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CLOVES Syndrome: A Review of Clinical, Genetic, and Therapeutic Aspects

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ABSTRACT

Purpose of Research: The research aims to provide an in-depth understanding of CLOVES syndrome, detailing its clinical features, epidemiology, etiology, and diagnostic criteria. It focuses on the role of PIK3CA gene mutations, challenges in diagnosis, and treatment options, including PI3K/AKT/mTOR pathway inhibitors.

Research Materials and Methods: This article is based on a review of the current literature and clinical reports from various sources. The methodology includes a collection and synthesis of clinical data, imaging findings, and genetic analyses from published case studies and medical literature. The primary materials used in the research include: clinical case reports and studies, imaging studies, genetic analysis, therapeutic interventions, epidemiological data, literature review and data analysis.

Basic Results: CLOVES syndrome affects fewer than 200 individuals worldwide, with symptoms appearing at birth or early childhood. It can lead to serious complications such as nerve compression, deep vein thrombosis, and pulmonary embolism. Diagnosis involves genetic testing and imaging, and sirolimus shows potential in managing symptoms.

Conclusions: CLOVES syndrome is a rare, non-hereditary overgrowth disorder caused by a PIK3CA gene mutation. Early diagnosis and a multidisciplinary approach are vital for managing this complex condition and improving patient outcomes.
Keywords: congenital lipomatous overgrowth, vascular malformation, epidermal nevi, skeletal anomaly syndrome, asymmetric overgrowth , lipoma, PIK3CA gene, mTOR inhibitors

Introduction and History

The acronym "CLOVES" stands for congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and spinal (scoliosis) and/or skeletal anomalies [6 7 8 9]. CLOVES syndrome is a rare, sporadic (non-hereditary) mosaic overgrowth disorder, first described in 2007 by Sapp et al. as a novel overgrowth syndrome, initially named “CLOVE” syndrome [1 2]. Although it shares characteristics with other overgrowth disorders such as Proteus syndrome, the patients did not fulfill the diagnostic criteria for those conditions[3 4]. After recognizing skeletal and spinal abnormalities (such as scoliosis) as components of the syndrome, Alomari revised the name to "CLOVES" [5]. The first documented account of the syndrome is a case report by German physician Hermann Friedberg in 1867, in which he described "gigantism of the right lower limb."

Epidemiology

Due to its rare and heterogeneous nature, fewer than 200 cases of CLOVES syndrome have been documented as of April 2022 [5 10 11]. Its estimated incidence is less than 1 in 1,000,000, with no gender preference, and it has been reported across all races and ethnic groups[11 12] . This inherited condition has a prenatal onset, usually manifesting at birth or in early childhood. Segmental excess growth is apparent in the majority of affected individuals by their first year [3 13 14].

Etiology

CLOVES syndrome is part of the PIK3CA-Related Overgrowth Spectrum (PROS), caused by postzygotic somatic mutations in the PIK3CA gene on chromosome 3q26.32 [5]. The PIK3CA gene encodes PI3K, a lipid kinase that regulates cell growth, proliferation, and survival [4 15]. This signaling pathway activates AKT1 (protein kinase B), stimulating cell proliferation through mTOR1, which drives unchecked growth [1]. In CLOVES syndrome, these mutations cause overgrowth mainly in mesodermal tissues (such as fat, blood vessels, lymphatic structures, muscles, and bone) and neuroectodermal tissues (including skin, brain, and head connective tissue) The overgrowth is generally localized, uneven, and limited to the areas affected by the mutation [6 11 16].Because these mutations occur after fertilization, CLOVES syndrome is not passed down through generations. It cannot be inherited by children, and relatives do not have an elevated risk of having a child with the condition. As a result, there is no transmission from parent to child or recurrence among siblings, and prenatal testing for family members is typically not required [17].

Clinical symptoms

Congenital Lipomatous Overgrowth

CLOVES syndrome is characterized by congenital overgrowth of adipose tissue, which affects all body regions and tissue spaces[11 18]. Lipomatous masses are congenital and usually grow progressively over time. A key characteristic is the asymmetric enlargement of the trunk or chest, noticeable at birth [11 16]. The visible tumefactions as unilateral or bilateral masses, primarily consist of lipomatous tissue, but may also include lymphatic and vascular components [5]. These masses are primarily found on the posterior-lateral chest wall and side, but may also spread to other regions, such as the front abdominal wall, groin, scrotum, retroperitoneal space, mediastinum, pleura, paraspinal muscles and epidural spaces [3 20 21 22]. In some cases, these lipomatous growths can also involve facial tissue, growing asymmetrically around areas such as the orbits, maxillary bone, or jawline [31].

The lipomatous tumors are commonly encircled by capillary, venous, lymphatic, or arteriovenous anomalies, which may lead to severe complications. These enlargements are typically invasive, resistant to treatment, and susceptible to reappearance after surgical excision. Additionally, their infiltration into the paraspinal and intraspinal spaces can lead to compression of the spinal cord or nerve roots[23 24 5].

Vascular Malformations

CLOVES syndrome is marked by a mix of vascular and fatty tissue abnormalities, involving various vascular malformations such as capillary, venous, lymphatic, and arteriovenous. [1 5 6 27]. Vascular malformations in CLOVES syndrome typically occur over lipomatous masses on the trunk but may also affect areas with skeletal overgrowth in the extremities. Capillary malformations, often appearing as port wine stains, are common and may be localized on the trunk, extremities, palms, soles, or fingertips [5 28 29 31]. These lesions present as smooth pink to reddish spots at birth and slowly evolve into a purplish, cobblestone, papulonodular texture as time progresses. Veins have an irregular, winding course, which heightens the likelihood of clot formation and calcification, potentially leading to severe complications like deep vein thrombosis and pulmonary embolism, particularly when phlebectasias involve the thoracic or cervical areas [5 25 31]. Lymphatic malformations, which may be microcystic or macrocystic, commonly appear as blisters filled with clear fluid [5 22 29].

These abnormalities can cause a variety of symptoms, such as digestive problems, nerve compression, radicular pain, muscle weakness, and, in some instances, changes in sphincter control or sexual dysfunction[31]. Magnetic Resonance Imaging, Computed Tomography, and Doppler ultrasound are valuable methods for the often intricate differential diagnosis of lymphatic and deep venous malformations [29 30].

Epidermal Nevi

Epidermal nevi, particularly linear keratinocytic nevi, are a characteristic feature of CLOVES syndrome, though they do not occur in every case [5 31]. These nevi commonly manifest as brown-gray, velvety, pigmented patches or thickened areas, usually found on the neck, abdomen, sides, or limbs. They may also be limited to areas with excess bone or fat tissue growth [5 29]. In CLOVES syndrome, these nevi usually exhibit a gradual progression during childhood, enlarging and becoming more raised and wart-like. By adolescence, they often transform into a rough, thickened texture, eventually reaching a stable state in adulthood [5 29 31]. In contrast to Proteus syndrome, CLOVES syndrome generally does not include connective tissue nevi (such as elastomas or collagenomas), with true epidermal nevi serving as a distinguishing characteristic of the condition [5]. In CLOVES syndrome, the growth is softer and often develops wrinkles, whereas in Proteus syndrome, the overgrowth is firmer and less elastic[29].

Scoliosis and/or Skeletal Abnormalities

Skeletal malformations in CLOVES syndrome can be severe, with varying degrees of scoliosis and asymmetric enlargement of the bones in the extremities [5]. Bony overgrowth primarily impacts the lower extremities, with the distal segments being more frequently affected than the proximal ones. As the condition advances, the proximal segments may also become involved. Scoliosis may be present from birth or develop during childhood, often associated with lower limb asymmetry. Unlike Proteus syndrome, the bone hypertrophy in CLOVES syndrome progresses slowly and does not cause distortion [5 6 22 23 32]. Bone overgrowth is typically less pronounced and progressive compared to the overgrowth of lipomatous tissue. The mosaic pattern of growth often impacts just one leg, leading to significant asymmetry that can be disabling. This may require interventions such as shoe lifts and, in some cases, epiphysiodesis [5 29].

Typical foot deformities include wide, triangular-shaped feet, broad forefeet, splayed toes with significant gaps between the metatarsal heads, and a sandal gap (a widened space between the first and second toes) [1 3 5 6 13 23 25 29]. In terms of skin appearance, the palms and soles may show furrows and creases, along with an overgrowth of the palmar and plantar skin [5 6 13 23]. Other associated conditions: hip dysplasia, spina bifida, chondromalacia patellae and dislocated knees [29 31].

Renal

Renal involvement in Cloves syndrome includes a variety of kidney-related issues, such as agenesis, hypoplasia, renal cysts, hydronephrosis, kidney stones, hematuria of unknown origin, and even cases of Wilms tumor [25 29 31]. Given these potential renal issues, renal ultrasound is a key diagnostic tool in monitoring kidney function and detecting abnormalities in affected individuals [25].

Neurological

Lipomatous masses or arteriovenous malformations are the primary causes of spinal cord involvement. These masses, located adjacent to the spinal cord, can gradually grow, resulting in compression of the spinal cord, thecal sac, and nerve roots, or even infiltrating them. The clinical symptoms will vary based on the level affected and the degree of infiltration or compression [31].

Arteriovenous shunts, a rare type of vascular anomaly, are the most common spinal cord issues. These can lead to radicular pain, sensory disturbances, lower extremity weakness, gait problems, sphincter control issues, and sexual dysfunction [29]. Vascular malformations or dilated dural veins can cause direct compression of the spinal cord, dural sac or nerve roots. This compression leads to spinal venous hypertension and congestive myelopathy, which may result in edema, ischemia, infarction, and necrosis [20 29]. Reports have also noted the presence of partial agenesis or aplasia of the corpus callosum and neuronal migration abnormalities [31]. These neurological manifestations can lead to intellectual disabilities and, more commonly, epileptiform symptoms [2 29 30].

Tumours

Cancers have a low incidence in CLOVES syndrome, affecting only about 1% of individuals. Tumor cases reported include choriocarcinoma, extraspinal medullary tumors, hemangiomas, multiple angiomatosis, and few cases of Wilms tumors [25 29 31].

Diagnostics

The diagnosis of CLOVES syndrome is determined through clinical evaluation, imaging studies, and genetic testing [5 6 27]. Given the rarity and complexity of PROS (PIK3CA-Related Overgrowth Spectrum) disorders, confirmation of CLOVES syndrome usually relies on detecting the specific PIK3CA mutation in the affected tissues [5 6 10 13]. If the mutation cannot be identified, the diagnosis is considered provisional [5]. Imaging methods, including cranial, spinal, and skeletal X-rays, abdominal ultrasound (for Wilms tumor), Doppler ultrasound, CT, MRI (for soft-tissue and bone hyperplasia or hypertrophy), and MR angiography (for vascular malformations), are used on a case-by-case basis. Radiologic imaging plays a crucial role in evaluating deformities and predicting long-term prognosis. Failure to detect a PIK3CA mutation does not rule out the diagnosis of a PROS disorder in individuals exhibiting characteristic clinical features [5 6 29 33]. The PIK3CA mutation is usually confirmed by biopsy. Since the mutation is somatic, it is important to choose tissues with higher mutation rates for accurate detection[31]. A fresh skin biopsy from overgrown tissue, vascular malformation, epidermal nevus or surgical excision from visibly affected areas, is recommended for diagnosis.

The main differential diagnoses include Proteus syndrome, Klippel-Trenaunay syndrome (KTS), and other PROS disorders. CLOVES syndrome and Proteus syndrome share similar clinical features, which historically led to misdiagnosis of many CLOVES cases as Proteus syndrome [5 23 27]. However, they vary genetically, with a PIK3CA mutation in CLOVES

syndrome and an AKT1 mutation in Proteus syndrome. Clinically, CLOVES syndrome can be identified by the absence of cerebriform connective tissue nevi and internal organ involvement, as well as the absence of pronounced postnatal overgrowth. In contrast, Proteus syndrome is characterized by fast, uneven postnatal growth, while CLOVES syndrome presents with slow, symmetrical, mild, and congenital overgrowth. CLOVES syndrome and KTS can be distinguished by the lack of truncal involvement in CLOVES syndrome and the tendency for KTS to affect the lower extremities [5 11 12 21]. Early identification of these syndromes is important because Proteus syndrome has a poorer prognosis, potentially resulting in pulmonary damage and deep vein thrombosis. Additionally, CLOVES syndrome must be distinguished from other overgrowth conditions like Beckwith-Wiedemann syndrome and Sotos syndrome.

Treatment

At this time there is no specific cure for CLOVES syndrome [34]. Until recently patients were managed palliatively by multidisciplinary (dermatologists, pediatric surgeons, orthopedists, neurologists, and radiologists) [29]. The management of vascular anomalies is crucial due to their potential complications, such as organ dysfunction, respiratory issues, hemoptysis, and gastrointestinal bleeding or obstruction, among others, depending on the affected organ [29]. Patients with low-flow malformations were prescribed anticoagulant medications for the prevention of thromboembolic disease [5]. The treatment of paraspinal arteriovenous malformations is a major therapeutic challenge for Neuroradiologists and Neurosurgeons [29 31]. Lipomatous masses can be quite large, and there is a risk of iatrogenic damage to the thoracic organs or spinal cord if they infiltrate these areas. The presence of paraspinal lipomatous masses and sometimes arteriovenous malformations increases the risk of iatrogenic neurological injury. Surgical treatment of scoliosis in patients with CLOVES syndrome typically involves posterior vertebral arthrodesis, sometimes requiring further correction through osteotomy. Treatment for limb length discrepancies varies greatly, from simple observation or epiphysiodesis in cases with minimal asymmetry to debulking or even amputation in the most severe cases [31]. Treatment of other deformations mainly involves partial or ray amputations of deformed fingers, toes or debulking methods.

The identification of PIK3CA mutations has led to the use of medications targeting this genetic pathway [5]. Sirolimus and related drugs, including everolimus and temsirolimus, are mTOR inhibitors initially developed for immunosuppression and cancer therapy. Oral sirolimus exhibits anti-angiogenic, anti-lymphangiogenic, and anti-proliferative properties [17]. It is

especially effective for treating low-flow vascular malformations and can help reduce lipomatous overgrowths. Several PI3K pathway inhibitors, originally developed for cancer treatment, are currently being evaluated for PROS disorders, such as alpelisib, taselisib, and pictilisib [35]. Preliminary evidence suggests that these inhibitors may reduce the size of lipomatous, vascular, and skeletal overgrowths, though the effects are temporary and partial. Long-term or even lifelong treatment is required, and clinicians face challenges with the long-term safety of these medications. Despite these challenges, the future holds promise for better therapies that could greatly improve the quality of life for individuals with CLOVES syndrome and other PIK3CA-related overgrowth conditions.

Summary

CLOVES syndrome is a rare disease that has distinctive clinical characteristics that make it noticeable in daily practice. CLOVES syndrome presents with a distinct set of clinical features, including asymmetric overgrowth, vascular malformations, and skeletal anomalies such as scoliosis. The overgrowth is often segmental, patchy, and confined to specific body parts affected by the mutation[5 23 25]. Diagnosis is typically made through clinical and radiographic examinations, distinguishing it from other overgrowth syndromes [25]. The syndrome is caused by somatic mosaic mutations in the PIK3CA gene, which are not inherited but occur sporadically during early embryonic development. These mutations activate the signaling pathway, leading to uncontrolled growth of various tissues [5 15].

Patients with CLOVES syndrome may experience serious complications for example patient with thoracic and central phlebectasia increased risk of pulmonary embolism [26]. Aggressive prophylactic measures are recommended before major interventions to mitigate these risks.

Treatment for CLOVES syndrome often involves managing symptoms and complications. Medications targeting the PI3K/AKT/mTOR pathway, such as sirolimus, have shown efficacy and safety. Interventional therapies, including sclerotherapy and laser treatment, have been used to control vascular anomalies [5].

CLOVES syndrome remains underdiagnosed and misdiagnosed, highlighting the need for increased awareness among healthcare providers. Further research is necessary to explore additional genetic causes and improve treatment strategies for this complex disorder [3 6].

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