WILSON'S DISEASE

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INTRODUCTION

• Genetically inherited disorders have gained importance in the last few decades primarily due to improved genetic and biochemical testing.

•An increasing emphasis of research is on the therapeutic aspects of these disorders.

•Wilson's Disease (WD)- a genetic disorder is an inborn errors of metabolism .

A number of aspects makes the disease especially interesting and important to Pediatricians viz.,

- Extremely varied clinical presentation giving rise to diagnostic difficulties.
- WD is a treatable cause of liver damage and cirrhosis, provided it is diagnosed early.
- Recent advances in molecular genetics have greatly facilitated early diagnosis in asymptomatic siblings.

What is Wilson's Disease(WD)?

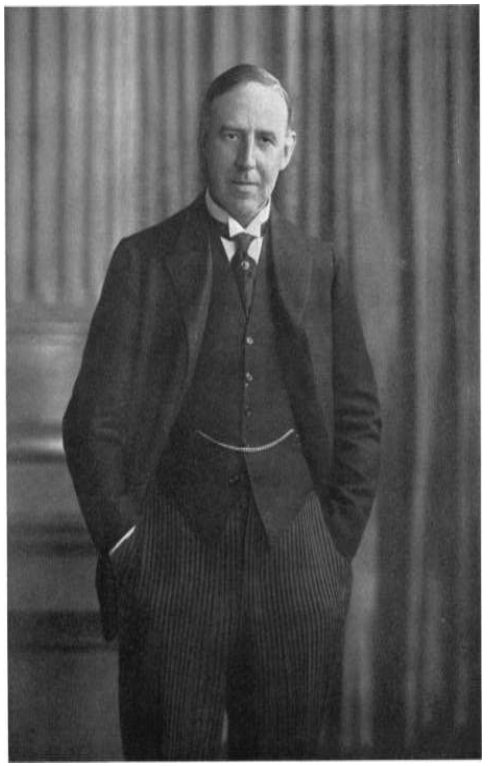
WD is

- An autosomal recessive disease
- Involving a defect of Cu transport
- Leading to excess Cu deposition in liver, brain, kidneys, and skeletal system
- Affecting most commonly children and young adults
- And running invariably a fatal course if not adequately treated by de-coppering therapy.

HISTORICAL MILESTONES

Corneal Copper deposits (KF rings)

Kayser(1902)
Fleischer(1903)



A familial nervous disease associated with cirrhosis of the liver

S.A.K.Wilson(1911)

Biological role for Copper postulated

Cumings (1948)

Contd……..,

Low levels of ceruloplasmin	Scheinberg & Gitlin (1952)
Chelation therapy with Pencillamine	Walshe (1956)
Gene location of WD on Chromosome 13	Frydman *et al* (1985)
Homologous Gene for WD published	Bull *et al* (1993)

Epidemiology

Global scenario

- The reported prevalence of WD varied between 12 and 29 per 100,000 in European population.

- Prevalence in Asian countries other than India varied between 33 and 68 per 100,000.

Contd…,

Indian scenario

- There are no community based incidence and prevalence studies of WD in India and most of the studies are Hospital based.

- In the study of Hepato-biliary Spectrum Disorders from Lucknow North India (235 patients over 31/2 years) showed that Wilson's disease accounted for 18 patients i.e., 7.6%

- Another large multicenter study, Pediatric Liver Study group of India in 11 medical colleges across the country showed- WD accounted for 19.4% of patients (etiological spectrum study) This was most common metabolic liver disease in this study.

Cont..,

- However, recent Indian literature has focused on neuropsychiatric form of WD

- At WD special clinics in NIMHANS, Bangalore , about 15-20 new cases of WD are registered annually.

Genetics

- A mutation in the ATP 7B gene located on chromosome 13 is responsible for WD.

- Hepatocyte copper trafficking is caused by impaired function of P type ATPase encoded by ATP 7B gene located on chromosome 13q14 and consists of 21 exons.

- Until now 400 mutations have been documented from various countries.

Contd…,

- Genetic analysis in India are mainly from Chandigarh, Kolkata and Vellore.

- C813A is the common mutation that is reported from our country.

- There is no single predominant mutation noted in the Indian population unlike the studies in other countries, thus suggesting **genetic heterogeneity** in India.

Pathogenesis and Pathology

Copper Balance

- The average intake of copper (Cu) in breast fed babies is 50 µ grams/ kg/ day and

- In older children and adults it is up to 5 mg / day.

- 60 to 70% of ingested Cu is absorbed normally depending on factors like ph, fiber, phytates, Zn etc.

Contd…,

- Absorbed Cu is transported via the portal vein loosely bound to albumin and transferrin.

- Most of the absorbed Cu is then taken up by the hepatocytes rapidly and used as a co-factor for Cu dependent intracellular enzymes such as cytochromes oxidase and superoxide dismutase.

Contd…,

- Biliary Cu which is not absorbable is lost in feces and regulated by sensitive mechanisms.

- As cerulo-plasmin – which contains 93% of plasma Cu and transport it to all tissues (brain, muscle, kidney) for their metabolic activities.

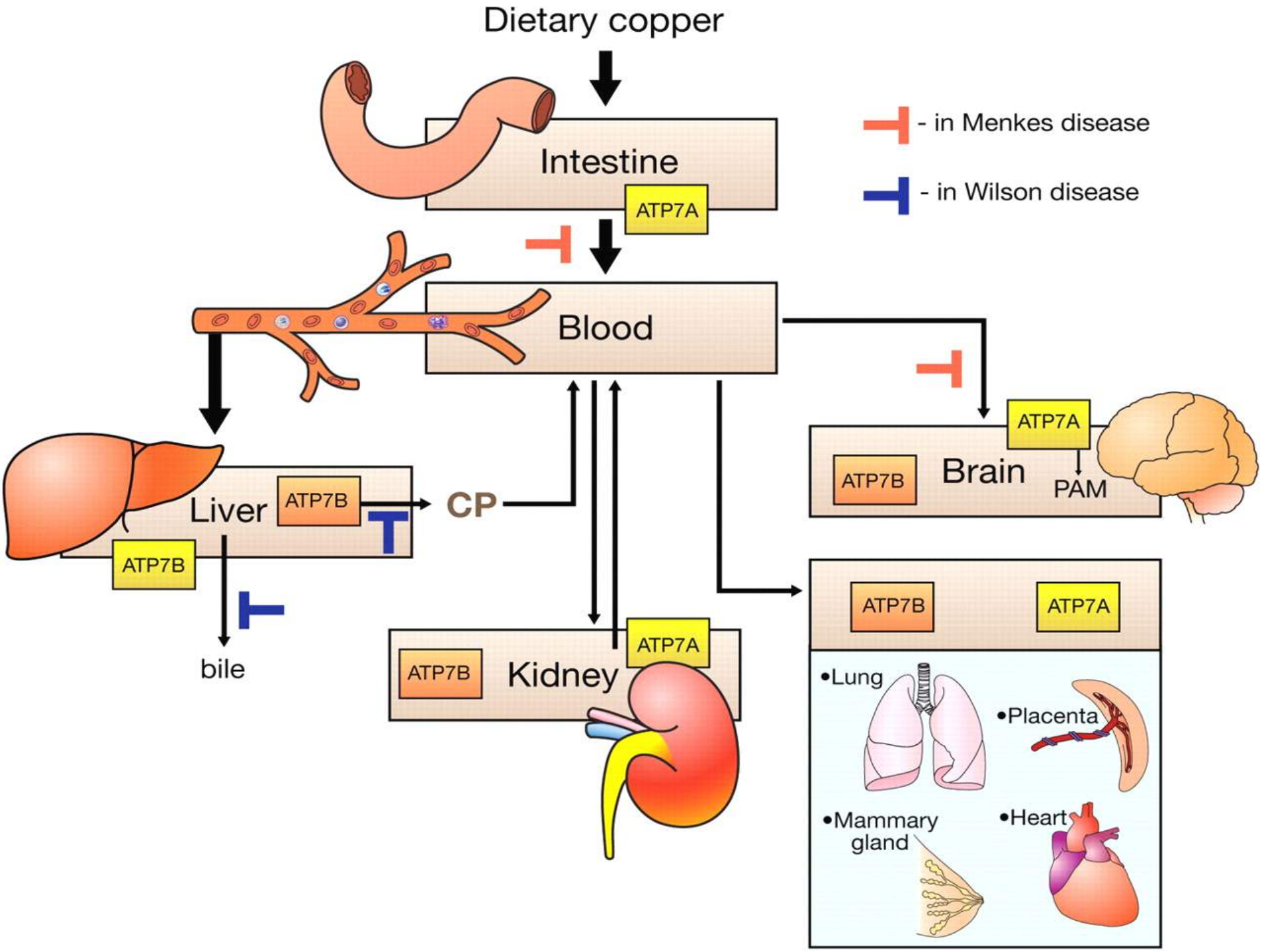
  Both the above mechanisms biliary Cu excretion and incorporation can be faulty in WD.

What happens to Cu in WD?

- As Cu failed to leave the cells , in the bile, or in Ceruloplasmin it accumulates to toxic proportions.

Where?

- This accumulation is first in cytosol bound to metallothionein and then to lysosomes while some free Cu is released to circulation.


Dietary copper
Intestine
ATP7A
- in Menkes disease
- in Wilson disease
Blood
Liver
ATP7B
ATP7B
CP
bile
Brain
ATP7A
ATP7B
PAM
Kidney
ATP7A
ATP7B
ATP7B
ATP7A
•Lung
•Placenta
•Mammary gland
•Heart

What is the result?

- If shift of intracellular Cu is sudden → acute symptoms of FHF and Hemolysis

- Gradual shift → Cirrhosis.

- Free Cu in circulation accumulates in brain and other tissues causing related symptoms.

What is the mode of Cu toxicity at cellular level ?

- It is hypothesized that excessive Cu deposited in various tissues leads to oxidative damage.

- Sinha et al., showed increased levels of serum Malonaldehyde (MDA), a test to detect such oxidative damage in 50% of cases.

- Tocopherol a naturally occurring antioxidant that might protect tissues from O2 derived free radicals was reduced in 59% cases,

- But did not correlate to clinical and bio-chemical status.

Contd…,

- Increased levels of pro and anti inflammatory cytokines were showed in some more studies.

- But cause and effect relationship of elevated cytokines could not be elicited.

- Hence the mechanism of Cu deposition leading to tissue damage is **unanswered.**

What is the Pathology?

- There is paucity of literature on the clinico-pathological correlation in WD in the international literature.

- In an autopsy study of 8 patients of WD the pathology described is --- *central-pontine-myelinolysis like changes*, *white matter cavitation, putaminal softening*, *ventricular dilatation* and *atrophy.*

- The *lenticular involvement* in WD was *not universal* as believed and pathological involvement was *far more diffuse* in character.

Clinical Manifestations

- The clinical presentations of WD are protean and varied.
- It has diverse manifestations.
- No two patients of WD may have similar clinical characters.
- The phenotypic variability of WD often leads to delay in diagnosis unless there is high index of suspicion.

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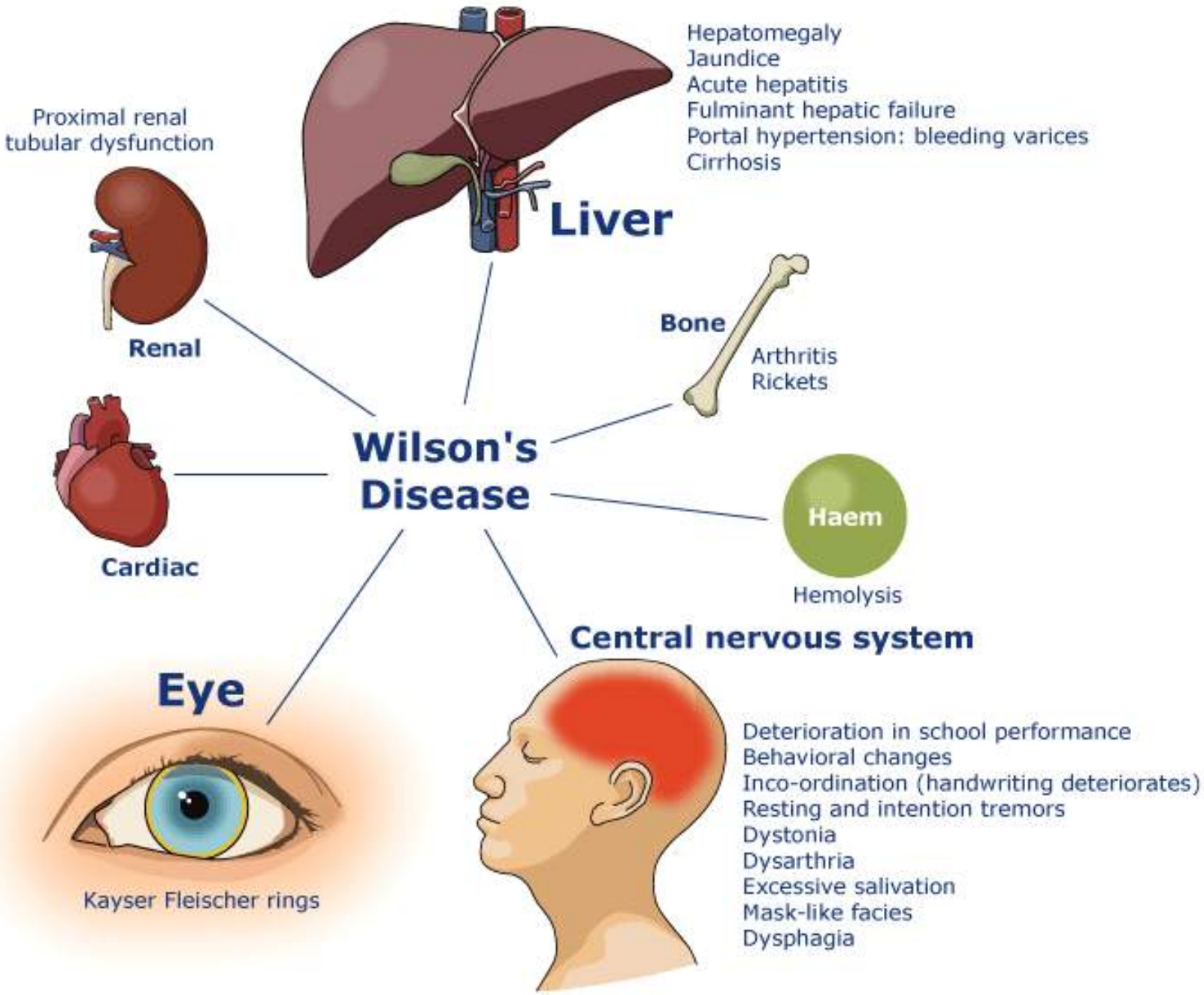
Most common presentations are

- with liver disease or with neuropsychiatric disturbances.
- Many systems are affected
- Asymptomatic patients are detected by family screening

Age at onset of symptoms:

- Can present at any age
- Majority at 5 and 35 yrs
- Youngest age of presentation 3 yrs and oldest at 8th decade.


Hepatomegaly
Jaundice
Acute hepatitis
Fulminant hepatic failure
Portal hypertension: bleeding varices
Cirrhosis
Liver
Proximal renal tubular dysfunction
Renal
Bone
Arthritis
Rickets
Wilson's Disease
Cardiac
Haem
Hemolysis
Central nervous system
Deterioration in school performance
Behavioral changes
Inco-ordination (handwriting deteriorates)
Resting and intention tremors
Dystonia
Dysarthria
Excessive salivation
Mask-like facies
Dysphagia
Eye
Kayser Fleischer rings

Contd…,

Hepatic WD

- Any type of liver disease may be encountered
- Highly variable ranging from asymptomatic to FHF

Chronic Liver Disease

Chronic hepatitis, hepatosplenomegaly, prolonged jaundice, edema, ascites, with signs PHT

Acute hepatitis: mimics acute viral hepatitis where presence of edema and ascites (with +ve family history) should suggest WD.

Fulminant hepatic failure is another presentation especially in younger age.

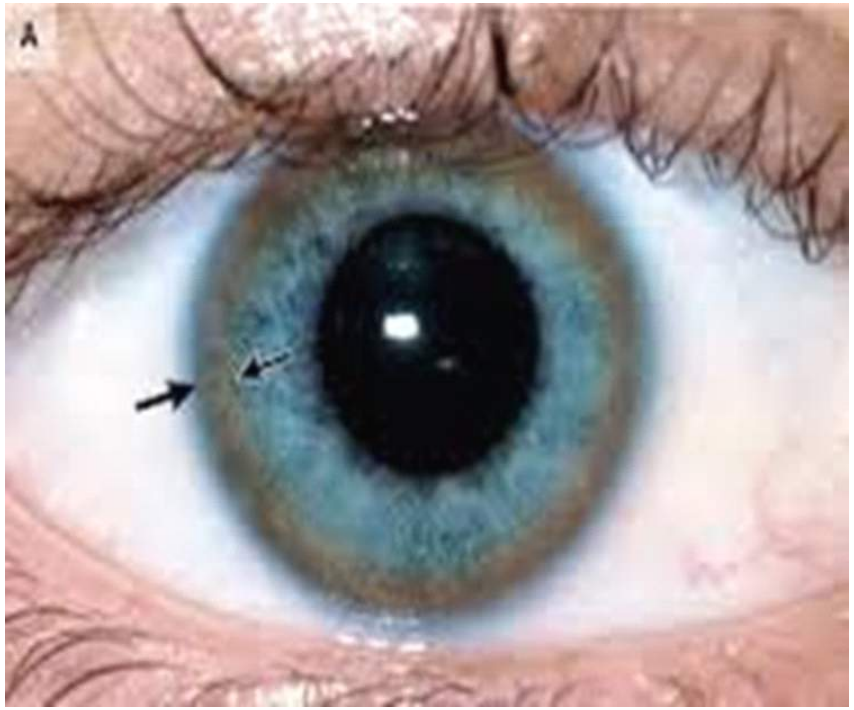
Contd…,

Neuropsychiatric manifestations:

- Neurological WD is typically seen in late teens
- Children as young as 5 or 6 years are occasionally affected
- Early symptoms are subtle
- Clumsiness, mild tremors, speech problems, difficulties in hand writing, deteriorating school performance, severe movement disorders - choreo- athetosis, dystonia, rigidity, and posture abnormalities, or with psychiatric disturbances
- Intelligence is not affected

Ophthalmic manifestations: Kayser-Fleischer Ring:

- Typically 1-3 mm in thickness.
- Green , yellow, or brown
- Located at the periphery of cornea
- Start as a small crescent at the top of limbus,
- Extends inferiorly and then medially until it becomes circumferential & broad



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•Although excess Cu is distributed through out the cornea

Sulphur- Cu complexes are seen only

in the Descemets membrane

•A complete ring indicates long standing disease and severe Cu

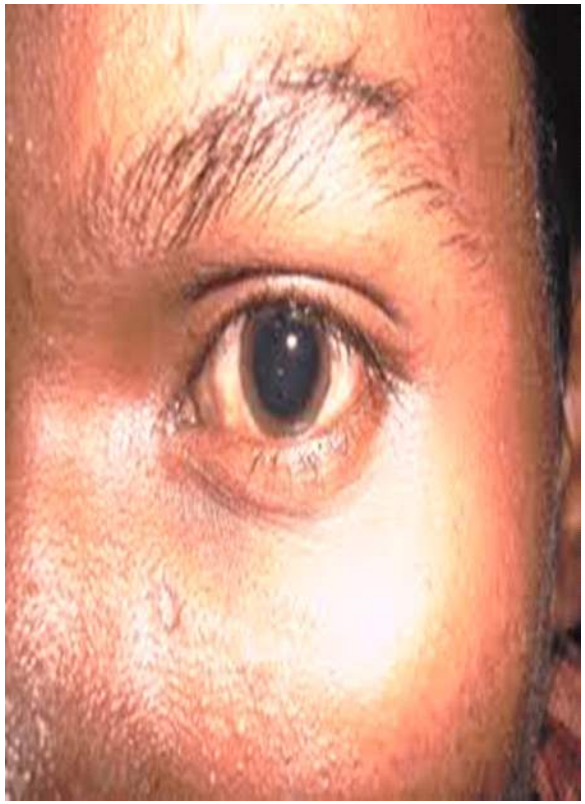
over load

•Present in 95%of neurological WD,

•Chelation therapy causes disappearance of the rings in 3 to 5 yrs

in the reverse order of appearance

•KF Ring does not affect the vision



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Other manifestations :

- Bone involvement as spontaneous fractures, osteoporosis

- Joint involvement especially knee joint , and with radiological abnormalities of vertebral column .

- Hemolytic anemia, and thrombocytopenia

- Kidney – Renal Tubular Acidosis of Fanconi type & nephrocalcinosis.

Clinical characteristics of Wilson's disease patients in various Indian studies

Group	Dastur et al.[6]	Singh et al. [67]	Raiamani et al.[12]	Murthy et al.[68	Pandit et al.[37]	Jha et al. [13]	Sinha et al. [14]	Taly et al. [1]
Year	1968	1978	1987	1988	2002	1998	2001	2007
Study period	1959-68	1972-75	1968-1986	1979-86	1980-2000	1984-93	1991-2000	1970-2000
Place of study	Bombay	Pondicherry	Vellore	Hyderabad	Pune	New Delhi	Ranchi	Bangalore
No. of cases (M:F)	23 (15:8)	08 (5:3)	30 (22:08)	12 (11:1)	124	22 (20:2)	49 (38:11)	282 (196:86)
Mean age at onset	13.4	13.3	NA	13.3	8.4	18.5	13	15.9
(Range)	(4-25)	(3-25)	(6-50)	(7-21)	(4-60)	(10-33)	(8-23)	(3-50)
Clinical pattern Hepatic	1	3	11	1	67		-	42
Neurological	10	3	13	10	28		34	195
Hepatic + Neurological	2	0	-	1	0		15	10

Contd…,

Group	Dastur et al.[6]	Singh et al. [67]	Raiamani et al.[12]	Murthy et al.[68	Pandit et al.[37]	Jha et al. [13]	Sinha et al. [14]	Taly et al. [1]
Musculoskeletal	3	2	6	0	0		-	6
Psychiatric	0	0	-	0	0		-	7
Others	5	0	-	0	10		-	7
Asymptomatic	2	0	-	0	19		-	15

The presenting symptoms in different series are variable.
The notable clinical features from NIMHANS study are

- ✓ Tremors (31.6%)
- ✓ Dysarthria (15.6%)
- ✓ Jaundice (12.4%)
- ✓ Abnormal gait (8.8%)
- ✓ Abdominal distension(7.8%)
- ✓ Musculo skeletal (5.2%)
- ✓ Seizures (4.9%)
- ✓ behavioral problems (4.6%)
- ✓ dystonia (3.6%)
- ✓ clumsiness (2.6%)
- ✓ generalized weakness (2%)
- ✓ bleeding diathesis (1.3%)
- ✓ chorea (0.3%)
- ✓ poor vision (0.9%)

Contd…,

- Hepatic involvement - predominant in younger age group
  It occurs early But may go unrecognized and may not be the first symptom.

- Neurological manifestations were the presenting symptoms in 60% of cases and

- Extrapyramidal features are the dominant disturbance followed by Psychiatric manifestations like bipolar affective disorder, psychosis

- Prone for malignancies like neuroblastoma, hepatocellular carcinoma, basal cell carcinoma, ALL, glioblastoma multiforme.

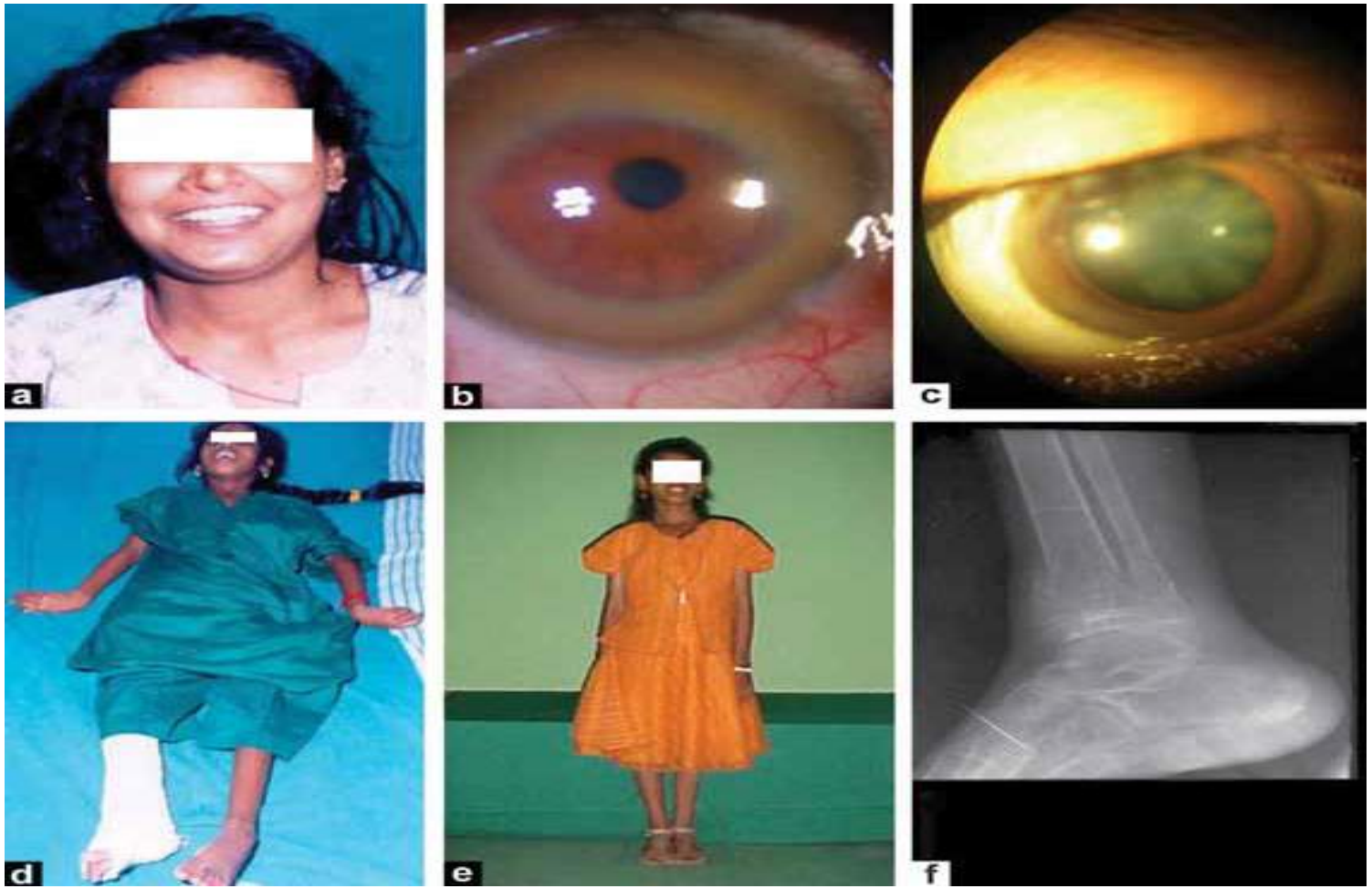
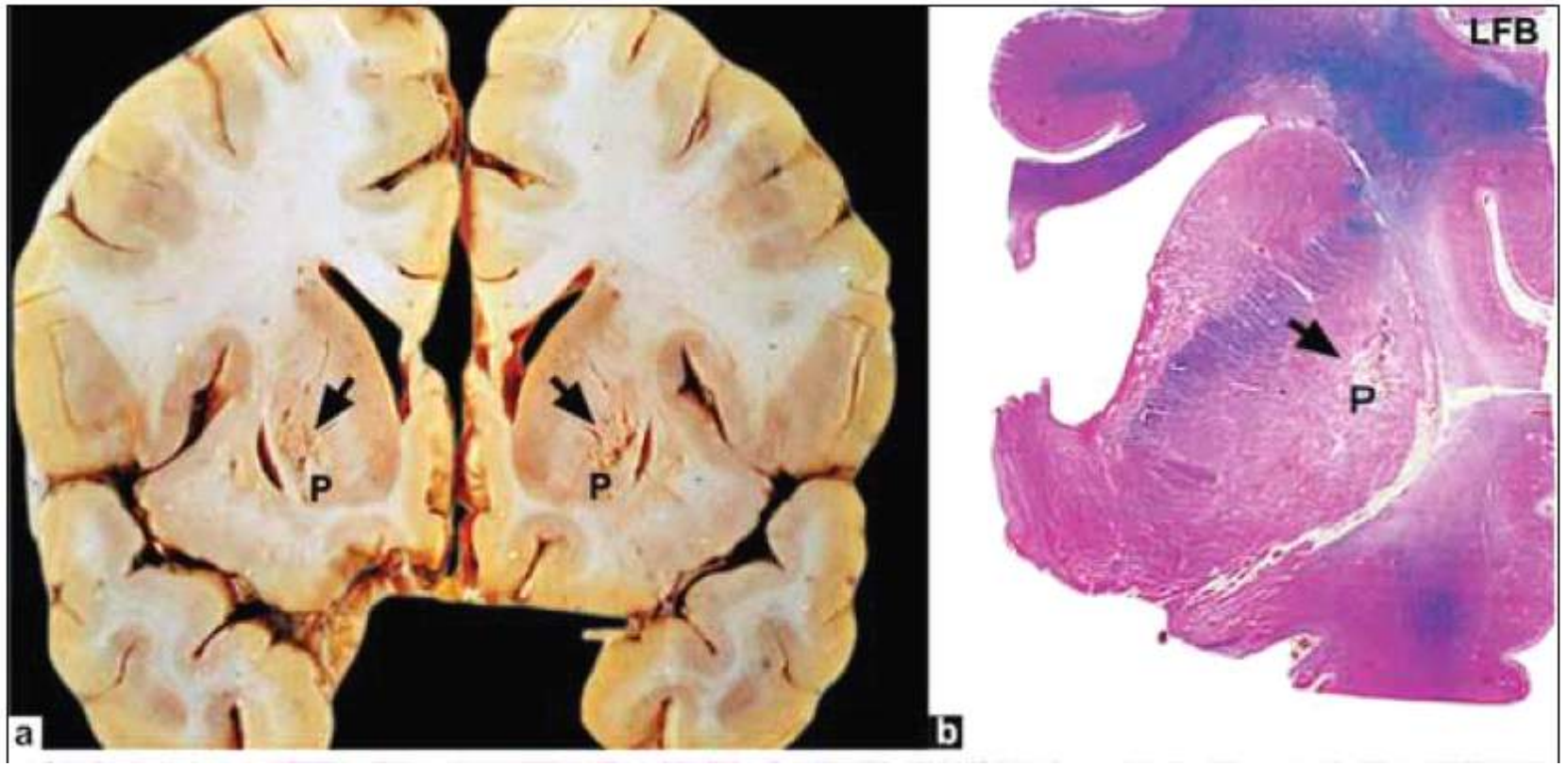
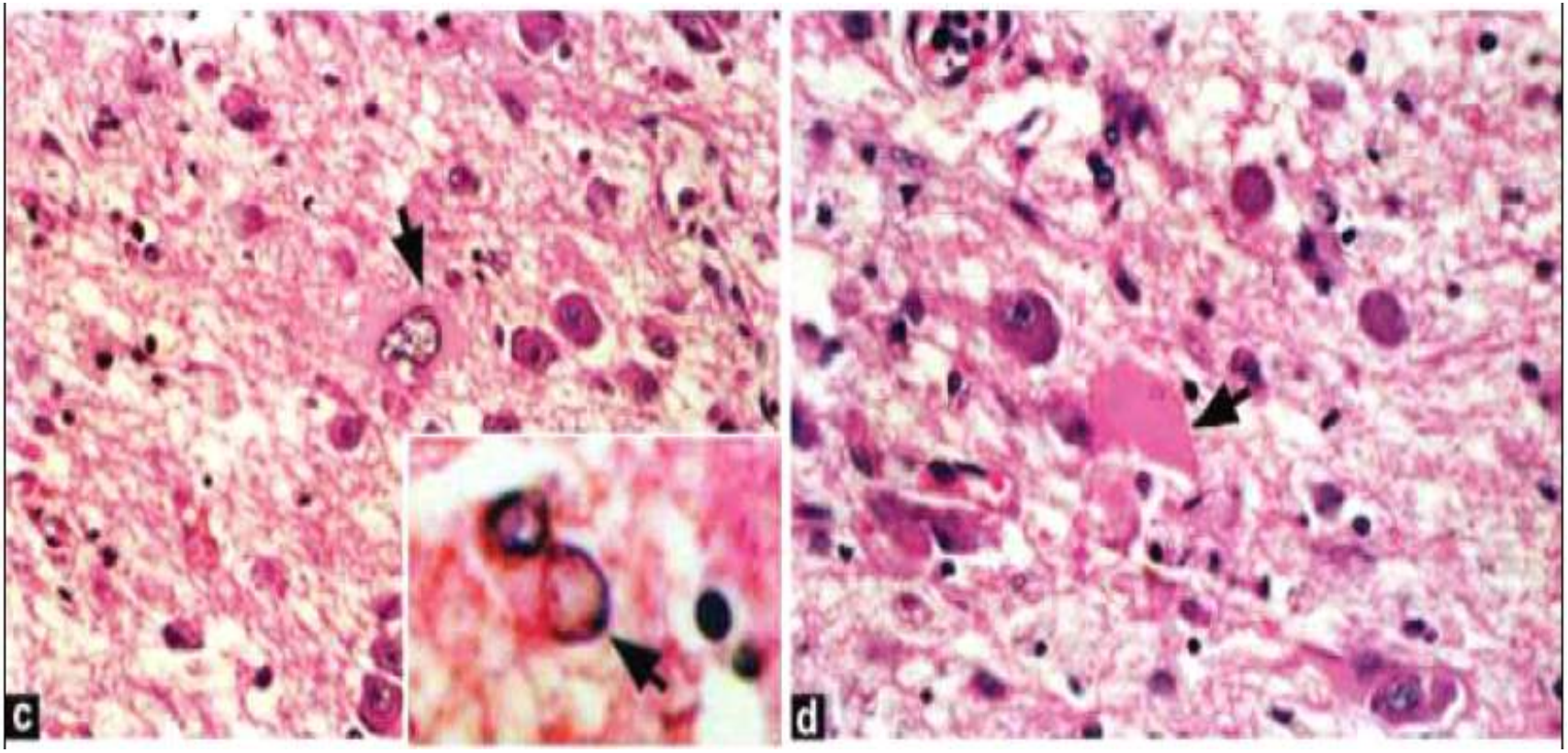


Figure 2: (a) Typical ‘Wilsonian’ dystonic smile; (b) KF ring-naked eye appearance; (c) Sunflower cataract; (d) Severe dystonia in a patient with WD, and with typical ‘Wilsonian smile’ with cast for pathological fracture; (e) improvement following specific treatment in the same patient and (f) X-ray showing features of osteomalacia including pathological fractures

(a) Coronal slice of the brain, from a case of Wilson's disease shows bilaterally symmetrical putaminal (P) softening (arrows) extending laterally up to the external capsule; (b) Whole mount preparation stained with Luxol Fast Blue shows relative preservation of internal capsule and pale and softened neuropil in the putamen (P, arrow).



(c) Softened area in the putamen has bizarre astrocytes with vesicular lobulated nuclei (arrow) with inset showing Alzheimer type 2 astrocytes in the neuropil (arrow). Inset: H and E, 3 300; (d) Large opalski cell characteristic of Wilson's disease has irregular eosinophilic cytoplasm and small peripherally placed pyknotic nucleus.



(e) Slice of enlarged liver shows microand macronodular cirrhosis. Inset demonstrates copper deposits within hepatocytes on rubeanic acid stain. Inset: Rubeanic acid 3 240

Diagnosis

Typically the combination of K.F rings and low serum Cp(0.1g/l) is sufficient to establish the diagnosis.

If K.F. rings are not present we need different tests.

No single test is diagnostic by itself and the key to diagnosis is by high index of suspicion.

Lab tests are broadly classified into

- Biochemical
- Ophthalmological
- Radiological

Contd…,

Biochemical : include estimation of

- Serum copper
- Serum ceruloplasmin
- 24 hour urinary Cu estimation

and others are

- LFT
- RFT
- Hematological
- And others to assess the status of other organs

Contd…,

- Serum cerulo-plasmin : Normal conc. of Cp (enzymatic assay) varies among labs.

- Lower limit between 0.15 and 0.2g/ l

- False positive→ severe malnutrition, protein losing states etc.

- False negative→ WD with marked hepatic inflammation, pregnancy etc.

- *Note: serum Cp is typically decreased in neurological WD.*

Contd..,

- Total serum Cu includes Cp bound and free Cu

  Normal range 70-150 µ gm/dl

  Not helpful in the diagnosis as they may be normal , low, or high.

- Hepatic parenchymal Cu Conc.:

  Usually elevated > 250 µ gm / gram dry wt (N: 15-55)

  Accurate available test but not pathognomonic as it is elevated in primary biliary cirrhosis, BA etc.

- *NOTE: Liver biopsy- not necessary for neurological WD as the other tests permit the diagnosis (and Cu already has been discharged to other tissues)*

Contd…,

- 24 hour urinary Cu excretion :

- Normal individuals < 70 micro gm/ day is excreted . Predominantly derived from the non-Cp (freely filtered from glomerulus)

- In symptomatic children with WD > 100 micro gm.

- Estimation of Cu after Pencillamine challenge has got many controversies.

Contd…,

Ophthalmological evaluation:

- Presence **of KF rings** in slit lamp examination- is corner stone of clinical examination.

- ***Presents in most cases of neurological WD***

- But in Hepatic WD it may not be present.

Contd…,

Neuroimaging :

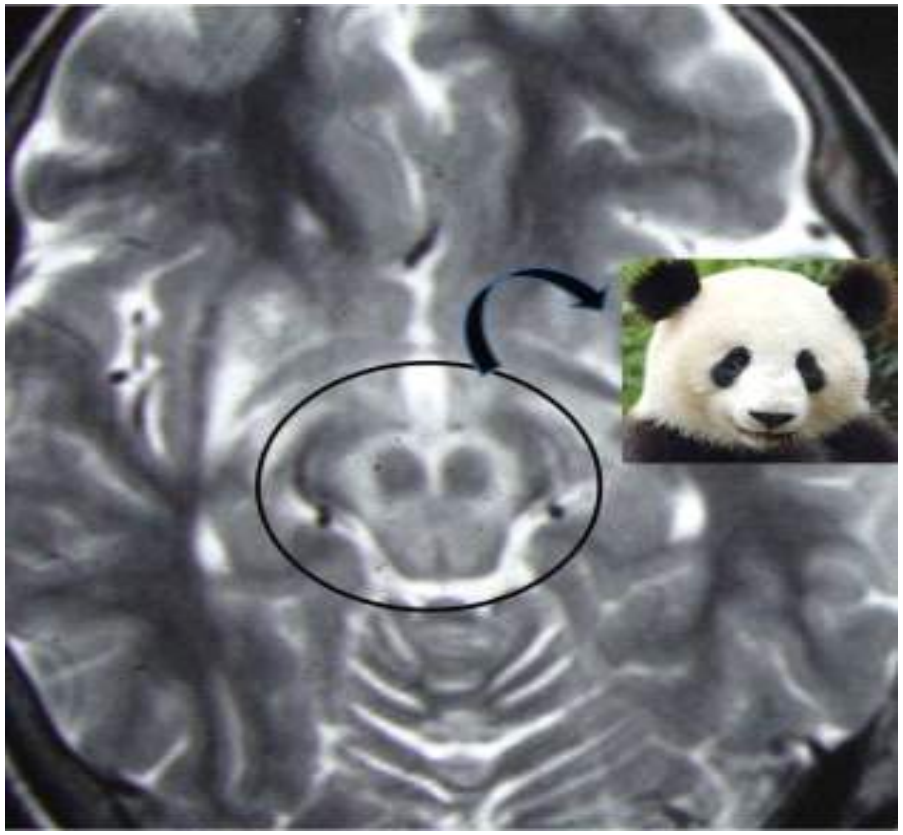
CT abnormalities : cortical atrophy, ventricular dilatation, caudate atrophy, brainstem and cerebellar atrophy and hypodensities in basal ganglia, thalami, hemispheres.

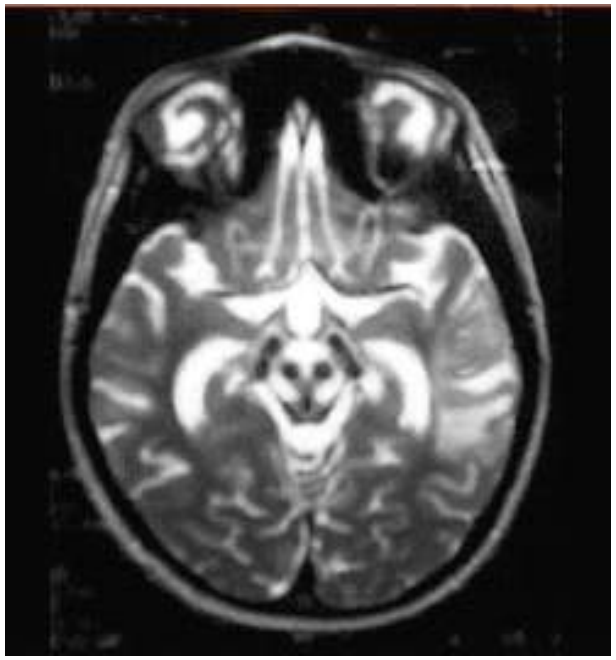
MRI : assists in diagnosis.

atrophy of cerebrum, brainstem, cerebellum, signal abnormalities in putamen , caudate, thalami, midbrain, pons, medulla, and cerebrum.

sign of "face of giant panda" is seen only a few cases.

MRI can be used as a tool to monitor therapy.





Scoring system developed at the 8th International Meeting on Wilson's disease, Leipzig 2001

Typical clinical symptoms and signs		Other tests	
KF rings		Liver copper (in the absence of cholestasis)	
Present	2	>5x ULN (>4 µmol/g)	2
Absent	0	0.8-4 µmol/g	1
Neurologic symptoms**		Normal (<0.8 µmol/g)	-1
Severe	2	Rhodanine-positive granules*	1
Mild	1	Urinary copper (in the absence of acute hepatitis)	
Absent	0	Normal	0
Serum ceruloplasmin		1-2x ULN	1
Normal (>0.2 g/L)	0	>2x ULN	2
0.1-0.2 g/L	1	Normal, but >5x ULN after D-penicillamine	2
<0.1 g/L	2	Mutation analysis	
Coombs-negative hemolytic anemia		On both chromosomes detected	4
Present	1	On 1 chromosome detected	1
Absent	0	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.

Treatment

Drugs available: D pencillamine

Zinc

Trientine

Tetrathiomolibdate

Contd…,

D Pencillamine (DP);

- promotes urinary excretion of Cu
- may also act by inducing metallothionein

- Initial dose: 250-500 mg and should be given on empty stomach (20mg/kg/ day in children)

- No consensus on the supplemental pyridoxin

- The propensity of DP to produce deterioration in neurological function on initiation of treatment is a subject of some disagreement.

Contd…,

Zinc :

- administered as acetate, sulfate, gluconate

- Acts by reducing intestinal absorption of dietary Cu via induction of metallothionein formation in intestinal erythrocytes.

- The increased metallothionein binds both Zn & Cu , traps them sloughed and excreted in feces.

- BUT - acts slowly and negative Cu balance is small.

- Hence used as maintenance at 50 mg tid.

Contd…,

- Trientine:

- Copper chelating agent with action similar to DP

- As it provokes less precipitous de-coppering safer than DP

- Should be taken on empty stomach

- 750- 2000 mg in three divided doses

- Experience is less extensive

Contd…,

Tetrathiomolibdate;

- Is another drug under consideration
- Acts by limiting absorption of Cu and also prevents cellular uptake of Cu.
- Dosing scheme is complicated as it binds with Cu in the gut when given with food and absorbed into the blood stream when given without food.
- Given 20 mg 6 times/ day – 3 times with meals & 3 times in between meals
- Not intended for long term therapy, only for 8 weeks
- To be followed by Zn maintenance

OUTCOME Measures

- Most of the patients with WD lead normal life following the institution of specific medications.

- But it has been found that patients with white matter lesions on MRI have poor response to de-coppering therapy.

- Rapid progressive course is noted in patients with hepatic WD

Conclusions

- WD perhaps more common than reported in India.

- There is a need for epidemiological studies and also multicentric genetic study in view of high degree of consanguinity in certain parts of India, particularly in south India.

- Patient and the care giver need to be educated regarding compliance and long term follow-up.

- Governments should see that drugs are available at subsidized rates as WD is a potentially curable disease.

REFERENCES

- Wilson's disease: an Indian Perspective - A.B. Taly, L.K.Prashanth. S.Sinha- Department of Neurology, NIMHANS, Bangalore, India

- Wilson's Disease by Anand et al liver unit, Department of Peditrics,KEM hospital Pune from IJP 2002

- EASL Clinical Practice Guide lines: Wilson's Disease from journal of Hepatology 2012 vol. 56/671-685 (European Association for the Study of Liver)

- Wilson's Disease- Ronald. F. pfeiffer, M.D from Seminars in Neurology/ vol.27, number 2-2007


Thank You