orphanaesthesia

Anaesthesia recommendations for

Zhu-Tokita-Takenouchi-Kim syndrome

Disease name: Zhu-Tokita-Takenouchi-Kim syndrome

ICD 10: Q87.8

Synonyms: ZTTK syndrome

Disease summary: Zhu-Tokita-Takenouchi-Kim (ZTTK) syndrome is a rare multi-organ disease. The first cases were mentioned in 2015. This syndrome is typically inherited in an autosomal dominant manner (typically de novo) and is caused by heterozygous mutations in the SON gene (21q22.11). Mutations in this gene lead to abnormal RNA splicing processes, which are essential for metabolic functions and neurodevelopment, including neural cell migration and/or renal development.

This disorder can be suspected prenatally through intrauterine growth retardation. ZTTK syndrome abnormalities include global development delay, brain abnormalities like corpus callosum abnormalities, ventriculomegaly or cerebellar abnormalities, seizures, and generalised hypotonia. Facial dysmorphism is presented by short philtrum, macrocephaly, wide nasal bridge, and midface retrusion. Other abnormalities include scoliosis, joint and muscle contractures, joint hypermobility, visceral malformations like a horseshoe or unilateral kidney, gastrointestinal malformations, or cardiac disorders like an atrial or ventricular septal defect.

Patients suffering from ZTTK syndrome can be indicated for corrections of cardiovascular or urogenital abnormalities in addition to surgery for musculoskeletal deformations. Anaesthesiologists have to focus on continual close monitoring due to the potential risk of perioperative complications like difficult airway management (DAM), anaesthesia-induced rhabdomyolysis (AIR), or inspiratory stridor after extubation. Rhabdomyolysis represents a potentially life-threatening complication, especially in these patients suffering from neuromuscular disorder. Anaesthesiologists should prefer total intravenous anaesthesia (TIVA), eventually with nondepolarising myorelaxants and, avoid volatile anaesthetics and succinylcholine.

Medicine is in progress

Perhaps new knowledge

Every patient is unique

Perhaps the diagnosis is wrong

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Typical surgery

Typical procedures include musculoskeletal corrections for scoliosis or extremities deformations, invasive and mini-invasive corrections of cardiovascular defects, or surgical repair of visceral malformations. Patients with development delay require sedation for central venous access or MRI.

Type of anaesthesia

Anaesthesia of patients suffering from Zhu-Tokita-Takenouchi-Kim (ZTTK) syndrome can be challenging for all members of a perioperative team. Theoretically, there are possible both general and regional anaesthesia. However, only general anaesthesia was described in the literature. There are no data about the use of regional anaesthesia in these patients.

Regional anaesthesia in patients with ZTTK syndrome has no specific contraindications. Cardiovascular abnormalities can be contraindicated for neuraxial blockade as well as in other patients with heart disease. Anaesthesiologists must count on limited cooperation in patients with developmental delay. Intravenous access, neuraxial blockade, or peripheral blocks can be challenging due to musculoskeletal deformations. Ultrasound navigated venous cannulation or regional anaesthesia can improve the success rate.

General anaesthesia, concretely total intravenous anaesthesia (TIVA), is a method of choice in patients with psychomotor development delay. Volatile anaesthetics, as well as succinylcholine, should be avoided for the potential risk of severe rhabdomyolysis or hyperkalaemia. TIVA, eventually in combination with non-depolarising muscle relaxants, has been described in the literature. The benefit of rocuronium in combination with sugammadex in patients with neuromuscular disease is described. This combination allows complete recovery from muscle relaxation. The data about the risk of malignant hyperthermia are not available, but the association between these syndromes is unlikely. They have different gene localization (SON gene located on chromosome 21).

Analgosedation has no specific contraindications to this syndrome. This anaesthetic approach should be considered individually by all members of a perioperative team. The sedation is unsuitable for patients with restrictive lung disease due to scoliosis, mental retardation, or muscle weakness with the risk of hypoventilation. On the other side, the potential benefits must be weighed against the risk of difficult airway management, especially in patients with facial dysmorphism.

Necessary additional pre-operative testing (beside standard care)

Patient´s history and the type of surgery are essential for determining the spectrum of pre-operative assessment. ZTTK syndrome typically has multi-organ involvement, and anaesthesiologists must consider indications for each examination individually to identify cardiovascular, pulmonary, or visceral disorders and neurological deficits.

Neurological examination, eventually including electroencephalography, with a detailed description of the neurological deficit, is a necessity. Also, the neurologist should recommend any specific therapy needed in patients suffering from epileptic seizures. In addition, a neurological examination can be helpful for juridical reasons in patients with neurological deficits before the surgery.

Electrocardiography is a standard part of the pre-operative assessment. Patients with ZTTK syndrome can suffer from heart disease. Cardiologist examination with echocardiography should be indicated in patients with heart disease symptoms, before high-risk surgery, or in case of doubts like a large scoliotic curve with possible pulmonary hypertension.

Respiratory functions evaluation includes arterial blood gas analysis with spirometry. This examination should be considered in patients with altered respiratory functions, for example, patients with restrictive lung disease due to musculoskeletal abnormalities, scoliosis, or muscle weakness. On the other hand, this examination will not be helpful in non-compliant patients.

Other specific pre-operative testing includes patients with hormonal imbalance with the recommendation of hormone substitution by an endocrinologist. Magnetic resonance imaging (MRI) for brain abnormalities describing can be helpful but not strictly necessary before surgery.

Particular preparation for airway management

ZTTK syndrome is a disorder that typically involves dysmorphic features in patients. Typical facial dysmorphism includes macrocephaly with midface retrusion, short philtrum, and wide nasal bridge. There is only one case that reports airway management. Endotracheal intubation was described in this case. The authors mentioned uncomplicated bag-mask ventilation. There were no complications with any mentioned airway securing.

There is no more data about airway securing. Anaesthesiologists must expect possible difficult airway management (DAM) due to facial dysmorphism in patients with ZTTK syndrome. Authors recommend preparing the equipment for DAM and more alternative plans for airway securing before every anaesthetic care.

Particular preparation for transfusion or administration of blood products

One case report indicated relatively high blood loss, about 20 % of total blood volume during long-time and extensive surgery. No other data about the administration of blood products are available. Some studies presented higher blood loss in patients with neuromuscular disease compared to patients without these syndromes. So Anaesthesiologists must expect higher blood loss in patients suffering from ZTTK syndrome with limited mobility and general hypotonia.

Particular preparation for anticoagulation

There is no data about thrombotic complications and administration of anticoagulation therapy in the literature. However, patients with ZTTK syndrome often have limited mobility. Therefore, the perioperative team should expect a higher risk of thrombotic complications during the perioperative period and individually consider the potential risk vs benefit of anticoagulation therapy with higher blood loss vs thrombosis in patients with low mobility.

Particular precautions for positioning, transportation and mobilisation

Patients with ZTTK syndrome can suffer from low mobility associated with a neuromuscular disorder, endocrine dysfunction, and/or secondary osteoporosis. There is often abnormal body constitution or contractures in these patients. The perioperative team should expect a higher risk of iatrogenic damage. We recommend using specific positioning pads and careful, coordinated positioning in patients with ZTTK syndrome.

Interactions of chronic disease and anaesthesia medications

There could be possible interaction with antiepileptic drugs, heart rhythm drugs, or other neurological medication, f. e. some interactions can cause prolonged QT symptoms, deepening the sedation… The perioperative team, in case of uncertainty, should consider neurologist or pharmacologist consultation to plan drugs administration before surgery and in postoperative period.

Anaesthetic procedure

General anaesthesia, especially total intravenous anaesthesia, is the preferred method for a patient with a severe mental alteration. The combination of propofol, opioid, and non-depolarising muscle relaxants was used safely in a patient with ZTTK syndrome. In case of need for muscle relaxation, rocuronium is a preferred relaxant because prolonged neuromuscular blockade can be reversed by sugammadex.

On the contrary, depolarising muscle relaxants or volatile anaesthetics should be avoided for the potential risk of rhabdomyolysis and severe hyperkalemia.

There are no specific contraindications for any type of regional anaesthesia. An anaesthetic team must consider limited cooperation in patients with altered mental status. The usual places for invasive access can be modified due to the changed body proportions, joint contractures, or scoliosis. Ultrasound-guided cannulation can significantly reduce the incidence of invasive access insertion failure.

Particular or additional monitoring

There is a potential risk of prolonged muscle relaxation in patients with general hypotonia. The anaesthetic team should always monitor the depth of neuromuscular blockade.

Invasive haemodynamic monitoring should be considered in high-risk or more extensive surgeries with major fluid shifts and in patients after cardiovascular corrections.

TIVA should be administered according to the depth of anaesthesia monitoring. Standard doses of sedatives can lead to overdosing and wake-up time prolongation after anaesthesia in patients with abnormal habitus. Depth of anaesthesia monitoring is helpful, and it shortens the time of anaesthesia.

Possible complications

Difficult airway management should be expected in patients with facial abnormalities. The anaesthetic team has to be prepared for this life-threatening complication and have alternative plans for airway securing, f. e. awake fibre-optic intubation, or to have prepared kit for invasive techniques for airway securing, such as bougie-assisted cricothyrotomy.

The inspiratory stridor with desaturation after the extubation was described in the literature. This complication was treated standardly.

There is a potential risk of rhabdomyolysis as well as other neuromuscular disorders, especially in long-time surgery with risk of muscle damage. Volatile anaesthetics or depolarising muscle relaxants should be avoided. Stress factors, like pain, should be eliminated. The rhabdomyolysis can be detected postoperatively by plasma creatine kinase and myoglobinuria monitoring.

Post-operative care

Patients suffering from ZTTK syndrome will profit from monitoring in ICUs after the surgery, especially in cases of high-risk or extensive surgery.

Rhabdomyolysis, as a possible postoperative complication, can be diagnosed by clinical examination in combination with the laboratory results.

Disease-related acute problems and effect on anaesthesia and recovery

There is no data about the risk of malignant hyperthermia. There are different gene localization in these two syndromes, so the association between ZTTK syndrome and malignant hyperthermia is unlikely.

Other complications and problems are mentioned above.

Ambulatory anaesthesia

Ambulatory anaesthetic care was not reported. The anaesthetic team should consider the potentially higher risk in ambulatory care settings for these patients.

Obstetrical anaesthesia

Not reported.

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