Aktiv Druck & Verlag GmbH | ISSN 0170 - 5334 I 02330

www.ai-online.info

64. Jahrgang | Oktober 2023

A&I

ANÄSTHESIOLOGIE & INTENSIVMEDIZIN

Offizielles Organ: Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin e. V. (DGAI)
Berufsverband Deutscher Anästhesistinnen und Anästhesisten e. V. (BDA)
Organ: Deutsche Interdisziplinäre Vereinigung für Intensiv- und Notfallmedizin e. V. (DIVI)

Von Hippel-Lindau disease

Zhu-Tokita-Takenouchi-Kim syndrome

orphananesthesia

a project of the German Society
of Anaesthesiology and Intensive Care Medicine

SUPPLEMENT NR. 12 | 2023

OrphanAnesthesia –
ein krankheitsübergreifendes Projekt des Wissenschaftlichen Arbeitskreises Kinderanästhesie der Deutschen Gesellschaft für Anästhesiologie und Intensivmedizin e.V.

Ziel des Projektes ist die Veröffentlichung von Handlungsempfehlungen zur anästhesiologischen Betreuung von Patientinnen und Patienten mit seltenen Erkrankungen. Damit will OrphanAnesthesia einen wichtigen Beitrag zur Erhöhung der Patientensicherheit leisten.

Patientinnen und Patienten mit seltenen Erkrankungen benötigen für verschiedene diagnostische oder therapeutische Prozeduren eine anästhesiologische Betreuung, die mit einem erhöhten Risiko für anästhesieassoziierte Komplikationen einhergehen. Weil diese Erkrankungen selten auftreten, können Anästhesistinnen und Anästhesisten damit keine Erfahrungen gesammelt haben, sodass für die Planung der Narkose die Einholung weiterer Information unerlässlich ist. Durch vorhandene spezifische Informationen kann die Inzidenz von mit der Narkose assoziierten Komplikationen gesenkt werden. Zur Verfügung stehendes Wissen schafft Sicherheit im Prozess der Patientenversorgung.

Die Handlungsempfehlungen von OrphanAnesthesia sind standardisiert und durchlaufen nach ihrer Erstellung einen Peer-Review-Prozess, an dem eine Anästhesistin bzw. ein Anästhesist sowie eine weitere Krankheitsexpertin bzw. ein weiterer Krankheitsexperte (z. B. Pädiaterin bzw. Pädiater oder Neurologin bzw. Neurologe) beteiligt sind. Das Projekt ist international ausgerichtet, sodass die Handlungsempfehlungen grundsätzlich in englischer Sprache veröffentlicht werden.

Ab Heft 5/2014 werden im monatlichen Rhythmus je zwei Handlungsempfehlungen als Supplement der A&I unter www.ai-online.info veröffentlicht. Als Bestandteil der A&I sind die Handlungsempfehlungen damit auch zitierfähig. Sonderdrucke können gegen Entgelt bestellt werden.

Bisher in A&I publizierte Handlungsempfehlungen finden Sie unter:

www.ai-online.info/Orphsuppl
www.orphananesthesia.eu

OrphanAnesthesia –
a project of the Scientific Working Group of Paediatric Anaesthesia of the German Society of Anaesthesiology and Intensive Care Medicine

The target of OrphanAnesthesia is the publication of anaesthesia recommendations for patients suffering from rare diseases in order to improve patients' safety. When it comes to the management of patients with rare diseases, there are only sparse evidence-based facts and even far less knowledge in the anaesthetic outcome. OrphanAnesthesia would like to merge this knowledge based on scientific publications and proven experience of specialists making it available for physicians worldwide free of charge.

All OrphanAnesthesia recommendations are standardized and need to pass a peer review process. They are being reviewed by at least one anaesthesiologist and another disease expert (e.g. paediatrician or neurologist) involved in the treatment of this group of patients.

The project OrphanAnesthesia is internationally oriented. Thus all recommendations will be published in English.

Starting with issue 5/2014, we'll publish the OrphanAnesthesia recommenations as a monthly supplement of A&I (Anästhesiologie & Intensivmedizin). Thus they can be accessed and downloaded via www.ai-online.info. As being part of the journal, the recommendations will be quotable. Reprints can be ordered for payment.

Find a survey of the recommendations published until now on:

www.ai-online.info/Orphsuppl
www.orphananesthesia.eu

Projektleitung
Prof. Dr. Tino Münster, MHBA
Chefarzt
Klinik für Anästhesie und operative Intensivmedizin
Krankenhaus Barmherzige Brüder Regensburg
Prüfeninger Straße 86
93049 Regensburg,
Deutschland
Tel.: 0941 369-2350
E-Mail: Tino.Muenster@barmherzige-regensburg.de

DGAI
Deutsche Gesellschaft für Anästhesiologie & Intensivmedizin
www.dgai.de

A&I
ANÄSTHESIOLOGIE & INTENSIVMEDIZIN
www.ai-online.info

www.orphananesthesia.eu

orphananesthesia
a project of the German Society of Anaesthesiology and Intensive Care Medicine

orphananesthesia

Anaesthesia recommendations for

Von Hippel-Lindau disease

Disease name: Von Hippel-Lindau disease

ICD 10: Q85.8

Synonyms: Morbus Hippel-Lindau, Familial cerebelloretinal angiomatosis, Lindau disease, Von Hippel-Lindau syndrome, VHL, VHLD

Disease summary: Von Hippel-Lindau (VHL) disease is a rare autosomal dominant genetic disorder with incomplete penetrance and variable expression, which is associated with the lifelong risk of development of malignant and benign tumours in the central nervous system (CNS) and viscera [1,6]. This syndrome belongs to the phakomatoses and is caused by highly penetrant mutations in the VHL tumour suppressor gene on the short arm of chromosome 3p25-26 [6,15,30]. Beside 20% de novo mutations, most cases are diagnosed by a germline mutation [6]. The protein encoded by this gene is involved in the ubiquitination and degradation of a hypoxia-inducible factor (HIF). Its dysregulation can lead to increased expression of tumour promoter proteins such as the vascular endothelial growth factor, e.g., which in turn leads to tumour development [1].

Depending on the type of mutation as well as an association with pheochromocytoma, two types of the familial disease are distinct. Type 1 VHL disease may present with retinal angioma, CNS haemangioblastoma, renal cell carcinoma (RCC), pancreatic cysts and neuroendocrine tumours, but carries a low risk of pheochromocytoma. Type 2 VHL disease is characterised by a high risk of pheochromocytoma. The latter one is furthermore classified in Type 2A (haemangioblastoma and pheochromocytoma with low risk of RCC), Type 2B (haemangioblastoma, pheochromocytoma and RCC) and Type 2C (pheochromocytoma as only manifestation).

Data of the disease's prevalence vary depending on particular regions between 1:35,000 – 91,000 [6,7,8,20,25,29]. The incidence is reported to range between 1:35,000 – 65,000 live births, whereby the incidence between the sexes appears to be similar [1,5,10,15,20,29]. Contrary to the overall population, the life expectancy is higher in men (59 years) than in women (48 years) [7]. There are no reports in the literature of demonstrable VHL features in foetal or neonatal life [1,9,26]. Clinical symptoms develop on average in the third to fourth decade of life [1,6,10]. Symptoms of VHL vary among patients, depending on size and location of the tumours and their clinical presentation. Especially in the CNS, the tumour reflects its mass effect [20,25]. Headaches, seizures, ataxia, gait imbalance, limb weakness, paraplegia, spasticity, numbness, dizziness, behavioural abnormalities, an altered mental status, progressive neurological impairment, visual impairment up to blindness, hearing loss, tinnitus, vertigo, palpitation, polycythaemia (due to erythropoietin production by cerebellar haemangioblastomas), fever, drenching sweats, vomiting, severe hypertension and acute abdomen arising from pancreatic cystadenoma have been reported [1,2,6,8,9,13,14,15,25,26,29]. Patients frequently have asymptomatic spinal cord and intracranial pathology as well as abdominal tumours, but nevertheless VHL disease may even lead to death [18,28]. The most common causes of death are complications associated

▶ **Citation:** Gaik C, Wiesmann T: Von Hippel-Lindau disease. Anästh Intensivmed 2023;64:S319–S331
DOI: 10.19224/ai2023.S319

with RCC and CNS haemangioblastomas [1]. Patients are also prone to the risk of unnecessary and extensive surgery with serious consequences in the long run, i.e. nephrectomy up to haemodialysis [29]. Generally, this complex multisystem disease requires input from multiple specialists to avoid preventable morbidity and mortality [1].

The mainly associated tumour entity in the CNS is the haemangioblastoma, which is a benign vascular tumour. It is commonly located in the cerebellum, brainstem, spinal cord, retina and nerve roots [1]. Its location in the supratentorial region or the endolymphatic sac of the middle ear is rare [1,29]. Visceral features of the disorder include renal cysts and renal cell carcinoma, pheochromocytomas, pancreatic cysts and neuroendocrine tumours, liver tumours as well as epididymal and broad ligament cystadenomas [1,6,15].

Definitive diagnosis is done by imaging in addition to genetic panel and testing of the VHL gene [1,6]. Computerised axial tomography scanning (CT), magnetic resonance imaging (MRI) and angiography are the imaging techniques of choice [8,28]. Ultrasonography of abdomen, ophthalmologic fundus examination, laboratory examination (i.e., raised vanillylmandelic acid or metanephrine in urine or plasma) as well as family history for cerebellar or retinal haemangioblastoma are of significant value, too [5,18,25].

VHL patients are recommended to undergo surveillance with the aim of early detection of asymptomatic manifestations. This strategy is considered essential to plan the most optimal treatment strategy to best prevent severe sequelae such as blindness, neurological damage and early death. There is no systemic treatment for VHL [19]. Therapeutic options include surgical resection of accessible lesions and focused high-dose radiation [25]. Tumours are often not removed before they become symptomatic [19]. Nevertheless, there is a recurrent risk after an apparently complete excision of a haemangioblastoma [9]. In case of pheochromocytoma, α-blockade with prazosin and a β-blocker is useful in the management of blood pressure control [6,12,25].

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

© Anästh Intensivmed 2023;64:S319–S331 Aktiv Druck & Verlag GmbH

Emergency information

	AIRWAY / ANAESTHETIC TECHNIQUE	Avoid sympathoadrenergic response during laryngoscopy (rupture of typical haemangioblastomas) – GA may be advantageous for controlled hyperventilation if ICP is raised – perform imaging before neuraxial / peripheral RA (CT / MRT / ultrasound → haemangio-blastoma?) – risk for PDA theoretical lower than in SPA (both techniques are basically feasible, consider neurosurgical advice) – tumour next to puncture side = absolute contraindication for PDA / SPA / CSE!
B	**BLOOD PRODUCTS (COAGULATION)**	No specific recommendations
C	**CIRCULATION**	Be aware of life-threatening haemodynamic crisis in type 2a-c due to typical pheochromocytoma – consider IBP before anaesthesia induction – check: any α- / β-adrenergic blocker therapy occurred pre-operatively?
D	**DRUGS**	No risk for MH – avoid drugs, which tend to raise ICP / CBF – consider drug dose adaptation in case of renal impairment
E	**EQUIPMENT**	Perioperative availability of dialysis may be necessary – 30-degree head-up position in case of (imminent) rise in ICP

Typical surgery

Stereotactic surgery and radiotherapy of the cerebral haemangioblastoma and resection of different, accessible tumours are related to neurosurgery, urology, surgical oncology, endocrine surgery, visceral surgery, endocrinology, radiology and ophthalmology [6,7,28]. Emergency interventions include neurosurgical decompression in case of imminent herniation or tumour embolisation via digital subtraction angiography (DSA) [14,15,27].

Type of anaesthesia

The anaesthetic management of VHL patients depends on location, peculiarity and severity of the lesions, clinical symptoms and planned procedure [15]. A general recommendation regarding an ideal anaesthetic approach cannot be given, as both general and regional anaesthesia techniques might present potential problems in VHL patients. Beside the patient's preference, the optimal mode of anaesthesia should be determined based on

patient-specific risk factors, results of imaging techniques, additional examination and an interdisciplinary approach with team members involved [6].

Techniques of regional anaesthesia may avoid the need for general anaesthesia and the pressor effects of laryngoscopy [8]. However, performance of spinal or epidural anaesthesia requires caution in patients with spinal haemangioblastomas as it might result in acute catastrophic events if needle puncture occurs [6]. If neuraxial anaesthesia is to be considered, CT or MRI imaging of the spinal column should be performed before neuraxial blockades as asymptomatic haemangiomas may be present [15].

Spinal cord involvement is estimated to occur in 28–100% of VHLD patients and lesions can be found at any level of the cord, but most commonly in the cervicothoracic or thoracolumbar regions [15,18]. They are usually intramedullary in the posterior columns close to the pia mater, but may also occur in the cauda equina, nerve roots or vertebrae [9,22]. It is often supposed that spinal anaesthesia has a greater potential of producing a spinal cord lesion because the needle is directed intrathecally, as compared to a needle or catheter intended for the epidural space [31]. However, this is a theoretical approach not supported by clinical data.

Space-occupying lesions with evidence of eliciting a significant mass effect or the existence of vascular lesions close to needle puncture sites are an absolute contraindication to neuraxial procedures. Although the risk of causing bleeding from distant lesions is low, neurosurgical advice should be sought before continuing [6,15]. Thereby, a neuraxial blockade could cause haemangioblastoma rupture or cerebellar herniation in patients with raised ICP. Either with a deliberate or inadvertent dural puncture, the pressure shifts caused by the leakage of cerebrospinal fluid (CSF) following dural puncture may be lethal [6,15,28]. Nevertheless, epidural anaesthesia has been successfully performed for labour and Caesarean delivery in VHL patients.

There are no case reports for peripheral regional anaesthesia in VHL patients, except one bilateral ultrasound-guided transversus abdominis blocks with bupivacaine [15]. As in neuraxial procedures, imaging techniques may help to rule out haemangioblastoma next to the puncture site. Thus, an ultrasound examination by the anaesthesist is the optimal approach for ruling out the existence of a local tumour in the prospected needle track.

In contrast, general anaesthesia allows hyperventilation, which can acutely decrease ICP and allows the possibility of combining surgeries to remove different VHL tumours [6]. In case of obstetrical or abdominal surgery, it also allows and facilitates emergency craniotomy or burr hole creation if required [15]. But when general anaesthesia is performed, the sympathetic response to laryngoscopy (gagging, adrenergic effects) must be avoided. All this could increase the risk of bleeding from vascular malformations of the cerebrum and retina [8,28].

Finally, the type of anaesthesia needs consideration of the nature of the surgical procedure, the circumstances associated with surgery and the patient's preferences [31].

Necessary additional preoperative testing (in addition to standard care)

These patients need comprehensive assessment before administration of anaesthesia [5].

Even if not associated with specific cardiac or respiratory pathologies, a thorough evaluation of the patient's history should focus on the cardiac and respiratory status.

© Anästh Intensivmed 2023;64:S319–S331 Aktiv Druck & Verlag GmbH

Specific laboratory results are usually not helpful in preoperative evaluation if no specific questions arise from anamnesis or clinical examination (e.g., potential bleeding disorder in the anamnesis unrelated to VHL).

If neuraxial anaesthesia is planned, an MRI to evaluate the presence, persistence or worsening of cerebellar and spinal tumours will be recommended [1,15]. Evidence of a tumour blocking the flow of CSF as well as any swelling or compression of vital structures due to tumour growth is of great importance [8].

Anamnestic symptoms or clinical examination results typical for the presence of a pheochromocytoma may be another indication for an imaging procedure. Perioperative mortality can be 25–50 % if pheochromocytomas remain undiscovered until the time of surgery [31]. The definitive diagnosis of an adrenal tumour may trigger a corresponding therapy, which allows the patient a better preparation for scheduled surgery and may help to avoid haemodynamic crises while anaesthesia and surgery are in progress.

Particular preparation for airway management

VHL is not associated with facial deformities or special airway difficulties. Nevertheless, a standardised approach for airway examination and detection of airway challenges is recommended. A particular preparation for airway management should be based on the examination results. A slower induction and manual hyperventilation with bag and mask may be indicated, due to the fact that the risk of large blood pressure increases resulting from rapid sequence induction and intubation might outweigh the likelihood of aspiration [9]. Blood pressure crises increase the risk for haemorrhages of typically existing haemangioblastomas in VHL [16].

Particular preparation for transfusion or administration of blood products

No specific recommendations are given. No typical bleeding disorders were reported for VHL patients.

Particular preparation for anticoagulation

No specific recommendations are given.

Particular precautions for positioning, transportation and mobilisation

Patients with an imminent rise in intracranial pressure (ICP) can be placed in a 30-degree head-up position and in case of pregnancy with a left lateral pelvic tilt [15]. As usual, it is recommended to avoid any position-related injuries and undue pressures on eye, neck, thorax and especially abdomen which could affect the ICP intraoperatively [25].

Interactions of chronic disease and anaesthesia medications

Not reported.

© Anästh Intensivmed 2023;64:S319–S331 Aktiv Druck & Verlag GmbH

Anaesthetic procedure

Preoperative evaluation: see details above.

Premedication and sedation might be performed by weighing the benefits and risks in individual patients. The use of diazepam and midazolam in VHL patients is reported [8,25].

Monitoring should include pulse oximetry, noninvasive blood pressure measurement and a four to five lead electrocardiogram [5]. Preinduction insertion of an arterial line might be helpful to get real-time information about the blood pressure response during induction, and thus might help to avoid excessive adrenergic responses [6,15].

IV line: Peripheral placement preinduction is recommended to ensure early intervention in case of haemodynamic instability. The placement of a central venous catheter depends on the individual patient's risk and scheduled surgery.

Anaesthesia: The induction of anaesthesia should be performed under consideration of patient-specific risk factors unrelated to VHL as well as lesions and pathologies due to VHL. The induction of anaesthesia requires careful planning to avoid haemodynamic changes and ICP increases. No specific anaesthetic agents are contraindicated in VHL, unless individual allergies exist [8]. There is no specific risk for malignant hyperthermia.

Few anaesthetic agents for intravenous induction were reported as uneventful in VHL patients, including fentanyl, alfentanil, remifentanil, pethidine, lidocaine, thiopental, propofol, midazolam, rocuronium, vecuronium [5,6,15,24,25,28]. Some case reports also include the use of succinylcholine [28]. Preferably, this relaxant should not be used to avoid additional ICP increase [6,15]. The latter may be blunted by pretreatment with small doses of a nondepolarising muscle relaxant [9]. It is recommended to ensure adequate amounts of anaesthetic agents to blunt the response to laryngoscopy in particular. Despite nephron-sparing approaches, progressive renal function loss may occur over time requiring dosage adjustment [29].

For the maintenance of anaesthesia, sevoflurane, isoflurane, halothane, nitrous oxygen, propofol, midazolam, sufentanil, remifentanil and morphine have been reported to be uneventful in VHL patients [5,6,14,18]. Intravenous anaesthesia for maintenance may be preferable instead of volatile agents because of the theoretical advantageous effects on cerebral circulation and ICP [6,15,25]. Halothane is known to sensitise the heart to catecholamines. It is advisable to avoid halothane if a pheochromocytoma is suspected, although there have been reports of uneventful anaesthesia despite its use in this condition [14].

Sugammadex, neostigmine and glycopyrrolate were reported to antagonise the effects of neuromuscular blocking agents in VHL patients [5,6,25].

For neuraxial anaesthesia: Bupivacaine has been used with diamorphine or fentanyl for spinal anaesthesia, and lidocaine, bupivacaine (in some cases with adrenaline) for an epidural anaesthesia of VHL patients [8,14,22,23,24]. There should be no special indication or contraindication for a specific local anaesthetic agent.

To prevent postoperative nausea and vomiting (PONV), the use of ondansetron has been reported to be uneventful [25,28].

© Anästh Intensivmed 2023;64:S319–S331 Aktiv Druck & Verlag GmbH

Dexamethasone may be considered to hinder and control cerebellar tumour or oedema swelling and as steroid replacement therapy in case of adrenal insufficiency [9,15,31]. Besides, in case of chronic corticoid therapy, hydrocortisone may be given preoperatively to prevent the inadequate adrenal gland from responding to stress [31].

Mannitol and furosemide were used as additional agents to control ICP [9].

In case of haemodynamic lability, phentolamine, labetalol, nicardipine, phenylephrine, prazosin and phenoxybenzamine, noradrenaline was used in VHL patients [5,6,9,14,18,25]. Vasodilators such as nitroglycerin and sodium nitroprusside may potentially increase cerebral blood flow and ICP in patients with intracranial hypertension. Therefore, metoprolol, esmolol, propranolol and propofol may be preferred until dura mater opening [12].

Especially in case of a preexisting pheochromocytoma, an adequate preparation with α- and β-blockers will be essential for maintaining haemodynamic stability [12]. Moreover, metoclopramide, droperidol and pentazocine should be avoided in these cases as they are supposed to induce an increased catecholamine release and inhibit the re-uptake of catecholamines into nerve terminals. This also applies to morphine and atracurium as well as other drugs known to be histamine releasers, which can provoke hypertensive crisis as a consequence of an elevation of circulating catecholamines [14].

Ventilation should be performed carefully with adequate low tidal volumes and properly adjusted ventilator settings to reduce baro- / volutrauma as usual. In case of an increased ICP a lower goal end-tidal carbon dioxide may be sought [6].

Particular or additional monitoring

Haemodynamic fluctuations should be anticipated especially during intubation and extubation. Therefore, invasive arterial blood pressure monitoring may be useful during the intraoperative and postoperative period, especially in patients with intracranial or spinal cord haemangiomas as well as pheochromocytoma and existing preoperative therapy with adrenergic blockers [9,12,18].

A perioperative close-meshed control of blood sugar is recommended, as this parameter may be unstable due to steroid therapy [15].

Measurement of ICP may be reasonable in particular cases as well as an interdisciplinary exchange with neurosurgeons [15].

Possible complications

Patients may be drowsy due to increasing ICP [6].

Pheochromocytomas can lead to catecholamine-induced, potentially life-threatening complications, including hypertensive crises, cardiac arrhythmias, pulmonary oedema and myocardial ischaemia. Therefore, elective surgery in VHL patients with pheochromocytoma may need a preoperative non-competitive α-adrenergic blockade with phenoxybenzamine or a selective blockade with prazosin, doxazosin or urapidil for 10–14 days. Calcium-channel blockers can also be applied. In case of additional tachyarrhythmias, a β-blocker may be

© Anästh Intensivmed 2023;64:S319–S331 Aktiv Druck & Verlag GmbH

added after a few days of α-blockade. β-blockers should never be used as monotherapy, because they can cause a sudden increase in blood pressure. Noradrenaline secreted by the tumour stimulates α1-receptors, causing severe vasoconstriction, while vasodilating β-receptors would be blocked [2,7].

Postoperative care

Postoperative care should be based upon the patient's preexisting conditions as well as the surgical or interventional procedure. Most case reports refer to a postoperative stay in PACU, IMC or ICU before transfer to the normal ward or discharge at home is acceptable [6,25]. Especially patients with adrenergic blockade due to a pheochromocytoma should be monitored postoperatively regarding haemodynamics, neurology, and blood sugar [7].

Postoperative analgesia can be performed by epidural anaesthesia, if possible and reasonable. As systemic analgesics paracetamol, diclofenac and morphine were reported as uneventful in VHL [12,15,28]. In patients with an increased ICP, they should be titrated carefully to avoid hypoventilation, hypercarbia and cerebral vasodilation [9].

Disease-related acute problems and effect on anaesthesia and recovery

Emergency-like situations: cerebral haemorrhage and / or herniation, spinal haemorrhage up to paraplegia, haemodynamic instability due to adrenergic crisis.

Differential diagnosis: (pre)eclampsia in pregnant women, cardiac / vascular impairment in haemodynamic instability, cerebral / spinal pathology due to other cause.

Ambulatory anaesthesia

Specific recommendations for or against ambulatory anaesthesia cannot be given as no published literature exists regarding this topic.

Obstetrical anaesthesia

The VHL disease has no negative impact on fertility besides the indirect consequences brought on by complications, i.e. multiple abdominal surgeries [9]. Clinical manifestation of the disease goes along with childbearing ages [1].

Overall, VHL-associated pregnancies have favourable outcomes with a 96.4% foetal survival rate and a 5.4% maternal morbidity rate [6,13].

Evidence regarding whether or not VHL-related tumours have new or accelerated growth during pregnancy is controversial [1,4,6,11,15,32]. It is under discussion whether progesterone may be responsible for any new occurrence or worsening of clinical features pertaining to this disease in pregnancy [1].

The hormonal and haemodynamic changes in pregnancy can accelerate the growth of haemangioblastomas, leading to increased symptoms [17]. For example, the significant

© Anästh Intensivmed 2023;64:S319–S331 Aktiv Druck & Verlag GmbH

increase in blood volume and cardiac output in pregnancy leads to an increased venous pressure within the haemangioma. The valveless veins that drain the spinal cord become engorged secondary to the gravid uterus' pressure on the inferior vena cava [9,17]. In addition, plasma osmolality and albumin concentration may predispose to the formation of cerebral oedema and amplify neurological symptoms in pregnancy [9].

The mode of anaesthesia and delivery should be determined based on an individual risk-to-benefit ratio, on a case-by-case basis with the presence or absence of CNS tumours (with or without ICP symptoms and signs) and pheochromocytoma taken into consideration [1]. In addition, one must also consider the potential for and adverse effects on placental perfusion and the effects on the foetus for each mode [9]. Recommendations for the management of pregnant patients with VHL as well as the timing of surgical intervention, anaesthesia and delivery of the foetus vary and are limited and inconsistent [28,32]. Moreover, VHL patients should undergo delivery at centres with the necessary expertise and availability of these various specialties [6]. Careful preoperative assessment and multidisciplinary planning are required to ensure maternal safety [15].

A successful vaginal mode of delivery has been reported, but its value compared to operative delivery is unclear [1,3,15,23]. It may cause cardiovascular stress and blood pressure fluctuations with the potential risk of rupturing a CNS haemangioblastoma [5,28]. In case of a vacuum-assisted vaginal delivery, the risk may even be higher [15,17].

Most reported cases of childbirth in mothers with VHL concerning the CNS involve Caesarean section [15]. Nevertheless, Caesarean delivery also includes a significant increased risk of cerebrovascular disease in VHL patients [30].

Anaesthetic management is challenging in pregnant VHL patients and general recommendations are not available. It depends on the location and severity of lesions, clinical symptoms, and the planned procedure [15].

Routine antacid prophylaxis should be performed, i.e., with ranitidine, metoclopramide and sodium citrate [5,6,15,28].

The cerebrospinal fluid pressure increases in normal labour and also increases with uterine contraction with or without Valsalva maneuver. This has been attributed to skeletal muscle contraction in response to pain and is prevented by regional analgesia [1,21].

Epidural techniques have been used in VHL patients to provide anaesthesia for Caesarean section, analgesia during labour and vaginal delivery [15,22,26]. In VHL, haemangioblastomas are usually not present in the epidural space. Most are located within the posterior medullary cord. Therefore, it has been proposed that epidural anaesthesia is preferable to spinal anaesthesia as the dura is not intentionally punctured, resulting in less chance of haemangioblastoma penetration [23].

Nevertheless, spinal anaesthesia has been successfully performed during an emergency Caesarean section even in patients having known stable vascular lesions affecting their thoracic spinal cords [23]. Because most haemangioblastomas are located in the cervical and thoracic region, the possibility of disrupting a tumour at the level of the lumbar region – the usual region of neuraxial anaesthesia placement – is minimal [1].

If there is a significant mass effect with an impending increase of the ICP, both neuraxial anaesthesia and vaginal delivery may worsen pressure ratio and patient's neurology. A Caesarean delivery with general anaesthesia may be reasonable in some cases [6]. Ultimately, if neuraxial anaesthesia is planned, an imaging study of spine (and brain) should be performed in advance. In the absence of contraindications, elective Caesarean section

under epidural anaesthesia appears to be a sensible choice for childbirth management in VHL patients [22]. An elective MRI before the scheduled delivery date might help in optimising the best approach for a neuraxial procedure.

In certain situations, general anaesthesia may be the only safe option, especially when emergent delivery in combination with lifesaving neurosurgical interventions is indicated [1,6]. However, the management in general anaesthesia may be aggravated due to hypertensive crises and the risk of cerebral haemorrhage [6,23]. The usual rapid sequence induction for general anaesthesia in pregnant patient may not be tolerated in patients with raised ICP [5]. The haemodynamic goals during induction should be based on an attempt to maintain the placental blood flow without risking severe hypo- or hypertension in a patient with the possibility of an intracranial mass [18].

In women with pheochromocytoma, surgical treatment is recommended before any pregnancy attempts. If the tumour is not resected before delivery, an α-blockade is recommended to reduce maternal and foetal mortality. There are also reports of a successful combined Caesarean delivery and resection of pheochromocytoma or craniotomy [5,6,17,18]. Besides, pheochromocytoma may mimic (pre)eclampsia with possible serious maternal and foetal consequences especially if undiagnosed [1]. Therefore, a magnesium should be continuously infused throughout the entire procedure. Unknown changes in placental perfusion which are secondary to chronically elevated catecholamine levels and the requirement of intravenous vasodilators with possible adverse foetal effects should also be taken into consideration [6,18].

Postpartum cerebellar haemorrhage or cerebellar tonsil herniation have been reported due to undiagnosed VHL. Haemangioblastoma is the most frequently described feature of the VHL disease complicating pregnancy in the literature [1,9,15,16,17]. Therefore, during pregnancy, repeated MRI should be performed to detect possible tumour recurrence or growth, i.e., the brain and spine of at-risk adolescents should be examined every 12–36 months [16,20]. It may show a dispersion of tumour mass in the brain and spine, especially the presence of space-occupying lesions with a significant mass effect. Besides, regular retinal checks and screening for plasma or urinary metanephrines each trimester may help to watch the disease's progress [6].

Finally, the maternal and foetal outcome mainly depends on the coordination of a skilled multidisciplinary team that may include obstetricians, anaesthesiologists, critical care physicians, radiologists, neurosurgeons, visceral surgeons, endocrinologists, neonatologists, a maternal-foetal medicine team and others [1,6]. The obstetric and anaesthetic management of women with VHL throughout their pregnancy and delivery involves vigilance for any change in neurological symptoms and signs or features of raised ICP [28].

© Anästh Intensivmed 2023;64:S319–S331 Aktiv Druck & Verlag GmbH

References

1. Adekola H, Soto E, Lam J, Bronshtein E, Chaiworapongsa T, Sorokin Y. Von Hippel-Lindau Disease and Pregnancy: What an Obstetrician Should Know. Obstetr Gynecol Survey 2013;68:655–662
2. Ben-Skowronek I, Kozaczuk S. Von Hippel-Lindau Syndrome. Horm Res Paediatr 2015;84:145–152
3. Berl M, Dubois L, Belkacem H, Dailland P, Carli P. Von Hippel-Lindau disease and obstetric anaesthesia. Ann Fr Anesth Reanim 2003;22:359–362
4. Binderup ML, Budtz-Jørgensen E, Bisgaard ML. New von Hippel-Lindau manifestations develop at the same or decreased rates in pregnancy. Neurology 2015;85:1500–1503
5. Boker A, Ong BY. Anesthesia for Cesarean section and posterior fossa craniotomy in a patient with von Hippel-Lindau disease. Can J Anaesth 2001;48:387–390
6. Burnette MS, Mann TS, Berman DJ, Nguyen TAT. Brain Tumor, Pheochromocytoma, and Pregnancy: A Case Report of a Cesarean Delivery in a Patient With Von Hippel-Lindau Disease. Anesth Analg 2019;13:289–291
7. Chittiboina P, Lonser RR. Von Hippel-Lindau disease. Handbook for Clinical Neurology 2015; 132:139–156
8. Demiraran Y, Özgon M, Utku T, Bozkurt P. Epidural anaesthesia for Caesarean section in a patient with von Hippel-Lindau disease. Eur J Anaesth 2001;18,330–332
9. Deslile MF, Valimohamed F, Money D, Douglas MJ. Central Nervous System Complications of von Hippel-Lindau Disease and Pregnancy; Perinatal Considerations: Case Report and Literature Review. J Matern-Fetal Med 2000;9:242–247
10. Feletti A, Anglani M, Scarpa B, Schiavi F, Boaretto F, Zovato S, et al. Von Hippel-Lindau disease: an evaluation of natural history and functional disability. Neuro-Oncol 2016;18:1011–1020
11. Frantzen C, Kruizinga RC, van Asselt SJ, et al. Pregnancy-related hemangioblastoma progression and complications in von Hippel-Lindau disease. Neurology 2012;79:793–796
12. Goel S, Johar N, Abraham M. Anesthesia for Emergency Craniotomy in a Patient with Von Hippel Lindau Disease With Pheochromocytoma. J Neurosurg Anesthesiol 2005;17:173–174
13. Grimbert P, Chauveau D, Remy SR, Grunfeld JP. Pregnancy in von Hippel-Lindau disease. Am J Obstetr Gynecol 1999;180:110–111
14. Gurunathan U, Korula G. Unsuspected Pheochromocytoma: Von Hippel-Lindau Disease. J Neurosurg Anesthesiol 2004;16:26–28
15. Hallsworth D, Thompson J, Wilkinson D, Kerr RSC, Russell R. Intracranial pressure monitoring and caesarean section in a patient with von Hippel-Lindau disease and symptomatic cerebellar haemangioblastomas. Int J Obstetr Anesth 2015;24:73–77
16. Hayashi S, Takeda N, Komura E. Symptomatic Cerebellar Hemorrhage From Recurrent Hemangioblastoma During Delivery. Neurol Med-Chir (Tokyo) 2010;50,1105–1107
17. Hayden MG, Gephart R, Kalanithi P, Chou D. Von Hippel-Lindau disease in pregnancy: a brief review. J Clin Neurosci 2009;16:611–613
18. Joffe D, Robbins R, Benjamin A. Caesarean section and phaeochromocytoma resection in a patient with Von Hippel Lindau disease. Can J Anesth 1993;40:870–874
19. Launbjerg K, Bache I, Galanakis M, Bisgaard ML, Binderup MLM. Von Hippel-Lindau development in children and adolescents. Am J Med Gen 2017;173: 2381–2394
20. Maher ER, Neumann HPH, Richard S. von-Hippel-Lindau disease: A clinical and scientific review. Eur J Hum Gen 201119:617–623
21. Marx GF, Zemaitis MT, Orkin LR. Cerebrospinal fluid pressures during labor and obstetrical anesthesia. Anesthesiology 1961;22:348–354
22. Matthews AJ, Halshaw J. Epidural anesthesia in von Hippel-Lindau disease. Management of childbirth and anesthesia for caesarean section. Anaesth Analg 1986;41:853–855
23. McCarthy T, Leighton R, Mushambi M. Spinal anaesthesia for caesarean section for a woman with von Hippel Lindau disease. Int J Obestetr Anesth 2010;19:461–462
24. Mugawar M, Rajender Y, Rurohit AK, Sastry RA, Sundaram C, Rammurti S. Anesthetic Management of von Hippel-Lindau Syndrome for Excision of Cerebellar Hemangioblastoma and Pheochromocytoma Surgery. Anesth Analg 1998;86:673–674
25. Murthy TVSP, Pratyush G, Prabhakar BT, Singh P, Mohan C. Anaesthetic Implication of Von Hippel Lindau Disease. Med J Armed Forces India 2006;62:181–183

© Anästh Intensivmed 2023;64:S319–S331 Aktiv Druck & Verlag GmbH

26. Ogasawara KK, Ogasawara EM, Hirata G. Pregnancy complicated by von Hippel-Lindau disease. Obstetr Gynecol 1995;85:829–831
27. Othmane IS, Shields C, Singh A, Shields J, Goldmann W. Postpartum Cerebellar Herniation in von Hippel-Lindau Syndrome. Am J Ophthalmol 1999;128:387–389
28. Razvi SAH, Stefak Y, Bird J. Caesarean section for a woman with Von Hippel-Lindau disease. Int J Obstetr Anesth 2009;18:294–295
29. Schmid S, Gillessen S, Binet I, Brändle M, Engeler D, Greiner J, et al. Management of Von Hippel-Lindau Disease: A Interdisciplinary Review. Onc Res Treat 2014;37:761–771
30. Terry AR, Merker VL, Barker FG, Leffert L, Souter I, Plotkin SR. Pregnancy complications in women with rare tumor suppressor syndromes affecting central and peripheral nervous system. Am J Obestr Gynecol 2015;213:108–109
31. Wang A, Sinatra RS. Epidural Anesthesia for Caesarean Section in a Patient with von Hippel-Lindau Disease and Multiple Sclerosis. Anesth Analg 1999;88:1083–1084
32. Ye DY, Bakhtian KD, Asthagiri AR, Lonser RR. Effect of pregnancy on hemangioblastoma development and progression in von Hippel-Lindau disease. J Neurosurg 2012;117:818–824.

© Anästh Intensivmed 2023;64:S319–S331 Aktiv Druck & Verlag GmbH

Date last modified: **February 2022**

This recommendation was prepared by:

Authors

Christine Gaik, Anaesthesiologist, University Clinic Marburg, Germany
gaikc@med.uni-marburg.de

Thomas Wiesmann, Anaesthesiologist, Diakonie-Clinic Schwaebisch Hall, Germany
thomas.wiesmann@diakoneo.de

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

This recommendation was reviewed by:

Reviewers

Markus Blankenburg, Paediatrist, Kinderschmerzzentrum Baden-Württemberg, Zentrum für Kinder-, Jugend- und Frauenmedizin, Klinikum Stuttgart, Olgahospital, Stuttgart, Germany
m.blankenburg@klinikum-stuttgart.de

Deniz Hos, Ophthalmologist, Zentrum für Augenheilkunde, University Clinic Köln, Germany
deniz.hos@uk-koeln.de

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

© Anästh Intensivmed 2023;64:S319–S331 Aktiv Druck & Verlag GmbH

Herausgeber

DGAI
Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin e. V.
Präsident: Prof. Dr. B. Pannen, Düsseldorf

BDA
Berufsverband Deutscher Anästhesistinnen und Anästhesisten e. V.
Präsidentin: Prof. Dr. G. Beck, Mannheim

Schriftleitung
Präsident/in der Herausgeberverbände

Gesamtschriftleiter/Editor-in-Chief:
Prof. Dr. Dr. Kai Zacharowski, ML FRCA FESAIC, Frankfurt

Stellvertretender Gesamtschriftleiter/Deputy Editor:
Prof. Dr. T. Volk, Homburg/Saar

CME-Schriftleiter/CME-Editor:
Prof. Dr. W. Zink, Ludwigshafen

Redaktion/Editorial Staff
Carolin Sofia Kopp B.A.
Korrespondenzadresse:
Neuwieder Straße 9 | 90411 Nürnberg | Deutschland | Tel.: 0911 9337812
E-Mail: anaesth.intensivmed@dgai-ev.de

Verlag & Druckerei

Aktiv Druck & Verlag GmbH
An der Lohwiese 36 |
97500 Ebelsbach | Deutschland
www.aktiv-druck.de

Geschäftsführung
Wolfgang Schröder | Jan Schröder | Nadja Schwarz
Tel.: 09522 943560 | Fax: 09522 943567
E-Mail: info@aktiv-druck.de

Anzeigen | Vertrieb
Pia Müller | Robert Kux
Tel.: 09522 943570 | Fax: 09522 943577
E-Mail: anzeigen@aktiv-druck.de

Verlagsrepräsentanz
Jürgen Distler
Neuwieder Straße 9 | 90411 Nürnberg
Tel.: 0171 9432534
E-Mail: jdistler@bda-ev.de

Herstellung | Gestaltung
Pia Müller | Robert Kux | Stefanie Triebert
Tel.: 09522 943570 | Fax: 09522 943577
E-Mail: ai@aktiv-druck.de

Titelbild
Dipl.-Designerin Monique Minde, Nürnberg

Erscheinungsweise 2023
Der 64. Jahrgang erscheint jeweils zum Monatsanfang, Heft 7/8 als Doppelausgabe.

Bezugspreise (inkl. Versandkosten):

- **Einzelhefte** 30,- €
- **Jahresabonnement:**
  Europa (ohne Schweiz) (inkl. 7 % MwSt.) 258,- €
  Schweiz 266,- €
  Rest der Welt 241,- €

Mitarbeiter aus Pflege, Labor, Studenten und Auszubildende (bei Vorlage eines entsprechenden Nachweises)
Europa (ohne Schweiz) (inkl. 7 % MwSt.) 94,- €
Schweiz 90,- €
Rest der Welt 94,- €

Für Mitglieder der DGAI und/oder des BDA ist der Bezug der Zeitschrift im Mitgliedsbeitrag enthalten.

Allgemeine Geschäfts- und Lieferbedingungen
Die allgemeinen Geschäfts- und Lieferbedingungen entnehmen Sie bitte dem Impressum auf www.ai-online.info

Indexed in **CINAHL; Current Contents®/ Clinical Medicine, EBSCO; EMBASE/ Excerpta Medica; Medical Documentation Service; Research Alert; Sci Search; Scopus; SUBIS Current Awareness in Biomedicine; VINITI: Russian Academy of Science.**

Wichtiger Hinweis
Für Angaben über Dosierungsanweisungen und Applikationsformen kann vom Verlag und den Herausgebern keine Gewähr übernommen werden. Derartige Angaben müssen vom jeweiligen Anwender im Einzelfall anhand anderer Literaturstellen auf ihre Richtigkeit überprüft werden. Gleiches gilt für berufs- und verbandspolitische Stellungnahmen und Empfehlungen.

Allein aus Gründen der besseren Lesbarkeit wird auf die gleichzeitige Verwendung männlicher, weiblicher und weiterer Sprachformen verzichtet. Sämtliche Personenbezeichnungen gelten für alle Geschlechterformen. Dies impliziert keinesfalls eine Benachteiligung der jeweils anderen Geschlechter, sondern ist als geschlechtsneutral zu verstehen.

Die Beiträge aus der A&I finden Sie online unter:
www.ai-online.info

CONTACT US

Please do not hesitate to contact us. We will be glad to answer and provide further information to you at any time.

.....
Name

.....
First Name

.....
Department / Hospital

.....
Place

.....
Telephone

.....
E-Mail

.....
Date / Signature

Please contact me for further information ○

I would like to participate in the project ○

ADDRESS

German Society of Anaesthesiology and
Intensive Care Medicine
Neuwieder Straße 9 I 90411 Nuremberg I Germany
Tel.: +49-911-933780
Email: info@orphananesthesia.eu