

## Anaesthesia recommendations for **Wolf-Hirschhorn syndrome**

**Disease name:** Wolf-Hirschhorn syndrome

**ICD 10: Q 93.3**

OMIM 194190, 602618, 602952, 604407, 605032, 605032, 605830, 606026

**Synonyms:** 4p deletion syndrome, 4p-syndrome, del (4p) syndrome, monosomy 4p, partial monosomy 4p, WHS

**Disease summary:** The disease was first described by Hirschhorn and Cooper in 1961, the second case was published in 1965 by Wolf et al. Wolf-Hirschhorn syndrome (WHS) is a rare congenital disorder with specific clinical features mostly caused by de novo microdeletion of the distal short arm of chromosome 4 (del 4p 16.3) involving the Wolf-Hirschhorn candidate gene (WHSC1 and WHSC2), but depending on the size of the deletion other genes can be involved as well (NELFA, LETM1, PIGG, CTBP1, FGFR1, MSX1) explaining the variability of clinical features. Only 10 % are caused by translocation. The Pitt-Rogers-Danks syndrome (another 4p deletion syndrome) is often considered as a mild clinical variation of WHS.

Typical clinical features (modified from Bösenberg (ref 9)):

Incidence > 75%:

typical facial feature of “Greek warrior helmet” appearance (prominent glabella extending into the broad bridge of the nose, high forehead), microcephaly, low set ears, intrauterine growth retardation, slow postnatal weight gain, failure to thrive, muscular hypotonia, seizures, febrile convulsions, typical EEG abnormalities, mental disability of variable degree.

Incidence 50-75%:

skeletal abnormalities such as scoliosis, congenital hip dislocation or clubfeet, craniofacial asymmetry, ptosis, microstomia, micrognathia, abnormal teeth, IgA or IgG2 deficiency.

Incidence 25-50%:

hearing loss, heart defect (mainly atrial or ventricular septal defect), eye or optic nerve anomalies, cleft lip and palate, genitourinary tract anomalies, structural brain anomalies, stereotypies (hand flapping, head-shaking, rocking...).

Incidence < 25%:

other anomalies concerning the liver, gallbladder, gut, diaphragm, oesophagus, lung and aorta, malignancies of the liver or the haematopoietic system.

The prevalence of the WHS is estimated at 1:20 000 – 1:50 000 births with a 2:1 female to male ratio. The severity of the phenotypic manifestation of WHS correlates with the amount

of chromosomal deletion. The mortality rate is about 30% within the first two years of life mainly due to aspirations leading to pulmonary infections or due to epileptic seizures. The seizures are often difficult to control, but tend to decline with age.

Congenital heart defects are usually not complex.

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Perhaps new knowledge

Every patient is unique

Perhaps the diagnosis is wrong

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**Find more information on the disease, its centres of reference and patient organisations on Orphanet: [www.orpha.net](http://www.orpha.net)**

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## Typical surgery

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Gastrostomy tube placement, fundoplication for gastroesophageal reflux disease, repair of cleft palate, cardiac surgery, tympanoplasty, myringotomy, hypospadias correction, cystoscopy, dental examination, orthopaedic surgery for foot and hip correction.

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## Type of anaesthesia

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Successful perioperative management has been reported with both inhalational and total intravenous anaesthesia in patients with WHS. However, two case reports describe an association between WHS and malignant hyperthermia, one of them with delayed onset. Children with WHS often present with infections, therefore perioperative hyperthermia could have other aetiologies. Association of malignant hyperthermia with WHS is unproven (no contracture tests performed, no ryanodine receptor genetically involved) and very unlikely as the generalized hypotonia is not caused by a muscle disease.

Regional anaesthesia like thoracic epidural anaesthesia for fundoplication is reported, but special care should be taken in case of vertebral abnormalities like scoliosis.

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## Necessary additional pre-operative testing (beside standard care)

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A thorough history and examination of the patient is important, as many organ systems (see above) can be involved. Careful evaluation of the airway patency (mouth opening, retrognathism) is essential. In case of congenital cardiac disease, ECG and echocardiography are necessary to evaluate the cardiac function. Blood coagulation and thrombocyte function should be checked if the patient receives valproate therapy, thrombelastography might be useful. Seizures should be well controlled by antiepileptic therapy. Therapeutic anticonvulsant levels should be checked before procedure.

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## Particular preparation for airway management

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Due to craniofacial deformities equipment for difficult airway management must be prepared. Mouth opening should be carefully evaluated as supraglottic devices and videolaryngoscopes require a minimum free interincisor distance to be introduced in the mouth. Radiographies of the cervical spine may be useful to evaluate the airway. A nasopharyngeal airway should be available. Some reports also mention successful conventional intubation without difficulties. A higher risk of aspiration and susceptibility to airway infections should be kept in mind. The size of the endotracheal tube should be chosen one size smaller than calculated per age due to growth retardation.

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## Particular preparation for transfusion or administration of blood products

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If the patient has IgA deficiency, he might be at risk of allergic or anaphylactic reactions when receiving a transfusion with a plasma-containing blood product.

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### **Particular preparation for anticoagulation**

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Coagulation disorders can develop in case of therapy with valproic acid. Careful review of coagulation parameters is recommended, as valproic acid influences both thrombocyte function (acquired von Willebrand's disease) and coagulation factors (fibrinogen). Therapy according to the laboratory test results is recommended in case of operations with anticipated significant blood loss, if valproic acid cannot be replaced.

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### **Particular precautions for positioning, transportation and mobilisation**

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Careful attention to intraoperative patient positioning is indicated in case of skeletal deformities like kyphosis, scoliosis or hip dysplasia.

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### **Interactions of chronic disease and anaesthesia medications**

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Most patients are under antiepileptic therapy, which should be continued throughout the perioperative period. Anticonvulsant medications should be given the morning of the procedure either by oral administration or by intravenous route. The anaesthetist must keep in mind possible pharmacological interactions. Especially older antiepileptic drugs like carbamazepine, phenobarbital, phenytoin induce hepatic enzymes leading to decreased plasma concentrations of many medications. Valproate is an inhibitor of microsomal hepatic enzymes and decreases the metabolism of many medications.

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### **Anaesthetic procedure**

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As WHS patients tend to be less cooperative and hearing loss is common, the presence of a parent/ caregiver is very helpful during induction of anaesthesia. If necessary, a pre-medication may be given carefully as the patient can be very sensitive and respiratory complications may occur. Successful inhalational inductions are described, but it should be kept in mind that patients with WHS often present with gastroesophageal reflux disease. The plan for management of the potentially difficult airway must be balanced carefully against the increased risk of aspiration.

Recurrent respiratory infections may lead to airway hyperreactivity during all phases of anaesthesia (induction, maintenance and awakening). Difficulties of ventilation and increased peak airway pressure may occur. The use of sevoflurane and bronchodilators can be helpful.

Doses of neuromuscular blocking agents should be titrated to effect when the patient presents with generalized hypotonia.

Regional anaesthesia may be applied using ultrasound guidance as malformations of the bony system are common.

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### **Particular or additional monitoring**

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According to the severity of cardiac disease, appropriate non-invasive and invasive haemodynamic monitoring should be planned for the surgical procedure.

Temperature monitoring is advisable to detect hyperthermia whether caused by infections or, unlikely, malignant hyperthermia.

Careful neuromuscular monitoring is recommended as hypotonic WHS patients probably have increased sensitivity to neuromuscular blocking drugs.

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### **Possible complications**

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Respiratory complications as pulmonary infection, aspiration pneumonia and atelectasis are common.

Prolonged duration of neuromuscular blocking agents is possible.

Perioperative seizures can occur if the patient has a history of severe convulsion disorder.

Hyperthermia should be treated promptly to avoid febrile seizures.

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### **Post-operative care**

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Continuous respiratory monitoring is recommended until the patient is fully awake and stable. Prolonged surveillance is advisable due to possible complications as mentioned above.

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### **Disease-related acute problems and effect on anaesthesia and recovery**

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If intra- or postoperative hyperthermia occurs, there are many differential diagnoses to be considered: infections, malignant hyperthermia, iatrogenic overheating, drug induced fever etc.

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### **Ambulatory anaesthesia**

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Usually may not be advisable. In case of mild presentation of the disease and very short procedure, ambulatory anaesthesia may be considered on an individual base.

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### **Obstetrical anaesthesia**

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No reports found.

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*This recommendation was prepared by:*

**Author(s)**

**Alaa Sabbahi**, Department of Anesthesiology and Intensive Care, Faculty of Medicine King Abdulaziz University, Jeddah, Saudi Arabia

**Heike Kaltofen**, Department of Anesthesiology and Critical Care, Medical Center-University of Freiburg, Faculty of Medicine, University of Freiburg, Germany  
heike.kaltofen@uniklinik-freiburg.de

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*This recommendation was reviewed by:*

**Reviewer 1**

**Francis Veyckemans**, Pediatric Anesthesia, Hopital Jeanne de Flandre, CHRU de Lille, France

**Reviewer 2**

**Burça Aydın**, Professor of Pediatrics and Pediatric Oncology, Department of Pediatrics, Division of Pediatric Oncology, Hacettepe University Faculty of Medicine & Cancer Institute, Sıhhiye-Ankara, Turkey

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