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Scimitar syndrome

Sotos syndrome

orphanaesthesia

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

SUPPLEMENT NR. 13 | 2022

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.

Bisher in A&I publizierte Handlungsempfehlungen finden Sie unter:

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OrphanAnesthesia –

a 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 recommenations 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.

Find a survey of the recommendations published until now on:

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Anaesthesia recommendations for

Sotos syndrome

Disease name: Sotos syndrome

ICD 10: Q87.3

Synonyms: Cerebral gigantism syndrome, Malan syndrome (Sotos syndrome 2)

Disease summary: Sotos syndrome is characterised by the presence of excessive growth during childhood, advanced bone age, macrocephaly, characteristic facial appearance and non-progressive learning difficulties [1]. It affects males and females in equal numbers. Its incidence is one in 14,000 live births. It was first described in 1964 by Dr. J.F. Sotos [2].

Until the early 2000s, diagnosis of Sotos syndrome was based upon the presence of characteristic clinical features as listed above [3]. It was subsequently discovered that mutations and deletions of the NSD1 (nuclear receptor-binding SET domain) gene – localised on chromosome 5q35.3, which codes for a histone methyltransferase implicated in transcriptional regulation – is responsible for more than 75 % of cases of Sotos syndrome [4]. In Europe and the USA, NSD1 mutations cause 60–80 % of cases of Sotos syndrome, whereby microdeletions of NSD1 cause approximately 10 % of cases. In contrast: in Japan, NSD1 microdeletions are the primary cause of Sotos syndrome in over 50 % of cases [4].

The function of the NSD1 gene has not yet been fully described. The gene codes for a histone methyltransferase, which acts as a transcriptional intermediary factor capable of both negatively and positively influencing transcription. NSD1 has been described as a "corepressor of genes that promote growth" [5]. While it remains unclear exactly how the malfunction of NSD1 leads to the features of Sotos syndrome, it is thought that mutations and microdeletions involving NSD1 disrupts the activity of genes involved in normal growth and development [4]. While over 95 % of cases are sporadic in aetiology, autosomal dominant inheritance has also been described in several cases [4].

As other genetic abnormalities were identified in patients with Sotos syndrome, patients with abnormalities of the NSD1 gene were later termed 'Sotos syndrome 1'. Heterozygous mutations in the NFIX (nuclear factor I, X type) on chromosome 19p13.3 were identified in a cohort of children with the Sotos syndrome phenotype. They were labelled 'Sotos syndrome 2' [6]. Furthermore, in 2015, a loss-of-function, frameshift mutation in the APC2 (adenomatous polyposis coli 2) gene was identified in two siblings with features of Sotos syndrome but without NSD1 mutations [7]. They exhibited intellectual disability, abnormal brain structure and typical facial features but no other features such as bone or heart abnormalities. The APC2 gene is a downstream regulator of the NSD1 gene and its expression is downregulated by abnormalities of the NSD1 gene, potentially explaining the resulting neurological manifestations [7]. This genotype-phenotype combination is now known as 'Sotos syndrome 3'.

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In Sotos syndrome, childhood growth is particularly advanced in the first year of life, after which it stabilises, before normalising in puberty. Height measurements are consistently above the 97th percentile in years 2–6, while final height is usually in the high normal range [4].

Craniofacial features are distinctive. The forehead tends to be overly prominent in infancy, while in adolescences an elongated face with a prominent chin is seen. Hypertelorism and down slanting palpebral fissures are common, as are receding hairline, prominent jaw, high arched palate, anteverted nostrils and long ears. Occipitofrontal circumference remains between the 98th and 99.6th percentile throughout life [8].

Most patients have a non-progressive neurological dysfunction, although the degree of learning disability appears to be extremely variable. Delay in motor development and expressive language is common [4].

Other manifestations of Sotos syndrome are variable. Delayed attainment of milestones of development is to be expected. Developmental delay is present in 80–85 % of the patients, for example excessive drooling; central nervous system abnormalities: enlarged ventricles, increased subarachnoid spaces that may require treatment, agenesis or hypoplasia of the corpus callosum, agenesis of the septum pellucidum, hypoplasia and atrophy of the cerebellar vermis, large cisterna magna and abnormalities of the Sylvian fissure. Among musculoskeletal abnormalities, hypotonia is the most frequent (84 %), pectus excavatum or carinatum has also been reported. Ophthalmologic manifestations are frequent: strabismus, nystagmus, retinal and optic nerve anomalies [9]. Hypothyroidism, hyperthyroidism, hypoparathyroidism and thyrotoxicosis has been reported [9,10]. There is an increased incidence of different tumours at a young age [9,11], non-progressive hypotonia [12]. About 14 % of patients present with auditory-related conditions [10] such as hearing loss, EMO, recurrent ear infections, cholesteatoma, and degenerative changes of the eardrum. About 24 % of individuals have congenital malformations or abnormalities of the head and neck [10], including high arched palate, auricular dysplasia, macroglossia, cleft lip and palate, and alveolar cleft. Feeding difficulties have also been reported [10]. It can be due to the hypotonia that may result in weakness in the muscles of swallowing and subsequent feeding difficulties or the associated congenital malformations of the head and neck. About 16 % of individuals were reported to have other conditions, including speech disorder, respiratory difficulties, laryngomalacia, severe OSA, gastroesophageal reflux disease, and parotitis [109].

Scoliosis and kyphoscoliosis are present in approximately 30 % of patients. Early detection of scoliosis is important to facilitate early intervention with back braces and/or surgery [8]. There is no reported or published data on pulmonary function capacity with the subset of patients with scoliosis compared to Sotos syndrome patients without scoliosis. Congenitally dislocated hips, genu vara/valga and propensity to fractures with minimal trauma have been described [8]. Childhood seizures are common in 50 %, frequently febrile in nature [4]. Behaviour abnormalities include social inhibition and attention deficit [13]. An increased occurrence of congenital heart disease is seen, the most common defects being patent ductus arteriosus and septal defects [8]. Renal anomalies (bifid, duplex, cystic or absent kidneys; vesicoureteral reflux; pelviureteric junction obstruction) and genital anomalies (hypospadias; cryptorchidism) are present in 15 % of children with NSD1 abnormalities [14]. Recurrent upper respiration tract infections and otitis media are also common, and constipation also often requires treatment [4].

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Typical surgery

Cardiac, neuro, ENT and urogenital surgery.

Nissen fundoplication with/without gastrostomy.

Type of anaesthesia

There are no definite recommendations regarding either general anaesthesia or regional anaesthesia for patients with Sotos syndrome.

The vast majority of published cases describes the use of general anaesthesia for procedures for Sotos syndrome patients. Regional anaesthesia is reported in Sotos syndrome. Neurostimulator and ultrasound guidance should be used to reduce the risk of complications. Most of the children with Sotos syndrome are uncooperative and possibly aggressive, so regional anaesthesia should be performed after GA induction [11]. One case report of regional anaesthesia has been published in a patient diagnosed with Sotos syndrome and sustaining mild hypotonia. No complications were observed [15].

Necessary additional preoperative testing (beside standard care)

A detailed preoperative assessment and an understanding of the comorbidities of patients with Sotos syndrome is essential for the anaesthetic management. Patients with Sotos syndrome exhibit a high incidence of heart defects and genitourinary abnormalities, so detailed assessment for cardiac and renal disease should be performed preoperatively.

Echocardiogram should be performed to assess for congenital heart defects, the most common being septal defects and patent ductus arteriosus. Renal ultrasound should also be considered if renal function is decreased.

Haematological investigations should include full blood count, urea, creatinine, electrolytes and coagulation profile.

Kyphoscoliosis may cause restrictive lung disease and require preoperative respiratory testing [11].

History of seizures should be documented, together with the anticonvulsive drugs and the possible interactions with the anaesthetic drugs.

Anaesthetic procedure

- Consider the option of an inhalation induction and intravenous catheter placement when the patient is already unconscious.
- Oral sedative premedication can be considered but should be individualised depending on patient conditions such as hypotonia, OSA, or respiratory difficulties.
- Drugs decreasing the seizure threshold should be avoided, even if there is no history of seizure disorder; many children with Sotos syndrome have EEG abnormalities without clinical seizures [11].

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- For general anaesthesia, parental presence during induction has been described as invaluable in achieving sufficient patient co-operation [16]. Tolerance of needles is variable, so oral sedative premedication can be considered [17].
- Despite the presence of craniofacial abnormalities including high arched palate, pointed chin and abnormally erupted teeth, endotracheal intubation has been performed without difficulty [16,18,19]. There are no documented cases of difficult intubation in the literature to date.
- Concern has been expressed regarding the use of muscle relaxants in patients with Sotos syndrome due to hypotonia. Muscle relaxants have been used in cases of Sotos syndrome without complications: succinylcholine, atracurium and vecuronium. It has been surmised that patients with Sotos syndrome do not have any significant aberrant clinical pharmacologic effects with the use of muscle relaxants [16,17,18]. Furthermore, the recovery trend of TOF post muscle relaxant administration appears to have been normal in the data to date [16].

Particular preparation for airway management

As detailed above, despite airway management concerns due to the craniofacial abnormalities associated with Sotos syndrome, the intubation in each case detailed in the literature to date has been straightforward [16,18,19]. Care should be taken, however, all the more so as a comprehensive airway assessment including Mallampati score is often not possible due to poor co-operation [16].

Of note: it has been reported that a depth of insertion of the orotracheal tube needs to be 3 cm deeper than that obtained through the standard formula (12 + age/2).

A previous case report had also demonstrated deeper endotracheal tube insertion in a child with Sotos syndrome. However, the tracheal tube sizes are appropriate for age, as predicted by usual formulae [11,12].

Macroglossia has been described [10].

Particular preparation for transfusion or administration of blood products

No particular concerns have been described.

Particular preparation for anticoagulation

No particular concerns have been described, but drug dosing should be adjusted if significant renal impairment is present.

Particular precautions for positioning, transportation and mobilisation

Extra care should be taken in positioning due to the above average height of these patients and laxity of joins. Head positioning may be difficult due to large occiput size [3]. These patients are prone to have fractures with minimal trauma.

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Interactions of chronic disease and anaesthesia medications

Anaesthetic agents which depend on renal excretion should be used with caution if renal impairment is present.

It may be better to choose anaesthetic agents that increase the seizure threshold due to the high prevalence of seizures in Sotos syndrome [16].

Seizures in Soto syndrome should be managed with standard protocols for anti-seizure medication. In drug resistant seizures, ketogenic diet and vagal nerve stimulator could also be considered [16].

Particular or additional monitoring

No definitive guidelines are available. The presence of cardiovascular, renal and cerebrovascular disease often associated with Sotos syndrome should guide the need for invasive monitoring with arterial and central venous pressures on a case by case basis.

Possible complications

None of note documented to date.

Post-operative care

Post-operative care should depend on the type of surgery and the clinical situation of the patient post-operatively. Presence of a parent/guardian during the post-operative period has been shown to greatly increase co-operation of patients [16].

Monitor the appearance of possible episodes of respiratory failure. Severe OSA has been described [10].

Disease-related acute problems and effect on anaesthesia and recovery

No acute or emergency situations have arisen from the documented cases of anaesthesia for patients with Sotos syndrome to date.

Ambulatory anaesthesia

Day case anaesthesia has not been described. Due to likelihood of distress caused by unfamiliar surroundings during an inpatient stay, it is reasonable to consider ambulatory anaesthesia when possible for small procedures.

Obstetrical anaesthesia

There are cases of patients with Sotos syndrome giving birth, but no cases describing their obstetrical anaesthesia management have been described to date. There are no known case reports of the use of regional anaesthesia in Sotos syndrome. There is no known contra-indication; however, the presence of scoliosis and cognitive impairment could make consent and performing neuroaxial anaesthesia difficult.

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