

Anaesthesia recommendations for patients suffering from

## Cerebrotendinous xanthomatosis

**Disease name:** Cerebrotendinous xanthomatosis

**ICD 10:** E75.5

**Synonyms:** cerebrotendinous xanthomatosis, CTX, cerebral cholesterosis

Cerebrotendinous Xanthomatosis (CTX; OMIM #213700) is a rare lipid storage metabolic disease with autosomal recessive inheritance. It is characterized by deficiency of mitochondrial sterol 27-hydroxylase (CYP27) which is a key enzyme in bile acid biosynthesis. The enzyme converts cholesterol into bile acids hence deficiency results in abnormal deposition of cholesterol and cholestenol in multiple tissues. The defect in CTX is located on CYP27A1 gene localized on the long arm of chromosome 2 [1].

Van Bogaert and colleagues first described CTX in 1937 [2]. It is estimated to occur in 3-5 out of 100,000 individuals worldwide and is more commonly seen in the Moroccan Jewish population with an incidence of 1 in 108 individuals in that group. It is also commoner in the in Druze population in Israel with incidence of 1:440.

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Medicine in progress



Perhaps new knowledge

Every patient is unique

Perhaps the diagnostic is wrong

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Find more information on the disease, its centres of reference and patient organisations on Orphanet: [www.orpha.net](http://www.orpha.net)

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## Disease summary

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See attachment 1

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## Typical surgery

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- Excision of xanthomas
- Bone fracture for open reduction and internal fixation
- Spinal surgery
- Cataracts
- Contracture release
- Cholecystectomy
- MRI scanning

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## Type of anaesthesia

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CTX is a disorder with multi-system involvement. Type of anaesthesia will depend on systems involved, severity of derangement and procedure planned.

General anaesthesia can be induced by intravenous or inhalational route. In the presence of spasticity, paresis and peripheral sensory-motor neuropathy, it may be wise to avoid Succinylcholine. Theoretical probability of extra-synaptic acetylcholine receptors poses risk of hyperkalaemia. Evaluation of patients for ischemic heart disease and autonomic neuropathy is important for the safe induction and maintenance of anaesthesia.

Patients with xanthoma of neck tendons can be difficult to ventilate and intubate [14].

Regional anaesthesia in presence of peripheral neuropathy could have medicolegal implications. Thorough neurological evaluation and documentation is recommended. The presence of autonomic neuropathy is a relative contraindication for a neuraxial block. Achilles tendon xanthoma removal under spinal anaesthesia has been reported [15].

Patients with bulbar palsy may not be able to maintain and protect airway when sedated for procedures like MRI.

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## Necessary additional diagnostic procedures (preoperative)

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Evaluation of neurological system by detailed clinical examination will play a very important role. Depending on the findings during clinical examination electromyography, electroencephalography or tests for autonomic neuropathy may be indicated.

Electrocardiogram, echocardiography and stress test for patients with ischemic heart disease.

In presence of neck xanthoma evaluation of airway with CT scan may be required.

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### **Particular preparation for airway management**

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In presence of neck xanthomas possibility of difficult airway should be kept in mind.

Patients with bulbar palsy are at high risk of aspiration.

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

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None.

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### **Particular preparation for anticoagulation**

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Prolonged coagulation times due to vitamin K deficiency may be present at diagnosis, but resolve after initiation of CDCA treatment. aPTT and PT should be checked at diagnosis and corrected if necessary prior to a surgical intervention.

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

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There is high incidence of osteopenia and osteoporosis in patients with CTX. Chronic treatment with CDCA (Chenodeoxycholic acid) leads to diarrhoea and nutritional impairment. One must take extra precautions during positioning and transport.

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

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There are no described interactions between CDCA and anaesthetic drugs. One must be aware of other drugs the patient may be taking for symptom control.

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### **Anaesthesiologic procedure**

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Literature for anaesthesia in patients with CTX is scarce; hence it is difficult to formulate guidelines.

It would be prudent to avoid Succinylcholine in the presence of neuromuscular involvement. Non-depolarizing muscle relaxants can be used safely. The availability of a specific reversal agent for Rocuronium (Sugammadex) makes this an attractive choice of muscle relaxant.

There is no contraindication to the use of opiates, intravenous, inhalational or local anaesthetic agents.

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### Particular or additional monitoring

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Monitoring of neuromuscular blockade.

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### Possible complications

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- Difficult airway.
- Hyperkalaemia in patients with motor neuropathy or paresis.
- Aspiration risk in patients with bulbar palsy.

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### Postoperative care

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The possibility of aspiration must be considered. In cases with bulbar palsy it is safer to extubate patients fully awake after ensuring full reversal of neuromuscular blockade.

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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 disease*

In the presence of neuromuscular symptoms Rocuronium rather than succinylcholine may be a better choice for rapid sequence induction of general anaesthesia. It would seem sensible to ensure Sugammadex is readily available in case of airway difficulty.

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### Ambulatory anaesthesia

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Regional including neuraxial anaesthesia avoids the airway issues associated with general anaesthesia. The possibility of neurological symptoms especially autonomic neuropathy must be kept in mind.

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### Obstetrical anaesthesia

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There are no specific data or recommendations for this group of patients.

## Literature and internet links

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## **Attachment 1**

### **Disease summary**

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#### **Pathogenesis:**

Deranged lipid metabolism causes huge deposition of cholesterol in tendons, central nervous system, vascular system, lungs, liver and kidney [3]. Cholesterol accumulation in the brain induces apoptosis of neuronal cells resulting in neurodegeneration [4], resulting in a diffuse decrease in total brain volume, principally in cortical grey matter rather than white matter.

#### **Clinical presentation:**

Clinical presentation is variable. A vast spectrum of symptoms includes childhood chronic diarrhoea, bilateral cataract and intellectual disability. In late adolescence and early adulthood it can present as progressive cerebellar ataxia, pyramidal signs, mental retardation, dementia, seizures, premature atherosclerosis and development of tendon xanthomas (particularly in the Achilles tendon).

#### **Eye:**

Up to 75 % of patients present with appearance of cataract during first decade of life [5]. Other ophthalmic findings include palpebral xanthomas, optic nerve atrophy and proptosis [6]. Dotti et al also reported optic disc pallor in about 50%, signs of premature scleral and retinal vessel sclerosis in 30% [7]. Cholesterol-like deposits along myelinated nerve fibres were seen in some patients.

#### **Cardiovascular system:**

Premature atherosclerosis and coronary artery disease have been reported. Lipomatous hypertrophy of the atrial septum has been described.

#### **Bone:**

Granulomatous lesions in the lumbar vertebrae and femur, impaired absorption of calcium, osteopenia with risk of bone fractures may be features. Some patients have marked thoracic kyphosis.

Tendon xanthomas particularly in the Achilles tendon commonly occur in CTX. They have been also described on the extensor tendons of elbow and hand, patellar and neck tendons, lungs, bones and central nervous system [8].

#### **Endocrine:**

Hypothyroidism has occasionally been reported.

#### **Central Nervous System:**

CNS involvement is commonly present in CTX and could be the presenting feature. Mental retardation and dementia develop following a slow deterioration in intellectual abilities in 2nd decade of life: this is seen in over 50% of patients. Some individuals show features of mental retardation from infancy. Rarely cognitive function can be normal. Common among neurologic features are epilepsy and Parkinsonism. The wide range of other neurological

features of CTX include dementia, pyramidal and extra-pyramidal signs, bulbar symptoms, progressive ataxia, pseudobulbar and bulbar symptoms, dystonia and palatal myoclonus.

Peripheral neuropathy, especially the subtype of axonal sensori-motor neuropathy, is common in patients with CTX. Histopathological evidence also suggests mild denervation characteristics in biopsied muscle. With adequate evaluation, a high incidence of autonomic nervous system abnormalities can be seen [9].

Psychiatric manifestation in CTX follows a bimodal/ bitemporal pattern. It can appear early in the disease course in the form of behavior/personality disorder associated with learning difficulties or mental retardation. Alternately it can manifest in advanced disease in the setting of dementia as rich neuropsychiatric syndrome such as frontal, orbitofrontal or frontotemporal syndrome of cortico-subcortical dementia encompassing behavior/ personality disorder, affective / mood disorder or psychotic disorder [10].

### **Gastrointestinal:**

Chronic infantile diarrhoea is a common presenting feature. Gallstones may be seen.

### **Medical investigations**

#### **Laboratory:**

Investigations reveal elevated levels of cholestanol in plasma and CSF, presence of bile alcohols (lathosterol, 7 $\alpha$ -hydroxylated bile acids) and bile alcohol glucuronides in plasma and/or urine [11]. However, plasma cholesterol and lipoprotein levels remain normal or below normal range.

Deficiency of fat soluble vitamins (A/D/E/K) may be present, which may result in prolonged coagulation times and osteopenia. Signs of cholestatic hepatitis (increased transaminases, bilirubin and  $\gamma$ GT) can be present in young children. An increase in transaminases may also be seen after initiation of CDCA therapy (see below), particularly in children, as supplementation of bile acids may induce hepatotoxicity at higher dosages.

#### **Neuroimaging:**

MRI brain shows symmetrical cerebellar white matter lesions.

#### **Neurophysiology:**

Electrophysiological examinations help in detection of peripheral neuropathy.

#### **Pathology:**

Histopathological examination reveals myelin destruction, gliosis and presence of xanthoma cells in brainstem and cerebellum along with occurrence of cholesterol crystals in white matter.

#### **Genetic testing:**

Mutation analysis of CYP27A1 for CTX is also available.

#### **Treatment:**

Treatment with chenodeoxycholic acid (CDCA) corrects the plasma cholestanol levels to nearly normal [12,13], although this may take some time due to the wash-out effect of

cholestanol from peripheral tissues. Early treatment with CDCA has been shown to stabilize the disease or even prevent symptoms when this is started at young age. Blood levels of cholestanol can further be decreased by adding HMG-CoA reductase inhibitors (e.g. statins) which also act as prophylaxis against atherosclerosis [12].

Treatment for end-organ damage is often required e.g. seizures, spasticity and cataracts.