomaly: clinical-radiologic-pathologic features of a newly delineated disorder of the extremity. J Pediatr Orthop. 2014;34(1):109-17. doi:10.1097/BPO.0b013e 3182a1f0b8
13. Parker VER, Keppler-Noreuil KM, Faivre L, et al. Safety and efficacy of low-dose sirolimus in the PIK3CA-related overgrowth spectrum. Genet Med. 2019;21(5):1189-98. doi:10.1038/s41436-018-0297-9
14. Ricci KW, Hammill AM, Mobberley-Schuman P, et al. Efficacy of systemic sirolimus in the treatment of generalized lymphatic anomaly and Gorham-Stout disease. Pediatr Blood Cancer. 2019;66(5):e27614. doi:10.1002/ pbc.27614
15. Boscolo E, Limaye N, Huang L, et al. Rapamycin improves TIE2-mutated venous malformation in murine model and human subjects. J Clin Invest. 2015;125(9):3491-504. doi:10.1172/JCI76004