= Thyrotoxic periodic paralysis =

Thyrotoxic periodic paralysis (TPP) is a condition featuring attacks of muscle weakness in the presence of hyperthyroidism (overactivity of the thyroid gland) . Hypokalemia (a decreased potassium level in the blood) is usually present during attacks . The condition may be life @-@ threatening if weakness of the breathing muscles leads to respiratory failure , or if the low potassium levels lead to cardiac arrhythmias (irregularities in the heart rate) . If untreated , it is typically recurrent in nature .

The condition has been linked with genetic mutations in genes that code for certain ion channels that transport electrolytes (sodium and potassium) across cell membranes . The main ones are the L @-@ type calcium channel ?1 @-@ subunit and potassium inward rectifier 2 @.@ 6 ; it is therefore classified as a channelopathy . The abnormality in the channel is thought to lead to shifts of potassium into cells , under conditions of high thyroxine (thyroid hormone) levels , usually with an additional precipitant .

Treatment of the hypokalemia , followed by correction of the hyperthyroidism , leads to complete resolution of the attacks . It occurs predominantly in males of Chinese , Japanese , Vietnamese , Filipino , and Korean descent . TPP is one of several conditions that can cause periodic paralysis .

= = Signs and symptoms = =

An attack often begins with muscle pain , cramping , and stiffness . This is followed by weakness or paralysis that tends to develop rapidly , usually in late evening or the early hours of the morning . The weakness is usually symmetrical ; the limb muscles closer to the trunk (proximal) are predominantly affected , and weakness tends to start in the legs and spread to the arms . Muscles of the mouth and throat , eyes , and breathing are usually not affected , but occasionally weakness of the respiratory muscles can cause life @-@ threatening respiratory failure . Attacks typically resolve within several hours to several days , even in the absence of treatment . On neurological examination during an attack , flaccid weakness of the limbs is noted ; reflexes are usually diminished , but the sensory system is unaffected . Mental status is not affected .

Attacks may be brought on by physical exertion , drinking alcohol , or eating food high in carbohydrates or salt . This may explain why attacks are more common in summer , when more people drink sugary drinks and engage in exercise . Exercise @-@ related attacks tend to occur during a period of rest immediately after exercise ; exercise may therefore be recommended to abort an attack .

There may be symptoms of thyroid overactivity , such as weight loss , a fast heart rate , tremor , and perspiration ; but such symptoms occur in only half of all cases . The most common type of hyperthyroidism , Graves ' disease , may additionally cause eye problems (Graves ' ophthalmopathy) and skin changes of the legs (pretibial myxedema) . Thyroid disease may also cause muscle weakness in the form of thyrotoxic myopathy , but this is constant rather than episodic .

= = Causes = =

= = = Genetics = = =

Genetic mutations in the L @-@ type calcium channel ?1 @-@ subunit (Cav1.1) have been described in Southern Chinese with TPP . The mutations are located in a different part of the gene from those described in the related condition familial periodic paralysis . In TPP , the mutations described are single @-@ nucleotide polymorphisms located in the hormone response element responsive to thyroid hormone , implying that transcription of the gene and production of ion channels may be altered by increased thyroid hormone levels . Furthermore , mutations have been reported in the genes coding for potassium voltage @-@ gated channel , Shaw @-@ related

subfamily , member 4 (Kv3.4) and sodium channel protein type 4 subunit alpha (Na41.4) .

Of people with TPP , 33 % from various populations were demonstrated to have mutations in KCNJ18 , the gene coding for Kir2.6 , an inward @-@ rectifier potassium ion channel . This gene , too , harbors a thyroid response element .

Certain forms of human leukocyte antigen (HLA) ? especially B46 , DR9 , DQB1 * 0303 , A2 , Bw22 , AW19 , B17 , and DRW8 ? are more common in TPP . Linkage to particular forms of HLA , which plays a central role in the immune response , might imply an immune system cause , but it is uncertain whether this directly causes TPP or whether it increases the susceptibility to Graves ' disease , a known autoimmune disease .

= = = Thyroid disease = = =

The most common underlying form of thyroid disease associated with TPP is Graves ' disease , a syndrome due to an autoimmune reaction that leads to overproduction of thyroid hormone . TPP has also been described in people with other thyroid problems such as thyroiditis , toxic nodular goiter , toxic adenoma , TSH @-@ producing pituitary adenoma , excessive ingestion of thyroxine or iodine , and amiodarone @-@ induced hyperthyroidism .

= = Mechanism = =

The muscle weakness and increased risk of irregular heart beat in TPP result from markedly reduced levels of potassium in the bloodstream . Potassium is not in fact lost from the body , but increased Na + / K + -ATPase activity (the enzyme that moves potassium into cells and keeps sodium in the blood) leads to shift of potassium into tissues , and depletes the circulation . In other types of potassium derangement , the acid @-@ base balance is usually disturbed , with metabolic alkalosis and metabolic acidosis often being present . In TPP , these disturbances are generally absent . Hypokalemia leads to hyperpolarization of muscle cells , making the neuromuscular junction less responsive to normal nerve impulses and leading to decreased contractility of the muscles .

It is not clear how the described genetic defects increase the Na + / K + -ATPase activity , but it is suspected that the enzyme becomes more active due to increased thyroid hormone levels . Hyperthyroidism increases the levels of catecholamines (such as adrenaline) in the blood , increasing Na + / K + -ATPase activity . The enzyme activity is then increased further by the precipitating causes . For instance , increased carbohydrate intake leads to increased insulin levels ; this is known to activate Na + / K + -ATPase . Once the precipitant is removed , the enzyme activity returns to normal levels . It has been postulated that male hormones increase Na + / K + -ATPase activity , and that this explains why males are at a higher risk of TPP despite thyroid disease being more common in females .

TPP is regarded as a model for related conditions , known as " channelopathies " , which have been linked with mutations in ion channels ; the majority of these conditions occurs episodically .

= = Diagnosis = =

Hypokalemia (low blood potassium levels) commonly occurs during attacks ; levels below 3 @.@ 0 mmol / l are typically encountered . Magnesium and phosphate levels are often found to be decreased . Creatine kinase levels are elevated in two thirds of cases , usually due to a degree of muscle injury ; severe elevations suggestive of rhabdomyolysis (muscle tissue destruction) are rare . Electrocardiography (ECG / EKG) may show tachycardia (a fast heart rate) due to the thyroid disease , abnormalities due to cardiac arrhythmia (atrial fibrillation , ventricular tachycardia) , and conduction changes associated with hypokalemia (U waves , QRS widening , QT prolongation , and T wave flattening) . Electromyography shows changes similar to those encountered in myopathies (muscle diseases) , with a reduced amplitude of the compound muscle action potentials (CMAPs) ; they resolve when treatment has commenced .

TPP is distinguished from other forms of periodic paralysis (especially hypokalemic periodic paralysis) with thyroid function tests on the blood . These are normal in the other forms , and in thyrotoxicosis the levels of thyroxine and triiodothyronine are elevated , with resultant suppression of TSH production by the pituitary gland . Various other investigations are usually performed to separate the different causes of hyperthyroidism .

= = Treatment = =

In the acute phase of an attack , administration of potassium will quickly restore muscle strength and prevent complications . However , caution is advised as the total amount of potassium in the body is not decreased , and it is possible for potassium levels to overshoot (" rebound hyperkalemia ") ; slow infusions of potassium chloride are therefore recommended while other treatment is commenced .

The effects of excess thyroid hormone typically respond to the administration of a non @-@ selective beta blocker , such as propranolol (as most of the symptoms are driven by increased levels of adrenaline and its effect on the ? @-@ adrenergic receptors) . Subsequent attacks may be prevented by avoiding known precipitants , such as high salt or carbohydrate intake , until the thyroid disease has been adequately treated .

Treatment of the thyroid disease usually leads to resolution of the paralytic attacks . Depending on the nature of the disease , the treatment may consist of thyrostatics (drugs that reduce production of thyroid hormone) , radioiodine , or occasionally thyroid surgery .

= = Epidemiology = =

TPP occurs predominantly in males of Chinese , Japanese , Vietnamese , Filipino , and Korean descent , as well as Thais , with much lower rates in people of other ethnicities . In Chinese and Japanese people with hyperthyroidism , 1 @.@ 8 ? 1 @.@ 9 % experience TPP . This is in contrast to North America , where studies report a rate of 0 @.@ 1 ? 0 @.@ 2 % . Native Americans , who share a genetic background with East Asians , are at an increased risk .

The typical age of onset is 20 ? 40 . It is unknown why males are predominantly affected , with rates in males being 17- to 70 @-@ fold those in females , despite thyroid overactivity being much more common in women .

= = History = =

After several case reports in the 18th and 19th centuries , periodic paralysis was first described in full by the German neurologist Carl Friedrich Otto Westphal (1833 ? 1890) in 1885 . In 1926 the Japanese physician Tetsushiro Shinosaki , from Fukuoka , observed the high rate of thyroid disease in Japanese people with periodic paralysis . The first English @-@ language report , in 1931 , originated from Dunlap and Kepler , physicians at the Mayo Clinic ; they described the condition in a patient with features of Graves ' disease . In 1937 periodic paralysis was linked with hypokalemia , as well as precipitation of attacks with glucose and insulin . This phenomenon has been used as a diagnostic test .

In 1974 it was discovered that propranolol could prevent attacks . The concept of channelopathies and the link with specific ion channel mutations emerged at the end of the 20th century .