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Bronchopulmonary dysplasia

Cerebrotendinous xanthomatosis

orphan**anesthesia**

a project of the German Society
of Anaesthesiology and Intensive Care Medicine

SUPPLEMENT NR. 11 | 2019

OrphanAnesthesia –

ein krankheitsübergreifendes Projekt des Wissenschaftlichen Arbeitskreises Kinderanästhesie der Deutschen Gesellschaft für Anästhesiologie und Intensivmedizin e.V.

Ziel des Projektes ist die Veröffentlichung von Handlungsempfehlungen zur anästhesiologischen Betreuung von Patienten mit seltenen Erkrankungen. Damit will Orphan Anesthesia einen wichtigen Beitrag zur Erhöhung der Patientensicherheit leisten.

Patienten mit seltenen Erkrankungen benötigen für verschiedene diagnostische oder therapeutische Prozeduren eine anästhesiologische Betreuung, die mit einem erhöhten Risiko für anästhesieassoziierte Komplikationen einhergehen. Weil diese Erkrankungen selten auftreten, können Anästhesisten damit keine Erfahrungen gesammelt haben, so dass für die Planung der Narkose die Einholung weiterer Information unerlässlich ist. Durch vorhandene spezifische Informationen kann die Inzidenz von mit der Narkose assoziierten Komplikationen gesenkt werden. Zur Verfügung stehendes Wissen schafft Sicherheit im Prozess der Patientenversorgung.

Die Handlungsempfehlungen von OrphanAnesthesia sind standardisiert und durchlaufen nach ihrer Erstellung einen Peer-Review-Prozess, an dem ein Anästhesist sowie ein weiterer Krankheitsexperte (z.B. Pädiater oder Neurologe) beteiligt sind. Das Projekt ist international ausgerichtet, so dass die Handlungsempfehlungen grundsätzlich in englischer Sprache veröffentlicht werden.

Ab Heft 5/2014 werden im monatlichen Rhythmus je zwei Handlungsempfehlungen als Supplement der A&I unter www.ai-online.info veröffentlicht. Als Bestandteil der A&I sind die Handlungsempfehlungen damit auch zitierfähig. Sonderdrucke können gegen Entgelt bestellt werden.

OrphanAnesthesia –

a common project of the Scientific Working Group of Paediatric Anaesthesia of the German Society of Anaesthesiology and Intensive Care Medicine

The target of OrphanAnesthesia is the publication of anaesthesia recommendations for patients suffering from rare diseases in order to improve patients' safety. When it comes to the management of patients with rare diseases, there are only sparse evidence-based facts and even far less knowledge in the anaesthetic outcome. OrphanAnesthesia would like to merge this knowledge based on scientific publications and proven experience of specialists making it available for physicians worldwide free of charge.

All OrphanAnesthesia recommendations are standardized and need to pass a peer review process. They are being reviewed by at least one anaesthesiologist and another disease expert (e.g. paediatrician or neurologist) involved in the treatment of this group of patients.

The project OrphanAnesthesia is internationally oriented. Thus all recommendations will be published in English.

Starting with issue 5/2014, we'll publish the OrphanAnesthesia recommendations as a monthly supplement of A&I (Anästhesiologie & Intensivmedizin). Thus they can be accessed and downloaded via www.ai-online.info. As being part of the journal, the recommendations will be quotable. Reprints can be ordered for payment.

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orphan**a**nesthesia

Anaesthesia recommendations for Cerebrotendinous xanthomatosis

Disease name: Cerebrotendinous xanthomatosis

ICD 10: E75.5

Synonyms: cerebrotendinous xanthomatosis, CTX, cerebral cholesterosis

Disease summary: Cerebrotendinous Xanthomatosis (CTX; OMIM #213700) is a rare lipid storage metabolic disease with autosomal recessive inheritance. It is characterised 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 localised 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 Druze population in Israel with incidence of 1:440.

Medicine is in progress



Perhaps new knowledge

Every patient is unique

Perhaps the diagnosis is wrong



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

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Disease summary

Pathogenesis:

Deranged lipid metabolism causes huge deposition of cholestanol in tendons, central nervous system, vascular system, lungs, liver and kidney [3]. Cholestanol 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 on. Rarely, cognitive function can be normal. Among neurologic features, epilepsy and Parkinsonism are common. 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 sensorimotor 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 behaviour/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 behaviour/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 α -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 γ 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 stabilise 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.

Typical surgery

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

Type of anaesthesia

CTX is a disorder with multi-system involvement. The 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 sensorimotor neuropathy, it may be wise to avoid Succinylcholine. Theoretical probability of extra-synaptic acetylcholine receptors poses risk of hyperkalaemia. The evaluation of patients for ischaemic 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.

Necessary additional pre-operative testing (beside standard care)

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 ischaemic heart disease.

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

Particular preparation for airway management

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

Patients with bulbar palsy are at high risk of aspiration.

Particular preparation for transfusion or administration of blood products

None.

Particular preparation for anticoagulation

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

Particular precautions for positioning, transportation and mobilisation

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.

Interactions of chronic disease and anaesthesia medications

No interactions between CDCA and anaesthetic drugs have been described. One must be aware of other drugs the patient may be taking for symptom control.

Anaesthetic procedure

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-depolarising 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.

Particular or additional monitoring

Monitoring of neuromuscular blockade.

Possible complications

Difficult airway.

Hyperkalaemia in patients with motor neuropathy or paresis.

Aspiration risk in patients with bulbar palsy.

Post-operative care

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.

Disease-related acute problems and effect on anaesthesia and recovery

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.

Ambulatory anaesthesia

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.

Obstetrical anaesthesia

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

References

1. Cali JJ, Hsieh CL, Francke U, Russell DW. Mutations in the bile acid biosynthetic enzyme sterol 27-hydroxylase underlie cerebrotendinous xanthomatosis. *J Biol Chem* 1991; 266:7779–7783
2. Van Bogaert L, Scherer H, Epstein E. Une Forme Cerebrale de la Cholesterinose Generalisee. Paris: Masson et Cie 1937
3. Bhattacharya AK, Lin DS, Connor WE. Cholesterol metabolism in patients with cerebrotendinous xanthomatosis: absorption, turnover and tissue deposition. *J Lipid Res* 2007;48:185–192
4. Inoue K, Kubota S, Seyama Y. Cholesterol induces apoptosis of cerebellar neuronal cells. *Biochem Biophys Res Commun* 1999;256:198–203
5. Cruysberg JR. Cerebrotendinous xanthomatosis: Juvenile cataract and chronic diarrhoea before the onset of neurological disease. *Arch Neurol* 2002;59:1975
6. Morgan SJ, McKenna P, Bosanquet RC. Case of cerebrotendinous xanthomatosis. I: Unusual ophthalmic features. *Br J Ophthalmol* 1989;73:1011–1014
7. Dotti MT, Rufa A, Federico A. Cerebrotendinous xanthomatosis: heterogeneity of clinical phenotype with evidence of previously undescribed ophthalmological findings. *J Inher Metab Dis* 2001;24:696–706
8. Cruysberg JR, Wevers RA, Van Encel BG, Pinkers A, Van Spreek A, Tolboom JJ. Ocular and systemic manifestations of cerebrotendinous xanthomatosis. *Am J Ophthalmol* 1995;120:597–604
9. Chen SF, et al. Neuromuscular abnormality and autonomic dysfunction in patients with cerebrotendinous xanthomatosis. *BMC Neurol* 2011;11:63
10. Fraidakis MJ. Psychiatric manifestations in cerebrotendinous xanthomatosis. *Transl Psychiatry* 2013;3:e302. DOI:10.1038/tp.2013.76
11. Menkes JH, Schimschock JR, Swanson PD. Cerebrotendinous xanthomatosis. The storage of cholesterol within the nervous system. *Arch Neurol* 1968;19:47–53
12. Salen G, Meriwether TW, Nicolau G. Chenodeoxycholic acid inhibits increased cholesterol and cholesterol synthesis in patients with cerebrotendinous xanthomatosis. *Biochem Med* 1975;14:57–74
13. Berginer VM, Salen G, Shefer S. Long-term treatment of cerebrotendinous xanthomatosis with chenodeoxycholic acid. *N Engl J Med* 1984;311:1649–1652
14. Habaragamuwa BW, Bajekal R. Cerebrotendinous xanthomatosis and anaesthesia. *Br J Anaesth* 2010;105:237–238
15. Kumar MK, Malve Gowda NR, Naveen N, Dhanraj P, Babu KR. A Case of Bilateral Achilles Tendon Xanthomas in Cerebrotendinous Xanthomatosis: Medically Unresponsive Treated by Surgical Excision and Reconstruction. *Int J Sci Stud* 2014;2:217–221.

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