

The interesting case— orphan diseases— double trouble

Ulrike Reuner¹, Wolfgang Stremmel², Ralf Weiskirchen³

¹Department of Neurology, University Clinic Dresden, Technische Universität Dresden, Dresden, Germany; ²Institute of Pharmacy and Molecular Biotechnology, University of Heidelberg, Heidelberg, Germany; ³Institute of Molecular Pathobiochemistry, Experimental Gene Therapy and Clinical Chemistry, RWTH University Hospital Aachen, Aachen, Germany

Correspondence to: Ulrike Reuner. Department of Neurology, University Clinic Dresden, Technische Universität Dresden, Fetscherstr. 74, 01307 Dresden, Germany. Email: Ulrike.Reuner@uniklinikum-dresden.de.

Abstract: With an incidence of 1:20,000–1:30,000, Wilson's disease is regarded as a rare disease. Yet rarer, however, is the co-occurrence of two unrelated orphan diseases in the same patient. By means of two case reports, we would like to illustrate the necessity of an appropriate differential diagnostic evaluation and treatment of these disorders.

Keywords: Wilson's disease; myasthenia gravis; McArdle's disease

Submitted Apr 09, 2019. Accepted for publication Apr 10, 2019.

doi: 10.21037/atm.2019.04.31

View this article at: <http://dx.doi.org/10.21037/atm.2019.04.31>

Case 1: female, 17 years old at the manifestation of the second disease

Wilson's disease was diagnosed at age 11 following the coincidental finding of moderately elevated transaminases. Apart from the elevated transaminases and other Wilson-typical laboratory abnormalities (low serum copper, increased free copper fraction, low ceruloplasmin, elevated basal copper excretion in 24-hour urine) there were no further signs of hepatic or neurological involvement.

Molecular genetic analysis

Detection of two pathogenic heterozygous mutations in the *ATP7B*-gene (exon 13: p.Arg969Gln, exon 14: p.His1069Gln).

Treatment with D-penicillamine (300 mg daily) and pyridoxine supplements (20 mg/week) led to normalization of transaminases and copper balance in 24-hour urine samples.

At the age of 17, the patient developed exercise-induced abnormalities of speech, mouth and tongue motility and swallowing difficulties, which were initially interpreted as a myasthenic reaction due to unwanted side effects of D-penicillamine.

Clinical findings

Dysarthria, impaired tongue motility and dysphagia, but otherwise normal neurological and general medical findings.

Additional investigations

Abdominal ultrasound and Fibroscan were normal, as was a cranial magnetic resonance imaging (MRI). An MRI of the mediastinum showed thymus hyperplasia. 3 Hz-repetitive nerve stimulation revealed a significant decrement in the orbicularis oris (38%) and trapezius (25%) muscle. Autoantibodies were strongly positive against acetylcholine receptors (>5 nM), but negative against titin (MGT-30).

Treatment

In addition to the Wilson-specific treatment (see above), pyridostigmine was added (180 mg immediate-release during daytime, 90 mg sustained-release at night) and entirely abolished the myasthenic symptoms. A robot-assisted endoscopic thymectomy (Da-Vinci-system) was performed and revealed marked lymphofollicular hyperplasia, but no evidence of a thymoma or malignant process.

During the course of the disease, the cholinesterase inhibitors could be reduced and eventually stopped, therefore no immunosuppressive therapy was required. Two years after cessation of the anticholinergic therapy, the patient remains asymptomatic. Despite the continuation of the Wilson-treatment (with D-penicillamine) the patient also remains asymptomatic with regard to Wilson-specific symptoms, both copper balance and abdominal ultrasound/Fibroscan also remain normal.

Diagnoses

- (I) Wilson's disease, molecular proven and clinically asymptomatic;
- (II) Seropositive generalized myasthenia gravis with predominant facio-pharyngeal weakness, asymptomatic after thymectomy even without anticholinergic medication.

Case 2: male, 30 years old at the manifestation of the second disease

Wilson's disease was diagnosed at age 5 following a toxoplasma infection. Despite falling toxoplasma antibody titres, plasma transaminases remained persistently elevated (4 times upper limit of normal) and the hepatosplenomegaly did not regress. Further investigations eventually confirmed Wilson's disease biochemically (low serum copper, increased free copper fraction, low ceruloplasmin, elevated basal copper excretion in 24-hour urine), histologically (perilobular hepatic fibrosis and fatty degeneration) and by radiocopper testing. On treatment with D-penicillamine the transaminase levels eventually dropped, but never returned to normal. The copper balance in 24-hour urine samples was normal. Unfortunately the patient was intermittently non-compliant and developed liver cirrhosis (Child B).

In addition to the moderately increased serum transaminases, also repeatedly elevated levels of CK (43–165 $\mu\text{mol/s}\cdot\text{L}$, reference range $<3.17 \mu\text{mol/s}\cdot\text{L}$) and myoglobin (151–336 $\mu\text{g/L}$, reference range $<72 \mu\text{g/L}$) with only mild myalgias were noted after age 28. There was no muscle weakness and no muscle atrophy. Electromyography (deltoid, vastus lateralis, quadriceps) showed normal recruitment of motor units, normal MUAPs and no pathological spontaneous activity.

Molecular genetic analysis

Detection of two known pathogenic mutations in

the *ATP7B*-gene (exon 14: p.His1069Gln, exon 20: p.Ser1365Cysfs*12). Detection of two known pathogenic mutations in the *PYGM* gene (OMIM: 608455): p.Arg50-to-ter(het) and p.Gly686Arg (het).

Diagnoses

- (I) Wilson's disease, molecular proven and clinically asymptomatic on treatment. By abdominal ultrasound and Fibroscan there was evidence of liver cirrhosis (stable over several years);
- (II) McArdle's disease (glycogenosis type V), molecular proven and with mild clinical course. A specific therapy is not available for McArdle's disease.

Take-home message

Rare diseases are rare, but nevertheless it is possible that two independent orphan diseases may co-exist at the same time in the same person. If the clinical findings do not appear plausible, a thorough diagnostic assessment is mandatory, because relevant or even causal therapeutic approaches may ensue as illustrated by case 1. Or else, as shown by case 2, only the correct diagnostic classification will permit an optimal management of the disease in the patient and adequate genetic counselling of the patient's family, thereby allowing the transfer of knowledge about respective genetic aspects of illnesses between trained professionals with those who are at risk or having a heritable disorder that can be passed on to their unborn offspring.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Informed Consent: Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

Cite this article as: Reuner U, Stremmel W, Weiskirchen R. The interesting case— orphan diseases—double trouble. *Ann Transl Med* 2019;7(Suppl 2):S74. doi: 10.21037/atm.2019.04.31