Rare disease

Behavioural and psychiatric disorders in paediatric Wilson's disease

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An 11-year-old boy was treated since 6-years-old with methylphenidate for combined attention deficit and hyperactivity disorder. At age nine his behaviour had worsened and he started to have phobias. One year later persistent hypertransaminasemia was found. Physical examination showed a dysidiadocokinesia. Laboratory investigation revealed a low caeruloplasmin and augmented basal urinary copper with a positive postpenicillamine test. Liver biopsy showed high liver copper (853 µg/g) and brain MRI was normal. D-penicillamine and zinc acetate were started without side effects. ATP7B gene mutation was confirmed after treatment initiation.

BACKGROUND

Wilson's disease (WD) is a rare autosomal recessive disorder of copper metabolism, with an estimated prevalence of 1 case in 30 000 births. It is characterised by impairment in biliary copper excretion and defective incorporation into caeruloplasmin, leading to copper accumulation in the liver, brain and kidneys. The causative gene Wilson's disease P-type copper-transporting adenosine triphosphatase (ATP7B) codes for a membrane-bound, P-type copper-transporting adenosine triphosphatase, expressed primarily in the liver.^{1–3} The most frequent mutation worldwide is p.H1069Q.²

WD clinical presentation is variable, depending in part upon age. In infancy and childhood, ongoing silent hepatic deposition of copper causes subclinical hepatitis, presented accidentally in liver tests. Rare before age six, clinical manifestations arise as copper deposition progresses. The majority of patients between age six to twelve present with liver disease, while neuropsychiatric symptoms become more significant in adolescence.^{1–4} Behavioural and psychiatric disorders (phobias, delusions, compulsive or aggressive behaviours, cognitive deterioration with worsening of school performance, poor memory, shortened attention span) account for less than 7–10% of the manifestations of WD.^{1–4–5}

No single diagnostic test can exclude or confirm WD with certainty. The diagnosis is based on a broad combination of laboratory tests and clinical features, gathered in a score system. The most helpful laboratory tests for diagnostic purposes are those measuring 24 h urinary copper excretion, hepatic copper concentration, serum free copper concentration and caeruloplasmin concentration. Screening individuals for mutations responsible for the disease are of great help for genetic counselling.^{5–6} The available treatments are chelating agents (D-penicillamine and trientine, tetrathiomolybdate) and zinc salts.

This case illustrates that even rare in young children, psychological or psychiatric manifestations in WD do occur at this age.

CASE PRESENTATION

The authors present the case of an 11-year-old boy who had been treated for attention deficit and hyperactivity disorder (ADHD) before he was admitted to the hepatology unit. At 6.5 years of age he had fulfilled Conner's criteria for combined ADHD. He presented with lack of attention, hyperactivity and impulsivity affecting both school performance and home behaviour. All improved after methylphenidate (20 mg per day) treatment. He had also suffered from primary nocturnal enuresis managed with desmopressin (0.2 mg per day).

Three years later his behaviour got worse and he started to have fear of dying. This phobia was related to the loss of one grandparent. After adjustment of methylphenidate dosage (36 mg per day) he was referred to the pedopsychiatric department. A year later, nocturnal enuresis resolved and desmopressin was withdrawn. A few months later, in the end of summer school break and under no methylphenidate medication, he complaint of unusual abdominal pain and laboratory evaluation disclosed moderate elevation of transaminases. Six months later he was referred to the hepatology unit with laboratory tests showing persistent hypertransaminasemia (peak values: aspartate aminotransferase (AST) 210 U/l, alanine aminotransferase (ALT) 470 U/l) and low caeruloplasmin (0.08 g/l; normal (N) 0.2–0.6 g/l).

The patient's medical history was unremarkable except for mild asthma since age two and later onset of allergic rhinitis, treated with topical corticosteroids. His parents were non-consanguineous. He had family history of depression of both mother and grandfather. The grandfather had had liver disease of unknown cause in childhood.

Figure 1 Patient liver histology demonstrating mild hepatitis, steatosis and complete septal fibrosis. Rhodanine stain shows copper and copper-associated protein. HE-Haematoxylin-eosin stain; TM-Masson trichrome stain.

He was then admitted to our unit for WD investigation. On physical and neurologic examination, a dysidiadochokinesia was present but no Kayser–Fleischer rings (KF) nor hepatosplenomegaly were found. The remaining examination was normal.

INVESTIGATIONS

Laboratory tests revealed a normal full blood count and negative Coombs test; AST 139 U/l (N 5–45 U/l); ALT 356 U/l (N 10–35 U/l); bilirubin (total/direct): 7.7/0.0 $\mu\text{mol/l}$ (N 3–22/ <5 $\mu\text{mol/l}$); γ glutamyl transpherase: 56 U/l (N 12–58 U/l); alkaline phosphatase (ALP): 307 U/l (N 135–530 U/l); lactic dehydrogenase 818 U/l (N 432–700 U/l); caeruloplasmin <0.02 g/l. Abdominal ultrasound disclosed a moderate hepatomegaly with hyperreflective homogeneous texture. Brain MRI was normal. During hospitalisation, both 24 h urine copper excretion test and a penicillamine challenge (oral penicillamine 500 mg every 12 h in two doses) were performed. Urine copper excretion was 2.1 $\mu\text{mol}/24$ h (N <0.9 $\mu\text{mol}/24$ h), increasing more than five times the normal upper limit (15.6 $\mu\text{mol}/24$ h) with penicillamine challenge. Serum copper level was 1.8 $\mu\text{mol/l}$ (N 11–24 $\mu\text{mol/l}$). Liver biopsy (figure 1) showed a liver copper value of 853 $\mu\text{g/g}$ (N <50 $\mu\text{g/g}$). Patient had a score of six points, according to the diagnostic score in WD five, turning highly likely the diagnosis, which was confirmed after a pathogenic homozygous mutation c.3061-12T>A in the ATP7B gene was found (table 1).

TREATMENT

D-Penicillamine (progressive doses), vitamin B6 and zinc supplement were started.

OUTCOME AND FOLLOW-UP

With treatment, the phobias disappeared in 3 weeks and improvement on behaviour, interaction and evoked memory occurred over 3 months. Because he had persistent elevated levels of transaminases, at month 5 of treatment, a compliance evaluation was performed. Urine excretion tests showed a good compliance with 3.3 $\mu\text{mol}/24$ h copper (N 3.2–7.9 $\mu\text{mol}/24$ h) and 1.9 mg/24 h zinc (N ≥ 2 mg/24 h) levels. He received increased doses of D-penicillamine with progressive improvement.

DISCUSSION

WD is usually asymptomatic in childhood before age five. Meanwhile, copper accumulation in the liver causes subclinical hepatitis. Progression to liver cirrhosis and development of neuropsychiatric symptoms usually occurs

Table 1 Patient diagnostic score for Wilson Disease (Ferenci Score)⁵

Serum caeruloplasmin		
Normal (>0.2 g/l)	0	0.02 g/l (2)
0.1–0.2 g/l	1	
<0.1 g/l	2	
Coomb's negative haemolytic anaemia		
Absent	0	(0)
Present	1	
Kayser–Fleischer rings		
Present	2	(0)
Absent	0	
Extrapyramidal signs and symptoms		
Severe	2	(0)
Mild	1	
Absent	0	
Liver copper		
Normal (<50 $\mu\text{g/g}$)	1	853 $\mu\text{g/g}$ (2)
<5xULN (50–250 $\mu\text{g/g}$)	1	
>5xULN (250 $\mu\text{g/g}$)	2	
Rhodanine stain*		
Absent	0	–
Present	1	
Mutation analysis		
2 chromosome mutation	4	homozygous
1 chromosome mutation	1	c.3061-12T>A (4)
No mutation detected	0	
Urinary copper		
Normal (<0.9 $\mu\text{mol}/24$ h)	0	2.1 $\mu\text{mol}/24$ h (2)
1–2x ULN	1	
>2x ULN	2	
>5x ULN after penicillamine	2	
Total score (after complete study)		10 points

Score interpretation—0–1: unlikely; 2–3: probable; ≥ 4 : highly likely.

*In absence of quantitative liver copper determination. ULN, upper normal limit.

around the second decade of life and it's rare before age 10.^{3–5} Psychiatric symptoms may occur 2 to 3 years before hepatic and neurological symptoms become manifest. Patients can develop psychiatric and behavioural abnormalities such as depression, paranoia, hallucinations and delusions, irritability or declining performance at school or at work.⁶ Lin *et al* described a 10-year-old male with an unusual presentation of WD that included psychological manifestations (impulsivity, lack of attention and hyperactivity at school, violence at home) and seizure disorder without hepatic involvement. He was treated initially for ADHD with progressive worsening of his bad temper and violence. Brain MRI and laboratory tests confirmed WD.⁷ In our patient hepatic disease was preceded by almost 4 years of ADHD and 1 year

of thanatophobia. Patients with neuropsychiatric symptoms show a late onset of symptoms and a longer diagnostic delay before definitive diagnosis than those with hepatic symptoms.³

Neither the absence of KF rings nor normal values for caeruloplasmin can exclude WD. Although KF rings are present in 90 percent of patients with neurologic manifestations of WD, only 50 percent of patients, with liver disease have them under age 10.⁵ In children, KF rings are rarely seen before the age of 8 years. According to Manoulaki *et al*, KF rings can be present in 38 percent of paediatric patients. They also found that caeruloplasmin concentration was low (<0.2 g/l) in 88 percent of patients, 73 percent according to EuroWilson.^{2 5} Despite our patient had behavioural and psychiatric manifestations, he did not have KF rings.

Although there are several biochemical tests, each of them have different limitations thus, no single diagnostic test can exclude or confirm WD with certainty. Liver copper content higher than 250 µg/g of dry weight is considered to be the gold standard in the diagnosis. However, false negative tests do occur as irregular distribution of copper in the liver parenchyma may be the reason why 20 percent of these patients have less than 250 µg/g of dry weight. Such is the case in early stage WD of infants and children, and of patients with severe cirrhosis.^{5 6} Mutation analysis is also an important diagnostic tool and may confirm the diagnosis in equivocal cases. Due to the high allelic heterogeneity observed in WD, it is not always diagnostic.² To provide objective criteria in WD diagnosis, a combination of clinical, biochemical and genetic tests were developed and proposed by Ferenci *et al*, as a scoring system.^{5 8} Family screening is effective in diagnosing patients with WD at an early, and most often asymptomatic stage of disease, with an excellent long-term outcome.³

Penicillamine or trientine is the first-choice therapy for children with liver disease. Zinc therapy is indicated for presymptomatic children and patients with neurological problems. During the last 10 years it has been shown that oral zinc is suitable as long-term maintenance therapy for children.^{5 9} In our patient penicillamine and zinc therapy were able to reverse psychiatric symptoms and improve behavioural and cognitive symptoms before 6 months of treatment. Fluctuation of serum transaminases levels led us to verify potential treatment failure as recommended, including non-compliance.³ Compliance can be monitored by 24 h urinary copper excretion measurement, which should rise up to 3.2–7.9 µmol/24 h (200–500 µg) on chelation therapy with D-penicillamine or trientine. During zinc therapy, 24 h urinary copper excretion should be between 0.8–2.0 µmol/24 h (50–125 µg/24 h), and zinc excretion should be at least 2 mg/24 h. Zinc overtreatment should be sought when urine copper drops below 0.8 µmol/24 h (50 µg/24 h).^{4 6}

Little is known regarding fluctuations of serum transaminases levels during treatment with penicillamine or zinc in children affected by WD. In our patient, the reason why serum transaminases levels were still high at 10 months treatment might be related to infratherapeutic doses of D-penicillamine. Other hypothesis could be high load of free copper due to quelation and high transaminases resulting from free copper excess. However, calculated free copper was systematically low.

Iorio *et al*, enrolled 109 patients and showed a normalisation of ALT level of 64 percent of children treated with penicillamine within a median time period of 17 months, and 50 percent of children with zinc in median of 6 months. Both penicillamine and zinc-treated patients with persistent hypertransaminasemia had the serum ALT level decreased from a basal median of 236 U/l to 78 U/l at the end of follow-up.⁹

Learning points

- ▶ Many affected children are asymptomatic so an early diagnosis of WD rests on a high index of suspicion.
- ▶ It is important to make a differential diagnosis in children with unexplained behavioural and/or neuropsychiatric problems, with or without any associated liver disease, at any age of onset.
- ▶ Any hypertransaminasemia during routine health maintenance should prompt the physician to WD diagnosis.
- ▶ Investigation of the diagnosis only ends with filling of a scoring system for WD diagnosis.

Competing interests None.

Patient consent Obtained.

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