

SHORT COMMUNICATION

Cognitive Abilities of Children With Neurological and Liver Forms of Wilson Disease

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*[†]Emilie Favre, [‡]Laurence Lion-François, [§]Marie Canton, ^{||}Claire Vanlemmens, [¶]Marjorie Bonneton, [#]Lise Bouillet, *Anne-Sophie Brunet, and ***Alain Lachaux

ABSTRACT

Cognitive impairment in adult patients experiencing Wilson disease is now more clearly described, even in liver forms of the disease. Although this condition can appear during childhood, the cognitive abilities of children have not yet been reported in a substantial case series. This retrospective study included 21 children with Wilson disease who had undergone general cognitive assessment. The results argue in favor of a poor working memory capacity in the liver form of the disease, and more extensive cognitive impairments in its neurological form. Extensive neuropsychological investigations on all children experiencing Wilson disease are thus required.

AQ6 Key Words: cognitive abilities, executive function, liver, pediatric, Wilson disease, working memory

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Wilson disease (WD) is a rare autosomal recessive disorder affecting copper metabolism that results in an accumulation of copper in organs such as the liver and brain. The signs of hepatic dysfunction that are consistently found in WD may be accompanied by brain lesions—predominantly located in the basal ganglia, brain stem, mid-brain, prefrontal cortex, and cerebellum (1)—and neuropsychiatric symptoms that include motor, cognitive, and behavioral impairments. The cognitive profile of adults

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From the *Department of Pediatric Gastroenterology, Hepatology and Nutrition, French National Centre for Wilson's Disease, ~~Children's Hospital of Lyon~~, the [†]Department of Neurology C, Pierre Wertheimer ~~Neurological Hospital~~, the [‡]Department of Pediatric Neurology, Children and Mother's Hospital of Lyon, Bron, the [§]Reference Centre for Inherited Metabolic Disorder, Children's Hospital of Nancy, Vandoeuvre-lès-Nancy, the ^{||}Department of Hepatology, Competency Centre for Wilson's Disease, ~~Hôpital Jean Minjoz~~, Besançon, the [¶]Department of Pediatric Gastroenterology, Hepatology and Nutrition, Children's Hospital of Nancy, Vandoeuvre-lès-Nancy, the [#]Regional Centre for Learning and Language Disorders of Children, Jean Minjoz Hospital, Besançon, and the ^{***}~~University Claude Bernard Lyon 1, Villeurbanne, France~~.

AQ3

AQ4 Address correspondence and reprint requests to Emilie Favre, PhD, Centre National de Référence pour la Maladie de Wilson, Service de Gastroentérologie, Hépatologie et Nutrition Pédiatrique HFME, 59 Boulevard Pinel, 69677 Bron Cedex, France (e-mail: e.favre@live.fr).

AQ5

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What Is Known

- Adult patients experiencing Wilson disease may have more or less severe cognitive impairment.

What Is New

- The intellectual abilities of children with Wilson disease are globally preserved.
- Those with a liver form may have poor working memory capacity.
- Those with a neurological form (motor symptoms and cerebral lesions) experience more extensive cognitive problems.
- Children with Wilson disease may have special educational and rehabilitation needs, such as requiring speech therapy.

experiencing the neurological form of WD is dominated by executive impairment, a slowing of visual motor speeds and a poor learning rate (1–4). Recent reports have indicated that patients with the liver form of WD—that is to say, patients without lesions and motor symptoms typical of cerebral copper accumulation—may also experience executive and attentional impairments, presumably due to mild hepatic encephalopathy (4–6). In other words, cognitive impairment in WD may be due to both copper toxicity affecting the brain and liver failure (7).

Although the initial manifestations of WD may appear during childhood (8), the cognitive abilities of pediatric patients have never yet been described in a case series. In particular, it is not clear whether cognitive impairment is due to the long-term effects of dysfunctional copper metabolism or its presence early in life. The present study was designed precisely to fill this gap by reporting on the general cognitive abilities of children experiencing both liver and neurological forms of WD.

METHODS

Methods are available online as Supplemental Digital Content (<http://links.lww.com/MPG/A748>) (Table 1).

~~Supplemental Data Methods~~

RESULTS

In this case series, ~~most~~ of the index scores were within the normal range (Fig. 1A). Interestingly, individual analyses revealed that the index scores were highly heterogeneous when compared with the general population. It was in particular noted that the working memory index (WMI) score was abnormally lower than the

TABLE 1. Demographic and clinical characteristics of children

	Age, y	Sex	Grade	Developmental history (reported before the diagnosis of WD)	Chelating agent	Liver symptoms*	INR [†]	Transaminases		Cerebral MRI abnormalities	Motor symptoms	Behavioral symptoms
								AST [‡]	ALT [‡]			
Liver form												
1.	12	m	Repetition	No	Tr.	Fibrosis	1.18	1.6	3.1	No	No	No
2.	13	m	Normal	No	Tr.	Compensated cirrhosis	1.20	1.4	2.3	No	No	No
3.	11	f	Normal	No	Pen.	Steatosis	1.00	n	n	No	No	No
4.	16	f	Normal	No	Pen.	Compensated cirrhosis	1.10	n	n	No	No	No
5.	15	m	Repetition	No	Tr.	Fibrosis	1.08	n	1.6	No	Tremor [§]	No
6.	14	m	Skipping	No	Tr.	Compensated cirrhosis	1.05	n	n	No	No	No
7.	13	f	Normal	Language delay	Pen.	Cirrhosis with portal hypertension	1.61	2.3	2.6	No	No	No
8.	13	m	Normal	Language delay	Pen.	Compensated cirrhosis	1.12	1.6	2.9	No	No	No
9.	11	m	Repetition	No	Pen.	Compensated cirrhosis	1.03	1.2	1.4	White matter [§]	No	No
10.	14	f	Repetition	No	Pen.	Compensated cirrhosis	1.08	n	n	No	No	No
11.	7	m	Normal	No	Zn.	Steatosis	1.02	n	n	MD	No	No
12.	12	f	Repetition	No	Pen.	Fibrosis	1.06	n	n	No	No	No
13.	13	f	Normal	No	Pen.	Fibrosis	1.11	1.2	n	No	No	No
14.	6	f	Skipping	No	Pen.	Steatosis	1.00	1.5	2.4	No	No	No
15.	12	m	Normal	No	Pen.	Steatosis	1.12	n	n	White matter [§]	No	No
16.	10	m	Additional specialized support	Dyslexia	Pen.	Compensated cirrhosis	1.00	1.3	5.8	No	No	Anxiety, withdrawn
17.	7	m	Repetition	Language delay	Pen.	Steatosis	1.02	4.4	5.2	No	No	No
Neurological form												
18.	14	f	Repetition + additional specialized support	Language delay	Pen.	Compensated cirrhosis	1.17	n	n	Brainstem, thalamus, caudate nucleus, putamen	Dystonia, anemia, extrapyramidal signs	Spasmodic laugh
19.	10	m	Repetition + additional specialized support	Speech delay	Pen.	Fibrosis	1.20	n	n	Putamen, caudate nucleus	Anemia, dysarthria, dystonia hypersialorrhea, extrapyramidal signs	Hyperactive behavior
20.	14	f	Normal	No	Pen.	Compensated cirrhosis	1.20	n	n	Brainstem, thalamus, putamen, pallidum, caudate nucleus	Dystonia, anemia, dysarthria, hypersialorrhea	Aggressive
21.	14	m	Additional specialized support	Dyslexia	Pen.	Cirrhosis with portal hypertension	1.00	n	n	Brain stem, putamen, pallidum	Anemia, dysarthria, hypersialorrhea	Apathy

f = female; INR = international normalized ratio; m = male; MD = missing data; n = within normal values range; Pen. = penicillamine; Tr. = trientine; WD = Wilson disease; Zn. = zinc acetate.

*Liver stiffness values were measured using a Fibroscan (steatosis: <7 kPa; fibrosis: 7–12 kPa; cirrhosis: >12 kPa). Criteria for portal hypertension were met if 2 of the 3 following signs were present: reduced platelet levels (<150,000/mm³), esophageal varices (endoscopy), ultrasound signs (Doppler ultrasonography).

[†]Normal values range: 0.97–1.30.

[‡]Numbers of times higher than the normal range (units per litter).

[§]Not specific to Wilson disease.

^{||}This patient was presenting with chronic liver failure.

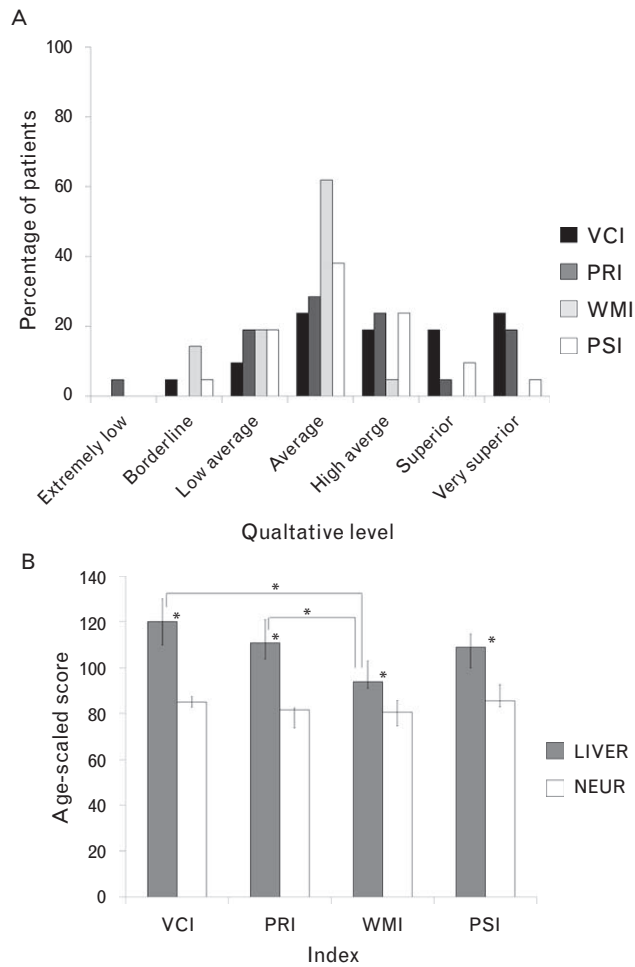


FIGURE 1. (A) Percentage of children with WD as a function of the qualitative level on WISC-IV index scores. (B) Median WISC-IV index scores in the liver and neurological forms of the disease. ~~MRI = abnormal magnetic resonance imaging; MRI = normal cerebral magnetic resonance imaging~~; PRI = perceptual reasoning index; PSI = processing speed index; VCI = verbal comprehension index; WMI = working memory index. Error bars represent the interquartile range. Asterisks (*) represent statistically significant differences.

verbal comprehension index (VCI) score in >45% of patients with the liver form of WD (Table 2).

Group analyses (Fig. 1B) confirmed the heterogeneity of index scores in patients with the liver form ($F[3, 48] = 20.96$; $P < 0.001$). More precisely, the WMI score (median \pm interquartile range: 94 ± 12) was lower than the VCI (120 ± 20 ; $P < 0.001$) and perceptual reasoning index (111 ± 17 ; $P = 0.001$) scores among patients in the LIVER group. Other comparisons did not reach the threshold of significance. Age-scaled index scores were also lower in patients with neurological WD than in those with the liver form of WD. The exact probability of the 2 groups differing was 0.001 for VCI (NEUR: 85 ± 4.75 vs LIVER: 120 ± 20), 0.001 for perceptual reasoning index (NEUR: 81.5 ± 8.75 vs LIVER: 111 ± 17), 0.049 for processing speed index (NEUR: 85.5 ± 9.5 vs LIVER: 109 ± 15), and 0.018 for WMI (NEUR: 80.5 ± 11.25 vs LIVER: 94 ± 12).

TABLE 2. Percentage of patients with an abnormally high discrepancy in index scores between them and the general population (<10% of the standardization sample with higher discrepancies)

	VCI > PRI	VCI > WMI	VCI > PSI	PRI > WMI	PRI > PSI	PSI > WMI
LIVER	76.5	47.06	23.53	29.41	11.76	0.00
NEUR	25	0.00	0.00	0.00	0.00	0.00
LIVER	5.88	0.00	5.88	0.00	11.76	23.53
NEUR	0.00	0.00	0.00	25.00	25.00	0.00

PRI = perceptual reasoning index; PSI = processing speed index; VCI = verbal comprehension index; WMI = working memory index.

DISCUSSION

The present study was designed to generate a picture of the general cognitive abilities of children with WD. In this series, the WISC-IV scores of most children with WD were within the normal range, confirming the global preservation of their intellectual abilities. A finer-grained analysis, however, suggested that slight specific impairments were common. AQ8

First of all, children with the neurological form scored less on all indexes than those with the liver form of WD. It is possible that extrapyramidal signs or dystonia might have contributed to the lower scores of written or timed subtests. This, however, could not account for all the difficulties experienced by children with the neurological form because their performance in the verbal comprehension test was also poorer than those with the liver form, and this index is wholly unaffected by motor abilities or time constraints. These data, therefore, indicate that lesions related to cerebral copper accumulation were responsible for both the motor and cognitive impairment of children experiencing WD.

Secondly, and most striking, was the discrepancy between the 4 WISC-IV indexes in children with the liver form of WD. Without falling into the abnormal range, their verbal working memory capacities were indeed consistently poorer than their verbal and visual-spatial reasoning. It is worth noting that working memory weakness can have a negative effect on numerous cognitive functions. For instance, working memory capacity is strongly linked to attentional and executive functioning, which in turn is responsible for coordinating goal-directed behavior (10). These problems have indeed been reported in adults (4–6) and children with other severe hepatic impairments or portal hypertension (11,12). Another example concerns the development of language abilities. It is well known that children experiencing specific language impairment and dyslexia often experience working memory difficulties (13,14). Language impairment has been described precisely in infants with other chronic hepatic diseases (15). In the present case series, a relatively high proportion of the children had a history of slight or more severe language difficulties (Table 1). Further studies need to confirm this point, but it is tempting to suggest that working memory difficulties may be linked to a certain delay in language development in the context of WD. Clues are therefore accumulating to suggest mild cerebral dysfunction among pediatric patients with just the liver form of WD.

Thirdly, the data reported here throw light on the functional effect of cognitive impairment in children with WD. The frequency of repetition of grades (38% in the present case series, see Table 1) did not differ from that seen in the general French population (16). Normal schooling remains possible in most of the cases, but additional specialized support is sometimes required, especially for children with the neurological form of WD.

The data reported here now need to be confirmed by further extensive neuropsychological studies. Nevertheless, they clearly argue for early mild cerebral dysfunction in the liver form and more general cognitive impairment in the neurological form of WD. In clinical practice, a close examination of cognitive capacities, and particularly working memory, is thus warranted in all children experiencing WD. This psychometric assessment would improve patient care by revealing those children with special educational and rehabilitation needs such as speech therapy.

REFERENCES

1. Frota N, Barbosa ER, Porto CS, et al. Cognitive impairment and magnetic resonance imaging correlations in Wilson's disease. *Acta Neurol Scand* 2013;127:391–8.
2. Portala K, Levander S, Westermarck K, et al. Pattern of neuropsychological deficits in patients with treated Wilson's disease. *Eur Arch Psychiatry Clin Neurosci* 2001;251:262–8.
3. Seniów J, Bak T, Gajda J, et al. Cognitive functioning in neurologically symptomatic and asymptomatic forms of Wilson's disease. *Mov Disord* 2002;17:1077–83.
4. Wensch E, De Tassigny A, Trocello J-M, et al. Cognitive profile in Wilson's disease: a case series of 31 patients. *Rev Neurol (Paris)* 2013;169:944–9.
5. Arguedas D, Stewart J, Hodgkinson S, et al. A neuropsychological comparison of siblings with neurological versus hepatic symptoms of Wilson's disease. *Neurocase* 2015;21:154–61.
6. Iwański S, Seniów J, Leśniak M, et al. Diverse attention deficits in patients with neurologically symptomatic and asymptomatic Wilson's disease. *Neuropsychology* 2015;29:25–30.
7. Ferenci P, Litwin T, Seniow J, et al. Encephalopathy in Wilson disease: copper toxicity or liver failure? *J Clin Exp Hepatol* 2015;5:S88–95.
8. Roberts EA, Schilsky ML. American Association for Study of Liver Diseases (AASLD). Diagnosis and treatment of Wilson disease: an update. *Hepatology* 2008;47:2089–111.
9. Wechsler D. ~~WISC-IV Echelle D'intelligence de Wechsler pour Enfants et Adolescents – Quatrième Edition. ECPA; 2005.~~ **AQ10**
10. McCabe DP, Roediger HL, McDaniel MA, et al. The relationship between working memory capacity and executive functioning: evidence for a common executive attention construct. *Neuropsychology* 2010;24:222–43.
11. Sorensen LG, Neighbors K, Zhang S, et al. Neuropsychological functioning and health-related quality of life: pediatric acute liver failure study group results. *J Pediatr Gastroenterol Nutr* 2015;60:75–83.
12. D'Antiga L, Dacchille P, Boniver C, et al. Clues for minimal hepatic encephalopathy in children with noncirrhotic portal hypertension. *J Pediatr Gastroenterol Nutr* 2014;59:689–94.
13. De Clercq-Quaegebeur M, Casalis S, Lemaitre M-P, et al. Neuropsychological profile on the WISC-IV of French children with dyslexia. *J Learn Disabil* 2010;43:563–74.
14. Kapa LL, Plante E. Executive function in SLI: recent advances and future directions. *Curr Dev Disord Rep* 2015;2:245–52.
15. Caudle SE, Katzenstein JM, Karpen SJ, et al. Language and motor skills are impaired in infants with biliary atresia before transplantation. *J Pediatr* 2010;156:936–40.
16. OECD. PISA à la loupe. Redoublement et transfert des élèves: quel impact pour les systèmes d'éducation? OECD Web site. <http://www.oecd.org/pisa/pisaproducts/pisainfocus/48391795.pdf>. Published July 6, 2011. Accessed June 28, 2016.

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