orphanaesthesia

Anaesthesia recommendations for

Hardikar syndrome

Disease name: Hardikar syndrome

ICD 10: Q87.8

Synonyms: Hardikar syndrome, HDKR

Disease summary: Hardikar syndrome (HS) is a very rare multiple congenital malformation syndrome (prevalence <1/1,000,000 (1,2)), characterized by an association of cleft lip and palate, patchy pigmentary retinopathy (cat's paw), obstructive liver disease (cholestasis, portal hypertension, etc.) and obstructive renal disease (ectopic ureteric insertion, obstruction, vesicouretral reflux and hydronephrosis). Gastrointestinal tract involvement (malrotation, gastresophageal reflux etc.) and cardiac involvement (coarctation of aorta, pulmonary artery stenosis, arrhytmia, cardiomyopathy, vascular malformations, etc.) have also been reported (1).

HS was first described in 1992 and is a female-specific, X-linked dominant disorder (Xq13.1) caused by truncating variants in the *MED12* gene. MED12 is a member of the Mediator complex that is involved in the regulation of transcription (5,6). Causal variants are *de novo* in all reported cases.

Until 2023, 13 cases have been reported of whom 10 cases have been genetically confirmed in the medical literature, mainly of genetics (3,4,5). The patients were diagnosed between the ages of 1 week and 20 years.

HS is allelic to a number of other *MED12*-related disorders, including Opitz–Kaveggia syndrome, Lujan syndrome (LS), Ohdo syndrome (XLOS), and nonsyndromic intellectual disability (NSDI). These syndromes primarily affect males, though manifesting females are increasingly recognized.

Regarding *MED12*-related disorders, clinical and anatomical characteristics include the phenotypes of FG syndrome type 1 (FGS1), LS, XLOS, HS, and NSID (table and appendix 1). Carrier females in families with FGS1 and LS are typically unaffected. In contrast to other previously described MED12-related syndromes, developmental and cognitive concerns have not been reported in females with HS. Variability in organ involvement is the rule.

HS strictly includes the clinical features listed in the table(1-15).

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**	Typical airway difficulties / anomalies / malformations? (Dis)Advantage for general (GA) or regional anaesthesia? (RA)
B	**BLOOD PRODUCTS (COAGULATION)**	Special preparation / storage of blood products necessary? Special haemostaseologic tests / consideration necessary? Coagulation disorders / pathologies?
C	**CIRCULATION**	Typical cardiopulmonary malformations, pathologies, arrhythmias…? Congenital heart disease/ anomaly? Special risk for heart failure? Haemodynamic specifics / risks?
D	**DRUGS**	Any drugs that should be avoided? Interactions with typical home medication? Special recommendations for premedication? Risk for MH/rhabdomyolysis?
E	**EQUIPMENT**	Special equipment (or care / assistance) needed for e.g., transport or within PACU/ IMC/ ICU?

Typical surgery

In the few cases reported, the pathologies were diagnosed and surgery performed in childhood and adolescence (between 4 days of life and 16 years) several of them in the same patient (4,8,13):

Ureteral stenosis requiring ureterostomy, PDA ligation, Ladd's procedure and gastrostomy tube placement, surgery for gut malrotation, gastrostomy, cleft lip and cleft palate repair, bilaterral ureterostomy, kidney transplant (for end stage renal disease secondary to obstructive uropathy); pharyngeal flap closure for velopharyngeal insufficiency; atypical coarctation of aorta needing angioplasty or stenting; abdominal hysterectomy and bilateral salpingectomy (for chronic lower abdominal pain, due to asymmetric rudimentary bicornuate noncommunicating uterus with hematosalpinx and hematometra).

Brain magnetic resonance angiography (MRA) is recommended following diagnosis of HS (in one patient a stable 3 mm left vertebral artery aneurysm and 2 mm right distal posterior cerebral artery aneurysm were found); and ear pressure equalization by tubes placement.

In one patient, unprecipitated intracranial haemorrhage occurred, resulting in lethal outcome.
Liver biopsy. Liver transplant was performed for biliary cirrhosis in tow cases (the risk of malignancy in biliary cirrhosis should be taken into account but is not specific for HS)
Surgery for femur fractures (demineralization) have been reported too.

Type of anesthesia

Anaesthesia management or procedures have not been reported despite surgeries performed in some patients, as stated before. So, extrapolation from the approach to syndromes with similar organ or anatomical malformations is the only way to find information.

Both general and regional anaesthesia might be performed. As spine malformations are possible, a previous X-ray exploration can be recommended (in one case spine X-rays were obtained at the age of 11 years for concern of spine deformity and revealed anomalies of the spine including C2/C3 retrolisthesis, incomplete fusion of S1 posterior elements, Sprengel deformity, and kyphosis).

Necessary additional pre-operative testing (beside standard care)

As neurodevelopment is preserved, full explanation of procedures can be made to patients. No other reported. However cardiac evaluation should be the rule due to the incidence of ECG alterations and structural deformities.

Particular preparation for airway management

As in other syndromes in whom the airway showed malformations (cleft lip and palate, facial anomalies), preparation for difficult airway is needed, and rapid sequence induction considered due to frequent intestinal malformations with significant gastroesophageal reflux.

Particular preparation for transfusion or administration of blood products

None has been reported. However, increased risk of bleeding due to impaired liver synthesis function should be considered in patients with liver involvement (7).

Particular preparation for anticoagulation

If the patient presents with aneurisms (carotid artery or others) anticoagulation is the rule.

Particular precautions for positioning, transportation and mobilisation

None reported. If spine deformities are present careful positioning and padding is mandatory.

Interactions of chronic disease and anesthesia medications

None reported. However, potential for chronic kidney disease, arrhythmia and cardiomyopathy should be considered.

Anesthetic procedure

If general anaesthesia is selected, airway difficulties should be considered and foreseen.

Drug metabolism could be affected provided biliary tract deformities alter drug excretion or liver function (drug metabolism) is affected by secondary cirrhosis or fibrosis. If aminosteroidal neuromuscular blocking agents are chosen, elimination might be delayed (both because liver and kidney organ disfunction).

Caution with gastric tubes or TEE probes due to possible bleeding risk - fibrotic liver with portal hypertension and esophageal varices have been described (14).

Particular or additional monitoring

Depending on the organ alterations and the surgical procedure, invasive monitoring is recommended (for instance in HS patients with vascular aneurysms in the head and neck for close blood pressure measurement and early detection of impending blood pressure peaks).

Neuromuscular blockade monitoring is recommended.

Possible complications

No specific complications reported related to the anaesthetic procedure.

Post-operative care

Mid or high dependence postoperative care is recommended depending on the magnitude of the surgical procedure and organ dysfunction.

Disease-related acute problems and effect on anesthesia and recovery

None reported.

Ambulatory anesthesia

Not reported.

Obstetrical anesthesia

Not reported.

Appendix 1. Characteristics of other MED-12 related syndromes.

FGS1 Cognitive impairment, hypotonia, abnormalities of corpum callosum. Absolute or relative macrocephaly, tall forehead, downslanted palpebral fissures, small and simple ears, constipation and/or anal anomalies, broad thumbs and hallucis. Characterisrtic behavior. LS Cognitive impairment, hypotonia, abnormalities of corpum callosum. Large head, tall thin body habitus, long thin face, prominent nasal bridge, high narrow palate and short philtrum. XLOS intelectual disability, blepharophimosis, facial coarsening HS (females) Cleft lip and/or palate, biliary and liver abnormalities, intestinal malrotation, pigmentary retinopathy, coarctation of the aorta

Appendix 2 (from ref 4).

System/Concern	Evaluations following initial diagnosis	Surveillance
Constitutional (measurements of growth parameters, assess for short stature)	✓	Annual
Neuro (MRI/MRA head and neck for aneurysms)	✓	Every 6 months to 1 year
Ophthalmology evaluation (retinal abnormalities, refractive error, strabismus, clinically significant ptosis)	✓	Every 1-2 years
Otolaryngology evaluation (cleft lip/palate and velopharyngeal insufficiency)	✓	As needed
Audiology evaluation (hearing loss)	✓	As needed
Endocrine evaluation (for growth hormone deficiency in children w/short stature) • Bone age, growth hormone & thyroid function studies	✓	As needed
Cardiovascular • Echocardiogram, EKG, and carotid ultrasound (congenital heart disease, aortic coarctation/ dilatation, carotid dilation)	✓	Annual
Gastroenterology (evaluation for intestinal malrotation and feeding issues)	✓	As needed
Hepatobiliary system (liver disease, choledochal cyst and cholangiocarcinoma) • Ultrasound abdomen • CT abdomen/MRCP • Tumor markers (AFP, CEA, CA 19-9) • Hepatic panel, GGT	✓ If abnormal ultrasound imaging ✓ ✓	Annual As needed Annual screening with tumor markers if abnormal imaging or screening labs Annual
Musculoskeletal (spine anomalies) • Clinical spine exam • Spine X ray	✓ As needed	✓ As needed
GU (renal and pelvic ultrasound for anomalies and reflux)	✓	As needed

References

1. https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=1415.
2. Hardikar W, Smith AL, Keith CG, Chow CW. Multisystem obstruction with cholestasis, pigmentary retinopathy, and cleft palate: a new syndrome? Am. J. Med. Genet. 1992;44:13-17.
3. Li D, Strong A, Shen KM, Cassiman D, Van Dyck M, Linhares ND, et al. De novo loss-of-function variants in X-linked MED12 are associated with Hardikar syndrome in females. Genet Med. 2021;23:637-644.
4. Pillai NR, Miller D, Bronken G, Salunke AK, Aggarwal A. MED12-related Hardikar syndrome: Two additional cases and novel phenotypic features. Am J Med Genet Part A, 2022;188A: 2231–2236. https://doi.org/10.1002/ajmg.a.62756.
5. Adams E, Adeleye M, Hussein M, Naravane A; Looysen T, Simmons M; Tang PH, Montezuma SR. Multimodal retinal imaging findings in Hardikar syndrome. Retinal Cases & Brief Reports ():10.1097/ICB.0000000000001476, August 15, 2023. | DOI: 10.1097/ICB.0000000000001476
6. van de Plassche SR; de Brouwer APM. MED12-Related (Neuro)Developmental Disorders: A Question of Causality. Genes 2021;1:663. https://doi.org/10.3390/genes 12050663.
7. Lyons MJ. MED12-Related Disorders. 2008 Jun 23 [Updated 2021 Aug 12]. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/
8. Ryan KM, Ellis AR, Raafat R, Bhoj EJ, Hakonarson H, Li D, et al. Aortic coarctation and carotid artery aneurysm in a patient with hardikar syndrome: cardiovascular implications for affected individuals. Am J Med Genet 2016;170(2):482-486. https://doi.org/10.1002/ajmg.a.37438.
9. OMIM # 301068. hardikar%20syndrome/Entry%20-%20%23301068%20-%20HARDIKAR%20SYNDROME%3B%20HDKR%20-%20OMIM.html
10. Cools F, Jaeken J. Hardikar syndrome: A new syndrome with cleft lip/palate, pigmentary retinopathy and cholestasis. Am J Med Genet 1997;71(4):472-474. https://doi.org/10.1002/(SICI)1096-8628(19970905)71:4<472::AID-AJMG19>3.0.CO;2-D
11. Poley JR, Proud VK. Hardikar syndrome: New features. Am J Med Genet 2008;146A(19): 2473-2479. https://doi.org/10.1002/ajmg.a.32266
12. Ejarque I, Uliana V, Forzano F, Marciano C, Merla G, Zelante L, et al. Hardikar syndrome distinct from Kabuki (Niikawa-Kuroki) syndrome? Clin Genet 2011;80(5):493-496. https://doi.org/10.1111/j.1399-0004.2011.01672.x
13. Maluf DG, Fisher RA, Fukcher AS, Posner MP. Hardikar syndrome: A case requiring liver transplantation. Transplantation 2002;74(7):1058-1061.
14. Nydegger A, Van Dyck M, Fisher RA, Jaeken J, Hardikar W. Hardikar syndrome: Long term outcome of a rare genetic disorder. Am J Med Genet 2008;Part A 146A:2468–2472.
15. Sastry AV, Abbadessa B, Wayne MG, Steele JG, Cooperman AM. What is the incidence of biliary carcinoma in choledochal cysts, when do they develop, and how should it affect management? World J Surg 2015;39:487-492.

Date last modified: February 2025

This recommendation was prepared by:

Author(s)
Carlos L. Errando. Anesthesiologist. Hospital Can Misses, Ibiza, IB, Spain, and Consorcio Hospital General Universitario de Valencia, Valencia, Spain.
Sociedad Española de Anestesiología y Reanimación (SEDAR), Grupo de trabajo de enfermedades raras. Spanish Society of Anesthesiology and Intensive Care, Rare diseases working group.
Email: errando013@gmail.com

Disclosure The authors have no financial or other competing interest to disclose. This recommendation was unfunded.

This recommendation was reviewed by:

Reviewers
Christine Gaik, Specialist in anaesthesia and intensive care medicine, University Hospital Marburg, Germany
gaikc@med.uni-marburg.de

Alanna Strong, Division of Human Genetics, Children's Hospital of Philadelphia, USA
strong.alanna@gmail.com

Disclosure The reviewers have no financial or other competing interest to disclose.