Recurrent Abdominal Pain, Vomiting, Velvet-Like Changes in the Small Intestine in a Patient with Multiple Acyl-CoA dehydrogenation Deficiency

Ziqing Ye
Department of Gastroenterology, Children's Hospital of Fudan University
Jieru Shi
Department of Gastroenterology, Children's Hospital of Fudan University
Xiaolan Lu
Department of Gastroenterology, Children's Hospital of Fudan University
Yingying Meng
Department of Gastroenterology, Children's Hospital of Fudan University
Wei Lu
Department of Pediatric Endocrinology and Inborn Metabolic Diseases, Children's Hospital of Fudan University
Bingbing Wu
Key Laboratory of Birth Defects, Children's Hospital of Fudan University, Shanghai, China
Ying Huang (yhuang815@163.com)
Children's Hospital of Fudan University

Research

Keywords: Multiple acyl-CoA dehydrogenation deficiency, exome sequencing, ETFDH genes

Posted Date: August 13th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-54093/v1

Abstract

Background

Multiple acyl-CoA dehydrogenation deficiency (MADD) is an inborn error of metabolism in fatty acid oxidation. We described an unusual case of recurrent vomiting and abdominal pain in a child with MADD, presenting with velvet-like changes in the small intestine.

Methods

Because of prominent gastrointestinal manifestations and small intestine ulcers, the patient was first diagnosed as Crohn's disease. The patient was admitted to our institution because of recurrent symptoms despite treatment. Upper and lower endoscopy, computed tomography and trios exome sequencing were performed.

Results

This patient underwent a repeated video endoscopy, which showed velvet-like changes in the small intestine rather than ulcers. Liver steatosis was identified by computed tomography. Serum tandem mass spectrometry showed elevated C8 and C10. Trios exome sequencing revealed compound heterozygous variants of c.250G>A, 524G>A in *ETFDH.* The diagnosis of multiple acyl-CoA dehydrogenation deficiency was made. Patient responded to oral riboflavin treatment.

Conclusion

With this case, we aimed to highlight the importance of tandem mass spectrometry and genetic sequencing, especially when the endoscopic findings are not pathognomonic in pediatric cases with recurrent gastrointestinal complaints. We confirmed the diagnosis with next generation sequencing, and described unusual findings of velvet-like changes mimicking ulcers in the small intestine in this patient with MADD.

Background

Multiple acyl-CoA dehydrogenation deficiency (MADD) is a ultrarare inborn error of metabolism in fatty acid oxidation and amino acid[1]. Patients with later-onset MADD develop progressive myopathy and heterogeneous symptoms of intermittent vomiting and hypoglycemia[2]. We present, for the first time in literature, a child with recurrent vomiting and abdominal pain and diffuse velvet-like lesions in the small intestine, who was diagnosed as MADD.

Methods

Patient

Clinical manifestations, laboratory results including abdominal computed tomography, upper and lower endoscopy, and video endoscopy results and treatment was retrieved from medical record. This study was approved by the Ethical Committee of Children's Hospital, Fudan University. Informed consent for participation and blood sample collection was obtained from the parent of the patient.

Genetic sequencing and variant assessment

Genomic DNA was extracted from the peripheral whole blood of the patient and parent using the Agilent SureSelectXT Human All Exon 50-Mb kit. Exome sequencing resulted in an average 100 × coverage using the Illumina HiSeq2000/2500 sequencer (Illumina, San Diego, CA, USA). Sequence read alignments were completed using Novoalign (V2.07.18) against the human reference genome GRCh37.p10 (http://www.novocraft.com). The bioinformatics pipeline has been previously described[3]. In brief, after quality control, variants were filtered by means of public databases, including Human Gene Mutation Database (HGMD) Professional, the Exome Aggregation Consortium (ExAC), and an in-house database. Sanger sequencing was performed with a Biosystems 3500 DNA Analyzer and analyzed by Mutation Surveyor V4.0.9.

Results

Case presentation

An 8-year-old girl from southern China with history of recurrent abdominal pain and vomiting since 4 years of age presented to the gastroenterology department. Colonoscopy was unremarkable, while multiple ulcers were identified in the small intestine on video capsule endoscopy. She was diagnosed with Crohn's disease, and initially treated with exclusive enteral nutrition, mesalamine and azathioprine in a local hospital. She still complained of abdominal pain and had multiple episodes of vomiting and was referred to our unit. Apart from gastrointestinal symptoms, she also reported muscle weakness during attacks.

On presentation, her physical examination was unremarkable. There was no sign of perianal diseases. Inflammatory markers, including C-reactive protein and erythrocyte sedimentation rate were within normal limits. Other laboratory investigations showed a lactate of 2.9 mmol/L, pH of 7.311, serum free fatty acid of 2,161 mmol/L. Serum tandem mass spectrometry showed C10 of 1.29uM, C8 of 0.57uM, C5/C3 of 0.362uM.

Upper endoscopy and colonoscopy was unremarkable. A repeat video capsule endoscopy revealed diffuse whitish velvet-like changes in several segments without apparent mucosal ulcerations (Fig. 1). Computed tomography only showed hepatic lipomatosis, indicating liver steatosis (Fig. 2). As a result, diagnosis of Crohn's disease cannot be supported in our patient.

Fatty liver might not be an usual cause of recurrent abdominal pain and vomiting in children. However, when associated with elevated free fatty acid, lactate and abnormal results of serum tandem mass spectrometry, metabolic disorders are of high suspicion. Endocrinology was consulted. Trios exome sequencing was performed, and compound heterozygous mutations of c.[250G > A]+[524G > A] were identified in *ETFDH*, which was confirmed by Sanger sequencing (Fig. 3). This patient was diagnosed with late-onset MADD.

Discussion

MADD (OMIM 231680) is an autosomal recessive inherited fatty acid and amino-acid metabolism disorder[4]. Most late-onset MADD can be corrected by therapeutic dosage of riboflavin, thus is regarded as riboflavin-responsive MADD[5]. Our patient was symptom-free soon after initiation of oral riboflavin treatment (100 mg/day).

Liver steatosis might be an important extra-muscular finding of late-onset MADD, and severe fatty liver was revealed by ultrasound in 4 out of 13 patients with MADD[6]. Liver steatosis and lipid storage myopathy in MADD are due to impaired fat oxidation and greater dependence upon carbohydrate oxidation[6]. Patients might be asymptomatic from liver steatosis. It is generally considered as a benign and stable condition. However, progression to cirrhosis and acute liver failure have been reported among three adult cases of late-onset MADD since 2013[7–9]. Liver involvment is associated with various fatty acid oxidation disorders, and steatosis is a reliable but non-sepcific sign[10]. Therefore, sytematic screening is encouraged if there is high index of suspicion.

Endoscopic findings of MADD or other fatty acid oxidation disorder have not been specifically reported yet. Intestinal fat accumulation was described in familial hypobetalipoproteinemia due to apolipoprotein B R463 mutation[11]. We speculated that velvet-like lesions in the small intestine were caused by similar pathogenesis of liver steatosis. Because our patient had prominent gastrointestinal complains of vomiting and abdominal pain, while the first video capsule endoscopy showed diffuse whitish changes mimicking ulcerations, she was misdiagnosed as Crohn's disease.

Primary MADD is caused by a genetic defect in electron transfer flavoproteins or in ETF dehydrogenase[4]. The c.250G > A and c. 524G > A variants in *ETFDH* have already been reported to be pathogenic[2]. In addition, the c.250G > A variant might be a possible founder mutation in southern China, and clustered in Fujian Province[2]. Our patient also came from this region. The estimated carrier frequency was about 1.35% among the normal population[2].

Our patient was responsive to riboflavin treatment. MADD patients demonstrate multiorgan dysfunction especially in the case of catabolism[12]. D,L-3-hydroxybutyrate treatment is effective in improving clinical symptoms and survival in severely affected MADD cases[1].

Conclusions

For children presenting with predominant gastrointestinal symptoms of recurrent abdominal pain and vomiting, pediatricians should consider possibility of metabolic disorders, especially when results of imaging and endoscopy are inconclusive. In this setting, tandem mass spectrometry and genetic sequencing should be timely engaged.

Abbreviations

MADD: multiple acyl-CoA dehydrogenation deficiency

Declarations

Ethics approval and consent to participate

Signed informed consent was obtained from the parents of the patients. Ethical approval was obtained from the Ethical Committee of Children's Hospital of Fudan University.

Consent for publication

Not applicable.

Availability of data and material

All data generated or analyzed during this study are included in this published article

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable.

Authors' contributions

Dr. Ye collected clinical data, carried out the initial analyses, drafted the manuscript, and reviewed and revised the manuscript. Dr. Shi, Dr. X Lu and Dr. Meng collected and interpreted clinical data and revised the manuscript. Dr. W Lu interpreted clinical data, reviewed and revised the manuscript. Dr. Wu interpreted sequencing data, reviewed and revised the manuscript. Dr. Huang was responsible for study supervision, enrollment of patient and critical revision of the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Acknowledgements

We express our gratitude to the patient.

References

1. van Rijt WJ, Jager EA, Allersma DP, et al. Efficacy and safety of D,L-3-hydroxybutyrate (D,L-3-HB) treatment in multiple acyl-CoA dehydrogenase deficiency. *Genet Med.* 2020;22(5):908-916.
2. Wang ZQ, Chen XJ, Murong SX, et al. Molecular analysis of 51 unrelated pedigrees with late-onset multiple acyl-CoA dehydrogenation deficiency (MADD) in southern China confirmed the most common ETFDH mutation and high carrier frequency of c.250G>A. *J Mol Med (Berl).* 2011;89(6):569-576.
3. Yang L, Kong Y, Dong X, et al. Clinical and genetic spectrum of a large cohort of children with epilepsy in China. *Genet Med.* 2018.
4. Olsen RK, Andresen BS, Christensen E, et al. Clear relationship between ETF/ETFDH genotype and phenotype in patients with multiple acyl-CoA dehydrogenation deficiency. *Hum Mutat.* 2003;22(1):12-23.
5. Xu J, Li D, Lv J, et al. ETFDH Mutations and Flavin Adenine Dinucleotide Homeostasis Disturbance Are Essential for Developing Riboflavin-Responsive Multiple Acyl-Coenzyme A Dehydrogenation Deficiency. *Ann Neurol.* 2018;84(5):659-673.
6. Zhu M, Zhu X, Qi X, et al. Riboflavin-responsive multiple Acyl-CoA dehydrogenation deficiency in 13 cases, and a literature review in mainland Chinese patients. *J Hum Genet.* 2014;59(5):256-261.
7. Soldath P, Lund A, Vissing J. Late-onset MADD: a rare cause of cirrhosis and acute liver failure? *Acta Myol.* 2020;39(1):19-23.
8. Scheicht D, Werthmann ML, Zeglam S, et al. Muscle weakness and early stages of liver failure in a 22-year-old man. *Internist (Berl).* 2013;54(8):1016-1022.
9. Shi W, Wu D, Si N, et al. The 463rd case: rhabdomyolysis, acute kidney failure and acute hepatic failure. *Zhonghua Nei Ke Za Zhi.* 2018;57(5):381-384.
10. Baruteau J, Sachs P, Broué P, et al. Clinical and biological features at diagnosis in mitochondrial fatty acid beta-oxidation defects: a French pediatric study of 187 patients. *J Inherit Metab Dis.* 2013;36(5):795-803.
11. Noto D, Cefalù AB, Cannizzaro A, et al. Familial hypobetalipoproteinemia due to apolipoprotein B R463W mutation causes intestinal fat accumulation and low postprandial lipemia. *Atherosclerosis.* 2009;206(1):193-198.
12. Olpin SE. Implications of impaired ketogenesis in fatty acid oxidation disorders. *Prostaglandins Leukot Essent Fatty Acids.* 2004;70(3):293-308.

Figures

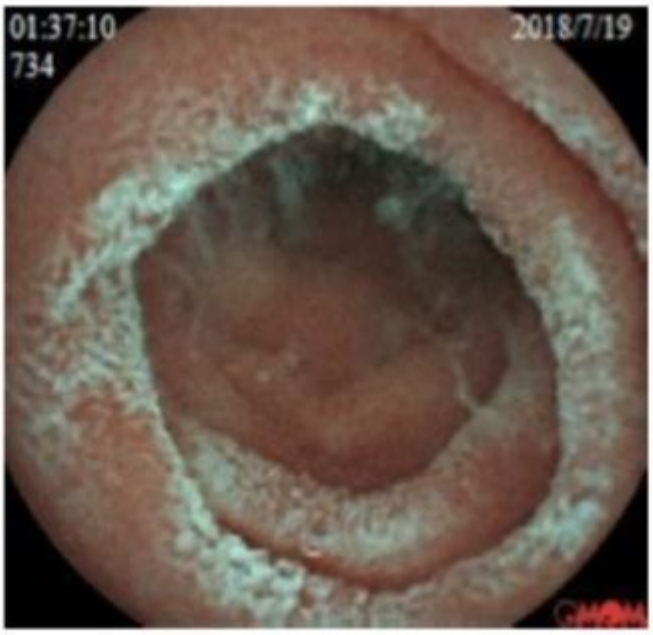

Figure 1

CT scan of the abdomen with contrast. There is hepatic lipomatosis and the liver is not enlarged. There is no splenomegaly.

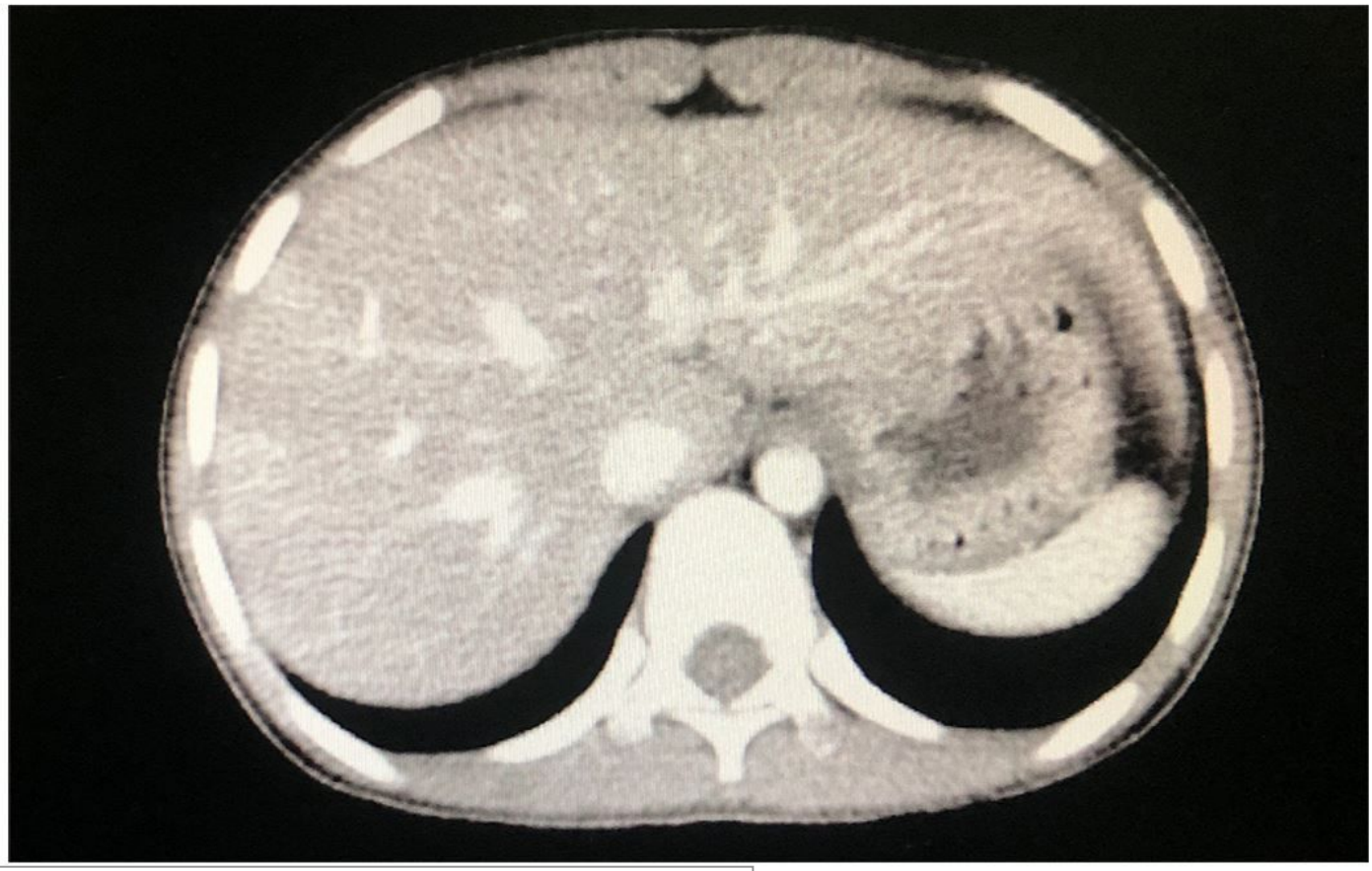

Figure 2

Findings of video capsule endoscopy. Diffuse velvet-like changes are present in multiple segments of the small intestine. There is no apparent ulceration or erosion.

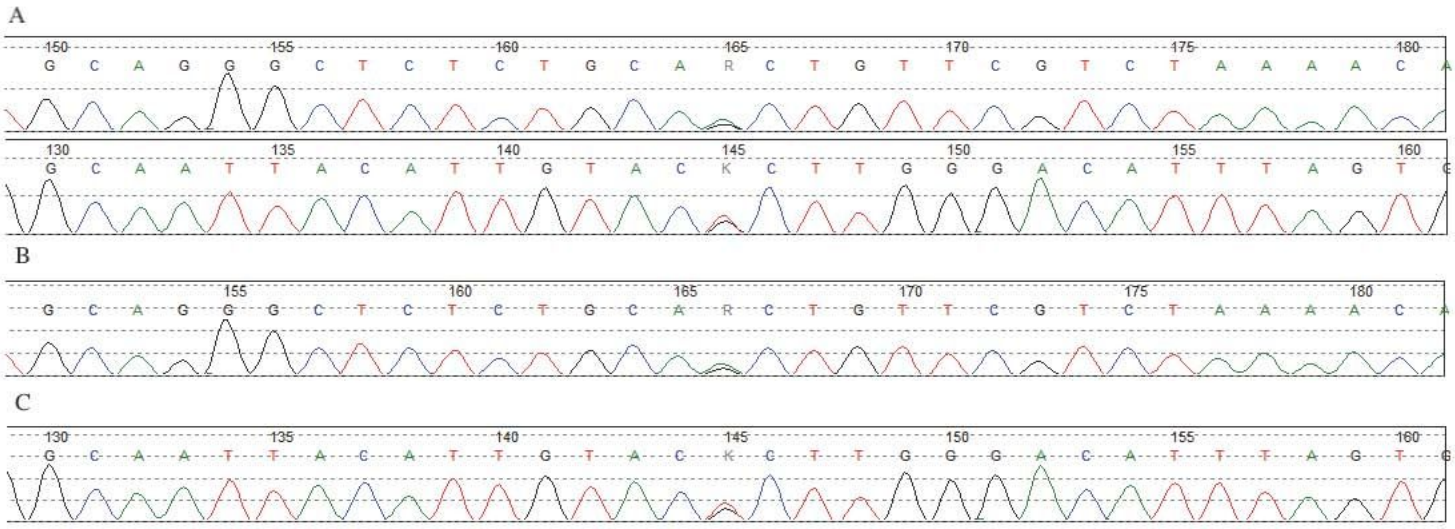

Figure 3

Sanger sequencing of ETFDH confirmed mutations in our patient. A, patient: ETFDH c.250G>A, c.524G>A; B, Father of the patient: ETFDH c.250G>A; C, Mother of the patient: ETFDH c.524G>A.