orphanaesthesia

Anaesthesia recommendations for

CLOVES syndrome

Disease name: CLOVES syndrome

ICD 10: Q87.3

Synonyms: Congenital lipomatous overgrowth-vascular malformation-epidermal nevi-skeletal anomaly syndrome, Congenital lipomatous overgrowth-vascular malformation-epidermal nevi-spinal anomaly syndrome.

Disease summary: CLOVES syndrome is characterized by congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and spinal/scoliosis/skeletal deformities [1].

It results from a somatic mosaicism in the phosphatidylinositol 3-kinase catalytic subunit alpha (PIK3CA) gene and is a PIK3CA related overgrowth spectrum (PROS) disorder that often presents at birth or childhood [2,3]. It is an extremely rare, nonhereditary disorder, with an estimated prevalence lower than 1:1,000,000 [4].

Skeletal abnormalities are in the upper and lower extremities and can include macrodactyly, sandal gap, leg-length discrepancy, hemihyperplasia, chondromalacia and furrowed soles [5]. Spinal abnormalities are common among affected individuals and can include tethered cord, scoliosis, and neural tube defects [6]. Other findings not included in the acronym include seizures, renal agenesis/hypoplasia, lymphatic malformations, splenic lesions, gastrointestinal involvement and an increased risk of developing Wilms tumours [6,7]. The vascular malformations typically present in childhood and include (venous, lymphatic and capillary) slow-flow and deeper (arteriovenous) high-flow vascular lesions [8]. Vascular and lymphatic lesions can lead to pain, hemarthrosis, bony abnormalities, bleeding, pulmonary embolism, thrombophlebitis, and even airway obstruction [9].

The prognosis of CLOVES syndrome depends on the severity of illness [5]. Mild disease tends to have a good prognosis. Treatment modalities for CLOVES syndrome includes supportive therapies, surgical interventions, and possible (mTOR) inhibitors [10].

Medicine is in progress

Perhaps new knowledge

Every patient is unique

Perhaps the diagnosis is wrong

Find more information on the disease, its centres of reference and patient organisations on Orphanet: www.orpha.net

Emergency information

A	**AIRWAY / ANAESTHETIC TECHNIQUE**	There is potential for airway difficulties related to malformations of lymphatic and vascular tissues. Many of the procedures require general anaesthesia. If regional anaesthesia is possible, consider ultrasound guidance given the vascular and tissue abnormalities. Consider spinal imaging for AVMs prior to neuraxial.
B	**BLOOD PRODUCTS (COAGULATION)**	There is an increased risk of perioperative anemia related to arteriovenous malformations (AVM) and unrecognized GI bleeding. There is also an increased risk of blood loss during surgeries around AVMs and considerations for multidisciplinary preoperative strategies should be completed.
C	**CIRCULATION**	There is a potential for significant physical limitations and compression of cardiovascular structures related to the masses. There is also the potential for significant scoliosis and alteration in respiratory mechanics affecting right ventricular pressures and function.
D	**DRUGS**	These patients may be on mechanistic target of rapamycin (mTOR) inhibitors, which may increase their risk of surgical site infections and wound breakdown.
E	**EQUIPMENT**	Potential need for difficult airway equipment. Ultrasound for vascular and regional techniques may be warranted. Assistance may be required during positioning as a significant number of patients are wheelchair users.

Typical surgery

MRI, endoscopic procedures, herniorrhaphy, orchidopexy, sclerotherapy, embolization, resections of truncal and limb masses, orthopedic surgery (amputation, resections, osteotomies), and neurosurgical interventions (spinal fixation, spinal cord detethering) [11,12].

Type of anaesthesia

There are very few case reports of anaesthetic management in CLOVES syndrome [13]. General anaesthesia would be required for many of these procedures and a balanced anaesthesia with volatiles, opioids, and/or propofol would be appropriate.

Paraspinal arteriovenous malformations (AVM), scoliosis, spinal cord tethering, and potential perioperative anticoagulation increase the risk of neuraxial anaesthesia in these patients. The use of ultrasound during peripheral regional anaesthesia should be considered given the potential for altered anatomy.

Necessary additional pre-operative testing (beside standard care)

A careful airway examination is essential. Any prior cervical spine and upper airway imaging should be reviewed to identify any possible lymphatic or vascular malformations that may make airway management difficult. Neurologic examination and documentation of pre-existing peripheral neuropathies is recommended.

Full blood count, coagulation profile, type and screen should be obtained. Standard liver and renal function tests should be ordered when appropriate. Glucose levels should be monitored to assess for hypoglycemia [14].

Patients with known pulmonary AVM, scoliosis, or masses affecting pulmonary mechanics may warrant pulmonary function testing, room air arterial blood gas, and/or an echocardiographic study. Exercise tolerance may be difficult to assess as many patients are wheelchair users [5]. Further testing to assess cardio-pulmonary status may be warranted. Patients are at an increased risk of venous thromboembolism and consideration of imaging to rule out thrombosis may be warranted prior to invasive procedures.

A preoperative hematology consultation may be beneficial to guide perioperative blood management.

Particular preparation for airway management

Patients with CLOVES syndrome may be at risk for difficult intubation. Truncal abnormalities may make positioning for airway manipulation challenging. Vascular and lymphatic abnormalities can affect the airway and cervical spine [15]. A thorough airway examination is indicated. Adjuncts should be immediately available for safe tracheal intubation.

Particular preparation for transfusion or administration of blood products

Evaluation of anaemia and coagulopathy should be determined preoperatively as they may have unrecognized anaemia secondary to angiodysplasia-related or phlebectasia-related gastrointestinal bleeding [16]. Blood transfusion risks should be taken into consideration, including transfusion related immunomodulation effects because of the increased risk of postoperative infection in these patients [4].

Blood conservation strategies are likely to be beneficial. Excision of truncal vascular malformations has resulted in significant blood loss, large-volume transfusions and non-invasive surgical treatments (embolization, sclerotherapy) should be considered prior to

surgical resection [17]. Topical and intravenous tranexamic acid may be helpful although not described in this population [18].

Particular preparation for anticoagulation

There is an association between phlebectasia and thromboembolism. This seems to apply above all to phlebectasia of the upper half of the body and operations in the prone position, because of decreased venous return, dependency, and direct compression [8]. Perioperative prophylaxis with anticoagulation and vena cava filters should be considered in patients with central and thoracic phlebectasia and should be addressed in a multidisciplinary fashion [8].

Prophylactic endovenous closure of ectatic veins in patients with CLOVES syndrome before major surgery has been recommended to reduce the risk of pulmonary embolism [19].

Particular precautions for positioning, transportation and mobilisation

Truncal and limb deformities can make positioning difficulty. There is a significant proportion of patients who are wheelchair users [5].

Interactions of chronic disease and anaesthesia medications

Not reported.

Anaesthetic procedure

There are few cases describing anaesthesia management in CLOVES syndrome [13]. Neuraxial anaesthesia may carry an increased risk due to the potential paraspinal AVM, scoliosis, and perioperative anticoagulation.

Intercostal nerve blocks and cryoneurolysis as well as paravertebral blocks have been used with success for chronic nociceptive and neuropathic chest wall pain [20, 21]. The use of ultrasound during regional techniques is likely beneficial given the potential for altered anatomy.

Particular or additional monitoring

Standard monitors should be used as appropriate (e.g., electrocardiogram, non-invasive blood pressure, pulse oximetry, capnography, gas analyzer). Neuromuscular monitoring is essential when patients require neuromuscular blocking agents. If intraoperative transesophageal echocardiography is indicated, consideration must be given to the possibility of esophageal phlebectasia or angiodysplasia [16].

The intraoperative use of thromboelastography has not been described but is likely helpful for managing acute hemorrhage.

Certain patients may be at high risk for pulmonary embolism, compromised cardiac function, and bleeding. Depending on the type of procedure, extended hemodynamic monitoring postoperatively may be warranted.

Possible complications

The majority of the reported perioperative complications occurred postoperatively with few complications occurring during the intraoperative period. Therefore, only a small proportion of reported complications are directly associated with anaesthesia.

One episode of intraoperative airway obstruction has occurred [13]. There is an increased risk of wound breakdown, infection, thromboembolism, and bleeding that continues into the postoperative period [4,16]. These patients may be on mechanistic target of rapamycin (mTOR) inhibitors, which may cause immunosuppression and impair wound healing. Therefore, a multidiscplinary discussion should be considered regarding the ongoing management of the condition.

Post-operative care

Thrombosis and coagulopathy risk assessment by haematology should be considered after any surgery, especially those with vascular malformations [3]. One single-centre cohort study demonstrated a 9% risk of post-operative pulmonary embolism [19].

Post-operative stridor has been reported in three patients [4].

Patients with significant scoliosis and pulmonary dysfunction may require prolonged ventilatory support in the intensive care unit.

Disease-related acute problems and effect on anaesthesia and recovery

Perioperative pulmonary embolism is a particular concern for these patients [19]. Multidisciplinary discussion regarding perioperative anticoagulation strategies should be discussed.

Ambulatory anaesthesia

Minor procedures can be considered as day cases, particularly in patients with limited systemic manifestations with CLOVES syndrome.

Obstetrical anaesthesia

There is no reported literature on obstetrical anaesthesia in patients with CLOVES syndrome. Neuraxial anaesthesia may be difficult and high risk (AVM, scoliosis, tethered cord, anticoagulation).

General anaesthesia may be necessary. Additional airway adjuncts should be available, given possible airway difficulties in CLOVES syndrome and pregnancy.

These patients are also at increased risk of thromboembolism events, which may be compounded in pregnancy.

References

1. 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.0b013e328317a71610.1097/MCD.0b013e328317a716.
2. Kurek KC, Luks VL, Ayturk UM, et al. Somatic mosaic activating mutations in PIK3CA cause CLOVES syndrome. Am J Hum Genet. 2012;90(6):1108-1115. doi:10.1016/j.ajhg.2012.05.006
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. McNeil J. Perioperative risk in patients with CLOVES syndrome. Published online 2015. https://open.bu.edu/handle/2144/16030
5. Alomari AI. Comments on the diagnosis and management of CLOVES syndrome. Pediatr Dermatol. 2011;28(2):215-216. doi:10.1111/j.1525-1470.2011.01396.x
6. Gucev ZS, Tasic V, Jancevska A, et al. Congenital lipomatous overgrowth, vascular malformations, and epidermal nevi (CLOVE) syndrome: CNS malformations and seizures may be a component of this disorder. Am J Med Genet A. 2008;146A(20):2688-2690. doi:10.1002/ajmg.a.32515
7. Kim JK, Hansen A, Peard L, Newsome M, Saltzman AF. Bilateral Wilms Tumor in CLOVES Syndrome [published online ahead of print, 2023 Feb 16]. Urology. 2023;S0090-4295(23)00090-0. doi:10.1016/j.urology.2023.01.034
8. 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
9. Alomari A, Dubois J. Interventional management of vascular malformations. Tech Vasc Interv Radiol. 2011;14(1):22-31. doi:10.1053/j.tvir.2010.07.006
10. de Grazia R, Giordano C, Cossio L, Downey C, Delucchi Á, Kramer D. CLOVES syndrome: Treatment with oral Rapamycin. Report of two cases. Rev Chil Pediatr. 2019 Dec;90(6):662-667. English, Spanish. doi: 10.32641/rchped.v90i6.1025.
11. Ballieux F, Modarressi A, Hammer F, et al. Reconstructive surgery in the management of a patient with CLOVES syndrome. J Plast Reconstr Aesthet Surg. 2013;66(12):1813-1815. doi:10.1016/j.bjps.2013.06.045
12. Uller W, Fishman SJ, Alomari AI. Overgrowth syndromes with complex vascular anomalies. Semin Pediatr Surg. 2014;23(4):208-215. doi:10.1053/j.sempedsurg.2014.06.013
13. Fishman S, Landrigan-Ossar M, Alomari A, Trenor C. Anesthesia and CLOVES Syndrome; A Single-Institution Experience. http://www2.pedsanesthesia.org/meetings/2014winter/syllabus/submissions/aandp/nonmods/NM-314.pdf [Accessed on: June 3rd, 2023]
14. Mirzaa G, Graham JM Jr, Keppler-Noreuil K. PIK3CA-Related Overgrowth Spectrum. 2013 Aug 15 [Updated 2023 Apr 6]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews®. Seattle (WA): University of Washington, Seattle; 1993-2025. https://www.ncbi.nlm.nih.gov/books/NBK153722/ [Accessed on: February 11, 2025]

15. 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;2021(4):rjab122. Published 2021 Apr 19. doi:10.1093/jscr/rjab122
16. St-Pierre J, Mirakhur A, Forbes N. Gastrointestinal Manifestations of CLOVES Syndrome. ACG Case Rep J. 2023;10(5):e01050. Published 2023 May 10. doi:10.14309/crj.0000000000001050
17. Weissler JM, Shubinets V, Carney MJ, Low DW. Complex Truncal Masses in the Setting of CLOVES Syndrome: Aesthetic and Functional Implications. Aesthetic Plast Surg. 2017;41(3):591-599. doi:10.1007/s00266-016-0771-1
18. Spencer SA, Sorger JI. Orthopedic issues in vascular anomalies. Semin Pediatr Surg. 2020;29(5):150973. doi:10.1016/j.sempedsurg.2020.150973
19. Reis J 3rd, Alomari AI, Trenor CC 3rd, et al. Pulmonary thromboembolic events in patients with congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and spinal/skeletal abnormalities and Klippel-Trénaunay syndrome. J Vasc Surg Venous Lymphat Disord. 2018;6(4):511-516. doi:10.1016/j.jvsv.2018.01.015
20. Javed S, Tabansi P. Use of intercostal nerve block for chest wall pain in a patient with CLOVES syndrome. Pain Manag. 2022;12(6):681-685. doi:10.2217/pmt-2021-0120
21. Sen S, De Haan JB, Mehrafza M, Hernandez N. Ultrasound-Guided Percutaneous Intercostal Cryoneurolysis for Acute-on-Chronic Pain in CLOVES Syndrome. Cureus. 2023;15(1):e34066. Published 2023 Jan 22. doi:10.7759/cureus.34066

Wang D, Eisen HJ. Mechanistic Target of Rapamycin (mTOR) Inhibitors. Handb Exp Pharmacol. 2022;272:53-72. doi: 10.1007/164_2021_553.

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