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Diagnosis

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

Tests performed for the diagnosis of Wilson disease

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 "free" copper Calculated on the basis that caeruloplasmin contains 0.3% copper	Free Copper >25µg/dl
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.

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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.

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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].

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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.

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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.

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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.

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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.

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Scoring system

In 2001 at the 8th international conference on WD and Menkes disease a scoring system for the diagnosis of WD was discussed[5]. 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 coper (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).

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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
- Elevated 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)

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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