Review Article

Classification and differential diagnosis of Wilson's disease

Wieland Hermann

Department of Neurology, SRO AG Spital Langenthal, Langenthal, Switzerland

Correspondence to: Prof. Dr. habil. Wieland Hermann, MD. Chief Physician of Neurology, SRO AG Spital Langenthal, St. Urbanstrasse 67, CH - 4900 Langenthal, Switzerland. Email: w.hermann@sro.ch.

Abstract: Wilson's disease is characterized by hepatic and extrapyramidal movement disorders (EPS) with variable manifestation primarily between age 5 and 45. This variability often makes an early diagnosis difficult. A classification defines different clinical variants of Wilson's disease, which enables classifying the current clinical findings and making an early tentative diagnosis. Until the unequivocal proof or an autosomal recessive disorder of the hepatic copper transporter ATP7B has been ruled out, differential diagnoses have to be examined. Laboratory-chemical parameters of copper metabolism can both be deviations from the norm not related to the disease as well as other copper metabolism disorders besides Wilson's disease. In addition to known diseases such as Menkes disease, occipital horn syndrome (OHS), Indian childhood cirrhosis (ICC) and ceruloplasmin deficiency, recently discovered disorders are taken into account. These include MEDNIK syndrome, Huppke-Brendel syndrome and CCS chaperone deficiency. Another main focus is on differential diagnoses of childhood icterus correlated with age and anaemia as well as disorders of the extrapyramidal motor system. The Kayser-Fleischer ring (KFR) is qualified as classical ophthalmologic manifestation. The recently described manganese storage disease presents another rare metabolic disorder with symptoms similar to Wilson's disease. As this overview shows, Wilson's disease fits into a broad spectrum of internal and neurological disease patterns with icterus, anaemia and EPS.

Keywords: Wilson's disease; classification; copper metabolism; ATPases; icterus

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Introduction

Wilson's disease often remains undetected due to its numerous symptoms which emerge at different times, as well as its individual character. Conversely, Wilson's disease can also be misdiagnosed as a result of misinterpreting the medical findings. To begin with, the autosomal recessive defect of the hepatic copper transporter ATP7B (chromosome 13q14.3; *ATP7B*; WND gene) (1,2) causes biochemical deviations followed by the fluctuating occurrence of hepatic and extrapyramidal symptoms (EPS) as well as the impairment of other organs (3-6).

Taking the clinical manifestation into account, primarily between age 5 and 45 (6), in some cases as early as age one or until age 70 (7-9), differential diagnostic considerations are required, which include Wilson's disease. At the same time, a nosological classification of Wilson's disease can be used for the allocation of typical and ruling out of atypical findings, to make a tentative diagnosis (10). In addition to starting treatment at an early stage, it is also necessary, from a therapeutic point of view, to make a correct diagnosis to justify treatment, which involves adverse reactions (5,11). In the case of the exclusion of an autosomal recessive disorder of the hepatic copper transporter ATP7B, the clarification of differential diagnoses based on the existing findings is paramount.

In this overview, classification and differential diagnostic consideration are conducted based on the findings. Significant biochemical parameters and clinical cardinal symptoms of Wilson's disease are taken into account. Age onset as well as the typical spectrum of hepatic or neurological findings serves isolating relevant differential diagnoses.

Classification of Wilson's disease

Wilson's disease is characterized by various manifestations

Table 1 Classification of Wilson's disease by clinical dominating symptoms [according to (15,19-22)]

Form of progression (clinical variant)	Key clinical symptoms
Non-neurological forms of progression	
Preclinical (asymptomatic)	None, diagnosis prior to onset of symptoms
Hepatic (abdominal)	Acute and chronic decompensated liver disease; cirrhosis of the liver
Neurological forms of progression	
Pseudoparkinsonism (tremulous and muscular rigidity)	Bradykinesia/hypokinesia, rigidity, hypomimia, minor resting tremor, postural/intention tremor, dysarthria, hypersalivation
Pseudosclerotic (tremulous)	Postural, flapping and intention tremor, cerebellar ataxia, acroataxia, dysarthria (scanning)
Mixed form (arrhythmic-hyperkinetic)	Choreatic, athetotic and torsion dystonia hyperkinesia, in part Parkinson's disease
Psychiatric form of progression (21,22)	

as a result of numerous qualitative and quantitative symptoms, which emerge at different times (10,12). Taking the individuality of each patient into consideration, it is a matter of additionally determining the essentials which are consistent in many patients.

Classification by age of onset

Until puberty, gastrointestinal symptoms with hepatic or haemolytic findings are predominant (6,12,13). Consequently, an indistinct elevation of transaminases and bilirubin, icteric flare-ups, signs of a virus—negative acute hepatitis as well as hepatosplenomegaly should lead to the suspicion (4). Acute liver failure is also possible. Haematologically, the occurrence of a Coombs-negative haemolysis and unclear anaemia, leukopenia as well as thrombocytopaenia, are suspicious (4,14).

Without an exact age limit and after overcoming undetected bland gastrointestinal findings, symptoms affecting the central nervous system appear from puberty onwards with dysarthric, extrapyramidal and mental manifestations (6,12,15-17). Laboratory-chemical involvement of the liver (transaminases, synthesis parameters albumin and coagulation factors, cholinesterase, ammonia), change in the sonographic liver texture and a Kayser-Fleischer ring (KFR) can support the suspicion (4,18).

Classification by cardinal symptoms in clinical forms of progression (clinical variants)

Based on the clinical and pathological-anatomical phenomena, Konovalov probably provided the most precise classification in his monograph published in 1960 (19). Following this, five clinical variants were distinguished (*Table 1*), modified according to Lössner *et al.* 1980 (15) and Bachmann *et al.* 1988 (20) based on clinical aspects.

Some authors additionally divide the mixed form into a dystonic and a choreatic form (1,23). Psychiatric symptoms are also variable and include personality changes, behavioural disorders to criminal activities, cognitive disorders, depression and schizophrenia (6,21,24,25). They correlate more with the occurrence of neurological symptoms than with the existence of hepatic symptoms (22,23). In nearly 10%, Wilson's disease manifests with psychiatric symptoms (24,26). An exclusive psychiatric presentation of Wilson's disease is also reported in literature (21,22). Oder *et al.* [1993] recommend a classification of the neurological form of progression into three subgroups for this purpose based on extrapyramidal symptoms and cognitive as well as psychiatric disorders (27). On the other hand, only the (pragmatic simple) classification in neurological and non-neurological disease course is common in daily clinical practice.

A specific differential diagnosis can be made with an exact classification of Wilson's disease based on the variable cardinal symptoms (10). Particularly in the case of unclear hepatic, extrapyramidal and psychiatric findings, Wilson's disease must be included in differential diagnostic considerations at an early stage according to the knowledge of its clinical variants.

A quantitative assessment of the EPS (neurological score, *Table 2*) serves the documentation of the severity of the disease. Imaging results [cMRI, (^{18}F)FDG-PET, ^{123}J-Beta-CIT-SPECT and ^{123}J-IBZM-SPECT], fine motor skills and electrophysiology support the classification in a neurological and non-neurological form of progression. They serve monitoring progression as well as defining differential

Table 2 Neurological score*

Symptoms	Assessment of the disorder
Extrapyramidal symptoms (EPS)	EPS in co-occurrence
Fine motor skills	
Diadochokinesia	
Resting/postural tremor	Very severe (5 points)
Elevated tonus	Severe (4 points)
Ataxia	Moderate (3 points)
Bradykinesia/hypokinesia	Mild (2 points)
Gait disorder	
Dysarthrophonia	Alone
Only dysarthrophonia	1 point
None	0 points

*, 5 points marked cerebellar and basal ganglionic findings; 2–4 points gradations of EPS findings; 1 point only speech disorder (may be the only neurological findings); 0 points no EPS.

Table 3 Standard values of copper metabolism in adults [according to (18,35)]

Parameters	SI unit	Other unit
Serum copper (adult)		
Men	12.4–20.6 µmol/L	79–131 µg/dL
Women	11.6–19.2 µmol/L	74–122 µg/dL
Ceruloplasmin copper*		>90% of the serum copper
Free serum copper**	<1.5 µmol/L	<10 µg/dL
Ceruloplasmin	0.200–0.600 g/L	20–60 mg/dL
Urine copper	<1.0 µmol/d	<65 µg/d
Liver copper***		<50 µg/g dry weight

*, calculated using the formula: Cp-Cu (µg/dL) = Cp (mg/dL) ×3; **, calculated using the formula: fCu (µg/dL) = Cu (µg/dL) – 3 × Cp (mg/dL), fCu (µmol/L) = Cu (µmol/L) – 53 × Cp (g/L); ***, physiologically extremely elevated in newborns.

diagnoses based on the profile of the diagnostic findings.

Differential diagnoses of Wilson's disease related to findings

Copper metabolism disorders

Deviations in parameters of copper metabolism are not exclusively attributed to Wilson's disease. Complex biochemical processes are involved in copper homoeostasis. Disruptions in these processes lead to separately described diseases contrary to the ATP7B defect. The following explanations regarding the physiology of copper regulation serve understanding them.

Discussion on standard values

Due to the mutation in the *ATP7B* gene, the balance of the key regulators for copper balance—the MNK and WND protein—is disrupted (28). The MNK protein (ATP7A, Menkes protein; located on the basal membrane of the small intestinal enterocytes) is responsible for intestinal copper absorption (29,30) and the WND protein (ATP7B; in hepatocytes) for the hepatobiliary excretion as well as copper uptake in the apoceruloplasmin in hepatocytes (31).

In the blood, reabsorbed copper binds loosely to albumin in relation of one atom per albumin molecule. In the process, special importance is attached to the histidine residue from the albumin for the complex formation with the copper atoms (32). Out of the amino acids in plasma, histidine has the highest affinity to copper (32) and transports it itself in small quantities as copper histidine (33). Furthermore, small quantities of copper are bound in the blood by transcuprein and other peptides (33). Ceruloplasmin, which is excreted into the serum, is formed with the covalent bond of 6–7 copper atoms in apoceruloplasmin (32). Approx. 95% of serum copper is transported to the other organs in this manner (34). There is only a small percentage of "free" serum copper.

The standard values in *Table 3* apply as a means of orientation for intact ATPase 7B.

Given that ceruloplasmin represents the largest copper fraction in serum, the disruption of its synthesis due to a lack of copper uptake (ATPase 7B—defect) results in a severe decrease of the overall serum copper level. Merely marginal shortfalls of the reference range are not indicative of Wilson's disease due to its broad spectrum. Free serum copper is higher because it is released from decomposing hepatocytes without a firm bond to other transport proteins. Another value is a matter of an (empirically) calculated value, which on its own is not very meaningful. This diagnostic finding can only be interpreted in a plausible manner in context with other findings.

Ceruloplasmin has a wide reference range and in the case of Wilson's disease, is decreased to basal values (typically <0.05 g/L) [(36), own data]. The decrease of ceruloplasmin is not 100% sensitive or specific (36). Marginal decreases

are often mistakenly considered an indicator for Wilson's disease. However, these are alimentary, in the case of bile acid synthesis disorders or caused by kidney disorders or individually without pathological significance. Even in the case of heterozygous genetic carriers of the *ATP7B* mutation, there is still sufficient ceruloplasmin synthesis without the clinical manifestation of Wilson's disease. Furthermore, aceruloplasminemia (see below) does not cause any symptoms related to Wilson's disease (37). In conformance with the increase of free copper, daily renal excretion increases to >1 µmol/d. This parameter should be confirmed by being tested twice.

The liver copper content is considered pathological as of a dry weight >250 µg/g (12,38). A representative biopsy specimen is required for a definitive conclusion of the liver biopsy; if applicable, multiple biopsies as a result of non-homogeneous hepatic copper distribution must be conducted (5).

A distinctive pathological profile of the copper metabolism parameter can already be verified prior to the onset of hepatolenticular clinical cardinal symptoms based on the toxic effect of the copper. One single pathological finding with other normal values or merely marginal deviations is not plausible for Wilson's disease. After clinical manifestation, the correlation to the cardinal symptoms (hepatopathy, EPS, KFR) must be tested, to support the validity of the diagnostic/laboratory tests (36).

Cellular enzymatic level

Bound to albumin, the copper is quickly transported to the liver and reaches the hepatocytes via an energy-dependent mechanism (hCtr1, high-affinity copper transporter) (31). Transport, excretion and storage, to maintain copper homoeostasis, are organized within the liver cells.

At the same time, glutathione is the most important cytosolic chelating agent; over 60% are in form of Cu(I)-GSH (14). Copper glutathione [Cu(I)-GSH] is the donator of copper to metallothionein and superoxide dismutase (31). Hepatic copper metallothionein serves as copper storage as well as copper supplier for other proteins (31). To prevent undesired toxic reactions triggered by copper ions, these are constantly escorted intracellularly by various chaperone proteins (chaperones such as HAH1, Cox17, CCS, Sco1/Sco2) (23,39,40).

Hepatic ATPase 7B acts as a central mechanism for copper homeostasis. It is an intracellular copper sensor with redistribution depending on the level (31). In the case of a low level of intracellular copper, the ATPase is located in the Golgi apparatus and communicates the copper uptake into enzymes containing copper, particularly in apoceruloplasmin (31,39). As soon as the copper level increases, it finds its way to the apical position, to ensure biliary copper excretion into the small ducts of the gall bladder (31,41). This complex function is disrupted by the mutations.

Two other intracellular proteins, XIAP (X-linked inhibitor of apoptosis, caspase inhibitor) and MURR1 (Copper Metabolism MURR1 Domain Protein 1, COMMD1), are involved in copper homeostasis (42,43). While MURR1 provokes vesicular compartmentalization and biliary excretion of copper (43), XIAP accelerates its proteasomal degradation through ubiquitination (42). The exact mechanism of the MURR1 effect is still unknown but an interaction with the ATP7B transporter is being discussed (44,45). MURR1 regulates the folding, stability and the proteasomal degradation of ATP7A, ATP7B as well as other proteins (45).

In regard to human pathogens, to date, the ATPases were known in this complex intracellular modulation. In 2012–2013, three new intracellular copper metabolism disorders were described; the MEDNIK syndrome, the Huppke-Brendel syndrome and chaperone deficiency CCS.

ATPases are enzymes (hydrolases) and simultaneously transport proteins, which use energy released through ATP hydrolysis, on a membrane (inside of a cell membrane, membrane-bound organelles) for active transport against a concentration gradient (46). They are substrate specific through a particular chemical and spatial structure and are distinguished in several types (ABC transporters, F-type, V-type, P-type, A-type, E-type among others) according to the substrate and occurrence in the cell or organisms (prokaryotes and/or eukaryotes, solely for bacteria or plants) (47). The formation of a phosphorylated intermediate is a characteristic feature of the P-type transporter, which also includes ATP7A and ATP7B (48).

The P-type ATPase 7B has substrate specificity for copper ions (47-51). Its structure is characterized by ATP binding sites, 8 transmembrane domains and amino-terminal by 6 copper-binding sequences (48,49). It is particularly found in the liver and kidneys, but to a small extent, also in the brain, lungs, placenta, skeletal muscle and pancreas (1,2,49-51). Its gene is located on the long arm of chromosome 13 (13q14-21-Locus) (52) and approx. 7.5 kilobases long. The encoded part for 1,411 amino acids is 4.3 kilobases allocated to 21 exons (33). Homozygous or compound heterozygous mutations lead to Wilson's disease.

There is a strong correlation in the functionally significant

regions between ATPase 7B and ATPase 7A, also a P-type ATPase with copper ion specificity (48,49,53,54). ATP7A is encoded x-chromosomal (Locus X 13.3). It is located in the intestine on the basal membrane of the enterocytes and responsible for copper absorption (23,49,51). Its defect causes Menkes disease (trichopoliodystrophy), which only occurs in boys (49). Disrupted copper-dependent enzymes in the CNS and connective tissue metabolism are responsible for the symptomology. Occipital horn syndrome (OHS; occurrence of occipital exostoses and calcifications) i*s consi*dered a milder variant of the ATP7A defect (55) (*Table 4*).

Remarkably, the ATP7A-associated distal motor neuropathy (X-linked dHMN) does not have any of the clinical or biochemical abnormalities of Menkes disease or the OHS. It resembles Charcot-Marie-Tooth disease type 2. This shows that the ATP7A plays a significant role in maintaining motor neurons. The still unknown pathomechanism of the ATP7A-associated distal motor neuropathy differs from the one in Menkes disease and OHS (55).

From other ATPase—defects, DYT 12 and the Kufor-Rakeb syndrome (PARK 9) with Parkinson's disease or extrapyramidal symptoms must be considered in differential diagnoses (*Table 4*).

It was assumed that Indian Childhood Cirrhosis (ICC) was endemic and unique in India. However, this disease has meanwhile been documented in children on non-Indian heritage (Non-Indian Childhood Cirrhosis, NICC) (65). An autosomal recessive defect of the Cirhin encoding CIRH1A gene was described as North American Indian Childhood Cirrhosis (NAIC) (67). Brewer also recognizes the analogy of ICC to Tyrolean Infantile Cirrhosis (TIC), an epidemic liver disease in children in Austria (3).

Adaptor proteins (AP) regulate the transport of transmembrane proteins and the clathrin-coated vesicles between Golgi apparatus, endosomes and plasma membrane. AP1 is responsible for normal ATP7A, ATP7B and clathrin function. A mutation in the AP1 gene—complex subunit sigma 1A (AP1S1), leads to a dysfunction of the ATP7A and ATP7B despite intact enzyme activities (69). Their mislocation results in dysfunctions in copper metabolism, a reduction of copper-dependent enzymes as well as a lack of copper transport. Patients with MEDNIK syndrome (acronym—see *Table 4*, autosomal recessive inheritance) have combined clinical and biochemical symptoms for Menkes disease as well as Wilson's disease (68).

The autosomal recessive mutation of the copper chaperone CCS (for SOD1) is another dysfunction of proteins for copper metabolism. CCS is responsible for escorting copper in an intracellular manner and for its delivery to Cu/Zn superoxide dismutase (SOD1) (*Table 4*). A lack of CCS leads to a defect of the SOD1 with a lethal outcome (74).

Alimentary disorder

Of the 2–4 mg of copper ingested daily with our food, 0.5–1.2 mg in total is reabsorbed in the upper segment of the small intestine; the rest leaves the body through our stool. As an integral part of at least 16 metalloproteins, copper has essential tasks, in particular in connective tissue metabolism, in the CNS and in haematopoiesis (75,76). Copper is also jointly responsible for enteral iron absorption (77).

Insufficient oral intake as well as malabsorption (e.g. as a result of bariatric surgery) are causes for a copper deficiency (78). An increased zinc uptake [through dietary supplements, denture adhesive cream (79)] also decreases the serum copper level (80). Taking valproic acid leads to a copper deficiency via a not yet clarified mechanism (81). A cause for copper deficiency cannot be found in approx. 20% of all patients; it is idiopathic.

Clinical manifestations of hypocupraemia are a sensorimotor polyneuropathy; damage to the optic nerve as well as the myelon with sensory ataxia and pyramidal tract signs (80,82,83). Blood work indicates microcytic hypochromic anaemia and there is cell dysplasia in the bone marrow (80,82,83). Anaemia, a low ceruloplasmin level as well as dysfunctions of the immune system (neutropenia), pigmentary abnormalities and disturbance of growth are also consequences of secondary iron deficiency (84). Moreover, osteoporosis as well as elevated glucose and cholesterol levels can occur.

A copper overload is rare, up to 10 mg/day are tolerated for longer periods of time. Larger doses of copper salts cause nausea, abdominal cramps and diarrhoea (85). High doses on a gram scale lead to liver and kidney damage, haemolysis, brain damage, coma and death (86,87).

Disorders in the formation of ceruloplasmin

Aceruloplasminemia and low ceruloplasmin

Ceruloplasmin (molecular weight of 151 kDa), an alpha-2-glycoprotein, is encoded on the long arm of chromosome 3 (CP gene, 3q23-q24) (33,34). It is primarily formed in the liver but also to a smaller extent in the brain and can transport up to 8 copper ions (Cu^{2+}) per molecule. Approx. 95% of the serum copper is bound to ceruloplasmin and give it its bluish colour (88,89). In addition to the function

Table 4 Differential diagnoses of ATPases—defects and cellular dysfunctions in copper metabolism

Disease	Age of manifestation/ pathophysiology	Symptoms	Laboratory	Treatment/prognosis
ATP7A mutation (x-chromosomal recessive)				
Menkes disease (56-58) (trichopoliodystrophy)	❖ Intrauterine damage of foetuses → age 0–1; ❖ Enteral copper absorption ↓; ❖ Disrupted copper distribution: elevated in intestines, heart, kidneys and pancreas, low in liver and CNS; ❖ Copper-dependent enzymes ↓: CNS damage, connective tissue disorder	❖ Epileptic seizures (56); ❖ Mental retardation, cerebral atrophy; ❖ At first, sparse and dull (silvery), later kinky and brittle hair (pili torti, trichorrhexis); ❖ Dry skin; ❖ Microgenia; ❖ Funnel chest; ❖ Hypermobile joints; ❖ Muscular hypotonia; ❖ Tortuosity; ❖ Often bladder diverticulum; ❖ Possible fractures	❖ Low: Cu^{2+} and cerulo-plasmin (CPL) in serum not until after 2–8 weeks, urine Cu^{2+} or ↔; dopamine β hydroxylase → noradrenaline still compensated in serum and cerebrospinal fluid (59); ❖ Elevated: beta-2 microglobulin in urine	❖ Copper histidine copper orotate; ❖ Good prognosis possible with residual activity of ATP7A and starting treatment early (55,58); ❖ Solely normalization of copper content; ❖ Neural tube defect, connective tissue disorder not improved; ❖ Usually lethal in childhood, rarely into adulthood
Occipital Horn syndrome (OHS) (60)	❖ Age 3–10; ❖ Milder variant of Menkes disease, rarely CNS involvement; ❖ Copper-dependent enzymes disrupted; lysyl oxidase ↓→ synthesis of collagen↓; dopamine β-hydroxylase noradrenaline↓	❖ Myasthenia; ❖ Calcification; on occipital bone (exostoses = "occipital horn"), of the trapezius muscle, sternocleidomastoid muscle; ❖ Hypermobile joints; ❖ Cutis laxa hernias, bladder diverticulum, tortuosity; ❖ Skeletal abnormalities; ❖ Unmanageable hair; ❖ Autonomic disorders	Low: Cu^{2+} and CPL in serum low or normal	❖ L-threo-dihydroxyphenylserine (L-threo-DOPS); ❖ Hypotonia treatment; ❖ Copper histidine connective tissue disorder not improved; ❖ Prognosis varies; ❖ However, life expectancy is significantly longer than in the case of Menkes disease
X-linked dHMN (61,62) (= distal hereditary motor neuropathy)	Age 5–50, ATP7A-related distal motor neuropathy (55)	❖ Loss of strength; ❖ Distal muscular atrophy; ❖ Peroneal nerve dysfunction; ❖ Axonal nerve lesion	No specific lab results	❖ Copper replacement; ❖ Prognosis unknown
ATP7B mutation (autosomal recessive)				
Wilson's disease	Primarily age 5–45	Hepatolenticular cardinal symptoms: hepatic insufficiency, EPS	❖ Low: Cu^{2+} and CPL in serum; ❖ Elevated: urine copper excretion	❖ Chelating agents: D-penicillamine, trientine; ❖ Zinc acetate/sulfate
Genetics still uncertain, likely autosomal recessive (63,64)				
Indian childhood cirrhosis (ICC) and non-Indian childhood cirrhosis (NICC) (65,66)	❖ From birth – age 3; ❖ Possible genetic disposition for copper-associated liver damage; ❖ CIRH1A—genetic defect (67) (encoded Cirhin); ❖ Copper accumulation in the liver	❖ Cirrhosis of the liver with Mallory-Denk bodies; ❖ Rapid cirrhosis progression → hepatic insufficiency; ❖ No neurological symptoms	❖ Cu^{2+} and CPL in serum normal; ❖ Elevated: cholestatic enzyme profile (total bilirubin); hepatic copper	❖ D-penicillamine (administration before cirrhosis required) reduces lethality (66); ❖ Fatal if untreated

Table 4 *(continued)*

Table 4 *(continued)*

Disease	Age of manifestation/ pathophysiology	Symptoms	Laboratory	Treatment/prognosis
Adaptinopathies (AP1S1 mutation, locus 7q22.1, autosomal recessive)				
MEDNIK (68,69)	From birth – age 1	Mental retardation, enteropathy, deafness, peripheral neuropathy, ichthyosis, keratoderma	❖ Low: Cu^{2+} and CPL in serum; ❖ Elevated: hepatic copper; very long chain fatty acid (VLCFA)	❖ Zinc acetate/sulphate; ❖ Liver disorder treatable; ❖ Neurological deficits persistent
Other ATPase defects with EPS				
DYT 12 (Orphanet) (70,71), autosomal–dominant	❖ Child–adult, age 4–55; ❖ Missense mutations in the *ATP1A3* gene (locus 19q13.2)	Rapid (sudden) onset of dystonia and parkinsonism	Homovanillylmandelic acid ↓ in the cerebrospinal fluid	❖ No treatment; ❖ Life expectancy unchanged; ❖ Quality of life negatively affected
Kufor-Rakeb syndrome (72,73) (rare hereditary variant of Parkinson's, PARK 9), autosomal—recessive	❖ Adolescence, age 10–19; ❖ *ATP13A2* mutation (locus 1p36); ❖ Neuronal lysosomal P-type ATPase: in the CNS, particularly, in substantia nigra, transmembrane transporters; ❖ NBIA (neurodegeneration with Brain Iron Accumulation)	❖ Axially stressed atypical Parkinson's disease with eye movement disorder, pyramidal tract signs, myoclonus, mental disorder; ❖ MRI (T2-weighted): hypointensity in the globus pallidus, putamen, caudate nucleus, indication of iron, accumulation	❖ No particular findings; ❖ Genetic testing	❖ No particular treatment; ❖ Slow progression
Chaperone disorder				
CCS deficiency (copper chaperone for SOD1) (74)	From birth to age 1	Developmental disorder; epilepsy; pericardial effusion; hypotonia	SOD1 activity ↓ (superoxide dismutase 1)	No treatment; infaust

as a copper transporter, it also has a copper-dependent oxidase activity (ferroxidase) (90). The iron oxidation of Fe^{2+} to Fe^{3+} enables its transport by transferrin. As an acute-phase protein, it acts as a strong antioxidant through inhibition of lipid peroxidation (88).

Aceruloplasminemia is a rare autosomal recessive neurodegenerative disease, which usually presents during late adulthood around age 50–60 (91). It belongs to the group of iron accumulation disorders (NBIA, Neurodegeneration with Brain Iron Accumulation) with iron accumulation in the brain, particularly in the basal ganglia and in the liver (92). There is a complete lack of ferroxidase activity in the case of the homozygous mutation (89). The serum indicates a low level of copper and iron with elevated ferritin. Renal copper excretion is normal (93). Neurologically, ataxia, dysarthria, hyperkinesia (tremor, chorea), dystonia as well as Parkinsonism accompanied by depression and cognitive disorders result (94). Anaemia, retinopathy, diabetes mellitus and in some cases, heart failure due to iron overload are internal characteristics (93). The prognosis is determined by heart failure.

Huppke-Brendel syndrome is an autosomal recessive defect of the *SLC33A1* gene for an Acetyl-coA transporter. This leads to a dysfunction of posttranslational ceruloplasmin modification and its decreased secretion into the blood. Before reaching age one, this disease presents with developmental delay, hypotonia, hypacusis, cerebral atrophy, cataract and nystagmus without basal ganglia and liver involvement (95,96). Serum copper and ceruloplasmin levels are low (95,96). The prognosis is poor as there currently is no treatment (96).

The serum ceruloplasmin concentration is severely decreased in the case of Wilson's disease and Menkes disease; also lower in the case of heterozygous trait carriers of

Table 5 Differential diagnosis of icterus [(99-101) refer to further literature]

Disease	Remarks
Inflammatory liver diseases	
Infectious causes—hepatitis B virus	Infection during the birthing process
Non-viral hepatitis—autoimmune hepatitis	Rare, age 5–30
Hepatobiliary excretion disorders	
Progressive familial cholestasis	3 types; genetic disorder in the transport of bile and lipids
Benign recurrent cholestasis	ATPase—mutation; bilirubin↑; good prognosis
Unconjugated hyperbilirubinemia	
Gilbert's syndrome	From age 15–30
Crigler-Najjar syndrome	Manifestation from birth on
Conjugated hyperbilirubinemia	
Dubin-Johnson syndrome	Spontaneous good prognosis
Rotor syndrome	Spontaneous good prognosis
Infantile metabolic disorders with icterus	
Cystic fibrosis (mucoviscidosis)	Mutation of a chloride channel
Tyrosinemia type I	Mutation → fumarylacetoacetase ↓
A1 antitrypsin deficiency	Mutation; proteinase inhibitor deficiency
Bile acid synthesis disorders	
Niemann-Pick disease type C	Autosomal—recessive; approx. from age 6; hepatosplenomegaly; vertical supranuclear palsy; cerebellar disorder, cognition ↓; epilepsy

Wilson's disease (97). Homozygote causes a ceruloplasmin synthesis dysfunction in Wilson's disease, so that there is inactive apoceruloplasmin without ferroxidase activity. On the other hand, the Menkes disease and OHS present a copper absorption disorder as cause for ceruloplasmin deficiency. Ceruloplasmin degradation also occurs in the case of hepatic insufficiency (hepatitis) and protein-losing enteropathy (97). Ceruloplasmin is physiologically low in infancy (98).

Ceruloplasmin elevation

Exogenous causes of ceruloplasmin elevation are copper intoxication, zinc deficiency and taking hormonal contraceptives. Endogenously, ceruloplasmin reacts as an acute-phase protein in the case of inflammation (88) and to hormonal changes (pregnancy). Oestrogens can stimulate its formation (97). Elevations in the serum ceruloplasmin concentration are also reported in the case of lymphoma, Alzheimer's disease and cholestasis. Clinical disorders caused by ceruloplasmin elevation itself are not described.

Differential diagnoses of typical clinical findings

Differential diagnoses of icterus and anaemia

If hepatic findings are made, in particular pertaining to icterus as well unclear anaemia, diseases with primary or possible manifestation in toddlers up to puberty are, in addition to Wilson's disease, significant in regard to differential diagnoses (*Table 5*).

Amongst others, hemoglobinopathies, iron deficiency, lymphatic leukaemia, erythroblastopenia, glucose-6-phosphate dehydrogenase deficiency and autoimmune haemolytic disorders must be taken into consideration in infantile types of anaemia. The occurrence of different forms of anaemia varies greatly. In Europe, iron deficiency anaemia and thalassemia minor represent the majority of all causes for anaemia in children and adolescents (102).

Differential diagnoses of neurological and psychiatric symptoms with manifestation starting in puberty

Unclear symptoms associated with basal ganglia and the cerebellum must be analysed in differential diagnoses for the presence of Wilson's disease, particularly before age 45, in exceptional cases even beyond that. Knowledge of the clinical forms of progression (clinical variants) of Wilson's disease helps recognize deviations in clinical findings (10). *Table 6* summarizes relevant neurological movement disorders at comparable ages of onset such as Wilson's disease.

Particularly unclear cognitive disorders (e.g., worsening of school-based performance) should include the possibility of a primarily psychiatric manifestation of Wilson's disease at puberty age (3,4). The psychopathological spectrum can include all ranges, so that a localization based on differential diagnoses is not possible a priori. An inclusion of extrapyramidal findings in the neurological status is a decisive factor.

Differential diagnoses of the KFR

The KFR is the macroscopically detectable phenomenon of copper deposition in the Descemet's membrane of the cornea.

Table 6 Differential diagnosis of extrapyramidal motor and cerebellar findings [(103,104); refer to further literature]

Disease	Remarks
Differential diagnosis of cerebellar ataxia	
Multiple sclerosis	Including sensory symptoms
Friedreich's ataxia	Autosomal—recessive; approx. from age 20
Ataxia telangiectasia (Louis-Bar syndrome)	Autosomal—recessive; from age 3
Creutzfeldt-Jakob disease	Prion disease
Gerstmann-Sträussler-Scheinker disease	Prion disease
SCA 2, 6, 12	Dominant ataxia symptoms
Niemann-Pick disease type C (105)	Autosomal—recessive; approx. from age 6 ceruloplasmin ↓
Differential diagnosis of Parkinson's disease/tremors	
Juvenile-onset Parkinson's disease (Hunt) (PARK 2)	Before age 45; autosomal recessive
Parkinson's (+)	
Kufor-Rakeb syndrome (PARK 9)	Iron deposition in basal ganglia
ALS Parkinsonism Dementia Complex	Motor deficits, fasciculations
SCA 3 (Machado-Joseph disease)	Including rigor, dystonia, spasticity among other things
Essential tremor	No additional EPS
Westphal variant	Initial hypokinesia
Progressive supranuclear palsy	Usually after age 45
Toxic (MPTP, methcathinone, CO)	
Differential diagnosis of choreoathetoid hyperkinesias/dystonia	
Neuroacanthocytosis (4 types)	Dyskinesias, dementia, acanthocytes
Huntington's disease	Distal hyperkinesias
Focal and generalized dystonia (DYT 3, 12, 16)	Complex of dystonia and Parkinson-syndrome
Fahr's syndrome	Cerebellar and basal ganglionic calcification
NBIA disorders (PKAN, PLAN, BPAN, FAHN)	Iron deposition in basal ganglia
Segawa syndrome	L-dopa response
Medication (antipsychotics)	Tardive dyskinesia and dystonia
Psychogenic	Dystonia, tremor, myoclonus

SCA, spinocerebellar atrophie; ALS, amyothrophic lateral sclerosis; EPS, extrapyramidal movement disorders; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridin; CO, carbon monoxide; NBIA, neurodegeneration with brain iron accumulation; PKAN, pantothenate kinase-associated neurodegeneration (form of NBIA); PLAN, PLA2G6-associated neurodegeneration (form of NBIA); BPAN, beta-propeller protein-associated neurodegeneration (form of NBIA); FAHN, fatty acid hydrolase-associated neurodegeneration (form of NBIA).

They were described as earlier as 1902 by Kayser (106) and therefore, 10 years prior to the publication of progressive lenticular degeneration by Wilson (107). They appear on the edge of the cornea as a brown ring, which is not always closed. They are always mentioned when findings of Wilson's disease are listed in textbooks and are considered a cardinal symptom (108). Nevertheless, there are numerous different aspects in literature. On the one hand, KFR belong to the initial symptoms (109), on the other hand, they are often not present in the early stages of the disease in children (105). In large populations of patients with Wilson's disease with hepatic symptoms, the occurrence of KFR was only reported

in 44–62% of patients (110,111) and they were usually not present in children with liver disease (112). Furthermore, they are more common in the case of the homozygous H1069Q mutation than in compound heterozygous patients at the time of diagnosis (113).

Initially, KFR was considered pathognomonic for Wilson's disease, however, they were rarely found in other liver diseases such as primary biliary cholangitis, chronic cholestasis (114,115) or in children with neonatal cholestasis (116). In regard to differential diagnoses, corneal opacities caused by other diseases, such as galactosialidosis (117), are possible. Other authors also refer to this occurrence in "non-Wilson patients" as pseudo-KFR (115,118). Despite these aspects, KFR are considered a classical ophthalmological manifestation of Wilson's disease, while the sunflower cataract caused by copper accumulation in the lens of the eye is rare (119,120). KFR can fade during decopperising therapy and disappear after years (121).

Differential diagnosis in heavy metal metabolism (manganese storage disease)

The recently recognized manganese storage disease is caused by an autosomal recessive mutation in the manganese transporter gene (*SLC30A10*) (122). It is considered the "new Wilson's disease" with the manifestation of a generalized dystonia in childhood (age 2–14) and asymmetrical Parkinson's disease with early postural instability before age 60 (123,124). The patients also develop liver cirrhosis and in doing so, "mirror" Wilson's disease (92).

Paraclinical findings include polycythaemia, low ferritin, increased total iron-binding capacity and an elevated serum manganese level (122). The basal ganglia show hyperintense lesions on T1-weighted images (122). Therapeutically, calcium-disodium EDTA infusions are used to boost renal excretion of manganese (92,125). This leads to a good neurological improvement if treatment is started in a timely manner (122,125).

Conclusions

If a clinical tentative diagnosis for Wilson's disease is made by allocating the current findings based on a classification scheme, considerations based on differential diagnoses must be taken into account until the genetic information has been ensured. Atypical symptoms as well as deviating progressions also require additional diagnosis. It must be taken into account, that a full presentation is not evident at the time of onset of the disease. As a result, differential diagnoses must be included in the respective clinical findings. An extensive understanding of copper metabolism and known disorders, in addition to Wilson's disease, is significant, in particular for the interpretation of the paraclinical data.

As this overview shows, Wilson's disease fits into a broad spectrum of internal and neurological disease patterns with icterus, anaemia and EPS. Recently discovered disease patterns pertaining to manganese and copper metabolism are relevant after ruling out an *ATP7B* mutation. On the one hand, starting treatment for Wilson's disease early on is required but on the other hand, only a reliable diagnosis justifies treatment, which involves adverse reactions. Starting treatment at an early stage, avoiding wrong medication and the prognostic assessment are also significant for differential diagnoses.

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Footnote

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