

Wilson Disease Watch

July-November 2011. vol 2

Abstracts of the European Wilson Disease Congress

European
Wilson Disease Congress

2011- November 14/15th

EuroWilson

PARIS

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Quality of life in patients with treated and clinically stable Wilson's disease

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Summary

Wilson's disease (WD), a rare autosomal recessive disease, has prevalence between 12 and 29 per 100,000 in European population. In the years 1980–2007, a cohort of 142 patients with WD (54 presented with neurologic symptoms, 49 with hepatic symptoms, 33 had mixed form, and data were missing for six patients) was followed-up (for patients alive mean duration was 11.1 ± 8.8 years). After initiation of treatment (d-penicillamine and zinc salts), 79% of patients had a stable or improved course of disease. Despite early diagnosis and appropriate therapy, 15 patients still had a relentlessly progressive course. Thirty patients died. The cumulative probability of survival in a 15-year period for the whole group was $76.7 \pm 4.9\%$. Better prognosis of WD was associated with male sex, younger age at onset, neurologic form of the disease, and treatment continuity.

In continuation, we were interested in the Health-related quality of life (HRQoL) in WD, since it has not been extensively studied. Therefore, the purpose of this cross-sectional study was to identify clinical and demographic factors influencing HRQoL in 60 treated, clinically stable patients with WD using a generic questionnaire, the Medical Outcomes Study Short-Form 36-Item Health Survey (SF-36). The level of disability and grading of WD multisystemic manifestations were assessed by the Global Assessment Scale for WD (GAS for WD). The Mini Mental State Examination (MMSE) and the 21-item Hamilton Depression Rating Scale (HDRS) scoring were also applied by the same trained interviewers. Lower scores on the SF-36 domains were found in patients with neurological compared with those with a predominantly hepatic form of WD. The HRQoL of patients with WD and psychiatric symptoms was also lower than that of those without them.

Finally, significant inverse correlations were obtained between the various SF-36 domains and all the following: period of latency from the first symptoms/signs appearance and treatment initiation, MMSE and HDRS scores, and different domains of the GAS for WD.

Wilson's disease in consecutive generations of one family

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Summary

Wilson's disease (WD) is an autosomal recessive disorder of copper metabolism caused by mutations in the *ATP7B* gene. Hepatic and neurological symptoms are the main clinical features of the disease.

We present the clinical and genetical analysis of non consanguineous family with affected members over two generations which were diagnosed after WD diagnosis in the proband. Twenty three individuals were studied prospectively. Retrospective data was obtained on 6 deceased family members. Among 32 analyzed family members, WD was confirmed by genetic testing in 4 persons: 2 of them had hepatic feature, 1 manifested with neurological symptoms and 1 was clinically asymptomatic.

Four other family members had clinical history which was suggestive of WD; but they weren't studied because they were deceased at the time of study.

We suggest that after WD diagnosing in the proband, a detailed interview should be performed on the history of neuropsychiatric / hepatic symptoms suggestive for WD in proband's siblings but also for more distant relatives.

Genetic variability in the methylenetetrahydrofolate reductase gene (*MTHFR*) affects clinical expression of Wilson's disease

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Summary

Wilson's disease (WND) is an autosomal recessive disorder of copper (Cu) transport, resulting from pathogenic mutations in the *ATP7B* gene. The reason for the high variability in phenotypic expressions of WND is unknown.

We recently documented that 5,10-methylenetetrahydrofolate reductase (one of the key folate/homocysteine pathway enzymes) gene (*MTHFR*) polymorphisms: C677T and A1298C in 245 WND effect the clinical expression of WND. *MTHFR* 1298C allele is related to earlier symptomatic WND manifestation compared with the 1298A allele. Carriership of the *MTHFR* "high activity" diplotype (double wild-type homozygous genotype 677CC/1298AA) is associated with delayed manifestation of WND.

Patients with the *MTHFR* 677T allele less frequently exhibit the neurological WND phenotype (31 (29.5%) vs. 36 (48.0%)), and more frequently present with hepatic WND (44 (41.9%) vs. 22 (29.3%)), compared with subjects *MTHFR* 677T(-).

Relative exchangeable copper: a new highly sensitive and highly specific biomarker for Wilson's disease diagnosis.

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Summary

Failure to diagnose WD can be dramatic leading to irreversible clinical damages. The Wilson disease gene codes for a copper transporting P-type ATPase (ATP7B) and the molecular genetic analysis of ATP7B gene is the reference test for diagnosis. The number of reported mutations of the *ATP7B* gene is on the rise. The analysis is cumbersome and requires tedious work. Other clinical and biological tests are proposed to diagnose WD but it is often difficult to interpret some patients' results. A rapid and reliable biological test for WD diagnosis is still needed.

We propose in this work a new biomarker, the relative exchangeable copper (REC) for the diagnosis of Wilson disease (WD). This test is designated to be used as a routine test in most laboratories. Analytical reliability of exchangeable copper (CuEXC) determination procedure is examined by studying the repeatability, the short stability and stability in frozen plasma. Relative exchangeable copper (REC = CuEXC/total copper %) is proposed and evaluated as a new diagnostic test and compared to classic tests used for WD diagnosis.

The determination procedure of CuEXC revealed to be analytically reliable and the CuEXC parameter is stable at room temperature for 24 hours and at -40°C for at least 7 days. Sixteen new Wilson disease patients were diagnosed in our institution between January 2009 and May 2011. The different biological tests used for WD diagnosis yielded lower sensitivity and specificity compared to our new biomarker, the REC. We believe that the relative exchangeable copper (REC) will facilitate the diagnosis of WD and will be a widely used test by laboratories.

Zinc-induced copper deficiency in Wilson's disease

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Summary

Introduction

Zinc intoxication has been reported in cases of therapeutic overdose for skin conditions, of coin ingestion and of chronic use of denture cream. Toxicity of zinc is mediated by copper deficiency, the former interfering with the intestinal absorption of copper, and it is responsible for hematologic abnormalities like sideroblastic anaemia, neutropenia and myelodysplasia. Neurological complications such as myelopathy and peripheral neuropathy have also been reported. No case of renal involvement has yet been published.

Case report

A 41-year-old patient had been treated by zinc-sulfate monotherapy for Wilson's disease for 10 years by 880 mg zinc-sulfate daily, and recently 1000mg/day (250mg zinc). He presented with a distal tetraparesis and hypoesthesia progressing for several months. Electroneuromyography confirmed a severe, axonal and predominantly motor polyneuropathie and somatosensory evoked potentials showed a myelopathy. He had anaemia, neutropenia and the bone marrow aspirates showed ringed sideroblasts; typical signs of copper deficiency. He had a severe yet asymptomatic albuminuria (8,300mg/24h) due to glomerulosclerosis with segmental hyalinosis. The daily-excreted urinary zinc amount was 200 times the normal upper limit. Serum and urinary copper levels and ceruloplasmine were low. Quantification in a liver biopsy showed tissue copper depletion. Once the zinc treatment was interrupted, the hematopoietic abnormalities normalized within a month, albuminuria decreased by 10 times within 3 months but the distal paresis remained unchanged.

Conclusions

This is a case of zinc intoxication in Wilson's disease due to chronic therapeutic overdose, resulting in the paradoxical situation of acquired copper deficiency in a genetic condition of copper overload. Besides typical and reversible hematologic abnormalities, the patient had a massive albuminuria that improved dramatically after zinc discontinuation. Neurological deficits remained unchanged. We suggest that Wilson disease patients treated with zinc undergo regular check-ups for blood counts and 24h urinary excretion of zinc and copper.

Long term follow-up of Wilson's disease – survival, clinical course, treatment, mutations analysis, and phenotypic correlation

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Summary

Background and Aims: Wilson disease (WD) is an inherited disorder of copper metabolism. When treated, the outcome can be excellent, although long-term survival has yet to be well documented. The aim of this study was to describe the long-term outcome of a cohort of patients with WD, and to assess those factors affecting the phenotypic manifestation of WD.

Methods: The presence of mutations to the ATP7B gene, the clinical manifestations, treatments, and the long-term outcomes were analyzed retrospectively in 117 patients with WD (59 men and 58 women, aged at evaluation 38.5 ± 11 , range 16-63 years).

Results: Fifty-five patients with a neurologic presentation, 51 patients with a hepatic presentation, and 11 asymptomatic patients were followed-up for an average of 15.1 ± 10 years (median 12 years, range 1 - 41 years). The H1069Q ATP7B gene mutation was the most frequent genetic variant (54.3%); the frequency of this mutation did not differ between patients with either the hepatic or neurological presentation ($p=0.099$). D-Penicillamine or zinc salts (81% and 17%, respectively) were used for treatment; and 3 patients underwent liver transplantation. The majority of symptomatic patients became asymptomatic, or improved, during the follow-up (82% patients with hepatic presentation, 69% with neurologic presentation). The long-term survival of patients with WD did not differ from that of the general Czech population ($p=0.95$).

Conclusions: Long-term follow-up shows a satisfactory response in the great majority of adequately treated patients with WD, and survival coincides with that of the general population.

Supported by by grant IGA MZ CR No. NT 12290/4 and NT 11247/4 provided by the IGA, Czech Ministry of Health.

Gene therapy in the LEC rat, animal model of Wilson's Disease

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Summary

Wilson's disease is an hereditary monogenic disease of the liver which represents an attractive candidate for a gene therapy. Indeed, the continuous turn-over of hepatocytes may results in a selective proliferative advantage for genetically corrected hepatocytes with ensuing repopulation with corrected cells.

The Long Evans Cinnamon (LEC) rat has a spontaneous mutation of the ATP7B gene and develops a phenotype that mimics the human liver disease. In the past 15 years, various attempts have been made to correct the genotype of these rats using cell or gene therapy, with improvements in biological and histo-pathological markers.

We will discuss here the potential of the LEC rat in the comprehension of Wilson's disease, and what new perspectives are currently developed to achieve gene correction in this disease, in particular using lentiviral vectors.

Medical therapy in Wilson disease

Karl Heinz Weiss

Summary 1/3

INTRODUCTION: The autosomal recessively inherited copper overload disorder Wilson disease remains a diagnostic and therapeutic challenge. The overall therapeutic approach is the generation of a negative copper balance.

A dilemma in Wilson Disease is the lack of controlled randomized trials with an optimal design. Still the choice of the “best” therapy remains an individual decision. Treatment options have not substantially changed within the last years, but some concepts are challenged by large cohort studies published recently. Medical therapy in Wilson disease should be life long following a theoretical, sequential treatment concept that has been suggested based on limited trials and experience. It differentiates between initial therapy and subsequent maintenance therapy, based on the hypothesis that after an initial treatment phase less dosage or an alternative treatment in decoppered patients might be sufficient to upkeep copper homeostasis.

TREATMENT: The treatment regimens, suggested by current guidelines [1], include copper chelators (namely D-penicillamine and Trientine) and/or zinc salts. The most fundamental differences between these is the distinct mode of function. While chelating agents bind copper directly and facilitate its excretion, zinc interferes with the intestinal uptake of copper [2, 3] and induces the endogenous chelator methallothionein [4, 5]. The decision which drug should now be used as first line therapy is driven by multiple considerations, but simplified it should be effective and safe.

Efficacy of medical therapy

Most data exist on the chelator D-penicillamine (DPA), which was the first oral chelating agent used to treat Wilson disease [6]. Various studies document the efficacy of D-penicillamine in symptomatic patients with liver disease [7-10]. The alternative chelator trientine has never been analysed in a head-to-head comparison to d-penicillamine but has also been shown to be an effective initial therapy for hepatic patients [7, 11-13]. Other chelating agents, including ammonium tetrathiomolybdate (TM) [14-19] remain an experimental therapy and are not commercially available. Judging from our experience more than 90% of patients with hepatic symptoms show an improvement under therapy with trientine or d-penicillamine. In the light of these overall encouraging and good results for chelating agents to control liver disease, the efficacy of these chelators is considered less favorable concerning neurologic disease.

Based on the distinct mode of action the overall decoppering potential of zinc salts is limited compared with D-penicillamine or Trientine. Consistently a lower or at least comparable rate of neurologic deterioration of neurologic patients under zinc monotherapy has been reported [10, 20-22]. However, studies or case series of patients receiving zinc salt as primary treatment are often restricted to asymptomatic [23, 24] or only neurologically [10, 22] affected patients. But even with this restriction the efficacy of zinc monotherapy is under debate. While some series suggest a favorable outcome of neurologic symptoms [10, 22], a non-response or neurologic worsening under zinc therapy seems to occur to a certain degree [25, 26] as well. In summary the use of zinc did not solve the problem of neurologic non-improvement or deterioration under medical therapy.

Medical therapy in Wilson disease

Karl Heinz Weiss

Summary 2/3

Concerning liver related symptoms the picture is more unambiguous. In a recent cohort study with 288 patients [27] we compared the hepatic outcome of treatment with chelating agents against zinc monotherapy. We found a significant higher rate of inadequate response to therapy (in terms of worsening of liver function tests and increasing urinary copper excretion) in patients under zinc than under chelation treatment. Concerning the elevation of ALT and gGT, these findings are in line with a recently published series of 17 patients who showed a similar, but not statistically significant, trend under zinc monotherapy [20]. Constitutional risk factors for the failure of zinc therapy were not evident in our cohort [27], as this event was not associated with sex, genotype, presentation, degree of liver dysfunction or age. However this emerging concept of “zinc non-responders” has implication for the choice of the treatment regimen as well for the monitoring of patients under zinc maintenance therapy. Further more, in our cohort study [27] neurological worsening occurred under all treatment regimens to a comparable amount, weakening the argument for the preferential use of zinc in these patients. But to finally elucidate this question of how to approach neurologic WD, prospective trials using standardized neurological rating scales would be desirable. In this context further efforts are also necessary to determine additional symptomatic treatment concept for these neurologic patients [28].

Safety of medical therapy

A clinically relevant limitation in the long-term use of every medication is the occurrence of adverse events necessitating a treatment change. This holds true for D-penicillamine where severe adverse events such as bone marrow toxicity, elastosis cutis, nephrotoxicity or lupus-like syndrome lead to the discontinuation of D-penicillamine in up to 30% of patients [29, 30] [27]. The alternative chelator trientine has been reported to have a better safety profile, although relevant adverse events like anemia have been observed. In our experience the rate of side effects demanding a treatment change is far less than under D-penicillamine ([27, 31] and unpublished data). So far only few adverse events, such as gastritis or copper deficiency anemia, have been reported under zinc therapy.

CONCLUSION:

In Wilson disease the choice of the medical therapy remains an individual decision, as only very few prospective data are available. While hepatic patients seem to benefit from the use of chelating agents, the primary role of zinc mono therapy may remain as a medical treatment alternative for asymptomatic or neurologically affected patients. An inadequate response to treatment, as well as signs of over treatment or the occurrence of relevant adverse events demand life long and continuous monitoring of the patients. This includes especially examination for new neurological or hepatic symptoms, as well as the assessment of liver function tests and urinary copper excretion. Despite neurological normalization, the restoration of normal liver function tests, namely AST, ALT and gGT, should be considered a primary treatment target.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

Medical therapy in Wilson disease

Karl Heinz Weiss

References 3/3

1. Roberts, E.A. and M.L. Schilsky, *Diagnosis and treatment of Wilson disease: an update*. Hepatology, 2008. **47**(6): p. 2089-111.
2. Brewer, G.J., et al., *Oral zinc therapy for Wilson's disease*. Ann Intern Med, 1983. **99**(3): p. 314-9.
3. Hoogenraad, T.U., R. Koevoet, and E.G. de Ruyter Korver, *Oral zinc sulphate as long-term treatment in Wilson's disease (hepatolenticular degeneration)*. Eur Neurol, 1979. **18**(3): p. 205-11.
4. Hill, G.M., et al., *Treatment of Wilson's disease with zinc. I. Oral zinc therapy regimens*. Hepatology, 1987. **7**(3): p. 522-8.
5. Cousins, R.J., *Absorption, transport, and hepatic metabolism of copper and zinc: special reference to metallothionein and ceruloplasmin*. Physiol Rev, 1985. **65**(2): p. 238-309.
6. Walshe, J.M., *Wilson's disease; new oral therapy*. Lancet, 1956. **270**(6906): p. 25-6.
7. Walshe, J.M., *Copper chelation in patients with Wilson's disease. A comparison of penicillamine and triethylene tetramine dihydrochloride*. Q J Med, 1973. **42**(167): p. 441-52.
8. Grand, R.J. and G.F. Vawter, *Juvenile Wilson disease: histologic and functional studies during penicillamine therapy*. J Pediatr, 1975. **87**(6 PT 2): p. 1161-70.
9. Lau, J.Y., et al., *Wilson's disease: 35 years' experience*. Q J Med, 1990. **75**(278): p. 597-605.
10. Czlonkowska, A., J. Gajda, and M. Rodo, *Effects of long-term treatment in Wilson's disease with D-penicillamine and zinc sulphate*. J Neurol, 1996. **243**(3): p. 269-73.
11. Dubois, R.S., D.O. Rodgeron, and K.M. Hambidge, *Treatment of Wilson's disease with triethylene tetramine hydrochloride (Trientine)*. J Pediatr Gastroenterol Nutr, 1990. **10**(1): p. 77-81.
12. Saito, H., et al., *Triethylene-tetramine (trien) therapy for Wilson's disease*. Tohoku J Exp Med, 1991. **164**(1): p. 29-35.
13. Scheinberg, I.H., M.E. Jaffe, and I. Sternlieb, *The use of trientine in preventing the effects of interrupting penicillamine therapy in Wilson's disease*. N Engl J Med, 1987. **317**(4): p. 209-13.
14. Brewer, G.J., et al., *Treatment of Wilson's disease with tetrathiomolybdate: V. Control of free copper by tetrathiomolybdate and a comparison with trientine*. Transl Res, 2009. **154**(2): p. 70-7.
15. Brewer, G.J., et al., *Treatment of Wilson disease with ammonium tetrathiomolybdate: IV. Comparison of tetrathiomolybdate and trientine in a double-blind study of treatment of the neurologic presentation of Wilson disease*. Arch Neurol, 2006. **63**(4): p. 521-7.
16. Brewer, G.J., et al., *Treatment of Wilson disease with ammonium tetrathiomolybdate: III. Initial therapy in a total of 55 neurologically affected patients and follow-up with zinc therapy*. Arch Neurol, 2003. **60**(3): p. 379-85.
17. Brewer, G.J., et al., *Treatment of Wilson disease with ammonium tetrathiomolybdate: II. Initial therapy in 33 neurologically affected patients and follow-up with zinc therapy*. Arch Neurol, 1996. **53**(10): p. 1017-25.
18. Brewer, G.J., et al., *Treatment of Wilson's disease with ammonium tetrathiomolybdate. I. Initial therapy in 17 neurologically affected patients*. Arch Neurol, 1994. **51**(6): p. 545-54.
19. Brewer, G.J., et al., *Initial therapy of patients with Wilson's disease with tetrathiomolybdate*. Arch Neurol, 1991. **48**(1): p. 42-7.
20. Linn, F.H., et al., *Long-term exclusive zinc monotherapy in symptomatic Wilson disease: experience in 17 patients*. Hepatology, 2009. **50**(5): p. 1442-52.
21. Hoogenraad, T.U., J. Van Hattum, and C.J. Van den Hamer, *Management of Wilson's disease with zinc sulphate. Experience in a series of 27 patients*. J Neurol Sci, 1987. **77**(2-3): p. 137-46.
22. Brewer, G.J., et al., *Treatment of Wilson's disease with zinc: XV long-term follow-up studies*. J Lab Clin Med, 1998. **132**(4): p. 264-78.
23. Brewer, G.J., et al., *Treatment of Wilson's disease with zinc. VI. Initial treatment studies*. J Lab Clin Med, 1989. **114**(6): p. 633-8.
24. Walshe, J.M., *Diagnosis and treatment of presymptomatic Wilson's disease*. Lancet, 1988. **2**(8608): p. 435-7.
25. Walshe, J.M. and N.A. Munro, *Zinc-induced deterioration in Wilson's disease aborted by treatment with penicillamine, dimercaprol, and a novel zero copper diet*. Arch Neurol, 1995. **52**(1): p. 10-1.
26. Lang, C.J., et al., *Fatal deterioration of Wilson's disease after institution of oral zinc therapy*. Arch Neurol, 1993. **50**(10): p. 1007-8.
27. Weiss, K.H., et al., *Zinc monotherapy is not as effective as chelating agents in treatment of Wilson disease*. Gastroenterology, 2011. **140**(4): p. 1189-1198 e1.
28. Holscher, S., et al., *Evaluation of the symptomatic treatment of residual neurological symptoms in Wilson disease*. Eur Neurol, 2010. **64**(2): p. 83-7.
29. Medici, V., et al., *Diagnosis and management of Wilson's disease: results of a single center experience*. J Clin Gastroenterol, 2006. **40**(10): p. 936-41.
30. Walshe, J.M., *Wilson's disease presenting with features of hepatic dysfunction: a clinical analysis of eighty-seven patients*. Q J Med, 1989. **70**(263): p. 253-63.
31. Merle, U., et al., *Clinical presentation, diagnosis and long-term outcome of Wilson's disease: a cohort study*. Gut, 2007. **56**(1): p. 115-20.

Wilson disease today and tomorrow

F Woimant

Summary

Prognosis of neurological forms of Wilson disease (WD) is highly variable. Some patients have marked clinical improvement and have excellent social and professional quality of life with normal life expectancy. Other patients will remain severely affected, with important dysarthria and diffuse dystonia.

The delay between the first symptoms and the diagnosis, the severity of the disease, the medical therapy resistance and the medication compliance seem to be among the main determinants for the prognosis.

The challenge for the next years is to improve prognosis of these patients. For that, we have:

1 To reduce the delay for diagnosis. Actually the mean delay for diagnosing Wilson disease in a neurological form is about two years. For reduce this delay, we have to organize formations, trainings and meetings for health professionals: paediatricians, hepatologists, neurologists, psychiatrists, ophthalmologists, gynaecologists , speech therapists, physiotherapists, psychologists ...

2 To develop highly sensitive and specific biomarker for WD diagnosis as relative exchangeable copper or REC. This technique allows diagnosing rapidly the patients affected by Wilson disease. It is also very important in the family screening. In our experience, this test allows to differentiate with efficiency WD patients and heterozygotes.

3 To determine best medical treatment with prospective trials. The ETC study will compare two chelators (D penicillamine et Trientine) . Further study could compare the best chelator with zinc salts or tetrathiomolybdate. Many patients with neurological forms of Wilson disease require rehabilitation with speech therapists, physiotherapist, ergotherapists and need psychological and social accompaniment. Every effort should be made to achieve optimal coordination between the health professionals, the reference hospitals and the patients' associations and to employ shared guidelines and protocols.

4 To improve management of patients who deteriorate despite medical therapy. The evolution of the exchangeable copper level will certainly help to adjust the posology of the treatment. We also have to determine for which patients the liver transplantation will be indicated, as the best time and the finest technique of transplantation.

5 To improve medication compliance. Non-compliance of the therapy is actually a very serious problem. Discontinuance of the treatment induces severe neurological deterioration even in previous stable patients. We have to follow up the patients during all their life and to carefully educate them, with the help of the patients' associations, because Wilson disease is a genetic disease for which we have several treatment strategies.

Diet in Wilson Disease

E. GARCIN (Paris, France)

Summary

In Wilson Disease, a low copper diet completes medical treatment which must be taken for life.

To have a specific alimentation means to avoid rich copper food (cacao and black chocolate, livers, some fish and selfish, some oleaginous fruits).

In general, the nutritional needs of WD patients are increased not only during the growth for teenagers, but also because of movement disorders frequently induced by the pathology...

In order to avoid any denutrition and to limit constrains for the patients, the National Reference Centre for Wilson Disease and the dieticians of Lariboisiere Hospital (Paris) have made this nutritional advice booklet.

This document gets together the copper content of several types of food including those to absolutely avoid with the WD. These contents have been found thanks to an existent bibliography including *The composition of foods-Mcance et Widdowson's-2002*.

Moreover, the dosages have been carried out by the toxicology laboratory of Lariboisiere Hospital by atomic absorption spectrometry of specific usual French food.

French medical experts advice to reduce copper in food to less than 1mg/day at the onset of the treatment and to less than 3mg/day when the symptoms are stable.

The objective of these advice is to help up WD patients in their food choices according to their habits and their living conditions.