Wilson's Disease in children

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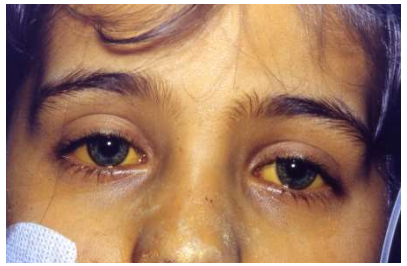
By your side

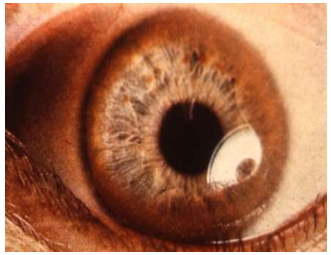
Wilson's Disease

- Hepatic presentation < 12 years
  - Acute or chronic hepatitis/Failure
  - Haemolysis
  - Low alkaline phosphatase



- Neurological > 12 years
  - Slurred speech/Tremor /poor co-ordination
- Kayser Fleischer rings

  -late childhood



Clinical features of Wilson's Disease

Acute hepatitis/Acute Liver Failure

- Jaundice and hepatitis
- Coagulopathy (INR $\geq$ 2)
- Encephalopathy
- Previous episodes of jaundice/haemolytic anemia
- Acute renal failure with rapid progression
- Cirrhosis in the explanted liver

Wilson's Disease

Chronic hepatitis

- Insidious onset of liver disease
- Similar to autoimmune hepatitis
- Low titre autoantibodies
  - ? exposure of antigens by hepatocyte necrosis
- Plasma immunoglobulins are normal

Neurological Wilson's Disease

Neurological or psychiatric

- Onset : acute or chronic
- Variable: Age of onset
  Speed of progression
  Deterioration in school performance
- Differential diagnosis
  - Late Niemann– Pick disease type C
  - Lafora disease
  - Congenital disorders of glycosylation.

Neurological Wilson's Disease

- Parkinsonian-like
  - mask-like facies,
  - Rigidity, and gait disturbance
- Pseudo-parkinsonian:
  - Bradykinesia/ cognitive impairment
- Pseudo-sclerotic
  - Tremor;
- Dyskinetic

Psychiatric Wilson's Disease

- Depression
- Neurotic behavior
  - Phobias/compulsive behavior
  - aggression/antisocial behavior
- Cognitive deterioration
  - Worsening school performance
  - Poor memory
  - difficulty in abstract thinking
  - shortened attention span

Wilson's Disease

- Skeletal manifestations
- Arthritis
  - ? Copper-mediated oxidative damage to collagen
- Rickets and osteoporosis:
  - Renal tubular phosphate leak and hepatic osteodystrophy
- Skeletal complications more frequent in Asian/Indian patients.

Wilson's Disease

Renal abnormalities

- Renal tubular abnormalities:
- Tubular copper deposition
- Glycosuria/Aminoaciduria
- Renal tubular acidosis
- Impaired phosphate reabsorption
- Fanconi syndrome
- Acute renal failure with rapid progression

Diagnosis of Wilson's Disease

- KF rings: rare in childhood.
- Family history or consanguinity
- Slurred or slow speech
- Jaundice
  - High bilirubin (>300 micromol/l)
  - Low transaminases (100–500 IU/l)
  - Low alkaline phosphatase(< 600 IU/l)
- Haemolysis

Differential diagnosis in Wilson's Disease

- Hepatitis A,B,C, EBV, CMV, Parvovirus, Indeterminate
- Auto-immune Liver Disease Type I or II
- Drugs (paracetamol/INAH)
- Metabolic : Tyrosinemia

Wilson's Disease

- Diagnosis:
  - Low serum copper & caeruloplasmin
  - Increased urinary copper (50-100 µg/24h)
  - Pre/post penicillamine* (x 5 normal)
  - Increased hepatic copper
    (>250 µg/g dry weight (normal <55)
  - Low alkaline phosphatase
- ATP7B mutation analysis
  - H1069Q mutation (exon 14) commonest

*not useful in pre-symptomatic siblings

Wilson's Disease

- Treatment
  - Penicillamine
  - Zinc
  - Trientine
  - Tetrathiomolybdate (TM)
- Transplantation
- Family screening and information

Prognostic index in ALF in Wilson's Disease

Score	Bilirubin μ/L	INR	AST IU/L	WCC X 10^{o}/L	Alb g/L
0	0-100	0-1.3	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	151-300	8.4-10.3	25-33
3	201-300	2.0-2.4	301-400	10.4-15.3	21-24
4	>301	>2.5	>401	>15.4	<20

Sensitivity 93%: Specificity 97%;PosPR 92%;NegPR 97%;
Score >11:- transplant indicated

Dhawan A, et al, Liver Transpl 2005;11:441–8

Wilson's Disease
BCH experience 1990 - 2018

- 62 patients
  - 32F:30M

  Clinical presentation

  29 acute liver failure

  14 chronic liver disease

  1 unknown (pre computerised records)

  12 screened as siblings had presented acutely

  - 6 Incidental

Wilson's Disease
BCH experience 1990 - 2018

Genetic analysis	62
ATP7B mutations	29
Not Known	26
Tested – but results not available	5
Other mutations	3

Wilson's Disease
BCH experience 1990 - 2018

- Acute presentations (29)
- Median age:12.2 yrs (7 – 16)
  - Previously investigated for other problems
    - Cardiac
    - Neurological
    - Deterioration in school work
    - Deterioration in motor skills
    - General malaise:
      - Fatigue, lethargy, previous viral infections, fever, jaundice, dizziness, vomiting, abdominal pain

Wilson's Disease
BCH experience 1990 - 2018

- Therapy and outcome: Acute Presentation (29)

Acute Presentation 29	**Therapy**	**Medical Therapy 8**	**Transplanted 21**
4	Pencillamine	2	2
11	Pencillamine and Zinc	4	7
3	Zinc	2	1
6	None	---	6
5	Unknown	---	5

Wilson's Disease
BCH experience 1990 - 2018

- Chronic Liver disease (14)
- Median age at presentation: yrs (3.4 – 16)
  - Fatigue, lethargy, fever, jaundice, dizziness, vomiting, abdominal pain
  - Deterioration in school work
  - previous viral infections
  - (1) Pain in Knees
  - (1) Neurological: ataxia/tremors, Parkinsonian facies

Wilson's Disease
BCH experience 1990 - 2018

- Therapy and outcome: Chronic Presentation (14)

Chronic **14**	**Therapy**	**Medical Therapy** **8**	**Transplanted** **3**
2	Pencillamine	2	0
6	Pencillamine and Zinc	4	2
1	Trientine and Zinc	2	0
4	Zinc	---	--
1	Not known	---	1

Wilson's Disease
BCH experience 1990 - 2018

- Transplanted (25)
  - 20 acute
  - 5 chronic
  - Median age at transplant (yrs) 11.5 (6.4 – 16)

  Med survival 15.5 yrs (0.02 – 28)

  3/25 died peri-operatively

  1 PNF following superurgent transplant aged 7yrs, ReTX, developed cerebral dysfunction 8 days post

  2 Multi organ failure 10 & 23 days post transplant

Wilson's Disease
BCH experience 1990 - 2018

Chronic Liver Disease (37)

- 36 alive
  - 1 Died - Variceal bleed on holiday; Died from septic shock

Long Term Maintenance Therapy (36)

- Penicillamine (5)
- Penicillamine and zinc (8)
- Zinc = (21)
- Trientine and zinc (1)
- Unknown (1) (lost to follow up)

14 transferred to adult care

Wilson's Disease
BCH experience 1990 – 2018

Transferred to adult services	35
Chronic Liver Disease	14
Post transplant Died post transfer to adults	21 3

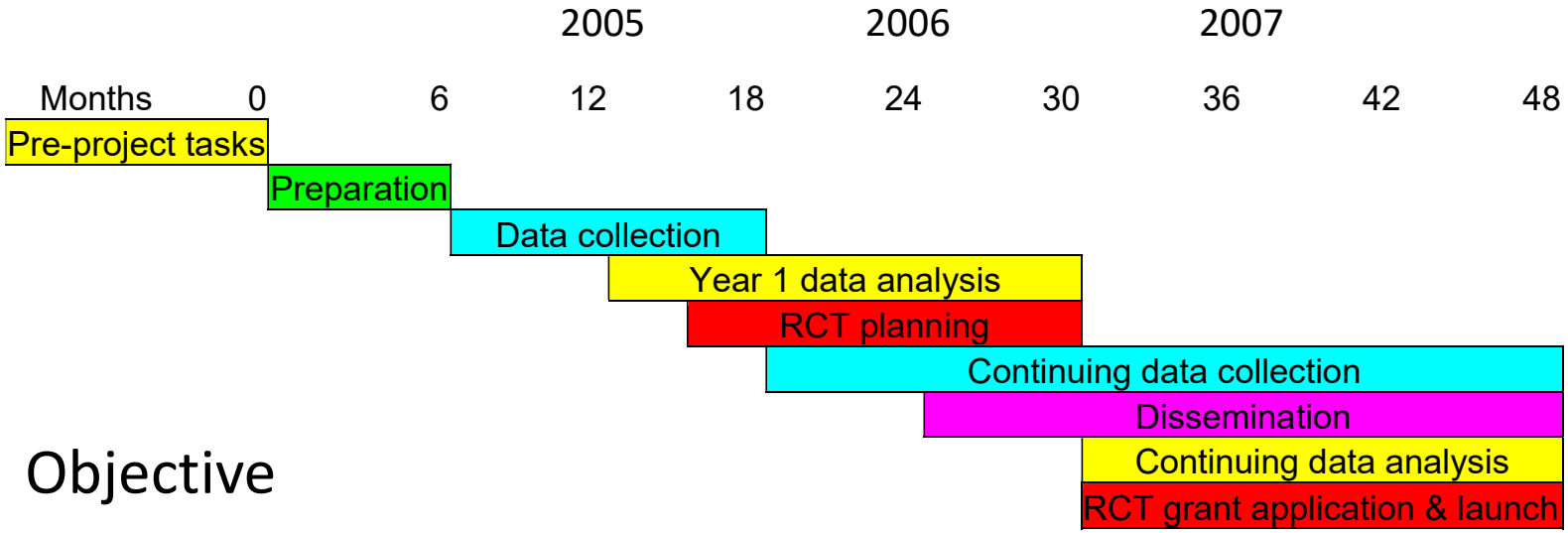
Wilson's Disease
BCH experience 1990 - 2018

- Initial Therapy (62)
  - Penicillamine (13)
  - Penicillamine and Zinc (19)
  - Zinc (14)
  - None (7)
  - Unknown (9)
- Long Term Maintenance Therapy (36)
  - Penicillamine (5)
  - Penicillamine and zinc (8)
  - Zinc = (21)
  - Trientine and zinc (1)
  - Unknown (1) (lost to follow up)

Wilson's Disease
BCH experience 1990 - 2018

- Transplant patients (n=25)
- Pre Tx therapy
  - Pencillamine (2)
  - Pencillamine and Zinc (9)
  - Zinc (2)
  - Unknown (6)
  - None (6)

EuroWilson: the plan in 2004



Objective

-to assess the feasibility of RCTs

-➔ epidemiology of WD in Europe

-➔ secondary purposes eg outcome measures

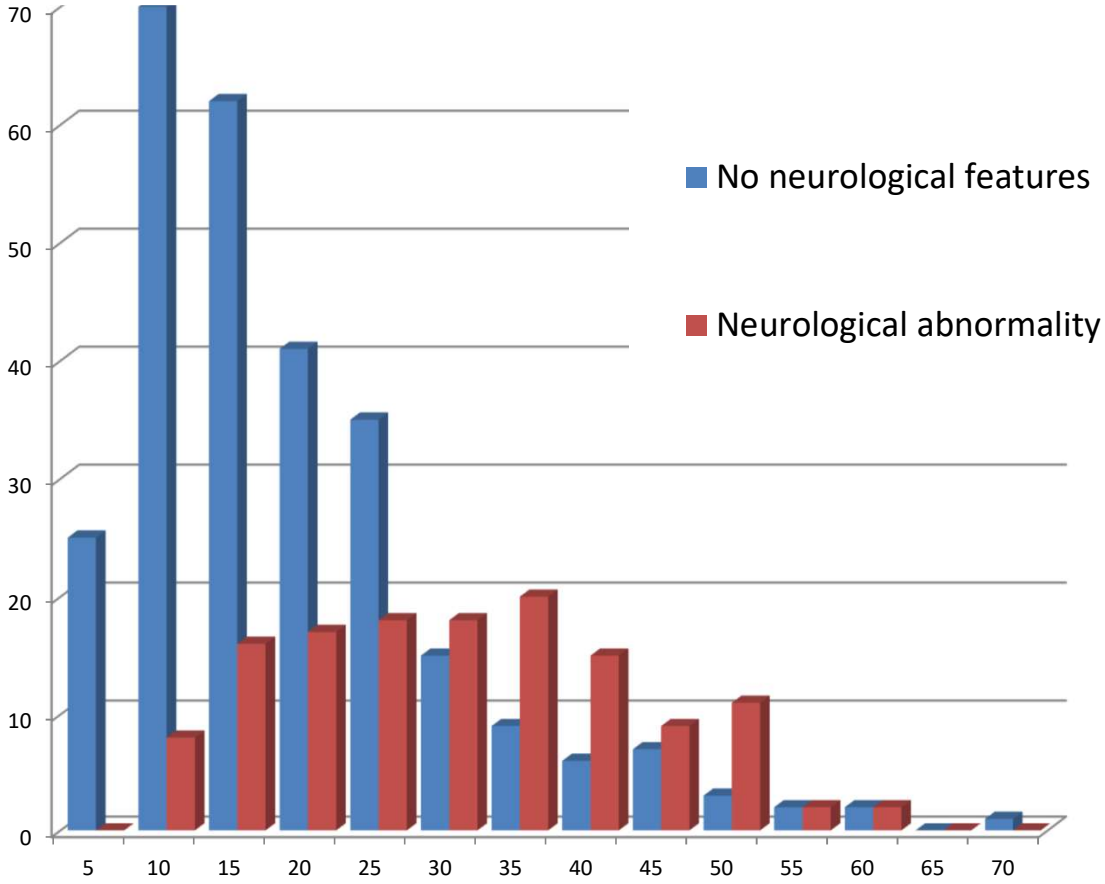
Eurowilson Diagnostic score in Wilson's Disease

Score	-1	0	1	2	4
Kayser-Fleischer rings		absent		present	
Neuropsychiatric symptoms typical brain MRI		absent		present	
Coombs negative haemolytic anaemia + high serum copper		absent	present		
Urinary copper		normal	1-2 x ULN	>2 x ULN >5 x ULN after penic	
Liver copper quantitative	normal		<5 x ULN	>5 x ULN	
Rhodanine positive hepatocytes		absent	present		
Serum ceruloplasmin		>0.2g/l	0.1-0.2g/l	<0.1 g/l	
Disease-causing mutations		None	1		2

Assessment of the Wilson Disease diagnostic score

0-1: unlikely **2-3: probable** **>4 : highly likely**

Age vs presence/absence of neurological abnormalities

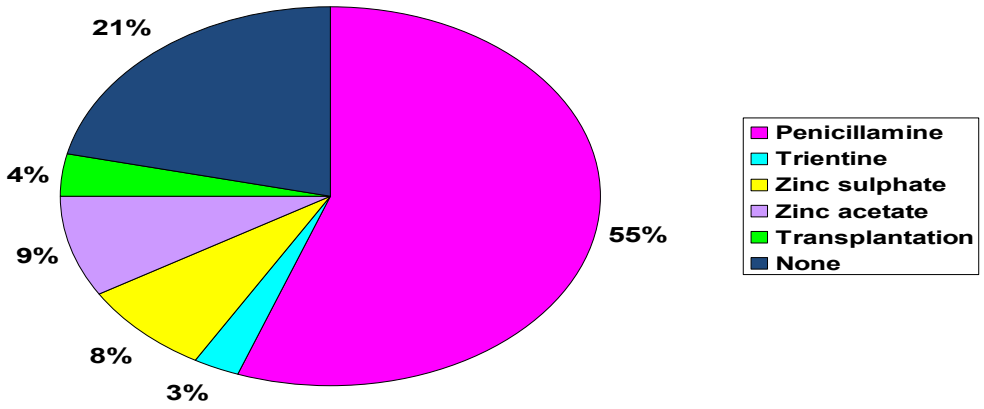


EuroWilson Database
Paediatric experience 2005-2009

219 new cases <18 years

- 5% had liver failure with encephalopathy
- 7% coagulopathy
- 21% jaundice, ascites, or haematemesis
- 16% hepato/spleno-megaly
- 39% abnormal LFTs
- 12% no hepatic features

Initial treatment of patients in EuroWilson database (2005-07)



Wilson's Disease
BCH experience 1990 - 2018

- Outcome of screened patients n = 12
  - 1 died post transplant (patient also had HHH mutation on same gene as Wilson's disease)
  - 11 alive and well, stable