

Wilson's disease – a six year long journey to a positive diagnosis

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Abstract. Progressive, adult-onset development of intricate signs for neurological deficit might be highly misleading, to the point of delaying positive diagnosis several years, costing valuable loss in efficiency for available treatment. Careful history and differential diagnosis led us from the referred motor neuron disease to the positive diagnosis: Wilson's disease.

Key Words: Wilson's disease, adult-onset, case report

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Introduction

Hepatolenticular degeneration, or Wilson's disease is an inherited, autosomal recessive disorder, affecting essentially the liver and central nervous system, but many other organs might be involved. The affected structures show functional and architectural changes given by the deposits of copper, which build up due to the lack of function of the ATP7B gene (Bandmann et al 2015). The mentioned gene encodes a membrane polypeptide responsible with copper transport, exporting copper from cells, to bind with apoceruloplasmine, and eventually to be eliminated (Bull et al 1993). Several mutations of the gene are described – twenty five allelic variants, causing different phenotypes, with higher or lesser severity. One in one hundred persons are carriers of a mutation, but disease prevalence reaches only 30 cases per million in the population; on the other hand, a minority of cases lack any known mutation (Cox et al 2005).

The disease gets to be diagnosed early during its course, usually in the first decade, if liver symptoms dominate. Second or third decade presentation is often characterized by neuro-psychiatric symptoms (Seniow et al 2002). This is sometimes misleading, because deficits caused by the disease might mimic symptoms and signs of other pathologies also. This was the case with our patient also (Loudianos et al 2000).

Treatment of the disease is oriented towards reduction of copper levels and symptomatic control.

Reduction of copper starts with limitation of its intake, by dietary adjustments, for example by avoiding shellfish, nuts, chocolate etc.

The base of the pharmacological treatment is represented by copper chelating drugs, the best known being D-penicillamine, but triethylenetetramine dihydrochloride and tetrathiomolybdate are

also promising derivatives. These drugs form stable complexes with copper and are eventually eliminated from the body along with the metal (Lorincz 2012). Another possibility is dimercaprol, but this requires periodical intramuscular injections, and the side effects profile is less tolerable.

After the copper levels are stabilized, Zn acetate treatment might be applied, this prevents absorption of copper by influencing metallothionein, an intestinal protein capable of binding copper. In case of severe hepatic disease, liver transplantation constitutes a risky but feasible approach; still it doesn't influence neurological signs.

Regardless the treatment option, if the symptoms already installed, little improvement is to be expected. This underlines the importance of early diagnosis (Brewer et al 2010).

Symptomatic pharmacological treatment improves slightly the quality of life in neurological manifestations (muscle relaxants, neuroleptics, anti-Parkinson drugs, benzodiazepins etc.). Physical therapy should also not be overlooked, in order to maintain an acceptable mobility of the patient (Lorincz 2010).

Case presentation

Clinical data

A 33 year old female patient presents with progressive spastic paraparesis, difficulty swallowing and speaking. The patient has a slowly developing history of around four years already; at this point she almost loses the capacity to walk independently (2-3 steps).

Interestingly, the first reported event in her disease course was a lower limb thrombophlebitis, which occurred in 2009; it was successfully treated with anticoagulant therapy. The exact underlying mechanism of her thrombosis was never properly

established, antiphospholipid syndrome and lupus were suggested (slightly raised anti double stranded DNA antibodies, and anticardiolipin antibodies – never reproducible since then), but even these results were obscured by the fact that she was then also under continuous birth-control treatment for two years already. Probably this episode has no real connection with the developing neurological disease, still, as the latter slowly uncovered, it represented a misleading element.

Afterwards, as the neurological signs occurred and became severe, she underwent several investigations, in six different centers, all of which raised different diagnostic possibilities: amyotrophic lateral sclerosis, multiple sclerosis, lupus erythematosus with neurological manifestations, antiphospholipid syndrome. There was no improvement of the existing symptoms, moreover, the disease seemingly progressed, even when she underwent several treatment approaches, including immunosuppressive drugs like prednisone, methotrexate.

At the neurological examination we've found tetraparesis, with the predominance of paraparesis, MRC scores were 3/5 for the lower limbs, better for the upper limbs. She presents no involuntary movements. Right long-beat nystagmus and convergence deficit on one hand, and difficulty swallowing, especially liquids, were present in the sphere of cranial nerves. Standing was possible, walking only a few steps, with assistance. The patient presented also diffusely hypertonic musculature but marked spasticity of the lower limbs. As for coordination, she had expressed dysmetria, more pronounced on the left side. Clonoid reflexes, clonus and spontaneous bilateral Babinski sign completed the clinical picture. Her speech was seemingly explosive. The patient showed bradypsychia, and alternation of disposition, sometimes accompanied by laughter or crying without an identifiable target or trigger.

From the above presented data one might identify pathologic signs affecting several systems, mainly central motor pathways.

Laboratory values

Usual laboratory values in normal range, including erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), and also liver function.

Anti DNA antibodies normal (one value of 45.5 UI/ml in 2011, never raised again since), anti-nuclear antibodies (ANA), even the extended ANA panel were negative, antiphospholipid antibodies positive at one examination (anti-cardiolipin antibodies aCL = 12.1, low positive).

Normal CSF, including immunology, negative for oligoclonal bands.

Negative for chronic hepatitis B, C, HIV, for *Borrelia burgdorferi* infection and a VDRL test found to be also negative.

She was negative for antibodies against serum NMDA receptor.

Copper metabolism:

Serum ceruloplasmine 61 IU/ml, 13.2 mg% (Normal range: 70-125 IU/ml, 15-35 mg%)

Serum copper 71 microg/dL (Normal range: 80-155 microg/dL)

Urinary copper 92 microg/24h (Normal range: 15-70 microg/dL)

Electrophysiology

Electroencephalography (EEG) showed no significant lesional or irritative changes.

Electroneurography (ENG) of the ulnar and median nerves showed parameters within normal limits, on both sides; peroneus nerve had a slightly altered F-wave on the right side, possibly indicating an L4-5 radiculopathy. Sensitive conduction was without any alterations.

Electromyography (EMG) performed at the right vastus lateralis, left deltoideus, right first dorsal interosseus muscle and mentalis muscle in normal limits.

Visual evoked potentials (VEP) using the pattern reversal technique revealed normal morphology, presence of the N75 and P100 components, with physiological parameters on both sides. Brainstem auditory evoked potentials (BAEP), recorded using the condensation technique, were also in normal limits.

Somatosensory evoked potentials (SSEP), evoked by stimulating the medianus nerve, showed the Erb, cervical and cortical response in normal limits; tibialis SSEP recorded cortically in normal ranges, slightly asymmetrical, minimally prolonged on the left side.

Imagery

Several investigations were made during the disease course, head, cervical, dorsal, lumbar MRIs, abdominal, cardiac and neck ultrasonography, chest X-ray. Pathological changes were noticed on the head MRI, revealing a medial hyperintensity of the pallidum, slight atrophy of the mesencephalon and pons mostly on the right side, "Giant Panda face" sign (see left), and when completed with angiography, discrete hypoplasia of the right sigmoid and transverse sinuses.

Another change was a left C6-C7 disc protrusion, without recommendation for neurosurgical approach (see below).

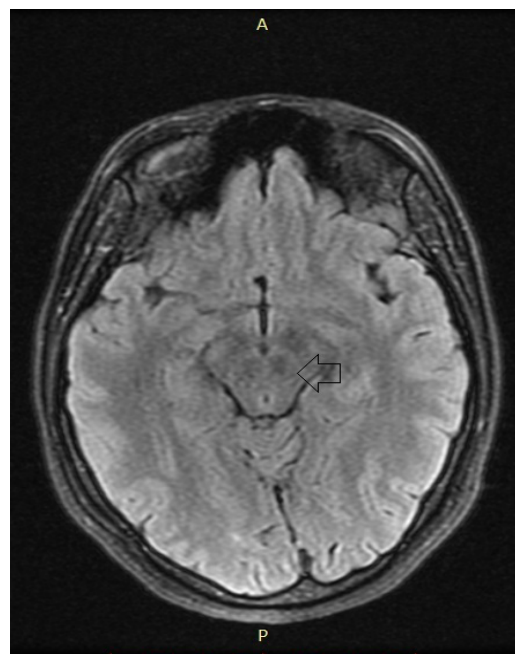


Figure 1. – Head MRI – “Giant panda face” – indicated with arrow

Abdominal and cardiac ultrasonography and chest X-ray were normal. A previously performed neck ultrasonography revealed a nodular struma, for which she already underwent surgery, histopathology being benign; she's since under hormone replacement therapy.

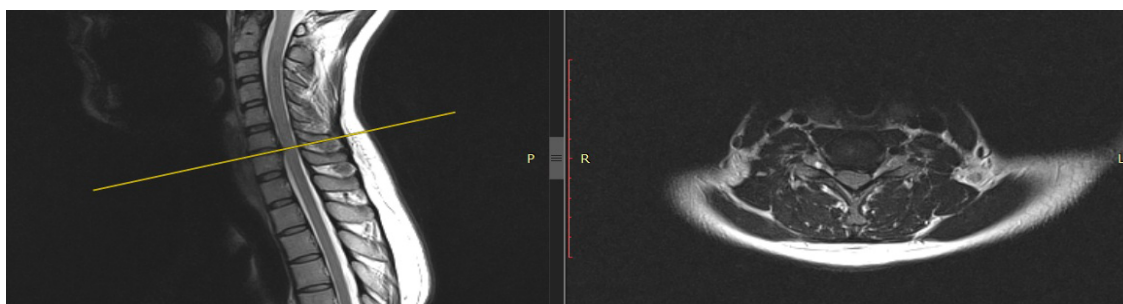


Figure 2. – Cervical spine MRI – C6-C7 discal protrusion

Other examinations

Ophthalmological assessment: she was negative for Kaiser-Fleisher ring.

Discussion

The case just presented was investigated in six different hospitals already, one abroad, without positive diagnosis. She was referred to us in order to examine the possibility of a motor neuron disease. Our first impression found this possibility improbable, the diagnosis being highly unlikely, given mostly the age of the patient. Still, we have performed the clinical examination and found no muscle wasting, no fasciculations, and the electromyography without significant and suggestive pathological change. The same observation – age, sex – and the clinical picture – progressive neurological deficits – suggested the possibility of a demyelinating disease. Several MRI investigations – performed on the whole extent of the central nervous system – failed to demonstrate suggestive lesions, she was negative for oligoclonal bands, she had no suggestive alterations of the evoked potentials, so the diagnosis was not sustained by the laboratory and the other investigations, moreover these elements were rather suggestive for hepato-lenticular degeneration (Hermann *et al* 2002).

Inflammatory or compressive myelopathy was also excluded considering on one hand imagery – the C6-C7 protrusion was not significant enough and doesn't cover the whole clinical picture – see voice, speech, coordination; on the other hand there were no laboratory signs of inflammation.

Antiphospholipid syndrome was not ruled out, still, its presence is questionable; on the other hand, the association of Wilson's disease with antiphospholipid syndrome is known, and was presented already in the literature (Atanassova *et al* 2006).

Neurolupus was suggested at a point as a possibility, but neither the clinical presentation, nor the imagery – no suggestive vasculitic signs on angio MRI – supports the diagnosis. Furthermore, all the specific antibodies were negative, which reduces this possibility even more.

She was never investigated for metabolic diseases, signs occurred in her third decade of life, motor system was mainly affected, and psychiatric symptoms just uncovered. These elements, together with the “Giant panda face” sign on the head MRI suggested the possibility of Wilson's disease, and we have investigated her accordingly, copper metabolism being suggestively influenced (see above). Abdominal ultrasonography was normal, this is the reason we have decided to postpone liver biopsy; the patient presented no Kaiser-Fleisher ring also – this is not a really peculiar feature, several cases are presented already

in the literature (Ross *et al* 1985; Demirkiran *et al* 1996). The most important prove for the positive diagnosis was that the reevaluation after six months of treatment (dietary changes, D-penicillamine and Zn acetate) showed no further deterioration and even a slight improvement of gait, she was able to walk a few more steps. Blood samples were taken for genetic testing and sent in a reference laboratory for Wilson's disease in Vienna, Austria. The results are not available yet, these will probably give us the definite support for the diagnosis.

Conclusion

Our case was referred as a motor neuron disease, after several inconclusive diagnostic steps. The careful investigation revealed another entity instead, Wilson's disease, but the positive diagnosis came after four years of continuous and possibly irreversible degradation. Wilson's disease should never be overlooked as a possibility, especially when other diagnostic quests fail.

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