orphanaesthesia

Anesthesia recommendations for

Neuromyotonia

Disease name: Neuromyotonia

ICD 10: G71.19

ORPHAcode: 84142

Synonyms: Isaac's syndrome, Continuous muscle fibre activity syndrome, Isaacs-Mertens syndrome, Quantal-Squander syndrome, Gamstorp-Wohlfar syndrome, Pseudomyotonia

Brief disease summary: Neuromyotonia is a rare condition (prevalence of fewer than 1 in 1,000,000) of peripheral nerve hyperexcitability [1]. There is a hereditary form through an autosomal dominant mutation of the KCNA1 gene on chromosome 12p13 [2]. This form commonly features tachycardia, excessive sweating, and it is sometimes associated with a congenital diaphragmatic hernia [2]. There is also an autosomal recessive form of the disease involving the HINT1 gene [3,4].

There is also an acquired form in which most patients have autoantibodies to CASPR2 and LGI1, which are proteins associated with the presynaptic voltage-gated potassium channel (VGKC) [5]. This leads to hyperexcitability of nerve membranes [5]. These autoantibodies are either of autoimmune origin (association with myasthenia, Hashimoto's thyroiditis or pernicious anemia) or a paraneoplastic syndrome (thymoma, lung, ovarian or bladder cancer, Hodgkin's lymphoma) [5].

Neuromyotonia typically presents with myokymia (muscle twitching), stiffness (approximately 30% present with pseudomyotonia, manifesting as delayed relaxation following muscle contraction), and muscle cramps [1]. Less common manifestations may include easy fatigability, hyperhidrosis, and ataxia [1]. Disease onset may occur at any age and is sometimes associated with myasthenia gravis and thymoma as noted above [5,6]. It can follow either a progressive course or a relapsing/remitting pattern [1]. Diagnosis is made by a combination of clinical symptoms such as myokymia in the presence of electromyography (EMG) showing doublet or triplet discharges [1].

Treatment with anticonvulsants, such as phenytoin, carbamazepine or gabapentin, is commonly used to relieve pain associated with the abnormal muscle firing [1].

Diagnosis may be incorrect; if uncertainty exists, the diagnosis should be re-evaluated.

Every patient is unique; individual circumstances must always guide clinical care.

Medicine is in progress; new clinical knowledge may not be yet reflected in this recommendation.

Recommendations are not rules or laws; they provide a framework to support clinical decision-making. Although this recommendation has passed a structured review process, it does not meet the formal criteria of a guideline.

Translations may not always reflect the most recent updates of the English version.

Find more information on the disease, its centers of reference and patient organizations on Orphanet: www.orpha.net

Emergency information

A	**AIRWAY / ANESTHETIC TECHNIQUE**	No typical airway malformations. Myokymia (including laryngeal/bulbar) may increase aspiration risk. Myokymia usually ceases after induction of anesthesia. Neuromuscular blockers are not required but may be used if needed to suppress myokymia. GA, RA, and TIVA have been used.
B	**BLOOD PRODUCTS (COAGULATION)**	No disease-specific coagulation disorders are described. No special preparation or storage of blood products is required.
C	**CIRCULATION**	No consistent structural cardiac abnormalities are associated with neuromyotonia. No specific increased risk of heart failure has been reported.
D	**DRUGS**	**Avoid:** succinylcholine. **Inhalational agents:** no proven risk; consider alternatives when available. **Interactions:** phenytoin and carbamazepine (CYP3A4 inducers) may reduce plasma levels of warfarin, beta-blockers and some antibiotics. **Premedication:** no specific recommendations. **MH / rhabdomyolysis:** no proven increased risk of MH; no reports of anesthesia-induced rhabdomyolysis.
E	**EQUIPMENT**	No disease-specific equipment is required. Neuromuscular monitoring may be useful to titrate blockade and suppress myokymia.

Additional disease information

Other imaging such as CT or MRI may be utilized to investigate the presence of thymoma or other malignancies associated with the paraneoplastic form of neuromyotonia with implications for perioperative planning and risk stratification. Plasma exchange, IVIG (intravenous immunoglobulin), and steroids have been reported to alleviate symptoms in some patients [7].

B-cell-depleting therapy with rituximab has been reported as effective treatment in refractory neuromyotonia, including antibody-negative cases, and may be considered as escalation option alongside plasma exchange, IVIG, and corticosteroids [8].

CASPR2 and LGI1 are the predominant antibodies in acquired neuromyotonia and malignancy screening may be negative even in antibody-positive patients. This suggests that an individualized rather than universal approach to oncological investigation is preferred [5].

Recent or ongoing immunomodulatory therapies may influence perioperative immune status, intravascular volume status, and drug pharmacokinetics, and should be considered during anesthetic planning [7,8].

Malignancy may require surgical work-up and intervention in affected patients, most commonly thymectomy, which may involve specific anesthetic considerations related to neuromuscular function and postoperative respiratory management.

Anesthetic case reports further support that peripheral nerve hyperexcitability, including myokymia, may persist despite adequate depth of general anesthesia and is abolished only following administration of neuromuscular blocking agents, with implications for intraoperative neuromuscular monitoring and management [9].

Typical surgery and procedures

Typical age of onset is from 15-40 years of age. Therefore, surgeries will be the same as the most common procedures in this age group (orthopedic, cosmetic, etc.). If the disease presents as a paraneoplastic syndrome, tumor biopsies and resections are also performed [10].

Type of anesthesia

Total intravenous anesthesia and peripheral anesthesia are the only reported modalities due to the small suggested risk of malignant hyperthermia as discussed below in the anesthetic procedure section. The use of both techniques has been reported without anesthetic complication [10,11]. Avoidance of succinylcholine is also recommended not only due to the suggested risk of malignant hyperthermia but mainly due to the risk of an exaggerated hyperkalemic response in patients with myopathies [12].

Necessary additional preoperative testing (beside standard care)

Aside from clinically indicated testing (for example related to an associated cancer or autoimmune disease), there is no specific testing that needs to be completed before anesthesia. CPK levels are usually moderately increased.

Particular preparation for airway management

Previous reports have described myokymia involving laryngeal and bulbar muscles, which may increase the risk of aspiration due to impaired coordination of airway protective reflexes. While this does not necessarily reflect an increased risk of laryngospasm, some authors have recommended gastric acid prophylaxis due to this potential aspiration risk. This muscle hyperexcitability typically improves following induction of anesthesia, which may reduce the risk of further aspiration events [11,6].

Particular preparation for transfusion or administration of blood products

Not reported.

Particular preparation for anticoagulation

None reported. However, some medications (phenytoin and carbamazepine) used in the treatment of this condition are CYP3A4 inducers, which may interfere with chronic anticoagulation therapy such as warfarin [13].

Particular precautions for positioning, transportation and mobilization

Not reported.

Interactions of chronic disease and anesthesia medications

Some of the medications utilized in the chronic management of neuromyotonia have interactions with medications used in the operating room. The most significant of these are phenytoin and carbamazepine which are CYP3A4 inducers [13]. These have the potential to decrease plasma levels of beta-blockers and some other drugs metabolized via CYP3A4, including certain antibiotics (e.g., macrolides such as erythromycin and clarithromycin, and azole antifungals such as ketoconazole and itraconazole). Other treatments, such as plasma exchange prior to operations, have a limited effect on anesthetic agents, except if performed the day before anesthesia (consider the risk of hypoproteinemia) [7]. The medical treatment for an associated cancer or autoimmune disease should also be taken into account.

Anesthetic procedure

Propofol, opiates, local anesthetics, midazolam and anti-nausea prophylaxis (ondansetron and dexamethasone) have been used without any adverse events [10,11,6,14]. Myokymia may persist despite adequate depth of general anesthesia and is reliably abolished by neuromuscular blockade, supporting the use of objective neuromuscular monitoring (e.g., train-of-four) with techniques such as acceleromyography or electromyography [9].

A risk of malignant hyperthermia with inhalational agents, as well as succinylcholine, has been alluded to in some reports. However, neuromyotonia is characterized by a defect in the pre-synaptic voltage gated potassium channel (VGKA). Malignant hyperthermia is most commonly caused by a defect in the ryanodine receptor (RYR1) or, more rarely, by mutations in the CACNA1S or STAC3 receptors, which are both associated with proteins in the T-tubule in calcium signaling [11]. This leads to a drastic increase in myoplasmic calcium. Therefore, the risk of malignant hyperthermia should not be greater in patients with neuromyotonia than in the normal population. Nevertheless, due to a paucity of anesthetic data and despite the absence of any report of any anesthesia-induced rhabdomyolysis with this rare condition, it may be prudent to avoid inhalational agents when an alternative is available [16].

Particular or additional monitoring

Intermittent or continuous neuromuscular monitoring (e.g., using train-of-four stimulation) is helpful to titrate the dose of non-depolarizing neuromuscular blocking agents, optimize surgical

conditions, and suppress myokymia. The patient may indeed be sensitive or resistant to the non-depolarizing neuromuscular blocking agent, depending for example on whether the disease is associated with myasthenia gravis or on the time elapsed since the last plasmapheresis [17].

Possible complications

The most common complications will be related to painful postoperative myokymia. There is also a risk for prolonged neuromuscular blockade in patients that have concurrent myasthenia gravis. Myokymia may lead to suboptimal surgical conditions and increase the risk of damage to surrounding structures during surgery. However, myokymia ceases in all reported cases with neuromuscular blockade. Other reports note that there is the potential for an increased risk of aspiration due to involvement of laryngeal muscles, but no cases have been reported so far [6].

Postoperative care

Case reports have described extended hospital stays due to painful myokymia, which may complicate postoperative pain management. A multimodal analgesic approach is recommended, and regional anesthesia techniques, including neuraxial approaches, may be considered on an individual basis to improve pain control, although data in this population remain limited [6,14,18].

Disease-related acute problems and effect on anesthesia and recovery

See above.

Ambulatory anesthesia

There are some reports of neuromyotonia patients being discharged the next day [5] or even the same day [14]. However, some patients have required prolonged stays for postoperative complications, including painful myokymia and respiratory complications related to neuromuscular dysfunction [6,14].

Obstetrical anesthesia

There are no current published reports on obstetrical anesthesia in neuromyotonic parturients. However, there is no reason to expect that epidural or spinal anesthesia could not be used, as neuraxial techniques have been successfully employed in other conditions associated with myokymia, leading to cessation of abnormal muscle discharges [2]. In addition, epidural analgesia may offer particular benefit in this population by reducing the need for general anesthesia in the event of an emergency cesarean section, thereby potentially decreasing the risk of aspiration.

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