Wilson's Disease Complicated with Massive Cerebral Infarction：A Case Report

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Abstract

Hepatolenticular degeneration, also known as Wilson's disease, is an autosomal recessive disorder of copper metabolism that causes rare diseases with significant morbidity and mortality. To our knowledge, no cases of hepatolenticular degeneration with massive cerebral infarction have been reported up to now. Here we present a case of hepatolenticular degeneration with massive cerebral infarction. Early, appropriate diagnosis and initiation of proper therapy could avoid further progression and reduce complications of the disease.

1. Introduction

The pathogenicity gene of WD is located in human chromosome 13[1], and the expressed product is p-type ATPase(*ATP7B*) involved in copper transport across membrane. The main clinical features are liver disease and neurological symptom[2]. The excretion of copper from biliary tract and its binding to ceruloplasmin are impaired,and then copper accumulates in the liver. When the liver's ability to store copper is exhausted, the copper is transported to the blood in the form of "free" copper (does not bind to ceruloplasmin) and deposits in organs and tissues such as the brain, heart, kidney, muscle and bone, causing extrahepatic copper toxicity, causing all sorts of clinical symptoms. The main changes in the brain are spongy degeneration, demyelination and gliosis caused by abnormal deposition of copper in the brain Parenchyma, which may involve putamen, caudate, thalamus, midbrain, Pons, etc[3], leading to extrapyramidal symptoms dominated by a variety of neurological symptoms. The levels of copper in brain tissue and cerebrospinal fluid (CSF) increased by a factor of 10. The toxicity of CSF is related to many mechanisms, such as mitochondrial toxicity, oxidative stress, membrane damage, DNA cross-linking and enzyme inhibition. Excess copper is initially absorbed and buffered by astrocyte and oligodendrocyte, but eventually leads to blood brain barrier dysfunction and demyelination. Wilson's disease with massive cerebral infarction is extremely rare[4].

Cerebral infarction, also known as ischemic stroke, mainly refers to a type of syndrome in which the blood supply in brain tissue stops or stops suddenly, resulting in hypoxia, ischemic necrosis in corresponding blood supply area, and corresponding nerve function defect. The main clinical features of large area cerebral infarction are contralateral complete hemiplegia of the lesion, hemidysesthesia and gaze palsy of the contralateral lesion were dominant. The symptoms will reach the peak within 6 hours or 6–24 hours after the onset of the disease, and the condition of the disease will become progressively worse, easy to appear obvious signs of brain edema and intracranial hypertension, and even brain herniation death.

A case will be presented in the following to provide reference for clinical diagnosis and treatment.

2. Case Presentation

2.1 History

A 19-year-old male was admitted to the Department of Encephalopathy in the First Affiliated Hospital of Anhui University of Traditional Chinese medicine in March 2018 due to "unclear speech, limb torsion for 16 years, sudden unable to speak, left limb weakness for 5 days ". The patient's sister died of Wilson's disease. The patient's vital signs were as follows: blood pressure, 110/70 mmHg; pulse rate, 80/minutes; respiration rate, 19/minutes; and body temperature, 36.6 °C. Conscious, unresponsive, lack of cooperation in physical examination, dysarthria, neck was rigid, K-F rings (+). All extremities muscle force were V grade. The muscle tension of the left limbs is decreased and reflexes reduced. The muscle tension of the right limbs is increased like a lead-pipe and hyperactivity of reflexes, right Babinski's sign (+).

2.2 Laboratory examination

The laboratory tests are as follows:CER:0.079 g/L(normal value 0.2–0.6 g/L); CP:0.01(normal value 0.26–0.59 vigor unit/L); Blood Routine: HGB 136 g/L, RBC 4.30×10^{12}/L, WBC 6.72×10^{9}/L, PLT 68×10^{9}/L;FIB 6.09 g/L; Serum Five elements: Cu 2.55 μmol/L, Ca 3.07 μmol/L, Fe 66.39 μmol/L; Urine 5 elements: Cu 932.18 μg/24 h, Zn 6031.84 μg/24 h, Ca 269.20 μg/24 h, Fe 5349.55 μg/24 h; CRP 18.95 mg/L; Blood Biochemistry: ALT 99 U/L, AST 78 U/L, TP 52.1 g/L, ALB 33.2 g/L, GLO 18.9 g/L;hs-CRP:18.95 mg/L(normal value 0–3 mg/L). Patients with rheumatic series, myocardial zymogram, full set of autoantibodies, triple myocardial infarction, anticardiolipin antibodies(ACA), electrolytes were not significantly abnormal.

2.3 Gene detection

Genetic detection: A homozygous nucleotide variation in the patient's ATP7B Gene c.2333G > T (coding region 2310 from C to G) that did not result in a change in the 770 amino acid Leu (p.Leu 770Leu), it is synonymous mutations .A homozygous variant of C. 2333G > T (coding region 2333 from G to T) that causes the mutation of Amino acid 778 from Arg to Leu (P.Arg778Leu), it is missense mutation(Fig. 1), which may affect the function of the protein. The father of the patient is heterozygous at the above sites. The patient and his father's gene are shown in Fig. 1

2.4 Neuroimaging

MRI enhancement of the brain: Consistent with hepatolenticular degeneration, right frontotemporal and parietal cerebral infarction to be discharged, chronic sphenoid sinusitis(Fig. 2);MRA: no obvious abnormity(Fig. 3).

Combined with patient history, family history, blood, MRI examination and genetic detection. According to "Wilson's disease: Clinical practice guidelines of the Indian National Association for Study of the Liver, the Indian Society of Pediatric Gastroenterology, epidemiology and Nutrition, and the Disorders Society of India"[5], he was diagnosed with Massive cerebral infarction (acute phase) and Wilson's disease.

3. Discussion

Any pathophysiological process leading to blood supply disorder of brain tissue may lead to stroke. The most common cause is cerebral artery disease, such as atherosclerosis, inflammation and artery dissection. In addition, the thrombus in the heart or extracranial vessels may transfer to the cerebral vessels and lead to cerebral ischemia.

The patient was 19 years old and lacked traditional stroke and young stroke related risk factors such as atherosclerosis, hypertension, diabetes, atrial fibrillation, heart disease, patent foramen ovale and positive-anticardiolipin antibody et al. He just had a family history of Wilson's disease.

The mechanism of Wilson's disease with massive cerebral infarction is not clear, and may be related to the following reasons: When the accumulation of Cu in the body exceeds the load capacity of various organelles containing copper protein in the tissues, unbound or loosely bound copper can induce oxidative stress and/or exert its toxicity through directly inhibited protein function[6]. The production of reactive oxygen species (Ros) far outpaces the removal of intracellular antioxidant defenses, the accumulation of free radicals leads to oxidative stress, which leads to damage or even apoptosis of brain cells, in turn leads to neurologic deficits. After oxidative stress occurs, ROS also triggers the release of Metalloproteinase-9 (MMP-9) through neurons, glial cells and endothelial cells, thereby digesting the endothelial basal layer and damaging the blood-brain barrier (BBB). The destruction of BBB can directly change the physiological neuron environment, and then cause neuroinflammation, brain edema, and aggravate the ischemic injury of brain tissue[7]. Patients with reduced platelets can significantly activate adhesion molecules and damage endothelial cells, which in turn activates neutrophils, macrophages, and microglia, which are expressed as increased levels of serum intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), both of which can directly damage endothelial cells and cause local brain tissue ischemia[8]. FIB increases, and FIB promotes the accumulation of Vascular smooth muscle cells and lipids, and contributes to the formation of arteriosclerosis plaque, which increases the formation and development of thrombus[9]. Patients with low ALB, the liver is activated by a compensatory increase in albumin, which is involved in the conversion of Arachidonic acid to thromboxane A2(TXA_2) in the blood. Normally, albumin binds to AA, and when albumin is reduced, the combined AA reduced, and free AA is further converted to TXA_2, which enhances platelet aggregation and promotes thrombosis. High-sensitivity C-reactive protein is a marker of inflammation and a direct factor inducing arterial thrombosis[10].The increase of hs-CRP can activate the complement system to act on endothelial cells to produce oxidative stress reaction, induce monocyte to produce procoagulant activity, promote the formation and development of thrombus in artery. In this patient, there were over deposition of Cu, thrombocytopenia, decrease of ALB ,increase of FIB and hs-CRP, decrease of ALB, it may lead to massive cerebral infarction through the above mechanism.

4. Conclusion

This case study suggests that Hepatolenticular Degeneration patients may have the related clinical symptoms and other neurological symptom, such as imaging manifestations of ischemic stroke. It is

suggested that clinicians should take the possibility of cerebral infarction into account when patients have neurological deficit symptoms, and neuroimaging examination should be carried out for such cases. Because large-area cerebral infarction with WD patients are relatively rare, so the pathological mechanism is unclear need to further study.

List Of Abbreviations

Wilson's disease WD

cerebrospinal fluid (CSF)

blood-brain barrier (BBB)

Metalloproteinase-9 (MMP-9)

thromboxane A2(TXA_2)

intercellular adhesion molecule-1 (ICAM-1)

vascular cell adhesion molecule-1 (VCAM-1)

Declarations

Ethics Approval and consent to participate

Not applicable.

Consent for Publication

Because the patient does not have the ability to write, the patient's father will sign the consent form instead. To be completed by the patient's father: I give my consent for all or any part of this material to appear in Journal of Neuroinflammation and all editions of Journal of Neuroinflammation, and any other works or products, in any form or medium.

Availability of Data and Materials

Authors do not wish to share the data because the case has been filed by the hospital and can not be viewed at will.

Acknowledgements

All authors contributed equally to this study.

Authors’disclosure of potential conflict of interest

No potential conflicts of interest relevant to this article were reported.

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Figures

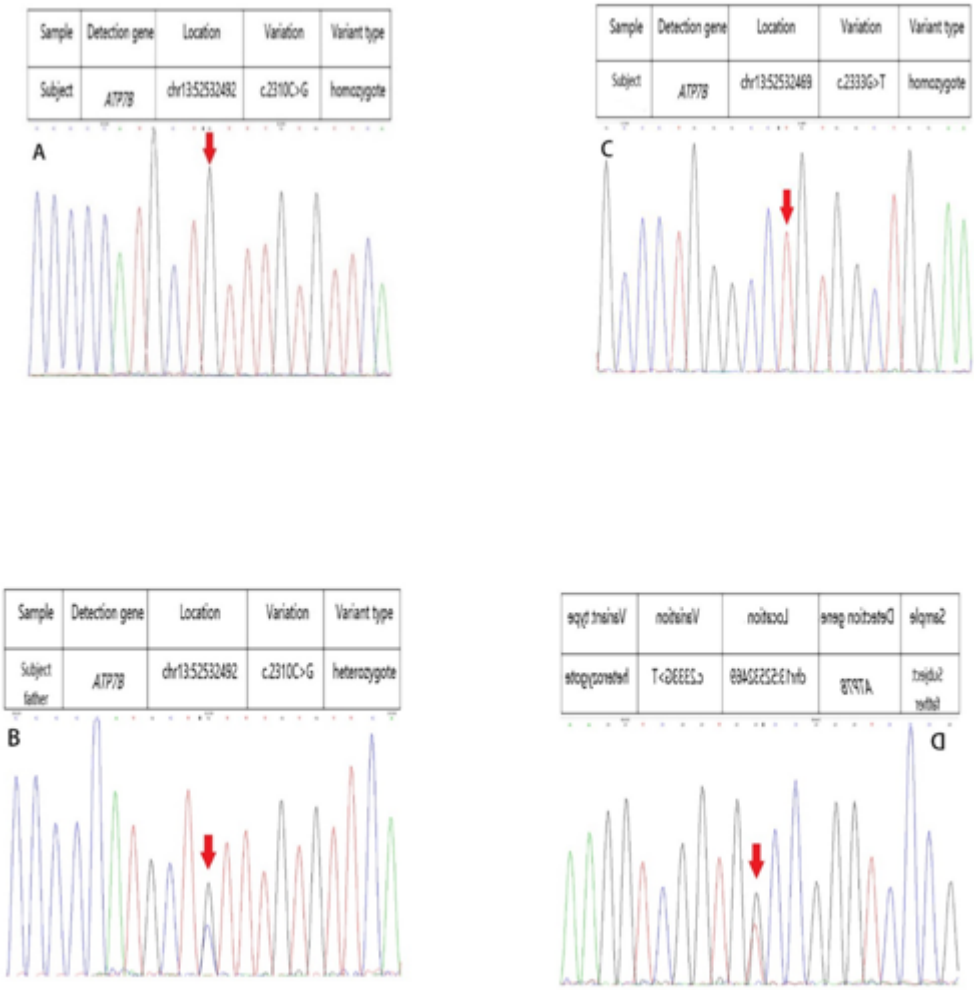

Figure 1

Sequence diagram: the comparison of c.2310C>G locus (A, B), c.2333G>T locus (C, D) of ATP7B gene

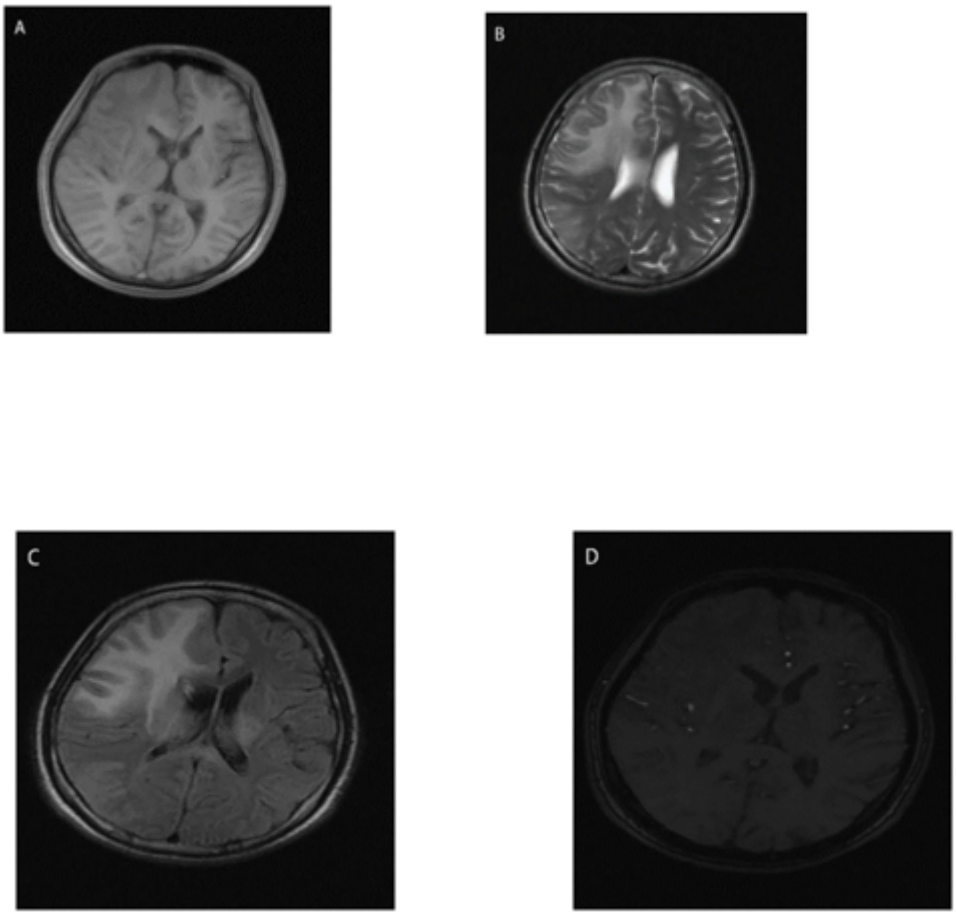

Figure 2

The right frontotemporal parietal lobe and left frontotemporal lobe on MRI showed patchy T1,long T2 signal intensity(A, B), Flair images show high signal intensity (C) ,and no obvious enhancement was observed on the enhancement scan (D) .

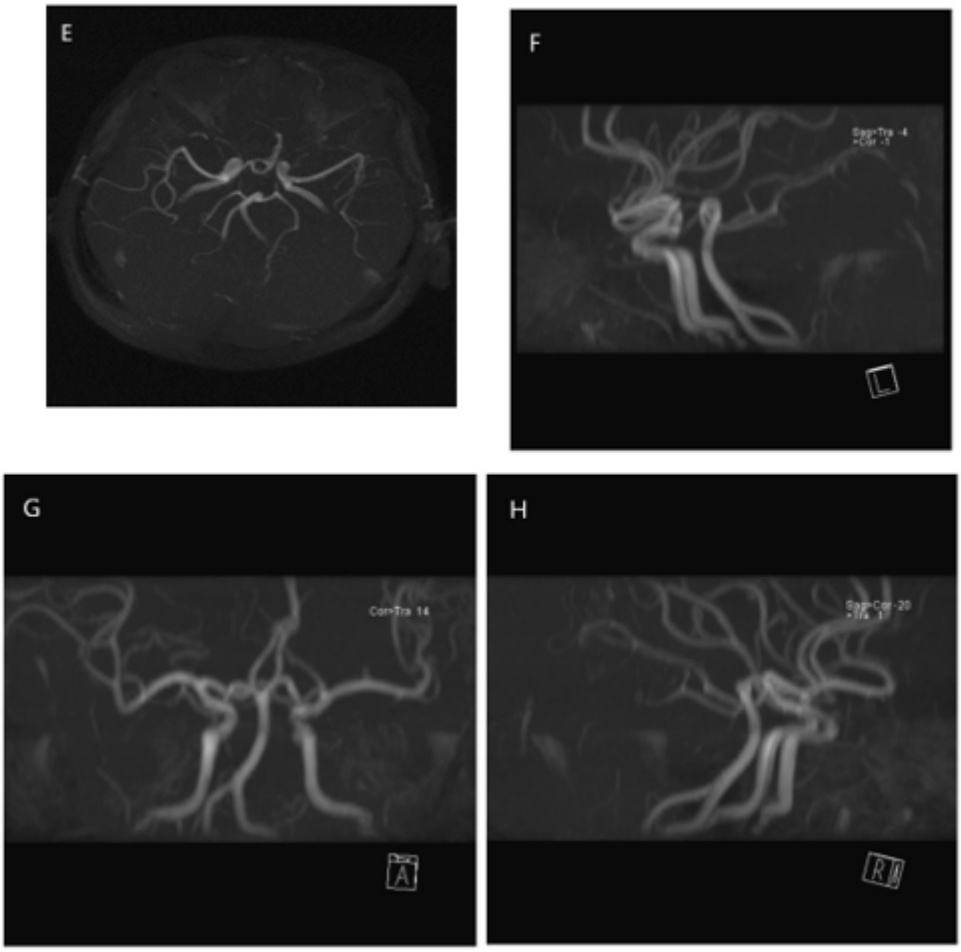

Figure 3

MRA: no obvious abnormity (E,F,G,H) .