

Anaesthesia recommendations for patients suffering from

Familial Dysautonomia

Disease name: Familial Dysautonomia

ICD 10: G90.1

Synonyms: Riley-Day syndrome, Hereditary Sensory and Autonomic Neuropathy Type III, HSAN III, HSAN3, HSN-III

Disease summary:

Familial Dysautonomia (FD) is a rare autosomal recessive genetic disorder, predominantly affecting the Ashkenazi Jewish population with the incidence of 1:3703 in this population and a carrier state of 1:32. It is characterised by sensory and autonomic neuropathy, and it is one of a group (Type 3) of clinically heterogeneous and genetically distinct disorders known as Hereditary Sensory and Autonomic Neuropathies (HSAN).

Also referred to as Riley-Day syndrome, the condition was first described in 1949 by the American paediatricians Conrad Milton Riley and Richard Lawrence Day. The incidence of FD in more than 600 patients has since been identified. Of these patients, 30% reside in the New York area, and 30% reside in Israel, with the remainder distributed internationally.

FD is an autosomal recessive disorder, and is the result of mutations in the IKBKAP gene on chromosome 9, which encodes for the IKAP protein. So far there have been 3 mutations identified, but the most common, which is present on more than 99.5% of all FD chromosomes, is a single T to C change at base pair 6 of intron 20.

Although penetrance is complete, there is marked variability in clinical expression of the disease. Signs of the disorder are usually apparent at birth, with the early signs presenting in neonates as hypotonia, swallowing difficulties, pallor, and failure to respond to nociceptive stimuli. Dyscoordination at the nasopharynx and gastroesophageal reflux lead to recurrent aspiration and pneumonia, resulting in chronic lung disease. There is also failure to thrive and delayed developmental milestones, labile blood pressure and body temperature, absence of overflowing tears, corneal anaesthesia, spinal curvature, and fractures. Later in life the patients develop renal insufficiency.

Clinical problems include familial dysautonomia crises. This manifests as intractable nausea and vomiting, high blood pressure, tachycardia, sweating, skin blotching (erythematous skin marks), agitated behaviour and ileus. These crises may be induced by any stress either emotional or physical (illness, menstrual period etc.). During a Dysautonomic crisis, norepinephrine and dopamine levels are increased, with a concomitant but smaller increase in epinephrine.

Pathology studies have shown a marked reduction in non-myelinated neuronal populations as well as a reduction in small diameter myelinated axons.

FD leads to progressive neuronal degeneration, with a survival rate of 50% at 40 years of age. Most commonly, death results from pulmonary complications and cardiovascular complications arising from autonomic instability.

Medicine in progress



Perhaps new knowledge

Every patient is unique

Perhaps the diagnostic is wrong



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

Typical surgery

Fundoplication, gastrostomy, jejunostomy, spinal fusion, fractures, joint replacement, tonsillectomy, adenoidectomy, herniorrhaphy, thoracotomy, pacemaker insertion, ophthalmic procedures such as tear duct closure and tarsoraphy (usually temporary), bronchoscopy, endoscopy, dental extraction, renal transplant and caesarean section.

Type of anaesthesia

Techniques include general anaesthesia, regional anaesthesia (a good technique for intra-operative and post-operative pain control), and sedation.

FD anaesthesia/sedation is high risk, as the cardiovascular system can be very unstable and the autonomic nervous system can react to the anaesthesia/sedation drugs unexpectedly. It should be carried out by a senior expert in this field who is familiar with this disease and its problems.

Choice of technique will depend upon:

1. The existence of pulmonary complications and their severity.
2. The presence of scoliosis – this may be a factor when considering neuroaxial blockade, as this is present in 90% of FD patients
3. Cardiovascular instability

4. The patient personality

5. Patient age

Necessary additional diagnostic procedures (preoperative)

Glucose, electrolytes, liver, pancreatic and renal function should be checked, due to the increased incidence of impaired renal function (glomerulosclerosis) in FD patients. In ambulatory dysautonomic patients, 32% have elevated serum creatinine and in older ages even more. Excessive vomiting and sweating, which can occur with crises, can lead to electrolyte imbalances. Metabolic seizures due to hyponatremia have also been observed. This is when fluid and salt intake have failed to compensate for losses, or when in crisis. Elevated diastase is common and may reflect gall bladder stones or sludging.

FBC, clotting screen, blood group, and CRP are needed for base line.

A preoperative ECG is needed, and anaesthetic precautions should be taken for possible QT prolongation, along with hypo- and hypertension. If a pacemaker has been placed for bradycardia or AV block, this will need to be checked.

Echocardiogram is required, as both chronic, and restrictive lung disease secondary to scoliosis, may result in pulmonary hypertension. FD patients have a diminished response to CO₂, therefore it is difficult for them to lower their increased CO₂ level. Cardiac remodelling or hypertrophy is also common in FD, which will be evident, particularly if hypertension is poorly controlled.

Many FD patients suffer from lung disease, due to recurrent aspiration pneumonia therefore chest X ray and arterial blood gases are needed.

Preoperative pulmonary function tests (PFT) are **not** recommended as FD patients do not have good coordination and therefore the results are usually not reliable.

Chest physiotherapy may be required to clean the lung as well as to strengthen respiratory muscles before and after surgery.

Sputum cultures are recommended.

Particular preparation for airway management

Rapid sequence induction has also been recommended in the literature, but this may not necessarily be required in practice.

FD is associated with decreased sagittal motion in the cervical spine. This **might** appear to translate to difficulty with airway management.

Particular preparation for preoperative drugs and fluids

FD patients commonly have gastroesophageal reflux disease, and a Nissen fundoplication and gastrostomy early in life helps reduce symptoms and complications. However, if the reflux has not been treated then a preoperative H₂-antagonist or proton pump inhibitor is

indicated. These medications should be continued for at least a month after the operation due to stress.

Extra IV fluids (30% more than maintenance) **should be given** 8-12 hours before the operation/procedure. The gastrostomy stoma (if present) should be **open** for 8-12 hours **before and during** the operation.

Particular preparation for transfusion or administration of blood products

If preoperative baseline haemoglobin is lower than 10 g/dl and particularly if there is going to be a major operation e.g. spinal fusion or gastrostomy and fundoplication, then packed red cell transfusion is recommended.

Particular preparation for anticoagulation

This will be as required, as a few patients have haematological problems or gastric bleeding.

Many FD patients are now taking Tocotrienol (Vitamin E like supplement) as it was shown to increase the IKAP FD protein. However, this supplement can decrease coagulation, and therefore patients should stop taking this **a week** before the operation.

Particular precautions for positioning, transport or mobilisation

Transport should be with running IV fluid in situ and with oxygen by nasal cannulae (if the patient requires this for any of the following reasons: existing lung disease, pre-operative sedation administered for anxiety, possible crisis before the operation due to stress). Oxygen supplementation before, and especially after the operation, should be given by nasal cannulae to avoid dryness of the eyes caused by the oxygen flow through a mask.

Particular attention should be paid to protecting the eyes during anaesthesia. FD patients have dry conjunctivae, absent corneal reflexes and are prone to corneal ulcers and perforations. Therefore it is very important to lubricate the eyes before and during the operation with effective artificial eye drops (not only saline eye drops) and secure the eyelids closed.

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

FD patients may be taking Glycopyrrolate, gastric antacid drugs, anticonvulsive and antihypertensive or hypertensive agents.

The most important point to remember regarding drugs, is that FD patients demonstrate an exaggerated response to exogenous adrenergic and cholinergic agents, particularly Noradrenaline, and so this, and related agents should be avoided. If required, they should be given in lower doses with caution. Dopamine/Dobutamine can be used with cardiac instability. Ipratropium bromide inhalation should be **avoided**.

Anaesthesiologic procedure

Eight hours preoperative fasting is recommended and IV fluids should be given during that period. Hypovolemic hypotension at the time of induction of anaesthesia is a major concern, and used to be a significant contributor to perioperative mortality. Preoperative IV over hydration with Hartmann's or Normal Saline is mandatory, and leads to increased haemodynamic stability during surgery. One to 1.5 litres, according to weight, is recommended during that preoperative 8 hours.

Anxiolysis is particularly important, as emotional stress may trigger a crisis, therefore Midazolam 0.5mg/kg orally preoperatively should be considered. If given IV in the anaesthetic room, then oxygen must be administered, and it should be given slowly, as hypotension and apnoea can occur.

Induction may be intravenous, or inhalational using Sevoflurane. Propofol, Ketamine, Dexmedetomidine, and muscle relaxants have all been used safely. Thiopentone has been associated with hypotension, and should be used with caution.

Anaesthesia can be maintained with inhalational agents and Fentanyl. Remifentanyl and TCI Propofol have also been used. Anaesthetic agents should be titrated to effect.

Although peripheral pain perception is reduced in FD patients, they have intact visceral and peritoneal pain perception. Therefore pain control, especially postoperatively, is important as crises can be induced by pain and stress.

At the end of the procedure, spontaneous breathing may be delayed due to chemoreceptor dysfunction, and initial respiratory efforts are weak. Therefore it is important to reverse neuromuscular blockade and continue support. If pulmonary disease is present, or if the procedure is complicated, postoperative ventilation may be required.

Particular or additional monitoring

The placement of an arterial line is recommended for long procedures for all FD patients.

CVP monitoring should be used for procedures where large volume shifts are expected.

There are case reports where BIS has been used, and this has been shown to reduce the amount of anaesthetic required.

Possible complications

Hypotension is a common complication in the setting of autonomic insufficiency. Major causes include: hypovolemia, bradycardia, hypoxemia, and/or hypercapnia. A fluid bolus is preferable to vasopressors in the first instance, but Fludrocortisone may need to be administered. One should remember that there is no compensatory tachycardia in FD patients when blood pressure drops.

Hypertension should be treated with deepening anaesthesia, and ensuring adequate

analgesia is administered. The management of a dysautonomic crisis is detailed below.

Postoperative care

The level of post-operative care required will depend on the severity of disease and the procedure performed. However, focus should be on maintaining good hydration and cardiovascular stability. This includes management of a dysautonomic crisis, which is why good pain control is vital, as it may help to prevent such a crisis occurring.

FD patients with restrictive lung disease because of kyphoscoliosis, and obstructive lung disease because of recurrent pneumonia, will require post-operative chest physiotherapy, especially for abdominal procedures. Periods of apnoea also tend to be longer than in normal patients and are associated with severe oxygen desaturation, and a significant drop in systolic and diastolic blood pressure.

Blood pressure, temperature and oxygen saturation should be monitored at all times and treatment should be given accordingly.

Lung congestion can be a result of over hydration, therefore a chest x-ray should be done 3-4 hours post operatively, and furosemide can be given at ¼ the normal dose if required.

Urine output can be monitored with a catheter.

The patients' drugs should be continued, especially the anticonvulsants.

Information about emergency-like situations / Differential diagnostics

Dysautonomic crises are a unique and fairly common problem in the FD population, occurring in about 40-50% of patients. Crises can occur in response to even mild stress, and are characterised by a range of symptoms as described before in "disease summary".

Management of a crisis involves Diazepam and Clonidine in an alternate mode every 2.5 hours. The initial dose of diazepam is 0.1-0.2 mg/kg, with a maximum dose of 10 mg. The subsequent drug will be Clonidine after 2.5 hours at a dose of 0.05-0.15mg (depending on the patient's weight and past sensitivity to this drug). These 2 drugs can be repeated every 2.5 hours, until resolution of the crisis. Before giving each drug, the blood pressure and heart rate should be checked - if BP is low then a fluid bolus should be given, and if blood pressure increases then the next drug in line should be given immediately. An IV proton pump inhibitor may reduce stress ulcers and emesis volume.

Oxygen supplementation is recommended.

The main causes of postoperative hypertension are: surgical stress, visceral pain, dysautonomia crisis and maybe supine position.

Ambulatory anaesthesia

This is possible for more minor, uncomplicated surgery, depending upon the severity of disease.

Obstetrical anaesthesia

The first two known instances of viable pregnancies in two patients with familial dysautonomia were described in a report in 1978. However, literature regarding anaesthesia in this population is very limited. There have been case reports of caesarean sections under local and regional anaesthesia.

Literature and internet links

Internet resources

Israeli familial dysautonomia centre at Hadassah Hospital Jerusalem Israel

Cmaayan@hadassah.org.il

Tel ++972 2 5844510, cell ++ 972 507874428

<http://www.hadassah-med.com/children-site/parents/chronic-deseases/familial-dysautonomia>

<http://www.hadassah-med.com/children-site/departments-and-units/familial-dysautonomia-center>

NYU FD centre

<http://www.med.nyu.edu/neurology/dysautonomia-center>

Patient organisations

fd-uk.org

fdnow.org

familialdyaautonomia.org

jewishgenetics.org

jewishfederations.org

fdhope.org

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