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Nemaline myopathy

Niemann-Pick Type C

orphan**anesthesia**

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

SUPPLEMENT NR. 9 | 2022

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 Patienten mit seltenen Erkrankungen. Damit will OrphanAnesthesia einen wichtigen Beitrag zur Erhöhung der Patientensicherheit leisten.

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 Anästhesisten damit keine Erfahrungen gesammelt haben, so dass 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 ein Anästhesist sowie ein weiterer Krankheitsexperte (z.B. Pädiater oder Neurologe) beteiligt sind. Das Projekt ist international ausgerichtet, so dass 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.

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 recommendations 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.

Bisher in A&I publizierte Handlungsempfehlungen finden Sie unter:

www.ai-online.info/Orphsuppl
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orphananesthesia

Anaesthesia recommendations for Nemaline myopathy

Disease name: Nemaline myopathy

ICD 10: G71.2

OMIM: 161 800, 256 030, 605 355

Synonyms: NM, rod myopathy, congenital rod disease, nemaline rod myopathy

Disease summary: Nemaline myopathy (NM) is a rare congenital myopathy that affects males and females. The incidence is estimated at 1 in 50,000 live births. NM is a genetic disorder (with the exception of sporadic late onset NM, which is an autoimmune disorder) with pathogenic variants that are either sporadic de-novo or else inherited in either an autosomal recessive or dominant fashion. Pathogenic variants in 11 genes have been identified, accounting for approximately 75% of the total genetic burden of the disease (see table). Recessive variants in the nebulin (NEB) gene are the most common cause and account for 50 % of the cases, while ACTA1 variants are the common dominant/de-novo cause (15–25 %). Muscle biopsy shows the presence of 'nemaline bodies', or rod-like structures. Nemaline bodies are extensions of the Z disc and may include aggregates of proteins such as alpha-actinin and actin. The cause of weakness in the majority of NM cases is abnormal thin filament function, including reduced thin filament length and impaired actin-myosin cross bridging. Of note, NM likely exists on a pathological spectrum and some patients with mutations in NM associated genes may have biopsies that, instead, show a congenital fibre-type disproportion or a mixed pattern with cores and rods.

The disease is clinically heterogeneous and can be divided into six clinical subtypes based on age of onset and severity. These subtypes are: severe congenital, Amish type, intermediate congenital, typical congenital, childhood-onset and adult-onset. The severe congenital and Amish type are life limiting and affected individuals typically do not survive beyond early childhood due to respiratory failure. The typical congenital type is the most common. It is mild and non-progressive, presenting with hypotonia, extremity weakness, and feeding difficulties in infancy. The childhood-onset and adult-onset are mild and present later. There are some genotype-phenotype correlations, with LMOD3, KLHL40, and KLHL41 related NM associated with the severe congenital subtype. NEB related NM can present with a range of severity, though most commonly it is associated with typical congenital NM. ACTA1 NM exhibits the most extreme variability, with individual presentations ranging from foetal akinesia and severe congenital to mild adolescent or adult onset. Important: with ACTA1, there can be variable expressivity even within families.

About 50 % of the adult forms are acquired and associated with the presence of a benign monoclonal gammopathy of undetermined significance (MGUS): they show good therapeutic response to corticotherapy with or without azathioprine or a bone marrow graft.

Clinical manifestations include craniofacial (high-arched palate, micrognathia, retrognathia, dental malocclusion and cleft palate) and musculoskeletal (kyphosis, scoliosis, talipes,

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pectus excavatum and pes cavus) abnormalities. Rarely it is associated with cardiac lesions; either congenital (atrial septal and/or ventricular septal defect, patent ductus arteriosus, aortic regurgitation or infundibular pulmonary stenosis) or direct involvement of the cardiac muscle leading to cardiomyopathy. Cardiac disease has been described in only certain genotypes, such as NEB11 (due to myopalladin mutation) and a small subset of ACTA1 patients.

Anaesthetic considerations are a potentially difficult airway (bag-mask ventilation and intubation), difficult intravenous access (due to contractures), poor respiratory reserve, potentially underappreciated chronic hypercapnia, risk of aspiration (potentially leading to pulmonary infection) and cardiac dysfunction. There is no convincing evidence of an association between NM and malignant hyperthermia. While no specific concerns have been noted in NM, neuromuscular blocking agents are best avoided (given the potential risk of exacerbating respiratory muscle weakness). In genetically undefined cases, particularly if there is biopsy evidence of cores with rods, MH precautions are logical. This is because pathogenic variants in RYR1 have been described in a small number of cases of core-rod myopathy or pure NM, and RYR1 variants are also a common cause of congenital fibre-type disproportion. However, if RYR1 variants have been excluded, there is no evidence to support MH risk associated with the other 11 known NM genetic subtypes.

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

Genetics

gene	locus	Mode of autosomic transmission	Protein involved	Incidence (%)	Clinical presentation
NEB	2q22	recessive	nebulin	50	all forms
ACTA-1	1q42.1	recessive or dominant	skeletal alpha actin	15-25 50 % severe neonatal forms	all forms
TPM3	2q22-q23	recessive or dominant	α -tropomyosin		distal limbs and neck muscles weakness
TPM2	9p13.2-p13.1	dominant	β -tropomyosin		typical form; sometimes arthrogryposis or cardiopathy
TNNT1		recessive	slow troponin T1	mainly in Amish population	Amish severe neonatal form
CLF2	14q12	recessive	cofilin	2 families	
KBTBD13	15q22.31	dominant	Kelch repeat and BTP domain containing 13		infancy, slow movements
KLHL 40	3p22.1	recessive	Kelch-like family member 40		severe congenital form (perinatal death)
KLHL 41		recessive	Kelch-like family member 41		typical form
LMOD3		recessive	Leiomodin-3		severe congenital form

Typical surgery

Muscle biopsy for diagnosis, oral and maxillofacial surgery (Le Fort level and mandibular osteotomies), orthopaedic surgery (correction of scoliosis, tendon releases and transfers), general surgery (gastrostomy insertion and orchidopexy), cleft palate repair, rarely cardiac surgery and ENT (tracheostomy insertion).

Type of anaesthesia

There is no recommendation for general or regional anaesthesia.

Halogenated agents and depolarising muscle relaxants (succinylcholine) are usually avoided due to the risk of anaesthesia-induced rhabdomyolysis (AIR) and life-threatening hyperkalaemia. Isolated NM (rod myopathy) is not thought to be susceptible to malignant hyperthermia (MH). The overlapping core-rod myopathies (CRM) and central core disease (CCD) are often caused by a mutation of the RYR1 gene and are at increased risk of MH. They are clinically indistinguishable from NM. Total intravenous anaesthesia (TIVA) is therefore recommended as the safest method of general anaesthesia in patients with NM.

There are successful reports of regional anaesthesia including spinal anaesthesia for gastrostomy insertion and epidural anaesthesia for orchidopexy.

Sedation should be used with caution due to the potential risk of a difficult airway and, with the severe phenotypes, the risk of aspiration and respiratory failure.

Difficult intravenous access has been described due to contractures.

Necessary additional pre-operative testing (beside standard care)

CK levels are usually normal or moderately elevated. Due to the possible association with congenital cardiac disease and the development of cardiomyopathy, echocardiogram and electrocardiogram (ECG) are recommended.

Lung function tests and arterial blood-gas sampling in patients with an advanced disease or severe subtypes are useful. This cohort can have a restrictive lung disease from scoliosis and/ or respiratory failure requiring night-time non-invasive ventilation.

Detailed pre-operative neurological assessment is prudent, especially when considering regional anaesthesia.

Particular preparation for airway management

A comprehensive pre-operative airway assessment is necessary. This condition is associated with a difficult airway. Features can include a cleft palate, micrognathia and retrognathia, dental malocclusion and limited mouth opening with a high arched palate. Difficult airway equipment should be available and a specific airway plan made for any anaesthesia.

There are reports of difficult bag-mask ventilation and mask fit due to cleft palate and micrognathia. Supraglottic airway devices may be required. Literature reports of grade 3 and 4 Cormack-Lehane views on laryngoscopy mean that a video-laryngoscope and fibre-optic scope should be available. However, reduced mouth opening can make a supraglottic airway or laryngoscope insertion problematic. In infants and children, such patients may require a fibre-optic intubation under general anaesthesia or deep sedation.

Awake regional techniques to avoid airway instrumentation have been successfully reported where the patient is co-operative and the surgery is appropriate. The patient may already have a tracheostomy for ventilation due to respiratory failure. Literature reports of neonatal tracheostomy appear to be performed electively to facilitate ventilation due to respiratory failure rather than in an emergency due to failure to intubate.

Particular preparation for transfusion or administration of blood products

There is no difference in the administration of blood products or pre-operative haematological/ coagulation tests.

Bleeding diathesis is associated with muscular dystrophy and certain myopathies but have not yet been reported in cases of NM.

Particular preparation for anticoagulation

There are no specific recommendations. General recommendations for venous thromboembolism prophylaxis apply.

Particular precautions for positioning, transportation and mobilisation

The anaesthetist should be vigilant about protecting pressure points and avoiding excess stress on joints, particularly where there are contractures and musculoskeletal deformities.

Pressure areas and neurovascular injury must be avoided.

Interactions of chronic disease and anaesthesia medications

Specific interactions have not been reported.

The mainstay of management is supportive.

Anaesthetic procedure

There is a potential risk for difficult oxygenation and intubation. Difficult airway equipment should be available along with a clear airway management plan. Intravenous access is secured for intravenous induction of anaesthesia. Case reports of the safe use of volatile anaesthetic agents without complication have been published, but due to the clinical heterogeneity of the disease and similarity with other myopathies (mainly core-rod myopathy and central core disease), a total intravenous anaesthetic technique is considered to be safer. This avoids the risk of MH, but also of rhabdomyolysis and hyperkalaemia even if AIR has so far been described only in patients with muscular dystrophy. Depolarising muscle relaxants (succinylcholine) tend to be avoided for the same reason. Non-depolarising muscle relaxants can be safely used with the caveat of neuromuscular monitoring and full reversal of blockade. Sugammadex has been used successfully in one case. Neostigmine can be safely used without causing myotonia. There are no contraindications to the use of propofol, opiates or local anaesthetics. Patients should be extubated fully awake with re-intubation equipment available if necessary.

Particular or additional monitoring

In major surgery or in case of patients with cardiac involvement, invasive blood pressure monitoring is recommended.

Monitoring neuromuscular blockade and ensuring full reversal of agents is prudent.

A central venous access may be necessary for major surgery or where venous access is difficult.

Temperature monitoring is advised to avoid hypothermia and shivering. A significant temperature increase could indicate MH.

Possible complications

Patients can develop life-threatening hyperkalaemia and rhabdomyolysis and in extreme cases cardiac arrest. This is related to the use of a halogenated agent and or succinylcholine use.

Patients are sensitive to non-depolarising muscle relaxants. Neuromuscular monitoring should be used and agents fully reversed.

Post-operative care

This depends on surgery type, clinical phenotype and stage of disease. Patients can be suitable for day-case surgery or ward management.

Intensive care or high dependency can be required after certain surgeries, for example, scoliosis surgery. If needed for respiratory failure, the aim should be using non-invasive ventilation and avoidance of prolonged controlled ventilation.

Multi-modal effective analgesia is essential to enable early mobilisation and reduce the risk of post-operative complications, for example, pneumonia and venous thrombo-embolism.

Disease-related acute problems and effect on anaesthesia and recovery

Respiratory failure can occur post-operatively requiring controlled or non-invasive ventilation. Sedative drugs, for example, benzodiazepines, should be used with caution. Dexmedetomidine is probably a better choice.

Due to bulbar dysfunction, there is a risk of pulmonary aspiration in the post-operative period. Some patients might have already had a gastrostomy sited.

Ambulatory anaesthesia

Ambulatory anaesthesia would only be recommended in patients with a mild or early disease who are not having major high-risk surgery. This should be decided on an individual case-by-case basis.

Obstetrical anaesthesia

Respiratory and cardiac function can deteriorate during pregnancy. Premature delivery is a risk. A caesarean section might be required due to muscle weakness and foetopelvic disproportion making spontaneous vaginal delivery difficult.

There are successful reports of epidural, spinal and general anaesthesia in parturient patients with NM.

Neonatal respiratory failure can occur after birth in severe phenotypes, requiring intubation and ventilation.

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