

One Case of Abnormal Liver Function with Unknown Reason

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Abbreviations:

ALT: glutamic-pyruvic transaminase; AST: glutamic oxalacetic transaminase; TB: total bilirubin; DB: direct bilirubin; IDB: indirect bilirubin; TBA: total bile acid; ALP: alkaline phosphatase; GGT: γ -glutamine transferase; DILI: Drug-induced liver injury; NAFLD: Non-alcoholic fatty liver disease; HBsAb: hepatitis B surface antibody; HBsAg: hepatitis B surface antigen; HBeAg: hepatitis B e antigen; HBeAb: hepatitis B e antibody; HBcAb: hepatitis B core antibody; HAV: hepatitis A; HCV: hepatitis C; HEV: hepatitis E; EBV: Epstein-Barr virus; CMV: cytomegalovirus; HSV: herpes simplex virus; DND: muscular dystrophy

1. Abstract

1.1. Background: One case of abnormal liver function with unknown reason was reported in this paper. It was a rare case with rare manifestations.

1.2. Case Presentation: A 6 years old boy, with a chief complain of "persistent abnormal liver function for one and a half years", admitted for a preliminary diagnosis as abnormal liver biochemistry index, reason to be investigated. After medical history collection, physical examination and routine examination, common causes of liver damage have been eliminated. Finally, the medical history was combed again, and it was found that the patient had poor motor function and some mental retardation. After genetic testing, the patient was diagnosed with progressive muscular dystrophy.

1.3. Conclusions: Transaminase increase is less seen as the first symptom in this kind of hereditary metabolic diseases, which reminds clinicians to pay attention.

2. Background

One case of abnormal liver function with unknown reason was reported in this paper. Abnormal liver function is a common clinical manifestation, which is mainly liver cell damage caused by

various pathogenic factors. However, this case is unique, and the ultimate cause is neither liver disease, nor a common clinical manifestation of this disease.

3. Case Presentation

3.1. Case Introduction

The patient, Xiao Tao, male, six years and ten months old, was admitted to our hospital mainly due to "persistent abnormal liver function for one and a half years". One and a half years ago, the child was found abnormal liver function (glutamic-pyruvic transaminase (ALT) is 435U/L, glutamic oxalacetic transaminase (AST) is 146U/L) during the routine examination before the prepuce operation. After then, he transferred to many hospitals, but the treatment effect is not good (specific schedule is not clear). His transaminases fluctuate repeatedly between 150-500U/L. This time he came to our outpatient department, then was admitted to hospital with "abnormal liver function". During the course of disease, there was no weakness, poor appetite, nausea, vomiting, yellow urine, yellow eye, yellow body, abdominal pain, diarrhea or other discomfort. Urine and feces of the patient are normal. Family history of the patient: his mother was an "HBeAg-positive" chron-

ic hepatitis B patient. There was no special in the patient's past history or personal history. Physical examination on admission: T 36.8°C, P 111 times/min, R 21 times/min, BP 110/72 mmHg. The patient had a sane consciousness, smooth breathing, and was irrelevant to the subject, vague in speech, slow in response, uncooperative in physical examination. There was no jaundice of the skin and mucous membrane, no enlargement of the superficial lymph nodes. Neck is soft, and no resistance feeling. No positive signs were found on cardiopulmonary examination. The whole abdomen was flat and soft, with no tenderness, rebound pain or muscle tension. There was no palpable enlargement of the liver, spleen and ribs. The signs of hepatic jugular venous reflux were negative, and there was no pitting edema in both lower limbs. After admission, liver function examination again showed: albumin 44.3g/L, ALT 568U/L, AST 216U/L, total bilirubin (TB) 14.2umol/L, direct bilirubin (DB) 2.6umol/L, indirect bilirubin (IDB) 11.6umol/L, total bile acid (TBA) 4.5umol/L, alkaline phosphatase (ALP) 203U/L, γ -glutamine transferase (GGT) 9U/L. Abdominal doppler ultrasound showed no obvious abnormalities.

Preliminary diagnosis: abnormal liver biochemistry index, reason to be investigated: 1. Virus infection? 2. Hereditary metabolic liver disease? 3. Autoimmune liver disease? 4. Drug-induced liver injury (DILI)? 5. Alcoholic fatty liver disease? 6. Non-alcoholic fatty liver disease (NAFLD)? 7. Other? To determine the reason of the disease, relevant auxiliary examinations were further carried out after admission. Hepatitis B markers: hepatitis B surface antibody (HBsAb) 1000IU/L, hepatitis B surface antigen (HBsAg), Hepatitis B e antigen (HBeAg), Hepatitis B e antibody (HBeAb) and core antibody (HBcAb) were all negative. Quantitative HBV DNA was negative. Antibodies to hepatitis A (HAV), C (HCV) and E (HEV) viruses were negative. Epstein-Barr virus (EBV) test: EBV-DNA (blood) $<1 \times 10^3$, EBV-DNA (lymphocyte) $<1 \times 10^3$, EBV-DNA (throat swab) $<1 \times 10^3$. Screening for common respiratory viruses: Legionella pneumoniae antibody IgM, mycoplasma pneumoniae antibody IgM, Q hot rickettsia antibody IgM, chlamydia pneumoniae antibody IgM, adenovirus antibody IgM, respiratory syncytial virus antibody IgM, influenza A virus antibody IgM, influenza B virus antibody IgM and parainfluenza virus antibody IgM were all negative. Torch1: Parvovirus B19, cytomegalovirus (CMV), herpes simplex virus (HSV), rubella virus and toxoplasma gondii

antibody IgM, were all negative. Inflammatory proteins detection: α 1-acid glycoprotein 0.64g/L, α 1-antitrypsin 1.40g/L, copper-blue protein 0.20g/L. Trace elements detection: copper 12.6umol/L, zinc 76.5umol/L, calcium 1.94umol/L, magnesium 1.22umol/L, iron 8.25umol/L. Autoimmunity antibody spectrum: all negative. Immunoglobulin test: Normal.

The diagnosis was not clear till then. After repeated communication with the parents, percutaneous liver biopsy guided by B-ultrasound was performed on the child. Pathological results (Figure 1) showed: (G1S1) the lobular structure was still recognisable, with 6 lobular structures visible. Hepatocytes were swollen and deformed, mainly watery degeneration, and glycogen nuclei were visible. Portal vein zone was enlarged, with mild chronic inflammation, and the inflammatory cells were mainly lymphocytes, with the slightly proliferated fibrous tissue. Copper staining was negative. Glycogen staining was negative, too. We asked for ophthalmic consultation, however, the child did not cooperate in the slit lamp examination, so no KF ring was found.

The diagnosis was still unclear. We retraced the medical history and physical examination again. And found that the child was 6 years old, but unable to do add and subtract within 10, also with a poor academic performance and mental retardation to a certain extent. He was short stature, unstable walking, easy to fall when walking and running. And he was unable to get out of bed lying on the back, when need to lie prone with both hands to support to get out of bed. Also he had poor muscle strength of both arms, which suggesting the possible existence of muscle diseases. Thus, blood creatine kinase examination was performed. The myocardial enzymogram was as follows: troponin 0.139ug/L, creatine kinase isoenzyme 246.60ug/L, myoglobin 614.50ug/L, and creatine kinase 24320.0U/L. The level of creatine kinase increased significantly. We communicate again with child's parents again of conducting relevant genetic testing. They agreed. Gene detection report showed that exon 1-57 of DMD/BMD gene was missing in the samples. At this point, the diagnosis of progressive muscular dystrophy (DND) in the children was confirmed. However, due to lack of specific treatment measures of this disease, poor overall prognosis and limited survival period, the child was discharged after his parents' consideration.

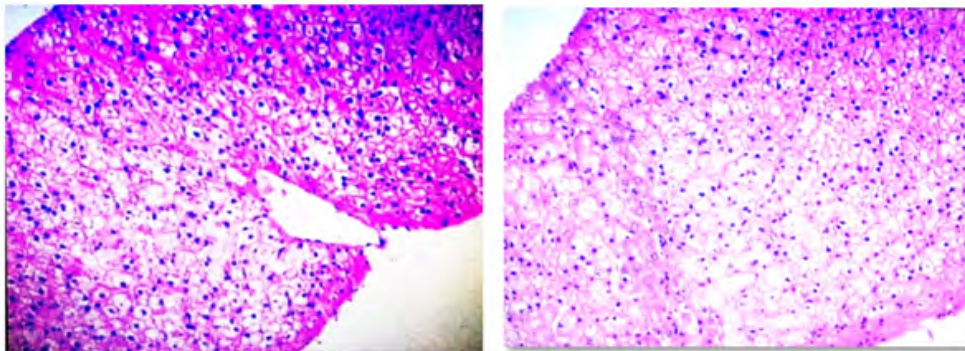


Figure 1: HE staining of the liver tissue.

4. Thinking Process of Diagnosis and Treatment

4.1. The Diagnosis

The child was admitted to hospital due to “persistent liver dysfunction for one and a half years”, with no obvious positive symptoms and signs. The liver dysfunction was mainly manifested as increased transaminase and normal bilirubin. Conventional symptomatic treatment is ineffective. From the perspective of clinical diagnosis of common and frequently-occurring diseases, the preliminary diagnosis considered after admission was as follows: the cause of abnormal liver biochemical indexes to be investigated: 1. Liver disease caused by viral infection? 2. Hereditary metabolic liver disease? 3. Autoimmune liver disease? 4. Drug-induced liver disease? 5. Alcoholic liver disease? 6. Nonalcoholic fatty liver disease? 7. Other? Subsequently, relevant auxiliary examinations were gradually carried out, and it was finally found that the persistent liver dysfunction of the child was not caused by the so-called “liver disease”, but a manifestation of genetic disease (progressive muscular dystrophy), thus making the diagnosis clear. Progressive muscular dystrophy is a group of primary skeletal muscle necrotizing diseases characterized by progressive skeletal muscle weakness, which is caused by genetic factors. The main clinical manifestations are progressive skeletal muscle atrophy and weakness of different degrees and distributions. It may also involve the myocardium [1]. Muscular dystrophy is divided into many subtypes. And according to the results of Xiao Tao’s gene test, it belongs to pseudohypertrophic muscular dystrophy. It is an X-linked recessive disorder, and is the most common type, which is found in men and carried in women. It can be classified as Duchenne or Becker type based on clinical manifestations. Becker type dystrophy (BMD): also known as benign pseudotrophic muscular dystrophy, it usually starts after the age of 10, with the first symptom of weak pelvic girdle and femoral muscle strength, slow progression and long course of disease. The patient cannot walk until 25 years or more after the onset of symptoms. Most patients still do not have paralysis when they are 30-40 years old. So the prognosis is better. Duchenne type dystrophy (DMD): also known as the severe pseudotrophic muscular dystrophy, it almost restricted to the boy. If the mother was a gene carrier, 50% male offspring got sick. Symptoms often starts in 2-8 years old, like early clumsy walk, easy to fall, cannot run and climb, the spinal cord lordosis when standing, belly stuck out and bipedal aside. Also the patient walks slowly, which was called a special “waddling gait”. When he lies on his back, it is very difficult to go immediately. He must turn on his stomach first, then climbing knees with his hands, and gradually support to stand up (“Gower” sign). It can also be seen in proximal limb muscles, quadriceps and arm muscle, predicting a poor prognosis [2]. Combining with clinical manifestations, Xiao Tao belongs to DND type. This disease has no specific treatment. A cupuncture, massage, body therapy and neuro-targeted repair therapy can be used, but the efficacy is not good.

4.2. Differential Diagnosis

(1) Liver disease caused by viral infection: this is a class of infectious diseases caused by various viral infections, mainly showed as liver damage. It is usually manifested as fatigue, poor appetite, oil aversion, nausea, vomiting and other digestive tract symptoms, with or without yellow urine, yellow eye and yellow body. Laboratory examination suggests abnormal liver function (increased aminotransferase, with or without increased bilirubin), and positive corresponding viral markers. In this case, the mother of the child was a chronic hepatitis B patient with positive HBeAg. Her viral load is high, and no effective mother-to-child blockade was conducted during the delivery of the child. Therefore, children are indeed at high risk of HBV infection. However, the subsequent HBV markers and HBV DNA tests were all negative. Further examination revealed negative IgM to HAV, HCV and HEV. In addition, the IgM of non-hepatotropic virus that commonly cause liver damage, including cytomegalovirus, rubella virus, herpes simplex virus, EBV, etc., are all negative. Therefore, liver disease caused by viral infection can be ruled out.

(2) Hereditary metabolic liver disease: This type of disease is relatively rare in adults, but should be considered in combination with the age of children. Hereditary metabolic liver disease is often characterized by multiple organ involvement. Because its essence is heredity gene problem, the high metabolism organ, such as nervous system, liver and kidney, is invaded and involve first. In China, the high incidence of genetic metabolic liver disease includes Wilson’s disease and glycogen accumulation disease. Wilson’s disease is caused by copper metabolism disorder. So, when copper is deposited in each tissue viscera, corresponding symptoms can occur, such as liver lesions and neurological lesions. To be specific, it is in the liver pathological change is diversification, can be the expression of acute hepatitis, chronic hepatitis, also can appear liver cirrhosis, it is the expression of liver function failure even. Some patients have neurological symptoms as the first symptom. And glycogen accumulation syndrome, which is essentially a group of diseases caused by metabolic disorders of sugar. At present, there are 12 types, of which 1, 2, 4, 6 and 9 types are mainly liver damage. Usually onset of this disease is early, even after the birth. The main performance was current hypoglycemia, accompanied by liver enlargement, lag growth and development and short stature, however little impact on intellectual development. The child showed liver and nervous system damage, but the serum copper and blood copper cyanin were negative. And there was no recurrent hypoglycemia. The copper staining and glycogen staining of liver biopsy were both negative, and there were no signs of hepatomegaly. Therefore, the above two types of genetic metabolic liver diseases could be excluded. Other common abnormal metabolic liver diseases, such as hemochromopathy, porphyria and cholesterol accumulation disease, can all be ruled out by combining the medical history, physical examination and relevant

auxiliary examinations.

(3) Autoimmune liver disease: this is a kind of autoimmune disease mainly caused by liver damage caused by immune dysfunction of the body. The common clinical types are autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), IgG4-associated cholangitis, and their overlapping syndromes. Only autoimmune hepatitis is seen in children. The incidence of autoimmune hepatitis in children is 0.4 per 100,000 and the prevalence is 3 per 100,000. Similar to adults, autoimmune hepatitis in children is also divided into two types. Type 1 is mainly positive for circulating anti-smooth muscle antibody (ASMA) and/or anti-nuclear antibody (ANA). Type 2 was mainly positive for liver cell solute antibody E and liver and kidney microsomal antibody E. Type 1, which accounts for two-thirds of children, usually develops after age 10. It is currently thought that the onset age of type 2 can be as early as infancy. However, the final diagnosis of any types need to be considered in combination with autoimmunity antibody spectrum, immunoglobulin and liver biopsy results on the basis of excluding other causes of liver damage. The relevant laboratory test results of this child are not supportive, so such diseases can be ruled out.

(4) Alcoholic liver disease: liver function damage caused by long-term heavy drinking. The child has no history of alcohol consumption, so it can be ruled out.

(5) Non-alcoholic fatty liver disease (NAFLD): this is a liver damage closely related to insulin resistance and genetic susceptibility to metabolic stress. Its pathological changes are similar to alcoholic liver disease, but patients have no history of heavy drinking. Its disease spectrum include non-alcoholic fatty liver (NAFL), non-alcoholic fatty hepatitis (NAFH) and its related liver cirrhosis and hepatocellular carcinoma (HCC). Combined with the history of the child, it can be ruled out.

(6) Drug-induced liver injures (DILI): it refers to the disease caused by the direct or indirect damage of some drugs to the liver. Its manifestations are the same as those of various human liver diseases, such as hepatocyte necrosis, cholestasis, intracellular lipid droplet deposition, chronic hepatitis, cirrhosis, etc. This child has no history of taking drugs of liver damage, so it can be ruled out.

5. Discussion and Conclusions

This case is a preschool male with a slow onset and long course of disease, mainly manifested by persistent liver function abnormalities, without obvious positive symptoms and signs. The effect of comprehensive liver protection in other hospital is not good. After admission, liver function examination still indicated elevated transaminase. First of all, from the thinking of common disease, frequently-occurring clinical diagnosis and treatment, the preliminary consideration was abnormal liver function (causes to be investigated). The most common causes include viral infection of the liver, genetic metabolic liver disease, autoimmune liver

disease, alcoholic liver disease, non-alcoholic liver disease, and drug-induced liver disease. During hospitalization, a series of relevant examinations were carried out centering on possible diseases, while continuing liver protection treatment.

Alcoholic liver disease, non-alcoholic liver disease, and drug-induced liver disease are easily excluded in the context of the child's history. Further examination revealed that antibodies to relevant viruses, including hepatotropic and non-hepatotropic, were negative. No abnormalities were found in screening for common genetic metabolic diseases, and autoimmune liver disease was not supported. At this point, the search for the cause of liver damage has reached an impasse. What is the next step for the diagnosis of this children?. Once again, we settled down to clear our minds and retraced the medical history. We found important clues: the child was 6 years old, but could not add and subtract within 10 years, had poor academic performance, and had certain mental retardation. He was short stature, unsteady walking, easy to fall when walking and running. And he was unable to get out of bed lying on the back, when need to lie prone with both hands to support to get out of bed normally. The muscle strength of both arms was poor, so we considered the possibility of myopathy. Subsequent tests of creatine kinase confirmed this hypothesis. So, is there some genetic disease that causes muscle damage that causes an increase in transaminases (which are not specific to liver cells but are also present in muscle cells) [3-5]? After further communication with the family of the child, relevant genetic testing was performed, and the diagnosis of progressive muscular dystrophy (DND) was finally confirmed. The disease of this child is a rare genetic metabolic disease, manifested as abnormal liver function, but the target organ damaged is outside the liver [6]. This has opened up a new horizon for us in the field of liver disease. In addition, we further recognize that thorough history and physical examination are essential for the diagnosis of disease. This also suggests that in our future clinical work, we should not only consider the liver disease as the cause of abnormal liver function, but also think carefully from various aspects. At the same time, in clinical work, we should first consider common diseases and frequently-occurring diseases according to patients' symptoms, signs and auxiliary examinations. However, when it is not feasible, we need to immediately change our thinking and look for a new breakthrough point.

6. Declaration

6.1. Ethics Approval and Consent to Participate

Not applicable.

6.2. Consent to Publish

All the authors signed consents for the publication, and written informed consent was obtained from the patient.

6.3. Competing Interests

The authors declare no competing interests.

6.4. Authors' Contributions

LSY wrote the article. ZKC was responsible for the collection of case data. WXH designed the idea of the article and revised the article. All authors have read and approved the manuscript.

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