orphanaesthesia

Anaesthesia recommendations for

Amyotrophic lateral sclerosis

Disease name: Amyotrophic lateral sclerosis

ICD 10: G12.2

Synonyms: Charcot disease, Lou Gehrig's disease

Disease summary: Amyotrophic lateral sclerosis (ALS) is a rare progressive, paralytic disorder characterised by degeneration of upper and lower motor neurons in the motor cortex, brainstem, and spinal cord. ALS is the most common form of degenerative motor neuron disease [1,3,6,11]. Involvement of the upper motor neurons leads to weakness, spasticity, hyperreflexia, and Babinski signs. Affection of the lower motor neurons causes weakness, muscular atrophy, fasciculations, and cramps [11]. Brain stem affection can lead to bulbar symptoms. The course of the disease varies according to the first affected region and clinical manifestation, and usually respiratory failure is the ultimate cause of death [4].

The worldwide incidence is approximately 1/50,000 per year and prevalence around 1/20,000. These numbers are relatively uniform in Western countries, although foci of higher frequency have been reported in the Western Pacific [23]. Incidence as well as prevalence increase with age [1]. The mean age of onset for sporadic ALS is late 50s, but earlier onset may occur in familial cases. There is a slight male preponderance (male to female ratio of around 1.5–2:1) in sporadic cases, but equal ratio in familial cases [1,23].

About 5–10 % of ALS cases are familial (typically autosomal-dominant inheritance), whereas the remaining 90–95 % of ALS cases occur sporadically, but these are phenotypically indistinguishable [1,6]. Over 100 genetic variants have been associated with the risk for developing ALS, but the pathogenetic mechanism(s) remain unknown [1]. Interestingly, different gene mutations can lead to distinct phenotypes (e.g., similar age at onset, site of onset, disease duration), while other single gene mutations can lead to multiple phenotypes [6]. Genes, influencing cytoskeletal dynamics or the protein and RNA homeostasis as well as trafficking processes, play an important role in the centre of current research [1].

Environmental factors undoubtedly influence the complex pathogenesis but it is incompletely understood. Environmental risk factors, which have been associated with ALS in varying levels of support, include e.g., military service, different kinds of (head) trauma, smoking and exposure to heavy metals and pesticides [1].

There is a marked phenotypic heterogeneity between patients with respect to the onset, location, and populations of involved motor neurons, resulting in diverse signs and symptoms [1,6,24]. "Classical" ALS usually begins in the limbs with focal weakness but progresses within weeks to months to involve most muscles. Until late in the disease, neurons innervating eye muscles, or the bladder are not affected [1,6]. Beside muscle weakness, muscle atrophy, fasciculations, spasticity and hyperreflexia may appear [24].

However, a third of patients present with bulbar symptoms, e.g., difficulties in chewing, speaking, swallowing, drooling of saliva as well as a slurred speech [1,26]. Dysphagia can result in symptomatic aspiration of solids, liquids and later for solid food [28]. Furthermore, emotional lability due to involvement of frontopontine motor neurons may indicate pseudobulbar palsy, which is characterised by facial spasticity and a tendency to laugh or cry excessively in response to minor emotional stimuli [1].

Up to 20 % of ALS patients show progressive cognitive abnormalities marked by behavioural changes, leading to (frontotemporal) dementia [1].

Beside “classical” ALS, there are several atypical ALS forms such as cases with pure limb involvement and these may have longer survival. In these atypical ALS forms, the pathological burden is predominantly at one (upper or lower) motor neuron level. These forms include Primary Lateral Sclerosis (PLS) or Progressive Muscular Atrophy (PMA), in which their independency or entity as a variant of ALS is under debate [5].

The degree of involvement of the upper and the lower motor neurons, the body regions affected, the degrees of involvement of other systems (e.g., cognition, behaviour), and the progression rates vary among patients [6]. The time from the first symptom of ALS to diagnosis is approximately 12 months. The diagnosis is primarily based on clinical examination. Imaging of the head and spine, electromyography and laboratory test particularly serve to exclude structural lesions and other causes for paralysis [1]. The ALSFRS-R questionnaire can be used to evaluate the course of the disease and especially the patient’s functional impairment [11].

Unfortunately, there is no causal therapy for ALS. Treatment options are usually palliative directed towards managing symptoms with temporary interventions (e.g., nasogastric feeding, surgical improvement of speech disorders, cough-assist devices, diaphragmatic pacing, ventilatory support or tracheotomy). Whether feeding via gastrostomy tube has a significant survival benefit is controversial [13,22,30]. Furthermore, pros and cons as well as consequences of a tracheostomy are part of an ethical discussion in the advanced care planning of ALS patients. Tracheostomy and ventilation may allow the patient to survive despite increasing paresis, but ALS may ultimately lead to a locked-in state with the inability to communicate. Drugs like edaravone and riluzole provide limited improvement [1].

Because no therapy offers substantial clinical benefit for ALS, the prognosis is poor [1,19]. As ALS progresses, there is further weakening of the diaphragm and respiratory muscles leading to dyspnoea, orthopnoea, hypoventilation, pneumonia and finally to death due to respiratory paralysis/failure or complications such as dysphagia or immobility within 3 to 5 years [1,11,24]. Mean life expectancy after symptom onset is about three years [11].

Medicine is in progress

Perhaps new knowledge

Every patient is unique

Perhaps the diagnosis is wrong

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Typical surgery

Tracheostomy.

Suprapubic bladder catheterisation.

Laparoscopic placement of diaphragmatic pacing systems [22,34].

Gastrostomy: percutaneous endoscopic gastrostomy (PEG), percutaneous radiologic gastrostomy (PRG), per-oral image-guided gastrostomy (PIG), surgical gastrostomy (laparotomy and laparoscopy approaches have higher complications and mortality rates and are therefore less common) [13,28,33].

Type of anaesthesia

Surgical interventions requiring (general/regional) anaesthesia may accelerate progression of ALS – referring to this, direct influence of anaesthetic drugs, inflammation and hypoperfusion among other things are under discussion as causing factors. Furthermore, repeated surgery and anaesthesia in these patients may lead to a considerable increase in respiratory complications [20]. Finally, each mode of anaesthesia carries specific problems in ALS patients, which should be carefully considered in this patient population [7,27].

General anaesthesia requiring invasive ventilation might result in respiratory complications in ALS patients like necessity of prolonged ventilation, perioperative progress of respiratory muscle weakness with respiratory failure, hypoventilation, an increased risk of aspiration due to progress of bulbar symptoms or finally a difficult weaning process.

Using short acting agents for general anaesthesia, if applicable without muscle relaxation, may help to avoid some of these problems [18,22,26]. Furthermore, a preferably restrictive use of opioids and sedative as well as neuromuscular blocking agents is recommended, due to an assumed increased sensitivity to opioids and sedative agents.

Depending on surgery, regional/neuraxial anaesthesia should be strongly considered as safe and feasible alternatives to avoid airway manipulation, invasive ventilation, sedative drugs, and muscle relaxants [17,24]. In cases of patients with preoperative existing severe respiratory weakness, the use of non-invasive ventilation techniques during regional/neuraxial anaesthesia, may help to support the respiratory effort [15,26]. Furthermore, regional/neuraxial anaesthesia can prevent perioperative surgical pain and reduce the need for analgetic medication with corresponding side effects [28].

The initiation of neuraxial (especially spinal) anaesthesia might result in hypotension and bradycardia due to local sympathectomy as in other patients undergoing neuraxial blockades. This phenomenon can theoretically be exacerbated due to associated autonomic dysfunction of different degree in ALS. Therefore, striving for an optimal fluid balance before spinal anaesthesia may lessen haemodynamic deviation. Further, (non)invasive monitoring (e.g., arterial line) and vasoactive medication should be available to monitor and treat haemodynamic abnormalities [24].

Besides, patients with pre-existing CNS disorders, including ALS patients, are supposed to be at an increased risk for an exacerbation of their preoperative neurologic symptoms (“double-crush” phenomenon), where patients with previous neural impairment may be prone to a secondary adversity from mechanisms, which are not fully understood (e.g., needle trauma, technical difficulties, drug toxicity and the selection of certain substances such as vasopressors

or lidocaine) [24,32]. Nevertheless, especially in cases in which surgery does not require deep muscle paralysis or is confined to the extremities, regional/neuraxial anaesthesia may be preferred compared to general anaesthesia to reduce the risk of respiratory complications [3,24]. Various regional/neuraxial techniques have been (solely) used successfully in the anaesthetic management of ALS patients, e.g., an open appendectomy or inguinal herniorrhaphy with an epidural anaesthesia, a radiologically inserted gastrostomy tube placement with paravertebral block, lumbar plexus and sciatic nerve blocks as well as a combined spinal-epidural (CSE) anaesthesia, a femur fracture as well as a baclofen pump replacement with transversus abdominis plane (TAP) block (even in outpatients) [3,7,8,10,17,28,31].

However, there is currently no ideal or evidence based universal agreement on the ideal anaesthetic technique (regional/general anaesthesia) for ALS patients. The decision for general or regional anaesthesia should be individualised on a case by case basis, considering a thorough risk-benefit analysis, respecting the patient's wishes and striving for a perioperative multidisciplinary approach [24].

Necessary additional pre-operative testing (beside standard care)

There is no general recommendation or protocol for an ideal preoperative assessment of ALS patients but it should be based on the individual patient as well as the attending anaesthesiologist with input from the managing neurologist/other primary clinician.

Depending on further comorbidities, preoperative assessment should focus on identifying organ dysfunction, particularly with special reference to the lung. ALS patients often pass through frequent pulmonary function tests (e.g., spirometry) – the results of these tests (e.g., SNIP, FVC, FEV 1, FEV 1 / FVC) should be reviewed preoperatively as a key indicator to determine whether these patients require post-operative monitoring, special support or non-invasive or even (prolonged) invasive ventilation [11,29]. It is useful if patients meet criteria for postoperative non-invasive ventilation that they are started on this therapy prior surgery so that they can develop tolerance to the mask before needing it in the immediate post-operative period [22].

Further diagnostics (e.g., chest X-ray, ECG, echocardiography, laboratory tests, blood gas analysis) should be performed on an individual basis and on clinical signs.

Particular preparation for airway management

Basically, evaluation and preparation for airway management in patients with ALS should follow common practice standards for airway management.

Airway examination should be performed carefully and with particular attention to the patient's anatomic and dysmorphic features (e.g., spasticity, tracheal constriction/scar after tracheotomy) with focus on mouth opening, jaw mobility as well as head and neck anatomy to evaluate potential airway problems.

In tracheotomised patients, the medical history should also include relevant complications of the artificial airway (scars, difficulties in changing the tracheostomy tube, regular frequency of suctioning the airway).

Difficult airway management should be anticipated with backup strategies planned in advance. Due to frequently pulmonary dysfunction, a sufficient preoxygenation is essential. Bag-mask-ventilation may be difficult due to spasticity and a frequent (severe) restrictive pattern in pulmonary dysfunction. Additional devices (e.g., oral {Guedel pattern} airway, nasopharyngeal airway) and adequate personal resources should be available.

Laryngoscopy and intubation may also be challenging. Therefore, video laryngoscopy or the use of a fibreoptic scope may be useful and necessary [11]. Further, oral/tracheal suction should be available during intubation due to dysphagia and secretion. There are reports of premedication with an antisialagogue (e.g., glycopyrrolate) to reduce secretion [4,34,37].

Although, most (non-tracheotomised) ALS patients get endotracheal intubation for airway protection, a laryngeal mask may be a viable option in selected patients [32].

Particular preparation for transfusion or administration of blood products

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

Particular preparation for anticoagulation

There are no specific suggestions for ALS. With respect to frequently restricted mobility up to being bedridden, anticoagulation should be considered in individual cases corresponding to current recommendations and depending on surgery and comorbidities. Furthermore, compression stockings and (limb) physiotherapy may be indicated for prevention of deep vein thrombosis.

Particular precautions for positioning, transportation and mobilisation

Many ALS patients need a different degree of help and support in their daily activity (including bedding and movement) due to physical disability/weakness. Spasticity, muscle cramps/ atrophy/weakness in many ALS patients requires extremely careful positioning and mobilisation on an individual basis.

Surgery in prone position (and spinal anaesthesia) is reported without complications, but this should be considered carefully in awake ALS patients without airway protection [25]. Supine position (e.g., in the post-operative setting) may also be stressful for ALS patient, because the use of accessory muscles to support respiration may be necessary [26]. Upper/semi-sitting position may help to relieve respiration [15].

Interactions of chronic disease and anaesthesia medications

Therapeutic ALS drug riluzole decreased the MAC of isoflurane in animal experiments [36]. There are no data/reports for interactions in humans. Especially in patients with chronic riluzole treatment, we recommend the use of anaesthetic-depth monitoring (e.g., BIS monitoring) to guarantee adequate levels of anaesthesia.

Anaesthetic procedure

Preoperative evaluation: see details above.

Premedication: might be performed weighing the benefits and risks in individual patients – be aware of an increased sensitivity to sedative drugs and a high risk for e.g., hypoxaemia, airway obstruction or aspiration. Specifically, benzodiazepines and gabapentinoids should only be used after careful consideration of risks and benefits [5]. Glycopyrrolate is sometimes used as an antisialagogue to reduce secretion in ALS patients.

Patient positioning and monitoring: act with caution due to spasticity and muscle weakness. In case of monitored sedation without invasive ventilation, an upper position may support the patient's respiration (as far as possible depending on surgery).

Vessel cannulation: might be difficult due to cramps or spasticity. Ultrasound or vein finder might facilitate cannulation.

(Monitored) sedation: e.g., fentanyl, midazolam, ketamine, dexmedetomidine and propofol may be used. Providers should consider a potential increased sensitivity to opioids and sedative agents. Ideally, sedation allows purposeful feedback to tactile and verbal stimulation – the loss of airway and gastric reflexes should strictly be avoided in patients getting sedation (e.g., for regional anaesthesia) [24].

Induction of anaesthesia: should be performed with consideration of patient-specific risk factors, especially regarding respiratory impairment. Furthermore, due to dysphagia and malnutrition/dehydration, anaesthesiologists should be aware of hypovolemia. (Severe) hypotension following induction of anaesthesia should be anticipated before induction (e.g., via clinical signs, passive leg raising, transthoracic echocardiography, haemodynamic monitoring, lactate). Involvement of autonomic nervous system (especially sympathetic disturbances) in ALS patients is under discussion and anaesthesiologists should be aware of unusual haemodynamic reaction/compensation in these patients with the risk of sudden instability [38].

Drugs: using established drugs for induction and maintenance of anaesthesia was reported as being uneventful. Drugs and doses should be selected carefully because adverse effects may be more distinctive and the likelihood of emergency situations occurring is higher than that in healthy patients [38]. Especially non-depolarising muscle relaxants (NDMR) should be used carefully and at the lowest possible doses (ideally controlled by relaxometry). Succinylcholine should be avoided whenever possible due to risk of hyperkalaemia [24,29]. After reversal of NDMR one should be aware of recurring or persistent muscle weakness and necessity of controlled ventilation. However, both sugammadex and neostigmine with glycopyrrolate have been used to reverse NDMR in ALS patients [2,3,11,14,37]. Using cholinesterase inhibitors, providers should keep in mind the longer duration of most NDMR compared to e.g., neostigmine [2]. Basically, an appropriate dose of reversal drug for the degree of muscle relaxation must be chosen. Furthermore, it is critical to monitor whether muscle relaxation is sufficiently reversed when using reversal drugs in ALS patients to avoid any residual block [4]. Weighing risks and benefits, anaesthesiologists may also consider general anaesthesia without the use of any muscle relaxants [18,22,35]. Total intravenous (TIVA) or balanced anaesthesia using volatile anaesthetics appears safe. However, inhaled anaesthetics are (controversially) discussed being responsible for residual muscle relaxation (despite drug reversal and inconspicuous neuromuscular monitoring) as well as the degree of disease progress in some ALS patients. Anaesthesiologists should keep this in mind, even if it is currently unclear whether TIVA provides significant advantages compared to inhalation anaesthesia in the management of ALS patients. Providing inhalational anaesthesia,

desflurane and sevoflurane should be preferred for maintenance due to their low lipid solubility allowing for rapid reversal and dose adjustment [3,29].

Regional/neuraxial/infiltration anaesthesia: using established drugs, no complications were reported among patients who underwent regional anaesthetic techniques [11,17,25]. Ultrasound guidance may help to identify target structures, primarily in patients with e.g., spasticity, deformities, and muscle atrophy. Furthermore, for cervical/brachial plexus block ultrasound can help to reduce the risk of inadvertent co-anaesthesia of e.g., N. phrenicus or N. recurrens with consequently progress of a pre-existing severe respiratory distress.

Ventilation: should be lung protective whenever possible. In patients with diaphragmatic pacing system, this device may be synchronised with the anaesthesia workstation ventilator to facilitate ventilation (and weaning) [22]. Preoperative consultation with the referral centre will improve the perioperative handling of these specific devices.

Particular or additional monitoring

Depending on the degree of pulmonary distress, an arterial line may be placed peri-operatively for blood gas monitoring [15]. Furthermore, the risk of sudden haemodynamic instability during anaesthesia may be increased in ALS patients due to affection of the autonomic nervous system [38].

Despite cognitive dysfunction/locked-in state in some ALS patients, bi-spectral index (BIS) monitoring is reported as useful for estimating the depth of anaesthesia concordant to healthy individuals [9].

Neuromuscular monitoring is indispensable when muscle relaxants are used as a part of general anaesthesia [3]. However, providers must consider a discrepancy between measured neuromuscular response and clinical symptoms [2,3,35]. A Train-of-Four stimulation (TOF) > 0.9 may not be used as the absolute criteria for safe extubation and full recovery from muscle paralysis in ALS patients [3,14].

Possible complications

Respiratory exhaustion and / or failure is the major concern in these patients (e.g., after residual muscle paralysis or mechanical ventilation). Respiratory distress may require prolonged mechanical ventilation as well as re-intubation [11,24]. Weaning is often prolonged and difficult [20].

Bulbar symptoms, primarily dysphagia, increase the peri-operative risk of aspiration.

Dysregulation or exacerbation of bulbar and autonomic nervous system involvement [24].

Post-operative care

Postperative care should be tailored to the individual’s disease severity and type of surgery and anaesthesia.

Basically, ALS patients may be more sensitive to muscle relaxants and opioids resulting in post-operative respiratory failure, aspiration pneumonia, electrolyte abnormalities and hypovolaemia due to poor nutrition intake, and exacerbation of neurologic symptoms and functional decline after surgery [24]. Therefore, a stay in intermediate or intensive care unit might be reasonable. Even if it is not mandatory, this may be useful for most ALS patients, especially if severe respiratory dysfunction pre-exists and controlled ventilation was necessary. The post-operative disposability of non-invasive ventilatory devices can help to accelerate extubation, further weaning and avoiding secondary respiratory deterioration [21]. However, weakness in the face or upper airway muscles can make it difficult or even impossible to introduce non-invasive ventilation in the first place [19].

Patients on non-invasive ventilation preoperatively should be placed back on this postoperatively and if they are routinely using cough assist/airway clearance devices should bring their own machine and resume their usual routine [22,29]. Handling of these devices may often be facilitated by having the patient's primary caregiver come to the post-anaesthesia care unit to help with the patient's machine. Communication may also be easier in presence of a patient's caregiver using their tools like an alphabet table or a text editor supported by a photomechanically controlled keyboard linked to a computer [16,22].

No post-operative routine use of oxygen is recommended because ALS patients have an inherent instability of respiratory control and their drive for respirations when sleeping is based on oxygen saturation [22,29].

Bulbar symptoms like dysphagia or dysarthria as well as cognitive impairment may lead to malnutrition and require intravenous or tube feeding in cases of prolonged inpatient admission. Because ALS is characterised by a hypermetabolic state, resulting in a greater demand on caloric intake, this may even more lead to weight loss [28].

Post-operative analgesia is essential for sufficient breathing (free of pain). This requires consideration in ALS patients, since opioids may cause respiratory depression and insufficient analgesia also adversely impacts respiration [15]. Nonsteroidal anti-inflammatory agents can be given considering the usual contraindications.

Disease-related acute problems and effect on anaesthesia and recovery

Differential diagnosis: e.g., peripheral neuropathy, Lyme disease, vitamin B12 deficiency, thyroid disease, metal toxicity [1].

Emergency-like situations: aspiration, pneumonia, respiratory exhaustion and/or failure, hypoxaemia.

Ambulatory anaesthesia

There are no general recommendations regarding outpatient procedures due to a lack of reports in the literature. However, ambulatory anaesthesia is possible and might be performed in institutions with adequate resources and expertise. Especially minor procedures that require limited sedation can be performed safely on an ambulatory basis [11].

Nevertheless, most complications are not attributable to the particular procedure per se, but rather a sequela of the underlying disease. Therefore, more extensive procedures and depending on pre-existing respiratory impairment, the intraoperative necessity of invasive

ventilation and the possibility of professional homecare (e.g., monitoring, healthcare/nursing service, oxygen disposability) ALS patients usually should be admitted to a hospital [11].

Obstetrical anaesthesia

Patients with ALS are fertile. However, the onset of disease usually is in the fifth or sixth decade, and therefore rarely applies fertile women. Due to this condition, there are rare data about ALS and pregnancy. The relationship between the hormonal change in pregnancy and increased susceptibility to ALS are under discussion and it is still unclear whether pregnancy influences the course of ALS or vice versa [15,26].

Depending on the progress of the ALS disease, pregnant women may be admitted to a (monitor) ward during pregnancy. The timing and mode of delivery at least depends on the course and progress of ALS in pregnant women. Since motor neurone diseases do not affect the motor and sensory nerves of the uterus, a vaginal delivery is basically possible (and preferred) [15,26]. Complications during pregnancy (especially progressive shortness of breath) may lead to (emergency) Caesarean section [15].

Respiration is the mostly affected component during pregnancy and respiratory deterioration must be assumed nearly independently from the delivery mode. The typical increase in cardiovascular work as well as tidal and minute ventilation in pregnancy may be affected due to weakness of diaphragmatic and costal muscles in ALS. Parturients with ALS may not be able to increase breathing appropriately to meet the oxygen demand during labour. Furthermore, in the last trimester of pregnancy, the diaphragmatic elevation leads to a decrease in in FRC. Therefore, recurrent testing of respiratory and pulmonary function is recommended. However, lower abdominal surgery like Caesarean section is associated with lung volume loss sustaining for nearly two weeks [12,26,35].

To avoid pregnancy-associated increased risks of difficult airway management and pulmonary aspiration of gastric content, which would cause further challenges in ALS patients, neuraxial anaesthesia (epidural/spinal/CSE) are preferred over general anaesthesia for delivery in pregnant women with ALS. Furthermore, an epidural analgesia during labour will minimise maternal respiratory efforts [15]. However, neuraxial anaesthesia can affect e.g., intercostal muscles and hinder spontaneous breathing [12]. Nevertheless, the recommended mode of anaesthesia in these cases is under discussion [35]. Depending on the degree of bulbar symptoms, general anaesthesia may be the only protective procedure against aspiration. The combination of local sprayed anaesthetics on trachea and vocal cords before intubation, TIVA (propofol, remifentanil) without using any muscle relaxants and local infiltration of the incision site (ropivacaine) is reported as successful for Caesarean section [35]. Considering succinylcholine as contraindicated in ALS and NDMR as critical for mother and neonate, this combination of short-acting agents may be an alternative strategy in these cases.

Riluzole as a proven therapy for ALS can be used during pregnancy [26].

Since motor neurone disease does not affect foetal development, neonatal outcomes are generally good [26].

In caring pregnant women with ALS, a multidisciplinary approach is required. This may include nutritionists and physiotherapy to avoid malnutrition and deep vein thrombosis as well as preservation of mobility [26]. Furthermore, obstetricians, neonatologists, anaesthetisologists, and neurologists should be part of the team.

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