Wilson's disease - Full Clinical Guideline

Reference no.: CG-T/2012/224

Wilson's disease is an inherited disorder in which defective biliary excretion of copper leads to accumulation, particularly in the liver and brain. The majority of patients present between ages 5 and 25, though 3% of patients present beyond the fourth decade.

Presentation (highly variable):

Acute liver failure - seen predominantly in young females (ratio 4:1)
- sometimes associated with Coombs-negative haemolytic anaemia and AKI
- suspect where deep jaundice, low Hb, mildly increased ALT and low ALP

Chronic hepatitis and cirrhosis

Haemolysis - Coombs negative haemolytic anaemia

Neurological - may be extremely subtle
- abnormalities include - Akinetic-rigid syndrome similar to Parkinsons, Tremor (coarse, proximal), Ataxia, Dystonic syndrome (often cranial region e.g dysarthria, drooling, facial grimacing)

Diagnosis:

Scoring system for diagnosis of Wilson's - Lepzig score (Ferenci et al. Liver Int 2003)

Typical clinical symptoms and signs	
KF rings	
Present	2
Absent	0
Neurologic symptoms**	
Severe	2
Mild	1
Absent	0
Serum ceruloplasmin	
Normal (>0.2 g/L)	0
0.1-0.2 g/L	1
<0.1 g/L	2
Coombs-negative hemolytic anemia	
Present	1
Absent	0

Other tests	
Liver copper (in the absence of cholestasis)	
>5x ULN (>4 µmol/g)	2
0.8-4 µmol/g	1
Normal (<0.8 µmol/g)	-1
Rhodanine-positive granules*	1
Urinary copper (in the absence of acute hepatitis)	
Normal	0
1-2x ULN	1
>2x ULN	2
Normal, but >5x ULN after D-penicillamine	2
Mutation analysis	
On both chromosomes detected	4
On 1 chromosome detected	1
No mutations detected	0

TOTAL SCORE	Evaluation:
4 or more	Diagnosis established
3	Diagnosis possible, more tests needed
2 or less	Diagnosis very unlikely

*If no quantitative liver copper available, **or typical abnormalities at brain magnetic resonance imaging. KF, Kayser–Fleischer; ULN, upper limit of normal.

Note that a mildly reduced caeruloplasmin (0.15-2.0g/L) is a frequent finding in other liver diseases resulting in reduced protein synthesis. Though a disease of copper overload the serum copper is often low as the total serum copper (which includes copper incorporated in caeruloplasmin) is usually decreased in proportion to the decreased caeruloplasmin.

Treatment:

Lifelong

Low copper diet for the first year of treatment

D-Penicillamine:

Chelator - main effect is to promote urinary excretion of copper

Start at 125-250mg/d and increase by 250mg increments every 4-7d to a maintenance dose of 750-1500mg/day in 2-3 divided doses

Absorption significantly reduced by taking with food, therefore, should be taken more than 1hr before or 2hrs after meals

Interferes with pyridoxine action, therefore, prescribe supplemental pyridoxine (25-50mg/day)

Side effects: 30% discontinue drug due to side effects
Early (1-3 wks): fever, rash, lymphadenopathy, neutropenia, thrombocytopenia, Proteinuria heralding nephrotoxicity
Late: nephrotoxicity, lupus like syndrome, skin disorders, myasthenia gravis, polymyositis, loss of taste, low IgA, serous retinitis.

Monitoring: 24hr urine copper a minimum of x 2/year
Efficacy = Normalisation of caeruloplasmin
24hr urine copper excretion in vicinity of 3-8μmol/day
and/ **or ≤≤1.6 μmol/day after cessation of Penicillamine for 2 days (preferred)**
(> 1.6 in those established on therapy may indicate non-adherence)

Non-caeruloplasmin bound copper (NCBC) levels can also be used to assess efficacy/ adherence and over treatment. Need to request caeruloplasmin and total copper.

NCBC = Total serum copper (μmol/l x 63.5) – caeruloplasmin bound copper (3.15 x (caeruloplasmin g/l x 1000)
Normal is < 150 μg/l. Values greater than this may suggest non-adherence, while levels < 50 μg/l suggest overtreatment leading to systemic copper depletion.

Reduce dose for surgery to promote wound healing and in pregnancy. Breast feeding not recommended

Trientene:
Chelator of copper - used as an alternative to Penicillamine if side effects
Typical dosage 900-2700mg/day in 2-3 divided doses
Poor GI absorption - take 1hr before or more than 3 hrs after meals

Side effects: Gastritis, siderolastic anaemia
Monitoring: As for Penicillamine
Trientene has a sole manufacturer, who significantly increased the cost of the drug in 2016. This may affect future availability.

Zinc:
Interferes with uptake of copper from the GI tract
Recommended dose is 150mg elemental zinc/day in 3 divided doses
If taken with chelators needs to be taken at different time
Probably less effective than chelators, therefore, usually reserved for maintenance treatment

Side effects: gastritis, elevations in lipase/ amylase without clinical pancreatitis
Monitoring; As for Penicillamine

Family screening:
The chance of a sibling being a homozygote is 25%, offspring 0.5%.
Analysis of ATP7B gene on chromosome 13 for mutations should be offered to siblings and offspring if genetic mutation identified in the index case.
This should be facilitated through referral to Dr Mohnish Suri, Consultant Geneticist, from the Nottingham Genetics department who runs clinics in Derby.

References:
Ferenci P et al. Diagnosis and pnenotypic classification of Wilson's disease. Liver Int 2003; 23:139-142
EASL Clinical Practice Guidelines: Wilson's disease. Journal of Hepatology 2012; 56: 671-685
AASLD Practice Guidelines: Diagnosis and treatment of Wilson disease. Hepatology 2008; 47(6) 2089-2111

1. Documentation Controls

Development of Guideline:	Dr Adam Lawson
Consultation with:	Hepatology consultant and specialist nurse team
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Key Contact:	Dr Adam Lawson