Internal Medicine Grand Rounds

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WILSON'S DISEASE

Evolving Insights Into Etiology, Clinical Presentation and Diagnosis, and Therapeutic Options

Burton Combes, M.D.

This is to acknowledge that Burton Combes, M.D. has disclosed no financial interests or other relationships with commercial concerns directly or indirectly related to this program. Dr. Combes will be discussing off-label uses in this presentation.

Burton Combes, M.D. is a Professor of Internal Medicine, Division of Digestive and Liver Diseases, at the University of Texas Southwestern Medical Center at Dallas.

His areas of interest are hepatic disease; autoimmune hepatitis; primary biliary cirrhosis; liver disease in pregnancy.

Introduction

Wilson's disease, an inherited disorder of copper metabolism, was first recognized in the early 1900's. It's clinical description evolved gradually as did elucidation of its diagnosis. A number of effective therapies have been developed, and more recently the site of its major genetic defect has been characterized. Despite these major advances, the diagnosis is often missed or delayed, even in excellent medical centers, in part because the disease is not considered, or because the physician uses a set of diagnostic tools that do not possess 100 percent positivity or specificity. Delay in diagnosis may lead to progression of the disease to an irreversible state, even when potentially effective treatment is instituted. In the current review, an effort will be made to highlight some of the important contributions to our understanding of Wilson's disease with the aim of improving our diagnostic and therapeutic skills.

Highlights of Wilson's Disease

A familial lethal neurological disease (lenticular degeneration) accompanied by cirrhosis (Wilson, 1912).

Associated with increased copper in liver and brain (Cumings, 1948).

Pigmented rings in cornea (Kayser-Fleischer) and sunflower cataracts earlier observed as reactions to copper foreign bodies are recognized as diagnostic features of Wilson's disease.

Characterized by increased excretion of copper in urine, further increased by BAL.

Ceruloplasmin, the major copper binding protein in plasma, found to be low (Scheinberg and Gitlin, 1952).

Reviews

Scheinberg IH, Sternlieb I. Wilson's disease. Major problems in internal medicine. Philadelphia, W. B. Saunders, Vol. 23, 1984.

Cuthbert JA. Wilson's disease. Update of a systemic disorder with protean manifestations. Gastroenterology Clinics North America 1998;**27**:655-681.

Loudianos G, Gitlin JD. Wilson's disease. Sem Liver Dis 2000;**20**:353-364.
Sternlieb I. Wilson's disease. Clinics in Liver Dis 2000;**4**:229-239

Brewer GJ. Recognition, diagnosis and management of Wilson's disease. Proc Soc Exp Biol Med 2000;**223**:39-46.

Signal - Early Contributions

Wilson SAK. Progressive lenticular degeneration: a familial nervous disease associated with cirrhosis of the liver. Brain 1912;**34**:295-509.

Cumings JN. The copper and iron content of brain and liver in hepato-lenticular degeneration. Brain 1948;**71**:410-415, 1948.

Mandelbrote BM, Stanier MW, Thompson RHS, Thruston MN. Studies on copper metabolism in demyelinating diseases of the central nervous system. Brain 1948;**71**:212-228.

Cumings JN. The effect of BAL in hepatolenticular degeneration. Brain 1951;**74**:10-12.

Denny-Brown D, Porter H. The effect of BAL (2,3-dimercaptopropanol) on hepatolenticular degeneration (Wilson's disease). New Engl J Med 1951;**245**:917-925.

Scheinberg IH, Gitlin D. Deficiency of ceruloplasmin in patients with hepatolenticular degeneration (Wilson's disease). Science 1952;**116**:484-485.

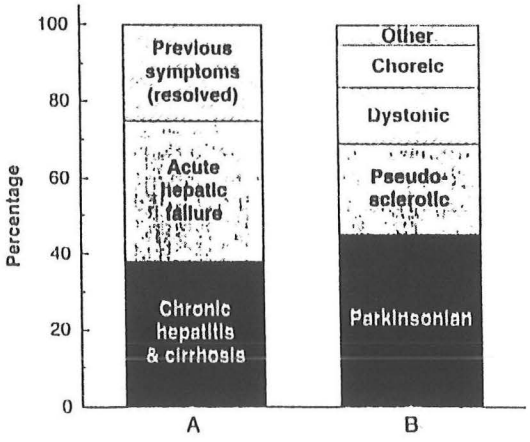
Clinical Presentation

Patients may be completely asymptomatic. They are usually uncovered during assessment of siblings of known cases, or by detection of abnormal physical findings such as splenomegaly and Kayser-Fleischer rings.

Hepatic presentations include episodes of self-limited acute hepatitis, findings of chronic hepatitis, cirrhosis with its complications, and fulminant liver failure.

Neurologic presentation includes the gamut of movement disorders including tremors, dystonia, ataxia and rigidity. Incoordination, dysphagia, dysarthria, and poor handwriting are common.

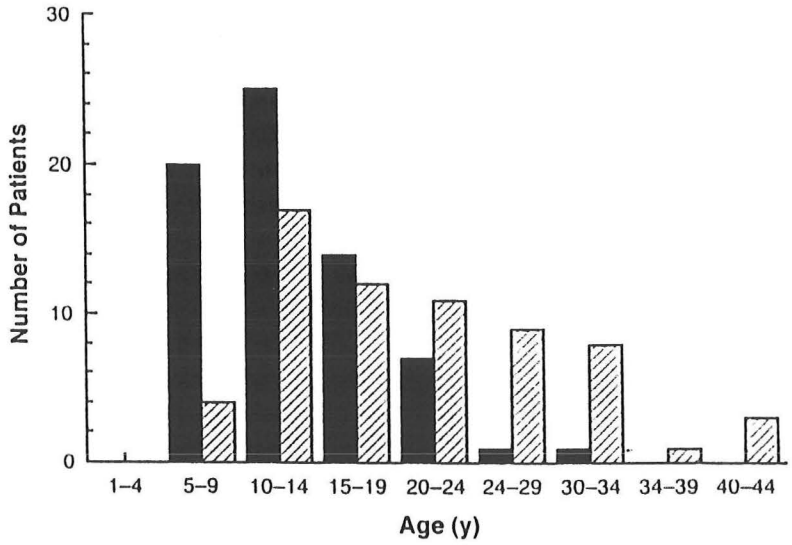
Psychiatric presentations are prevalent and quite diverse. They include behavioral disturbances, inability to concentrate, mood swings, and even psychotic behavior.



Clinical manifestations of Wilson's disease. Presentation subtypes of patients with initial (A) hepatic disease (n=87) and (B) neurologic disease (n=136) are shown. (Data from Walshe JM: Wilson's disease presenting with features of hepatic dysfunction: A clinical analysis of eighty-seven patients. QJM 70:253-263, 1989; and Walshe JM, Yealland M: Wilson's disease: the problem of delayed diagnosis. J Neurol Neurosurg Psychiatry 55:692-696, 1996).

From: Cuthbert JA. Wilson's disease. Update of a systemic disorder with protean manifestations. Gastroenterology Clinics North America 1998;**27**:655-681.

In general, hepatic disease presents earlier by almost 5-10 years than neuropsychologic disease. Most patients are recognized by age 40, but there are well documented cases through the sixth decade.



Overlap of age in years at initial presentation between patients with hepatic disease *(black bars)* and patients with neuropsychiatric symptoms initially *(hatched bars)*. (*Data from* Scheinberg IH, Sternlieb I: Wilson's disease. *In* Smith Jr LH (ed): Major Problems in Internal Medicine, vol 23. Philadelphia, WB Saunders, 1984, p 1.)

From: Cuthbert JA. Wilson's disease. Update of a systemic disorder with protean manifestations. Gastroenterology Clinics North America 1998;**27**:655-681.

The adage is to always think of Wilson's disease in patients with hepatic disease, in those with neurologic disease presenting with any type of movement disorder, and with new behavioral disturbances in persons 40 years or less.

Nazer H, Ede RJ, Mowat AP, Williams R. Wilson's disease: clinical presentation and use of prognostic index. Gut 1986;**27**:1377-1381.

Walshe JM. Wilson's disease presenting with features of hepatic dysfunction: A clinical analysis of eighty-seven patients. Quart J Med 1989;**NS70**:253-263.

Steindl P, Ferenci P, Dienes HP, Grimm G, Pabinger I, et al. Wilson's disease in patients presenting with liver disease: A diagnostic challenge. Gastroenterology 1997;**113**:212-218.

Dufour J-F, Kaplan MM. Muddying the Water: Wilson's disease challenges will not soon disappear. Gastroenterology 1997;**113**:348-350.

Schilsky ML, Sternlieb I. Overcoming Obstacles to the diagnosis of Wilson's disease. Gastroenterology 1997;**113**:350-353.

Gow PJ, Smallwood RA, Angus PW, Smith AL, Wall AJ, Sewell RB. Diagnosis of Wilson's disease: an experience over three decades. Gut 2000;**46**:415-419.

Chronic Active Hepatitis

Sternlieb I, Scheinberg IH. Chronic hepatitis as a first manifestation of Wilson's disease. Ann Intern Med 1972;**76**:59-64.

Scott J, Gollan JL, Samourian S, Sherlock S. Wilson's disease, presenting as chronic active hepatitis. Gastroenterology 1978;**74**:645-651.

Schilsky ML, Scheinberg IH, Sternlieb I. Prognosis of Wilsonian chronic active hepatitis. Gastroenterology 1991;**100**:762-767.

Fulminant Hepatic Failure

McCullough AJ, Fleming CR, Thistle JL, Baldus WP, Ludwig J, McCall JT, Dickson ER. Diagnosis of Wilson's disease presenting as fulminant hepatic failure. Gastroenterology 1983;**84**:161-167.

Shaver WA, Bhatt H, Combes B. Low serum alkaline phosphatase activity in Wilson's disease. Hepatology 1986;**6**:859-863.

Davies SE, Williams R, Portman B. Hepatic morphology and histochemistry of Wilson's disease presenting as fulminant hepatic failure: a study of 11 cases. Histopathology 1989;**15**:385-394.

Berman DH, Leventhal RI, Gavaler JS, Cadoff EM, van Thiel DH. Clinical differentiation of fulminant Wilsonian hepatitis from other causes of hepatic failure. Gastroenterology 1991;**100**:1129-1134.

Sallie R, Katsiyiannakis L, Baldwin D, Davies S, O'Grady J, Mowat A, Mieli-Vergani G, Williams R. Failure of simple biochemical indexes to reliably differentiate fulminant Wilson's disease from other causes of fulminant liver failure. Hepatology 1992;**16**:1206-1211.

Durand F, Bernuau J, Giastra E, Mentha G, Shouval D, Degott C, Benhamou JP, Valla D. Wilson's disease with severe hepatic insufficiency: beneficial effects of early administration of D-penicillamine. Gut 2001;**48**:849-852.

Late Onset Wilson's Disease

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Czlonkowska A, Rodo M. Late onset of Wilson's disease. Report of a family. Arch Neurol 1981;**38**:729-730.

Ross ME, Jacobson IM, Dienstag JL, Martin JB. Late-onset Wilson's disease with neurological involvement in the absence of Kayser-Fleischer rings. Ann Neurol 1985;**17**:411-413.

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Hefter H, Weiss P, Wesch H, Stremmel W, Feist D, Freund HJ. Late diagnosis of Wilson's disease in a case without onset of symptoms. Acta Neurol Scand 1995;**91**:302-305.
Wang X-P. Wilson disease: asymptomatic or late-onset type? Acta Neurol Scand 1996;**94**:421-422.

Pilloni L, Lecca S. Coni P, Demelia L, Pilleri G, Spiga E, Faa G, Ambu R. Wilson's disease with late onset. Digest Liver Dis 2000;**32**:180.

Neuropsychological

Rathbun JK. Neuropsychological aspects of Wilson's disease. Intern J Neuroscience 1996;**85**:221-229.

Genetics of Wilson's Disease

Genetics of Wilson's Disease

Inheritance is autosomal recessive.

- **Familial incidence**
- **High consanguinity rate**
- **Absence of disease in parents**
- **Heterozygote is phenotypically normal**

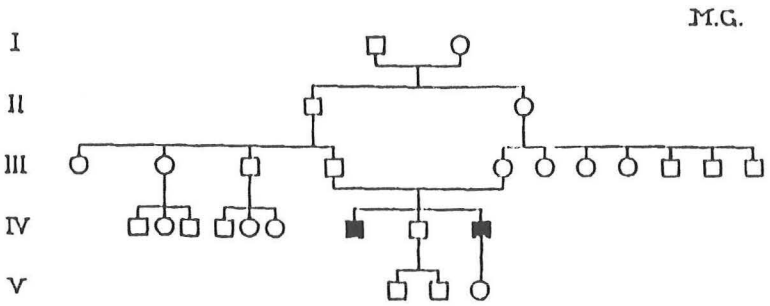


FIG. 1. Pedigree of affected siblings whose parents were first cousins. The single offspring of affected individual is clinically and biochemically normal (age six years).

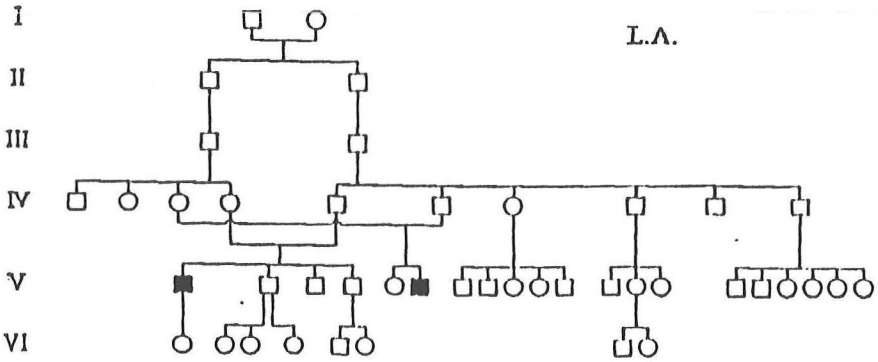
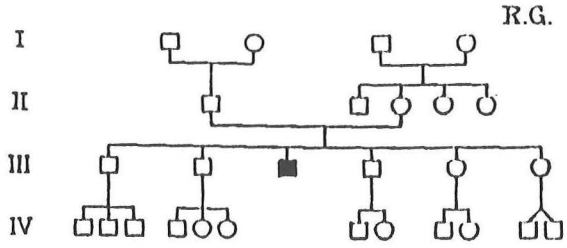


FIG. 2. Pedigree showing two instances of second cousin marriages, each having an affected offspring.



Pedigree of affected sibling with unrelated parents.

From Bearn AG, Amer J Med 1953;**15**:442-449.

Bearn AG. Genetic and biochemical aspects of Wilson's disease. Amer J Med 1953;**15**:442-449.

Bearn AG. A genetic analysis of thirty families with Wilson's disease (hepatolenticular degeneration). Ann Hum Genet Lond 1960;**24**:33-43.

Wilson's Disease Gene Abnormalities

Abnormal gene mapped to chromosome 13q 14.3

Gene is a copper transporting P-type ATPase

Heterogeneous at the molecular level

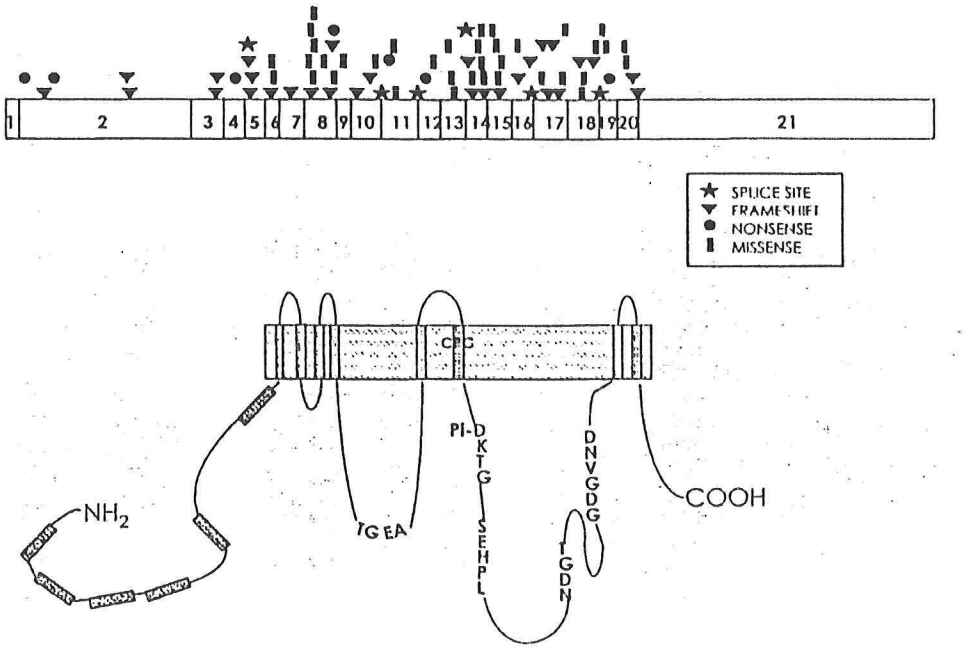
At least 200 different disease-specific mutations

- **Single base insertions and deletions**
- **Frame-shifts, missense, nonsense and splice shift mutations**

Limited number of frequent mutations - inbred populations

Large number of rare mutations

Mutation of the Wilson Disease Gene



Summary of all published WD mutations in exonic and splice-site-junction sequences (Bull et al. 1993; Tanzi et al. 1993; Figus et al. 1995; Thomas et al. 1995; Loudianos et al. 1996; Waldenström et al. 1996; Kemppainen et al. 1997).

From Shah at al, Am J Hum Genet 1997;**61**:317-328.

Wilson's Disease Gene Abnormalities

Most mutations are in compound heterozygote state and rarely homozygous.

No correlation between the genotype and phenotype.

Clinical symptoms appear earlier in patients with hepatic presentation than in those with neurological presentation, no matter what the type of mutation.

Wilson's Disease Gene

Bull PC, Thomas GR, Rommens JM, Forbes JR, Cox DW. The Wilson disease gene is a putative copper transporting P-type ATPase similar to the Menkes gene. Nat Genet 1993;**5**:327-337.

Petrukhin K, Fischer SG, Pirastu M, Tanzi RE, Chernov I, Devoto M, et al. Mapping, cloning and genetic characterization of the region containing the Wilson disease gene. Nat Genet 1993;**5**:338-343.

Tanzi RE, Petrukhin K, Chernov I, Pellequer JL, Wasco W, Ross B, et al. The Wilson disease gene is a copper transporting ATPase with homology to the Menkes disease gene. Nat Genet 1993;**5**:344-350.

Shah AB, Chernov I, Zang HT, Ross BM, Das K, Lutsenko S, et al. Identification and analysis of mutations of the Wilson disease gene (ATP7B): Population frequencies, genotype-phenotype correlation, and functional analyses. Am J Hum Genet 1977;**61**:317-328.

Riordan SM, Williams R. The Wilson's disease gene and phenotypic diversity. J Hepatol 2001;**34**:165-171.

Solioz M, Vulpe C. CPx-type ATPases: a class of P-type ATPases that pump heavy metals. Trends in Biochem Sci 1996;**21**:237-241.

Pathophysiology of Wilson's Disease

Untreated patients are in positive copper balance.

Cause related to an abnormal copper transporting P-type ATPase.

Increased copper in liver, brain, other organs, and tissues.

Chronic copper intoxication.

Progressive anatomical and physiologic disease leading to overt hepatic and cerebral manifestations, and when untreated, to death, usually before the age of 40.

Ceruloplasmin

The major copper containing protein in serum has been a major player in the diagnosis of Wilson's disease because its concentration in serum is low in the vast majority of patients. Alone, it is not diagnostic of the disease because low values may also be present in up to 20 percent of heterozygote carriers. Moreover, there are a number of other conditions that can lead to low concentrations of ceruloplasmin.

Deficiency of Ceruloplasmin

May be acquired or inherited in people who do not have Wilson's disease.

Acquired:

- **Excess urinary loss (nephrotic syndrome)**
- **Excess intestinal loss (protein losing enteropathy)**
- **Interference with intestinal absorption of copper (sprue)**
- **Interference with protein synthesis in severe malnutrition (kwashiorkor)**
- **Severe hepatic dysfunction**

Inherited:

- **Heterozygotes for Wilson's disease**
- **Aceruloplasminemia**

Curiously, concentrations of ceruloplasmin in serum may be elevated into the normal range during the course of severe or active liver disease, thereby obscuring the diagnostic value of a low serum concentration. In part, these changes can be mediated by elevated values of female hormones, and by stimulation of ceruloplasmin synthesis in inflammatory states (phase reactant).

Wilson's Disease with Normal Ceruloplasmin Concentration

Severe or active liver disease

- **Pregnancy**
- **Estrogen**
- **Inflammatory diseases**

Ceruloplasmin has also been implicated in the pathogenesis of Wilson's disease with the impression that impaired secretion from liver into blood and even into bile contributed importantly to copper retention in liver. The recent discovery that copper metabolism is essentially normal in a separate genetic disorder, aceruloplasminemia, which in turn is complicated by abnormal storage of iron, has refocused on the contribution of ceruloplasmin through its oxidase activity to iron metabolism.

Ceruloplasmin

Copper-containing glycoprotein - the major copper protein in serum.

Molecular weight 132 kDa

Single polypeptide chain of 1046 amino acid residues.

6 copper atoms per molecule;

3 form a trinuclear cluster
3 exist as mononuclear domains

The trinuclear cluster and one of the mononuclear coppers (in domain 6) form a complex, essentially the same as that found in ascorbate oxidase, strongly suggesting an oxidase role in ceruloplasmin.

Ceruloplasmin

Scheinberg IH, Sternlieb I. Wilson's disease and the concentration of caeruloplasmin in serum. Lancet 1963;**i**:1420-1421.

Gibbs K, Walshe JM. A study of the caeruloplasmin concentrations found in 75 patients with Wilson's disease, their kinships and various control groups. Quart J Med 1979;**NSXLVIII**:447-463.

Cauza E, Maier-Dobersberg T, Polli C, Kaserer K, Kramer L, Perenci P. Screening for Wilson's disease in patients with liver diseases by serum ceruloplasmin. J Hepatol 1997;**27**:358-362.

Edwards CQ, Williams DM, Cartwright GE. Hereditary hyperceruloplasminemia. Clinical Genetics 1979;**15**:311-316.

Harris ZL, Klomp LWJ, Gitlin JD. Aceruloplasminemia: an inherited neurodegenerative disease with impairment of iron homeostasis. Am J Clin Nutr 1998;**67(suppl)**:972S-977S.

Miyahjima H, Nishimura Y, Mizoguchi K, Sakamoto M, Shimizu T, Honda N. Familial apoceruloplasmin deficiency associated with blepharospasm and retinal degeneration. Neurology 1987;**37**:761-767.

Logan JI, Harveyson KB, Wisdom GB, Hughes AE, Archbold GPR. Hereditary caeruloplasmin deficiency, dementia and diabetes mellitus. Quart J Med 1994;**87**:663-670.

Morita H, Ikeda S, Yamamoto K, Morita S, Yoshida K, Nomoto S, Kato M, Yanagisawa N. Hereditary ceruloplasmin deficiency with hemosiderosis: A clinicopathological study of a Japanese family. Ann Neurol 1995;**37**:646-656.

Kawanami T, Kato T, Daimon M, Tominaga M, Sasaki H, Maeda K, Arai S, Shikama Y, Katagiri T. Hereditary caeruloplasmin deficiency: clinicopathological study of a patient. J Neurol Neurosurg Psychiatry 1996;**61**:506-509.

Servan J, Elghozi D, Gaynot S, Duclos H. Hemosiderose cerebrale liee a un deficit hereditaire en ceruloplasmine. Rev Neurol (Paris) 1998;**154**:158-162.

Jones RJ, Lewis SJ, Smith JM, Neuberger J. Undetectable serum caeruloplasmin in a woman with chronic hepatitis C infection. J Hepatol 2000;**32:**703-704.

Meyer LA, Durley AP, Prohaska JR, Harris ZL. Copper transport and metabolism are normal in aceruloplasminemic mice. J Biol Chem 2001;**276**:36857-36861.

Calabrese L, Carbonaro M, Muci G. Presence of coupled trinuclear copper cluster in mammalian ceruloplasmin is essential for efficient electron transfer to oxygen. J Biol Chem 1989;**264**:6183-6187.

Zaitseva I, Zaitsev V, Card G, Moshkov K, Bax B, Ralph A, Lindley P. The x-ray structure of human ceruloplasmin at 3.1 A: nature of the copper centres. J Biol Inorg Chemistry 1996;**1**:15-23.

Diagnosis

Kayser-Fleischer Rings

Copper in cornea at limbus in Descemet's membrane.

Virtually diagnostic in patients with neurologic findings.

Absence in patients with neurologic findings virtually excludes diagnosis.

Present rarely in some patients with a cholestatic syndrome that causes copper retention.

Urine Copper

(Normal <50 microgram/24 hours)

Increased to >100 micrograms/24 hours in most symptomatic patients.

Young asymptomatic patients may excrete less

Heterozygote carriers may excrete more

50-100 micrograms per 24 hours a difficult range

Even more difficult are reports of excretion of <50 micrograms/ 24 hours in otherwise well documented cases of Wilson's Disease.

Must avoid contaminated collection containers (false high) and assure complete collection (false low).

Hepatic Copper Concentration

Often said to be gold standard

Normal liver <50 micrograms/gram dry weight

Wilson's disease liver >250 micrograms/g dry weight

Heterozygote carriers <250 micrograms/g dry weight

Confounding States

Hepatic copper high in

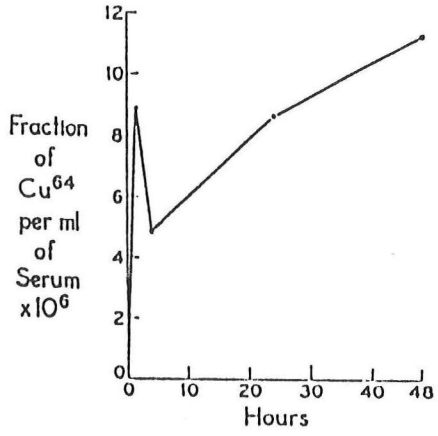
Cholestatic liver diseases
Non-Wilsonian copper disease(s)

Hepatic copper found low and attributed to sampling problem.

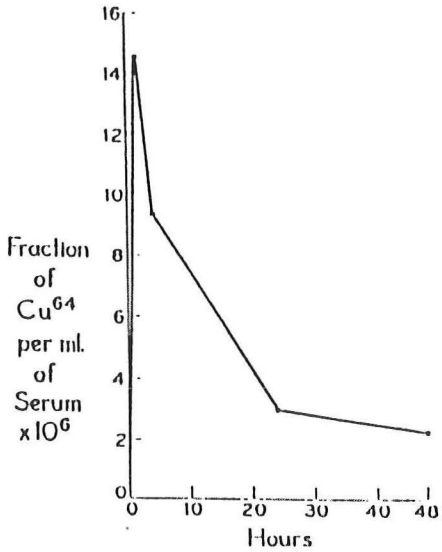
Radiocopper Tests

Based on the principle that after early absorption and disappearance of radiocopper into liver, radioactivity reappears in serum largely in ceruloplasmin.

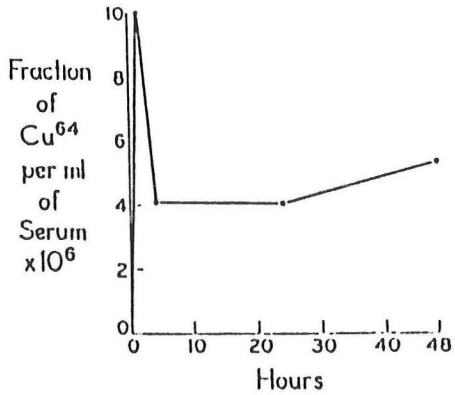
False positivity may occur in heterozygotes; the isotopes are difficult and expensive to obtain.



THE MEAN CONCENTRATIONS IN SERUM OF Cu^{64}, EXPRESSED AS FRACTIONS OF THE ADMINISTERED DOSE PER MILLILITER, OF 19 CONTROL SUBJECTS AT VARIOUS TIMES AFTER THE INGESTION OF 2.0 MG OF CUPRIC^{64} ACETATE OR SULFATE.



THE MEAN CONCENTRATIONS IN SERUM OF Cu^{64}, EXPRESSED AS FRACTIONS OF THE ADMINISTERED DOSE PER MILLILITER, OF 7 PATIENTS WITH WILSON'S DISEASE AT VARIOUS TIMES AFTER THE INGESTION OF 2.0 MG OF CUPRIC^{64} ACETATE OR SULFATE.



THE MEAN CONCENTRATIONS IN SERUM OF Cu^{64}, EXPRESSED AS FRACTIONS OF THE ADMINISTERED DOSE PER MILLILITER, OF 19 KNOWN HETEROZYGOTES (PARENTS OF PATIENTS WITH WILSON'S DISEASE) AT VARIOUS TIMES AFTER THE INGESTION OF 2.0 MG. OF CUPRIC^{64} ACETATE OR SULFATE.

From Sternlieb I et al. J Clin Invest 1961;**40**:707-715.

Therapies for Wilson's Disease

Overt illness can be improved, stabilized, or prevented by therapies that remove excess copper from the body, and prevent accumulation of new copper.

BAL

Of historic importance. Initially introduced as an antidote for the effects of arsenic gases, injection of BAL was found to increase copper excretion in urine and to improve neurological findings in some patients. Treatment is painful. More effective oral agents have replaced BAL. Scheinberg and Sternlieb continued to use BAL in patients with severe neurologic disease that did not respond to penicillamine, trientine, or both simultaneously. Approximately one-third demonstrated improvements that were then maintained by these latter agents.

Cumings JN. The effect of BAL in hepatolenticular degeneration. Brain 1951;**74**:10-12.

Denny-Brown D, Porter H. The effect of BAL (2,3-dimercaptopropanol) on hepatolenticular degeneration (Wilson's disease). New Engl J Med 1951;**245**:917-925.

Cumings JN. The treatment of hepatolenticular degeneration. Proc Royal Soc Med 1958;**52**:62-64.

Scheinberg IH, Sternlieb I. Treatment of the neurologic manifestations of Wilson's disease. Arch Neurol 1995;**52**:339-340.

Penicillamine

This agent, introduced by Walshe, revolutionized the management of Wilson's disease. it is a potent chelator of copper and markedly increases its urinary excretion. It may also increase hepatic proteins such as metallothionein that bind copper in the liver. It can prevent the development of overt disease in asymptomatic patients as well as improve and stabilize hepatic and neuropsychiatric disease.

Its downside is the relatively high incidence of complications including the development of acute and chronic severe hypersensitivity reactions and the nephrotic syndrome. During initial therapy, it may be accompanied by worsening of neurologic findings.

Walshe JM. Penicillamine, a new oral therapy for Wilson's disease. Am J Med 1956;**21**:487-495.

Sternlieb I, Scheinberg IH. Prevention of Wilson's disease in asymptomatic patients. New Engl J Med 1968;**278**:352-359.

Walshe JM. Penicillamine: The treatment of first choice for patients with Wilson's disease. Movement Disorders 1999;**14**:545-500.

Brewer GJ. Penicillamine should not be used as initial therapy in Wilson's disease. Movement Disorders 1999;**14**:551-554.

LeWitt PA. Penicillamine as a controversial treatment for Wilson's disease. Movement Disorders 1999;**14**:555-556.

Brewer GJ, Terry CA, Aisen AM, Hill GM. Worsening of neurologic syndrome in patients with Wilson's disease with initial penicillamine therapy. Arch Neurol 1987;**44**:490-493.

Glass JD, Reich SG, DeLong MR. Wilson's disease: Development of neurological disease after beginning penicillamine therapy. Arch Neurol 1990;**47**:595-596.

Trientine

This agent chelates copper and increases its excretion in urine. It also decreases intestinal absorption of copper. Initially introduced as an alternative to penicillamine in patients who developed toxicity, and with considerable success, it has been shown to be as effective as penicillamine in management of all phases of Wilson's disease. Because of low rates of toxicity, it is being used more and more as a first choice agent.

Walshe JM. Copper chelation in patients with Wilson's disease. A comparison of penicillamine and triethylene tetramine dihydrochloride. Quart J Med 1973:**NSXLII**;441-452.

Walshe JM. Treatment of Wilson's disease with trientine (triethylene tetramine) dihydrochloride. Lancet 1982;**i**:643-647.

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Dubois RS, Rodgerson DO, Hambidge KM. Treatment of Wilson's disease with triethylene tetramine hydrochloride (trientine). J Pediatr Gastroenterol Nutr 1990;**10**:77-81.

Loessner SR, Kuehn GK, Bachmann H. Mode of action of triethylenetetramine dihydrochloride on copper metabolism in Wilson's disease. Acta Neurol Scand 1991;**83**:364-366.

Condamine L, Hermine O, Alvin P, Levine M, Rey C, Courtrecuisse V. Acquired sideroblastic anaemia during treatment of Wilson's disease with triethylene tetramine dihydrochloride. British J Haematol 1993;**83**:166-168.

Dahlman T, Hartvig P, Loefholm M, Nordlinder H, Loof L, Westermark K. Long-term treatment of Wilson's disease with triethylene tetramine dihydrochloride (trientine). Quart J Med 1995;**88**:609-616.

Zinc

While using zinc as an antisickling agent, Brewer and associates produced copper deficiency. Using the same dose and regimen of zinc in Wilson's disease, Brewer, Hill, Prasad and their associates were able to produce negative copper balance in their patients. In unrelated studies, Hoogenraad and associates in the Netherlands, building on the initial thesis work of Schouwink, also demonstrated the usefulness of zinc in Wilson's disease. Zinc has now been shown to be an effective agent in the management of most presentations of Wilson's disease.

Zinc induces intestinal cell metallothionein, which has a high affinity for copper and blocks movement of copper into the circulation. Intestinal cells which turn over fairly rapidly take bound copper with them into the stool. The absorption of copper in food, and in the endogenous secretions of saliva, gastric juice and the upper intestinal tract are blocked, putting the patient in negative copper balance. Zinc also induces hepatic metallothionein with the potential of binding toxic copper in the liver. Zinc has been shown to be effective in treatment of patients who have been presymptomatic from the beginning; and in maintenance therapy. This compound is probably best used in conjunction with a chelator in the initial therapy of patients with symptomatic hepatic and/or neurologic disease.

Toxicity is low, consisting mainly of abdominal discomfort in about 10 percent of patients.

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Tetrathiomolybdate

This compound (TM) forms a stable complex between protein, copper and itself. When given with food, TM complexes copper in the intestine and prevents its absorption. When given between meals, TM is absorbed, and in the circulation complexes with albumin bound copper, preventing its access into cells. TM acts quickly. It is estimated to halt copper toxicity within 2 weeks of its administration. Currently it is felt to have great potential in the initial management of patients with neurologic presentation. The only human toxicity is related to induction of copper deficiency leading to a reversible anemia felt to be related to copper deficiency in the bone marrow.

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Therapy During Pregnancy

Therapy should be continued during pregnancy, since the disease may worsen. Penicillamine, trientine and zinc have proven to be useful in this setting.

Scheinberg IH, Sternlieb I. Pregnancy in penicillamine-treated patients with Wilson's disease. New Engl J Med 1975;**293**: 1300-1302.

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Guidelines for Medical Therapy

Brewer has provided valuable guidelines for medical management of different clinical presentations of Wilson's disease. He admittedly is down on penicillamine because of (1) its high incidence of toxicity, (2) the risk of worsening of neurologic disease, and (3) the availability of other effective medications that have little or no toxicity.

Anticopper Therapy for Different Categories of Wilson's Disease Patients

Category of patient	Treatment of choice
Initial presentation	
Neurological	Tetrathiomolybdate
Psychiatric	Tetrathiomolybdate
Hepatic	Trientine and zinc
Maintenance therapy	
Maintenance after initial therapy	Zinc
Presymptomatic	Zinc
Pregnant	Zinc
Pediatric	Zinc

From Brewer GJ, Proc Soc Exp Biol Med 2000;**223**:39-46.

Liver Transplantation

This is an effective mode of therapy for patients with decompensated liver disease unresponsive to medical treatment. Severe neurologic disease has also improved after transplantation. Transplantation is not recommended as initial therapy for neurologic disease.

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