orphanaesthesia

Anesthesia recommendations for patients suffering from

Börjeson-Forssman-Lehmann syndrome

Disease name: Börjeson-Forssman-Lehmann syndrome

ICD 10: Q87.8

OMIM: 301900

Synonyms: -

Disease summary:
The Börjeson-Forsmann-Lehmann syndrome (BFLS) is a very rare genetic disorder. This disease was first described in 1962 by Börjeson, Forssman and Lehmann [3]. The pattern of inheritance was confirmed in 1989: BFLS is a relatively uncommon type of syndromic X-linked mental retardation [7,14,15].

In 2002 a mutation in the zinc finger gene PFH6 has been identified as the cause of BFLS [7,11,12]. This gene seems to play a role in neuronal migration in the cerebral cortex [8]. Up to now there is no evidence for genetic heterogeneity of BFLS. Males are predominantly affected but milder manifestations may be seen in females [7].

The genotype-phenotype correlations have not yet clearly emerged [12]. The main and most constant clinical features are mental retardation, big ears, underdeveloped genitalia, (truncal) obesity, tapering fingers, and short toes. “Gynecomastia” may also appear, but it is unclear whether this is caused by breast tissue hyperplasia or lipomastia [4,16]. Social skills in BFLS are good and behaviour is in general friendly but can be challenging with externalising and even thrill-seeking features. However, variation among patients is wide [17].

Basically, the phenotype and the main clinical features evolve with age and show considerable variation both within and between affected families [7,16]:

Infancy / childhood:
Developmental delay in achieving typical milestones, retarded growth, floppy appearance, failure to thrive, hyperpigmentation, seizures, hyperopia, nystagmus, respiratory illness, large ears, an arched palate, cleft lip and palate, ankyloglossia, hypotonia, jaundice, hypoglycaemia, poor feeding, small external genitalia, cryptorchidism, hypopituitarism, inguinal hernia [4,6,12,16,18].

Adolescence:
Short stature, (truncal) obesity, gynecomastia, micro- macrocephaly, large ears and fleshy earlobes, protruding cheeks, broad feet with bilateral e.g., syndactyly, underdevelopment of toes and fingers (short, tapered, malleable), small external genitalia (impalpable or small

testes), hearing impairment (requiring aids), mental retardation, delayed development in both speech and motor skills, learning problems with need for attending special schools and education, attention deficit hyperactivity disorder (ADHD) and reactive attachment disorder. The degree of intellectual handicap is usually moderate [4,12,16].

Adult life:
Short stature, coarse facial features like big and long ears and earlobes or prominent supraorbital ridges and chin, swelling of subcutaneous tissue of the (e.g., cheeks and forehead), ptosis, deep-set eyes, cataract, narrow palpebral fissures, hearing impairment, sensory impairment in the legs, axonal / generalized polyneuropathy (moderate), seizures, clumsiness in running, cubitus valgus, short and tapering fingers (and toes), clinodactyly, flat, broad feet, knock-knees, kyphosis / kyphoscoliosis, thickening of the skin, scant body hair, hypotelorism, obesity, gynecomastia, small external genitalia, hypogonadism, oligomenorrhea / amenorrhea in women, hypothyroidism, hypopituitarism, significant learning problems, severe intellectual disability, micro- as well as macrocephaly and epilepsy [12,16]. Some heterozygous females may be entirely normal or show milder-to-moderate clinical features and 95% have skewed X inactivation [3,7,10,11,13,14,15,16].

Usually, BFLS patients require a varying degree of supervision. They often live in their parent's home or in group / nursing homes [16].

BFLS is considered a rare entity. Nevertheless, it is expected to be underdiagnosed [16]. The syndrome is mainly clinically diagnosed and complemented by genetic testing. Family history should be considered to support the suspected clinical diagnosis. Especially an X-linked pattern of inheritance may be worthwhile. Diagnostic investigation with e.g., EEG or MRI may be normal [7,12,16].

There is no specific treatment in BFLS. Beside the frequent need for special education, therapeutic management is symptomatic and may especially be needed for seizures, hearing impairment or (associated) Perthes disease. Genetic counselling is indicated [7].

Medicine in progress

Perhaps new knowledge

Every patient is unique

Perhaps the diagnostic 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**	Both general anaesthesia (GA) (balanced/TIVA) and regional anaesthesia (RA) are possible / anticipate difficult airway (characteristic facial features may complicate airway management) / RA may be challenging due to limited patient compliance / (Kypho)scoliosis, lumbar lordosis, and vertebral anomalies may complicate neuraxial techniques and cause restrictive lung function (lung-protective ventilation)
B	**BLOOD PRODUCTS (COAGULATION)**	Not reported
C	**CIRCULATION**	Potential cardiac complications due to dilated cardiomyopathy and persistent ductus arteriosus (both with sporadic reports), as well as kyphoscoliosis / ECG, TTE, TEE, or IBP may be helpful based on individual risk assessment
D	**DRUGS**	Continue anticonvulsant/psychiatric medication (consider drug monitoring and watch for interactions with anesthetics) / No risk for MH
E	**EQUIPMENT**	Consider ultrasound-guided IV access and caregiver presence in PACU in case of behavioral/attachment disorders or severe intellectual disability / Postoperative hypoxemia may occur due to airway difficulties, scoliosis, or obesity – anticipate and monitor accordingly

Typical surgery

Surgery of ankyloglossia and orchidopexy are reported [4].

Type of anesthesia

Up to now there are no data or case reports for anesthesia in BFLS. Therefore, a general recommendation regarding an ideal anesthetic approach cannot be given.

General anesthesia might be performed as well as peripheral or neuraxial anesthesia but the latter require the patient's collaboration which may be difficult to achieve without sedation.

There are structural CNS abnormalities described for BFLS with brain abnormalities and seizures [10]. Spinal or epidural anesthesia may be challenging due to kyphoscoliosis,

lumbar lordosis and further vertebral anomalies reported in BFLS [19]. Characteristic facial features may complicate airway management for general anesthesia.

Necessary additional diagnostic procedures (preoperative)

A thorough physical examination is essential in the perioperative setting. A meticulous evaluation of the patient's airway is necessary because of distinctive facial features in BFLS, which may impede airway management.

If neuraxial procedure is planned, the anesthesiologists should focus on the anatomy of the back, spine and chest. In BFLS vertebral anomalies like kyphoscoliosis and lumbar lordosis are indeed reported.

There are sporadic case reports of dilated cardiomyopathy and a persistent ductus arteriosus [4,9,19,20] or kyphoscoliosis may have cardiac consequences. Additional diagnostic like i.e., an ECG or transthoracic / -oesophageal echocardiography (TTE / TEE) may be useful.

As panhypopituitarism has been reported in cases of BFLS, the results of patient's endocrine status should be checked in its files and the appropriate treatment should be adapted in the perioperative period, if necessary: thyroid hormones, steroids etc. [2]

Particular preparation for airway management

Distinctive facial features in BFLS may impede mask ventilation as well as classic laryngoscopy. Therefore, a thorough airway examination is necessary. This should include evaluation of fat distribution within the face, neck and chest, mobility of the temporomandibular joint and neck, mouth opening, size and mobility of the tongue (ankyloglossia), presence of prognathism and dental status. Teeth anomalies or malposition as well as hypodontia are reported in BFLS and may lead to dental or gingival damage during airway management [1,6,19].

Truncal obesity and bilateral breast enlargement / gynecomastia may lead to reduced oxygen reserve during induction of anesthesia.

Basically, a standardized approach for airway examination and detection of airway challenges is recommended. A thorough preparation for airway management should be based on the examination results. Availability of video-laryngoscopes, supraglottic airway, fiberoptic intubation and, if applicable surgical airway, may be required.

Particular preparation for transfusion or administration of blood products

Not reported.

Particular preparation for anticoagulation

Not reported.

Particular precautions for positioning, transport or mobilization

Basically, all team members should act with caution because hyperextensibility of the joints is reported in BFLS [4,6,19]. Furthermore, there are no specific recommendations for patients with BFLS.

Probable interaction between anaesthetic agents and patient's long-term medication

Epilepsy (and anticonvulsant medication) is an inconsistent feature in BFLS [4].

Psychiatric disorders and ongoing mood changes or behavioral problems are often treated with antipsychotic drugs (i.e., risperidone, methylphenidate) [4,17].

If applicable, drug-monitoring of anticonvulsant or psychiatric medication may be reasonable. Continuation of these medications is recommended. Pharmacological interactions with anesthetic drugs should be considered.

Anaesthesiologic procedure

Preoperative Evaluation: see details above.

Premedication: might be performed weighing the benefits and risks in individual patients.

Patient positioning: should be performed with respect to hyperextensible joints [4,6,19].

IV line: deformities / malformations usually concern fingers and toes – so peripheral placement of IV line should not be impeded. Nevertheless, obesity may complicate central venous access. Ultrasound-guided central venous access is therefore recommended.

Invasive blood pressure measurement: should be based upon the patient's pre-existing conditions as well as the surgical or interventional procedure.

(Mechanical) Ventilation: a pulmonary restrictive syndrome due to e.g., (kypho) scoliosis or truncal obesity may occur in BFLS. Lung-protective ventilation should be to avoid baro- / volutrauma.

Anesthesia: there are no case reports of anesthesia in BFLS published so far. Theoretically, there are no contraindications for anesthesia-related drugs just because of BFLS. Total intravenous or balanced anesthesia using volatile anesthetics can be performed safely considering their usual contraindications. There is no specific risk for malignant hyperthermia.

Regional anesthesia can be performed as described above.

Particular or additional monitoring

The degree of hemodynamic monitoring (invasive or non-invasive) should be based upon the patient's pre-existing conditions as well as the surgical or interventional procedure.

Possible complications

Not reported. Possibly hypoxemia in case of airway difficulties (see above) or postoperatively because of scoliosis and obesity.

Postoperative care

Postoperative care should be based upon the patient's pre-existing conditions as well as the surgical or interventional procedure.

In case of pre-existing behavioral / attachment disorders or severe mental retardation, it may be helpful to allow assistance / caregivers to the PACU.

Information about emergency-like situations / Differential diagnostics

Emergency-like situations: difficult airway due to distinctive facial features.

Differential diagnostics: Coffin-Lowry syndrome, Coffin-Siris syndrome, Klinefelter syndrome, Prader-Willi syndrome, Wilson-Turner syndrome, Bardet-Biedl syndrome, Smith-Lemli-Opitz syndrome and pseudohypoparathyroidism [5,7,13,19].

Ambulatory anesthesia

Specific recommendations for or against ambulatory anesthesia cannot be given as no published literature exists regarding this topic. Ambulatory procedures are possible weighing the benefits and risks in individual patients regarding local infrastructure and the patient's comorbidities.

Obstetrical anesthesia

Female carriers of BFLS mutation are usually only mildly or not at all affected [19]. They are usually fertile, however, hypogonadism and genital or endocrine anomalies in BFLS may impair fertility [4,20].

In general, neuraxial as well as general anesthesia might be performed in this patient population. However, there are no reports of obstetrical anesthesia. Therefore, selection of anesthesia techniques should be performed for the individual woman and with respect to potential problems for each procedure (see above) and typical anesthetic risks in pregnancy (e.g., aspiration).

Literature and internet links

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Last date of modification: May 2025

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