12.7.2 Inherited diseases of copper metabolism Wil

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12.7.2 Inherited diseases of copper metabolism: Wilson’s disease and Menkes’ disease 2115 12.7.2 Inherited diseases of copper metabolism: Wilson’s disease and Menkes’ disease Michael L. Schilsky and Pramod K. Mistry ESSENTIALS Copper is an essential metal that is an important cofactor for many proteins and enzymes. Two related genetic defects in copper trans- port have been described, each with distinct phenotypes. Wilson’s disease An uncommon disorder (1 in 30 000) caused by autosomal re- cessive loss-of-function mutations in a metal-transporting P-type ATPase (ATP7B) that result in defective copper excretion into bile and hence copper toxicity. Typical presentation is in the second and third decade of life with liver disease (ranging from asymptomatic to acute fulminant hepatic failure or chronic end-stage liver dis- ease) or neurological or psychiatric disorder (dystonia, dysarthria, parkinsonian tremor, movement disorder, a spectrum of psychiatric ailments). While no single biochemical test or clinical finding is suf- ficient for establishing the diagnosis, typical findings include low serum caeruloplasmin, high urinary copper excretion, and elevated liver copper content. Corneal Kayser–Fleischer rings may be seen. Treatment is with copper chelating agents and zinc. Liver transplant- ation is required for fulminant hepatic failure and decompensated liver disease unresponsive to medical therapy. Menkes’ disease A rare disorder (1 in 300 000) caused by X-linked loss-of-function mutations in a P-type ATPase homologous to ATP7B (ATP7A) that result in defective copper transport across intestine, placenta, and brain and hence cellular copper deficiency. Clinical presentation is in infancy with facial dimorphism, connective tissue disorder, hypo- pigmentation, abnormal hair, seizures, and failure to thrive, usually followed by death by age 3 years (although some variants with a milder phenotype result from milder mutations, e.g. occipital horn syndrome). Treatment, which is only effective

when presymptomatic diagnosis is made in a sibling after florid presentation in a previous affected sibling, is with intravenous copper histidine. Introduction Copper is an essential metal that is an important cofactor for many proteins and copper-containing enzymes involved in cellular res- piration, antioxidant defence, pigment production, neurotrans- mitter formation, connective tissue synthesis, and iron homeostasis. Therefore, in states of impaired copper homeostasis resulting in copper excess or copper deficiency, tissue injury and organ dysfunc- tion ensue. The average diet provides substantial amounts of copper, typically between 2 and 5 mg/day, most of which is eventually ex- creted in the bile and then in the stool. Copper is absorbed by en- terocytes mainly in the duodenum and proximal small intestine and transported in the portal circulation bound to albumin and histidine to the liver where it is avidly removed from the circulation. The liver utilizes some copper for metabolic needs, synthesizes and secretes the copper containing the protein caeruloplasmin, and excretes ex- cess copper into the bile (Fig. 12.7.2.1). Wilson's disease (OMIM 277900) Introduction and historical perspective Wilson's disease (hepatolenticular degeneration) was first described in detail in 1912 by Kinnear Wilson as progressive lenticular de- generation, a familial, lethal neurological disease accompanied by chronic liver disease leading to cirrhosis. Over the next few decades, the role of copper in pathogenesis was established, and the pattern of inheritance was determined to be autosomal recessive. Wilson's disease was uniformly fatal until treatments were devel- oped just over half a century ago, when it became one of the first liver diseases for which effective pharmacological treatment was identified. The first chelating agent, introduced in 1951 for the treat- ment of Wilson's disease, was the intramuscularly administered compound British Anti-Lewisite (BAL or dimercaptopropanol). The identification and testing of an orally administered chelator, d-penicillamine, by John Walsh in 1956 revolutionized treatment. Other treatment modalities have since been introduced, including the use of zinc salts to block enteral copper absorption, trientine and tetrathiomolybdate to chelate copper, and liver transplantation, which may be life-saving and curative because the liver is the pri- mary site of the metabolic disorder. Genetic defect In 1993, the gene defect in Wilson's disease was identified. The ATP7B gene encodes a metal-transporting P-type ATPase, which is expressed mainly in hepatocytes and functions in the transmembrane transport of copper. The absent or reduced function of ATP7B protein leads to im- paired excretion of excess copper into the bile, leading to copper accu- mulation and toxicity. Eventually copper is released into the bloodstream and deposited in extrahepatic tissues. Failure to incorporate copper into caeruloplasmin is an additional consequence of the loss of functional ATP7B protein. Caeruloplasmin devoid of copper, apocaeruloplasmin, has a short half-life, which causes decreased plasma levels found in most patients with Wilson's disease (Fig. 12.7.2.1). Wilson's disease occurs worldwide with an average incidence of approximately 30 per million. The carrier frequency is approxi- mately 1 in 90. However, a recent study of the frequency of ATP7B mutations in the United Kingdom suggested that this established figure may underestimate the frequency of affected individuals and carriers, and estimated a disease incidence of 1:8000. Clinical features There is protean phenotypic presentation comprising various com- binations of liver disease, progressive neurological disorder, and psychiatric disorder. Presentation with liver disease occurs more frequently in children and younger adult patients than in older adults. Overt liver disease is the most common presenting feature in childhood with the most common age of presentation between 10 and 13 years, but manifestations may be present as early as age 3 to 5 years in rare individuals. In contrast, neurological disease oc- curs as the initial presenting feature in adults, usually in the third

section 12 Metabolic disorders 2116 or fourth decade of life. This sequence reflects the natural history of primary hepatic involvement followed by neurological and other extrahepatic organ dysfunction. Symptoms at any age can be non- specific and there is considerable overlap between distinct hepatic and neurological presentations frequently cited in the literature. A patient presenting with liver disease aged between 5 and 40 years with decreased serum caeruloplasmin and detectable Kayser–Fleischer rings represents the classic form of Wilson's dis- ease. However, about one-half of patients presenting with liver dis- ease do not possess two of these three criteria and pose a challenge in trying to establish the diagnosis. Moreover, as with other liver dis- eases, patients may not come to medical attention when their clin- ical disease is comparatively mild. Even when presymptomatic siblings are excluded, the age at which Wilson's disease may present is both younger and older than generally appreciated, though most present between the ages of 5 and 35 years. Wilson's disease is increasingly diagnosed in children younger than 5 years old, with atypical findings in children under 2 years old that include cirrhosis in a 3-year-old and fulminant hepatic failure in a 5-year-old. The oldest patients diagnosed with Wilson's disease were in their early 70s. With new molecular testing capabilities, testing for Wilson's disease can be performed even in utero or in newborns, and cases are now being diagnosed earlier than ever before.

Liver presentations The diversity of liver disease encountered in patients with Wilson's disease is summarized in Table 12.7.2.1. Wilson's disease should be considered in the differential diag- nosis of patients with unexplained liver disease and when neuro- logical and/or psychiatric symptoms occur concurrently with liver disease. Liver involvement can range from asymptomatic, with only biochemical abnormalities or an isolated clinical finding of hepatomegaly, to acute fulminant hepatic failure or chronic end- stage liver disease. Children may be entirely asymptomatic, with hepatomegaly or abnormal serum aminotransferases found only in- cidentally. Some patients may have a brief clinical illness resembling an acute viral hepatitis or mononucleosis, and others may present with features indistinguishable from autoimmune hepatitis. Some may present with only biochemical abnormalities or histological findings of steatosis on liver biopsy and many others with signs of chronic liver disease with advancing fibrosis and inflammation and evidence of compensated or decompensated cirrhosis. Patients may present with isolated splenomegaly due to clinically unapparent cir- rhosis and portal hypertension. Wilson's disease may also present as acute fulminant hepatic failure with an associated Coombs'-negative haemolytic anaemia and acute kidney injury. Some patients have transient episodes of jaundice, due to haemolysis. Low-grade haemolysis may be associ- ated with Wilson's disease when liver disease is not clinically evident. Neurological presentations Neurological manifestations of Wilson's disease typically present later than the liver disease, most often in the third decade of life. However, earlier subtle findings may appear in paediatric patients, including changes in behaviour, deterioration in school work or the inability to perform activities requiring good hand–eye coordination. Patient may exhibit small handwriting as in Parkinson's disease (micrographia). Other common findings in those presenting with neurological dis- ease include tremor, lack of motor coordination, drooling, dysarthria, dystonia, and spasticity or athetosis. Because of pseudobulbar palsy, transfer dysphagia may also occur, with a risk of aspiration if severe. Dysautonomia may be present, but usually in concert with other neurological findings. Migraine headaches and insomnia may be re- ported, but seizures are infrequent. Along with behavioural changes, Cu CPN Golgi +Cu Lysosome −Cu Cu Cu Cu ATP7B ATP7B Hepatocyte canalicular membrane hCTR basolateral membrane caeruloplasmin Cu-albumin hCTR Cu Cu-GSH bile bile cMOAT Trans Golgi Endosome +Cu ATOX1 Cu Golgi ATP7A Enterocyte basolateral membrane hCTR apical membrane hCTR Cu Trans Golgi ATOX1 Cu Cu Cu +Cu −Cu Fig. 12.7.2.1 Cellular copper trafficking in the hepatocyte and enterocyte depicting the

contrasting metabolic defects in Wilson’s disease and Menkes’ disease. ATP7B is the major copper transporter in the hepatocyte, and ATP7A fulfils this role in the enterocyte. Copper gains access to both cell types via copper transporter 1, hCTR, and is delivered by the copper chaperone ATOX1 to ATP7B and APT7A, respectively, residing in the trans- Golgi network. Increasing cell copper content is associated with trafficking of ATP7B towards the apical canalicular membrane and copper excretion in bile in the hepatocyte. In contrast, in the enterocyte, increasing dietary copper leads to net absorption of copper via the basolateral surface. While significant amounts of ATP7B expression are relatively restricted to hepatocytes and a few other cell types, ATP7A expression is more ubiquitous except that it is minimally expressed in the liver. In the other cells that express ATP7A, the basolateral presence of ATP7A when copper is abundant, and this protein’s copper transport activity, result in the cellular excretion of excess copper. In the kidney, ATP7A and ATP7B are active in copper reabsorption or excretion from the body.

12.7.2 Inherited diseases of copper metabolism: Wilson’s disease and Menkes’ disease 2117 other psychiatric manifestations include depression, anxiety, and even frank psychosis. Many but not all individuals with neurological or psychiatric manifestations may have cirrhosis, but frequently they are not symptomatic from their liver disease. Eye manifestations Kayser–Fleischer rings represent deposition of copper in the Descemet’s membrane of the cornea (Fig. 12.7.2.2). When they are visible by direct inspection, they appear as a band of golden- brownish pigment near the limbus. A slit-lamp examination by an experienced observer is required to identify Kayser–Fleischer rings in most patients. Rarely, they may be found in patients with chronic cholestatic diseases and in children with neonatal cholestasis; how- ever, these disorders can usually be distinguished from Wilson’s dis- ease on clinical grounds or on histology. Kayser–Fleischer rings are present in approximately 95% of patients with a neurological presen- tation but in only approximately 40 to 50% of patients with predom- inant hepatic disease at the time of diagnosis. Sunflower cataracts, also found by slit lamp examination but with a lower frequency, represent deposits of copper in the lens. These typic- ally do not obstruct vision, and—along with Kayser–Fleischer rings— will gradually disappear with effective medical treatment or following liver transplant. Reappearance of either of these ophthalmological findings in a medically treated patient in whom these had previously disappeared suggests noncompliance with therapy. Diagnostic testing A diagnosis of Wilson’s disease should be considered in any patient with unexplained liver disease, especially if associated with neurological and psychiatric disease; patients with acute fulminant liver failure, especially if haemolysis is present; and first-degree relatives of affected patients. No single biochemical test or clinical finding is sufficient to establish the diagnosis. A combination of clinical and biochemical evaluation is necessary to make the diagnosis, and this has led to the use of a scoring system that uses these findings and tests to determine the probability of establishing a diagnosis of Wilson’s disease (Leipzig criteria). Biochemical liver tests Serum aminotransferase activities are generally abnormal in Wilson’s disease except at a very early age. In many patients, the degree of ele- vation of aminotransferase activity may be mild compared to other liver injuries and does not reflect the severity of the liver disease. Measures of liver synthetic function such as coagulation factors and proteins such as albumin may be reduced significantly in such cases. Caeruloplasmin Caeruloplasmin is a 132-kDa protein synthesized mainly in the liver and is also an acute phase reactant. The vast majority of caeruloplasmin is secreted into the circulation from hepatocytes as a copper-carrying protein containing six copper atoms per mol- ecule (holocaeruloplasmin), and the remainder as the protein lacking copper (apocaeruloplasmin). Caeruloplasmin is the major carrier for copper in the blood, accounting for 90% of the circulating

copper in normal individuals. It is also a ferroxidase and a nitric oxide oxidase, so it influences nitric oxide homeostasis. Levels of serum caeruloplasmin may be measured enzymatically by their copper-dependent oxidase activity towards these substrates, or by antibody-dependent assays. Results generally are regarded as equivalent, but it should be noted that immunological assays routinely in clinical use may overestimate caeruloplasmin concentrations since they do not discriminate be- tween apocaeruloplasmin and holocaeruloplasmin. A serum caeruloplasmin level of less than 200 mg/L (<20 mg/dl, although the lower level of the normal range can vary between la- boratories) is considered consistent with Wilson's disease. Low caeruloplasmin levels are found in approximately 95% of cases. However, serum caeruloplasmin alone as a screening test for Wilson's disease in patients referred with liver disease has a low positive Table 12.7.2.1 Clinical patterns of hepatic, neurological, and psychiatric disease in patients with Wilson's disease Hepatic Asymptomatic hepatomegaly Isolated splenomegaly Persistently elevated serum aminotransferase activity (AST, ALT) Fatty liver Acute hepatitis Resembling autoimmune hepatitis Cirrhosis—compensated or decompensated Fulminant hepatic failure Neurological Movement disorders (tremor, involuntary movements) Drooling, dysarthria Rigid dystonia Pseudobulbar palsy Dysautonomia Migraine headaches Insomnia Seizures Psychiatric Depression Neurotic behaviours Personality changes Psychosis Other systems Renal abnormalities: aminoaciduria and nephrolithiasis Skeletal abnormalities: premature osteoporosis and arthritis Cardiomyopathy, dysrhythmias Pancreatitis Hypoparathyroidism Menstrual irregularities; infertility, repeated miscarriages Fig. 12.7.2.2 Florid Kayser–Fleischer ring in a patient with Wilson's disease. Courtesy of Dr Susan Hall Forster, Yale School of Medicine.

section 12 Metabolic disorders 2118 predictive value (approximately 6%), although the very lowest values have a slightly higher predictive value than levels near or at the lowest limit of normal. Moreover, a low caeruloplasmin level is found in 20% of healthy heterozygote carriers of Wilson's disease, and in other disorders including protein-losing states (gut and kidney), poor hepatocellular synthetic function, and in another genetic disorder where the caeruloplasmin gene is affected, acaeruloplasminaemia. Serum copper Although a disease of copper overload, the total serum copper in Wilson's disease is usually decreased in proportion to the decreased caeruloplasmin in the circulation. In patients with severe liver injury, serum copper may be within the normal range or even elevated des- pite a decreased serum caeruloplasmin level. In the setting of acute fulminant hepatic failure due to Wilson's disease, levels of serum copper may be markedly elevated due to the sudden release of the metal from tissue stores. Normal or elevated serum copper levels in the face of decreased levels of caeruloplasmin indicate an increase in circulating 'free' or noncaeruloplasmin-bound copper. Urinary copper excretion The amount of copper excreted in the urine in a 24-h period, which reflects the amount of noncaeruloplasmin copper in circulation, may be helpful for diagnosing Wilson's disease and for monitoring treatment. Basal measurements can provide useful diagnostic infor- mation so long as copper does not contaminate the collection ap- paratus (this is less problematic with current plastic disposables) and the urine collection is complete. Basal 24-h urinary excretion of copper in Wilson's disease is typically more than 100 µg (1.6 µmoles) in symptomatic patients, but a level above 40 µg (>0.6 µmoles) may indicate Wilson's disease and requires further investigation. Liver copper concentration Liver copper content of more than 250 µg/g dry weight provides crit- ical diagnostic information and should be obtained in cases where the diagnosis is not straightforward and in younger patients. In untreated patients, normal hepatic copper content (<40–50 µg/g dry weight) almost always excludes a diagnosis of Wilson's disease. Further diag- nostic testing is indicated for patients with

intermediate copper con- centrations (70–250 μg/g dry weight), especially if there is active liver disease or other symptoms of Wilson's disease. The major problem with attempting diagnosis based on hepatic parenchymal copper concentra- tion is that in the later stages of Wilson's disease distribution of copper within the liver is often inhomogeneous. Furthermore, copper con- centrations may seem falsely low in those with significant amounts of fibrosis in the biopsy, and—since this is a weight-based measurement— the error is potentially greater in smaller specimens. Liver biopsy findings The earliest histological abnormalities in the liver include microvesicular and macrovesicular steatosis, glycogenated nu- clei, and focal hepatocellular necrosis. The liver biopsy may show classic histological features of autoimmune hepatitis. With pro- gressive parenchymal damage, fibrosis and subsequently cirrhosis develops and is frequently found in most patients by the second decade of life. Cirrhosis is usually macronodular, although occa- sionally micronodular. In the setting of fulminant hepatic failure, there is marked hepatocellular degeneration, hepatocytes apoptosis, and parenchymal collapse, typically on the background of cirrhosis. Detection of copper in hepatocytes by orcein or rhodanine staining is highly variable. In extreme cases, nodules lacking histochemically detectable copper are found next to cirrhotic nodules with abundant copper, and negative histochemistry for copper does not exclude the diagnosis. Electron microscopy reveals characteristic mitochondrial abnormalities, dilated cristae and crystalline deposits, in hepatocytes in the early phase of the disease (when steatosis is evident). Neurological findings and radiological imaging of the brain Neurological disease may manifest with parkinsonian features of dystonia, hypertonia, and rigidity, with tremors and dysarthria. Muscle spasms, which can lead to contractures, dysarthria, dys- phonia, and dysphagia can be incapacitating. Movement disorder may be present as well. At this stage of the disease, MRI or CT scan- ning of the brain may detect structural abnormalities in the basal ganglia. Most frequently found are increased density on CT and hyperintensity on T2-weighted MRI in the region of the basal gan- glia, but other regions of the brain may be involved. Genetic studies ATP7B mutation analysis can be difficult because of the multiplicity of mutations, the occurrence of mutations in noncoding sequences, and the large size of the gene that spans around 80 kb. Pedigree ana- lysis using haplotypes of polymorphisms flanking the Wilson's dis- ease gene can be used but it is mostly replaced by methods relying on high-throughput sequencing. Most patients are compound heterozy- gotes. Currently, over 500 mutations of ATP7B have been identified. Mutation analysis is an especially valuable diagnostic strategy for certain well-defined populations harbouring prevalent ATP7B mutations. Populations with a single predominant mutation in- clude those of Iceland, Japan, Korea, Sardinia, Spain and the Canary Islands, and Taiwan. Certain populations in Eastern Europe also show predominance of the H1069Q mutation, accounting for nearly 40% of disease alleles. Genotype–phenotype correlation is imperfect as in most other inherited metabolic diseases of the liver, indicating an important role for modifier genes and environmental factors in the determination of phenotypic characteristics. However, a large multinational study and a meta-analysis suggest that homozygosity for the H1069Q mutation is associated with neurological presenta- tion in adults. The H1060Q Wilson ATPase resides in a highly con- served sequence in the cytoplasmic loop, SEHPL, and appears to result in defective trafficking of the mutant protein. Diagnostic considerations in specific target populations Liver diseases which mimic Wilson's disease Patients with Wilson's disease, especially younger ones, may have clin- ical features and histological findings on liver biopsy indistinguishable from autoimmune hepatitis. All children with apparent autoimmune hepatitis and any adult patient with the presumptive diagnosis of autoimmune hepatitis failing to respond appropriately to cortico- steroids must be evaluated for Wilson's disease. Hepatic steatosis in Wilson's disease is rarely as severe as in nonalcoholic fatty

liver dis- ease. Nevertheless, occasional patients with Wilson's disease closely resemble nonalcoholic fatty liver disease or have both diseases. Acute fulminant liver failure A high level of clinical suspicion is essential because transplant re- ferral is required given the poor prognosis for medical management

12.7.2 Inherited diseases of copper metabolism: Wilson's disease and Menkes' disease 2119 of these patients, and there are disease-specific management and family screening that should follow. Most patients with the ful- minant hepatic failure presentation of Wilson's disease have a char- acteristic pattern of clinical findings: • Coombs'-negative haemolytic anaemia with features of acute intravascular haemolysis • Coagulopathy unresponsive to parenteral vitamin K administration • Rapid progression to renal failure • Relatively modest rises in serum aminotransferases (typically <2000 IU/litre) from the beginning of clinical illness • Normal or markedly subnormal serum alkaline phosphatase (typ- ically <40 IU/litre) with alkaline phosphatase to bilirubin ratio of less than 4:1. • AST-to-ALT ratio of greater than 2:1. • Female-to-male ratio of greater than 2:1. Serum caeruloplasmin is usually decreased, but the predictive value of this test in the setting of acute liver failure is poor. Serum copper and 24-h urinary excretion of copper are greatly elevated. The serum copper is usually greater than 200 µg/dl (31.5 µmol/litre). Kayser–Fleischer rings may be identified to support the diagnosis of Wilson's disease but are absent in approximately 50% of these pa- tients. Expeditious diagnosis is critically important since, without timely liver transplantation, death is almost inevitable. Management of these patients awaiting transplantation includes measures to sup- port their liver injury and specifically is geared to reduce the removal of the excess circulating copper to prevent further liver and renal injury, reduce haemolysis, and help stabilize the patient. Family screening First-degree relatives of any patient newly diagnosed with Wilson's disease must be screened. Assessment should include serum copper, caeruloplasmin, liver function tests, slit-lamp examination of the eyes for Kayser–Fleischer rings, and basal 24-h urinary copper. Individuals without Kayser–Fleischer rings who have subnormal caeruloplasmin and abnormal liver tests undergo liver biopsy to confirm the diag- nosis. Molecular analysis of the ATP7B gene is increasingly available and should be used as primary screening tool, especially for sibling screening once the proband is identified. Treatment should be initi- ated for all individuals over 3 years old identified as patients by family screening, and individualized for younger patients. Perspective on diagnosis Over the years, diagnostic advances have enabled a more system- atic evaluation of individuals suspected to have Wilson's disease, and unlike the early description by Wilson, many patients are now diag- nosed before they develop neurological symptoms. These include the recognition of corneal Kayser–Fleischer rings, 50% of patients with hepatic presentations, and 98% of those with neurological or psychiatric presentation of disease. Molecular diagnostic studies have made it feasible to identify presymptomatic and symptomatic individuals by analysing for disease-specific mutations of the ATP7B gene. However, since de novo genetic diagnosis is currently expen- sive, not universally available, and (most importantly) sometimes inconclusive, a combination of clinical findings and biochemical testing is still necessary to establish the diagnosis of Wilson's disease. Treatment In general, the approach to treatment is dependent upon whether there is active disease or symptoms, whether neurological, psychiatric, or hepatic, or whether the patient is identified prior to the onset of clinical symptoms. This distinction helps in determining the choice of therapy and the dosages of medications utilized. The recommended initial treatment of symptomatic patients or those with active disease is with chelating agents. The largest treatment experience worldwide is with penicillamine; however, there is more frequent consideration of trientine for primary therapy.

Combination therapy, in which zinc is utilized in conjunction with a chelating agent (temporally separated), has a theoretical basis in both blocking copper uptake and eliminating excess copper. Past studies of the use of tetrathiomolybdate as an alter- native chelating agent for the initial treatment of neurological Wilson's disease suggest that this drug may be useful as initial therapy for pa- tients presenting with neurological symptoms, and newer studies are underway to revisit this treatment (Table 12.7.2.2). Table 12.7.2.2 Pharmacological treatments of Wilson's disease Drug/dose in adults Mode of action Neurological deterioration Side effects Comments Penicillamine 750–1500 mg in 2 or 3 divided doses; requires supplemental pyridoxine General chelator Induces cupruria 10–20% during the initial phase of treatment Fever, rash, proteinuria, lupus-like reaction Aplastic anaemia Leucopenia Thrombocytopenia Nephrotic syndrome Degenerative changes in skin; Elastosis perforans serpiginosa Serous retinitis Hepatotoxicity Colitis (rare) Reduce dose for surgery to promote wound healing and during pregnancy to reduce teratogenicity Trientine 750–1500 mg in 2 or 3 divided doses General chelator Induces cupruria 10–15% during the initial phase of treatment Gastritis; aplastic anaemia rare Sideroblastic anaemia Colitis (rare) Reduce dose for surgery to promote wound healing and during pregnancy Zinc 75–150 mg in 3 divided doses Metallothionein inducer Blocks intestinal absorption of copper Can occur during the initial phase of treatment; infrequent hepatic decompensation Gastritis; biochemical pancreatitis; zinc accumulation; possible changes in immune function No dosage reduction for surgery or pregnancy Tetrathio-molybdate 120 mg in 6 divided doses (with meals and apart from meals) Chelator Blocks copper absorption Reports of rare neurological deterioration during the initial treatment Anaemia; neutropenia Hepatotoxicity Experimental in the United States of America and Europe

 Once the disease symptoms or biochemical abnormalities have stabilized, typically in 2 to 6 months after the initiation of therapy, a reduced dosage of chelators or zinc therapy can be used for main- tenance treatment. Patients presenting without symptoms may be treated with either maintenance dosages of a chelating agent or with zinc from the outset. Failure to comply with lifelong therapy has led to recurrent symptoms and liver failure, the latter requiring liver transplant for survival. Monitoring of therapy includes monitoring for compliance as well as for potential treatment-induced side effects. Liver transplantation Liver transplantation is the only effective option for those with Wilson's disease who present with acute fulminant hepatic failure and is indicated for all Wilson's disease patients with decompensated liver disease unresponsive to medical therapy. In acute fulminant liver failure due to Wilson's disease, interventions to rapidly reduce elevated free circulating copper may reduce secondary organ injury while the patient awaits a suitable organ donor. Liver transplantation corrects the hepatic metabolic defects of Wilson's disease and over time reverses extrahepatic copper disposition. Living donor liver transplantation has been successfully performed for Wilson's dis- ease, including the use of donor livers from heterozygote carriers for Wilson's disease. One-year survival following liver transplantation ranges from 79 to 87%, and those who survive this early period con- tinue to survive long term. A liver transplant is not recommended as the primary treatment for neurological Wilson's disease since the liver disease is stabilized by medical therapy in most of these individuals and outcomes with a liver transplant in the setting of advanced neurological disease are not always beneficial. Menkes' disease (OMIM 309400) Menkes' disease is an X-linked recessive neurodegenerative disorder presenting in infancy due to mutations in the ATP7A gene, which encodes a P-type ATPase homologous to ATP7B (Fig. 12.7.2.1). The pathology and disease manifestations reflect decreased activities of enzymes that require copper as a cofactor, such as dopamine-β- hydroxylase, cytochrome c oxidase, and lysyl oxidase. Affected infants appear healthy at birth but by the age of approxi- mately 2 months develop hypotonia, seizures, skin and joint

laxity, hair twisting (pili torti), and failure to thrive, usually followed by death by 3 years of age from end-stage neurodegenerative disease. Treatment with daily injections of copper histidine may im- prove the outcome if started presymptomatically soon after birth. However, newborn screening is not routinely available and early detection is difficult because clinical abnormalities in affected new- borns are absent or subtle, hence this type of pre-emptive treatment is only possible when presymptomatic diagnosis is made in a sibling after florid presentation in a previous affected child. The usual biochemical markers, low serum copper and caerulo plasmin, are unreliable in the neonatal period. Molecular diagnosis is the preferred option when available, but this is rendered difficult by the large size of ATP7A (150 kb) and diversity of mutation types, including large deletions and chromosomal rearrangements. A useful test for neonatal diagnosis of Menkes' disease has been developed involving the measurement of serum neurotransmitter levels. Dopamine-β-hydroxylase converts dopamine to noradren- aline and these transmitters in turn can be further metabolized to dihydroxyphenylacetic acid to dihydroxyphenylglycol, respectively. In Menkes' disease, deficiency of dopamine-β-hydroxylase (an en- zyme that depends on copper for its activity) leads to a high ratio of dopamine to noradrenaline as well as of dihydroxyphenylacetic acid to dihydroxyphenylglycol. These characteristic abnormal- ities can be used to identify presymptomatic disease, allowing pre- emptive therapy with copper histidine and resulting in delay in the development of typical neurodegeneration and other changes, but most often not the arrest of the disease. Trials of gene therapy are in development. Occipital horn syndrome is a milder allelic variant of Menkes' dis- ease that may present later in life without the same neurodegenerative changes observed in the typical early presentation described preiously. Clinical features include skeletal deformity (including exostoses of the occipital bone—the 'horns'), looseness of the skin, and joint laxity, features which previously led the condition to be considered a variant of Ehlers–Danlos syndrome. FURTHER READING Bandmann O, Weiss KH, Kaler SG (2015). Wilson's disease and other neurological copper disorders. Lancet Neurol, 14, 103–13. Beinhardt S, et al. (2014). Long-term outcomes of patients with Wilson disease in a large Austrian cohort. Clin Gastroenterol Hepatol, 12, 683–9. Coffey AJ, et al. (2013). A genetic study of Wilson's disease in the United Kingdom. Brain, 136, 1476–87. Ferenci P. (2014). Phenotype-genotype correlations in patients with Wilson's disease. Ann N Y Acad Sci, 1315, 1–5. Ferenci P, et al. (2012). EASL Clinical Practice Guidelines: Wilson's disease. European Association for Study of Liver. J Hepatol, 56, 671–85. Guillaud O, et al. (2014). Long term results of liver transplantation for Wilson's disease: experience in France. J Hepatol, 60, 579–89. Kaler SG (2011). ATP7A-related copper transport diseases-emerging concepts and future trends. Nat Rev Neurol, 7, 15–29. Kaler SG, et al. (2008). Neonatal diagnosis and treatment of Menkes disease. N Engl J Med, 358, 605–14. Lorincz MT (2018). Wilson disease and related copper disorders. Handb Clin Neurol, 147, 279–92. Lutsenko S (2014). Modifying factors and phenotypic diversity in Wilson's disease. Ann N Y Acad Sci, 1315, 56–63. Roberts EA, Schilsky ML, American Association for Study of Liver Diseases (2008). Diagnosis and treatment of Wilson disease: an up- date. Hepatology, 47, 2089–111. Schilsky ML (2017). Wilson disease: diagnosis, treatment and follow- up. Clin Liver Dis, 21, 755–67. Zimbrean PC, Schilsky ML (2014). Psychiatric aspects of Wilson dis- ease: a review. Gen Hosp Psychiatry, 36, 53–62

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