Anaesthesia and familial dysautonomia with congenital insensitivity to pain

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Synopsis of the patient: A six year old boy presented for cosmetic surgery to his nose, which had been fractured some months previously. The trauma had resulted in some deviation of the nasal septum and ugly scarring on the bridge of his nose. Mother explained that he was accident prone and very emotionally labile. Significantly he had developed a compartment syndrome following a tibial fracture at 4 years of age. The fracture went unnoticed initially because he continued to run around unperturbed. His mother was somewhat aggressive and distrustful of the medical fraternity as she had been suspected of child abuse in the past.

On examination he was a hyperactive young man with a short attention span. He was small for his age and had bruising of different stages on his legs, arms and body. There was an obvious deformity of his nose, deviation of his septum and scarring over his nasal bridge. His skin was mottled, dry and pale. The haemoglobin was 9g/dl.

No premedication was given. Anaesthesia consisted of halothane 0.5% in nitrous oxide: oxygen 60:40. The skin in the area of the scar was infiltrated with 2% lignocaine and 1:200000 adrenaline by the surgeon. In addition to the standard monitors, a BIS monitor was used. No additional analgesia was given. The BIS (bispectral index) score remained below 50 throughout, despite refracturing the nose under light anaesthesia. He was comfortable in recovery.

Background

Familial dysautonomia (FD), which was first described in 1959, is also known as Riley-Day syndrome (named after an early 20th century American paediatrician and physician) or HSAN - hereditary sensory and autonomic neuropathies and has only been described in children of Ashkanazi Jews. (see footnote)

It is a rare neuro-developmental genetic disorder that is transmitted via an autosomal recessive gene. The disease affects the central nervous system and is characterised by pathological deficits in peripheral autonomic and sensory neurones (decreased unmyelinated and small-fibre neurons). Progressive multiorgan dysfunction occurs secondary to this demyelination in the brainstem and posterior columns of the spinal cord as well as degeneration of the autonomic ganglia.

Familial dysautonomia is classified within a broad group of hereditary sensory and autonomic neuropathies, each caused by a different genetic error.[1] Recent studies have shown that two mutations in the gene IKBKAP on the long arm of chromosome 9 are responsible for the disease. IKAP, the IKBKAP-encoded protein, is a member of the recently identified human Elongator complex.[1,2] The genetic error probably affects development, as well as maintenance of neurons, because there is neuropathological and clinical progression.[1]

Inherited autonomic neuropathies are a rare group of disorders associated with sensory dysfunction. As a group they are termed the "hereditary sensory and autonomic neuropathies" (HSAN). Classification of the various autonomic and sensory disorders is ongoing.[3] Phenotypic expression varies and overlap between different entities makes the classification difficult. In recent years, identification of specific genetic mutations for some disorders has aided both the diagnosis and classification. The best known and most intensively studied of the HSANs are familial dysautonomia (Riley-Day syndrome or HSAN type III) and congenital insensitivity to pain with anhidrosis (HSAN type IV) Diagnosis of the HSANs depends primarily on clinical examinations and specific sensory and autonomic assessments.[3]

Clinical features

Clinical features, which begin in early childhood, reflect widespread involvement of sensory and autonomic neurons. Sensory loss includes poor perception of pain and temperature. The sensory impairment affects peripheral sensation but not visceral or peritoneal sensation. Autonomic features include dysphagia, vomiting crises, blood pressure lability with hypertension and profound sweating, postural hypotension, and excessive vagal reflexes. Central dysfunction includes emotional lability and poor motor co-ordination and ataxia. Intelligence is normal although they may behave immaturely. Speech may also be delayed.[1-3]

Cardiovascular problems: These are related to both sympathetic and parasympathetic instability. Profound fluctuations in vasomotor response and blood pressure have been described, particularly under anaesthesia.[4,5] Despite the impaired peripheral pain perception, appropriate pain management is essential. Epidural analgesia, previously considered a contraindication, has been shown to prevent the paroxysmal hypertension and exaggerated vasovagal responses.[4]

Respiratory problems: Affected individuals are prone to recurrent respiratory infections that may lead to chronic lung disease or bronchiectasis. The causes are multifactorial. Initially, recurrent aspiration plays a major role and many present for anti-reflux procedures (Nissen fundoplication). Hypotonia and kyphoscoliosis are compounding factors that develop as the disease progresses. These children therefore run a significant risk of developing postoperative respiratory complications.[5,6]

Orthopaedic problems: Spinal deformity is a common orthopaedic problem which begins at approximately four years of age, with a prevalence of 86 percent (forty-eight of fifty-six) by the age of fifteen years.[7,8]

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Patients with FD have a higher prevalence of fractures and one or more neuropathic joints than do their peers. The neuropathic joints are secondary to the peripheral sensory neuropathy. The fracture pattern also is different, with a higher incidence of proximal femoral fractures.[7]

Anaesthetic considerations

Children with this condition present for a variety of dental, endoscopic, orthopaedic and ophthalmic surgical procedures.[7-9] Despite the apparent insensitivity to pain it is essential to provide adequate anaesthesia to reduce the surgical stress and the "dysautonomic" events. These patients are known to have an increased sensitivity to endogenous or exogenous catecholamines.[4]

A variety of anaesthetic techniques have been described with varying degrees of success. Morbidity is high.[5,6] In a recent publication, Challands found that epidural anaesthesia contributed to the cardiovascular and autonomic stability of three children who required a revision of their anti-reflux procedure. Furthermore the postoperative pain management was substantially better and respiratory complications fewer. These children had previously received an opiate-based general anaesthetic for the initial surgical procedures that were remarkable for their haemodynamic instability, poor pain control and respiratory complications.[4]

Premedication should be considered against a background of the emotional lability that may be precipitated by the surgical procedure, the cardiovascular lability and the risk of respiratory depression. These children may have a blunted response to hypoxia and hypercarbia and are thus sensitive to opiates.

Careful management of hydration is necessary. Patients may become dehydrated secondary to swallowing difficulties, excessive sweating and episodes of diarrhoea and vomiting (the latter being GIT manifestations of autonomic instability). Prolonged preoperative starvation may compound the problem. These children may not respond to hypovolaemia appropriately and the haemodynamic lability may add to the confusion. Cardiac arrest has been described in response to profound hypotensive episodes and dysautonomic crises.[4]

Respiratory support and pulmonary protection is an essential part of the perioperative management. A multimodal approach should include a proper preoperative assessment, perioperative physiotherapy, antibiotics and the judicious use of opiate analgesia. Epidural analgesia is ideal but may be difficult in the presence of kyphoscoliosis. Intraoperative ventilatory support is mandated even for minor procedures.

Affected children have an impaired gag reflex, impaired oesophageal motility, gastric distension and are prone to reflux. All the necessary precautions should be instituted on induction, extubation and postoperatively to prevent aspiration. There are no specific contraindications to muscle relaxants including suxamethonium. Reduced doses should be considered in those children who are hypotonic.

Eye protection is important since affected individuals lack tears, have absent corneal reflexes and are thus prone to corneal injuries[9] irrespective of whether they are under anaesthesia or not. Temperature regulation is also impaired. Both hypo and hyperthermia have been reported.[4] Temperature must be monitored and controlled as far as possible.

Deep sedation with midazolam and propofol has been used successfully for endoscopic procedures. However all the problems previously mentioned may occur and monitoring is therefore essential.[10]

Postoperative complications centre mainly around the autonomic lability and respiratory dysfunction. Persistent vomiting, orthostatic hypotension, paroxysmal hypertension and hyperthermia may need to be addressed. Respiratory problems include aspiration, hypoventilation or hypoxemia, and are a cause for concern. Diazepam has been used for management of the dysautonomic crises and is considered the drug of choice.

Conclusion

These children are unusual anaesthetic challenges. Intuitively one would consider that analgesia would not be necessary. Although light general anaesthesia may prove adequate in some situations, inadequate anaesthesia may have severe repercussions. The emotional lability must be understood. Affected children, and their parents, should be treated with understanding and the same compassion as any other child.

Footnote[11]

The word Ashkenazi is derived from the Hebrew word for "Germany," in particular to the area along the Rhine where the allemani tribe once lived. Ashkenazi is used to refer to Jews who have ancestors from Eastern and Central Europe, such as Germany, Poland, Lithuania, Ukraine, and Russia. Today, there are Ashkenazi Jews all over the world and many are marrying outside of the Jewish community. However, for centuries political and religious factors ensured their genetic isolation from the population at large

In the aftermath of World War II and the Holocaust, most of the world's 10 million Ashkenazi Jews live in the U.S., Israel, South America, South Africa, Australia, and New Zealand. About 80 percent of the six million ethnic Jews in the U.S. are of Ashkenazi Jewish descent.

People of Ashkenazi Jewish descent have a higher incidence of a number of mutations for specific diseases. Examples include mutations in the genes that increase the risk of developing breast and ovarian cancer as well as mutations that cause the childhood neurological disorders Tay-Sachs disease and Gaucher disease. Other hereditary diseases include cystic fibrosis, Crohn's disease, Fanconi's anaemia, Niemann Pick disease, Mucolipidosis IV, Haemophilia C and congenital adrenal hyperplasia.

References

1. Axelrod FB Familial dysautonomia. Muscle Nerve. 2004;29(3):352-63.
2. Slaugenhaupt SA, Gusella JF. Familial dysautonomia. Curr Opin Genet Dev. 2002;12(3):307-11.
3. Axelrod FB, Hilz MJ Inherited autonomic neuropathies. Semin Neurol. 2003;23(4):381-90.
4. Challands JF, Facer EK Epidural anaesthesia and familial dysautonomia (the Riley Day syndrome). Three case reports. Paediatr Anaesth. 1998;8(1):83-8.
5. Stubbig K, Schmidt H, Schreckenberger R, Bohrer H, Motsch J. Anesthesia and intensive therapy in autonomic dysfunction. Anaesthesist. 1993; 42(5):316-9.
6. Dell'oste C, Vincenti E, Torre G. Multiple and various anaesthetics, ketamine included, in a young patient with familial dysautonomia, Case report. Minerva Pediatr. 1996; 48(3):113-6.
7. Laplaza FJ, Turajane T, Axelrod FB, Burke SW. Non spinal orthopaedic problems in familial dysautonomia (Riley-Day syndrome). J Pediatr Orthop. 2001;21(2):229-32.
8. Bar-On E, Floman Y, Sagiv S, Katz K, Pollak RD, Maayan C Orthopaedic manifestations of familial dysautonomia. A review of one hundred and thirty-six patients. J Bone Joint Surg Am. 2000; 82-A(11):1563-70.
9. Francois J. The Riley-Day syndrome. Familial dysautonomy, central autonomic dysfunction. Ophthalmologica. 1977; 174(1):20-34
10. Wengrower D, Gozal D, Goldin E.Familial dysautonomia: deep sedation and management in endoscopic procedures. Am J Gastroenterol. 2002; 97(10): 2485-6.
11. www.dnadirect.com/resource/ genetics_101/GH_Ashkenazi.jsp.