

Anaesthesia recommendations for **Alkaptonuria**

Disease name: Alkaptonuria

ICD 10: E70.2

Synonyms: Hereditary ochronosis, endogenous ochronosis, homogentisate dioxygenase deficiency

Disease summary: Alkaptonuria (AKU) is a rare autosomal recessive disorder with an incidence of 1:250 000 to 1:1000 000 live births. AKU is caused by a deficiency of the enzyme homogentisate 1,2-dioxygenase (HGO). This enzyme converts homogentisic acid (HGA) to maleylacetoacetic acid in the tyrosine degradation pathway. Accumulated HGA is rapidly cleared in the kidney and excreted in the urine. HGA blood levels are kept very low through rapid kidney clearance, but over time HGA is deposited in cartilage throughout the body and converted to a pigment-like polymer. This occurs through an enzyme-mediated reaction in collagenous tissues like ligaments, tendons, cartilage, and sclera. As a result, AKU has three major features:

Darkening of the urine upon contact with air.

HGA is oxidized to form a pigment-like polymeric material responsible for the black color of standing urine, or after exposure to an alkaline agent.

Ochronosis (bluish-black pigmentation of connective tissue).

Accumulation of HGA and its oxidation products (e.g., benzoquinone acetic acid) in connective tissue leads to ochronosis – brown pigmentation of the sclera which does not affect vision, blue or gray discoloration and calcification of ear cartilage, possible discoloration on the skin of the hands, corresponding to underlying tendons and gray and black discoloration of cartilages in the joints.

Arthritis.

It often begins in the spine. Degenerative changes, mainly in intervertebral disks, may be seen throughout the entirety of the vertebral column, where the lumbar spine is the most commonly affected region. With the progression of the disease it may cause changes resembling those of ankylosing spondylitis. Patients may complain of stiffness in their lower back with no other symptoms or signs of lumbar spine disease. The culprit of spinal abnormalities could possibly be disk space narrowing, widespread disk calcifications and mild osteophytosis with minimal calcification of the intervertebral ligaments. Radiographs of the large joints may show joint space narrowing, subchondral cysts, and infrequent osteophyte formation. Knees, hips, and shoulders are frequently affected. Fifty percent of individuals require at least one joint replacement by age 55 years.

Pigment deposition can be also seen in heart endocardium, valves, and kidneys. Therefore, patients may have valvular disease, nephrolithiasis, and other renal complications in the advanced age.

Impaired renal function can accelerate the development of arthritis and ochronosis due to inability to excrete HGA and worsen the progression of the disease. By around the age of 60, 50% of the individuals with AKU have a history of renal stones.

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

Typical surgery

Hip or knee replacement, shoulder joint replacement, lumbar laminectomy, valve replacement. Any synovial joint may require arthroplasty. Renal stone disease may require urological procedures including nephrostomy. Repair of ruptured ligaments and tendons may require a surgical approach. Any surgery required in non-alkaptonuric patients may also be needed in AKU patients.

Type of anaesthesia

The systemic manifestations of AKU resemble other musculoskeletal disorders such as osteoarthritis, ankylosing spondylitis, and collagen vascular diseases such as rheumatoid arthritis. Anaesthetic considerations for these disorders can serve as a useful guide to the management of a patient with AKU. The anaesthetic considerations presented address each organ system as they pertain to the anaesthetic management of a patient with AKU. A thorough evaluation of the type and severity of systemic dysfunction is essential before providing anaesthesia to these patients. Organ and tissue involvement will influence the anaesthetic technique to be used.

Valvular heart disease is common in patients with ochronosis, and preoperative evaluation should be concerned primarily with determining the location and severity of the lesion and its hemodynamic significance. General anaesthesia may be not appropriate in case of severe valvular regurgitations. Limitation in the range of motion of the cervical spine most likely would cause certain problems with tracheal intubation. Deep sedation can provoke respiratory insufficiency in compromised patients. For unclear reasons, hypotension during and after surgery complicates surgery including arthroplasty.

Since there may be early puncture difficulties, interspinous spaces and other anatomical landmarks can be located with the help of an ultrasound.

Degenerative changes of the lumbar spine would make the regional technique unsuccessful. Calcification of interspinous ligaments makes epidural approaches to anaesthesia difficult if not impossible. Caution should be kept while performing spinal anaesthesia because of the fact that the dura and arachnoid membrane can be damaged by HGA what predisposes to post-puncture headaches.

Necessary additional pre-operative testing (beside standard care)

- Assessment of the mobility of the lumbar spine (ROM: Schober test) as well as the cervical spine, X-ray of the lumbar spine.
- Pulmonary function tests should be done in patients with respiratory complaints which may be impaired due to ochronotic fibrosis of the costal cartilages and correspond to restrictive pulmonary diseases.
- Evaluation of the cardiovascular system is required and assessment of heart valves is crucial. Preoperative echocardiography would be a prudent course of action because it will provide information regarding valvular function, chamber filling, wall contractility and motion, and regional and global ventricular function. However, in patients who are severely debilitated (recent signs and symptoms of ischemic heart disease or history of congestive heart disease), cardiac catheterization may be warranted. Ultimately, the

degree of cardiovascular involvement will dictate the need for invasive monitoring during a proposed surgical procedure. Cardiovascular abnormalities such as generalised atherosclerosis, and conduction blocks may also be associated with ochronosis. Reports exist of calcification and stenosis of the aortic annulus leading to coronary artery disease, and the risk of myocardial infarction is higher than normal in older patients with ochronosis. Therefore, electrocardiogram and echocardiogram should be done in all individuals older than the age of 40 years.

- Impairment of renal function can manifest with frequent urinary tract infections and nephrolithiasis. Renal ultrasound examination or helical abdominal CT to evaluate for the presence of renal calculi is recommended if renal involvement is suspected.

Particular preparation for airway management

Limitation in the range of motion of the cervical spine most likely would cause certain problems with tracheal intubation. Because of strong evidence, the possibility of difficult airway should be taken into account.

The depositions of pigments make the cartilage of the joints prone to destruction and make the joints painful. The cartilage of the airway and respiratory system may also be affected in ochronosis. Heavy deposition of the pigment in the laryngeal, tracheal, and bronchial cartilages may result in hoarseness, dysphagia, and a difficult airway.

Difficult airway cart should be readily available.

Particular preparation for transfusion or administration of blood products

There is no special consideration for transfusion or administration of blood products in patients with AKU. However, these patients may be on long-term aspirin or NSAID therapy which may result in platelet dysfunctions, prolonged bleeding time, and gastrointestinal bleeding. Parenteral fluid administration may be needed for hypotensive complications.

Particular preparation for anticoagulation

There is no evidence to support the need of particular anticoagulation.

Particular precautions for positioning, transportation and mobilisation

Patients with AKU may have some joint and spine deformity due to cartilage destruction and thus difficulty may be faced during positioning and pressure points should be adequately padded to prevent any undue pressure on the diseased joints.

Interactions of chronic disease and anaesthesia medications

Such patients may be on long-term aspirin or NSAID therapy which may result in platelet

dysfunctions, prolonged bleeding time, and gastrointestinal bleeding.

Anaesthetic procedure

Dosages of intravenous anaesthetics and muscle relaxants should be modified according to the existing renal dysfunction.

Neuraxial sonography can be considered with or without a real-time ultrasound-guided approach in spinal anaesthesia.

Particular or additional monitoring

Caution should be exercised in pulse oximeter monitoring of patients with excessive pigment deposition.

The deposition of HGA products in the tissues renders them resistant to the near-infrared photons, making near-infrared spectroscopy cerebral oximetry technically unfeasible. The pigmentation of the forehead, the systemic connective tissues degeneration, the pigmentation of the periosteum, or even the possibility of dura mater involvement in AKU may explain the inability of NIR spectroscopy photons to penetrate the frontal cortex.

In case of high risk surgery especially in patients with cardiac abnormalities arterial cannulation for invasive blood pressure measurement and central line placement is recommended.

Possible complications

There is a report of a 24-year-old alkaptonuric man with severe decreased kidney function who developed fatal metabolic acidosis and intravascular haemolysis. Haemolysis may have been caused by rapid and extensive accumulation of HGA and subsequent accumulation of plasma soluble melanins. Toxic effects of plasma soluble melanins, their intermediates, and reactive oxygen side products are increased when antioxidant mechanisms are overwhelmed. A decrease in serum antioxidative activity has been reported in patients with chronic decreased kidney function. However, despite administration of large doses of an antioxidant agent and ascorbic acid and intensive kidney support, haemolysis and acidosis could not be brought under control and haemolysis led to the death of the patient.

Increased predisposition to post-puncture headaches should be taken into account because the dura and arachnoid membrane are made vulnerable by HGA and could be damaged.

Hypotensive complications during and after surgery requiring general anaesthesia is frequently seen requiring aggressive fluid therapy.

Post-operative care

Failure to wean from mechanical ventilation after general anaesthesia or dyspnea can develop due to stiffness of cartilage in the chest wall.

Disease-related acute problems and effect on anaesthesia and recovery

Disk herniation at the lumbar level is rare but it can cause symptoms resembling those in spinal anaesthetic toxicity or other post-punctural complications.

In general, disease-triggered emergency-like situations are not common in AKU.

Ambulatory anaesthesia

Ambulatory anaesthesia can be performed according to common guidelines in patients without severe cardiac, respiratory and renal abnormalities.

Obstetrical anaesthesia

Obstetrical anaesthesia can be performed according to common guidelines in patients without severe cardiac, respiratory and renal abnormalities.

References

1. Abdulrazzaq YM, Ibrahim A, Al-Khayat AI, et al. R58fs mutation in the HGD gene in a family with alkaptonuria in the UAE. *Ann Hum Genet.* 2009 Jan;73(1):125-30. doi: 10.1111/j.1469-1809.2008.00485.x. Epub 2008 Oct 20
2. Ahmed S, Shah Z, Ali N. Chronic low backache and stiffness may not be due ankylosing spondylitis. *J Pak Med Assoc.* 2010 Aug;60(8):681-3
3. Al-Mahfoudh R, Clark S, Buxton N. Alkaptonuria presenting with ochronotic spondyloarthropathy. *Br J Neurosurg.* 2008 Dec;22(6):805-7. doi: 10.1080/02688690802226368
4. Argiriadou H, Anastasiadis K, Antonitsis P, et al. The inability of regional oxygen saturation monitoring in a patient with alkaptonuria undergoing aortic valve replacement. *J Cardiothoracic Vasc Anesth* 2009; 23:586–588
5. Brueck M, Bandorski D, Kramer W, et al. Aortic valve stenosis due to alkaptonuria. *J Heart Valve Dis.* 2008 Jan;17(1):127-9
6. Capkin E, Karkucak M, Yayli S et al. Ochronosis in differential diagnosis of patients with chronic backache: a review of the literature. *Rheumatol Int.* 2007 Nov;28(1):61-4. Epub 2007 Jun 13
7. Carrier DA, Harris CM. Bilateral hip and bilateral knee arthroplasties in a patient with ochronotic arthropathy. *Orthop Rev.* 1990 Nov;19(11):1005-9
8. Collins E, Hand R. Alkaptonuric ochronosis: a case report. *AANA J.* 2005 Feb;73(1):41-6
9. Cox TF, Ranganath L. A quantitative assessment of alkaptonuria: testing the reliability of two disease severity scoring systems. *J Inherit Metab Dis.* 2011 Dec;34(6):1153-62. doi: 10.1007/s10545-011-9367-8. Epub 2011 Jul 9
10. Drakoulakis E, Varvitsiotis D, Psarea G et al. Ochronotic arthropathy: diagnosis and management: a critical review. *Am J Orthop (Belle Mead NJ).* 2012 Feb;41(2):80-3
11. Effelsberg NM, Hügler T, Walker UA. A metabolic cause of spinal deformity. *Metabolism.* 2010 Jan;59(1):140-3. doi: 10.1016/j.metabol.2009.06.034. Epub 2009 Sep 17
12. Gercek A, Koc D, Erol B, et al co-existence of Pott's disease and alkaptonuria in a 21-month-old child. *Paediatr Anaesth,* 2008 Jun;18(6):569-71. doi: 10.1111/j.1460-9592.2008.02495.x. Epub 2008 Feb 2
13. Gonzales ME. Alkaptonuric aortic stenosis: a case report. *AANA J.* 1999 Apr;67(2):145-51.
14. Grasko JM, Hooper AJ, Brown JW, et al. A novel missense HGD gene mutation, K57N, in a patient with alkaptonuria. *Clin Chim Acta.* 2009 May;403(1-2):254-6. doi: 10.1016/j.cca.2009.03.032. Epub 2009 Mar 21
15. Gupta A, Jayanti A, Prasanna K. Premature arthritis in an elderly woman. *Int J Clin Pract.* 2006 Jul;60(7):858-60
16. Hamdulay SS, Finegold J, Boyer L, et al. Clinical images: Magnetic resonance imaging appearance of alkaptonuria. *Arthritis Rheum.* 2012 Jan;64(1):129. doi: 10.1002/art.33357
17. Hegedus ZL. The probable involvement of soluble and deposited melanins, their intermediates and the reactive oxygen side-products in human diseases and aging. *Toxicology.* 2000 Apr 14;145(2-3):85-101
18. Heng AE, Courbebaisse M, Kemeny JL, et al. Hemolysis in a patient with alkaptonuria and chronic kidney failure. *Am J Kidney Dis.* 2010 Jul;56(1):e1-4. doi: 10.1053/j.ajkd.2009.11.023. Epub 2010 Mar 6
19. Kalevski SK, Haritonov DG, Peev NA. Alcaptonuria with lumbar disc prolapse: case study and review of the literature. *Spine J.* 2007 Jul-Aug;7(4):495-8. Epub 2006 Dec 29
20. Kastsichenka S, Mikulka A. Anaesthesia and orphan disease: a patient with alkaptonuria. *Eur J Anaesthesiol* 2013 Dec; Vol 30(12):779-80 doi: 10.1097/01.EJA.0000434959.14590.46
21. Kopeć K, Kusz D, Wojciechowski P, et al. Orthopaedic problems in patients affected by alkaptonuria. A case report. *Ortop Traumatol Rehabil.* 2007 Mar-Apr;9(2):206-14
22. Laxon S, Ranganath L, Timmis O. Living with alkaptonuria. *BMJ.* 2011 Sep 29;343:d5155. doi: 10.1136/bmj.d5155
23. Liu W, Prayson RA. Dura mater involvement in ochronosis (alkaptonuria). *Arch Pathol Lab Med.* 2001 Jul;125(7):961-3
24. Mannoni A, Selvi E, Lorenzini S, et al. Alkaptonuria, ochronosis, and ochronotic arthropathy. *Semin Arthritis Rheum.* 2004 Feb;33(4):239-48
25. Morava E, Kosztolányi G, Engelke UF, et al. Reversal of clinical symptoms and radiographic abnormalities with protein restriction and ascorbic acid in alkaptonuria. *Ann Clin Biochem.* 2003 Jan;40(Pt 1):108-11

26. Parambil JG, Daniels CE, Zehr KJ, et al. Alkaptonuria diagnosed by flexible bronchoscopy. *Chest*. 2005 Nov;128(5):3678-80
27. Paul R, Ylinen SL. The "whisker sign" as an indicator of ochronosis in skeletal scintigraphy. *Eur J Nucl Med*. 1991;18(3):222-4
28. Raaijmakers M, Steenbrugge F, Dierickx C. Ochronosis, arthroscopy of a black knee: a case report and review of the literature. *Knee Surg Sports Traumatol Arthrosc*. 2008 Feb;16(2):182-4. Epub 2007 Sep 25
29. Rallis E, Kintzoglou S. Ashy ears. *ScientificWorldJournal*. 2010 Aug 3;10:1530-1. doi: 10.1100/tsw.2010.147
30. Ranganath LR, Cox TF. Natural history of alkaptonuria revisited: analyses based on scoring systems. *J Inherit Metab Dis*. 2011 Dec;34(6):1141-51. doi: 10.1007/s10545-011-9374-9. Epub 2011 Jul 12
31. Reddy DR, Prasad VS. Alkaptonuria presenting as lumbar disc prolapse: case report and review of literature. *Spinal Cord*. 1998 Jul;36(7):523-4
32. Sag AA, Silbergleit R, Olson RE et al. T1 hyperintense disc in alkaptonuria. *Spine (Phila Pa 1976)*. 2012 Oct 1;37(21):E1361-3
33. Shimizu I, Hamada T, Khalpey Z, et al. Ochronotic arthropathy: pathological evidence of acute destruction of the hip joint. *Clin Rheumatol*. 2007 Jul;26(7):1189-91. Epub 2006 Jun 20
34. Steinmann B, Gnehm HE, Rao VH, et al. Neonatal severe primary hyperparathyroidism and alkaptonuria in a boy born to related parents with familial hypocalciuric hypercalcemia. *Helv Paediatr Acta*. 1984 May;39(2):171-86
35. Suwannarat P, O'Brien K, Perry MB et al. Use of nitisinone in patients with alkaptonuria. *Metabolism*. 2005 Jun;54(6):719-28
36. Suwannarat P, Phornphutkul C, Bernardini I, et al. Minocycline-induced hyperpigmentation masquerading as alkaptonuria in individuals with joint pain. *Arthritis Rheum*. 2004 Nov;50(11):3698-701
37. Tsunashima T, Arima T, Tsuboi S, et al. A case of alkaptonuria with fatal cardiovascular disturbance. *Acta Med Okayama*. 1976 Apr;30(2):87-94
38. Yancovitz M, Anolik R, Pomeranz MK. Alkaptonuria. *Dermatol Online J*. 2010 Nov 15;16(11):6
39. Zaraa I, Labbène I, Trojjet S, et al. Endogenous ochronosis with a fatal outcome. *J Cutan Med Surg*. 2012 Sep-Oct;16(5):357-60.
40. Pratheeba N, Singh N, Ranjan RV, et al. Anesthetic management of a case of alkaptonuria. *Anaesth Pain & Intensive Care* 2013;17(2):179-181
41. Pandey R, Kumar A, Garg R et al. Perioperative management of patient with alkaptonuria and associated multiple comorbidities. *J Anaesthesiol Clin Pharmacol*. 2011; 27(2): 259-261 <http://dx.doi.org/10.4103/0970-9185.81839> PMID:21772695 PMCID:PMC3127314
42. Bilgi K, Jagadeeshan S, Venugopal P. Difficult epidural in a patient with undiagnosed alkaptonuria. *Indian J Anaesth* 2016;60:523-5.
43. Argiriadou H, Anastasiadis K, Antonitsis P, et al. The inability of regional oxygen saturation monitoring in a patient with alkaptonuria undergoing aortic valve replacement. *J Cardiothorac Vasc Anesth*. 2009;23(4):586-588. doi:10.1053/j.jvca.2008.08.014
44. Kozanhan B. Anesthetic management of two patients with alkaptonuric ochronosis for total knee arthroplasty. *Rev Bras Anesthesiol*. 2018;68(3):307-310

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