CRMR
Maladie de Wilson
et autres maladies rares liées au cuivre

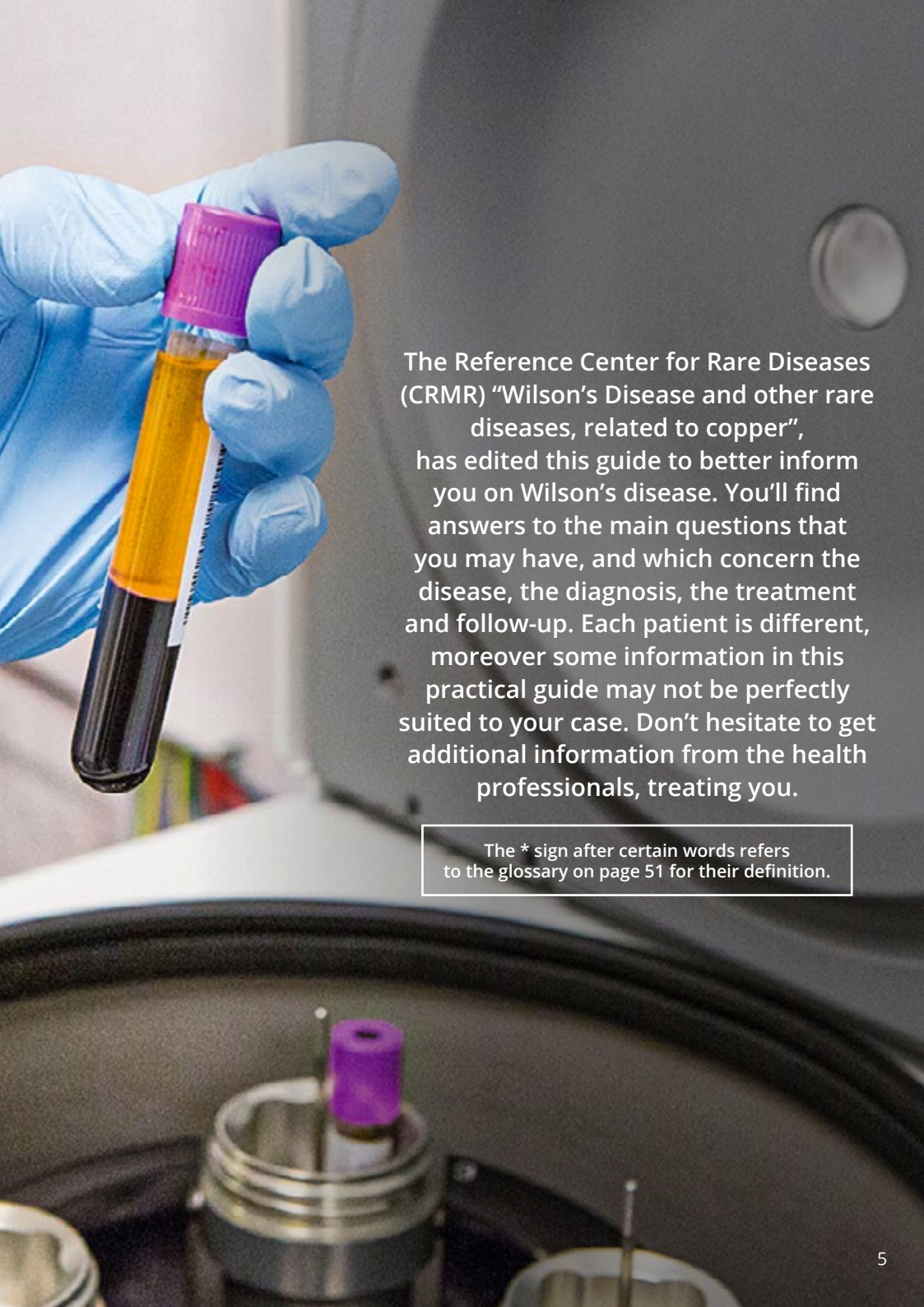
Wilson's disease in 60 questions

Produced by the team of the coordinating site of the Wilson's disease and other rare copper-related diseases (Paris).

www.crmrwilson.com

Seconde edition – September 2021

SUMMARY



The Reference Center for Rare Diseases (CRMR) "Wilson's Disease and other rare diseases, related to copper", has edited this guide to better inform you on Wilson's disease. You'll find answers to the main questions that you may have, and which concern the disease, the diagnosis, the treatment and follow-up. Each patient is different, moreover some information in this practical guide may not be perfectly suited to your case. Don't hesitate to get additional information from the health professionals, treating you.

The * sign after certain words refers to the glossary on page 51 for their definition.

THE DISEASE

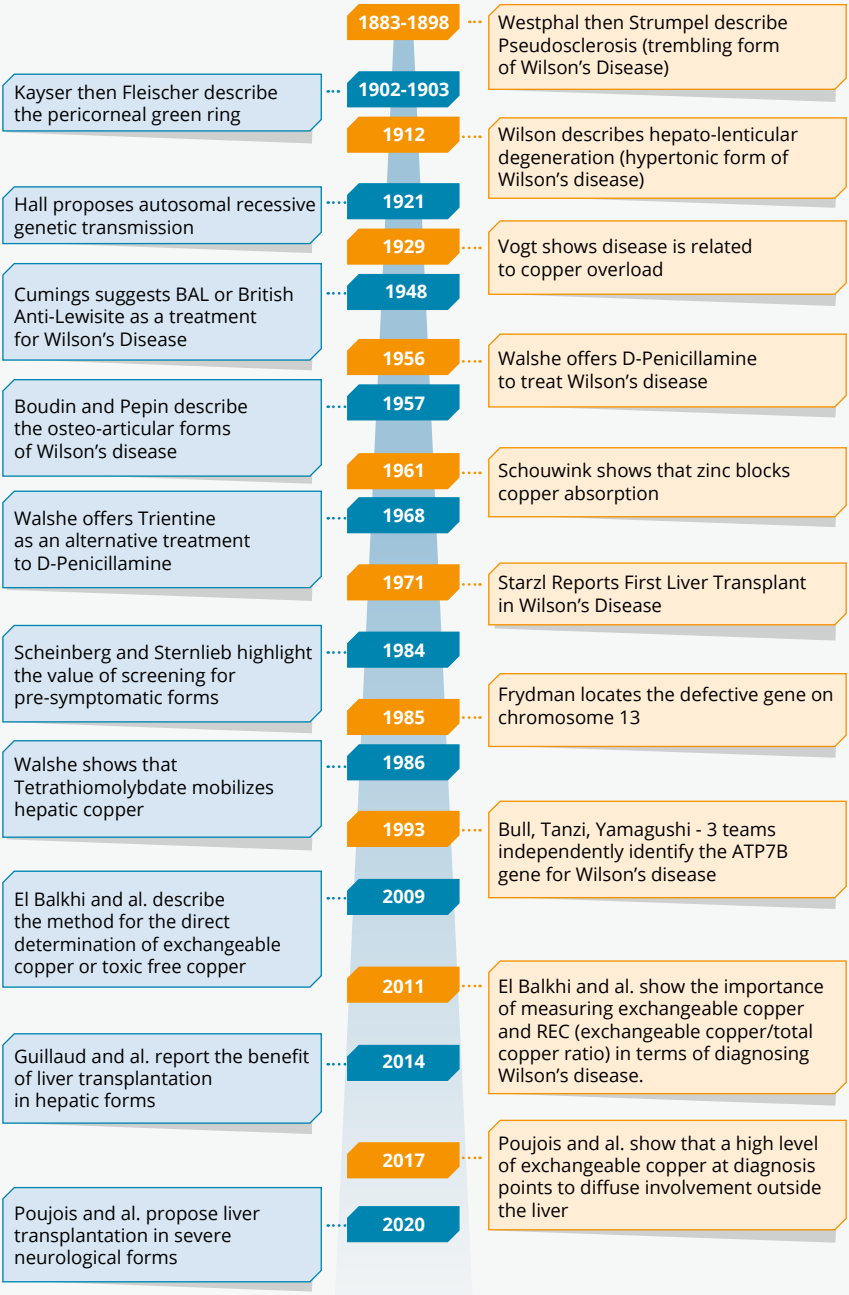
1. What is Wilson's disease?

Wilson's disease is a rare disease, characterized by the accumulation of copper in the body, mainly in the liver and brain. An exceptional fact for such a genetic disease*, is that an efficient medical treatment exists, provided that the treatment is established at an early stage and carried on during the entire lifetime. If the disease is not treated, Wilson's disease could be fatal.

2. Since when do we know of Wilson's disease?

Wilson's disease was named in 1912 by an English neurologist, Samuel Alexander Kinnier Wilson (1878-1937), under the term « Hepatolenticular progressive degeneration. Nervous family disease related to liver cirrhosis ». He describes that this disease can affect children and adults, with lesions of the liver and the brain. He hypothesizes that the brain abnormalities are linked to a toxic generated by the diseased liver.

The main stages of knowledge concerning Wilson's disease

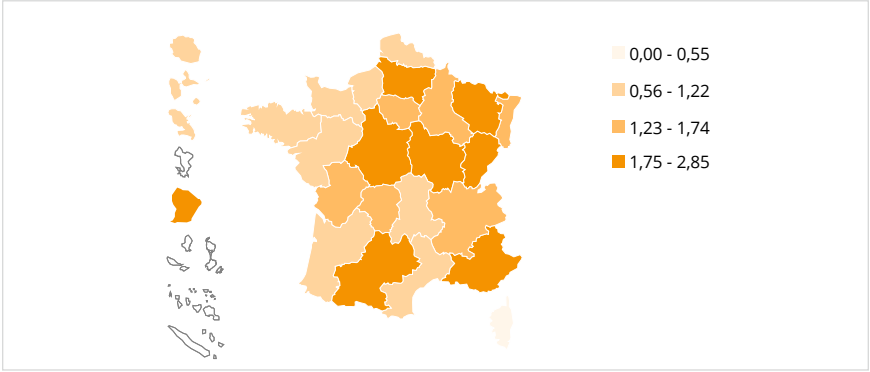


3. How many people suffer from Wilson's disease in France?

The number of people with Wilson's disease is estimated to be between 1 to 3 people out of 100,000, i.e. between 640 and 2100 in France. A national epidemiological study identified 907 people with Wilson disease in 2013, i.e. 1.5 people out of 100,0000[1].

However, recent English and French studies show that the genetic prevalence* of Wilson's disease may be higher: 14 to 26 in 100,0000[1].

Some patients with Wilson's disease may not be diagnosed, especially if they present with mild and not very progressive forms.



Distribution of Wilson's disease prevalence in France in 2013 (per 100,000 population).

4. Can Wilson's disease be inherited*?

Wilson's disease is a genetic disease. It's related to a faulty gene, namely ATP7B gene localized on the 13th chromosome. This gene allows to manufacture protein (ATP7B protein) which regulates the concentration of copper in the body. Each individual possesses two units of each gene, one from the father and the other from the mother. To develop this sickness, one has to have received two faulty ATP7B genes, one from each parent. One faulty gene alone doesn't cause Wilson's disease. Moreover, parents who have passed on a faulty gene, don't suffer from Wilson's disease, they are known as "healthy carriers" or healthy heterozygotes.

TO FIND OUT MORE SEE QUESTION 22

1- Characteristics and prevalence of Wilson's disease : A 2013 observational population-based studyin France. Poujois A, Woimant F et al. Clin Res Hepatol Gastroenterol. 2017.

5. How does copper accumulate in the body?

Copper is present in several foods that we ingest on a daily basis. The latter is important in little quantity for the body (between 1,3 and 1,6 mg/day), to manufacture several proteins and to remain in good health.

Ingested copper is then transported to the liver, where it is stocked.

When too much copper is received by the liver, the surplus copper is eliminated by the bile*, through the intervention of a protein copper carrier, known as ATP7B. This protein also allows another part of copper which is present in the liver, to stick to a molecule called ceruloplasmin; the latter then transports the copper in the blood and to the various other organs in the body.

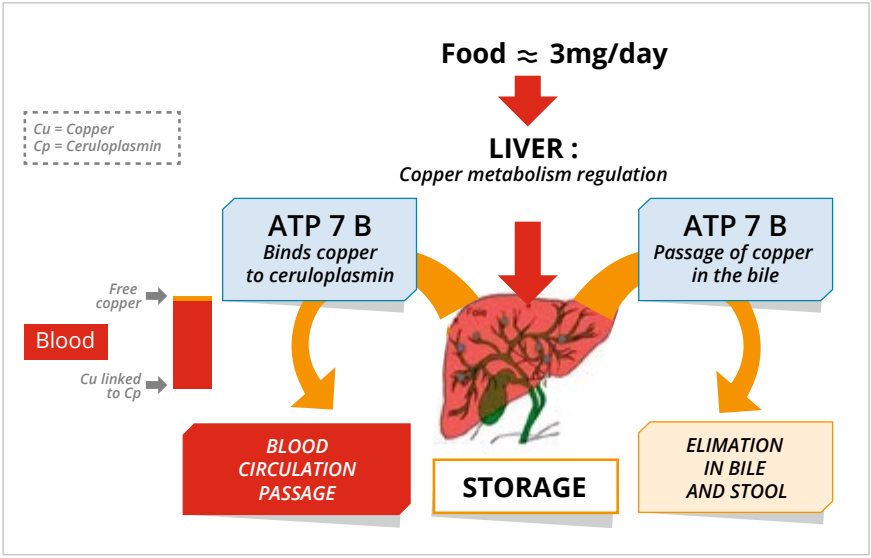
In case of Wilson's disease, the ATP7B protein is defaulted and it's not easy eliminating the excess copper in the liver towards the bile, which leads to a toxic accumulation of copper in the liver. Moreover, copper in the blood doesn't stick well with ceruloplasmin and circulates under a "free" form, which is toxic for the various organs such as the eye, brain, kidneys, etc... As excess copper cannot be eliminated through bile and stools, it is then eliminated through urine.

This is the reason why Wilson's diseases is a liver disease during the initial stage. But when the capacity to stock copper in the liver have been surpassed, copper is carried out in a free and toxic form, within the blood and it then accumulates in various organs, like the brain or the eye cornea. Wilson's disease turns into liver, eye, brain disease and at times affects other organs.

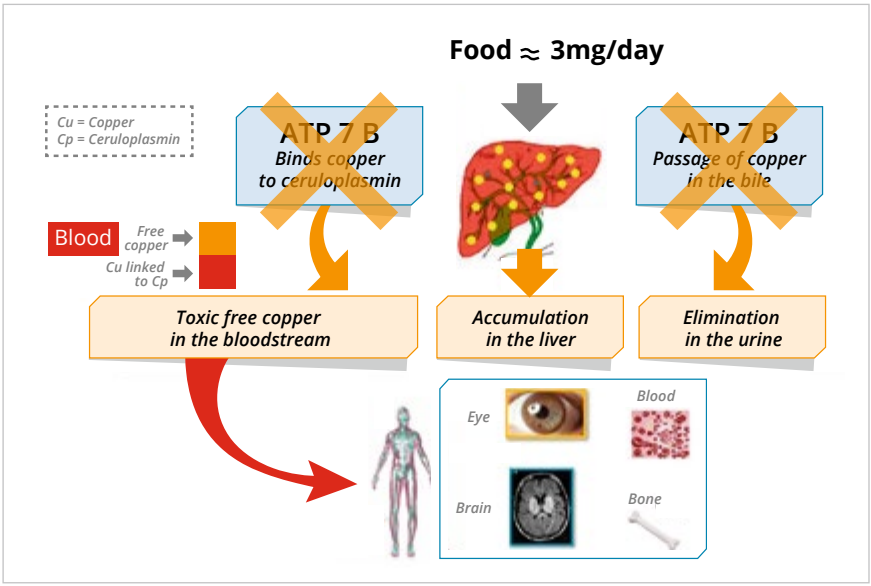
The medical treatment allows to:

-either capture the excess copper or eliminate it through urine (treatments known as copper chelators*).

-either curb intestinal absorption of the ingested copper and eliminate through stools (zinc's function).



Normal metabolism of copper in the body



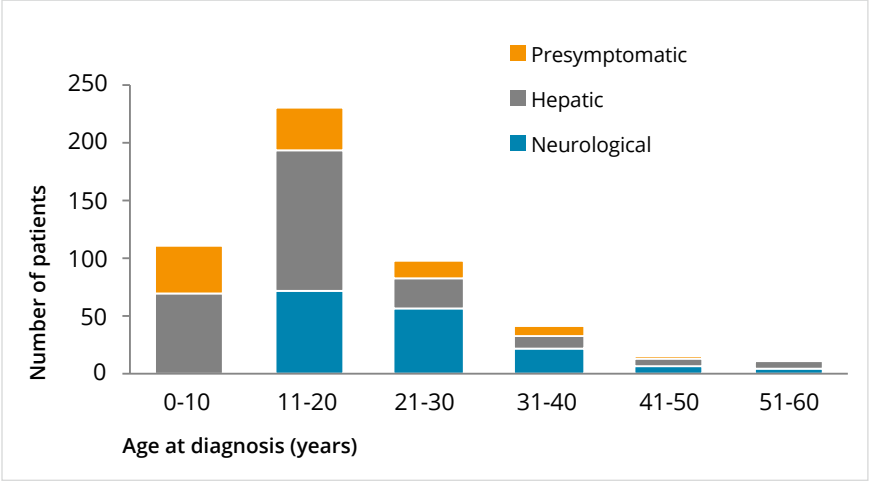
Altered copper metabolism in Wilson's disease

6. How to explain the symptoms?

The symptoms appear due to the accumulation of copper in various organs. This begins at birth, but it takes several years for the accumulation to become symptomatic. Copper first accumulates in the liver, leading to hepatic* symptoms, and if no treatment is given, it affects other organs and mainly the brain and eye.

7. At what age do the initial symptoms of Wilson's disease appear?

The initial symptoms tend to appear between the age of 10 and 20 but the first forms could be at an early or later stage. Moreover, one must raise awareness of Wilson's disease at any age.



Age at diagnosis according to the different forms of Wilson's disease (France Register 2016)

Initially the illness is a liver disease, patients for whom the illness is discovered due to hepatic symptoms are younger than those for whom the sickness is discovered due to neurological symptoms.

8. What are the main revealing symptoms of Wilson's disease?

Accumulation of copper begins in the liver. For 47% of the patients, the initial symptoms are going to be related to liver damage: tired, loss of appetite, nausea, icterus, abdominal swelling due to the presence of an liquid (ascites*), edema of lower limbs.

In 32% of the cases, the illness is going to become obvious through neurological symptoms which gradually become worse, such as tremor, difficulties speaking, also known as dysarthria*, muscle stiffness also known as dystonia, a decrease in scholar or professional efficiency. The initial symptoms can also concern a behavioral modification and irritability, anxiety, depression...

Among other symptoms which could highlight the sickness, for women: repeated miscarriages or spontaneous abortions, irregularity or a complete stop for menstruation.

In 20% of the cases, the disease is diagnosed during a family screening, as the patients are asymptomatic.

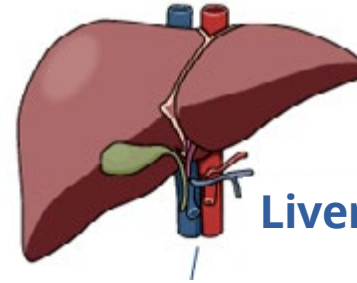
9. How does Wilson's disease evolve?

We have treatments for Wilson's disease. Treatments which are more effective than those which begin early and are carried out continuously throughout one's life. In these cases, life expectancy is the same as the general population. The patients followed-up in France are between 5 and 83 years old (the average age is 25 years). When the diagnosis is carried out later, treatment most often improves the symptoms, although some patients continue experiencing the remaining symptoms which vary in intensity.

If left untreated, symptoms worsen and can lead to death.

THE VARIOUS SYMPTOMS: HEPATIC, OCULAR, NEUROLOGICAL AND OTHERS...

10. How is the liver affected in Wilson's disease?



In all the people who suffer from Wilson's disease, copper usually begins to accumulate in the liver, at first.

The intensity of liver damage varies a lot; it can remain dormant for a long time and manifest itself in a progressive or brutal way.

Liver damage may seem like viral hepatitis: significant fatigue, loss of appetite, increase in hepatic enzymes known as transaminase* (AST and ALT).

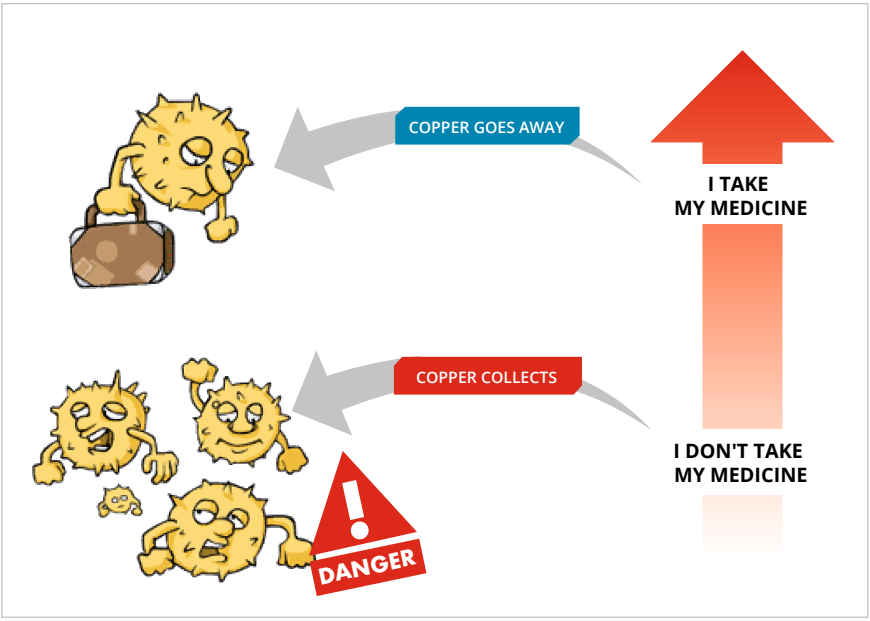
At times this damage is expressed through jaundice (icterus with a yellow color of the skin, white eyes) along with stomach swelling, due to accumulation of liquid (ascites), and/or swelling of ankles (edema of lower limbs).

When the liver is severely damaged and its function is deeply impacted, this is known as liver failure, which can jeopardize a patient's life.

Last but not least, the liver can turn into a chronic liver disease. This concerns the progressive transformation of liver into a "hard" organ, made up of fibrous "scarred" tissue. Liver disease can at times increase the spleen size and dilate esophageal veins (esophageal varices).

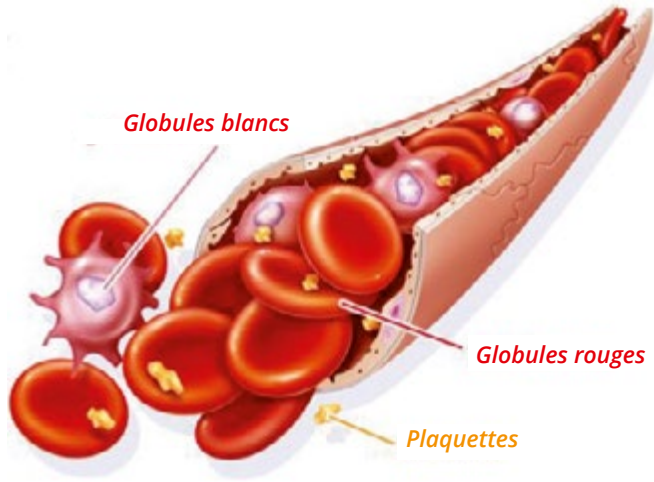
11. When Wilson's disease is diagnosed with hepatic symptoms, can it evolve towards a neurological form?

The hepatic forms can turn into a neurological one. This is mostly observed when treatments are stopped or aren't taken on a regular basis.



12. Which tests can help diagnose liver disease?

- **Blood tests** can confirm liver damage, by showing a high rate of hepatic transaminases, but it should be noted that this blood work for the liver's function can be normal. In case of liver failure, the rates of prothrombin* (TP) and albumin* are lowered. In case of icterus, the rate of bilirubin* is high, in case of severe chronic hepatic disease, the rate of platelets* can be low. Last but not least, the increase in « toxic » copper in the blood can accompany anemia*, through the abnormal destruction of red blood cells.

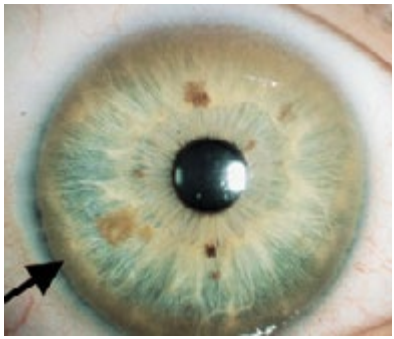


- **Hepatic ultrasound** is carried out with a probe placed on the abdomen, allowing a better assessment of liver damage, and look for an increase in the volume of the spleen. This painless test can in some cases be complemented with a hepatic MRI.
- **Fibroscan** helps measure the elasticity or stiffness of the liver; this is related to liver damage. This examination is painless and is carried out with a probe placed on the abdomen.
- **Liver biopsy** is carried out in cases of difficult diagnoses or wosseming of the disease. This helps measuring the level of copper in the liver and to properly analyze the lesions which are found. It is done under local or general anesthesia.

13. Do patients with severe liver damage tend to develop other diseases?

Patients suffering from liver damage can at times develop liver tumors. Therefore, regular screening through a liver ultrasound or even magnetic resonance imaging (MRI) exams are essential. Ultrasound follow-up is at least annual, or even semi-annual if there are signs of cirrhosis.

14. What is the Kayser-Fleischer ring?



Kayser-Fleischer ring

Eye exam is extremely important when it comes to Wilson's disease. Indeed, 40 % of the patients with hepatic symptoms and almost all those who have neurological symptoms have a peri corneal ring, which is a greenish brown golden feature, namely the Kayser-Fleischer ring. This ring which is exceptionally visible to the naked eye, needs to be sought in ophthalmology, through a specific exam which is completely painless, using a slit lamp*. This ring doesn't change the visual acuity*.

15. How does the Kayser-Fleischer ring evolve?

The Kayser-Fleischer ring disappears with treatment, first on the sides, then at the bottom, and finally at the top. This could take several years.

Kayser-Fleischer ring
at diagnosis: circumferential

Reduction of the Kayser-Fleischer ring after several years of treatment

16. How does brain damage manifest itself in Wilson's disease?

Neurological symptoms vary depending on the areas of the brain which are damaged ; symptoms can be isolated or associated

Following a frequency order, symptoms can be :

- tremors in the arms, legs, head
- speaking difficulties (dysarthria)
- abnormal contractions of the muscles which cause twisting of the hands, feet, face (dystonia)
- slow movements
- difficulty writing
- difficulty swallowing: dysphagia
- coordination and balance disorders (cerebellar syndrome)
- behavioral changes with loss of inhibition, addiction, mood swings, irritability, impulsivity, depression...
- neuropsychological disorders along with difficulties focusing, paying attention, affecting school results or professional issues.

It is important to know that patients with neurological symptoms always suffer from liver damage.

17. How do the neurological symptoms evolve in Wilson's disease?

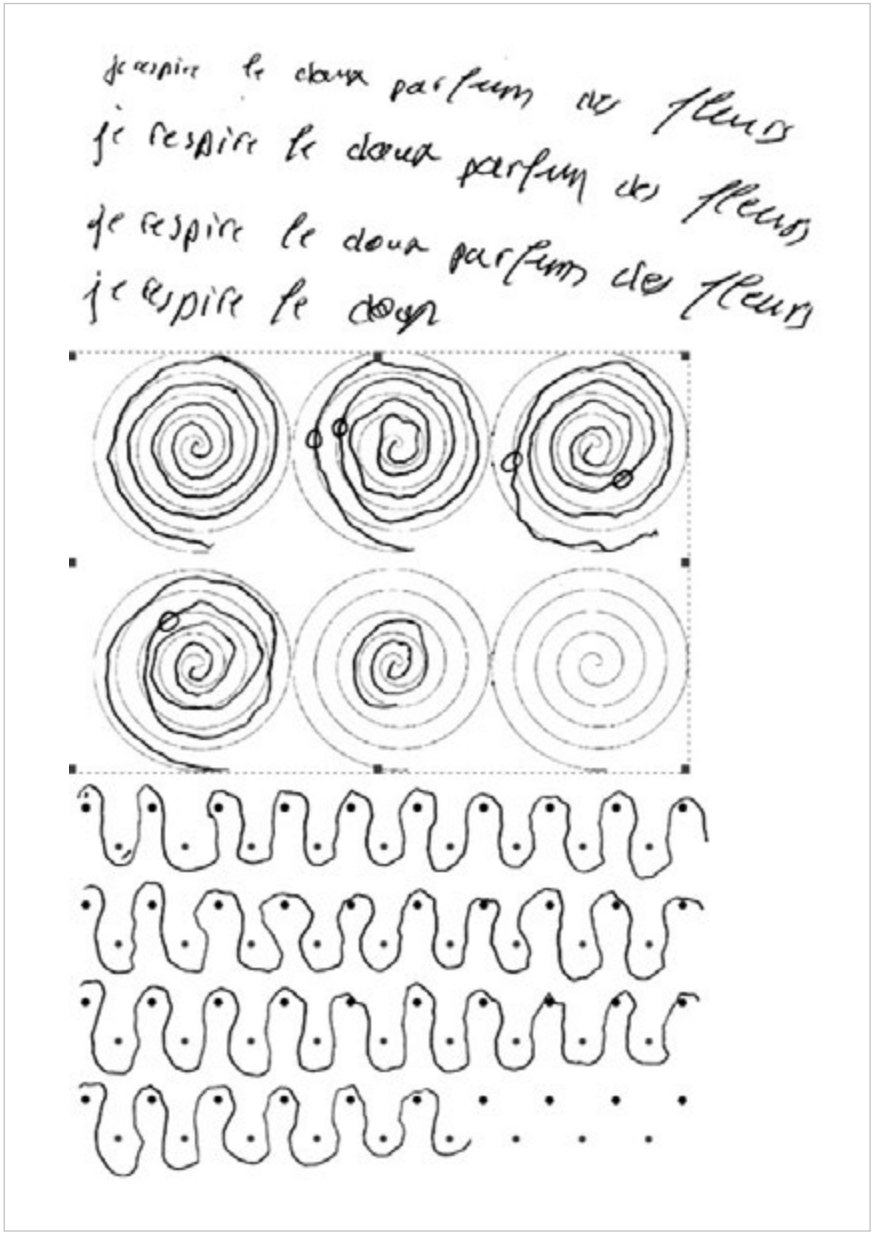
The neurological symptoms worsen, if there is no treatment.

With treatment, there is slow improvement that only appears after several months. Moreover, after starting the treatment, symptoms may worsen which is most often reversible.

Neurological scales make it possible to follow evolution in a precise manner, for example the Unified Wilson Disease Rating Scale (UWDRS).

Assessing tremor or distal stiffness, can be carried out through writing tests like DPRE (Flow rate Accuracy Rhythmicity Analog visual scale; *T. Peron-Magnan*). This test is used to see how the patient feels while writing.

Writing the sentence as quickly as possible "I breathe the sweet smell of flowers", trace the inside of spirals and finally slalom between points under the same conditions.

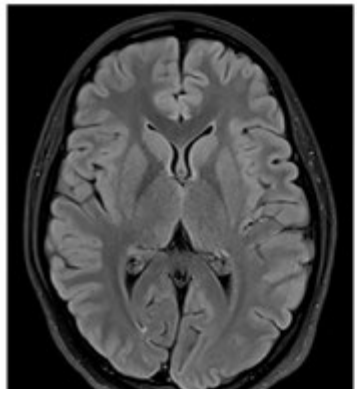


DPRE test (Flow Accuracy Rhythmicity Visual Analog Scale)

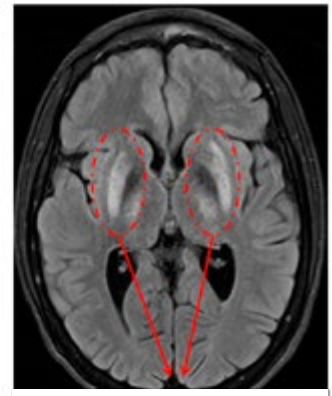
18. Which tests help diagnosing brain damage?

In addition to the neurological examination, the baseline examination is **the brain MRI**, as it allows to view the lesions of the brain, showing the cerebral accumulation of copper, which is most often abnormal in patients with neurological signs.

Normal brain MRI



Brain MRI pathological Wilson's disease



White areas = Accumulation of copper in the basal ganglia

19. Can other organs be affected by Wilson's disease?

Menstruation can be irregular for women. This may be the first symptom. Before diagnosis, miscarriages are also common.

Some patients may suffer from kidney malfunction. Urinary or kidney stones* (lithiasis*) are common.

Patients with a serious form, with prolonged bed rest may develop bone damage. A vitamin D deficiency is frequent in winter and requires an adapted supplementation, in every patient.

THE DIAGNOSIS

20. How is Wilson's disease diagnosed?

The diagnosis of Wilson's disease leans on a range of clinical, biological and radiological arguments.

Clinical arguments

Liver damage is associated with **brain damage**, in some patients.

The eye exam is rather important in Wilson's disease. In fact, almost 40 % of patients and almost all those who have neurological symptoms, have a greenish-brown peri-corneal ring feature. This ring, which is exceptionally visible to the naked eye, should be checked through a slit lamp test.

TO FIND OUT MORE SEE QUESTION 14

Biological arguments

Blood tests can confirm liver damage by revealing a high level of liver transaminases: but it should be known that this liver function test may be normal.

Associated copper assessment:

- **The dosage of ceruloplasmin:** the concentration of ceruloplasmin is lowered in the blood
- **Determining total copper in the blood or cupremia:** total copper includes copper related to ceruloplasmin and free copper. It is lowered.

TO FIND OUT MORE SEE QUESTION 26

Wilson's disease is an overloaded copper disease localized in certain organs, including the liver, but the overall copper in the blood is low.

• **Following the publications of the coordinating site team (Paris)**, REC or Relative Exchangeable Copper must be added to the cupric assessment*. It's the ratio of free or exchangeable copper (which is the toxic copper) over the total copper in the blood. It is higher than 18.5% for patients suffering from Wilson's disease[1].

• **The copper levels in the urine** collected over a 24-hour period is an important part of the diagnosis. There is an increase in the urinary copper level.

• **Research for gene mutation* (molecular diagnosis)**

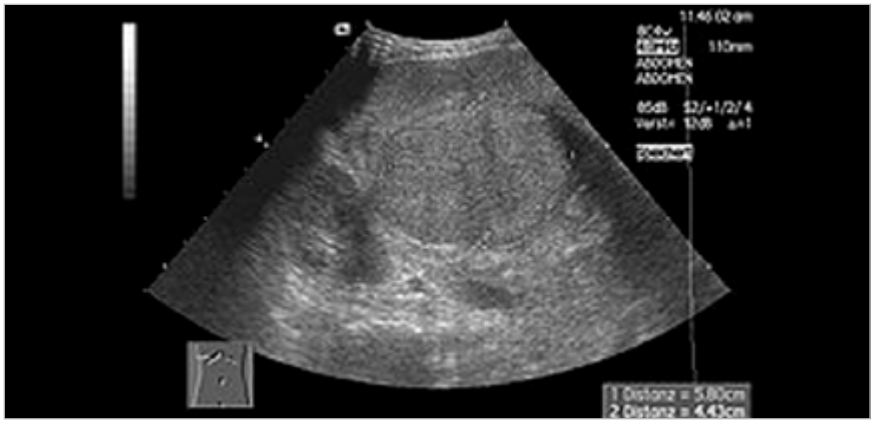
Searching for gene mutation confirms the diagnosis. Over 900 different mutations have been described in Wilson's disease and all of them aren't known.

TO FIND OUT MORE SEE QUESTION 22

1- Woimant et al. New tools for Wilson's disease diagnosis : exchangeable copper fraction. Ann. Trans. Med. 2019.

Radiological arguments

- Hepatic ultrasound helps understanding the liver damage better, look for an increase in the spleen size, in some cases this can be completed with a hepatic MRI.



Example of liver ultrasound

- Brain MRI helps looking for brain damage which may show an accumulation of copper in the brain, the latter is abnormal along with neurological signs.

21. Can Wilson's disease be diagnosed, before the symptoms emerge?

One can diagnose the disease before symptoms appear, in a so-called pre-symptomatic stage, amongst the siblings of the affected person. In this so-called autosomal recessive* disease, the risk of being sick for the brothers/sisters of a patient with Wilson's disease is 25%

It is therefore key to look for the disease in brothers/sisters of the patients, in order to start treatment as quickly as possible. This research is also offered to other family members (parents, uncles, aunts, cousins).

Familial Screening: A blood test and urine test are carried out, to measure copper. More specifically, dosing of ceruloplasmin, total cuprumia, REC - Relative Exchangeable Copper and 24-hour cupremia, not to mention a genetic test is carried out. These tests* are made within the CRMR Wilson disease and other rare copper-related diseases. If the disease is diagnosed, treatment is implemented, to prevent the emergence of symptoms.

GENETICS

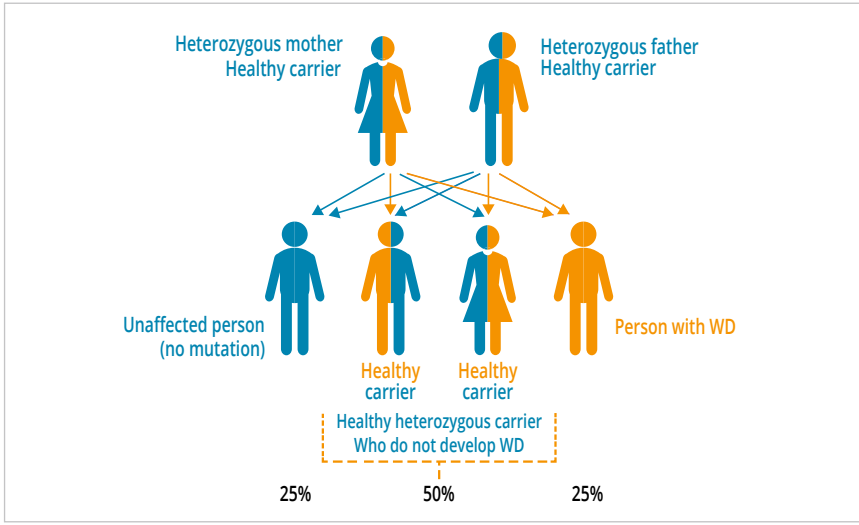
22. What is an autosomal recessive disease?

We all have 46 chromosomes: a set of 23 chromosomes is inherited from our mother and a set of 23 chromosomes is inherited from our father.

- Each chromosome contains thousands of different genes
- Each gene has 2 alleles (1 inherited from the father and 1 from the mother)
- The Wilson disease gene is located in chromosome 13
- More than 900 abnormalities of the Wilson gene (ATP7B) have been described

One has Wilson's disease when the 2 alleles of the Wilson gene are altered.

Parents of someone with Wilson's disease, have a single abnormal allele. They are said to be heterozygous or healthy carriers, because they shall not develop the disease.



Autosomal recessive transmission

23. What are the genetic studies?

Genetic study is about looking for mutations in the ATP7B gene on the 2 alleles on chromosome 13. Screening for mutations can be quick, if the patient has the most common mutations; otherwise, screening for mutations may take several weeks.

24. Can the genetic study always confirm the diagnosis?

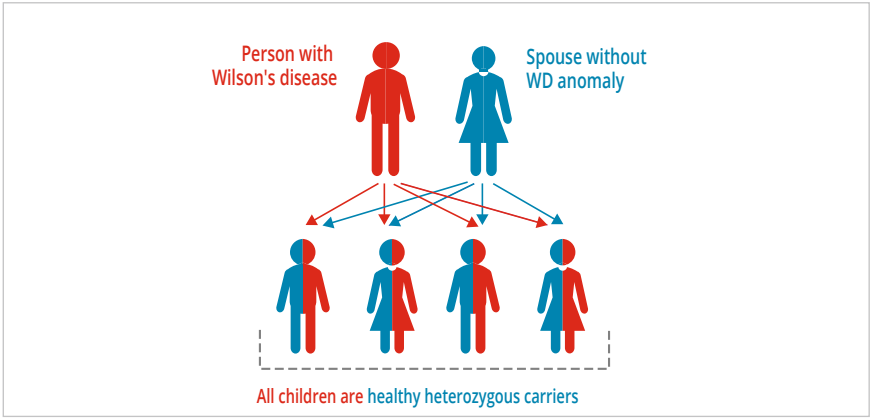
Over 900 mutations in the ATP7B gene have been described. Some are not yet known. The experience of geneticians working with the CRMR Wilson's disease shows that the precise identification of the 2 mutations, was only possible in 98% of the cases. For 2% of patients with Wilson's disease, only 1 of the 2 mutations are currently found. If the clinical symptomatology and the cupric assessment are very suggestive of Wilson's disease, the diagnosis is not questioned, and the treatment shall begin.

25. What are the risks for patients with Wilson's disease to transmit the disease to their children?

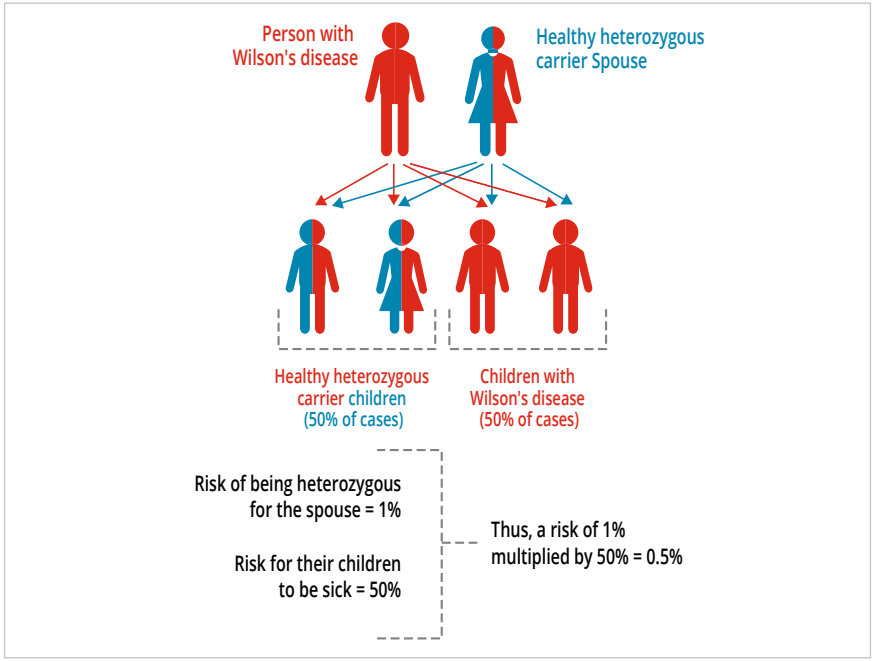
The risk for children to have Wilson's disease, is estimated at 0.5%. Therefore, the risk is rather low, but it is essential to screen for the disease in children to begin treatment. This screening is done from the age of 3 years.

Theoretically, there are 2 possibilities:

- The spouse has no abnormality in the ATP7B gene (most common, 99%). All children are heterozygous - therefore healthy carriers; they will not develop Wilson's disease.



- The spouse is heterozygous (probability 1%), a healthy carrier. In this case, the risk for the child of being sick is 0.5%.



Apart from inbred marriage, we do not know the "genetic" status of the spouse. Currently, it is not recommended to look for genetic anomalies in an unrelated spouse; as not all of the Wilson gene abnormalities are known, the results of the genetic analysis could be falsely reassuring.

COPPER BALANCE

26. In this overloaded copper disease, why is the concentration of copper in the blood (or cupremia) low?

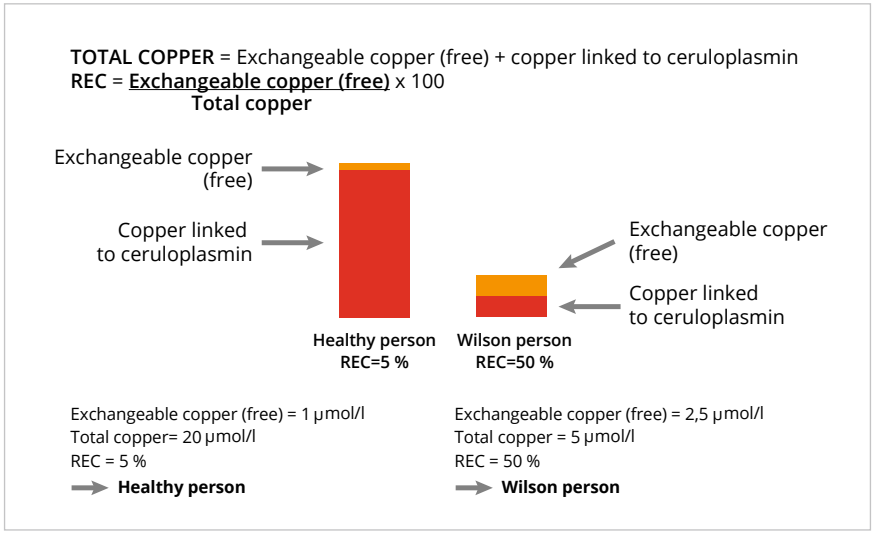
Copper in the blood is mainly related to a protein called ceruloplasmin.

In the absence of Wilson's disease, the total cupremia or copper level in the blood is mainly a reflection of the copper linked to the ceruloplasmin, the free circulating copper being in small quantity.

In Wilson's disease, copper is difficult to attach to ceruloplasmin and circulates through a free form. The total cupremia is low because it mainly reflects the amount of copper linked to ceruloplasmin. Copper in free form increases but in much lower proportions than the decrease in copper, which is linked to ceruloplasmin.

The assessment of exchangeable copper (a technique which was implemented by the Lariboisiere Hospital team, Paris AP-HP, in 2009) allows free copper to be screened. In patients with Wilson's disease, the relative exchangeable copper (REC), which is the ratio of free copper to total copper, is increased (> 18,5%).

Wilson's disease is a disease with excessive copper located in some organs like the liver but the total amount of copper in the blood is low!



Definitions' reminder

27. Is copper concentration in urine always high?

The amount of copper in the urine collected over a 24-hour period is an important element, when it comes to a diagnosis. There is an increase in the urinary copper level.

In Wilson's disease, copper can no longer be eliminated by bile and stool, it is eliminated by urine. The level of copper in a 24-hour urine (or 24-hour cupruria) is increased during the time of diagnosis.

Under treatment, monitoring of cupruria (copper in the urine) is important:

• **under chelator,** [D-Penicillamine (Trolovol®) or Trientine 2HCL (Cufence®) or Trientine 4HCL (Cuprior®)], it remains high. In this case, the chelating drug catches copper and eliminates it through the urine

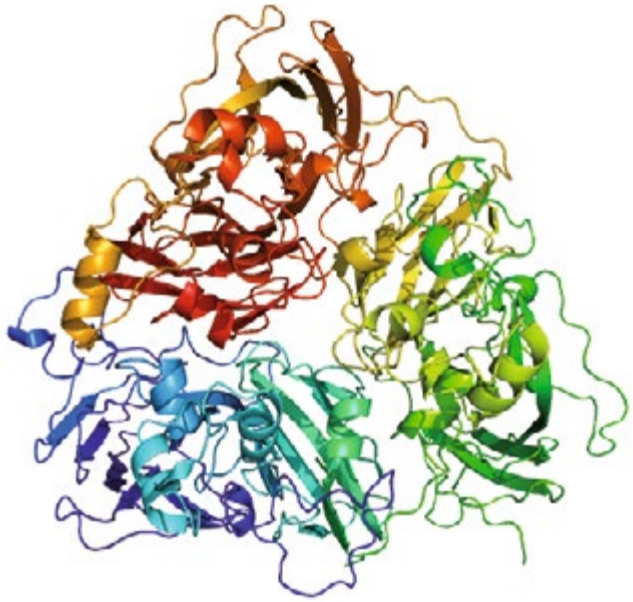
• **under zinc,** [(Zinc acetate (Wilzin®), zinc sulfate (magistral preparation)] digestive absorption of copper is reduced, it is eliminated in the stool. In this case, the 24-hour cupruria is low.

28. Is ceruloplasmin always reduced in Wilson's disease?

Ceruloplasmin is most often low in Wilson's disease. In fact, the ATP7B protein being deficient, it does not make it possible to fix the copper on this protein. In some liver forms of Wilson's disease, ceruloplasmin may be high. Hormonal treatments like the pill or pregnancy can increase the level of ceruloplasmin.

FEATURES OF THE COPPER BALANCE DURING DIAGNOSIS:

- Low ceruloplasmin
- Low total cupremia
- High exchangeable copper in neurological forms[2] (>2µmol/l)
- High REC
- High cupruria



Structure of ceruloplasmin seen by electron microscope

2. Poujois and al. Exchangeable copper: a reflection of the neurological severity in Wilson's disease. Eur J Neurol. 2016

TREATMENTS

29. How do we treat Wilson's disease?

Once the diagnosis of Wilson's disease has been confirmed, whether or not the patient has symptoms, **medical treatment must be started quickly**, combined with a low-copper diet.

This treatment should be continued throughout life. In fact, any interruption of treatment leads to a reappearance or worsening of the symptoms, sometimes brutally and most often seriously.. The aim of the medical treatment for Wilson's disease, is to reduce the damage from copper and prevent further damage.

There are two stages for the treatment:

- **The initial stage** which tries to eliminate the copper accumulated in the organism
- **The maintenance stage**, when the sickness has been stabilized

If necessary, physiotherapy, speech therapy and psychological support is combined.

In a few rare cases, a liver transplant is proposed.

30. What is a low copper diet?

In Wilson's disease, experts advise to reduce copper intake in food:

- **less than 1 mg/day** at the beginning of treatment
- **less than 2 mg/day** (1,3 mg/day for women and 1,6 mg/day for men) when the disease has been stabilized

Foods that contain a lot of copper are organ meats, dark chocolate, shellfish, and dried fruit.

This document shows the copper content of the main foods

GROUPS		ALLOWED WITHOUT RESTRICTION < 0,30 mg of copper/100 g
Beverages		• **All sparkling and mineral waters** (Contrex®*, Volvic®, Evian®) et gazeuzes • **Sodas:** Coca cola®, Limonade, Schweppes® (*0,00 mg /100 ml) • **Fruit juices and nectars:** Ex : orange, peach, apricot nectar U© (*0,24mg/l), Carrefour© organic orange juice (*0,25 mg/l), Granini© (1l) strawberry juice (30%) (*0,12mg/l) • **Coffee and tea:** Ex: powder for cappuccino coffee (*0,01mg/100g), Lipton© herbal tea (*0,002 to 0,004mg/1 cup of 150 ml) • **Chocolate beverages:** Ovomaltine© (*0,14mg/1 tablespoon = 20 g), Nesquick© (*0,20mg/1 tablespoon = 20 g)
Meats, cured meats & offals		• All fresh, frozen, or canned meats, all poultries except duck, all game birds, rabbit • Cured meats: salami, sausages...
Seafood		• Lean and fatty fish, shrimps (*0,25mg/1 handful = 100g), smoked salmon (*0,05mg/2 slices = 80g), canned natural tuna (*0,03mg to 0,07mg/100g), sardines in oil (*0,20mg/100g)
Eggs		• They are all authorized in all forms
Vegetables & dried vegetables		• **All green vegetables: fresh, natural frozen, canned:** Ex: fresh brocolis (*0,18mg/200g), fresh green beans (*0,26mg/200g), canned green beans (*0,16mg/200g), field peas (*0,30mg/200g), canned corn (*0,05mg/100g), carrots (*0,04mg/100g), tomatoes (*0,02 to 0,15mg/100g), tomato sauce (*0,08mg/20 cl carton), parsley (*0,07mg/100g)
Bread & starches		• Pasta, semolina, rice (except whole rice) • **Potatoes**: Ex: French fries (0,11mg/100g), chips (*0,026mg/10 chips, i.e. 23g) • **Bread**: Ex: White bread (*0,13mg/100g)
Fruits & dried fruits		• All authorized: fresh, canned, natural, frozen: ex: fresh grapefruits (0,39mg/100g), fig (0,15mg/1 fig), average banana (0,15mg/banana), fresh blackberries (*0,10mg/100g), canned pineapple (*0,05mg/100g), fresh mango from Peru (*0,03mg/100g)
Dairy products		• Whole, half-skimmed, skimmed, liquid, concentrated, fresh, pasteurized, powder, UHT sterilized milk, soya-based dairy products, yoghurts, cottage cheese... • All cheeses except parmesan: Ex: La vache qui rit (*0,00mg/serving), Tenery cheese for toasted sandwiches (*0,00mg/slice).
Sugar, desserts & sugar-based products		• **Chocolate**: Ex: white chocolate, milk chocolate (0,02mg/100g), Lindt Pyrénéens© milk chocolate (*0,019mg/1 chocolate = 7g), Ferrero Rocher© (0,080mg/1chocolate = 12,5g), Chocolate bars: Ex: Mars© (*0,07mg/1 bar = 50g), Milky Way© (0,03mg/1 bar), Chocolate desserts: Ex: milk chocolate pudding (0,08g/pot), industriel milk chocolate mousse (0,07mg/1 pot), chocolate Dany© (*0,13mg/pot), chocolate and hazelnut sundae (0,05mg/100g), Chocolate breakfast cereals: Ex: Choco pops© (*0,21 mg/60g) • **Pastries, Viennese pastries, cakes** without chocolate or with milk chocolate for home-made cakes. • **Ice creams and sorbets** without chocolate • **Compotes, jams for example:** Vergers gourmand© apples-strawberries compote (*0,04mg/100g), strawberry jam (*0,03mg/100g), Carrefour© currant jelly (*0,02mg/100g), Valade© currant jelly (*0,03mg/100g), chestnut cream (*0,10mg/100g), apple compote (*0,04mg/100g) • **Other desserts:** pudding (except chocolate), Nestlé© semolina pudding (*0,01mg/100g), mix for egg custard (*0,01mg/100g)
Fats		• **All oils, butter, margarine, sour cream**

WITH MODERATION	EXCEPTIONALLY	TO AVOID
0,30 to 1 mg of copper/100g	1 to 3 mg of copper/100g	≥ 3 mg of copper:100g
• **Fruit juices and nectars:** Réa© grapefruit juice (*0,48mg/l) • **Chocolate beverages:** Poulain© chocolate powder (*0,41mg/ 1 tablespoon = 20g)		• **Chocolate beverages:** Van Houten© cocoa (*4,8mg/100g)
• Duck (0,46mg/150g) • Kidneys (0,68mg/100g), heart (*0,33mg to 0,66mg/100g) • Duck liver pate (*0,38 mg/100g)	• Pork liver (2,5 mg/100g), poultry gizzards (*1,15 mg/ 100g) • Poultry liver paste	• **Livers:** veal (*from 13 to 18mg/ 100g), lamb (20,4mg/100g), poultry (*6,4mg/100g), beef (3,75mg/100g)
• Calamari (0,52mg/100g), mussels (0,40mg/200g), small lobsters (0,85mg/3 small lobsters = 100g)	• Crayfish (2mg/100g), crab (1,8 mg/100g), periwinkles (1,7mg/2 handfuls = 100g edible), lobster (1,35mg/100g)	• Scallops (10mg/3 = 100g), clams (6,1mg/120g), common welks (6mg/100g), oysters (4mg/6 to 10 oysters)
• Fresh mushrooms (0,4mg/100g), cooked soya (0,32 mg/ 100g) • Canned lentils (*0,60mg/200g) • Cooked lentils (0,66mg/200g)		
• Whole rice (*0,38mg/200g)		
• **Dried fruits:** dried prunes (*0,33mg/5 prunes = 100g), nuts (0,44mg/10 nuts or 1,34mg/100g), coconut (0,56mg/ 100g), pistachios (*0,66mg/about 66 pistachios = 100g), peanut butter (0,70mg/100g or 0,07mg/1 teaspoon), almond paste (0,50mg/100g) • **Fresh fruits:** currants (0,81mg/100g)	• **Dried fruits:** sunflower seeds (2,27 mg/100g), cashews (2mg/3 handfuls = 100g), Brazil nuts (1,76mg/ 25 nuts = 100g), sesame seeds (1,46mg/100g), pine nuts (1,32 mg/3 handfuls = 100g), hazelnuts (1,2 mg/about 65 hazelnuts = 100g), pecan nuts (1,07mg/ 3 handfuls = 100g), almonds (0,50 mg/50g), peanuts (1,02mg/3 handfuls = 100g)	
• Parmesan (0,34mg/40g)		
• **Chocolate:** Crunch© (*0,45mg/100g), Nutella© (*0,60mg/100g i.e. 7 teaspoons, Chocolate bars: Ex: Bounty© (0,26mg/ 1 bar), Snickers© (0,24mg/1 bar), Kit Kat© (0,13mg/1 pack of 4 bars), Smarties© (0,1mg/1 pack = 40g), Twix© (*0,22mg/ 1 pack of 2 bars), Milka© chocolate bar (*0,10mg/1 bar of 30g), Chocolate desserts: Ex: chocolate profiteroles (0,18mg/100g) • **Pastries, Viennese pastries, cakes:** ginger bread (*0,5mg/50g i.e. 2 slices), breakfast wheat pops cereals (0,33mg/60g), Favorini© hazelnut wafers (*0,39mg/100g = 4 wafers)	• **Chocolate:** black (0,65mg/2 squares, Côte d'Or© black chocolate 70 % (*0,27mg/2 squares) • **Chocolate Viennese pastries:** Ex: chocolate roll	• **Chocolate:** Van Houten© cocoa (*4,81mg/100g) (a maximum of 10g of cocoa can be used in a mix)
• All oils, butter, margarine, sour cream		

31. Are there several kinds of medicines?

There are two types of treatments:

• **Copper chelators** [D-Penicillamine (Trolovol®), Trientine 2HCL (Cufence®) and Trientine 4HCL (Cuprior®)] which collect copper and eliminate it through the urine.

• **zinc salts** [Zinc acetate (Wilzin®), zinc sulfate (magistral preparation)] which increase the elimination of copper from the digestive tract, in the stool

Other treatments, such as tetra thiomolybdate, are being explored.

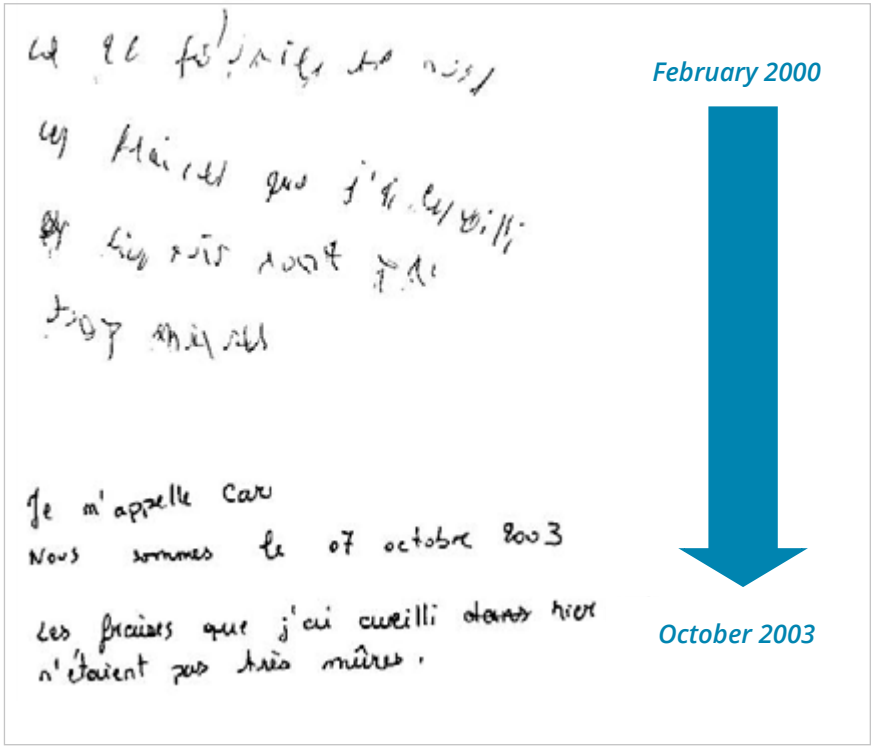
32. What does the initial treatment of Wilson's disease involve?

In the hepatic forms, the treatment is increased progressively over about one month.

In neurological forms, the initial treatment must be initiated by very gradually increasing the dosage* in order to reduce the risk of neurological worsening at the beginning of treatment. This aggravation is observed with all treatments; it is most often reversible. A very close clinical and biological monitoring is essential at the beginning of treatment.

The risk of initial neurological aggravation may be reduced with tetra thiomolybdate, which reduces the intestinal absorption of copper and forms a complex with copper and albumin in the blood; this complex is eliminated through bile. The treatment is currently subject to international studies and is not yet marketed in France.

Improvement under treatment may only appear after several months (3-6 months or more).



Improvement of writing after 5 years of treatment

33. What is the criteria to choose the treatment?

Wilson's disease is a rare disease and no studies have compared the various treatments.

The choice of treatment is based on symptoms during diagnosis:

- **in severe neurological forms and in hepatic forms,** the treatment usually begins with D-Penicillamine (Trolovol®). If D-Penicillamine (Trolovol®) doesn't suit, it is replaced by Trientine 2HCL (Cufence®) or 4HCL (Cuprior®), salts.
- **in moderate neurological forms,** the treatment usually begins with Trolovol®, or zinc (Wilzin®).
- **in symptomless forms,** the treatment is usually based on zinc (Wilzin®).

The decision is made on a case-per-case basis and the French National Authority for Health (HAS) recommends getting the opinion from the Reference Center for Rare Diseases, when it comes to Wilson's disease before beginning the treatment[3].

34. What are the side effects related to the treatment?

Trolovol® or D-Penicillamine may trigger a decrease in the number of white blood cells and blood platelets, the appearance of protein in the urine and more rarely autoimmune diseases* (lupus*, myasthenia*). All are reversible when the treatment is stopped. After several years of treatment, one notices in some patients, that the skin is abnormally wrinkled. The appearance of these side effects leads to stopping D-Penicillamine and replacing it either by Trientine 2HCL (Cufence®) or 4HCL (Cuprior®) or Zinc salt.

Zinc salts, on the other hand, can cause nausea or even vomiting, at the beginning of the treatment.

One should make note that the major risk is the one of not taking the treatment, as this inevitably leads to aggravating the disease.

35. Which patients candidate for a liver transplant?

Liver transplantation is offered to some patients with fulminant hepatitis or severely decompensated chronic liver disease.

Liver transplantation remains controversial in severe neurological forms, without liver decompensation, but resistant to all medical treatment. It could stop the worsening of certain fulminant neurological forms, resistant to usual treatments[4].

The new transplanted liver has a functional ATP7B protein, to make metabolism of copper in the liver normal. Moreover, treatments specific to Wilson's disease are most often stopped; but the patient shall follow a lifelong anti-rejection immunosuppressive treatment and will continue a follow-up, on a regular basis.

3- Protocole National de Diagnostic et de Soins – Maladie de Wilson : **http://www.cnrwilson.com/maladie-wilson/**

4- Poujois, A. et al. Liver transplantation as a rescue therapy for severe neurologic forms of Wilson disease. Neurology 2020.

36. What does the maintenance therapy of Wilson's disease involve?

Once the disease has been stabilized, we become part of the so-called maintenance phase. Treatment should be continued for life.

The dosage of the treatment is to be adapted depending on the individual, according to clinical and biological data including the copper balance (exchangeable copper and cupruria). Adjusting the dosage during this maintenance phase is very important, in order to avoid excess-treatment and copper deficiency.

When the disease has stabilized after several years of follow-up, initial treatment with a chelator may be replaced by zinc salts (Wilzin®), as these are better tolerated.

The main difficulty is complying with the treatment. Indeed, if one stops taking medication, this makes the disease much worse, which can be brutal and not reversible under medical treatment.

Physiotherapy, speech therapy and psychological support is often combined.

37. Can one interrupt the medical treatment?

In Wilson's disease, treatment should never be stopped. Indeed, if one were to stop treatment, it can lead to a re-emergence or re-aggravation of symptoms, within very variable time-periods, but constantly. These relapses (hepatic and/or neurological) are often brutal and can be very serious, especially since the response to treatment is often poor. They can also occur in patients who were initially treated for an asymptomatic form.

38. Is the medical treatment always efficient?

Under treatment, at times spectacular regressions of a pronounced symptomatology can be observed. Most often, liver damage stabilizes and then improves. Tremor, hypertonia* of the limbs, akinesia* often respond better to treatment than axial dystonia*, dysarthria and behavioral disorders. The Kayser-Fleischer ring first fades away at the lateral edges, and then most often completely disappears. However, some patients have a disease which is resistant to the usual drug treatments. In these cases, a liver transplant may be discussed.

39. Is the treatment different for children?

Amongst children, the treatment is the same as in adults; the medical dosage (chelators or zinc salts) is to be adapted depending on the weight.

40. Can one pursue treatment during pregnancy?

During pregnancy, it is key to continue treatment, any discontinuation may lead to quick worsening and symptoms may reoccur. Treatments through Trolovol®, Cufence®, Cuprior® or Wilzin® are therefore continued at reduced doses, most often. The frequency of clinical follow-up consultations and biological assessments (including copper assessment) is much more during pregnancy. After delivery, the usual dose of treatment is resumed.

41. Can a woman suffering from Wilson's disease breastfeed?

There isn't much information available in medical literature when it comes to the risks of breastfeeding under treatment. This is generally not recommended. However, short-term breastfeeding can be decided with the doctor on a case-per-case basis, with most often a proposal to alternate between breast milk and powdered milk (breastfeeding is done just before taking the medication). The dosage of copper in breast milk can be proposed to adapt the recommendations for breastfeeding.

42. Vaccines: should you be vaccinated against hepatitis, against COVID-19 or influenza, when you have Wilson's disease?

When you have Wilson's disease, it is highly recommended that you get vaccinated against hepatitis A and B viruses; catching viral hepatitis may worsen Wilson's disease. There is no vaccination for hepatitis C, which is mainly spread through the blood. **Beware of tattoos and piercings, as these are sources of infections...!!!**

Vaccination against COVID-19 is strongly recommended, especially if the patient has had a liver transplantation, or has cirrhosis or neurological impairment. From similarly, for influenza vaccination.

43. What additional treatments can be offered in case of liver damage?

When there is liver damage, other treatments can be offered:

• **esophageal and/or gastric varices** come with portal hypertension that complicated liver damage. This is treated with beta-blockers, ligation* or sclerosis* of varicose veins

- edema of the lower limbs or ascites is treated with a low-sodium* diet and diuretics

44. What additional treatments can be offered in case of brain damage?

When it comes to neurological forms, treatments can be suggested for:

• **Dystonia** (anticholinergics, benzodiazepines, botulinum toxin injections)
• **Tremor** (beta-blockers)
• **Depressive syndrome** (antidepressant drugs, benzo)
• **Psychiatric disorders** (preferably atypical neuroleptics, benzodiazepines)
• **Symptomatic epilepsy** (antiepileptic drugs)

Orthopedic interventions can be considered, in case of deformations and retractions, related to dystonic postures.

45. How does one carry out the speech therapy treatment?

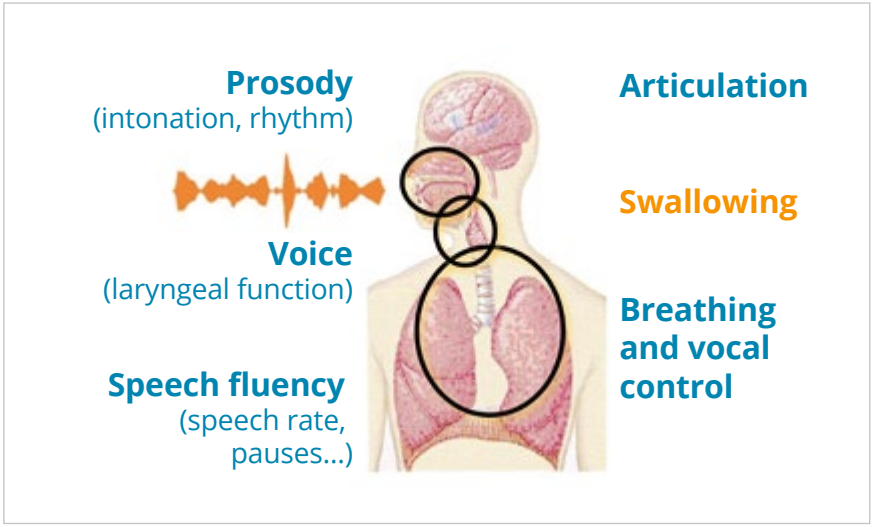
The speech-language pathologist prevents, assesses, diagnoses, and treats speech, language, social communication, cognitive-communication, and swallowing disorders. Different dimensions such as pneumophonic control (breathing for voice and speech production), articulation, laryngeal function (voice), resonance (in case of nasation), prosody (intonation, rhythm of speech), as well as speech fluency (speech rate, pauses) are evaluated and analyzed.

Following the assessment, advice and strategies can be provided to the patient and their family to facilitate communication and swallowing.

A speech therapy follow-up can be organized by taking into account the results of the assessment, the patient's request and his/her overall care with the observations of the medical and non-medical team for Wilson's disease.

The speech-language pathologist of the CRMR is thus in contact with the professionals in private practice or of the patient's institution, speech-language pathologists or others if necessary.

The patient is then regularly re-assessed during his/her visits at CRMR, in order to properly adjust the speech-language pathology management.



Dimensions considered in the speech-language pathology assessment

46. What is the neuropsychological rehabilitation?

Neuropsychological treatment is offered to patients with cognitive and behavioral disorders.

Cognitive impairment concerns difficulties affecting various intellectual functions such as:

• **Memory:** immediate memory or oldest memory, forgetting appointments often or everyday chores, lacking words.

• **Executive functions:** organizing daily lives, paying attention during single and dual tasks, focusing...

• **Gestures and the meanings**, organizing space

The neuropsychological assessment makes it possible to assess each of these functions but also assess behavioral disorders (irritability, lack of motivation, etc.) and offer patients specific rehabilitation for the difficulties which have been pinpointed.

47. What is the physiotherapeutic approach?

The physiotherapist assesses the locomotory functional aspect of patient. Minimal signs, such as stiffness, tremor, can come in the way of delicate gestures (ex: writing), but can also be a major handicap (ex: impaired walking).

The physiotherapist establishes a physiotherapeutic diagnosis and offers recommendations as far as possible, in the form of rehabilitation strategies. He is in contact with his colleagues who take care of the patients near their homes. The latter has the mission of giving information and training with his colleagues, which is part of the initial and in-service training of physiotherapists.

48. What is the psychological approach?

The clinic psychologist offers punctual or regular individual or family interviews to:

• **Support patients and their families confronted with emotional reactions** (stress, anxiety, sadness), questions and changes which may be a result due to being aware of the disease.

• **Support patients in difficult situation, to take their treatment:** Indeed, taking a treatment for life isn't always easy. There are many patients who have a tough time understanding why taking treatment is a problem. This situation can trigger a feeling of shame, guilt and even make patients run away from the medical sector and postpone their consultations. If this is the case, it must be noted

that this is a common problem and there are many solutions for as many patients. One shouldn't hesitate talking to a psychologist or any other medical team member.

• **Supporting loved ones**, mainly those loved ones for whom being diagnosed with the disease is at times a source of guilt or their children, if need be.

• **Or any other request for help** in terms of psychology.

49. What can relaxation techniques and hypnosis provide?

Relaxation has a part to play in rehabilitation. It allows the patient to favor relaxation, channel and alleviate anxiety, pain and stress which is triggered by the disease. Various techniques exist, one can quote Jacobson, Schultz, relaxation which leans on mental imagery.

Medical hypnosis performed by a hypnotherapist (most often Ericksonian) can be offered to help patients manage anxiety, stress or pain.

50. What is the role of social worker?

The social worker supports patients who require help in terms of being part of their social and professional life, to resume or maintain their self-sufficiency, in coordination with partners involved in the therapeutic project.

He/she informs and guides, optionally educates about administrative paperwork, in order to access rights or benefits in the case of a disability. He/she receives people and/or their relatives for an interview, so as to assess the social issues. He/she participates in the development of home support aids but also looks for an establishment, if need be.

51. What are the dietary recommendations?

Dieticians at CRMR Wilson have developed a booklet, with the aim of giving patients advice to restrain the amount of copper in their diet, while respecting a balanced diet. (cf. Question 30)

A recipe book, poor in copper « Recipe, the Wilson way » was written by CRMR Wilson's disease in partnership with patients' association, created and illustrated with a patient suffering from Wilson's disease. It is available on request via **cnr.wilson@for.paris**.

52. How are the patients suffering from the Wilson's disease followed-up?

Regular monitoring of patients with Wilson's disease is key, in order to make sure the efficacy, tolerance and compliance with the treatment. The frequency of consultations is established by the doctors: first pluri-monthly, then half-yearly.

Clinical follow-up is multidisciplinary, carried out by specialized doctors (pediatricians, hepatologists and neurologists) and needed by nurses, physiotherapists, speech therapists, psychologists, neuropsychologists, social workers, dieticians.

Biological follow-up involves:

- **dosage of liver enzymes**, bilirubin, prothrombin level, blood count cells
- **dosage of urinary copper of 24 hours** which is high (until 8 µmol/day) under chelator treatments by D-Penicillamine (Trolovol®) or Triethylenetetramine (Cufence®, Cuprior®) and low (lower than 2 µmol/day) under zinc salts
- **dosage of exchangeable copper;** treatments lead to a decrease in exchangeable copper or serum "toxic" free copper
- **proteinuria of 24h** and **anti-nuclear antibodies** for patients taking D-Penicillamine (Trolovol®)

Clinical and biological worsening should suggest poor compliance with the treatment.

Hepatic monitoring means, in addition to being examined by a doctor and a blood test, the carrying out of an annual or bi-annual abdominal ultrasound (if there is a sign of severe chronic liver disease) associated with a fibro scan which measures the elasticity of the liver.

In the long run, not many patients seem predisposed into developing liver tumors, therefore it is required to regularly monitor via a hepatic ultrasound or even liver MRI.

Clinical neurological monitoring is accompanied, but depends on the neurologist's decision, through a cerebral MRI but also an ophthalmological test, especially if they were abnormal during the diagnosis. Copper-related brain and eye damage usually fades over time.

53. How to benefit from Long Term Conditions (LTC), in France?

The general practitioner must complete the care protocol at a 100%, for a Long-Term Condition (LTC 17: Hereditary* metabolic diseases requiring specialized prolonged treatment), which must then be sent to the medical adviser at the Social Security fund. It takes about 2 months to get the care approval, which usually lasts around 5 years. Therefore, it is required to renew the latter. Since 2020, the renewal of the LTC is conditional on the patient's consultation in one of the centers or competence centers of the Wilson CRMR within the last five years.

This protocol makes it possible to be exempt from the advance fees for treatment, care, tests ... related to Wilson's disease and subject to the use of a professional, who do not charge excess fees.

DAILY LIFE

54. What are the consequences of Wilson's disease on daily life?

The consequences depend on how quickly one is diagnosed and the daily compliance with the treatment. A patient who is diagnosed and treated at an early stage, may have little or no symptoms. On the other hand, when the disease is not treated early enough, it can be disabling, at times leading to a loss of self-sufficiency with difficulties walking, language impairment and swallowing. Luckily, these cases are rare, as the disease is diagnosed much more quickly.

Any patient with Wilson's disease will have to take treatment for life, in 2 to 3 doses per day, most often away from meals, which can be restrictive when it comes to everyday life.

One treatment is available by hospital pharmacies: Wilzin®.

The Trolovol®, Cuprior® and Cufence® are available in local pharmacies.

55. Can patients suffering from Wilson's disease, carry on their professional life?

Except in the case of severe neurological disorders, patients with Wilson's disease keep or resume their professional activity after a few months of treatment.

Students continue or resume their studies with potential support.

56. What are the consequences of Wilson's disease for children?

It's important to explain Wilson's disease to children through simple words, as soon as they are old enough to understand. A booklet for children and their families has been created by the CRMR Wilson's disease. It is available at the hospital or via **cnr.wilson@for.paris (in french)**. A video "Hugo" is also available on the site www.crmrwilson.com.

Most children go to school. Schooling can be arranged through an individualized welcome project (IWP) or a personal schooling project (PSP).

Treatment may be difficult to accept, especially during teenage years. The family team at CRMR Wilson's disease and psychologists are available to help you. The transition between the follow-up among pediatric teams and adults, can also be difficult and must be supported.

57. In case of a persistent handicap, what is the social help within reach, in France?

In the case where the patient is employed or is entitled to unemployment benefits, under certain conditions he can receive daily compensation (IJ) during his sick leave. The daily compensation is paid by the Primary Health Insurance Funds and the maximum payment period is of 3 years.

If the patient's condition does not allow him to go back to work, disability is possible after a certain period of sick leave. This gives access to a pension, subject to affiliation and the latter is calculated depending on the income.

Depending on the loss of work capacity, one can be classified as a 1st or 2nd disability category, situations in keeping with part-time work. The patient or the general practitioner requests for the latter. The Social Security medical offices give the approval.

In other situations, you can receive the Disabled Adult Allowance (DAA), and the request needs to be carried out at the Departmental Center for the Disabled, subject to disability and resources.

58. Do the entourage of caregivers receive help?

These measures apply in France:

• **If the loved one receives the Increment for Third Party**, any family member who supports him may be compensated. On the other hand, when the assisted person benefits from the **Disability Compensation Benefit** (human aids), he can only pay (or compensate) his spouse, ascendant or descendant, if he requires constant help for daily actions. Regardless of the state of health, the latter can pay other family members, provided that they are retired or have partially or totally given up their professional activity.

• **Parental attended leave** is open to all employees, whose dependent child is under the age of 20 and requires continuous presence by their side and compulsory medical care.

This leave can be a maximum of 3 years, through instalments or full time. A request needs to be made to the Family Allocation Fund, in order to obtain payment of the **Daily Allowance for Parental Presence (DAPP)** which replaces the income, but the amount is limited.

• **Family caregiver leave, is an unpaid leave for employees**. The family caregiver of a disabled person can stop their professional activity, in order to take care of their loved one. For a period of 3 months which can be renewed, this leave cannot exceed one year, for the entire career.

• **The free affiliation of a family** caregiver with pension insurance, allows the family caregiver to validate quarters for his retirement for the entire period, during which he shall take care of his loved one without the need to pay premiums, to one's pension fund (subject to conditions related to the handicap of the person receiving assistance and the resources of the household).

TO FIND OUT MORE

59. What is the progress on the Wilson's Disease research? What is the impact on the patient?

While a lot of progress has been made in the recent years, which helps better understand the mechanisms of the disease, there are still some gray areas left, mainly those concerning the metabolism of copper in the brain. Research on Wilson's disease seeks to better understand these mechanisms.

The objective is to develop new treatments such as chelators, specifically taking action on the liver cells, to form a complex with the copper, eliminated in the bile.

Of course, many questions still continue: in which patients can we expect the disease to worsen, at the beginning of treatment? What is the best treatment depending on the form of the disease and its course? How much copper should be reduced in the body?

Research also concerns gene therapy, the initial results on animal models are promising, and the first clinical studies in humans started in 2021.

Treatments which stimulate certain areas of the brain are also being studied, in order to reduce disabling dystonia, which some patients may have.

You can help research on Wilson's disease by making a donation to the "**ALIAGE**" Copper and other metals" association, whose headquarters are at Adolphe de Rothschild Foundation Hospital, 29 rue Manin, 75019 Paris

ALIAGE
ASSOCIATION FOR
WILSON'S DISEASE RESEARCH

60. Where can one get additional information?

The National Reference Center for Wilson's disease strives to improve patient management, for those suffering from Wilson's disease.

This is coordinated by Doctor Aurélia Poujois and is located at the Rothschild Foundation Hospital, 29 rue Manin 75019 Paris.

Contact: cnr.wilson@for.paris or **+331 48 03 62 52**

Web site: www.crmrwilson.com

The Rare Diseases Reference Center "Wilson's disease and other rare copper-related diseases" has been included in the G2M sector, since April 2016.

Web site: www.filiere-g2m.fr

SFEIMA is the French Society for the Study of Innate Errors of Metabolism in Adults.

Web site: www.sfeima-asso.fr

Information server for rare diseases.

Web site: www.orpha.net

The Bernard Pepin association for Wilson's disease is the patients' association in France dedicated to WD and has the following objectives:

- To help patients suffering from Wilson's disease and their families by helping them morally and materially.
- To inform the population about this disease
- To educate the medical profession for an early diagnosis
- To contribute to research: genetics, pathophysiology and therapy

Contact : communicationbpwilson@gmail.com
+335 45 91 12 29 or **+336 47 43 22 71**
Web site: www.abpmaladiewilson.fr

The European EuroWilson site contains information about Wilson's disease, which may be of interest to patients, their families and healthcare professionals.

Web site: www.eurowilson.org

European Alliance of Patient and People Associations active in the field of rare diseases.

Web site: www.eurordis.org

Where can one get additional information?

Association law 1901 created in October 2011, «Rare Diseases Info Services» is a health telephony device, devoted to rare diseases. It is meant for the sick, their loved ones and healthcare professionals.

You can speak freely and be heard during a conversation, where your anonymity shall be respected.

Contact : +331 56 53 81 36
Web site: www.maladiesraresinfo.org

The mission of the Alliance Rare Diseases is to encourage, develop, on issues common to rare diseases and rare disabilities, genetic or not, any information, training, mutual aid, advocacy and of research.

Web site: www.alliance-maladies-rares.org

The objective of the Rare Disease Foundation is to develop research in the field of rare diseases, in order to promote the emergence of new therapies and also improve the life course of patients and their entourage.

Web site: www.fondation-maladiesrares.org

SPECIFICITY OF THE MANAGEMENT OF WILSON'S DISEASE WILSON'S DISEASE IN FRANCE

The National Plan for Rare Diseases (PNMR):

France plays a pioneering role in the field of rare diseases: it is the first country in Europe to have developed and implemented a national plan. In 2003, a strategic plan to improve the care of people suffering from rare diseases was implemented. This 1st PNMR (2005-2008) has, among other things identified centers of reference and competence. The 2^{d} PNMR (2011-2016) saw the creation of rare disease health networks. The 3rd PNMR (2018-2022) is a continuation of the 1st PNMR with the creation of 23 health networks based on 387 centers of reference and 1,800 centers of competence for a global follow-up as close as possible to the patients.

The network of the reference center:

Patients with Wilson's disease are managed within the network of the Centre de Référence Maladies Rares (CRMR) «Wilson's disease and other rare copper-related diseases».

The CRMR is coordinated by Doctor Aurélia Poujois and is located in the Department of Neurology of the Adolphe de Rothschild Foundation Hospital, 29 rue Manin 75019 Paris.

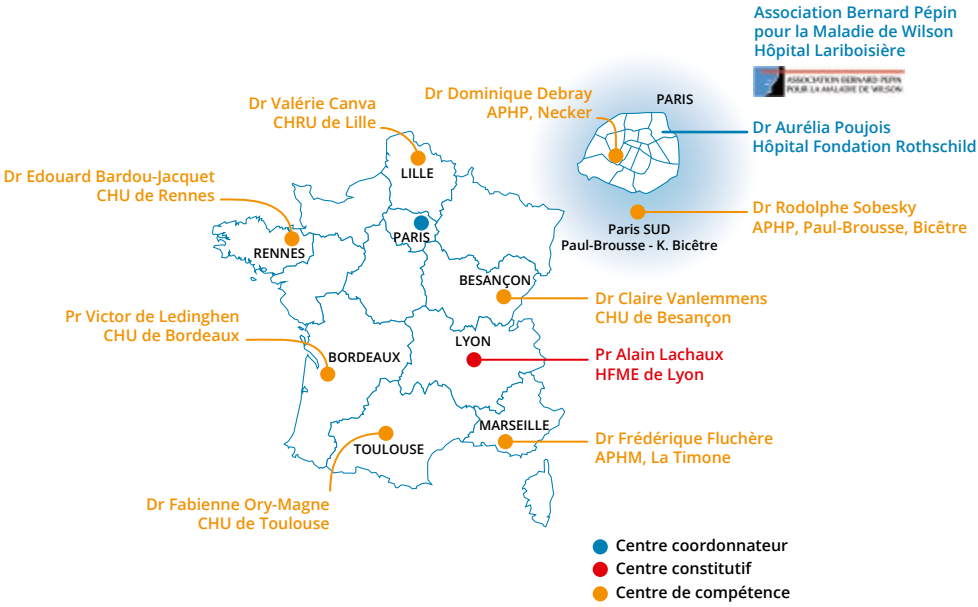
The CRMR was accredited by the Ministry of Health and Solidarity in October 2005 and re-labeled in September 2017. Since June 2016, it is part of the Filière G2M (Groupement des Maladies Héditaires du Métabolisme).

The CRMR brings together clinical teams with complementary skills to provide optimal care for patients with Wilson's disease, from the beginning to Wilson's disease, from children to adults.

The missions of the CRMR are to:

- Structure the care offer
- Coordinate patient care
- To take charge of the patients because the diagnosis and the treatment are particularly complex
- Organize multidisciplinary consultations
- Define the referentials and therapeutic protocols
- Inform and train professionals
- Coordinate research activities
- Ensure epidemiological monitoring and patient follow-up (National Registry)

On the territory, the network is made up of a coordinating center, a constituent center and eight competence centers.



GLOSSARY

Akinesia: Akinesia is a slow initiation and realization of movements.

Albumin: Albumin is the most common protein in the blood. A drop in albumin in the blood mainly occurs during liver failure or kidney disease.

Anemia: Anemia is an abnormal drop in red blood cell count.

Ascites: Ascites is defined as the presence of a bloodless fluid in the abdominal cavity.

Auto-immune disease: Autoimmune diseases result from a dysfunction of the immune system which attacks the normal constituents of the body.

Autosomal recessive: Autosomal transmitted disease also affects boys and girls. Recessive disease occurs when the subject has received 2 mutated genes, one from his father and the other from his mother.

Bile: Bile is a viscous liquid, yellow or greenish in color, produced by the liver.

Bilirubin: Bilirubin is a yellow pigment, a degradation product of hemoglobin but also of other hemoproteins, which abnormal accumulation in the blood and tissues determines jaundice, which can arise from very various causes.

Chelator: Substance capable of forming with copper or other metals an removable complex in the urine.

Cupric assessment: The cupric assessment is a blood and urine assessment, used to determine the level of copper in the blood and urine.

Dose: A medication dose, which needs to be taken and observed in order to be effective.

Dysarthria: Dysarthria is a disorder concerning speech performance and control. It results in impaired speech, articulation, speed and speech melody. Dysarthria can make patients difficult to understand.

Dystonia: muscle tone disorder characterized by involuntary, prolonged muscle contractions, of one or more parts of the body, responsible for abnormal behavior.

Genetic disease: Genetic diseases are the set of diseases which are caused by one or more defective genes or by a chromosomal abnormality. This can be hereditary or not.

Genetic mutation: A genetic mutation is an alteration of the cell's genetic material, which can be at the origin of a genetic disease.

Hepatic: which makes up the liver or which relates to liver.

Hereditary: Which is transmitted according to the genetic laws of heredity.

Heredity: Transmission of genetic characteristics from parents to their descendants.

Hypertonia: Exaggeration of muscle tone which is expressed by an increase in the resistance of the muscle, during stretching.

Kidney stones: Kidney stones are stone-like formations which develop in the kidneys and urinary tract.

Ligation: Surgical operation that involves tightening a link around a vessel.

Lithiasis: Constitution, formation of stones in the kidneys or urinary tract (nephritic lithiasis), in the gallbladder (vesicular lithiasis), ...

Low-sodium: Low sodium diet limits salt intake in the diet.

Lupus: Lupus is a chronic autoimmune disease, of various manifestations, which can affect one or more organs.

Myasthenia: Myasthenia is a neuromuscular disease, which causes muscle weakness of varying intensity and duration.

Platelets: Blood platelets are small cells found in the blood just like red blood cells and white blood cells. They have an essential role in coagulation.

Prevalence: Number of people affected by an illness. It generally speaks for 100,000 people.

Prothrombin: Prothrombin level is a medical biology analysis used to assess blood clotting.

Sclerosis: Varicose sclerosis is the intravenous injection of a product which shall create a vein's inflammatory lesion and lead to its occlusion.

Slit lamp: Kind of microscope equipped with a lighting device, a light slit, allowing to examine the cornea and the lens.

Transaminases: Transaminases are enzymes found in many organs. An increased level of transaminases translates to liver, heart or muscle damage.

Visual acuity: Visual acuity is the ability to clearly distinguish small details at close or long distance.

This practical guide, coordinated by Dr. France Woimant,
Dr. Aurélia Poujois and Ms. Emeline Ruano, was developed in 2018
by professionals from the coordinating site of the Lariboisière Hospital (Paris)
under the aegis of the CRMR Wilson disease and other rare copper-related diseases.

In September 2021, it was updated by the professionals of the coordinating site
of the Adolphe de Rothschild Foundation Hospital.

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Wilson's disease in 60 questions

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