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Uncertain pathogenicity of mutations in Wilson gene

Wilson's disease is caused by an autosomal recessive disorder of the hepatic copper transport of ATP 7B. The responsible gene is located on the long arm of chromosome 13. Currently more than 500 mutations are known which in the case of homozygous or compound heterozygous incidence lead to the outbreak of the disease. Adversely affected are the biliary copper excretion and the incorporation of copper in ceruloplasmin. This leads to a toxic copper accumulation primarily in liver and basal ganglia.

Hepatic and extrapyramidal motoric leading symptoms with variable clinic manifestation mainly occur between the age of 5 and 45. Individual cases have been described in the 1st and with later manifestation in the 70th year of life.

In the present case the diagnose could not be confirmed despite genetic evidence of a heterozygous mutation.

Casuistry

A progressive gait disorder began in a 64-year-old female patient. Over time dysarthria (staccato like speech) and dysphagia appeared as well. Differential diagnosis included Wilson's disease and molecular genetics was arranged for.

The genetic diagnosis showed two compound heterozygous mutations in gene ATP7D (Tab. 1). Thereupon Wilson's disease was diagnosed and the D-Penicillamine therapy was initiated. This did not lead to any improvement and was stopped due to incompatibility. Consequently, the diagnosis of Wilson's disease had to be questioned.

Mutation	Amino acid exchange	Inheritance	MAF (%)
Point mutation 1915 C > T	His639Tyr	autosomal - recessive	0.02
Point mutation 3688 A > G	Ile1230Val	autosomal - recessive	0.06

Tab. 1. Mutations present in ATP7B. MAF: minor allele frequency – rarity of a mutation variety; the rarer, the more likely pathogenic.

Diagnosis for verification of the diagnosis

The neurological examinations showed a cerebellar, pyramidical and polyneuropathetic syndrome. Psychopathologically, a depressive disorder was present while the internal findings were unconspicuous (Tab. 2).

Examination	Results
Family history	No neurological disorder No Wilson's disease
Neurological status	Cerebellar syndrome with - delayed saccade initiation, slowed saccadic pursuit - incomplete vertical gaze paresis upward - dysrhythmic tongue motility, dysarthria (staccato like speech), dysphagia - hypotonic muscle tone of the arms - slightly atactical – dysmetric finger – nose – attempt and bradydysdiadochokinesis double sided - heavily atactical knee – heel – attempt double sided, astasia, abasia - truncal ataxie Pyramidal tract syndrome with - vigorous muscle proprioceptive reflexes of the arms, double sided positive finger bend and wrist reflex, double sided positive Léri reflex - unusual abdominal skin reflexes on three levels - slight extension spasm and increased muscle self-reflexes of the legs, double sided inexhaustible patella clonus, double sided positive Babinski polyneuropathic syndrome - sensitive: pallhypaethesia malleolar (4/8), hypesthesia - autonomous: hypohidrosis plantaris Signs of neurodegeneration - glabella tap reflex non-habituating - palmomental reflex double sided positive
Internal findings	Reduced general condition, good nutritional condition, no icterus, no oedemas Abdomen – liver soft, at costal arch free round the kidneys no liver skin signs
Eyes	No Kayser-Fleischer rings
Fine motor test	Handwriting sample: macrography Drawing a spiral: atactic clear lines double sided Tracking – test: atactic clear lines double sided
cMRT	No lesions of basal ganglia Slight accentuation of cerebellum fissures Vascular gliose like white matter lesion
Abdomen sonography	Normal findings for liver, gall bladder, pancreas, spleen, kidneys
Electrophysiology	Sympathic skin response and: correlation with axonal sensitive and autonomous polyneuropathy (legs more affected than arms) MEP to arms and legs: no measurable disorder of the motor tract MSEP: no disorder of the sensitive tract EEG: normal frequency modulated alpha - EEG
Laboratory diagnostics	Blood count normal Liver values: - in the reference area: ALAT, ASAT, cholinesterase, albumin, ammoniac, bilirubin (total) Quick 88 %, INR = 1.09 - reduced: transferrin 1.77 g/l (norm > 2.2 g/l) Kidney values: - in the reference area: Crea, sodium in serum - Urine diagnostics: nitrite and protein negative Copper metabolism: - Coeruloplasmin 0.18 g/l (Norm: 0.2 – 0.6 g/l) - Copper total in serum 10.3 µmol/l (Norm: 11.6 – 19.2 µmol/l) - Free copper in serum 0.67 µmol/l (Norm: < 1.5 µmol/l) - Copper in unrin < 1.0 µmol/d (Norm: < 1.0 µmol/d)

Tab. 2. Diagnostic constellations.

On the basis of the criteria used by Sternlieb und Lössner (Kayser-Fleischer ring, typical neurological symptoms, decreased level of serum coeruloplasmin, increased liver copper, decreased serum copper, increased urine copper) the constellation of clinical and paraclinical results, according to table 2, excludes Wilson's disease.

The absence of a Kayser-Fleischer ring and a normal urinary copper excretion are important arguments against Wilson's disease. The level of coeruloplasmin is only marginally lower and sufficient for normal function. Patients of Wilson's disease have typical levels of < 0.02 g/l. The copper level in the serum has a wide reference range. It too is only slightly decreased and does not justify the diagnosis.

Veritable liver enzymes, intact synthesis and detoxication function including normal ultrasound texture as well as normal clinical findings prove the absence of a hepatic leading pathology.

In the CMRT no basal ganglia lesions (spongious dystrophy of the putamen) which are typical for patients of Wilson's disease can be found.

Summary and Conclusions

1. The patient does not have Wilson's disease despite the compound heterozygous presence of His639Tyr and Ile1230Val in the ATP 7B gene. A late manifestation of Wilson's disease at the age of 64 is rare although it cannot be ruled out. But without hepatolenticular and pathognomonic findings it is not present here.
2. In heterozygous constellation these two pathogenic variants are no evidence of a sufficient functional disorder of ATPase 7B. The mutation His639Tyr was described as probably pathogenic by Gromatzke et al 2005 as well as Braiterman et al 2014. The same is assumed for the second mutation Ile1230Val. It cannot be ruled out completely that the second change Ile1230Val de novo occurred on the same allele.
3. In case of an only marginally reduced level of coeruloplasmin in our patient a sufficient hepatic synthesis of coeruloplasmin (incorporation of copper-ions in apocoeruloplasmin) has to be present despite the two pathogenic changes (mutations). This can support the assumption of both mutations on the same allele or question the pathogenicity of one of the two mutations.
4. In case the presence of variants which are not pathogenic with absolute certainty can be verified a solely genetic diagnosis of Wilson's disease is not sufficient. The clinical constellation of typical and pathognomic findings has to be included in the diagnosis.
5. From a therapeutic point of view a correct diagnosis is essential to justify the therapy with d-penicillamin which has side effects.
6. From a differential diagnostic point of view an SCA of the ADCA I according to Harding should be considered for our patient.

Wieland Hermann
SRO AG Langenthal, St. Urbanstraße 67, 4900, Langenthal, Switzerland

Publication

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