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Screening and Monitoring for Wilson Disease (WD)

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Paediatric WD

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- Most children present with liver disease:
  - Asymptomatic: coincidental finding or family screening
  - Symptomatic - non acute
  - Symptomatic - Acute liver failure

- Neurological and psychiatric symptoms are extremely rare

Diagnostic Tools: similar

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- Overall clinical/biochemical picture – raises suspicion
- Ceruloplasmin levels
- Total serum copper
- Urinary copper excretion/Penicillamine challenge
- Mutation analysis:
  - More than 500 mutations within the *ATP7B* gene
  - Most patients are compound heterozygotes
  - Next-generation sequencing can identify both mutant alleles in 95% of patients (risk is identifying variants of unknown significance)

- Liver biopsy and quantitative copper analysis
  - If molecular testing inconclusive or not available (although we usually end up doing a liver biopsy)
  - Only few studies evaluating diagnostic accuracy of liver copper content in children
  - Liver copper content is increased:
    - In early infancy (physiological)
    - In healthy heterozygotes
    - In chronic cholestatic disease (eg EHBA)
  - Liver histology alone cannot be used to establish a diagnosis of WD

Paediatrics specific Challenges

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- The diagnosis of WD is very difficult particularly in young and/or asymptomatic children or in mild disease
- Show atypical or insufficient findings of biochemical and clinical tests for WD:
  - Ceruloplasmin levels:
    - Can be normal
    - Age impact: low in neonates, gradually rises with age with peak in mid childhood, then declines again during puberty
  - Urinary copper excretion:
    - Often normal in asymptomatic children or children with mild liver disease
    - Penicillamine challenge: unreliable to rule out diagnosis in asymptomatic children
  - KF-rings are absent

Family screening

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- Genetic counseling is essential
- Screening of first degree relatives
  - Siblings (as early as 2 years of age)
  - Parents
  - Offspring of affected parent, particularly in consanguineous families (Wd in 2 consecutive generations in non-consanguineous families has been reported)
- Physical examination, serum ceruloplasmin, liver function tests,
- molecular genetic testing (mutation analysis or haplotype analysis)

Sibling screening challenges

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- Parental willingness for siblings to be screened – safeguarding issue
- Uncertainty if unusual or no mutations are found in index case
- Screening will only report if WD confirmed in sibling. Labs will not report carrier status or no mutations unless sibling requests results when reaching adulthood

Treatment

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- Aim: normal physical examination and normal liver function tests

- Options:
  - removal of copper excess by chelating agents (D-penicillamine or Trientine) or
  - blocking intestinal copper absorption with zinc salts

Monitoring Practice

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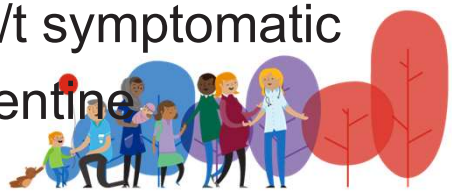
Purpose is Two-fold:

- Efficacy & side effects –
  - Routine FBC/Biochem/Coag (not copper/ceruloplasmin) at each visit
  - proteinuria
  - Occasional LBx to watch copper content (never serial)

- Compliance - Practice within our unit varies
  - no monitoring
  - 24hrs urine collection (zinc/copper): how often and how to interpret
    - Annual monitoring
    - Presymptomatic children excrete less copper c/t symptomatic
    - Different for zinc therapy c/t penicillamine or trientine



Practice Guidelines

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- EASL – Journal of Hepatology 2012 vol.56: 671 – 685
- ESPGHAN – JPGN, Vol 66, Number 2, February 2018

Diagnostic approach to WD (ESPGHAN PG 02/2018)

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Step 1

- Clinical evaluation for HSM, KF rings, ascites
- Liver tests: AST/ALT, SBR, INR, AP
- Biochemical tests of copper metabolism: ceruloplasmin, 24hr copper excretion

Step 2

- Molecular testing (common mutations, whole gene sequencing)

Step 3

- Liver copper (if molecular testing inconclusive or unavailable)

ESPGHAN – Ferenci score (consensus 2001) – diagnostic score in WD (adopted for EuroWilson Database)

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Score	-1	0	1	2	4
KF rings		Absent		Present	
Neuropsychiatric symptoms		Absent		Present	
Coombs –ve hemol anaemia + high serum copper		Absent	Present		
Urinary copper		Normal	1-2 xULN	> 2x ULN or normal but >5x ULN 1 day after penicillamine challenge	
Quant Liver copper	normal		<5 x ULN	> 5x ULN	
Rhodanine+ve hepatocytes (if no quant Copper available)		Absent	Present		
Serum ceruloplasmin		>0.2 g/L	0.1- 0.2 g/L	<0.1 g/L	
Disease causing mutation detected		None			2

0-1: unlikely 2-3: probable 4 or more: highly likely

King's Wilson index (2005)

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Scoring system to predict outcome of children with hepatic decompensation:

Score	SBR (µmol/L)	INR	AST	Leuco's, 10^9/L	Albumin g/L
0	0-100	0-1.29	0-100	0-6.7	>45
1	101-150	1.3-1.6	101-150	6.8-8.3	34-44
2	151-200	1.7-1.9	151-200	8.4-10.3	25-33
3	201-300	2.0-2.4	201-300	10.4-15.3	21-24
4	>300	>2.5	>300	>15.3	0-20

Score ≥ 11 = urgent listing for transplant

Conclusion

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- Similarities in approach to diagnostics, screening and monitoring

- Paediatric specific challenges