orphanaesthesia

Anaesthesia recommendations for

Macrophage activation syndrome

Disease name: Macrophage activation syndrome

ICD 10: D76.2

Synonyms: Haemophagocytic lymphohistiocytosis, reactive haemophagocytic syndrome, hemophagocytic syndrome

Disease summary: Macrophage activation syndrome (MAS) is a potentially life-threatening complication of rheumatic disease that, for unknown reasons, occurs much more frequently in individuals with Systemic onset juvenile idiopathic arthritis (SOJIA) and in those with Adult-onset Still disease and Systemic lupus erythematosus (SLE). Macrophage activation syndrome is characterised by pancytopenia, liver insufficiency, coagulopathy, and neurologic symptoms and is thought to be caused by the activation and uncontrolled proliferation of T-lymphocytes and well-differentiated macrophages, leading to widespread haemophagocytosis and cytokine overproduction.

The incidence of MAS is unknown as there is a wide spectrum of clinical manifestations, and episodes may remain unrecognised. It is characterised by sustained fever, hyper-ferritinemia, pancytopenia, fibrinolytic coagulopathy, and liver dysfunction.

Diagnosis: A patient of SOJIA or suspected SOJIA with fever and serum ferritin level > 684 ng/ml should have any two of the following criteria for a diagnosis of MAS: Platelet count < 181 x 10^9/L; Aspartate aminotransferase > 48 units/L: Triglyceride concentration > 156 mg/dL; or Fibrinogen levels < 360 mg/dL.

On histopathologic examination, high haemophagocytic activity (engulfment of blood cells) is noted in bone marrow, liver, and spleen, with positive CD163 (histiocyte) staining.

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Perhaps new knowledge

Every patient is unique

Perhaps the diagnosis is wrong

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General information

Recent findings in haemophagocytic lymphohistiocytosis, a disease that is clinically like MAS, highlight the possible pathogenetic role of a defective function of *perforin*, a protein involved in the cytolytic processes and control of lymphocyte proliferation. Defect in lymphocyte cytolytic activity is proposed as a hypothesis for its pathophysiology. There is a pro-inflammatory cytokine environment along with the inability of NK (natural killer) cells and cytolytic CD8 T-cells to lyse infected cells. This results in cytokine storm, causing activation of macrophages (haemophagocytosis) and causes multi-organ failure.

Primary, MAS is the most typical manifestation of rare autosomal-recessively inherited disorders due to several genetic defects involved in granule-mediated cytotoxicity, killing of infected cells and termination of immunologic responses. It has been shown that mutations of the *perforin gene* (PRF-1,10q21) can explain 20-40% of primary forms of MAS.

Secondary or acquired forms of MAS can break out at any time during a primitive disease and occasionally it might be its presenting manifestation. In cases of acquired MAS, no underlying immunologic deficiency can be identified. Acquired forms of MAS are most frequent in children with Systemic onset juvenile idiopathic arthritis: some authors suggest an association rate of 5-10%, and MAS is believed to contribute significantly to the mortality rate in this category of juvenile idiopathic arthritis.

Both primary and acquired forms of MAS can be triggered by viral, bacterial, fungal infections, parasitic infestations, or specific drug administrations. MAS can complicate several inflammatory conditions, malignancies, primary immunodeficiencies and infective pathologies.

Although the clinical features of MAS have been well documented, early diagnosis can be difficult. Measurement of the serum ferritin level may assist in the diagnosis and may be a useful indicator of disease activity, therapy response, and prognosis. The recognition that MAS belongs to the secondary or reactive haemophagocytic syndromes has led to the proposal to rename it according to the contemporary classification of histiocytic disorders.

The principal challenge for treating patients with HLH is making a timely diagnosis. It is also critical to search for and treat underlying triggers of HLH, and institute specific antimicrobial therapy.

Although HLH appears to be a disease of excessive immune activation, the ideal form of immune suppression/anti-inflammatory therapy remains unknown. Although somewhat responsive to corticosteroids and clearly responsive to etoposide or anti-T-cell serotherapy (ATG or alemtuzumab), HLH remains difficult to treat. Generally, HCT is recommended in the case of documented familial HLH, recurrent or progressive disease despite intensive therapy, and CNS involvement.

Typical surgery

Bone marrow aspirate, long-term central venous catheter positioning, pleural tube positioning, abdominal tube positioning, liver biopsy.

Other incidental surgeries apart from disease or for diagnosis may be rarely required in such children.

Type of anaesthesia

There is no definite recommendation for either general or regional anaesthesia. Macrophage activation syndrome starts often with very low platelet count and reduced coagulation activity due to liver failure. To perform safe anaesthesia, regional anaesthesia should be performed under tight evaluation of coagulation parameters.

The main concerns in patients with MAS are its perioperative risk of flare and thus avoidance of trigger factors. The role of anaesthetic drugs as trigger factor for MAS has not been reported in literature. It must be remembered that only emergency surgery and anaesthesia be advisable in a patient with MAS, due to the life-threatening nature of the condition. Elective procedures may be delayed until stabilisation of the patient is achieved.

In SOJIA, MAS is a life-threatening complication and accounts for a significant proportion of the morbidity and mortality (8–22%). It is triggered by viral infections, drugs [non-steroidal anti-inflammatory agent (NSAID), disease-modifying agents such as gold salts, sulpha-salazine and penicillamine] and external stresses such as exposure to cold.

The anaesthetic drugs that are histamine releasers such as morphine and atracurium need to be avoided.

Various trigger factors (NSAIDs, drugs releasing histamine and cold) that may lead to MAS need to be avoided in the perioperative period. Elective procedures should be scheduled during remission phase of disease.

Necessary additional pre-operative testing (beside standard care)

Routine pre-anaesthetic evaluation and investigations are recommended, apart from system-specific tests.

Cardiac function tests like electrocardiography and echocardiography.

Blood examinations, coagulation profile, blood lactate level, kidney function tests with serum electrolytes, and liver function tests are required.

BNP blood level is useful to monitor cardiac failure.

X-ray of the thorax, lung ultrasound, and blood gas analysis to focus on atelectasis, pleural effusion and PaO2/FiO2 ratio, respectively.

Specialist consultation with rheumatologist, cardiologist or neurologist may be required in the peri-operative period for optimisation of systemic abnormalities, to be decided on a case-to-case basis.

Particular preparation for airway management

There are not reported difficulties in airway management in literature. Nevertheless, difficult airway cart and expertise must be readily available, as the pre-existing rheumatological condition can affect the laryngeal cartilages and cervical spine.

Particular preparation for transfusion or administration of blood products

Ensure availability of fresh frozen plasma, platelets, cryoprecipitate and packed red cells, depending upon the surgical requirements, extent of liver dysfunction, and other haematologic abnormalities. Tranexamic acid and coagulation factors may be necessary.

Particular preparation for anticoagulation

There is no evidence to support the need of a particular anticoagulant. But the impaired mobility of severe clinical presentation may suggest a higher risk of post-operative thrombosis. Deep vein thrombosis (DVT) prophylaxis is required during the peri-operative period, especially in major surgeries.

Particular precautions for positioning, transportation and mobilisation

There is no reported literature on specific precautions for positioning and transportation. But extreme caution needs to be exercised in view of pre-existing rheumatoid affliction of the bones and joints. It is recommended to adequately pad all bony prominences during surgical positioning for minimising neuropathies.

Interactions of chronic disease and anaesthesia medications

Not reported.

Anaesthetic procedure

Balanced general anaesthesia with controlled ventilation is usually recommended. In case of present cardiac failure and/or pericardiac effusion, avoid nitrous oxide because of cardio-depressant effects.

Inotropic drug support is required usually, for haemodynamic stabilisation.

Opiates, propofol and local anaesthetics have been used without any complication. Patients may require a lower dose of propofol or opiates. Intravenous induction agent, Etomidate can be particularly useful for haemodynamic stability in critical cases.

Hoffman's reaction dependent drugs such as remifentanil and cis-atracurium are suggested to facilitate drugs' metabolism and elimination. Avoid histamine releasing agents.

Mechanical ventilation or non-invasive ventilation are recommended to limit atelectasis development.

For pain management, ultrasound-guided nerve blocks may be undertaken in expert-hands after ruling out or correcting coagulopathy.

Particular or additional monitoring

Monitor body temperature to avoid hyperthermia and increased oxygen demand.

Neuromuscular monitoring with peripheral nerve stimulator and meticulous intake-output charting (urine output measurements) are recommended.

As MAS has a life-threatening nature, arterial cannulation for invasive blood pressure monitoring & serial ABGs along with central venous line placement (under ultrasound-guidance) with pressure measurement is recommended. In case of cardiac failure, trans-oesophageal echocardiography and SviO2 catheter are very useful.

Possible complications

As patients with MAS are at risk for acute cardiac, respiratory, and renal failure, they require post-operative intensive care unit admission and vigilant monitoring. All supportive measures must be undertaken to prevent multiple organ failure syndrome.

Sedative drugs (benzodiazepines) can worsen respiratory insufficiency and hence they are to be used sparingly.

Post-operative care

The degree of post-operative monitoring depends on the surgical procedure and the pre-operative condition of the patient. Intensive care is mandatory. Invasive monitoring is to be continued along with serial ABGs and coagulation profile to be done in the ICU.

Disease-related acute problems and effect on anaesthesia and recovery

Though not reported so far, MAS can result in multi-organ dysfunction, coagulopathy, renal shut-down, and unpredictable downhill course, which can be exacerbated by the stress of surgery and anaesthesia. There can be delayed recovery and prolonged post-operative ventilation and ICU stay.

Ambulatory anaesthesia

Not reported. In general, ambulatory surgeries cannot be recommended in critical patients of Macrophage activation syndrome.

Obstetrical anaesthesia

There has been no known literature about obstetric anaesthesia in a patient of MAS. Early obstetrical and foetal medicine/neonatology consult is recommended along with routine management of MAS.

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