

# orphananesthesia

## Anaesthesia recommendations for patients suffering from **Multiminicore disease**

**Disease name:** Multiminicore disease

**ICD 10:** G71.2

**Synonyms:** MmD, Multi-minicore disease, Minicore myopathy, Multicore myopathy, Multiminicore myopathy, Minicore myopathy with hand involvement, antenatal onset minicore myopathy with arthrogryposis, Minicore myopathy with external ophthalmoplegia, Multicore myopathy with external ophthalmoplegia, Multiminicore disease with external ophthalmoplegia, SEPN1-related congenital muscular dystrophy, rigid spine syndrome, rigid spine muscular dystrophy.

MmD - the most common synonym introduced following the European Neuromuscular Centre dedicated workshops (1,2) - will be used throughout this paper.

The number of synonyms cited above reflect the wide variability in histological findings, clinical penetrance, as well as the genetic heterogeneity of this disorder. MmD is one of the congenital myopathies (overall group prevalence of 3.5 – 5.0/100,000 in the paediatric population), recessively inherited, and morphologically defined by the presence of multiple small well-circumscribed areas devoid of oxidative activity and oxidative staining on muscle biopsy. In contrast to central cores in 'Central Core Disease' (CCD), minicores are multiple, excentric and only extend for a short distance along the long axis of the muscle fibre.

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Medicine in progress



Perhaps new knowledge

Every patient is unique

Perhaps the diagnostic is wrong

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### Disease summary

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Several clinical forms have been identified: The “classic form”, “minicore myopathy with external ophthalmoplegia”, “minicore myopathy with moderate hand involvement” and “minicore myopathy antenatal onset with arthrogryposis” [3]. The “classic form of MmD” – formerly also called “rigid spine syndrome” or “rigid spine muscular dystrophy” - presents in infancy with hypotonia, delay in achieving motor milestones (though most children are able to walk independently by 2.5 years), feeding difficulties, and a myopathic facies. Ophthalmoparesis in this group is rare. The muscle weakness, which mainly affects trunk and neck flexors, is associated with spinal rigidity, and secondarily results in progressive scoliosis, lateral trunk deviation and severe restrictive respiratory impairment by the second decade. This may require non-invasive ventilation, even in still ambulant patients. Secondary right ventricular function impairment often evolves. In quite a number of these severe cases, the course becomes stable in late childhood and many continue to walk into adulthood despite the above-mentioned problems and the requirement for assisted ventilation.

Muscle MR imaging shows a selective involvement of thigh muscles, with adductors, sartorius and biceps femoris more markedly involved and rectus femoris and gracilis relatively spared [4]. This phenotype is related to several mutations in the selenoprotein-N1 gene (SEPN1-gene, chrom 1p36.13), a protein involved in protecting cells from damage caused by oxidative free radicals and probably crucial in myogenesis before birth.

Other, less severe, clinical forms result from recessive mutations in the RYR1 gene (chrom 19q13.1) encoding for the calcium-release channel of the sarcoplasmic reticulum (5.038 amino-acids - 106 exons) and implicated in malignant hyperthermia susceptibility. These appear to be part of a clinical spectrum rather than true distinct entities. The clinical features comprise external ophthalmoparesis, associated or not with proximal and axial weakness, and mild-to-moderate respiratory and bulbar involvement; some present with hip girdle weakness as predominant and more or less isolated feature. Respiratory involvement is mild or absent, and impairment of cardiac function does only rarely occur in RYR1-related MmD. Primary cardiomyopathies are not a recognized feature of either SEPN1- or RYR1-associated MmD but have been reported with other genetic backgrounds [5].

The pattern of selective involvement of muscles on MRI is distinct from MmD due to SEPN1-mutations and comparable to the selective pattern of involvement found in CCD [6]. It is now clear that muscle MRI is a powerful predictor of RYR1 involvement.

The variable clinical spectrum is reflected in the number of recessive homozygous and compound heterozygous mutations in the RYR1 gene. In MmD the mutations (missense, nonsense and splice mutations as well as deletions and duplications) appear to be distributed throughout the huge RYR1 gene, whereas in CCD and MH the dominantly inherited mutations – most often mis-sense - have been found to cluster in 3 “hot spots” (MHS/CCD region 1, 2 and 3).

Some MmD patients are, clinically as well as histologically, difficult to distinguish from dominantly inherited CCD. They present with moderate, non- or slowly progressive weakness in the hip girdle and axial musculature, and multiple larger lesions or ‘multicores’ on histology as a sort of continuum with the histopathologic findings of CCD. Therefore distinction between MmD and CCD can only be made based on a comprehensive clinical, radiological (MRI), histopathological and genetic assessment.

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### Typical surgery

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Correction of scoliosis, strabismus surgery, placement of gastrostomy feeding tube, orchidopexy, muscle biopsy.

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### Type of anaesthesia

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In MmD, secondary to SEPN1-mutations, the main concerns for anaesthetists are the axial weakness, scoliosis, severe restrictive lung disease with possible cor pulmonale and the potential for postoperative pulmonary complications. In view of the muscle wasting and risk of "anaesthesia induced rhabdomyolysis", succinylcholine is contra-indicated even for rapid sequence induction. MH-susceptibility has not been reported in MmD due to SEPN1-mutations.

Patients with MmD due to mutations of the RYR1 gene, however are at increased risk of Malignant Hyperthermia. Even though this association is less well documented as in CCD, and the risk smaller, a number of clinical MH-crises have been reported in these patients. Therefore avoidance of volatile anaesthetics and/or succinylcholine is mandatory. Total intravenous anaesthesia with propofol, morphinomimetics and, if need be, non-depolarizing neuromuscular blockers is the technique of choice. Dexmedetomidine (+/- ketamine) use for procedural sedation is reported to be safe [7]. Uneventful epidural anaesthesia and peripheral (femoral) nerve block, using bupivacaine and ropivacaine, respectively, have been reported [8,9].

Likewise, if in a patient with MmD the genetic background is unknown - as is most often the case - non-MH-triggering anaesthesia is also mandatory.

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### Necessary additional diagnostic procedures (preoperative)

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Pronounced respiratory impairment due to muscle weakness and/or scoliosis is typically present and underestimated in the classic form of MmD due to SEPN1 mutations. Nocturnal hypoventilation and desaturation is reported [3]. The intercostal-accessory group of respiratory muscles is affected more than the diaphragm [10]. Severe respiratory impairment has to be anticipated with a high degree of suspicion. Preoperative lung function tests including blood gas analysis are advised.

In these patients right ventricular dysfunction secondary to marked respiratory involvement evolves over time and regular cardiac assessment by echocardiography and/or other tests is recommended.

Preoperative neurological consultation may be helpful for juridical reasons. Nutritional assessment is advised for major surgery.

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### Particular preparation for airway management

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No increased incidence of difficult intubation reported. However, some patients with the SEPN1-related form may have marked neck extension contractures.

Patients with weakness of the pharyngeolaryngeal muscles are at increased risk of pulmonary aspiration of gastric content.

Preoperative training in the use of non-invasive positive pressure ventilation (NPPV) and assisted cough techniques are advised if FVC < 50% of predicted [11]. Preoperative or intraoperative tracheostomy is not recommended even if FVC is < 40% [12].

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#### **Particular preparation for transfusion or administration of blood products**

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Not reported but scoliosis surgery is often associated with important blood loss. A Cochrane Review in 2009 concluded that antifibrinolytic drugs reduce blood loss and the amount of blood transfused. Aprotinin, tranexamic acid and aminocaproic acid were found to be similarly effective [14].

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#### **Particular preparation for anticoagulation**

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Not reported. In patients with reduced mobility a higher than normal risk of perioperative thrombosis is present.

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#### **Particular precautions for positioning, transport or mobilisation**

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Early mobilization following surgery is advised in order to avoid the detrimental effects of prolonged immobilization on muscle mass and strength. Exercise induced myalgia may necessitate analgesic management [5].

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

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Not reported.

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#### **Anaesthesiologic procedure**

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Propofol, midazolam, opioids and ketamine have been used without complications. A normal course of neuromuscular block was reported with the administration of mivacurium in adults and children [15].

Avoid succinylcholine at all times. Avoid volatile anaesthesia in all RYR1-related MmD patients and if in doubt about genetic background. Guidelines for safe anaesthesiological management of potentially MH-susceptible patients have recently been published [16]. Local guidelines also have to encompass correct preparation of the anaesthetic workstation [17] and availability of sufficient quantities of dantrolene.

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### Particular or additional monitoring

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Monitoring of temperature and ETCO<sub>2</sub> is mandatory. Neuromuscular monitoring strongly advised. Measurement of preoperative and postoperative CK advised.

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### Possible complications

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Patients with MmD due to mutations of the RYR1 gene are at increased risk of Malignant Hyperthermia. Prompt recognition is essential. The European Malignant Hyperthermia Group recently published a consensus document on recognizing and managing a MH crisis [18]. In SEPN1-related MmD respiratory impairment has to be anticipated.

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### Postoperative care

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In the classic form with scoliosis and restrictive respiratory impairment postoperative non-invasive ventilator support is recommended (NIPPV –intermittent positive ventilation applied by nasal mask or BIPAP – bilevel positive airway pressure delivered by nasal or facial mask). Use the patient's home device if applicable.

In this same group extubation directly to NIPPV/BIPAP is recommended if FVC < 50% of predicted and for patients using NIPPV/BIPAP preoperatively (12).

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### Information about emergency-like situations /Differential diagnostics

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*caused by the illness to give a tool to distinguish between a side effect of the anaesthetic procedure and a manifestation of the diseases*

Exertional rhabdomyolysis caused by exercising in a humid and hot climate is occasionally associated with a RYR1-mutation [19].

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### Ambulatory anaesthesia

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Feasible in patients with stable disease and without respiratory impairment. Prolonged monitoring for signs of MH is not advised if non-triggering anaesthesia is used.

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### Obstetrical anaesthesia

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Worsening of weakness during or after pregnancy has been reported in congenital myopathies [20].

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