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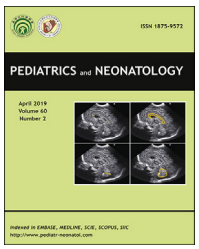

Short Communication

Monitoring of liver stiffness by transient elastography during the treatment of Gaucher disease

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Gaucher disease (GD) is a sphingolipid storage disease, that is caused due to a deficiency in β-glucocerebrosidase (EC 3.2.1.45, acid β-glucosidase, GBA) activity. A deficiency in GBA activity leads to the accumulation of glucocerebroside in macrophages (Gaucher cells) in the bone marrow, liver, spleen, and brain. Children affected with GD show the symptoms of a failure to thrive, thrombocytopenia, anemia, and hepatosplenomegaly. Enzyme replacement therapy (ERT) with recombinant human GBA (rhGBA) can reduce hepatosplenomegaly, increase hemoglobin level and platelet count, and increase bone mineral density.[1] Infiltrations of Gaucher cells in the liver may progress to chronic liver disease and cirrhosis, which have been reported to be the causes of death in patients with GD without ERT.[2] Liver fibrosis can be evaluated through a liver biopsy, which is an invasive procedure and has the risk of severe complications. Liver transient elastography (FibroScan® 502 touch, Echosense Paris, France) is a noninvasive procedure that can evaluate liver stiffness and monitor treatment efficacy in pediatric liver disease. We describe a case of a child with GD with decreased liver stiffness that was monitored by liver elastography after ERT.

A 3-year-11-month-old girl presented with a short stature, abdominal distension, and splenomegaly since the age of 2 years. Abdominal sonography showed that the long axis of spleen measured 10.4 cm and the liver span was 6.3 cm over the right midclavicular line with homogeneously increased hepatic echogenicity. Hepatic color Doppler revealed a biphasic hepatic vein flow pattern. At the age of 2 years 3 months, her laboratory data revealed anemia (hemoglobin level: 11.3 g/dL) and borderline thrombocytopenia (platelet count: 160,000/μL). Liver function tests such as alanine transaminase, bilirubin, prothrombin time, and partial thromboplastin time were within normal limits, except aspartate transaminase that showed a mildly elevated level (51 U/L). Polymerase chain reaction for detecting serum Epstein–Barr virus and cytomegalovirus showed negative results. Abdominal magnetic resonance

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imaging (MRI) revealed only mild-to-moderate splenomegaly without any evidence of portal vein abnormality.

During the follow-up, oculomotor apraxia and developmental delay of the gross motor function with normal cognition were noted at the age of 3 years. Progressive thrombocytopenia (109,000/μL) and splenomegaly (long axis: 12 cm) were also detected at the age of 3 years 2 months. Liver transient elastography (FibroScan®) done at this age revealed increased liver stiffness measurement (LSM) of up to 8.2 kPa [normal: 3.4 (range: 2.3 to 4.6) kPa at the ages of 1−5 years[3]] that progressed to 9.4 kPa at the age of 3 years 4 months.

Due to idiopathic splenomegaly with oculomotor apraxia, a GD screen test performed by tandem mass spectrometry in a multiplex assay was applied, which revealed a deficiency in GBA activity in the dried blood spot sample [GBA activity was 0.44 μM/h (normal mean: 11.54 μM/h); the ratio of neutral alpha-glucosidase to GBA activity was 62.8 (normal: <30)]. A further confirmatory test showed a deficiency in leukocyte GBA activity (0.46 nmol/mg protein/h, pH 5.0; normal range: 12.91 ± 4.95 nmol/mg protein/h, pH 5.0), confirming the diagnosis of GD. Her GBA gene analysis revealed a p.L483P (c.1448T > C, also known as p.L444P) homozygous mutation. A liver biopsy performed at 3 years 6 months revealed enlarged Kupffer cells in the liver parenchyma, which was consistent with the diagnosis of GD. Electroencephalography, echocardiography, and spine and femur X-ray were all unremarkable. The liver function test showed progressive elevation of aspartate transaminase level by up to 80 U/L, which was the highest level before ERT, at the age of 3 years 7 months. Other liver function tests were within normal limits.

ERT with rhGBA (Cerezyme®) 60 IU/kg every other week was started since the age of 3 years 7 months. After 3 months of treatment, the liver elastography showed significant improvement of LSM to 3.8 kPa. Thrombocytopenia and splenomegaly (11.1 cm at the age of 3 years 10 months) were also improved (Fig. 1), with normal liver span (8.3 cm over the right midclavicular line). Plasma chitotriosidase activity[4] revealed improvement from 1906.47 to 1429.56 and to 1096.79 nmol/mL/h (normal: <98 nmol/mL/h). The aspartate transaminase level was decreased to 23 U/L after ERT.

In type 1 GD without ERT, chronic liver disease and cirrhosis have been identified as the causes of death.[2] MRI can detect hepatic and splenic infiltration in GD, which can be correlated with disease severity.[5] It is also recommended to use MRI or ultrasound to monitor the response of hepatosplenomegaly to therapy and adjust the ERT dosage. However, the application of MRI for monitoring cirrhosis and hepatic fibrosis may be difficult due to the need of sedation in younger children, cost, and the consumption of time.

Transient elastography (FibroScan®) can be used to evaluate liver stiffness and hepatic fat deposition in adult patients with cirrhosis, chronic hepatitis, and liver transplantation.[6] The advantages of FibroScan® include noninvasiveness, a highly successful rate, and the reduced requirement of sedation in children. However, measurement failure occurs due to excessive subcutaneous adipose tissue in obese patients and the poor cooperation of younger children.

In our patient, the first measurement of liver stiffness was done at the age of 3 years 2 months (LSM: 8.2 kPa), and the second measurement was done at the age of 3 years 4 months (LSM: 9.4 kPa), as shown in Fig. 1, which were done within 2 months of the confirmation of GD. The LSM value might be increased according to the trend before the ERT, which may reveal a more significant therapeutic effect after the ERT, in trend with the improvement of thrombocytopenia and plasma chitotriosidase activity. Transient elastography can serve as a useful tool for the evaluation of liver and spleen stiffness in adult patients with GD. It is also

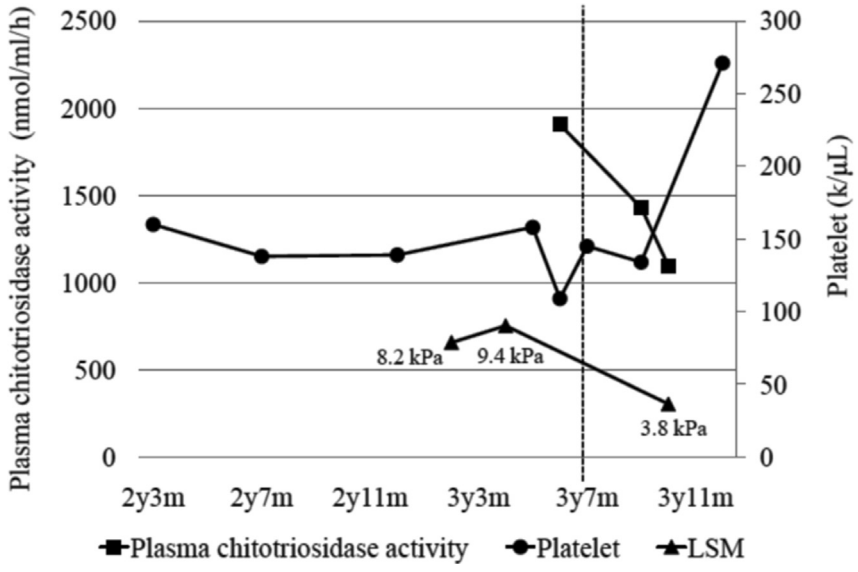

Figure 1 Plasma chitotriosidase activity, platelet count, and LSM showed improvement during ERT since the age of 3 years 7 months (indicated by the dashed line). Plasma chitotriosidase activity (normal: <98 nmol/mL/h); LSM: liver stiffness measurement (normal value: 3.9 ± 0.9 kPa); ERT: enzyme replacement therapy.

reported an increase in liver stiffness of adult patients with GD compared to that of healthy controls (7.1 and 5.0 kPa, respectively),[7] which was compatible with our patient. However, no study has yet evaluated the therapeutic effect of liver stiffness in pediatric GD during ERT.

This is the first study to demonstrated through transient elastography that ERT may reverse the liver elastic texture within 3 months of therapy in pediatric patients with GD. Further studies are warranted to assess whether the changes are universal to pediatric patients with GD, especially if the changes could guide the treatment for late-treated patients with GD.

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Conflict of interest

The authors declare that they have no potential, perceived, or real conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.pedneo.2018.05.002.