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Case report

Multiple sclerosis and Wilson disease: A rare coincidence

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1. Introduction

Wilson's disease is an inherited disorder in which defective biliary excretion of copper leads to its accumulation, particularly in liver and brain. WD is caused by a mutation in the ATP7B gene located on chromosome 13, which encodes a copper-transporting P-type ATPase residing in the trans-Golgi network of hepatocytes. ATP-ase7B is involved in copper transport in the trans-Golgi network in hepatocytes and the incorporation of copper into the apoceruloplasmin [1,2]. Several studies indicate that iron (Fe), copper (Cu) and other trace metals are involved in the pathogenesis of various neurodegenerative disorders including the demyelinating disorder MS [2]. Demyelination in MS is presumably associated with autoimmune reactions however progression of the disease seems to be influenced by oxidative stress, since the invasion of immune cells is accompanied by release of soluble factors including cytokines and ROS leading axonal loss. On the other hand excessive levels of free Cu and Fe ions may catalyze the formation of reactive oxygen species (ROS) [2]. We report a 44 year old male patient initially diagnosed as MS, who additionally developed typical WD proven with liver biopsy and genetic testing.

2. Case report

A 42-year-old man with no previous medical history presented with a 5 day history of numbness in right side of his body and face and right arm weakness. His neurologic examination was remarkable for impaired pain and crude touch sensation in the right side of body and slightly weakness on right arm. Additionally deep tendon reflexes were brisker on right arm and leg. Extrapyramidal system examination revealed normal findings. Brain MRI demonstrated multiple white matter high signal lesions on T2 and FLAIR images in corpus callosum, periventricular regions and cervical spinal cord without gadolinium enhancement suggestive for demyelinating disorders (Fig. 1A). Patient's symptoms gradually resolved with intravenous methylprednisolone treatment. He was asymptomatic for 2 years until he experienced his second relapse which presented with double vision and unsteady gait. MRI revealed a new area of abnormal signal intensity in the subcortical white matter of the right frontal lobe and in the left side of pons (Fig. 1B). The cerebrospinal fluid (CSF) examination revealed normal cell numbers and protein concentration while CSF was positive for oligoclonal bands. Also the patient was checked for anti-MOG and anti-AQP4 antibodies. And there were no antibodies against MOG and AQP4.Therefore, the patient was diagnosed as definite MS according to the 2010 McDonald criteria. Baseline liver enzymes, thyroid function tests and complete blood count tests were within normal limits. IFN beta-1a (44 mcg subcutaneously three times per week) was initiated. Liver function tests gradually elevated during interferon treatment and did not reach normal levels despite discontinuation of therapy. Liver ultrasonography revealed surface nodularity and heterogeneous echotexture and liver biopsy was performed by courtesy of gastroenterology consultation. Liver biopsy exhibited histological findings of cirrhosis which stained with rhodanine. 24 -h urinary excretion of copper was 112 µg/24 h (normal range: 3–35 µg/24 h), ceruloplasmin was 26.5 mg/dl (normal range: 22–58 mg/dl) and serum copper was 93 µg/dl (normal range: 70–160 µg/dl). Furthermore dried liver tissue copper level was 436 µg/g (normal range: 15–55 mcg/g in dry tissue). Kayser–Fleischer rings were detected on ophthalmological examination. Patient experienced hepatic encephalopathy periods several times. Repeated MRI revealed basal ganglia hyperintensity on T1 weighted images (Fig. 1 C). Also WD diagnosis was confirmed with genetic testing. When the ATP7B gene was analyzed, the patient proved to be homozygous for c.2333 G > T (p.Arg778Leu). It was also learned that no one in the family suffered from WD.

Consequently liver function tests reached normal levels after diet

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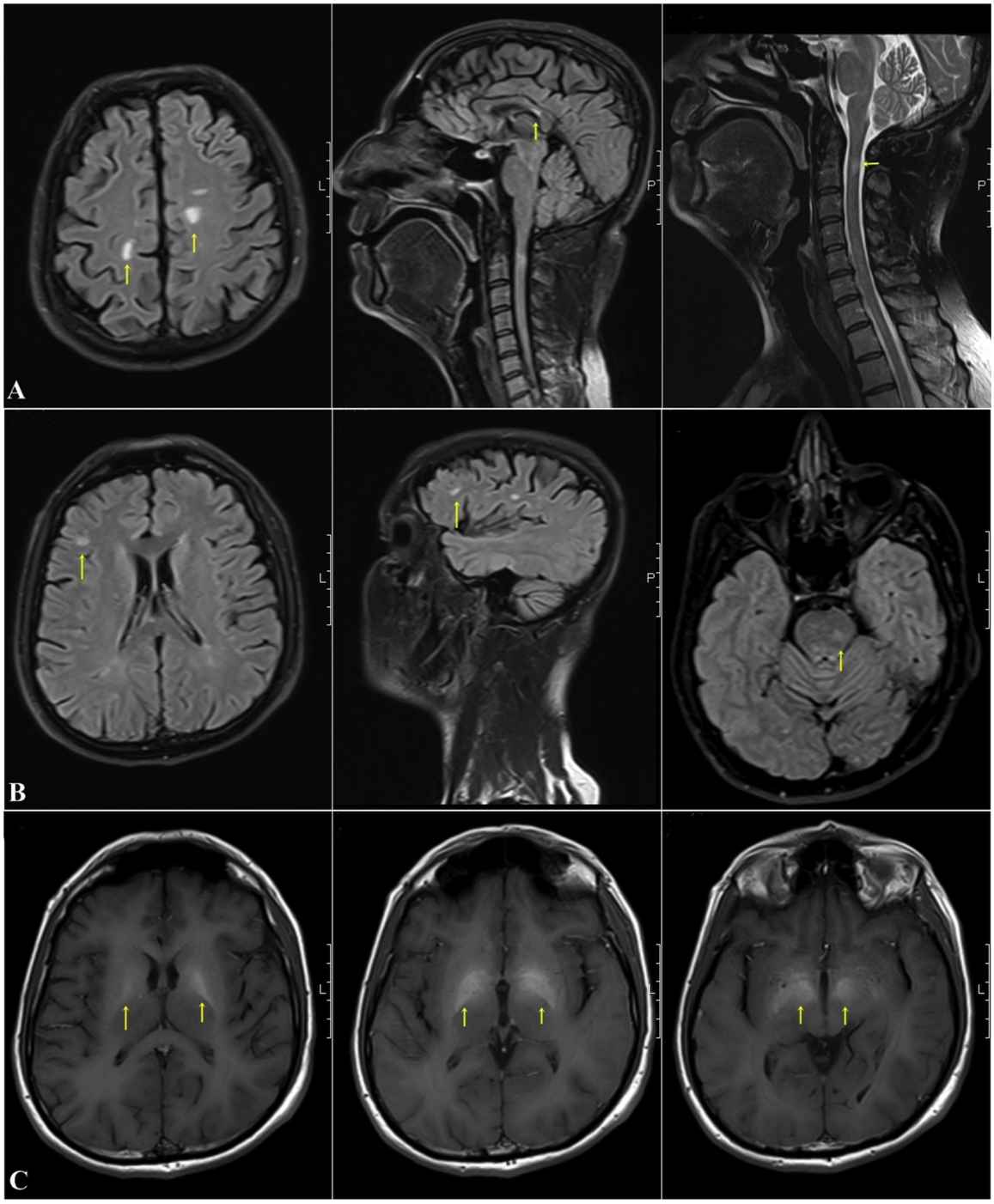

Fig. 1. Initial brain MRI revealed multiple white matter high signal lesions on T2 and FLAIR images in corpus callosum, periventricular regions and cervical spinal cord without gadolinium enhancement suggestive for demyelinating disorders (A).
MRI revealed a new area of abnormal signal intensity in the subcortical white matter of the right frontal lobe and in the left side of pons (B).
Repeated MRI revealed basal ganglia hyperintensity on T1 weighted images (C).

and chelation therapy via D-penicillamine however fasting blood glucose levels were elevated indicating diabetes mellitus. Afterwards glatiramer acetate (GA) was initiated by monitoring liver function tests closely. GA is well tolerated without any side effects including liver toxicity and patient has no evidence of disease activity in terms of relapse, MRI activity and disability progression for four years with GA and GA treatment is still ongoing. Recent neurological examination revealed normal findings except slightly impaired tandem walk.

3. Discussion

Here we present a case of MS patient developing liver failure several weeks after initiation of IFN beta treatment. To our best knowledge it is the fourth case demonstrating the co-occurrence of MS and WD. Günther P. et al. reported first case that was diagnosed with a hepatic form of Wilson's disease at age 12 and with multiple sclerosis at age 38 [3]. And Dzieżyc K. et al. reported two patients initially diagnosed as MS and subsequently WD [1]. Likewise our case, liver failure was unmasked by interferon treatment in one of the cases and did not

presented any neurological symptoms of WD.

In the brain, copper toxicities leads to neuronal degeneration and astrocyte changes, probably due to hyperammonemia with the occurrence of pathologic astrocytes and astrogliosis. Oligodendrocytes are more sensitive to oxidative and nitrative stress in vitro than are astrocytes and microglia, seemingly due to a diminished capacity for antioxidant defense. Multifocal demyelination areas were previously demonstrated in autopsy studies in patients with WD. Oxidative and nitrative stress might therefore result in vivo in selective oligodendrocyte death, and thereby demyelination [3].

In our case, patient experienced two relapses prior to the WD diagnosis and did not experience any relapses after initiation of cupper chelation and later on GA treatment while EDSS remain stable during 4 years follow-up. This stable course of MS can be either explained by immunomodulatory effect of D-penicillamine or the altered immune function of hepatocytes during the natural course of WD. Anna Członkowska's early study revealed previously untreated patients with WD showed an exaggerated humoral immune response, however after D-penicillamine treatment the humoral and cell-mediated response returned to almost normal levels [4]. Hence D-penicillamine may act as an immunomodulatory agent which could slow down the course of MS likewise zinc. It has been well demonstrated that matrix metalloproteinases (MMPs) play an important role in the immunopathogenesis of MS, in part through the disruption of the blood–brain barrier and the recruitment of inflammatory cells into the CNS. Norga et al. [5] has shown that a MMP inhibitor D-penicillamine inhibits acute and chronic relapsing experimental allergic encephalomyelitis in mice.

On the other hand hepatocytes, the major parenchymal cells in the liver play a crucial role on activating innate immunity by secreting wide variety of innate immunity proteins including pro-inflammatory mediators (e.g. interleukin (IL)-6, IL-22, IL-1b and tumor necrosis factor-a). It can be postulated that hepatocyte injury induced by excessive levels of cupper may hamper the immune functions of hepatocytes and consequently immune system may be suppressed. Additionally free copper in blood, which is increased in serum in WD patients, could cause immunosuppressive effect on T-cells [1].

In conclusion, although WD and MS are different diseases, they may have some effects on each other when they rarely appear in the same individual. In addition to immune-mediated demyelination in the pathophysiology of MS, elevated levels of copper in the central nervous system contribute to neurodegeneration. As WD progresses, the progression of MS may be slowed down by multisystemic immunosuppressive effects of copper as well as the immunomodulatory effects of drugs in the treatment of WD such as D-penicillamine. GA or another non-liver metabolized disease modifying drug may be a suitable treatment option for individuals with MS and WD.

Consent

A written informed consent was obtained from patient.

Declaration of Competing Interest

All of the authors have no conflict of interest.

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