= Wilson 's disease =

Wilson 's disease , also called Wilson disease or hepatolenticular degeneration , is an autosomal recessive genetic disorder in which copper accumulates in tissues ; this manifests as neurological or psychiatric symptoms and liver disease . It is treated with medication that reduces copper absorption or removes the excess copper from the body , but occasionally a liver transplant is required .
The condition is due to mutations in the Wilson disease protein (ATP7B) gene . A single abnormal copy of the gene is present in 1 in 100 people , who do not develop any symptoms (they are carriers) . If a child inherits the gene from both parents , the child may develop Wilson 's disease . Symptoms usually appear between the ages of 6 and 20 years , but cases in much older people have been described . Wilson 's disease occurs in 1 to 4 per 100 @,@ 000 people . It is named after Samuel Alexander Kinnier Wilson (1878 ? 1937) , the British neurologist who first described the condition in 1912 .

= = Signs and symptoms = =

The main sites of copper accumulation are the liver and the brain , and consequently liver disease and neuropsychiatric symptoms are the main features that lead to diagnosis . People with liver problems tend to come to medical attention earlier , generally as children or teenagers , than those with neurological and psychiatric symptoms , who tend to be in their twenties or older . Some are identified only because relatives have been diagnosed with Wilson 's disease ; many of these , when tested , turn out to have been experiencing symptoms of the condition but have not received a diagnosis .

= = = Liver disease = = =

Liver disease may present itself as tiredness , increased bleeding tendency or confusion (due to hepatic encephalopathy) and portal hypertension . The latter , a condition in which the pressure in the portal vein is markedly increased , leads to esophageal varices , blood vessels in the esophagus that may bleed in a life @-@ threatening fashion , as well as enlargement of the spleen (splenomegaly) and accumulation of fluid in the abdominal cavity (ascites) . On examination , signs of chronic liver disease such as spider angiomata (small distended blood vessels , usually on the chest) may be observed . Chronic active hepatitis has caused cirrhosis of the liver in most by the time they develop symptoms . While most people with cirrhosis have an increased risk of hepatocellular carcinoma (liver cancer) , this risk is relatively very low in Wilson 's disease .
About 5 % of all people are diagnosed only when they develop fulminant acute liver failure , often in the context of a hemolytic anemia (anemia due to the destruction of red blood cells) . This leads to abnormalities in protein production (identified by deranged coagulation) and metabolism by the liver . The deranged protein metabolism leads to the accumulation of waste products such as ammonia in the bloodstream . When these irritate the brain , the person develops hepatic encephalopathy (confusion , coma , seizures and finally life @-@ threatening swelling of the brain) .

= = = Neuropsychiatric symptoms = = =

About half the people with Wilson 's disease have neurological or psychiatric symptoms . Most initially have mild cognitive deterioration and clumsiness , as well as changes in behavior . Specific neurological symptoms usually then follow , often in the form of parkinsonism (cogwheel rigidity , bradykinesia or slowed movements and a lack of balance are the most common parkinsonian features) with or without a typical hand tremor , masked facial expressions , slurred speech , ataxia (lack of coordination) or dystonia (twisting and repetitive movements of part of the body) . Seizures and migraine appear to be more common in Wilson 's disease . A characteristic tremor described as " wing @-@ beating tremor " is encountered in many people with Wilson 's ; this is

absent at rest but can be provoked by extending the arms .

Cognition can also be affected in Wilson 's disease . This comes in two , not mutually exclusive , categories : frontal lobe disorder (may present as impulsivity , impaired judgement , promiscuity , apathy and executive dysfunction with poor planning and decision making) and subcortical dementia (may present as slow thinking , memory loss and executive dysfunction , without signs of aphasia , apraxia or agnosia) . It is suggested that these cognitive involvements are related and closely linked to psychiatric manifestations of the disease .

Psychiatric problems due to Wilson 's disease may include behavioral changes , depression , anxiety and psychosis . Psychiatric symptoms are commonly seen in conjunction with neurological symptoms and are rarely manifested on their own . These symptoms are often poorly defined and can sometimes be attributed to other causes . Because of this , diagnosis of Wilson 's disease is rarely made when only psychiatric symptoms are present .

= = = Other organ systems = = =

Medical conditions have been linked with copper accumulation in Wilson 's disease :

Eyes : Kayser ? Fleischer rings (KF rings) , a pathognomonic sign , may be visible in the cornea of the eyes , either directly or on slit lamp examination as deposits of copper in a ring around the cornea . They are due to copper deposition in Descemet 's membrane . They do not occur in all people with Wilson 's disease . Wilson 's disease is also associated with sunflower cataracts exhibited by brown or green pigmentation of the anterior and posterior lens capsule . Neither cause significant visual loss . KF rings occur in approximately 66 % of diagnosed cases (more often in those with neurological symptoms rather than with liver problems) .

Kidneys : renal tubular acidosis (Type 2) , a disorder of bicarbonate handling by the proximal tubules leads to nephrocalcinosis (calcium accumulation in the kidneys) , a weakening of bones (due to calcium and phosphate loss) , and occasionally aminoaciduria (loss of essential amino acids needed for protein synthesis) .

Heart : cardiomyopathy (weakness of the heart muscle) is a rare but recognized problem in Wilson 's disease ; it may lead to heart failure (fluid accumulation due to decreased pump function) and cardiac arrhythmias (episodes of irregular and / or abnormally fast or slow heart beat) .

Hormones : hypoparathyroidism (failure of the parathyroid glands leading to low calcium levels) , infertility , and habitual abortion .

= = Genetics = =

The Wilson 's disease gene (ATP7B) has been mapped to chromosome 13 (13q14.3) and is expressed primarily in the liver , kidney , and placenta . The gene codes for a P @-@ type (cation transport enzyme) ATPase that transports copper into bile and incorporates it into ceruloplasmin . Mutations can be detected in 90 % . Most (60 %) are homozygous for ATP7B mutations (two abnormal copies) , and 30 % have only one abnormal copy . Ten percent have no detectable mutation .

Although 300 mutations of ATP7B have been described , in most populations the cases of Wilson 's disease are due to a small number of mutations specific for that population . For instance , in Western populations the H1069Q mutation (replacement of a histidine by a glutamine at position 1069 in the protein) is present in 37 ? 63 % of cases , while in China this mutation is very uncommon and R778L (arginine to leucine at 778) is found more often . Relatively little is known about the relative impact of various mutations , although the H1069Q mutation seems to predict later onset and predominantly neurological problems , according to some studies .

A normal variation in the PRNP gene can modify the course of the disease by delaying the age of onset and affecting the type of symptoms that develop . This gene produces prion protein , which is active in the brain and other tissues and also appears to be involved in transporting copper . A role for the ApoE gene was initially suspected but could not be confirmed .

The condition is inherited in an autosomal recessive pattern . In order to inherit it , both of the

parents of an individual must carry an affected gene . Most have no family history of the condition . People with only one abnormal gene are called carriers (heterozygotes) and may have mild , but medically insignificant , abnormalities of copper metabolism .

Wilson 's disease is the most common of a group of hereditary diseases that cause copper overload in the liver . All can cause cirrhosis at a young age . The other members of the group are Indian childhood cirrhosis (ICC) , endemic Tyrolean infantile cirrhosis and idiopathic copper toxicosis . These are not related to ATP7B mutations : for example , ICC has been linked to mutations in the KRT8 and the KRT18 gene .

= = Pathophysiology = =

Copper is needed by the body for a number of functions , predominantly as a cofactor for a number of enzymes such as ceruloplasmin , cytochrome c oxidase , dopamine ? @-@ hydroxylase , superoxide dismutase and tyrosinase .

Copper enters the body through the digestive tract . A transporter protein on the cells of the small bowel , copper membrane transporter 1 (CMT1 ; SLC31A1) , carries copper inside the cells , where some is bound to metallothionein and part is carried by ATOX1 to an organelle known as the trans @-@ Golgi network . Here , in response to rising concentrations of copper , an enzyme called ATP7A releases copper into the portal vein to the liver . Liver cells also carry the CMT1 protein , and metallothionein and ATOX1 bind it inside the cell , but here it is ATP7B that links copper to ceruloplasmin and releases it into the bloodstream , as well as removing excess copper by secreting it into bile . Both functions of ATP7B are impaired in Wilson 's disease . Copper accumulates in the liver tissue ; ceruloplasmin is still secreted , but in a form that lacks copper (termed apoceruloplasmin) and is rapidly degraded in the bloodstream .

When the amount of copper in the liver overwhelms the proteins that normally bind it , it causes oxidative damage through a process known as Fenton chemistry ; this damage eventually leads to chronic active hepatitis , fibrosis (deposition of connective tissue) and cirrhosis . The liver also releases copper into the bloodstream that is not bound to ceruloplasmin . This free copper precipitates throughout the body but particularly in the kidneys , eyes and brain . In the brain , most copper is deposited in the basal ganglia , particularly in the putamen and globus pallidus (together called the lenticular nucleus) ; these areas normally participate in the coordination of movement as well as playing a significant role in neurocognitive processes such as the processing of stimuli and mood regulation . Damage to these areas , again by Fenton chemistry , produces the neuropsychiatric symptoms seen in Wilson 's disease .

It is not clear why Wilson 's disease causes hemolysis , but various lines of evidence suggest that a high level of free (non @-@ ceruloplasmin bound) copper has a direct effect on either oxidation of hemoglobin , inhibition of energy @-@ supplying enzymes in the red blood cell , or direct damage to the cell membrane .

= = Diagnosis = =

Wilson 's disease may be suspected on the basis of any of the symptoms mentioned above , or when a close relative has been found to have Wilson 's . Most have slightly abnormal liver function tests such as a raised aspartate transaminase , alanine transaminase and bilirubin level . If the liver damage is significant , albumin may be decreased due to an inability of damaged liver cells to produce this protein ; likewise , the prothrombin time (a test of coagulation) may be prolonged as the liver is unable to produce proteins known as clotting factors . Alkaline phosphatase levels are relatively low in those with Wilson 's @-@ related acute liver failure . If there are neurological symptoms , magnetic resonance imaging (MRI) of the brain is usually performed ; this shows hyperintensities in the part of the brain called the basal ganglia in the T2 setting . MRI may also demonstrate the characteristic " face of the giant panda " pattern .

There is no totally reliable test for Wilson 's disease , but levels of ceruloplasmin and copper in the blood , as well of the amount of copper excreted in urine during a 24 @-@ hour period , are together

used to form an impression of the amount of copper in the body . The gold standard ? or most ideal test ? is a liver biopsy .

= = = Ceruloplasmin = = =

Levels of ceruloplasmin are abnormally low (< 0 @.@ 2 g / L) in 80 ? 95 % of cases . It can , however , be present at normal levels in people with ongoing inflammation as it is an acute phase protein . Low ceruloplasmin is also found in Menkes disease and aceruloplasminemia , which are related to , but much rarer than Wilson 's disease .

The combination of neurological symptoms , Kayser ? Fleischer rings and a low ceruloplasmin level is considered sufficient for the diagnosis of Wilson 's disease . In many cases , however , further tests are needed .

= = = Serum and urine copper = = =

Serum copper is low , which may seem paradoxical given that Wilson 's disease is a disease of copper excess . However , 95 % of plasma copper is carried by cerulopasmin which is often low in Wilson 's disease . Urine copper is elevated in Wilson 's disease and is collected for 24 hours in a bottle with a copper @-@ free liner . Levels above 100 ?g / 24h (1 @.@ 6 ?mol / 24h) confirm Wilson 's disease , and levels above 40 ?g / 24h (0 @.@ 6 ?mol / 24h) are strongly indicative . High urine copper levels are not unique to Wilson 's disease ; they are sometimes observed in autoimmune hepatitis and in cholestasis (any disease obstructing the flow of bile from the liver to the small bowel) .

In children , the penicillamine test may be used . A 500 mg oral dose of penicillamine is administered , and urine collected for 24 hours . If this contains more than 1600 ?g (25 ?mol) , it is a reliable indicator of Wilson 's disease . This test has not been validated in adults .

= = = Liver biopsy = = =

Once other investigations have indicated Wilson 's disease , the ideal test is the removal of a small amount of liver tissue through a liver biopsy . This is assessed microscopically for the degree of steatosis and cirrhosis , and histochemistry and quantification of copper are used to measure the severity of the copper accumulation . A level of 250 ?g of copper per gram of dried liver tissue confirms Wilson 's disease . Occasionally , lower levels of copper are found ; in that case , the combination of the biopsy findings with all other tests could still lead to a formal diagnosis of Wilson 's .

In the earlier stages of the disease , the biopsy typically shows steatosis (deposition of fatty material) , increased glycogen in the nucleus , and areas of necrosis (cell death) . In more advanced disease , the changes observed are quite similar to those seen in autoimmune hepatitis , such as infiltration by inflammatory cells , piecemeal necrosis and fibrosis (scar tissue) . In advanced disease , finally , cirrhosis is the main finding . In acute liver failure , degeneration of the liver cells and collapse of the liver tissue architecture is seen , typically on a background of cirrhotic changes . Histochemical methods for detecting copper are inconsistent and unreliable , and taken alone are regarded as insufficient to establish a diagnosis .

= = = Genetic testing = = =

Mutation analysis of the ATP7B gene , as well as other genes linked to copper accumulation in the liver , may be performed . Once a mutation is confirmed , it is possible to screen family members for the disease as part of clinical genetics family counseling . Regional distributions of genes associated with Wilson 's disease are important to follow , as this can help clinicians design appropriate screening strategies . Since mutations of the WD gene vary between populations , research and genetic testing done in countries like the USA or United Kingdom can pose problems as they tend to

have more mixed populations .

= = Treatment = =

= = = Dietary = = =

In general , a diet low in copper @-@ containing foods is recommended with the avoidance of mushrooms , nuts , chocolate , dried fruit , liver , and shellfish .

= = = Medication = = =

Medical treatments are available for Wilson 's disease . Some increase the removal of copper from the body , while others prevent the absorption of copper from the diet .

Generally , penicillamine is the first treatment used . This binds copper (chelation) and leads to excretion of copper in the urine . Hence , monitoring of the amount of copper in the urine can be done to ensure a sufficiently high dose is taken . Penicillamine is not without problems : about 20 % experience a side effect or complication of penicillamine treatment , such as drug @-@ induced lupus (causing joint pains and a skin rash) or myasthenia (a nerve condition leading to muscle weakness) . In those who presented with neurological symptoms , almost half experience a paradoxical worsening in their symptoms . While this phenomenon is observed in other treatments for Wilson 's , it is usually taken as an indication for discontinuing penicillamine and commencing second @-@ line treatment . Those intolerant to penicillamine may instead be commenced on trientine hydrochloride , which also has chelating properties . Some recommend trientine as first @-@ line treatment , but experience with penicillamine is more extensive . A further agent , under clinical investigation by Wilson Therapeutics , with known activity in Wilson 's disease is tetrathiomolybdate . This is regarded as experimental , though some studies have shown a beneficial effect .

Once all results have returned to normal , zinc (usually in the form of a zinc acetate prescription called Galzin) may be used instead of chelators to maintain stable copper levels in the body . Zinc stimulates metallothionein , a protein in gut cells that binds copper and prevents their absorption and transport to the liver . Zinc therapy is continued unless symptoms recur or if the urinary excretion of copper increases .

In rare cases where none of the oral treatments are effective , especially in severe neurological disease , dimercaprol (British anti @-@ Lewisite) is occasionally necessary . This treatment is injected intramuscularly (into a muscle) every few weeks and has unpleasant side effects such as pain .

People who are asymptomatic (for instance , those diagnosed through family screening or only as a result of abnormal test results) are generally treated , as the copper accumulation may cause long @-@ term damage in the future . It is unclear whether these people are best treated with penicillamine or zinc acetate .

= = = Physical and occupational therapies = = =

Physiotherapy and occupational therapy are beneficial for patients with the neurologic form of the disease . The copper chelating treatment may take up to six months to start working , and these therapies can assist in coping with ataxia , dystonia , and tremors , as well as preventing the development of contractures that can result from dystonia .

= = = Transplantation = = =

Liver transplantation is an effective cure for Wilson 's disease but is used only in particular scenarios because of the risks and complications associated with the procedure . It is used mainly in

people with fulminant liver failure who fail to respond to medical treatment or in those with advanced chronic liver disease . Liver transplantation is avoided in severe neuropsychiatric illness , in which its benefit has not been demonstrated .

= = Prognosis = =

Left untreated , Wilson 's disease tends to become progressively worse and is eventually fatal . With early detection and treatment , most of those affected can live relatively normal lives . Liver and neurologic damage that occurs prior to treatment may improve , but it is often permanent .

= = History = =

The disease bears the name of the British physician Samuel Alexander Kinnier Wilson (1878 ? 1937) , a neurologist who described the condition , including the pathological changes in the brain and liver , in 1912 . Wilson 's work had been predated by , and drew on , reports from German neurologist Carl Westphal (in 1883) , who termed it " pseudosclerosis " ; by the British neurologist William Gowers (in 1888) ; and by Adolph Strümpell (in 1898) , who noted hepatic cirrhosis . Neuropathologist John Nathaniel Cumings made the link with copper accumulation in both the liver and the brain in 1948 . The occurrence of hemolysis was noted in 1967 .

Cumings , and simultaneously the New Zealand neurologist Derek Denny @-@ Brown , working in the United States , first reported effective treatment with metal chelator British anti @-@ Lewisite in 1951 . This treatment had to be injected but was one of the first therapies available in the field of neurology , a field that classically was able to observe and diagnose but had few treatments to offer . The first effective oral chelation agent , penicillamine , was discovered in 1956 by British neurologist John Walshe . In 1982 , Walshe also introduced trientine , and was the first to develop tetrathiomolybdate for clinical use . Zinc acetate therapy initially made its appearance in the Netherlands , where physicians Schouwink and Hoogenraad used it in 1961 and in the 1970s , respectively , but it was further developed later by Brewer and colleagues at the University of Michigan .

The genetic basis of Wilson 's disease and linkage to ATP7B mutations was elucidated in the 1980s and 1990s by several research groups .

= = Other animals = =

Hereditary copper accumulation has been described in Bedlington Terriers , where it generally only affects the liver . It is due to mutations in the COMMD1 (or MURR1) gene . In non @-@ Wilsonian copper accumulation states (such as Indian childhood cirrhosis) , no COMMD1 mutations could be detected to explain their genetic origin .