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Case Report on Cloves Syndrome with Uncertained Significance of Sotos Syndrome

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Abstract:
CLOVES syndrome is an uncommon non-inherited mosaic disorder involving segmental tissue overgrowth. The acronym CLOVES stands for Congenital Lipomatous Overgrowth, Vascular malformations, Epidermal nevi, and Spinal/skeletal deformities. SOTOS syndrome, commonly referred to as Cerebral gigantism. It is marked by excessive growth before and after birth, along with the recognizable facial appearance, advanced bone development, and delays in cognitive development. A 9-year-old female presented with recurring complaints of similar nature. Clinical findings raised the suspicion of mosaic somatic overgrowth disorder, with CLOVES syndrome, Klippel-Trenaunay syndrome, and Parker-Weber syndrome as potential differentials. The combined clinical, genetic, and imaging findings illustrate the complexity of patient's condition and coexistence of characteristics of both SOTOS syndrome and CLOVES syndromes. We aimed to describe the phenotypic considerations between CLOVES and SOTOS syndrome, and reach out the novel management for the complications and the conditions associated with these syndromes.

Keywords: CLOVES syndrome, PIK3CA gene, SOTOS syndrome, NSD1 gene, Kippel-Trenaunay syndrome, Parker-Weber syndrome, Genetic investigation (pathogenic mutation), Ultrasonography, Scoliosis, Vascular overgrowth, Port-wine stains.

INTRODUCTION:

CLOVES syndrome is an uncommon non-inherited mosaic disorder involving segmental tissue overgrowth [1,2,3]. The acronym CLOVES stands for Congenital Lipomatous Overgrowth, Vascular malformations, Epidermal nevi, and Spinal/Skeletal deformities [4,5,6,7,8,9]. This condition is extremely rare with an occurrence rate estimated at less than one case per million people globally, has an equal incidence in both females and males [12][13][16][17]. Individuals with CLOVES syndrome often present with vascular malformations (commonly affecting the trunk),abnormal fat accumulation, curvature of spine(scoliosis)[Figure 1], and enlarged bones (especially in legs), though the bone overgrowth is typically non-progressive and not associated with significant deformities[10][11][Figure 2]. Complications that may develop include consumptive Coagulopathy, Thrombophlebitis, Thromboembolic events, and lymphatic malformations [18-23].

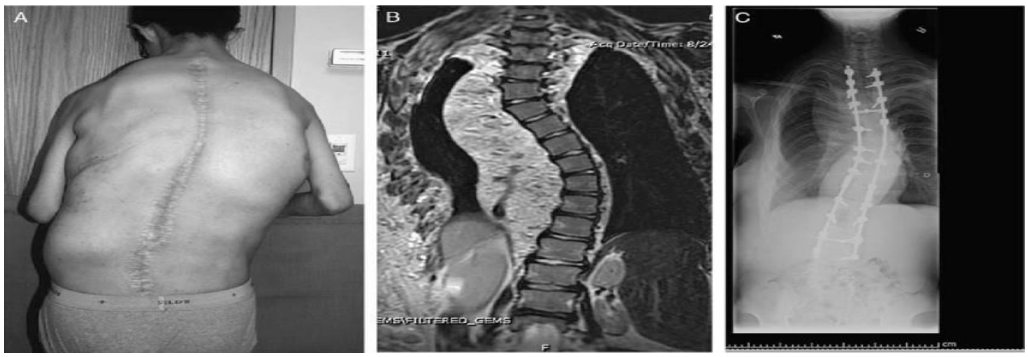

Figure 1.: Representation of the scoliosis(cervical hypertrophy) in a patient diagnosed with CLOVES syndrome.

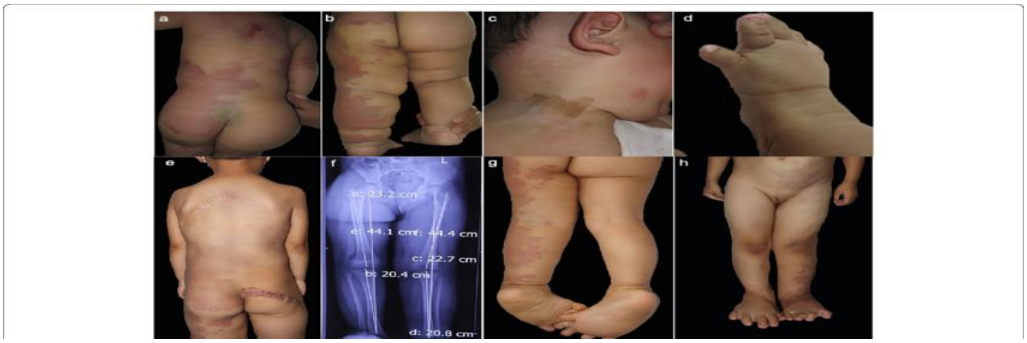

Figure 2: Overgrowth, skin hyperpigmentation over the body and the skeletal deformities of a patient with CLOVES syndrome.

This syndrome usually arises by somatic mutations during the embryonic development and as it is a non-inherited, there are no known environmental or lifestyle risk factors. The somatic(post-zygotic) mutation in the **PIK3CA** gene(phosphatidylinositol-4,5-Bisphosphate 3-kinase catalytic alpha subunit) which is found on chromosome 3q26.32 results in CLOVES syndrome [12][13]. The PIKC3A gene encode the p110-alpha catalytic subunit of the enzyme plays a key role in cell signalling by converting phosphatidylinositol (3,4)-bisphosphate (PIP2) into phosphatidylinositol (3,4,5)-triphosphate (PIP3). This conversion triggers a cascade that results in activation of AKT through phosphorylation by PDK1, which in turn activates the mTORC1 (mechanistic target of rapamycin complex 1) pathway. The aberration of PI3K/AKT/mTOR cascades promotes anomalous cellular processes, including metabolism, growth, proliferation, and even oncogenesis [14][15].

Diagnosis of CLOVES syndrome is established through imaging studies that assess the extent and characteristics of overgrowth, such as MRI (to evaluate soft tissue and vascular abnormalities), Ultrasound (for superficial venous malformations), and CT scan or X-rays (to detect bone involvement & calcification) [24][25]. Confirmation is further supported by detecting somatic mutations in the PIK3CA gene within affected tissues, using techniques like Targeted next-generation sequencing(NGS) panels, Droplet digital PCR (ddPCR), or Ultra-deep sequencing methods[26][27]. Owing to the rarity and complexity of CLOVES syndrome, a universally accepted standard treatment protocol has yet to be established. Management typically involves a multidisciplinary approaches such as Targeted therapy (Alpelisib-PIK3 inhibitor)[28-30],(Sirolimus-mTOR inhibitor)[31-35]; Surgical and interventional procedures (surgery or debulking, embolization)[36-40]; Supportive and symptomatic care (physical therapy, pain management and monitoring for complications) [42][43].

SOTOS syndrome, commonly referred to as **Cerebral gigantism**[Figure 3]**,** was initially identified by Jaun Sotos in 1964 and the key diagnostic standards for detecting the SOTOS syndrome were established by Cole and Hughes in 1994[44][45][47][48]. It is marked by excessive growth before and after birth, along with the recognizable facial appearance, advanced bone development, and delays in cognitive development[46]. This condition, listed as OMIM#117550, is a genetically diverse disorder primarily resulting from mutations, deletions, or duplications in the NSD1 gene. In some cases, alterations in the NFIX or APC2 genes may also be responsible. The syndrome is most commonly associated with the following three key clinical features-Accelerated growth and an abnormally large head (macrocephaly); Distinctive characteristics; Varying levels of intellectual or developmental delay[49-56].

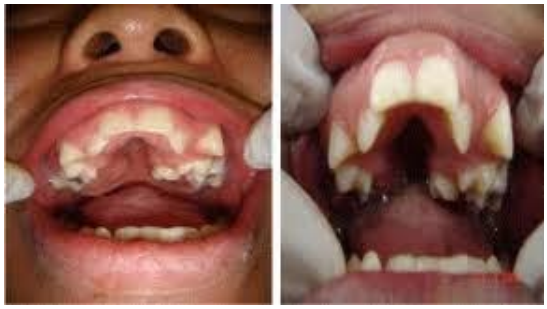

Figure 3: SOTOS syndrome or Cerebral gigantism.

CASE PRESENTATION:

A 9-year-old female child was presented to hospital with complaints of granulomatous lesions present over the posterior 1/3rd of the tongue since birth, bleeds with touch/pressure; congenital disproportionate limb growth (R>L); swollen lower limbs-hemihypertrophy; multiple hyperpigmented patches over b/l upper and lower limb since birth; cervical lymph nodes are palpable(non-tender); dental caries since past 3 years. The child is with the history of recurrent Respiratory tract infection with no previous hospital admission. Uneventful birth, developmentally normal child studying in 2nd standard. Immunised as per NIS and 3rd born child to non-contagious married couple.

Clinical evaluation:

Organ	**Site of involvement**	**Abnormalities**
Mouth and Oral cavity	Lips	Pink stains over lower lip @centre.
	Gums	Hypertrophy.
	Tongue	Granulomatous lesions.
	Teeth	Dental carries.
Limbs (R>L)	Finger	Hypertrophy of thumb and index finger over right side.
	Toes	Hypertrophy of 2nd and 3rd toe (Syndactyly-toes fused together).
Skin	Neck	Large hyperpigmented patch over left side of neck.
	Arms and Legs	Hyperpigmentation over right fore arm and legs.
	Palms	Port wine stains over right palm.

	Lower back	Port wine stains over lower back.
Spine	Spinal curvature	Scoliosis. Cervical hypertrophy over right upper back.

The clinical examination demonstrated possible mosaic somatic overgrowth syndrome-CLOVES syndrome, Klippel-Trenaunay syndrome (KTS), Parker Weber syndrome. The 2D echocardiogram revealed mild to moderate Tricuspid regurgitation[Figure 4] and severe PAH; venous doppler imaging of lower limbs demonstrated diffuse mild skin thickening in b/l lower limbs with multiple round to ovoid hyperechoic lesions, suggestive of diffuse lipomatosis[Figure 5]. Mild ascites was noted on abdominal and pelvic ultrasound.

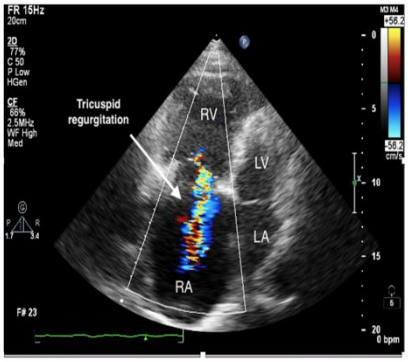

Figure 4.: Echocardiogram revealing the mild to moderate Tricuspid regurgitation(Tr).

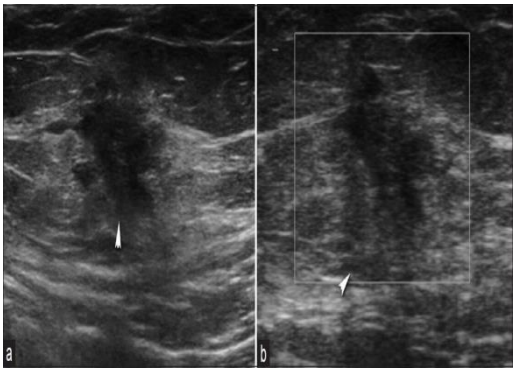

Figure 5.: Venous doppler of lower limbs demonstrated the skin thickening in both b/l lower limbs with hypoechoic lesions.

DISCUSSION:

The hallmark clinical feature of the CLOVES syndrome is the presence of trunkal lipomas, or paravertebral fat deposits, which envelop the paraspinal muscles and flanks. However, during early months or years of life, these regions of dysregulated adipose tissue may be difficult to identify through the physical examination, and the core clinical features of SOTOS syndrome comprise distinctive cranio-facial characteristics, developmental or learning difficulties, and abnormal somatic overgrowth[57-59]. We aimed to describe the phenotypic considerations for differentiation between CLOVES and SOTOS syndrome, and reach out the novel management for the complications and the conditions associated with these syndromes.

The patient exhibited multiple distinguishing features, including scoliosis (cervical hypertrophy), dental caries, hyperpigmented patches over the right forearm and lower limbs; port-wine stains involving the right palm and lower back. Genetic investigations were performed using two independent analyses. The first one, sequencing of **NSD 1** gene revealed a previously reported zygosity variant associated with **SOTOS syndrome**, classified as a **Uncertain significance**. The second one, concurrent analysis of PIK**3CA** gene identified a pathogenic mutation consistent with **CLOVES syndrome**. These genetic findings were corroborated by imaging studies. A 2D echocardiogram demonstrated mild to moderate tricuspid regurgitation accompanied by severe PAH (pulmonary arterial hypertension); venous doppler examination of the lower limbs revealed diffuse

lipomatosis. Additionally, abdominal and pelvic ultrasonography identified mild ascites.
Furthermore, the clinical history suggested phenotypic overlap with other rare vascular and overgrowth syndromes, including Klippel-Trenaunay syndrome and Parker weber syndrome, due to similarities in presentation. The combined clinical, genetic, and imaging findings illustrate the complexity of patient's condition and coexistence of features characteristics of both SOTOS and CLOVES syndromes.

CONCLUSION:

CLOVES syndrome is exceptionally rare disorder that requires a better understanding of its clinical features and etiopathogenesis, so as to differentiate from other overgrowth syndrome with similar presentation. Here in this we report a case of 9-year-old child with CLOVES and SOTOS syndrome, to reach out the novel management for the complications and the conditions associated with this syndrome. We are presenting this case to contribute to medical literature by providing a comprehensive account on CLOVES syndrome.

DECLARATION OF CONSENT:

I hereby declare that the guardian reviewed the clinical details and provided written informed consent for their publication. The patient was assured that their identity would remain confidential and that only anonymized information would be used. All ethical standards regarding patient privacy were strictly followed. Consent documentation has been securely maintained.

ABBREVATIONS:

AKT- Alpha serine/threonine-protein kinase**.**
APC2-Adenomatous polyposis coli 2.
B/L- Bilateral.
CLOVES- Congenital Lipomatous Overgrowth, Vascular malformations, Epidermal nevi, Spinal/Skeletal deformities.
CT scan- Computerized Tomography Scan.
DdPCR- Droplet digital polymerase chain reaction.
mTORC- Mechanistic target of rapamycin complex 1 pathway.
MRI- Magnetic Resonance Imaging.
NFIX- Nuclear factor I X.
NGS- Next Generation sequencing panel.
NIS-National Immunization Schedule.
NSD1- Nuclear receptor binding SET domain protein 1.
OMIM#117550- Online Mendelian Inheritance in Man (This refers to SOTOS syndrome).
PDK 1- 3-Phosphoinositide-dependent protein kinase 1.
PI3K- Phosphatidylinositol 3-kinase.
PIKC3A - Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.
PIP3- Phosphatidylinositol-(3,4,5)-triphosphate.
PIP2-Phosphatidylinositol-(3,4)-bisphosphate.
(R>L)- Right limb is greater then the left.

REFERENCES:

1. Mahajan VK, Gupta M, Chauhan P, Mehta KS. Cloves syndrome: a rare disorder of overgrowth with unusual features - an uncommon phenotype? *Indian Dermatol Online J*. 2019;10(4):447–452. doi:10.4103/idoj.IDOJ_418_18.
2. Alomari AI, Burrows PE, Lee EY, Hedequist DJ, Mulliken JB, Fishman SJ. CLOVES syndrome with thoracic and central phlebectasia: increased risk of pulmonary embolism. J Thorac Cardiovasc Surg. 2010;140(2):459–463. doi:10.1016/j.jtcvs.2010.04.023.
3. Keppler-Noreuil KM, Rios JJ, Parker VE, et al. PIK3CA-related overgrowth spectrum (PROS): diagnostic and testing eligibility criteria, differential diagnosis, and evaluation. Am J Med Genet A. 2015;167A(2):287–295. doi:10.1002/ajmg.a.36836.
4. Hanafusa H, Morisada N, Nomura T, et al. A girl with CLOVES syndrome with a recurrent PIK3CA somatic mutation and pancreatic steatosis. Hum Genome Var. 2019;6:31. doi:10.1038/s41439-019-0063-9.
5. Gopal B, Keshava SN, Selvaraj D. A rare newly described overgrowth syndrome with vascular malformations-Cloves syndrome. Indian J Radiol Imaging. 2015;25(1):71–73. doi:10.4103/0971-3026.150166.
6. Puvabanditsin S, Memon N, Chekmareva M, Di Stefano V, Mehta R. Cloves syndrome: a case report and perinatal diagnostic findings. Genet Couns. 2014;25(3):265–270.
7. Alomar S, Khedr RE, Alajlan S. CLOVES syndrome in a nine-month-old infant. Cureus. 2019;11(9):e5772. doi:10.7759/cureus.5772.
8. Alomari AI, Chaudry G, Rodesch G, et al. Complex spinal-paraspinal fast-flow lesions in CLOVES syndrome: analysis of clinical and imaging findings in 6 patients. AJNR Am J Neuroradiol. 2011;32(10):1812–1817. doi:10.3174/ajnr.A2349.
9. Vahidnezhad H, Youssefian L, Baghdadi T, et al. Phenotypic heterogeneity in PIK3CA-related overgrowth spectrum. Br J Dermatol. 2016;175(4):810–814. doi:10.1111/bjd.14618.
10. de Grazia R, Giordano C, Cossio L, et al. CLOVES syndrome: treatment with oral rapamycin. Report of two cases. Rev Chil Pediatr. 2019;90(6):662–667. doi: 10.32641/rchped.v90i6.1025.
11. Ferreira J, Gutiérrez JCL, Carneiro A, et al. CLOVES syndrome diagnosis and treatment in an adult patient. Ann Vasc Surg. 2021;75:533.e5–533.e9. doi: 10.1016/j.avsg.2021.03.044.
12. **Anderson S**, **Brooks SS**, **Schierholz E**. An Extremely Rare Disorder of Somatic Mosaicism. *Adv Neonat Care*. 2016;16:347-59.
13. **Kurek KC**, **Luks VL**, **Ayturk UM**, **Alomari AI**, **Fishman SJ**, **Spencer SA**, et al. Somatic Mosaic Activating Mutations in PIK3CA Cause CLOVES Syndrome. *Am J Hum Genet*. 2012;90:1108-15.
14. Madsen RR, Vanhaesebroeck B, Semple RK. Cancer-associated PIK3CA mutations in overgrowth disorders. Trends Mol Med. (2018) 24:856–70. doi: 10.1016/j.molmed.2018.08.003.
15. Zhang Y, Kwok-Shing Ng P, Kucherlapati M, Chen F, Liu Y, Tsang YH, et al. A pan-cancer proteogenomic atlas of PI3K/AKT/MTOR pathway alterations. Cancer Cell. (2017) 31:820–32.e3. doi: 10.1016/j.ccell.2017.04.013.
16. Sapp JC, Turner JT, van de Kamp JM, et al. Newly delineated syndrome of congenital lipomatous overgrowth, vascular malformations, and epidermal nevi (CLOVE syndrome) in seven patients. Am J Med Genet A 2007; 143A(24): 2944–2958.
17. Alomari AI. CLOVE(S) syndrome: expanding the acronym. Am J Med Genet A 2009; 149A(2): 294–295.

18. Samo S, Sherid M, Husein H, Sulaiman S, Yungbluth M, Vainder JA. Klippel-trenaunay syndrome causing life-threatening GI bleeding: A case report and review of the literature. Case Rep Gastrointest Med. 2013;2013:1–6.
19. Tetangco EP, Arshad HMS, Silva R. Klippel-Trenaunay syndrome of the rectosigmoid colon presenting as severe anemia. ACG Case Rep J. 2016;3(4):e161.
20. Servelle M, Bastin R, Loygue J, et al. Hematuria and rectal bleeding in the child with Klippel and Trenaunay syndrome. Ann Surg. 1976;183(4):418–28.
21. Azizkhan RG. Life-threatening hematochezia from a rectosigmoid vascular malformation in Klippel-Trenaunay syndrome: Long-term palliation using an argon laser. J Pediatr Surg. 1991;26(9):1125–7; discussion 1128.
22. Myers BM. Treatment of colonic bleeding in Klippel-Trenaunay syndrome with combined partial colectomy and endoscopic laser. Dig Dis Sci. 1993;38(7):1351–3.
23. Wang Z-K, Wang F-Y, Zhu R-M, Liu J. Klippel-Trenaunay syndrome with gastrointestinal bleeding, splenic hemangiomas and left inferior vena cava. World J Gastroenterol. 2010;16(12):1548–52.
24. Alomari A.I., Chaudry G., Rodesch G., Burrows P.E., Mulliken J.B., Smith E.R., Fishman S.J., Orbach D.B. Complex spinal-paraspinal fast-flow lesions in CLOVES syndrome: Analysis of clinical and imaging findings in 6 patients. AJNR Am. J. Neuroradiol. 2011;32:1812–1817.
25. Christodoulou D.C., Gorham J.M., Herman D.S., Seidman J.G. Construction of normalized RNA-seq libraries for next-generation sequencing using the crab duplex-specific nuclease. Curr. Protoc. Mol. Biol. 2011;94:4.12.1–4.12.11.
26. Kurek KC, Luks VL, Ayturk UM, Alomari AI, Fishman SJ, Spencer SA, Mulliken JB, Bowen ME, Yamamoto GL, Kozakewich HP, Warman ML. Somatic mosaic activating mutations in PIK3CA cause CLOVES syndrome. Am J Hum Genet. 2012 Jun 8;90(6):1108-15. doi: 10.1016/j.ajhg.2012.05.006. Epub 2012 May 31. PMID: 22658544; PMCID: PMC3370283
27. Green AM, Angelaki DE. Multisensory integration: resolving sensory ambiguities to build novel representations. Curr Opin Neurobiol. 2010 Jun;20(3):353-60. doi: 10.1016/j.conb.2010.04.009. Epub 2010 May 12. PMID: 20471245; PMCID: PMC2901182.
28. Venot, Q. · Blanc, T. · Rabia, S.H. Targeted therapy in patients with PIK3CA-related overgrowth syndrome Nature. 2018; 558:540.
29. Keppler-Noreuil, K.M. · Rios, J.J. Parker, V.E. PIK3CA-related overgrowth spectrum (PROS): diagnostic and testing eligibility criteria, differential diagnosis, and evaluation. Am J Med Genet A. 2015; 167A:287
30. Triana, P. · Dore, M. · Cerezo, V.N. Sirolimus in the treatment of vascular anomalies. Eur J Pediatr Surg. 2017; 27:86
31. Parker VER, Keppler-Noreuil KM, Faivre L, Luu M, Oden NL, De Silva L, et al. Safety and efficacy of low-dose sirolimus in the PIK3CA-related overgrowth spectrum. Genet Med. 2019;21(5):1189–98.
32. Adams DM, Ricci KW. Vascular anomalies: diagnosis of complicated anomalies and new medical treatment options. Hematol Oncol Clin North Am. 2019;33(3):455–70.
33. Van Damme A, Seront E, Dekeuleneer V, Boon LM, Vikkula M. New and emerging targeted therapies for vascular malformations. Am J Clin Dermatol. 2020;21(5):657–68.
34. Dompmartin A, Acher A, Thibon P, Tourbach S, Hermans C, Deneys V, et al. Association of localized intravascular coagulopathy with venous malformations. Arch Dermatol. 2008;144(7):873–

7.
35. Hammer J, Seront E, Duez S, Dupont S, Van Damme A, Schmitz S, et al. Sirolimus is efficacious in treatment for extensive and/or complex slow-flow vascular malformations: a monocentric prospective phase II study. Orphanet J Rare Dis. 2018;13(1):191.
36. Wang S, Yuan S. Combined surgery and sclerotherapy for 13 years: a case report of a patient with CLOVES. Front Pediatr. 2024 Mar 4;12:1336358. doi: 10.3389/fped.2024.1336358. PMID: 38500592; PMCID: PMC10944971.
37. Kim, L.J. · Spetzler, R.F. **Classification and surgical management of spinal arteriovenous lesions: arteriovenous fistulae and arteriovenous malformations** Neurosurgery. 2006; **59**:S195-S201.
38. Boroumand MR, Kalani MY, Spetzler RF. Combined endovascular and microsurgical treatment of a complex spinal arteriovenous fistula associated with CLOVES syndrome in an adult patient. J Clin Neurosci. 2016 Dec;34:232-234. doi: 10.1016/j.jocn.2016.09.001. Epub 2016 Oct 8. PMID: 27729180.
39. Alhazzab A, Alkhaibary A, Khairy S, Alshaya W. CLOVES syndrome and cervical arteriovenous fistula: a unique association managed by combined microsurgical and endovascular therapy. J Surg Case Rep. 2021 Apr 19;2021(4):rjab122. doi: 10.1093/jscr/rjab122. PMID: 33927860; PMCID: PMC8055267.
40. Hedequist D, Spencer S, Richards BS, Fishman S, Alomari A. Surgical Treatment of Spinal Deformity in Patients With CLOVES Syndrome: A Report of 4 Cases. J Pediatr Orthop. 2015 Oct-Nov;35(7):682-6. doi: 10.1097/BPO.0000000000000351. PMID: 25393573.
41. Javed S, Tabansi P. Use of intercostal nerve block for chest wall pain in a patient with CLOVES syndrome. Pain Manag. 2022 Sep;12(6):681-685. doi: 10.2217/pmt-2021-0120. Epub 2022 Jul 8. PMID: 35801429.
42. Alomari, Ahmad I. et al.The Journal of Thoracic and Cardiovascular Surgery, Volume 140, Issue 2, 459 - 463
43. Budge EJ, Khalil Allam MA, Mechie I, Scully M, Agu O, Lim CS. Venous malformations: Coagulopathy control and treatment methods. *Phlebology: The Journal of Venous Disease*. 2020;36(5):361-374. doi:10.1177/0268355520972918.
44. E.B. Hook et al.Cerebral gigantism: endocrinological and clinical observations of six patients including congenital giant, concordant monozygotic twins, and a child who achieved adult gigantic size.J Pediatr(1967).
45. T.R.P. Cole et al. Sotos syndrome, J Med Genet(1990).
46. J.H. Hersh et al. Risk of malignancy in Sotos syndrome, J Pediatr(1992).
47. Sotos JF, Dodge PR, Muirhead DD, Crawford JD, Talbot NB: A syndrome of excessively rapid growth and acromegalic features and a nonprogressive neurologic disorder. N Engl J Med 1964; 271: 109 – 116.
48. Cole TR, Hughes H: Sotos syndrome: a study of the diagnostic criteria and natural history. J Med Genet 1994; 31: 20 – 32.
49. Lapunzina P. Síndrome de Sotos. Protoc Diagn ter Pediatr. (2010) 1:71–9.
50. Cole TR, Hughes HE. Sotos syndrome: a study of the diagnostic criteria and natural history. J Med Genet. (1994) 31(1):20–32. doi: 10.1136/jmg.31.1.20.
51. Ko JM. Genetic syndromes associated with overgrowth in childhood. Ann Pediatr Endocrinol Metab. (2013) 18(3):101–5. doi: 10.6065/apem.2013.18.3.101.

52. Türkmen S, Gillessen-Kaesbach G, Meinecke P, Albrecht B, Neumann LM, Hesse V, et al. Mutations in NSD1 are responsible for sotos syndrome, but are not a frequent finding in other overgrowth phenotypes. Eur J Hum Genet. (2003) 11(11):858–65. doi: 10.1038/sj.ejhg.5201050.
53. Cecconi M, Forzano F, Milani D, Cavani S, Baldo C, Selicorni A, et al. Mutation analysis of the NSD1 gene in a group of 59 patients with congenital overgrowth. Am J Med Genet A. (2005) 134(3):247–53. doi: 10.1002/ajmg.a.30492.
54. Tatton-Brown K, Douglas J, Coleman K, Baujat G, Chandler K, Clarke A, et al. Multiple mechanisms are implicated in the generation of 5q35 microdeletions in sotos syndrome. J Med Genet. (2005) 42(4):307–13. doi: 10.1136/jmg.2004.027755.
55. Tatton-Brown, K.; Cole, T.R.P.; Rahman, N. Sotos Syndrome. In GeneReviews®; Adam, M.P., Feldman, J., Mirzaa, G.M., Pagon, R.A., Wallace, S.E., Bean, L.J.H., Gripp, K.W., Amemiya, A., Eds.; University of Washington, Seattle: Seattle, WA, USA, 1993.
56. Tatton-Brown, K.; Rahman, N. Clinical features of NSD1-positive Sotos syndrome. Clin. Dysmorphol. 2004, 13, 199–204.
57. Alomari AI. Characterization of a distinct syndrome that associates complex truncal overgrowth, vascular, and acral anomalies: a descriptive study of 18 cases of CLOVES syndrome. Clin Dysmorphol. 2009;18(1):1–7. doi: 10.1097/MCD.0b013e328317a716.
58. Alomari AI. Comments on the diagnosis and management of cloves syndrome. Pediatr Dermatol. 2011;28(2):215–16. doi: 10.1111/j.1525-1470.2011.01396.x.
59. Ocansey S, Cole TRP, Rahman N, et al. Sotos Syndrome. 2004 Dec 17 [Updated 2025 Jun 5]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025.