Pediatric Wilson's Disease: Phenotypic, Genetic Characterization and Outcome of 182 Children in France

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ABSTRACT

Objectives: To describe a cohort of Wilson disease (WD) pediatric cases, and to point out the diagnostic particularities of this age group and the long-term outcome.

Methods: Clinical data of 182 pediatric patients included in the French WD national registry from 01/03/1995 to 01/06/2019 were gathered.

Results: Diagnosis of WD was made at a mean age of 10.7 ± 4.2 years (range 1–18 years). At diagnosis, 154 patients (84.6%) had hepatic manifestations, 19 (10.4%) had neurological manifestations, and 9 patients (4.9%) were asymptomatic. The p.His1069Gln mutation was the most frequently encountered (14% of patients).

Neurological patients were diagnosed at least 1 year after they presented their first symptoms. At diagnosis, the median urinary copper excretion (UCE) was 4.2 μmol/24 hours (0.2–253). The first-line treatment was D-penicillamine (DP) for 131 (72%) patients, zinc salts for 24 (13%) patients, and Trientine for 17 (9%) patients. Liver transplantation was performed in 39 (21.4%) patients, for hepatic indications in 33 of 39 patients or for neurological deterioration in 6 of 39 patients, mean Unified Wilson's Disease Rating Scale of the latter went from 90 ± 23.1 before liver transplantation (LT) to 26.8 ± 14.1 ($P < 0.01$) after a mean follow-up of 4.3 ± 2.5 years. Overall survival rate at 20 years of follow-up was 98%, patient and transplant-free combined survival was 84% at 20 years.

Conclusion: Diagnosis of WD can be challenging in children, particularly at the early stages of liver disease and in case of neurological presentation; hence the support of clinical scores and genetic testing is essential. Diagnosis at early stages and proper treatment ensure excellent outcomes, subject to good long-term treatment compliance. LT is a valid option for end-stage liver disease not responding to treatment and can be discussed for selected cases of neurological deterioration.

Key Words: copper, liver transplantation, Wilson disease

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What Is Known

- The presentation of Wilson disease in children is mainly hepatic and rarely neurological.
- Copper chelating therapy is the treatment of choice in children with hepatic manifestations.
- Liver transplantation may be indicated in cases of acute liver failure and non-response to medical therapy.
- While very rare, neurological Wilson disease may occur in late childhood and deteriorate despite chelation therapy. The benefits of liver transplantation are uncertain.

What Is New

- Overall survival rate of children with Wilson disease and who received medical therapy or a liver transplant is excellent.
- In children with a neurological Wilson disease, liver transplantation could be a good option. Indeed, the neurological status of such children improved significantly after liver transplantation.

Wilson disease (WD) is a rare autosomal recessive genetic disorder (prevalence 1 per 30,000) causing an impaired biliary copper elimination and consequently a copper accumulation, mainly in the liver and the brain. Clinical expressions are variable; the hepatic manifestations prevail during childhood, and the first

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neurological signs classically appear in the second and third decades of life as the copper accumulation progresses (1,2).

The diagnosis of WD is based on a pattern of clinical signs, laboratory results, and genetic analysis (2,3). Making a WD diagnosis can be particularly challenging in pediatric cases since young children often do not display clinical and laboratory hallmarks (elevated urinary copper excretion, Kayser-Fleischer ring, abnormal brain magnetic resonance imaging [MRI]) (2). Moreover, diagnosis is often delayed in case of neurological manifestations at pediatric ages considering the overall rarity of this form.

Chelating agents and zinc salts are the recommended treatments for WD, they are chosen according to the clinical form. Liver transplantation (LT) is a valid therapeutic option in case of acute liver failure or advanced liver disease. Indication of LT for neurological WD has been proposed as a rescue therapy in some patients, mostly adults, but remains controversial. Previous reports about LT in WD do not include this indication in children (4,5).

In order to improve the diagnosis and the treatment of WD disease, a National Plan for rare diseases has organized the medical care for WD in France through selected multidisciplinary units distributed nationwide since 2005. This organization has allowed the creation of a national registry for WD patients in 2006 and the release of the first WD national guidelines in 2008 to unify practices among physicians. Herein we report the results of a large cohort of WD children included in the French national registry for WD, to highlight the diagnosis particularities and the long-term outcome, with a particular focus on neurological patients, some of them having required LT.

PATIENTS AND METHODS

Clinical data of all children reported in the French WD national registry were gathered from 01/03/1995 to 01/06/2019 (retrospective collection between 1995 and 2005 and prospective collection since 2006). Data included epidemiological, clinical, laboratory, genetics, and follow-up information.

The patients were followed by pediatricians, hepatologists and neurologists in the two reference centers (Paris and Lyon) and the eight centers of competence (Bicetre/Paul Brousse Hospitals (Paris), Necker hospital (Paris), Besançon, Lille, Aix/Marseille, Toulouse, Bordeaux and Rennes).

The diagnosis of WD was based on clinical manifestations, biochemical parameters, and/or genetic analysis as previously published (1,2,6,7). All patients included in the registry had a clinical score >4 using the score proposed by Ferenci et al (3), with a mean score of 7.8 ± 2.4.

Collected data included: family history and clinical data, presence of a Kayser-Fleischer ring, biochemical liver tests and hematologic data, immuno-nephelometric measurement of serum ceruloplasmin levels, 24-hour urinary copper excretion (UCE), brain MRI, hepatic copper content from liver biopsy if available. Brain MRIs were recorded as pathological when the typical features of bilateral high intensities were found on Flair-weighted images in the basal ganglia, the mesencephalon, and the cerebellum.

Treatments and adherence to treatment (good, regular, poor) were also reported. Adherence was self-reported by the patients and it was considered as good when less than two doses were missed in a month, regular when two to four doses were missed in a month, and poor when there were more than four doses missed per month.

First-line treatment was decided by the physicians in charge of each patient in accordance with French WD guidelines that recommend starting zinc therapy for asymptomatic or mild hepatics forms. Trientine is advised as a second-line treatment in cases of intolerance to D-penicillamine. Listing for LT was decided by a multidisciplinary team according to French guidelines.

Depending on the primary clinical manifestations, cases were classified as hepatic (H), neurological (N), or asymptomatic (AS). We considered as asymptomatic patients those diagnosed after family screening having normal liver tests and no liver or neurological symptoms. The hepatic group was subdivided into three subgroups: presymptomatic, that is, finding of isolated elevation of serum transaminases (between two and five times upper limit of normal, ULN) either fortuitous or at family screening, and no signs of chronic disease at ultrasound; chronic hepatic manifestations, such as liver fibrosis or cirrhosis, portal hypertension, hepatomegaly; acute liver failure at diagnosis with coagulopathy (international normalized ratio > 1.5) with acute presentation of signs and symptoms of liver disease with or without encephalopathy in absence of any pre-diagnosed liver disease. Decompensated cirrhosis that may have indicated LT was defined as the development of symptomatic complications such as jaundice, ascites, hepatic encephalopathy or variceal hemorrhage in patients with known chronic liver disease.

Genetic analyses, available in the study centers after 1994, were performed for patients and their families by bi-directional sequencing on the 21 exons and intron-exon boundary regions of *ATP7B* gene. For the detection of large deletions, a multiplex ligation-dependent probe amplification (MLPA) assay was performed using the SALSA MLPA P098 for Wilson Disease kit (MRC-Holland, Amsterdam, Netherlands).

Ethics and Regulatory Aspects

The study received approval from the INSERM (Institut National de la Santé et de la Recherche Médicale) Ethics evaluation committee (IRB 00003888, authorization No.19-550/January 24, 2019). Written informed consent was obtained from parents or adult patients.

Statistical Analysis

Normally distributed quantitative variables were expressed as mean ± SD; non-normally distributed quantitative variables were expressed as mean (range), and were compared using the Student *t*-test or non-parametric tests (Mann-Whitney, Kruskal-Wallis) when appropriate. Qualitative variables were expressed as count (percentage), and compared using the χ^2 test or Fischer exact test when appropriate. Patient survival was analyzed using the Kaplan-Meier method. Statistical analyses were performed with SPSS version 23.0 (IBM, New York, USA); *P* values lower than 0.05 were considered as statistically significant.

RESULTS

Study Population

A total of 182 children were included in the register analysis. Among them, 91 (50.0%) were male, 65 were siblings (35.7%) and consanguinity was reported for 21 children (11.5%).

Diagnosis was made at a mean age of 10.7 ± 4.2 years (range 1–18 years). At diagnosis, 154 patients (84.6%) had hepatic manifestations (H), 19 (10.4%) had neurological manifestations (N), and 9 patients (4.9%) were asymptomatic (AS). Mean age at diagnosis was 10.5 ± 4.0 years (range 2–18) for H patients, 14.5 ± 1.9 years (range 11–18) for N patients ($P < 0.001$), and 7 ± 5.5 years (range 1–17) for AS patients; Table 1.

N patients were diagnosed with WD significantly later after onset of first symptoms than H patients: 15 of 19 N patients (78.9%) versus 22 of 154 H patients (14.2%) were diagnosed after a delay of one year ($P < 0.01$). A total of 15 (78.9%) N patients presented with

TABLE 1. Characteristics of the study population (n = 182)

Demographic data and clinical profile	Expressed as mean ± SD; median (range) or count (%)
Total patients, n	182
Male sex	91 (50.0%)
Age at diagnosis (y)	10.7 ± 4.2
Consanguinity	21 (12%)
Number of families, n	147
Kayser-Fleischer ring*	58 (38.9%)
Serum ceruloplasmin (mg/dL)	8 ± 6
Urinary copper excretion (μmol/24 hours)	4.2 (0.2–253)
Urinary copper excretion after DP (μmol/24 hours†)	18 (0.3–187)
Clinical manifestation	
Asymptomatic	9 (5%)
Hepatic	154 (85%)
Neurological	19 (10%)
Clinical manifestation/initial treatment	
Asymptomatic, *n* (DP/Ttn/zinc/LT)	3/0/6/0
Hepatic	114/12/18/10
Neurological	14/5/0/0
All groups	131/17/24/10
Follow-up (y): median (range)	7.85 (0.4–21.8)
LT, n (%)	39 (21%)
Death, n (%)	3 (2%)

Normal ceruloplasmin: 20–35 mg/dL. Normal urinary copper excretion: 20–35 mg/dL. DP = D-penicillamine; LT = liver transplantation; SD = standard deviation; Ttn = Trientine. *149 of 182 children (81.8%) had ophthalmologic evaluation at diagnosis. †n = 45.

symptoms of dysarthria, 14 (73.6%) with writing troubles, 9 (47.4%) with dystonia, 9 (47.4%) with tremor, 8 (42.1%) with gait disorders, 8 (42.1%) with drooling. Psychiatric symptoms were described in one patient with behavioral problems. One of 19 (5.2%) N patients was diagnosed in the period from 1995 to 2004 and 18 of 19 (94.8%) in the period from 2005 to 2019.

At diagnosis, 149 (81.8%) children had an ophthalmologic evaluation. Among them, 58 (38.9%) had a detectable Kayser-Fleischer (KF) ring: 40 of 129 (31.0%) were H patients and 18 of 19 (94.7%) were N patients (Table 2). The youngest patient with a detectable KF ring was 7-year old (H), and a total of eight patients (13.7%), with detectable KF rings were younger than 10 years, all H patients.

A brain MRI was performed in 92 (50.5%) patients, which revealed abnormalities in 26 of 92 (28%) patients.

Laboratory at Diagnosis

The mean serum ceruloplasmin level was 8 ± 6 mg/dL. A total of 10 patients (6%), all H patients, had serum ceruloplasmin levels within the normal range (24 ± 5 mg/dL), including five (50%) with chronic hepatic manifestations, three (30%) with mildly elevated serum transaminases, and two (20%) with acute liver failure at diagnosis.

At diagnosis, the median basal urinary copper excretion (UCE) was 4.2 μmol/24 hours (0.2–253). The median basal UCE was significantly lower for AS patients (1.3 μmol/24 hours [0.2–4.1] compared to H patients [4.5 μmol/24 hours (0.2–254)], $P < 0.001$) and to N patients (5.4 μmol/24 hours [1.2–15.9], $P < 0.001$), Table 2. For 19 (10%) patients, basal UCE was below 1.6 μmol/24 hours. The latter patients with low UCE had a median age of 9 years (1–18), 14 of 19 (73.7%) were H patients, 4 of 19 (21.1%) were AS patients, and 1 of 19 (5.3%) was an N patient. For five (2.7%) patients ages 1–6 years, basal UCE was <0.6 μmol/24 hours: two of five (40.0%) were H patients with mild elevation of transaminases diagnosed after family screening and three of five (60.0%) were AS patients.

Data from the penicillamine challenge were available for 45 (24.7%) patients. The median UCE after the challenge was 18 μmol/24 hours (0.3–187). For three (6.7%) patients (3–6 years of age), UCE values after challenge were below 3.2 μmol/24 hours: two were H patients, one was an AS patient. For 10 patients with

TABLE 2. Demographic and laboratory findings according to the type of presentation at diagnosis

	Demographic and laboratory parameters comparison between clinical groups								
		H patients				N patients	AS vs H	AS vs N	H vs N
Variables expressed as mean ± SD, median (range) or count (%)	AS patients	a	b	c	Total H patients				
Total patients (n)	**9**	36	92	26	**154**	**19**			
Male sex	**4 (44.4%)**	23 (63.9%)	46 (50.0%)	8 (30.1%)	**77 (50.0%)**	**10 (52.6%)**			
Age at diagnosis	**7.0 ± 5.5**	8.9 ± 4.7	10.7 ± 3.8	12.2 ± 2.9	**10.5 ± 4.0**	**14.5 ± 1.9**	$P < 0.001$	$P < 0.001$	$P < 0.001$
Kayser-Fleischer ring*	**0**	3 (8%)	22 (24%)	15 (58%)	**40 (31%)**	**18 (95%)**	NS	$P < 0.001$	$P < 0.001$
Sérum céruloplasmin (mg/dL)	**6.8 ± 4.7**	8.1 ± 7.1	8.6 ± 5.6	11.6 ± 7.4	**9.0 ± 6.4**	**5.1 ± 3.3**	NS	NS	$P = 0.001$
Urinary copper excretion (μmol/24 hours)	**1.3 (0.2–4.1)**	2.9 (0.2–51)	3.3 (1.0–94.9)	57.4 (2.0–254)	**4.5 (0.2–254)**	**5.4 (1.2–15.9)**	$P < 0.001$	$P < 0.001$	NS
Urinary copper excretion after DP (μmol/24 hours†)	**2.2 (1.1–3.3)**	11.4 (3.0–32.9)	17.9 (1.9–54.5)	90.6 (37.2–187.9)	**18.0 (1.9–187.9)**	**31.2 (12.4–54)**	$P < 0.001$	NS	NS
Aspartate aminotransferase (IU/L)	**37.4 ± 13.6**	107.3 ± 83.2	136.8 ± 128.0	327.3 ± 299.4	**163.5 ± 181.6**	**41.3 ± 14.8**	$P < 0.001$	NS	$P < 0.001$
Alanine aminotransferase (IU/L)	**26.0 ± 4.9**	191.4 ± 178.9	175.4 ± 191.1	109.5 ± 102.7	**167.5 ± 177.9**	**39.7 ± 44.5**	$P < .001$	NS	$P < 0.001$

a: asymptomatic but with isolated elevation of serum transaminases (between 2 and 5 times upper limit of normal, ULN); b: chronic hepatic manifestations such as persistent elevated serum aminotransferases (<5× ULN), hepatomegaly or compensated cirrhosis; c: acute liver failure at diagnosis, coagulopathy (international normalized ratio > 1.5) with acute presentation of signs and symptoms of liver disease with or without encephalopathy in absence of any pre-diagnosed liver disease. Groups values are showed in bold, subgroups in standard text. AS = asymptomatic; DP = D-penicillamine; H = hepatic; N = neurological; SD = standard deviation. *149 of 182 children (81.8%) had ophthalmologic evaluation at diagnosis. †n = 45.

TABLE 3. The most frequent mutations detected in children with Wilson disease in this study

Mutation	Nucleotide sequence	Exon	Mutation type	Domain of ATP7B	Number of patients	Number of alleles	Age of disease onset (y)	Clinical form: H: hepatic; N: neurological
p.His1069Gln	c.3207C>A	14	Missense	ATP loop	20	18	11 (4–18)	12 H 6 N
p.Gln111*	c.330delA	2	Nonsense	Cu 1	5	5	13 (10–16)	3 H 2 N
c.2865 + 1G>A		Intron 12	Splicing		4	4	13 (11–15)	3 H 1 N
p.Arg1319*	c.3955C	19	Nonsense	TM 7	4	4	7 (4–11)	4 H
p.Asn1270Ser	c.3809A>G	18	Missense	ATP hinge	4	4	9.5 (3–18)	3 H 1 N
p.Val890Met		11	Missense	TM 5	3	5	9 (7–13)	3 H
p.Arg226Trp		1	Missense		3	4	10 (8–12)	2 H 1 N
p.Met769HisFs*26	c.2304dupC	8	Nonsense	TM 4	3	4	14.5 (14–45)	3 H
c.51 + 4A>T		Intron 1	Splicing		3	3	10 (5–14)	3 H
p.Ile1148Thr	c.3443T>C	16	Missense	ATP loop	3	3	10 (4–16)	2 H 1 N
c.1708–1G>A		Intron 4	Splicing		2	3	11 (9–13)	2 H
p.Arg778Trp		8	Missense	TM 4	2	2	10.5 (10–11)	2 H

H = hepatic; N = neurological.

low basal UCE levels (<1.6 μmol/24 hours), UCE values increased >5ULN after the penicillamine challenge.

A liver biopsy was performed in 34 H and 2 N patients, at a mean age of 10.6 ± 4.2 years for diagnostic purposes. The median liver copper content was 13.80 μmol/g (0.48–42.66), including five patients (mean age 10.2 ± 4.1 years) with a liver copper content below 4 μmol/g, and two with a liver copper content within the normal range (<0.8 μmol/g).

Genetic data obtained by direct sequencing or MLPA analysis were available for 143 (79%) patients. All patients had a least one mutation identified: two mutations were found in 131 of 143 (92%) patients, three mutations were found in 2 of 143 (1.7%) patients, and a single mutation was detected in 10 of 143 (7%) patients. A total of 109 different mutations were identified. The p.His1069Gln mutation was the most frequently encountered (ie, in 20 [14%] patients). The other most frequent mutations were listed in Table 3. In our pediatric WD cohort, only five patients with a deletion in exons 1 or 4 have been identified using an MLPA assay. There are no large genetic rearrangements in the ATP7B gene in Wilson patients compared to the ATP7A gene in Menkes patients.

Treatment

The first-line treatment was D-penicillamine (DP) for 131 (72%) patients, zinc salts for 24 (13%) patients, and Trientine for 17 (9%) patients. A total of 10 (5.5%) patients who presented with acute liver failure (ALF) did not receive any treatment before liver transplantation. When considering N patients, 14 of 19 (73.7%) started treatment with DP and 5 of 19 (26.3%) started treatment with Trientine. None received zinc salts as first-line treatment. Among AS patients, six of nine (66.7%) started treatment with zinc salts and three of nine (33.3%) with DP.

When considering N patients, 5/19 (26.3%) started treatment with Trientine; among AS patients, six of nine (67%) started treatment with zinc salts.

Adverse effects to DP treatment leading to discontinuation were reported in 17 (13%) patients. They included dermatologic reactions (6/17), nephropathies (4/17), and hematologic toxicity (3/17). No adverse effects were reported in patients treated with Trientine or zinc salts.

At last follow-up, treatment information was available for 111 of 143 non-LT patients. Treatments included DP for 52 of 111 (46.8%) patients, zinc salts for 34 of 111 (30.6%) patients, and Trientine for 24 of 111 (21.6%) patients. Among the 131 patients treated initially with DP, 22 of 131 (16.8%) required LT. Of the 18 H patients who started treatment with zinc salts, 7/18 (38.8%) switched to a chelator because of treatment inefficacy and 1 of 18 (5.6%) eventually required LT. Among the 17 patients who received Trientine as a primary treatment, 3 of 17 (17.6%) switched to zinc salts, 2 of 17 (11.8%) switched to DP, and 6 of 17 (35.3%) required LT because of neurological deterioration in four patients. Among AS patients, all patients who started treatment with zinc salts (n = 6) continued with the same treatment, though two of six of them (33%) displayed some degree of abnormal transaminases at the last follow-up.

Adherence to treatment was reported as good in 48 of 88 patients (55%), regular in 29 of 88 (33%) patients, and poor in 11 of 88 (13%). The rate of adherence to treatment was not found to be related to The different clinical forms, type of treatment or age.

Outcome

Liver Transplantation

Liver transplantation was performed in 39 (21.4%) patients, for hepatic indications in 33 of 39 patients and for neurological deterioration in 6 of 39 patients. LT occurred within the first year after diagnosis for 34 of 39 (87.2%) patients, and 1 of 39 (2.6%) patient required re-transplantation. Among the transplanted patients for hepatic indications, 26 of 33 (78.8%) had an acute liver failure (ALF) and 7 of 33 (21.2%) had decompensated cirrhosis. The mean age of patients in the ALF group was 12.7 ± 3.1 years; there were 18 females and 8 males.

Retrospective calculation of the new King's Wilson score was >11 for 37 of 39 patients listed for LT for hepatic indications. The two patients with scores <11 presented with decompensated cirrhosis and uncontrolled HTP indicating LT.

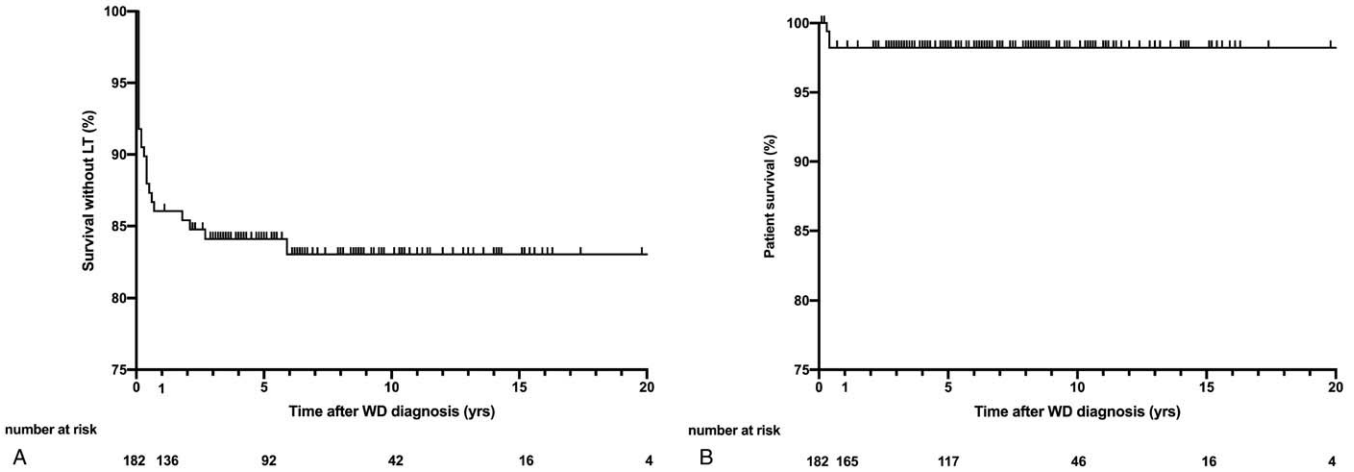

FIGURE 1. (A) Combined patient and transplant-free survival. (B) Overall survival rate.

Two patients, listed for ALF, died from immediate complications related to LT. All other patients progressed well, had no major complication from LT, and had normal liver tests at the last follow-up.

Regarding the patients transplanted for neurological involvement, the indication was for all of them unresponsiveness or deterioration of neurological symptoms despite the medical treatment. Among them, four of six patients had Trientine as first-line treatment and two of six had DP. The median time between diagnosis and LT was 7 (2–31) months, the mean Unified Wilson's Disease Rating Scale (UWDRS) was 26.8 ± 22.9 at diagnosis and 90 ± 23.1 before LT. Improvement after LT was satisfactory. After a mean follow-up of 4.3 ± 2.5 years, the mean UWDRS was 35.2 ± 14 (range 13–77), which was significantly lower compared to UWDRS at LT ($P < 0.01$). A total of four of six patients had a mean UWDRS decrease of 77% after LT and the other two, a decrease of 41%; among the latter two patients who were less neurologically improved after LT, one had persistent behavioral abnormalities after LT. No major hepatic complication was reported and all patients had normal transaminase levels at the last follow-up.

Overall transplant-free progression was 86.0%, 84.1%, 83.1%, 83.1%, and 83.1% at 1, 5, 10, 15, and 20 years, respectively (Fig. 1A).

Follow-up

At last follow-up, liver tests were available for 101 non-transplanted patients (6 AS patients, 84 H patients, and 11 N patients) of whom 41 of 101 (41%) had some degree of abnormal liver tests (2/6 [33%] AS patients, 36/84 [42%] H patients, and 3/11 [27%] N patients).

Fourteen of the 22 patients still on Trientine (64%) at last follow-up had increased transaminases levels: 1.5–2.5 × ULN in 12 patients, and >2.5 × ULN in two patients. This proportion was significantly higher compared to those treated with DP (18/49 [37%], $P = 0.040$) and zinc (9/28 [32%], $P = 0.045$).

All 13 N patients who did not undergo LT reported stabilized or improved symptoms.

Survival

Three of 182 (2%) patients died, one of three because of a non-disease-related event (car accident), two of three from complications following liver transplantation. Overall patient survival was 98% at 1 year and 20 years after the diagnosis of WD (Fig. 1B).

DISCUSSION

We describe herein the characteristics of one of the largest published pediatric cohort of WD patients corresponding to a nationwide report, which represent a major strength of the presented data. Our results illustrate the natural progression of the steady accumulation of cooper in WD over time with a continuous increase of the urinary cooper excretion with age and the progression of clinical forms according to age: asymptomatic and mild-forms of liver disease at around 7 years of age, followed by all the stages of liver damage at around 10 years of age, and finally neurological symptoms appearing during the half of the second decade of life. Distribution of clinical forms in pediatric cohorts of WD have classically a predominance of hepatic manifestations but the percentage of neurological cases is very variable, ranging from 0 to 20% (8–10). These differences are likely due to the specialty of the reporting centers (hepatologist or neurologist), the mean age of the patients included, and maybe also the experience in diagnosing neurological forms. The present report gathered data from diverse multidisciplinary centers, so we consider being thoroughly exhaustive reporting 10% of neurological cases.

The diagnosis of WD in children may be difficult, particularly at early stages, given the absence of a single clinical characteristic or available biochemical test that would confirm or rule out the diagnosis. Indeed, in our cohort, many patients did not have an elevated urinary copper excretion (basal or after DP), neither high liver copper nor a KF ring, some patients even had normal ceruloplasmin levels. These equivocal findings have been well described in the literature (7,11–18) and highlight the importance of the use of clinical scores, and the value of genetic testing for mutations identification. Diagnosis of neurologic WD in children is even more complicated and a high index of suspicion is necessary since symptoms can be very varied and subtle. In the present cohort, the diagnosis delay from onset of symptoms was longer for neurological forms, and this delay has been previously reported to be from 3 to 6 years (19). We are convinced that the centralization of WD care in multidisciplinary services, has largely contributed to an earlier diagnosis and improved management of the patients.

The long term prognosis in patients surviving >10 years after diagnosis and treatment initiation is excellent, especially if patients can be diagnosed before the development of cirrhosis or neurological symptoms and if they are adherent to therapy (20). Survival rates in the present study were better than in most published studies; however, these data are hardly comparable since the latter were mostly performed from adult populations (11,20–22), which are characterized by a higher proportion of neurologic patients and a minor proportion of ALF. In any case, early diagnosis is essential to improve outcome.

Regarding medical therapy, ESPGHAN recommends the use of chelators (DP or Trientine) for symptomatic WD patients as first-line therapy (2). DP is the most broadly chosen first-line treatment for symptomatic WD cases but its main inconvenience is the high frequency of adverse effects that has been reported to up to 30% (23–25) in most studies. In the present study, only 10% of adverse effects due to DP were reported, but an under-report from the patients and the referring physician is highly likely since mostly major adverse effects leading to treatment change were systematically reported in the registry. Under-reporting is also presumable for Trientine and zinc salts treatments, nonetheless, there was no report of severe adverse effects requiring treatment discontinuation with these two medications.

Although Trientine is not officially approved as a first-line treatment for WD in France, 17 children were treated with Trientine right after diagnosis, probably due to its better safety profile compared to DP, and particularly to the general acknowledgment from initial reports of less frequent neurological worsening (13). In the present study, it was the treatment choice for 5 of 19 children with neurological symptoms, four of whom later required LT for neurological deterioration, in contrast to 2 of 14 under DP who presented this complication. More recent studies have suggested that neurological deterioration rates are comparable between DP, Trientine, and zinc salts treatments (23,26). Several reports have confirmed the efficacy of Trientine for all clinical forms of WD (23,27,28) but in our study it is interesting to note that Trientine was associated a with a higher frequency of initial neurological worsening and of increased transaminases at last follow-up; however, it is not possible to draw any definite conclusion in this non controlled and observational study, with a quite small number of patients treated with Trientine. Furthermore, reliable informations about adherence to treatment and compliance with the recommendations of fasting and adequate refrigerated storage are lacking, which may impact the efficacy of Trientine (29).

Treatment with zinc has been validated for asymptomatic children, but is not recommended for symptomatic presentations (1,2). In this study, all asymptomatic patients who started zinc as initial treatment were still using it at last follow-up, whereas a third of them displayed transaminases abnormalities at the last follow-up. Previous reports revealed a progressive aggravation on zinc therapy even in asymptomatic patients (30–32) underlying the importance of a close surveillance.

In case of ALF, LT is often required. The predominance of female patients in the ALF group has been reported before (5,33) and the hormone-related theory seems to be the most likely explanation for this difference; however, other studies including pediatric patients have not reported a similar biased sex ratio (34,35), suggesting that process is more complex (35). The LT requirement was almost 2-fold higher and the ALF rate was about 3-fold higher in the study herein compared to the Austrian cohort of adults and children (20). This discrepancy may be due to an over-representation of LT patients in the present study as the registry includes all the French pediatric centers performing liver transplantation. On the contrary, it is possible that some patients, especially those with mild forms of WD, were not followed by the referral centers, and thus not included in the registry.

To explain the high rate of LT patients we also verify the absence of futile indications. Listing for LT in France has evolved through time and since 2007 is based on a scoring system using points that are assigned according to severity, age, and other factors including points granted after a board review of each case. Nazer score (36) and later the Revised King score for LT (34) were used to establish LT criteria in WD; the retrospective calculation of the Revised King score was >11 for >97% of the patients listed for hepatic indications confirming the gravity of the transplanted patients.

On the other hand, some severe neurological patients received LT. The topic of LT for neurological indications has been thoroughly weighed by Poujois et al (37) in an adult and children series who conclude that it could be used as rescue therapy allowing to regain autonomy in most cases. Herein, the results were rather reassuring as the neurological symptoms of these patients improved after LT. The number of patients was very limited to draw conclusions, yet this option should be prudently evaluated in selected cases of neurologic deterioration.

The main limitations of the present study are its retrospective design, the variable practice of physicians in the same country, the lack of complete data set for some patients and the probable over-representation of the more severe forms of the disease.

In conclusion, the diagnosis of WD can be challenging in children, particularly at the early stages of liver disease and in the case of neurological presentation; hence the support of clinical scores and genetic testing is essential. Diagnosis at early stages and proper treatment ensure excellent outcomes subject to good long-term treatment compliance. LT is a valid option for end-stage liver disease not responding to treatment and can be discussed for selected cases of neurological deterioration.

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