Chapter

17 Metal Storage Disorders: Inherited Disorders of Copper and Manganese Metabolism and Movement Disorders

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Copper Metabolism and Transport, Deficiency, and Toxicity

Copper is one of the six transition metals that have important biochemical roles in humans, particularly in catalysis and electron transport [1, 2]. Because it can exist in two redox states (Cu^{2+}/Cu^{+}), it can participate in redox reactions involving transfer of an electron, but if it builds up it can also generate potentially toxic reactive oxygen species by Fenton chemistry. Examples of copper in redox enzymes include: complex IV of the mitochondrial respiratory chain, copper–zinc superoxide dismutase, ceruloplasmin (ferroxidase), lysyl oxidase, dopamine beta-hydroxylase, and tyrosinase.

Copper is present in many foods and in drinking water. The content is particularly high in organ meats (e.g. liver), shellfish, chocolate, nuts, and mushrooms. The content in food may be increased by cooking in copper-containing vessels. Copper absorption is reduced by gastric bypass surgery and this can lead to a myelopathy [3].

Copper is transported into the enterocyte via the CTR1 transporter. Export from the enterocyte is regulated by the copper-transporting ATPase, ATP7A. This protein is synthesized in the endoplasmic reticulum and resides in the trans-Golgi network, but, as intracellular copper levels rise, it translocates to the basolateral membrane where it allows copper export into the plasma. Mutations in *ATP7A* give rise to generalized copper deficiency, deficient activity of copper enzymes, and the symptoms of Menkes syndrome and variants [4].

On arriving at the liver, copper is taken up through CTR1 at the basolateral membrane and rising copper levels lead to translocation of ATP7B from the trans-Golgi network to the apical membrane where the copper is excreted into the bile canaliculus [4]. ATP7B is also required for the secretion of copper bound to ceruloplasmin from the liver into plasma. Mutations in *ATP7B* (Wilson disease) cause an accumulation of copper in the liver with reduced plasma concentrations of ceruloplasmin and ceruloplasmin-bound copper (normally the major fraction of plasma copper). As the disease progresses, levels of free copper in the plasma increase; urinary copper excretion is higher than normal. Copper deposition in the basal ganglia of the brain is responsible for the movement disorder, copper deposition in Descemet's membrane at the corneoscleral junction in the eye give rise to Kayser–Fleischer rings, copper deposition in the kidneys can cause a tubulopathy, and high free plasma copper can cause hemolysis.

Within the cell, chaperones are important in conveying copper to copper-dependent enzymes such as copper–zinc superoxide dismutase (chaperone: CCS) and complex IV of the respiratory chain (chaperones: SCO1 and SCO2). *SCO1* mutations in the mouse lead to severe cellular copper deficiency because, in addition to its role in complex IV assembly, SCO1 is required for expression of CTR1 and hence copper uptake [5].

Copper Toxicity Disorders

Wilson Disease (*ATP7B* Mutations)

Wilson disease is an autosomal-recessive disorder caused by bi-allelic mutations in the *ATP7B* gene on chromosome 13q14.3. The incidence is approximately 1 in 30,000 live births. As discussed, there is a failure of excretion of copper from the liver into the bile and of ceruloplasmin-bound copper into the plasma. The build-up of copper in the liver causes inflammation and fibrosis. Copper is deposited in the brain (particularly the basal ganglia), the eye (Kayser–Fleischer rings), and the kidney (tubulopathy).

In a series of 400 adult patients with Wilson disease, 50% presented with neurological and psychiatric

symptoms, 20% with neurological and hepatic symptoms, and 20% with purely hepatic symptoms [6].

In patients with neurological presentations, movement disorders are prominent. Dysarthria (speech difficulty) and dysgraphia are particularly characteristic. Major movement disorders include dystonia, rigidity, tremor, and choreiform movements.

Dystonia is common, present in about two-thirds of patients, and can be focal, multifocal, or generalized as the disease progresses. Focal forms of dystonia include blepharospasm, cervical dystonia, or *risus sardonicus*. With orofacial dystonia or oropharyngeal dyskinesia, patients may develop dysphonia, dysarthria, or dysphagia. Parkinsonism and ataxia are also found in Wilson disease although they are rarely an isolated clinical feature and are typically accompanied by other neurological deficits. Chorea is more common in children and adolescents with Wilson disease.

In patients with psychiatric presentations, common features include changes in personality (irritability, anger, poor self-control), depression, and anxiety. Frank psychosis can occur.

Ninety-five percent of patients with neurological signs have Kayser–Fleischer rings. Slit lamp examination may be required to visualize the golden/greenish-brown pigmentation in the early stages. It starts as a superior crescent and progresses inferiorly to become circumferential.

T2-weighted and fluid-attenuated inversion recovery MRI images typically show changes in the striatum but abnormalities can be present in other brain regions (Figure 17.1). In one recent series the incidence of

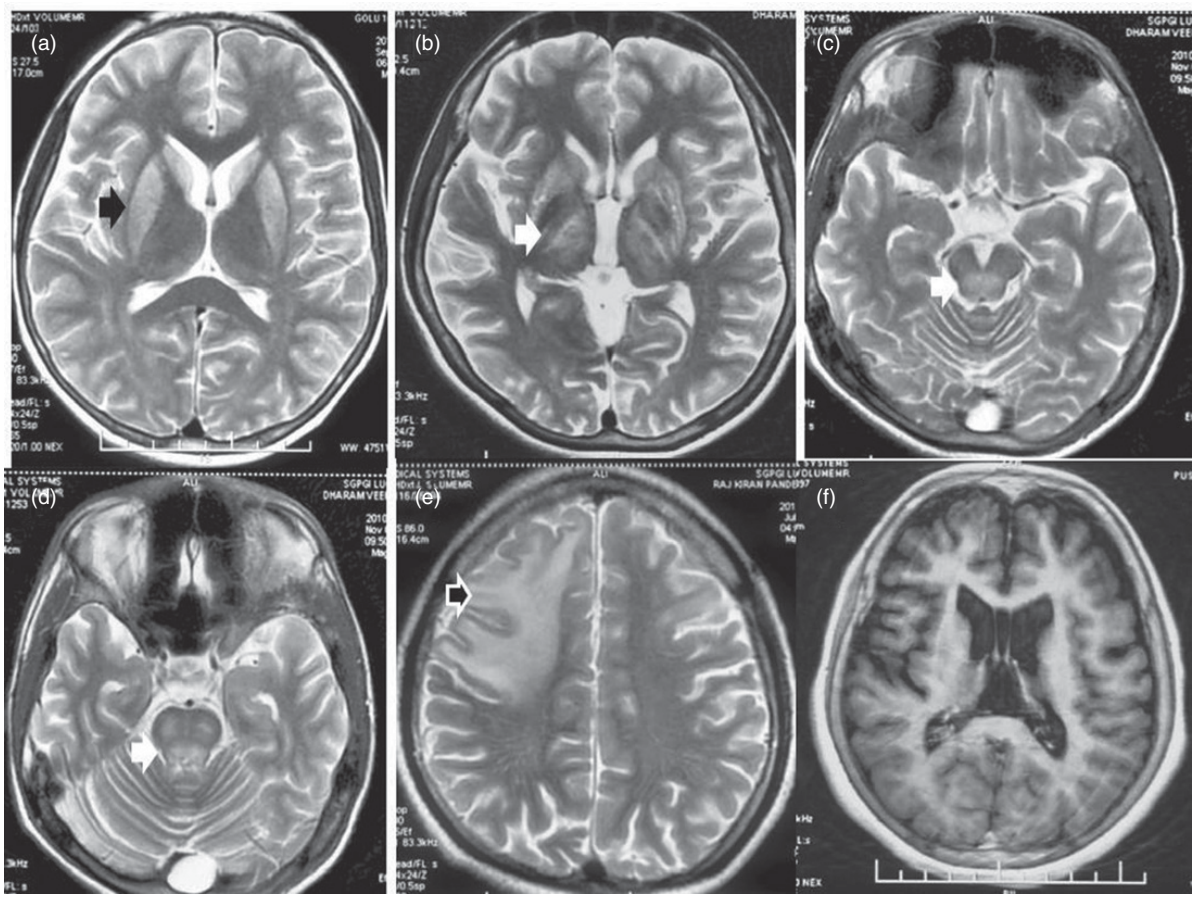

Figure 17.1 Representative cranial MRI findings in patients with Wilson disease having neurological manifestation in axial section. (a) Basal ganglia T2 hyperintensity (putamen, 85.3%; caudate, 67.6%; globus pallidus, 61.8% of patients). (b) Thalamus (58.8% of patients) and corpus striatum T2 hyperintensity. (c) Midbrain T2 hyperintensity (61.8% of patients). (d) Pontine T2 hyperintensity (61.8% of patients). (e) Frontoparietal subcortical white matter (23.5% of patients) and cortical (26.5% of patients) T2 hyperintensity. (f) Cortical atrophy in T1 sequence (20.5% of patients). From: Ranjan A, Kalita J, Kumar S et al. A study of MRI changes in Wilson disease and its correlation with clinical features and outcome. Clin Neurol Neurosurg 2015;138:31–6. Reproduced with permission.

Table 17.1 Diagnostic biochemical measurements in Wilson disease

	Wilson disease	Normal
Serum ceruloplasmin (mg/L)	0–200	200–400
Serum copper (μmol/L)	<11	11–24
Urinary copper (μmol/24 h)	>1.6	<0.6
Liver copper (μg/g dry weight)	>250	<50

abnormalities (percentage of patients) was: putamen, 85.3%; caudate, 67.6%; brainstem and globus pallidus, 61.8% each; thalamus, 58.8%; cerebral cortex, 26.5%; subcortical white matter, 23.5%; and cerebellum, 5.9% [7]. Both hyperintense and hypointense signals can be seen. Choreoathetosis correlated with thalamic, pallidal, and putaminal lesions; mini mental state examination, with subcortical white matter changes. MRI load correlated with age, tremor, psychiatric disorder, choreoathetosis, and severity of Wilson disease [7].

Laboratory investigations usually show abnormalities of liver function tests (even with a pure neurological presentation) although the levels of transaminases tend to be lower than other causes of chronic hepatitis (e.g. autoimmune). Clotting times may be prolonged. Plasma copper and ceruloplasmin are low; urinary excretion of copper is elevated (Table 17.1).

A liver biopsy shows chronic inflammation with fibrosis, with increased staining for copper-associated protein. The liver copper content is increased (Table 17.1).

Many different mutations in the *ATP7B* gene have been described (>500). Most patients are compound heterozygotes. R778L is a common mutation in Asian patients whereas H1069Q is a common mutation in Europeans. R778L causes complete loss of function of the copper ATPase; homozygotes present early with hepatic disease. H1069Q mutations are associated with some residual activity and homozygotes present with neurological disease at around 21 years of age [4].

The treatment options for Wilson disease include drugs that chelate copper and increase its excretion, and zinc. Zinc induces metallothionein synthesis in the intestinal epithelium and the metallothionein binds copper in the villus cells (preferentially over zinc). This reduces copper absorption and increases losses into the feces as the villus cells are shed into the intestinal lumen.

Treatment of neurological Wilson disease presents a major challenge. It may save the patient's life but make their movement disorder significantly worse and in 34% of cases where neurological deterioration occurs, it is irreversible. A recent study confirmed that worsening of neurological symptoms can occur in 35% of patients treated with D-penicillamine (n = 35) and 19% of patients treated with zinc sulphate (n = 21), a difference that was not statistically significant [8, 9]. On the other hand, a study in 2006 by Brewer et al. showed that neurological deterioration on treatment occurred in 27% of patients treated with trientine (n = 23) but in only 4% of patients treated with ammonium tetrathiomolybdate (n = 25), a difference that was significant at the $p < 0.05$ level [10]. Bis-choline tetrathiomolybdate is currently in a Stage III clinical trial (ClinicalTrials.gov).

Hepatic Wilson disease may require treatment of acute liver failure or end-stage chronic liver disease by liver transplantation. Liver transplantation for neurological Wilson disease remains controversial; there is a wide spectrum of outcomes post liver transplant – some with neurological recovery and others with continued disability and an overall increased mortality [11].

MEDNIK Syndrome

MEDNIK syndrome is an autosomal-recessive disorder caused by bi-allelic mutations in *AP1S1*, which encodes a protein that is needed for translocation of ATP7A and ATP7B from the trans-Golgi network to the cell membrane and other organelles. Plasma copper and ceruloplasmin concentrations are reduced but liver copper is elevated. The clinical features are those constituted in the acronym MEDNIK: "Mental retardation, Enteropathy, Deafness, peripheral Neuropathy, Ichthyosis, and Keratoderma" plus brain atrophy and cholestatic hepatopathy. Although brain atrophy is the most common finding on MRI, three patients have been described with symmetrical T2 hyperintensity of the basal ganglia, mainly affecting the caudate and putamen. However, a specific movement disorder has not been described. The disorder responds to treatment with zinc acetate [12, 13].

Copper Deficiency Disordes

Menkes Disease, Occipital Horn Syndrome, X-Linked Distal Hereditary Motor Neuropathy (*ATP7A* Mutations)

The *ATP7A* gene is on the X-chromosome, so mutations give rise to X-linked disorders. Menkes disease is

the most severe form; the milder forms are the occipital horn syndrome and X-linked distal hereditary motor neuropathy [4].

Many of the manifestations of Menkes syndrome can be understood in terms of the effect of copper deficiency on copper-dependent enzymes (see below). The reduced activity of complex IV of the respiratory chain, copper–zinc dismutase, and ceruloplasmin probably contribute to neurological disease; the reduced cross-linking of elastin and of collagen by lysyl oxidase contribute to cutis laxa, tortuosity of the arteries, and bladder and bowel diverticulae; the reduced activity of dopamine beta-hydroxylase impairs synthesis of adrenaline and noradrenaline and contributes to hypothermia and orthostatic hypotension; and the reduced activity of tyrosinase contributes to pallor of skin and hair.

Menkes disease occurs with an incidence of approximately 1 in 250,000 live births and is a progressive neurodegenerative disorder. Major neurological signs are hypotonia progressing to hypertonia and epilepsy.

Infants with Menkes syndrome may be born prematurely and some exhibit a large cephalhematoma and/or skin laxity. The hair breaks easily. Hypothermia can be a problem in the neonatal period. By 1–2 months, hypotonia is apparent as is the characteristic appearance with sagging cheeks and loose skin over the neck. Examination of the hair under the microscope reveals the characteristic pili torti. Feeding difficulties, chronic diarrhea, and failure to thrive are common problems although linear growth is usually preserved. Seizures tend to start at about 2 months. Many seizure types have been described, including infantile spasms with hypsarrhythmia on EEG. During the first year of life hypotonia is replaced by hypertonia, and a delay in achieving motor milestones becomes increasingly apparent. In one series from China, all patients were reported to have dystonia [14]. Urinary-tract infections are common and may be difficult to treat because of bladder diverticulae; chest infections are also common. Umbilical and inguinal hernias occur frequently as does pectus excavatum. In the past, most patients died before the age of 3 years of infections or vascular complications, although with good care, especially attention to feeding, better survival could be achieved.

Skeletal X-rays often show osteopenia and Wormian bones in the skull. MRI shows cerebral atrophy, ventriculomegaly, and cerebellar atrophy at first imaging in the majority of patients, and focal lesions in the basal ganglia also occur early in the course of the disease, between 2 months and 16 months of age [15]. These lesions are typically asymmetrical and involve the caudate and anterior putamen; they are hyperintense on T2-weighted images. Subdural collections are seen in under one-fifth of scans.

Serum copper is <11 μg/dL and ceruloplasmin <200 mg/L but low values like this can be seen in the first few months of life in normal (and especially premature) infants. The abnormalities of catecholamines and their metabolites provide better diagnostic markers in young infants. Examples of useful diagnostic parameters are the ratios in plasma of dopamine to noradrenaline or of dihydroxyphenylacetic acid to dihydroxyphenylglycol or the ratio of homovanillic acid (HVA) to vanillylmandelic acid (VMA) in the urine [16]. The latter has been proposed as a test that could be used for neonatal screening; early diagnosis is important for treatment to be successful.

Treatment with parenteral copper, usually in the form of copper histidine, can improve neurological outcomes. However, some patients show no significant improvement despite early treatment initiation [17].

The occipital horn syndrome is a milder form of Menkes syndrome seen in about 10% of cases. The connective-tissue abnormalities are similar to those seen in Menkes but development is much less affected. Exostoses are palpable at the sites of some muscle insertions; the occipital horn is at the site of insertion of the paraspinal muscles. Skin and joint laxity are common problems as are the bladder diverticulae. Chronic diarrhea and orthostatic hypotension are probably both consequences of dysautonomia, particularly impaired synthesis of adrenaline and noradrenaline.

The mildest phenotype caused by *ATP7A* mutations is X-linked distal hereditary motor neuropathy. Affected individuals present in late childhood/adult life with weakness associated with distal muscular atrophy.

All three phenotypes of ATP7A deficiency show an X-linked mode of inheritance but approximately one-third of patients have a new mutation. The mutations producing Menkes disease vary considerably from chromosomal abnormalities (principally X-autosome translocations) through intragenic deletions involving more than one exon to single base-pair changes. These mutations are predicted to lead to a non-functional

protein. In contrast, the occipital horn syndrome is usually caused by splice site mutations that permit small amounts of ATP7A protein to be produced and X-linked distal hereditary motor neuropathy is caused by a small number of missense mutations with even higher residual ATP7A activity [4].

Disorders of Specific Copper-Dependent Enzymes or Chaperones

Aceruloplasminemia

Aceruloplasminemia is an autosomal-recessive disorder caused by bi-allelic mutations in the *CP* gene encoding the copper-dependent enzyme ceruloplasmin [18]. Ceruloplasmin is undetectable in plasma. Patients have an accumulation of iron in the liver, islets of Langerhans, and brain. They present in adulthood with neurological symptoms (chorea, ataxia, dystonia, parkinsonism, and psychiatric disorders), retinal degeneration, and diabetes mellitus. Ceruloplasmin is a ferroxidase enzyme that converts ferrous iron (Fe^{2+}) into ferric iron (Fe^{3+}). It is believed to also be important in the conversion of Mn^{2+} to Mn^{3+} (see below). Patients have low serum iron (mostly transferrin-bound Fe^{3+}), high serum ferritin (produced from excess cellular Fe^{2+}), and low serum copper. Hepatic iron is increased.

Aceruloplasminemia is normally classified as one of the neurodegeneration with brain iron accumulation (NBIA) group and is discussed in Chapter 16.

Treatment with iron chelation and fresh frozen plasma may be useful to reduce the iron load in the central nervous system and to improve the neurological symptoms [19].

Deficiency of the Copper Chaperone for Superoxide Dismutase

The copper chaperone for superoxide dismutase (CCS) acts as a copper chaperone, delivering the metal to the copper–zinc superoxide dismutase (SOD1) enzyme. One patient with Huppke–Brendel syndrome and a homozygous truncating mutation in the *SLC33A1* gene, who was reported as having congenital cataracts, hearing loss, and neurodegeneration (see the next section), also had a variant of unknown significance in *CCS* [20]. The patient with the *CCS* variant had additional symptoms not present in the other patients with *SLC33A1* mutations, including neonatal hypotonia, hypoglycemia, and a pericardial effusion. At age 18 months, he had rapid developmental regression and epilepsy with persistent bilateral thalamic lesions on brain MRI. The activity of SOD1 was reduced in the fibroblasts.

Deficiency of Copper–Zinc Superoxide Dismutase

Mutations in *SOD1* encoding the copper–zinc superoxide dismutase enzyme cause amyotrophic lateral sclerosis (motor neuron disease) [21]. This suggests that a reduced activity of this enzyme caused by copper deficiency may contribute to the motor neuropathy of X-linked distal motor neuropathy.

Deficiency of the Cytochrome C Oxidase Assembly Protein SCO1

SCO1 is a copper chaperone involved in the assembly of complex IV of the mitochondrial respiratory chain and also plays a role in copper homeostasis. Bi-allelic mutations cause neonatal-onset hepatic failure and encephalopathy (with or without hypertrophic cardiomyopathy), with profound lactic acidosis and reduced activity of complex IV in the liver and muscle [22]. Affected infants are profoundly hypotonic. A patient who survived to 4 months initially had very poor truncal tone with increased peripheral tone but progressed to dystonic posturing [23].

Deficiency of the Cytochrome C Oxidase Assembly Protein SCO2

SCO2 is a paralogue of SCO1 and it also participates in the assembly of complex IV of the mitochondrial respiratory chain and in copper homeostasis. Bi-allelic mutations in *SCO2* cause neonatal encephalocardiomyopathy [24, 25]. Profound hypotonia and dystonia may be apparent. Recently, it has been shown that bi-allelic mutations in *SCO2* can also cause an axonal polyneuropathy with predominantly motor involvement [26]. Affected individuals have evidence of cellular copper deficiency.

Dopamine Beta-Hydroxylase

Bi-allelic mutations in *DBH* cause the isolated failure of autonomic noradrenergic neurotransmission because a defect in the beta-hydroxylation of dopamine in peripheral nerves leads to a failure of synthesis of

adrenaline and noradrenaline [27]. The main symptom is orthostatic hypotension. Hypothermia and hypoglycemia can occur in infancy. In two patients with lifelong orthostatic hypotension due to DBH deficiency, the oral administration of DL-dihydroxyphenylserine led to remarkable improvement [28].

Lysyl Oxidase

Heterozygous mutations in the *LOL* gene encoding lysyl oxidase cause autosomal-dominant familial thoracic aortic aneurysms [29].

Tyrosinase

Bi-allelic mutations in the *TYR* gene encoding tyrosinase cause autosomal-recessive oculocutaneous albinism [30]. Tyrosinase catalyzes the first two steps, and at least one subsequent step, in the conversion of tyrosine to melanin.

Disorders with Secondary Effects on Copper Levels

SLC33A1 Mutations/AT1 Deficiency/ Huppke–Brendel Syndrome, and Autosomal-Dominant Hereditary Spastic Paraplegia 42

Mutations in *SLC33A1* lead to a deficiency of the acetyl-coenzyme A (CoA) transporter AT1 that is required for entry of acetyl-CoA into the lumen of the Golgi apparatus where it participates in many acetylation reactions involving proteins and their glycans. The impaired synthesis and/or secretion of ceruloplasmin leads to low serum copper and ceruloplasmin. There is no evidence of copper deficiency or copper toxicity.

Homozygous mutations in *SLC33A1* have been reported in children with autosomal-recessive congenital cataracts, hearing loss, and neurodegeneration (Huppke–Brendel syndrome) [31]. Heterozygous mutations in *SLC33A1* have been described in autosomal-dominant hereditary spastic paraplegia type 42 [32].

Manganese Metabolism and Transport, Toxicity and Deficiency

Manganese is another of the six transition metals essential for human metabolism. It participates in group transfer reactions such as phosphorylation and glycosylation. Deficiency can lead to defective glycosylation of serum proteins such as transferrin. It can exist in a number of oxidation states; Mn^{2+} and Mn^{3+} are important in the body and their interconversion can facilitate redox reactions including manganese superoxide dismutase, the important mitochondrial scavenger of reactive oxygen species. Other enzymes for which manganese is a cofactor are involved in amino acid metabolism (e.g. arginase), lipid and carbohydrate metabolism, immune function, bone and connective-tissue growth, and blood clotting [33, 34].

Manganese is present in water supplies and in many foods. Foods particularly rich in manganese include cloves, saffron, nuts, mussels, dark chocolate, sesame, and sunflower seeds [35].

Uptake of manganese (Mn^{2+}) into cells can be facilitated by a number of transporters including SLC39A8 and SLC39A14, divalent metal transporter 1 (DMT1; SLC11A2), dopamine transporter (DAT), and citrate transporters [2, 36]. Iron competes with manganese for uptake by DMT1 and also at several other stages of manganese metabolism (e.g. binding to transferrin). This explains why increasing oral iron uptake can be used in the treatment of hypermanganesemia [37, 38]. Uptake by SLC39A8 probably also contributes to the uptake of manganese from the gut and the uptake of manganese into the cells that need it; hence, SLC39A8 deficiency leads to low plasma manganese levels and signs of cellular manganese deficiency, e.g. impaired glycosylation of transferrin [39–41]. On the other hand, the uptake of manganese into the liver, facilitated by SLC39A14, appears to be important in facilitating the biliary excretion of manganese; SLC39A14 deficiency is a cause of hypermanganesemia and deposition of manganese in the brain [42].

After uptake of Mn^{2+} from the gut, it is oxidized in the blood by ceruloplasmin to Mn^{3+}, which is then bound to transferrin, the major manganese-binding protein. Uptake of transferrin-bound Mn^{3+} occurs when it binds to the transferrin receptor and is internalized in an endocytotic vesicle (receptor-mediated endocytosis). In the endosome, Mn^{3+} is reduced to Mn^{2+} and uptake into the cytoplasm probably occurs mainly via DMT1 [36]. Stable tissue concentrations of manganese are maintained by tight homeostatic control of intestinal absorption and biliary excretion. When blood levels of manganese are elevated manganese may be deposited in the

brain, particularly in the basal ganglia. Affected areas of the brain can be visualized as they produce a hyperintense signal on T1-weighted MRI [42]. Brain manganese accumulation leads to a condition known as manganism, an extrapyramidal movement disorder characterized by dystonia, bradykinesia, and rigidity, accompanied by psychiatric and cognitive defects [42].

Manganese neurotoxicity has been attributed to impaired dopaminergic, glutamatergic, and GABAergic neurotransmission, mitochondrial dysfunction, oxidative stress, and neuroinflammation. While excessive levels of copper and iron can lead to the generation of reactive oxygen species by Fenton chemistry, manganese might increase reactive oxygen species production indirectly. Feeding rats a high manganese diet leads to an increase in markers of oxidative stress as well as a shift in the ratio Fe^{2+}/Fe^{3+} in the brain [43]. This suggests that the change in Fe^{2+}/Fe^{3+} might favor iron-induced production of reactive oxygen species.

Disorders Leading to Manganese Accumulation in the Brain

Manganese Poisoning

High levels of manganese in the blood can occur due to a high manganese intake, which is particularly likely if the mechanisms restricting entry through the gut are by-passed. Examples include parenteral nutrition, intravenous abuse of drugs contaminated with manganese, working in mines and battery factories, and welding [42].

Acquired Hepatocerebral Syndrome/ Acquired Hepatocerebral Degeneration

In patients with chronic liver disease (particularly cirrhosis), manganese excretion is impaired and blood manganese rises with the deposition of manganese in the basal ganglia and subsequent motor impairment. Clinical characteristics include movement disorders, mainly parkinsonism and ataxia-plus syndrome, as well as cognitive impairment with psychiatric features. Neuroimaging studies of acquired hepatocerebral degeneration (AHD) with parkinsonism show hyperintensity in the bilateral globus pallidus on T1-weighted magnetic resonance images, consistent with manganese accumulation. Ataxia-plus syndrome in AHD may demonstrate high-signal lesions in the middle cerebellar peduncles on T2-weighted images [44]. Iron deficiency is common in patients showing brain MRI abnormalities compatible with manganese deposits in thr basal ganglia. This observation suggests that iron deficiency could be an important risk factor for manganese-induced neurotoxicity and should, therefore, be carefully considered and treated [45].

Dystonia–Parkinsonism, Hypermanganesemia, Polycythemia, and Chronic Liver Disease (SLC30A10 Deficiency)

In 2012, it was shown that an autosomal-recessive syndrome of dystonia–parkinsonism, hypermanganesemia, polycythemia, and chronic liver disease was caused by bi-allelic mutations in *SLC30A10* [37, 38, 46]. By 2017, 22 affected families had been described and it is now clear that the disease can present with liver disease, a movement disorder, or a combination of the two [47, 48].

The movement disorder can present as early as the second year or as late as the sixth decade of life. Difficulty with walking is a common early symptom. Extrapyramidal signs are variable, from severe dysdiadochokinesis but sparing of face and tongue (Video 17.1) and pure four-limb dystonia with a cock-walk, i.e. high-stepping, gait (Video 17.2), to typical parkinsonism with bradykinesia, cogwheel rigidity, hypomimia, and dysarthria [49]. One patient has spastic paraparesis without dystonia and two siblings have hypotonia with sensorimotor axonal neuropathy [38, 46]. The rate of progression of the movement disorder can be slow in adults but quite rapid in patients presenting in the second year of life.

MRI of the brain shows areas of hyperintensity on T1-weighted images consistent with increased levels of manganese. These are particularly seen in the globus pallidus, putamen, and subthalamic region (but sparing the thalamus), in the brainstem (but sparing the lower pons), and in the dentate nucleus and cerebellar white matter. In some, but not all, patients there is also hyperintensity of the cortical white matter and anterior pituitary (Figure 17.2).

MRI of the liver also shows hyperintenstiy on T1-weighted images consistent with raised manganese levels; this is not seen in SLC39A14 deficiency [42].

Clinical evidence of liver disease may be apparent, ranging from mild hepatomegaly to hepatic failure in early adulthood. Liver function tests show raised transaminases in most cases.

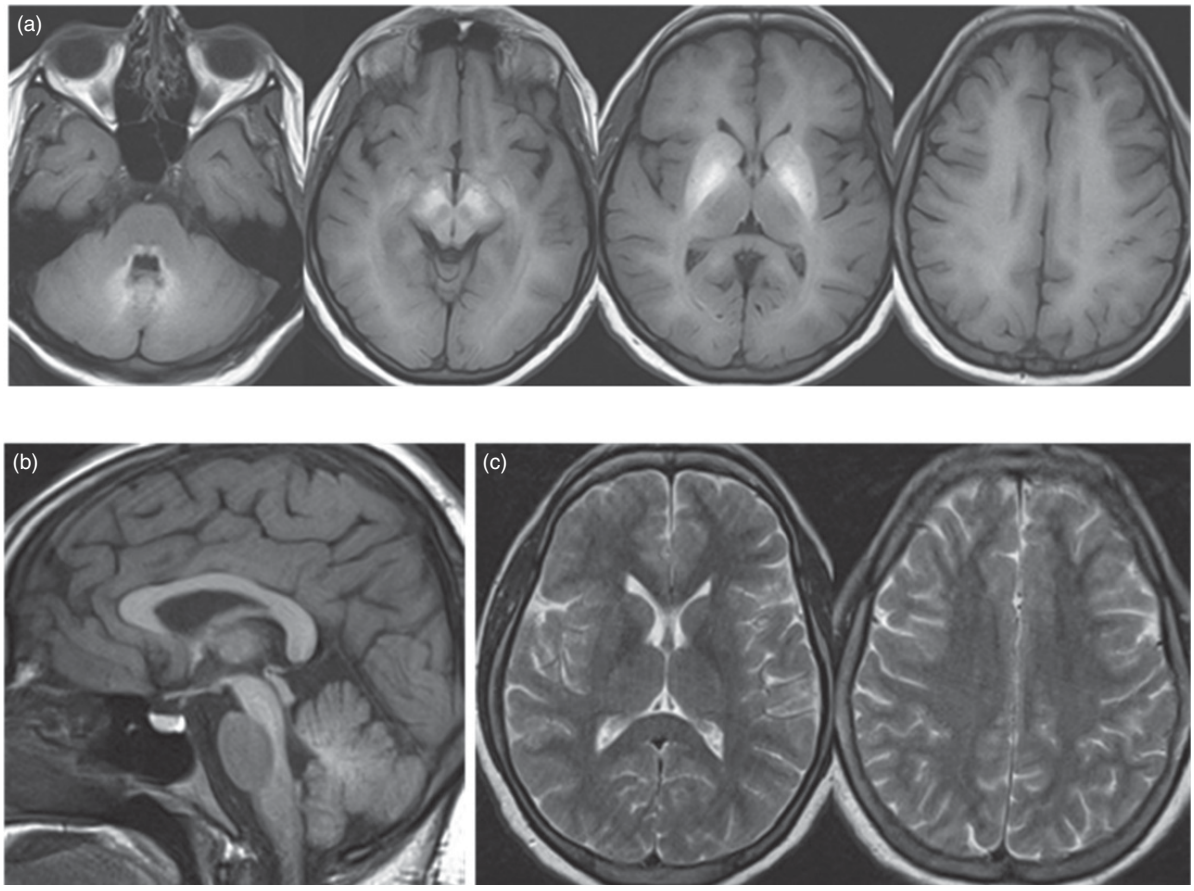

Figure 17.2 MRI brain appearances in SLC30A10 deficiency: T1-weighted MRI shows abnormally high signal on (a) transaxial images from the white matter, putamen, and globus pallidus bilaterally; and (b) on sagittal images from the anterior pituitary and white matter, particularly the corpus callosum, midbrain, dorsal pons, and medulla. (c) Transaxial T2-weighted images show abnormally low signal from the globus pallidus in the same distribution as the regions of highest signal on the T1-weighted images. From: Tuschl K, Clayton PT, Gospe SM Jr et al. Syndrome of hepatic cirrhosis, dystonia, polycythemia, and hypermanganesemia caused by mutations in *SLC30A10*, a manganese transporter in man. Am J Hum Genet. 2012; 90:457–66.

Other laboratory investigations usually show polycythemia, although in a patient with severe liver disease and gastrointestinal bleeding this may be masked. Whole blood manganese is usually >2000 nM (normal <320 nM).

The first successful treatment was achieved by the chelation of manganese with intravenous disodium calcium edetate together with an iron supplement to reduce manganese absorption. Chelation treatment led to the improvement of neurological symptoms, the halt of liver disease progression, the normalization of hemoglobin levels, and the reduction of manganese blood levels [37, 38, 46].

More recently, treatment using 2,3-dimercaptosuccinic acid as a manganese chelating agent showed satisfactory results with improvement of biochemical markers, hepatic manifestations, and relative amelioration of the neurological symptoms [47].

Infantile/Early-Childhood-Onset Dystonia with Hypermanganesemia (SLC39A14 Deficiency)

In 2016, patients with infantile/early-childhood-onset parkinsonism–dystonia with hypermanganesemia and MRI indicating increased manganese in the basal ganglia were shown to have bi-allelic mutations in *SLC39A14* [42]. To date, 29 cases from 11 families have been described [50, 51]. Individuals with SLC39A14 deficiency do not have liver disease or polycythemia.

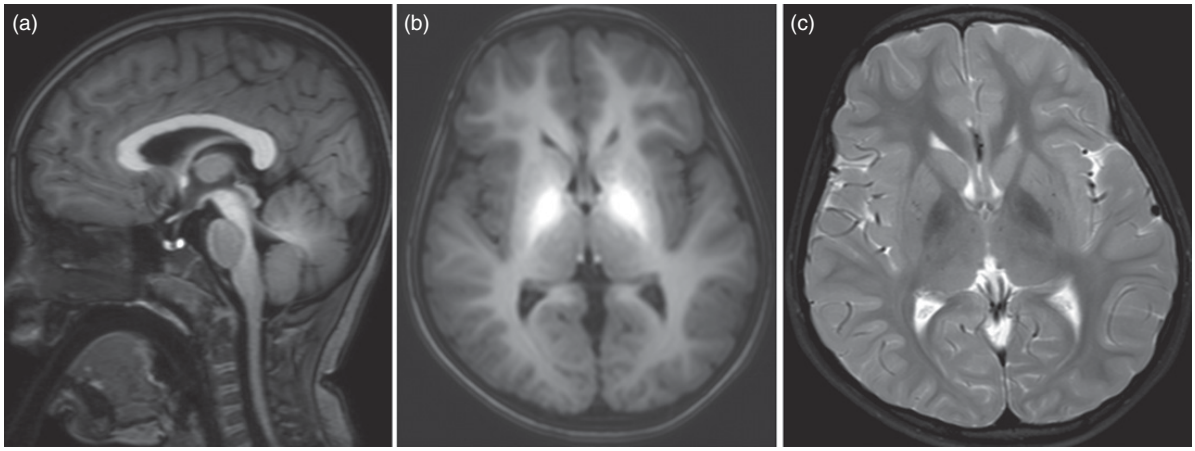

Figure 17.3 MRI brain appearances in SLC39A14 deficiency. Generalized T1 hyperintensity of (a) the white matter, including the dorsal pons and cerebellum, and the pituitary gland, on sagittal images; and (b) the cerebral white matter, globus pallidus, and striatum, on transaxial images, can be observed. (c) Hypointensity of the globus pallidus is also evident on T2-weighted imaging. From: Tuschl K, Meyer E, Valdivia LE et al Mutations in SLC39A14 disrupt manganese homeostasis and cause childhood-onset parkinsonism-dystonia. Nat Commun. 2016 May 27;7:11601

The median age of onset of the dystonia is younger than for SLC30A10 deficiency. Patients typically present between 5 months and 3 years with delayed walking or gait disturbance. Examination in the early course of the disease shows principally hypotonia. Later, examination reveals dystonia, spasticity, dysarthria, bulbar dysfunction, and parkinsonian features (bradykinesia, tremor, and hypomimia). It is a progressive disorder leading, by the age of 10 years, to generalized severe drug-resistant dystonia, limb deformities, scoliosis, and loss of independent walking. Patients may even die before the age of 10 years from complications (e.g. chest infection) [42].

MRI of the brain shows hyperintense areas on T1-weighted images, consistent with increased manganese levels. The areas principally affected are the globus pallidus and striatum with sparing of the thalamus; the T2-weighted images of these areas show hypointensity. In addition, the white matter T1 intensity is increased in the white matter. including the cerebellum, spinal cord, and dorsal pons (with sparing of the ventral pons) (Figure 17.3) [42].

Laboratory investigations show a markedly elevated whole blood manganese level (usually >1000 nM; reference range <320 nM).

Sequencing of *SLC39A14* in patients with infantile/early childhood-onset dystonia with hypermanganesemia has revealed missense mutations, nonsense mutations, and frameshift mutations, causing premature termination of translation.

Attempts to treat SLC39A14 deficiency with chelation therapy have met with some success [42]. A 5-year old girl was treated with intravenous disodium calcium edetate (20 mg/kg per dose) twice daily for 5 days a month (similar to the regimen that had been successful in SLC30A10 deficiency). After 6 months of treatment, the neurological signs had improved and the child had regained the ability to walk independently (Videos 17.3 and 17.4). In contrast, the attempted treatment of a 17-year-old girl with advanced disease was not successful. Prior to the start of treatment, she had severe generalized dystonia with prominent oromandibular involvement, contractures, and scoliosis. On treatment, her disease continued to progress with worsening tremor and stiffness. It is likely that, to be effective, chelation treatment for SLC39A14 deficiency will need to be started early in the course of the disease [42].

Other approaches to treatment include decreasing dietary manganese intake (using a manganese-depleted synthetic formula) and symptomatic treatment of dystonia such as oral trihexyphenidyl, botulinum toxin injections, and tendon-lengthening surgery [51].

Disorders Leading to Manganese Deficiency

SLC39A8 Deficiency

Two papers published simultaneously in 2015 described the effects of *SLC39A8* mutations [39, 40]. Six patients from the Hutterite community and an Egyptian sibling pair presented with developmental delay/intellectual disability, hypotonia, strabismus, and variable short stature. MRI scans showed cerebellar atrophy. Concentrations of manganese and zinc were variably reduced in plasma and increased in urine [39]. They all had a homozygous mutation (p. Gly38Arg) in *SLC39A8.* A further affected individual presented with cranial asymmetry, disproportionate (short-limbed) dwarfism, severe infantile spasms with hypsarrhythmia, hearing loss, and severe developmental delay. The blood manganese was below the limit of detection. The patient's plasma showed an abnormal transferrin glycosylation profile (type II pattern); this was consistent with the reduced activity of a manganese-dependent enzyme required for N-glycosylation – beta-1,4-galactosyltransferase [40]. The transferrin glycosylation profile improved with galactose treatment.

In 2017, two further patients with mutations in *SLC39A8* (homozygous p.Cys113Ser) were described [41]. They presented with features suggestive of Leigh syndrome: profound developmental delay, dystonia, seizures, and failure with to thrive, with basal ganglia T2 hyperintensities and elevated cerebrospinal fluid lactate (in one). This sibling was shown to have reduced activities of complexes II/III and IV in liver. However, the second sibling also had a type II abnormal transferrin pattern and blood and urine manganese levels were undetectably low. Interestingly, the brain imaging findings in both siblings were opposite to those seen in the disorders in which manganese accumulates (SLC30A10 and SLC39A14 deficiencies); the basal ganglia were hypointense on T1-weighted images and hyperintense on T2. The abnormal transferrin pattern was attributed to the reduced beta-1,4-galactosyltransferase activity, and the mitochondrial damage to a build-up of reactive oxygen species as a result of the reduced activity of manganese-dependent superoxide dismutase [41].

Treatment with high-dose manganese sulphate (15–20 mg/kg per day) led to a marked improvement in blood manganese, and transferrin glycosylation in two patients. In a child whose treatment was started at 8 months, previously intractable seizures came under control and there was an improvement in hearing, vision, and motor function (reduction in hyperextension, improved head control, and progress in motor milestones). Infantile spasms were fully controlled. In a 19-year-old woman with global psychomotor disability, seizures, strabismus, scoliosis, and cerebellar atrophy on MRI, motor function improved. Previously observed repetitive movements of the head were observed less frequently and she became able to perform the finger-to-nose test, indicating reduced ataxia. Muscle strength improved and she became able to sit without support [52]. Interestingly, a missense variant in *SLC39A8* was recently found to be associated with severe idiopathic scoliosis [53].

Disorders of Other Manganese Transporters

ATP13A2 Mutations (Kufor–Rakeb Syndrome)

ATP13A2 encodes a lysosomal transporter for divalent transition metals required to maintain intracellular manganese homeostasis [54]. Bi-allelic mutations cause two phenotypes. The first type is the autosomal-recessive Kufor–Rakeb syndrome, which presents in childhood with atypical parkinsonism, supranuclear gaze palsy, spasticity, and dementia [55]. MRI indicates the features of iron accumulation in the basal ganglia in some (so it is classified as one of the NBIA disorders, see Chapter 16). The second phenotype is spastic paraplegia type 78, a paraplegia plus disorder. Onset of spastic quadriplegia with bilateral pes cavus in the second decade is associated with other neurological abnormalities such as cognitive decline, ataxia, nystagmus, ophthalmoplegia, and axonal sensory and motor neuropathy. One patient has shown progressive parkinsonism but others have had no signs of basal ganglia dysfunction. MRI shows cerebral atrophy and changes in the basal ganglia, and dopamine transport scintigraphy may show marked depletion of dopamine transporter density in the putamen, even in the absence of extrapyramidal symptoms [56].

ATP13A1 Mutations

ATP13A1 encodes a transporter in the membrane of the endoplasmic reticulum. The yeast homolog was

shown to regulate manganese transport into the endoplasmic reticulum [57]. In a study of a cohort of individuals with intellectual disability, mutations in this gene have been reported in children with, in addition to intellectual disability, dysmorphic features (downslanting palpebral fissures, prominent nose, hyperplasia of the maxilla, abnormal finger nails), attention hyperactivity disorder, and recurrent respiratory infections [58].

Disorders of Individual Manganese-Dependent Enzymes

Deficiency of Manganese Superoxide Dismutase (SOD2)

In mice, homozygous mutations of *Sod2* lead to premature death within the first 10 days of life with a dilated cardiomyopathy, accumulation of lipid in liver and skeletal muscle, and metabolic acidosis [59]. The role of SOD2 in clinical disease remains under intense study [60].

Arginase Deficiency

Arginase deficiency is a urea cycle defect, causing high plasma arginine and episodic hyperammonemia. Untreated individuals develop spastic diplegia or tetraplegia, plateauing of cognitive development, epilepsy, and the subsequent loss of developmental milestones. Plasma arginine was normal in a severely affected infant with SLC39A8 deficiency [40].

Glutamine Synthase Deficiency

Glutamine synthase deficiency leads to low plasma glutamine, chronic hyperammonemia, epileptic encephalopathy, diarrhea, an erythematous skin rash, and multi-organ failure. Plasma glutamine was normal in a severely affected infant with SLC39A8 deficiency [40].

Prolidase Deficiency

Homozygous mutations in *PEPD* cause skin lesions (including skin ulcers and telangiectasias), recurrent infections, dysmorphic facial features, variable intellectual disability, and hepatomegaly. Biochemically, it is characterized by massive urinary excretion of imidodipeptides; this has not been reported in SLC39A8 deficiency.

Pyruvate Carboxylase Deficiency

Pyruvate carboxylase (PC) deficiency is characterized by failure to thrive, developmental delay, recurrent seizures, and lactic acidosis. However, infants with type B PC deficiency ("French phenotype") also present with neonatal-onset hypothermia, hypotonia, lethargy, convulsions, vomiting, and hepatomegaly. Bizarre ocular eye movements and especially rigidity and hypokinesia (hypokinetic–rigid syndrome) are important hallmarks and may suggest PC deficiency when associated with severe lactic acidosis [61].

Glycosyl Transferases

Glycosyl transferases are known to be manganese-containing enzymes. Hence, it is not surprising that manganese deficiency leads to defects in glycosylation [47]. The galactosyl transferase whose compromised activity is thought to give rise to the abnormal transferrin pattern in SLC39A8 deficiency is encoded by *B4GALT1*. Mutations in this gene cause congenital disorder of glycosylation type IId – described in a boy, born of non-consanguineous parents, who presented with macrocephaly due to Dandy–Walker malformation, hypotonia, coagulopathy, myopathy with elevated creatine kinase, mild developmental delay, motor retardation, and an abnormal serum transferrin pattern by isoelectric focusing [62].

Key Points and Clinical Pearls

- Copper and manganese perform essential roles in the basal ganglia and elsewhere in the nervous system.
- Neurological disease (particularly movement disorders) can result from deficiency or excess of copper/manganese.
- Maintenance of optimal levels of copper and manganese in the nervous system requires whole-body as well as local homeostatic mechanisms. Liver uptake and excretion are particularly important in preventing high levels in the blood and, as a result, in the brain
- Wilson disease can present with neurological disease, or liver disease or both. Kayser–Fleischer rings are an important clinical sign indicating that a movement disorder is due to Wilson disease. Low plasma copper and ceruloplasmin and increased urinary copper excretion provide confirmation.

- Movement disorders caused by manganese toxicity produce characteristic MRI images with high intensity of the basal ganglia (and other brain areas) on T1-weighted images – raised blood manganese provides confirmation.
- Deficiency of copper/managnese can be treated with supplements of the metal and toxicity due to high levels can be treated with chelators.

Directions for Future Research

- Better understanding of the basic science of how levels of copper and manganese are controlled in different organs and subcellular organelles.
- Improved early detection; therapies are most effective if started early.
- Improvement in therapy for Wilson disease: avoidance of the risk of neurological deterioration.
- Improvement in therapy for the disorders causing high levels of manganese in the brain, e.g. orally active chelation agents.

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