orphanaesthesia

Anaesthesia recommendations for

Birt-Hogg-Dubé syndrome

Disease name: Birt-Hogg-Dubé syndrome (BHDS)

ICD 10: D23.9

Synonyms: Hornstein-Knickenberg syndrome

Disease summary: Birt-Hogg-Dubé syndrome (BHDS) is a rare autosomal dominant inherited disease characterised by skin lesions, renal tumours and pulmonary cysts with or without pneumothorax [13]. In 1975 a pedigree with cutaneous tumours ("perifollicular fibromas" on face, neck and trunk) in combination with adenomatous colon polyps (one being transformed into carcinoma) was primarily published by Otto P. Hornstein and Monika Knickenberg [5]. Finally, the syndrome was named after Arthur R. Birt, Georgina R. Hogg and W. James Dubé, who in 1977 described a family with similar skin tumours named "fibrofolliculomas" [2].

BHDS is caused by mutations in the gene that encodes folliculin (FLCN) on chromosome 17p11.2 [10]. Except some trends, no clear correlation between type of mutation or location within the FLCN gene and any of the phenotype manifestations has been identified [18]. However, two FLCN mutations were identified in a German cohort of 197 patients with increased risk for pneumothorax [15].

Folliculin is expressed in many organs and tissues (i.e., skin, distal nephron of the kidney, and the pneumocytes of the lung). In consequence, BHDS is clinically characterised by a typical triad of skin lesions (i.e., fibrofolliculomas, trichodiscomas and acrochordons) predominantly in the midface, renal tumours, and pulmonary cysts, with or without spontaneous pneumothorax [2,6,9]. Despite several theories, the development of each of these pathologies in BHDS like, i.e., lung cysts and the relationship between lung cysts and pneumothorax is not fully clarified [4,7]. Generally, clinical appearance of BHDS may vary and some patients do not show any skin lesions [6,12].

Skin: lesions in the field of nose, cheeks, neck and sometimes on upper trunk or ears. These benign hair follicle tumours are also called fibrofolliculomas. Furthermore, trichodiscomas, acrochordons or angiofibromas may appear. Mucosal lesions may occur as papules involving lips, buccal mucosa, and gingiva [9].

Lungs: more than 80 % of patients with BHDS show pulmonary cysts, (in contrast to other cystic lung diseases), mostly located in basal and paramediastinal regions [9,17]. However, lung function is usually not impaired due to these (often multiple) cysts [7,9,12]. Nevertheless, there is a highly increased risk of spontaneous, sometimes recurrent, pneumothorax in comparison to patients without BHDS [9,17].

Kidneys: patients with BHD are at risk for multiple renal tumours that are often malignant and may metastasise [14]. In up to 34 % of the patients, renal neoplasms (bilateral or multifocal) can appear and is usually the most threatening component of BHDS [17]. Most renal cell

tumours are oncocytomas or renal cell carcinoma (RCC) of chromophobe or hybrid chromophobe-oncocytoma histology [1,9,14].

Other clinical findings: there are a lot of benign as well as malignant tumours, that are associated with BHDS. However, a causal relationship between these tumours (i.e., colorectal carcinoma / adenoma, arteriovenous malformation) and BHDS has not been proven yet [8,9,16].

Skin lesions as well as renal and pulmonary affection usually appear after the age of 20 years in BHDS [4,9].

BHDS is found worldwide, but clinical appearance differs depending on the region. Skin lesions are very frequent in patients from the USA or Europe, but rare in Asian patients with BHDS. An equal distribution was found for renal impairment. There are only a few hundred affected families with BHDS described worldwide. However, the disease is probably underdiagnosed due to its clinically varying appearance [9,12].

Diagnosis is usually based on clinical presentation and, i.e., histological examination of skin lesions or genetic testing, primarily to confirm the diagnosis [9]. One should be aware of BHDS in case of bilateral or multifocal renal tumour in patients with accompanying (family) anamnesis of pneumothorax, lung cysts or skin lesions [8,9]. There is no clear indication for chest CT as a routine screening in these patients, but pulmonary cysts and pneumothorax are found in 90 % and 24 % of patients with BHDS [8]. In summary, there are diagnostic criteria proposed for BHDS – patients should fulfill one major or two minor criteria for diagnosis [9]:

Major criteria [9]:

– at least five fibrofolliculomas or trichodiscomas, at least one histologically confirmed, of adult onset,

– pathogenetic FLCN germline mutation.

Minor criteria [9]:

– multiple lung cysts: bilateral basally located lung cysts with no other apparent cause, with/without spontaneous primary pneumothorax,

– renal cancer: early onset (< 50 years) or multifocal/bilateral renal cancer, or renal cancer of mixed chromophobe and oncocytic histology,

– a first-degree relative with BHD.

To date there is no causative therapy for patients with BHDS. Generally, skin lesions are resected for cosmetic reasons only. Therapy of choice for renal tumours is usually surgical intervention. Whenever possible (after a period of active surveillance), growing kidney tumours (> 3 cm diameter) should be removed in a nephron-sparing way, but nevertheless hemodialysis may be necessary post-operative in some cases [18]. Moreover, renal transplantation is discussed for patients with BHDS and severe renal impairment [3,11]. Pneumothorax needs to be relieved if clinically apparent and in patients with recurrent pneumothorax, i.e., pleurodesis is recommended to reduce the risk of new episodes. Furthermore, affected patients should avoid activities with fluctuations in air pressure (i.e., diving).

Genetic testing in patients suspected of having BHDS may help to verify diagnosis as well as allow identification and counselling of family members at risk.

Although there is no generally recommended surveillance programme for patients with BHDS, surveillance and a personalised follow-up of these patients (as well as lifelong screening of relatives) is important, especially to monitor progress of renal cancer [8,9,18].

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

	AIRWAY / ANAESTHETIC TECHNIQUE	no special airway anomalies, but typically multiple pulmonary cysts (however, lung function is usually not impaired) – prefer peripheral / neuraxial RA to avoid mechanical / positive pressure ventilation whenever applicable (high risk for pneumothorax / cyst rupture!) – perform careful mask-ventilation – if GA (TIVA / balanced) is necessary, use lung-protective ventilation – be aware of sudden desaturation in case of (spontaneous / tension) pneumothorax
B	**BLOOD PRODUCTS (COAGULATION)**	no specific recommendations
C	**CIRCULATION**	be aware of haemodynamic crisis in case of tension pneumothorax
D	**DRUGS**	no risk for MH – consider drug dose adaption in case of renal impairment –adequate PONV prophylaxis recommended (pneumothorax due to vomiting)
E	**EQUIPMENT**	use neuromuscular monitoring and ultrasound for RA, vessel cannulation and catheter placement (to avoid pneumothorax) – perioperative availability of dialysis may be necessary

Typical surgery

Surgical excision or laser ablation of skin lesions.

Nephron-sparing surgery, open/laparoscopic nephrectomy (with or without the assistance of a surgical robot), cryo-/radiofrequency ablation as nephron-sparing techniques, percutaneous kidney biopsy [3,6,9,11,18].

Segmental lung resection, lobectomy, video-assisted thoracic surgery (VATS), bronchoscopies for routine surveillance or to receive transbronchial biopsies, any kind of lung biopsy, pleurectomy, chemical pleurodesis [3,6,7,11].

Type of anaesthesia

There is no definite recommendation for either general or regional anaesthesia. However, exposure to positive pressure ventilation could precipitate pneumothorax in patients with

BHDS [9]. Therefore, whenever possible general anaesthesia with necessity of mechanical ventilation should be avoided. Neuraxial/peripheral regional anaesthesia may be a suitable alternative in many cases. In either case, precautions should be taken for BHDS patients of being at high risk for pneumothorax when undergoing general anaesthesia, especially in presence of pulmonary cysts [18]. To avoid high pressure values and peaks, a thorough lung protective ventilation strategy should be followed when general anaesthesia is necessary.

General anaesthesia can be performed as balanced anaesthesia with volatile anaesthetics or as total intravenous anaesthesia (TIVA). Monitoring of neuromuscular blockade is advised before emergence of the anaesthesia, especially in cases of impaired renal function.

Using ultrasound visualisation of correct wire localisation within the blood vessel for placement of central venous line in V. jugularis interna/externa or V. subclavia is strictly recommended to avoid accidental pneumothorax or lung injury with respect to an already increased risk of pneumothorax.

Adequate prophylaxis of postoperative nausea and vomiting is recommended as well as in patients without BHDS. Vomiting causes high intracorporeal pressure variations with unknown effects on the pneumothorax risks.

Necessary additional pre-operative testing (beside standard care)

Blood testing: may show high level of waste products as well as elevated blood urea nitrogen (BUN) and serum creatinine levels (which may indicate kidney dysfunction) [3].

Pulmonary assessment: based on a detailed anamnesis, the pulmonary capacity should be investigated [18]. Eventually, a pulmonary function test might complete this assessment. CT may be useful when general anaesthesia is planned, especially to detect pulmonary cysts. Moreover, an examination via ultrasound may help to exclude a pneumothorax in symptomatic patients.

Particular preparation for airway management

As far as known there are no anatomic peculiarities due to BHDS itself. Nevertheless, a standardised approach for airway examination and detection of airway challenges is recommended. A thorough preparation for airway management should be based on the examination results.

However, mask ventilation should be performed carefully to avoid large ambient pressure differences as well as high pressure values and peaks. Due to a high risk of rupture of pulmonary cysts in patients with BHDS, one should be aware of sudden desaturation in case of pneumothorax in airway management.

Particular preparation for transfusion or administration of blood products

Not reported. No specific recommendations referring to BHDS.

Particular preparation for anticoagulation

Not reported. No specific recommendations referring to BHDS.

Particular precautions for positioning, transportation and mobilisation

Not reported. No specific recommendations referring to BHDS.

Interactions of chronic disease and anaesthesia medications

Not reported.

Anaesthetic procedure

Preoperative evaluation: see details above.

Premedication: might be performed weighing the benefits and risks in individual patients (especially alterations in drug metabolism in patients with moderate to severe kidney dysfunction).

Patient positioning: no specific recommendations.

IV line: no specific recommendations for peripheral IV line. Using ultrasound visualisation of correct wire localisation within the blood vessel for placement of central venous line in V. jugularis interna/externa (or V. subclavia) is strictly recommended to avoid accidental pneumothorax or lung injury with respect to high risk of frequently multiple lung cysts in these patients.

Invasive blood pressure measurement: facilitates frequent arterial blood gas analysis, especially in case of pulmonal impairment.

(Mechanical) ventilation: should strictly be performed lung-protective with adequate low tidal volumes to avoid baro-/volutrauma. Especially in presence of lung cysts, high pressure values and peaks should be avoided due to high risk of cyst rupture and (tension) pneumothorax [18].

Anaesthesia: total intravenous or balanced anaesthesia using volatile anaesthetics can be performed safely. There are no absolute or known relative contraindications for anaesthesia-related drugs just because of the disease BHDS. Depending on renal impairment in the individual patient, the choice of the particular anaesthetic substance and its dosage should be adapted to current blood values. There is no specific risk for malignant hyperthermia.

There are no reports about peripheral/regional/neuraxial anaesthesia in patients with BHDS. However, to our knowledge there are no contraindications for these anaesthetic procedures. They may rather be favoured to avoid general anaesthesia and mechanical ventilation whenever applicable.

Particular or additional monitoring

Extended heamodynamic monitoring may help to optimise intraoperative fluid management, because it can be detrimental in patients with severe renal or pulmonary dysfunction.

Possible complications

Severe respiratory failure/hypoxaemia, usually due to (tension) pneumothorax.

Postoperative necessity of haemodialysis due to renal dysfunction.

Post-operative care

Post-operative care should focus on respiratory and renal function in the individual patient. If necessity of haemodialysis is foreseeable, post-operative stay should be performed at an ICU. In patients with BHDS and no pulmonary/renal impairment depending on further complicative diseases, post-operative care may be done at PACU or IMC before transfer to the normal ward (or discharge at home) is acceptable.

Disease-related acute problems and effect on anaesthesia and recovery

Emergency-like situations: During pre-procedure time-out, the team should be made aware of hypoxaemia or haemodynamic instability due to (tension) pneumothorax.

Differential diagnostics: tuberous sclerosis [9], Cowden syndrome, von Hippel-Lindau disease [11], lymphangioleiomyomatosis (LAM), pulmonary endometriosis, α1-antitrypsin deficiency, Marfan syndrome [4].

Ambulatory anaesthesia

Not reported. Nevertheless, depending on respiratory and renal function as well as accompanying diseases in the individual BHDS patient, ambulatory anaesthesia may be acceptable.

Obstetrical anaesthesia

Patients with BHDS are fertile, thus the obstetrical anaesthetist might face women with BHDS for labour analgesia. Pulmonary and renal manifestation in the women's fertile age may aggravate pregnancy and labour.

There are no general recommendations or even case reports about pregnancy or delivery in women with BHDS yet. Nevertheless, recommendations referring to performance of general or neuraxial anaesthesia should be considered as described above.

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Please note that this recommendation has not been reviewed by an anaesthesiologist and a disease expert but by three disease experts instead.