For medical professionals

Clinical presentation

HOW MAY WILSON DISEASE PRESENT?

Wilson disease may come to light in an individual in a variety of different ways. Indeed, one of the mysteries of this condition is that the same genetic abnormality can produce such different clinical problems in different people.

ASYMPTOMATIC

- When brothers and sisters of a patient with Wilson disease are tested, they are sometimes found to be affected. This usually applies to younger brothers and sisters. Genetic testing can be done immediately after birth.
- If the blood tests which primary care practitioners take in patients with minor illnesses include liver function tests, abnormalities can occasionally be found which on further investigation prove to be Wilson disease

ACTION POINT

If "routine liver function tests" are inexplicably abnormal in a child, test for Wilson disease

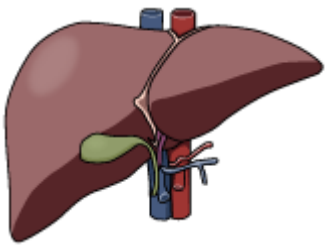
HAEMOLYSIS

- Haemolysis can sometime be the first manifestation of Wilson disease, without clinical evidence of liver disease. It may resolve spontaneously, and liver problems may not appear until a year or more later.
- Haemolysis may present simultaneously with liver disease

ACTION POINT

In a child with haemolysis and negative Coombs test, remember to exclude Wilson disease

HEPATIC



The liver manifestations of Wilson disease may be of almost any variety and severity. The important practical message therefore is: suspect Wilson disease in any child with undiagnosed liver disease.

Presentations include:

- finding abnormal liver function tests as above, even as early as the first year of life
- finding enlargement of the liver on clinical examination, either in a routine check of an asymptomatic child or during examination of a

CLUES suggesting Wilson disease in a child with fulminant liver failure are:

- absence of other known causes
- a relevant family history
- disproportionate rise in bilirubin (>300micromol/l)
- haemolysis on blood film
- relatively low alkaline phosphatase (<600iu/l) or transaminases (100-500iu/l)

neurologically affected case.

- an acute hepatitis which appears to resolve. Failure to find a viral aetiology for an acute hepatitis, or delayed or incomplete resolution, should raise the possibility of Wilson disease
- "chronic hepatitis" i.e. continuing abnormality of liver function tests, clinically indistinguishable from an autoimmune hepatitis, though usually not having raised plasma globulin or autoantibodies in the serum
- variceal haemorrhage from unsuspected portal hypertension
- signs of decompensated chronic liver failure
- fulminant liver failure (FHF). This, the most urgent presentation, causes the most difficulty in diagnosis and management. It usually occurs without antecedent illness but may occasionally be precipitated by an infection. Previous episodes of haemolysis or 'hepatitis' may have occurred.

NEUROLOGICAL

The neurological manifestations of Wilson disease generally present between the ages of 10 and 35 years; however a patient presenting at 55 years has been published. The neurological manifestations are diverse and may present as movement disorders which can be quite difficult to differentiate from other neurological disorders.

CLUES suggesting Wilson disease are:

- Wing-beating
- Postural tremor of the arms
- Dystonic posture of the stretched arm behind the back
- Fixed pseudo-smile (risus sardonicus)
- Dysarthria

They include:

1. A dystonic syndrome characterized by dystonic postures and choreoathetosis
2. An ataxic syndrome with postural and intentional tremor and ataxia of the limbs
3. A parkinsonian syndrome with hypokinesia, rigidity and resting tremor

These three syndromes often occur in the same patient or develop as the disease progresses. Experience in 188 patients (Czlonkowska unpublished data) suggests that the most frequent

symptoms are:

- Dysdiadochokinesia (present in all investigated patients)
- Dysarthria (93%)
- Salivation (93%)
- Gait disturbances (79%)
- Postural tremor (wing-beating in 56%)

OPHTHALMIC

Usually, the ophthalmologist is asked to look for eye abnormalities in a patientalready suspected of having Wilson disease. Occasionally the optometrist or ophthalmologist may be the first to suspect Wilson disease because of findingthe characteristic eye abnormalities
The Kayser-Fleischer ring is a gold or gray-brown opacity in the peripheral cornea. It first develops superiorly in the cornea (12 o'clock), then inferiorly, and finally in the horizontal meridian. It represents a deposit of copper and sulfur-rich granules in Descemet's membrane, and is reversible with treatment.Additional later ocular findings in Wilson disease include sunflower cataracts,saccadic pursuit movements, loss of accommodation response, and apraxia of opening the eyelid.

RENAL OR SKELETAL ABNORMALITIES

They are very occasionally the first signs of Wilson disease.

Diagnosis

Tests performed for the diagnosis of Wilson disease

The diagnosis of WD is based on a combination of clinical, biochemical and genetic tests.

TEST	COMMENTS
Urinary Copper	24 hour copper excretion >100µg in 65% of WD patients
Urinary copper penicillamine challenge with two dosages of 500mg 12 hours apart and measure urine copper	24 hour copper excretion > 1600 µg in patients with active liver disease
Serum Copper	Serum copper may be low in asymptomatic cases (because caeruloplasmin is low) or high in cases with active liver disease (because free copper is raised)
Serum Copper	Serum copper may be low in asymptomatic cases (because caeruloplasmin is low) or high in cases with active liver disease (because free copper is raised)
Serum Caeruloplasmin	< 20 mg/dl (in 95% of WD patients)
KF rings	Identification in most patients requires an experienced observer
Liver Copper	>250 µg/gm of dry weight liver
Coombs negative haemolytic anaemia	
Biochemical indices	Abnormal liver function tests
MRI scan	Abnormal
Molecular diagnosis	Over 200 mutations are known

24h urinary copper

The 24h urinary copper value may be misleading because of incorrect 24h urine collection, especially in pediatric patients, for whom 24h urine collection is not very easy. The penicillamine challenge test was evaluated in patients presenting with liver disease, in whom it has high sensitivity, but its sensitivity in asymptomatic patients is low and it has not been evaluated in adult neurologically presenting cases.

Serum copper

The total serum copper varies in different clinical scenarios in Wilson disease, because it may be low as a result of low caeruloplasmin, or elevated as a result of release of free copper from a damaged liver. Free serum copper, calculated as [total copper - 0.3%
caeruloplasmin] suffers from the fact that is is based on two laboratory measurements and thus has wide confidence intervals. It is no longer considered to be a reliable diagnostic tool.

Plasma Caeruloplasmin

Although, low plasma caeruloplasmin is reported in 73% of WD patients[1], false negatives have been observed in cases of infection, pregnancy and estrogens intake, because it is an acute phase reactant. On the other hand, false positive data may be observed in heterozygotes (20%), protein-losing enteropathy, aceruloplasminemia and severe hepatic insufficiency. The method used by the laboratory (the oxidative assay or nephlometric assay) may also affect the results of caeruloplasmin measurement[2].

Liver copper

Liver copper values equal to or higher than 250 µg/gm of dry weight are considered to be the gold standard in the diagnosis of Wilson's disease. In chronic cholestatic conditions the liver copper content is also elevated, but in childhood this usually does not cause diagnostic confusion. (Ferenci P, Steindl-Munda P, Vogel W, et al. Diagnostic value of quantitative hepatic copper determination in patients with Wilson's Disease. Clin Gastroenterol Hepatol 2005;3:811-8) assessed the hepatic copper content of 106 patients at the time of diagnosis of Wilson disease. The distribution of hepatic copper concentration as a function of histological findings showed that 19 Wilson disease patients had a liver copper concentration below 250 µg/g dry weight. The sensitivity analysis based on comparison of these 106 patients to 244 other patients without Wilson disease showed that the upper limit of diagnosis (>250µg/g dry weight) has a poor sensitivity (82%) and very good specificity. The low range (50µg/g dry weight) has a higher sensitivity, but lower specificity as well as a positive predictive value. The negative predictive value shows a major gain. Further studies are required to confirm these data.
There are fewer data on liver copper in patients with a neurological presentation.

Liver histology

Hepatic manifestations of Wilson disease are very similar to those observed in autoimmune hepatitis, steatosis, and fulminant hepatic failure. Copper and copper-associated protein may be seen histochemically, but their absence does not exclude a diagnosis of Wilson disease, particularly in childhood.

Neuroimaging

Neuroimaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI) of the brain, play an important role in the diagnosis of Wilson disease presenting neurologically. In CT, ventricular dilatation, cortical atrophy and brainstem atrophy is seen more frequently than

bilateral hypodense areas in the basal ganglia. Experience from 109 cases shows that cortical atrophy was found in 83 (76%) of patients with a neurological presentation (basal ganglia hypodensity in 28 of 109)(Czlonkowska unpublished data)
MRI is the most important diagnostic tool in patients with neurological presentation. Almost all patients show an MRI abnormality. MRI detects non-specific changes in the brain such as diffuse brain atrophy and focal abnormalities. These are shown as increased signal activity on T2-weight images in lenticular, thalamic and caudate nuclei as well as in the brain stem, cerebellum and white matter. It has been shown that the most frequent abnormalities are (Czlonkowska, unpublished data):

- Putamen (61%)
- Globus pallidus (59%)
- Brainstem and cerebellum (34%)

Magnetic resonance spectroscopy (MRS) can also detect heavy copper accumulation in brain matter and be a noninvasive study of brain metabolism. By this technique N-acetylasparatate (NAA), choline containing compounds (Cho), creatine and phosphocreatine (Cr), lactate and other amino acids can be observed noninvasively. In adult patients with Wilson disease the MRS study shows decreased NAA/Cr and Cho/Cr ratios in the left and right globi pallidus.

Molecular biology

In recent years the developments of new techniques in genetic and molecular biology have provided useful tools in the diagnosis of Wilson disease. Ferenci et al. have studied DNA from 754 patients.

Using polymerase chain reaction (PCR), mutation analysis was first performed to detect the H1069Q mutation, which is the most common mutation among the WD patients of central, eastern and northern European origin. Further mutation analysis was performed in the absence of the H1069Q mutation. Amongst 635 index cases studied so far, 87% of patients had at least one known mutation (in 54% both mutations were identified, 33% had only one known mutation). In 13% of cases no mutation was identified. This is to some extent due to the fact that this is an ongoing study, where exons 2 to 7, 9, and 21 were not yet analysed.
The distributions of WD mutations according to clinical presentation of the disease as well as the age at onset of either neurological or hepatic symptoms were also assessed:

	H1069Q/ H1069Q	H1069Q/ Exon 14	H1069Q/ Exon 8	H1069Q/ 3400 delc	H1069Q/ Exon 13	H1069Q/ ?	H1069Q/ Other	Exon 8§	Exon 15§	Other	?/?
Clinical presentation											
Neurologic	97	1	13	12	2	52	13	25	5	27	33
Hepatic	75	5	29	6	13	58	12	39	14	43	51
Other	1	-	-	-	-	-	-	-	1	-	-
Age of onset neurological symptoms											
<10	0	-	1	-	-	2	2	2	1	3	-
10-20	28	-	5	8	1	22	7	13	3	12	12
1321-35	60	-	6	4	1	32	4	8	1	12	13
>35	6	-	1	-	-	2	-	1	0	5	8
Age of onset hepatological symptoms											
<10	11	-	4	2	1	11	2	2 5	3	11	9
10-20	38	4	22	2	4	16	5	7 12	7	27	21
21-35	24	-	4	1	5	10	2	4	3	13	16
>35	2	-	1	1	3	6	-	1	-	2	4

§Homozygote or second mutation unknown

In this series the H1069Q homozygote mutation, associated with late onset neurologic disease, was mainly detected in neurological presentations. This was also the case of the H1069Q/ 3400delC mutation. Hepatic presentation of WD mutations was mainly associated with mutations affecting exon 8.

Clinical tests : the Kayser Fleischer ring

The diagnostic value of the KF ring is not the same for patients with neurological and hepatic disease. In a study conducted by Steindl et al only 50% of hepatic patients were found to have KF rings, while KF rings were detected in 90% of neurological patients.

Scoring system

In 2001 at the 8th international conference on WD and Menkes disease a scoring system for the diagnosis of WD was discussed[3]. The aim was to provide objective criteria with high sensitivity and specificity for the diagnosis of Wilson disease. A combination of clinical and biochemical tests with a score ranging from 0 to 4 for each test were developed.

Liver copper (in absence of cholestasis)		**Serum caeruloplasmin**	
Normal (<50µ/g)	-1	Normal (>0,2 g/l)	0
<5xULN (50-250µ/g)	1	0.1-0.2 g/l	1
>5xULN (250µ/g)	2	<0.1 g/l	2
Rhodanine stain (in absence of quantitative liver copper determination)			
absent	0		
present	1		
Mutation analysis		**Clinical symptoms and signs**	
2 chromosomes mutations	4	KF rings	
1 chromosome mutation	1	present	2
no mutation detected	0	absent	0
Urinary copper (in absence of acute hepatitis)			
normal (<0.9µmol/d or <100mg/d)	0	severe	2
1-2x ULN	1	mild	1
>2x ULN	2	absent	0
normal but >5x ULN after penicillamine	2	Coomb's negative haemolytic anemia	
		present	1
	2	absent	0

The patients with a total score of at least 4 were diagnosed with Wilson's disease. The patients with a total score of two to three were considered as "likely to have Wilson's disease, yet more investigations had to be performed". The diagnosis of Wilson's disease was judged to be improbable for scores between zero and one. With respect to molecular analysis, it should be noted that more than 200 different mutations have been identified. It has been difficult to devise a simple genetic screening test for the disease. Thus only the H1069Q (exon 14), was researched.
In order to test this scoring system, 143 children with chronic liver disease, aged at least 5 years, were reviewed. All patients had urinary copper assessments and a liver biopsy as part of the diagnostic work up.
Evaluation of the Leipzig meeting score:

	Score			
	≥4	**2-3**	**≤1**	**Total**
Wilson's disease Patients	50	3	0	53
Other diagnosis	5	40	45	90
	True +	**False -**	**False +**	**True -**
Wilson's disease Patients	50	3		
Other diagnostic	94%	94%	91%	97%
	Sensitivity	**Specificity**	**+ Predictive value**	**Predictive value**
	94%	94%	91%	97%

Fifty patients with Wilson disease had a score >= 4 (true positives). A total of 85 true negatives with a score of either 2-3 (40 children) or < 1 (45 children) were observed. Only 3 patients with Wilson disease had a score of 2 to 3 (false negatives), while 5 non Wilson disease patients had a score of at least 4 (false positives). Both sensitivity and specificity of this scoring system was higher than 94%. In addition, positive predictive value and negative predictive values were higher than 90% (90.9% and 96.59% respectively).

Fulminant hepatic failure

As previously mentioned, hepatic failure is a common feature of WD, predominantly reported in females (75% versus 25% in males). The patients with fulminant presentation of WD, defined as acute liver disease with encephalopathy, have a high mortality (almost 100%) in the absence of transplantation. In order to assess survival in FHF patients a prognostic index based on the SBR, AST and INR values has been developed[4]. The results showed that among the 27 patients included in this study all patients with a score of at least 7 died. The sensitivity and specificity of the test were respectively 87% and 90%, with a likelihood ratio of 8.7. This scoring system has been re-evaluated by Dhawan et al. The medical records of children with Wilson disease, in particular those with fulminant Wilson disease, admitted to King's College Hospital (London, UK) were reviewed retrospectively. Between 1967 and 2000, 74 children (46 boys and 28 girls) with a median age of 11.7 years
(2.6-17.9 years) were admitted to the hospital. All children with at least two positive tests out of the following list were diagnosed with Wilson disease.

- Family history
- KF rings
- Low Caeruloplasmin
- Coombs' negative haemolytic anaemia
- levated 24-Urinary copper
- Elevated liver copper
- Positive penicillamine challenge

Elevated urinary copper, low caeruloplasmin, KF rings and anemia were reported in half of patients. Elevated liver copper and family history were noted in respectively 76% and 17% of patients.

Diagnosis of Wilson disease :

	Number (%)	Media (range)
Family History	17 (22.7)	
Kaiser-Feisher Rings	38 (50.7)	
Coombs' negative haemolytic anaemia	1	
Serum Caeruloplasmin (g/l)	45/58 (77.6)	0.07 (0-0.82)
24 Urinary Copper (µmol/24h) Post-penicillamine	54/57 (94.7) 21.30 (70)	10.3 (0.7-192) 34.9 (12.6-381.6)
Liver Copper (µg/g of dry weight)	20/25 (80)	458 (5-2358)

More than half of the children (54.7%) had jaundice. Acute liver failure and abdominal pain were reported in respectively 36% and 32% of patients. Lethargy and encephalopathy were observed in almost one third of patients.
Clinical presentations of Wilson's disease 74 children admitted to King's college Hospital

Major Symptoms			
Jaundice	54.7%	Ascites	25.3%
Acute Liver Failure	36%	Hepatomegaly	24%
Abdominal pain	32%	Splenomegaly	22.7%
Gastrointestinal Symptoms n(%)			
Abdominal Distension	16 (21.3)	Pale Stools	8 (10.7)
Anorexia	15 (20)	Diarrhoea	7 (9.3)
Vomiting	13 (17.3)	Melaena	1 (1.3)
Neurological Symptoms			
Lethargy	22 (29.3)	Vertigo	2 (2.7)
Encephalopathy	20 (27)	Tremors	1 (1.3)
Behavioural changes	5 (6.7)	Developmental delay	1 (1.3)
Headaches	4 (5.3)		
Other			
Peripherial Oedema	13 (17.3)	Puritus	6 (8)
Dark Urine	10 (13.3)	Gynaecomastia	4 (5.3)
Fever	10 (13.3)	Joint Pain	4 (5.3)
Epistaxis	6 (8)		

Among these patients, 17 fulminant presentations of WD were observed. Nine were male and 8 female, with a median age of 11.9 (8.6-16) years. In WD patients with fulminant presentation, diagnosis is even more challenging, due to the lethal condition of the disease, which requires a rapid diagnosis associated with difficulties performing biochemical tests, especially the 24H urinary copper (caused by renal insufficiency).

The data obtained in all patients were analysed retrospectively, using bilirubin, white cell counts, INR, albumin and AST values at presentation as predictors of mortality. Authors proposed a new predictive index value of 11 with a higher likelihood ratio than the previous scoring system (22.8 vs 8.7), as well as higher sensitivity and specificity (93% and 96% compared to 87% and 90% respectively)

1 - Steindl P., Ferenci P., Dienes HP., Grimm G., Pabinger I., Madl Ch., Maier-Dobersberger Th., Herneth A., Dragosics B., Meryn S., Knoflach P., Granditsch G., Gangl A. Wilson´s disease in patients presenting with liver disease: a diagnostic challenge. Gastroenterology, 1997, 113 : 212-18.
2 - Cauza E., Maier-Dobersberger Th., Kaserer K., Kramer L., Ferenci P.Screening for Wilson´s disease in patients with liver

diseases by serum ceruloplasmin. J. Hepatol., 1997, 27 : 358-362
3 - 8th International conference on Wilson's disease and Menkes Disease. Leipzig/ Germany, April 16-18, 2001
4 - Nazer H., Ede RJ., Mowat., Williams R. Wilson's disease: clinical presentation and use of prognostic index. Gut. 1986, 27 : 1377-1381

Treatment

The treatment of Wilson disease was impractical until J.M. Walshe, in 1956, described the favourable effects of this copper-chelating therapy in Wilson disease. In almost all asymptomatic patients and many symptomatic patients penicillamine therapy can prevent or repair the devastating effects of the copper overload. However, side effects and toxic reactions are frequently observed and in 10% of the patients therapy has to be stopped. Also, a significant proportion of the patients with neurological disease experience worsening of their neurological symptoms after starting penicillamine, and some of them will never return to their pre-penicillamine base-line again. Therapeutic alternatives have therefore been sought. The first to appear was trientine, another copper-chelating agent, which probably will give the same results as penicillamine, but with less side effects. However experience with this medication is limited so far.

In 1961 Schouwink introduced zinc as an alternative to penicillamine. He described that during zinc treatment the amount of copper excreted with the stools increased, making overall copper balance negative. This effect is now known to be based on zinc-induced metallothionein synthesis in the small intestinal epithelium. The metallothionein binds copper and the complex is sloughed off into the faeces together with the intestinal cell. Especially during the last 10 years zinc has gained increasing acceptance as it has been shown sufficiently that oral zinc is a suitable alternative to penicillamine as long-term maintenance therapy both for adults and children with Wilson disease. Zinc seems to be safe in presymptomatic patients too. It is currently investigated whether it is also a good alternative for patients with neurological problems.

A special treatment problem is the patient with severe liver disease and impending liver failure. In these patients penicillamine will fail in up to 50%. Nevertheless this medication should be started as soon as the diagnosis has been made. However when, despite therapy, liver synthesis function deteriorates further, liver transplantation should be performed. Liver transplantation is also done in patients with end-stage liver disease due to advanced cirrhosis.

Present therapy will improve symptoms and prevent a fatal outcome in most patients. However, for patients with neurological disease the symptoms may not all be reversible. For patients presenting with mild liver problems, residual morbidity seems to be confined to the presence of cirrhosis in some, while in pre-symptomatic patients, therapy prevents the onset of symptoms altogether. For all patients compliance with the life-long continuous treatment is of paramount importance. Stopping medication will lead to severe organ damage, or even death, within a time-period that can be as short as a couple of months.

Pregnancy in WD

Wilson disease itself is not a reason for avoiding pregnancy. It is very important that treatment is continued throughout the pregnancy, because of the risk of deterioration of liver or neurological disease if it is stopped. Your physician will guide you about choice of medicines and doses, and about monitoring your treatment throughout pregnancy. However, before embarking on a pregnancy, women with Wilson disease need to have a detailed discussion with their physician about all aspects of their health. For example, severe liver disease may pose significant problems.

Laboratory services

A small number of specialist laboratories have developed molecular diagnostic tests for Wilson disease. As a part of the EuroWilson project, these laboratories have formed a network in which there is collaboration and a quality assurance scheme www.emqn.org. Techniques have rapidly improved, and there are now rapid methods for detecting the common mutations. Rapid sequencing has also

made it much easier to detect less common or previously unknown mutations.
Consideration will also be given to the availability of facilities for liver copper assay and its quality assurance.
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This booklet has been developed as part of the EuroWilson project.
Eurowilson is an academically governed organisation which received support from the European Commission Framework 6 Programme.
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