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ANDERSEN-TAWIL SYNDROME

Andersen-Tawil syndrome (ATS) is a rare disorder which is estimated to affect 1 in one million people. ATS has three distinct characteristics, episodes of muscle weakness (periodic paralysis), changes in heart rhythm (arrhythmia), and developmental abnormalities. The most common changes affecting the heart are ventricular arrhythmia, which is a disruption in the rhythm of the heart's lower chambers, and long QT syndrome. Long QT syndrome is a heart condition that causes the heart (cardiac) muscle to take longer than usual to recharge between beats. The cardiac involvement varies from non-symptom causing arrhythmias to sudden death. If untreated, the irregular heartbeats can lead to discomfort, fainting (syncope), or cardiac arrest.

Arrhythmia - any of a group of conditions in which the electrical activity of the heart is irregular. The heartbeat may be too fast (over 100 beats per minute) or too slow (less than 60 beats per minute), and may be regular or irregular. A heart beat that is too fast is called tachycardia and a heartbeat that is too slow is called bradycardia. Although many arrhythmias are not life-threatening, some can cause cardiac arrest.

FEATURES OF ANDERSEN-TAWIL SYNDROME

Periodic Paralysis is a group of rare genetic diseases that lead to weakness or paralysis (rarely death) from common triggers such as cold, heat, high carbohydrate meals, not eating, stress or excitement and physical activity of any kind. This is due to malfunctions in part of the muscle cell that controls ions (a charged atom) entering or leaving the cell (an ion channel). Electrically charged ions leak in or out causing the cell to become unable to move.

ATS is one of the conditions in this group and is distinguished from the others by the coexistence of abnormalities in both skeletal muscle and cardiac muscle and periodic paralysis that can occur in either hyperkalemic (when the amount of potassium ion in the blood is elevated) or hypokalemic (when the amount of potassium ion in the blood is low) conditions. 15% of people with ATS experience periodic paralysis when their potassium levels are high, 20% with normal potassium levels and the rest experience the paralysis in association with low potassium ions These different concentrations of potassium also affect the person’s heart and causes arrhythmia which can be fatal. There are also characteristic facial features which are often a diagnostic clue but these may be very subtle.

Muscular Dystrophy New Zealand

There are two types of ATS. Andersen-Tawil syndrome Type 1 (ATS1) has a detectable defect in the gene KCNJ2. This accounts for approximately 60% of the individuals with ATS. Andersen-Tawil Syndrome Type 2 (ATS2) has all the same clinical features but no defect detected in the KCNJ2 gene.

CAUSE OF ANDERSEN-TAWIL SYNDROME

Individuals with a detectable mutation in gene KCNJ2 (ATS1) have an error in a protein which controls the entry and exit of potassium ions into their cells. The specific name for this is a voltage gated, inward rectifying potassium channel or Kir2.1 channel. These are found predominantly in skeletal muscle, heart and brain cells. The incorrectly functioning channels 'leak' or fail to bind with another protein which regulates its activity which means that their electrical charge is not controlled properly. These cells lose their charge and take a long time to get it back. The individual experiences this as muscle weakness or paralysis.

Because people with ATS2 have no known genetic mutation the specific mechanism of the defective potassium ion channel is not known but the result is the same.

GENETICS

We each have two copies of the KCNJ2 gene in each cell. To be affected with the condition only one copy needs to be defective. Around half of all people diagnosed with ATS will have one parent who also has the condition. This type of inheritance pattern is called Autosomal Dominance. The other half are thought to have a new mutation (they are the first person in their family with the faulty gene). People with ATS1 have a genetic confirmation of the condition and a 50% chance in each pregnancy that the baby will also have the condition.

Genetic counseling is available to these individuals and families. This service provides information, helps families understand inheritance patterns and what this means in their family, as well as enabling people to make more informed family-planning decisions. Because other members in a family can be affected and not know it, early diagnosis and treatment is of benefit

Muscular Dystrophy New Zealand

DIAGNOSIS OF ANDERSEN-TAWIL SYNDROME

Affected individuals present in the first or second decade with either cardiac symptoms (palpitations and/or fainting) or weakness that occurs spontaneously following prolonged rest or following rest after exertion. Mild permanent weakness is common. The present of the Long QT heartbeat as well as distinctive physical features which can be mild and include a characteristic face, dental issues (e.g. slow loss of baby teeth), skeletal findings such as mild joining of toes and mild learning difficulties. The presence of a KCNJ2 disease causing mutation confirms the diagnosis.

MANAGEMENT OF ANDERSEN-TAWIL SYNDROME

For episodic weakness the treatment depends on the concentration of potassium in the blood. If serum potassium concentration is low, administration of oral potassium every 15-30 minutes until the serum concentration normalizes can assist. If serum potassium concentration is high, ingesting carbohydrates or continuing mild exercise may shorten the attack.

There can be a reduction in frequency and severity of episodic attacks of weakness with lifestyle/dietary modification to avoid known triggers. Other options are; use of carbonic anhydrase inhibitors; daily use of slow release potassium supplements and implantable cardioverter-defibrillator for those with tachycardia-induced syncope.

Cautious use of antiarrhythmic drugs (particularly class I drugs) is recommended as although they are being used to treat the irregular heart beat they may actually make the neuromuscular symptoms worse.

Individuals who have no symptoms but have a positive diagnosis via genetic testing are recommended to have annual screening with a 12-lead ECG and 24-hour Holter monitoring.

People with ATS are also encouraged to avoid medications known to prolong QT intervals such as ; salbutamol inhalers (which may exacerbate cardiac arrhythmias); thiazide and other potassium-wasting diuretics (which may provoke drug-induced hypokalemia and could aggravate the QT interval).

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RESEARCH

The University of Rochester, USA with collaboration from the Office of Rare Disorders, the Rare Diseases Clinical Research Network and the National Center for Research Resources has completed a 2 year observational study into the characteristics of ATS over time. They were looking to see if symptoms progress and if they are related to a mutation in the KCNJ2 Gene. The study was started in 2007 and completed in October 2013.

The University of Rochester and the National Institute of Neurological Disorders and Stroke have completed a study on the effectiveness of a drug called Dichlorphenamide on the periodic paralysis experienced by people with ATS. This trial lasted 65 weeks and was completed in April 2013.

Results for both of these studies are yet to be published.

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