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A case of abdominal pain with dyslipidemia: difficulties diagnosing cholesterol ester storage disease

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Abstract. – Cholesterol ester storage disease is an exceptionally rare dyslipidemia with less than 150 cases reported in the medical literature. The diagnosis of Cholesterol Ester Storage Disease is often missed by virtue of the fact that the symptoms mimic both inborn metabolic defects and hepatic steatosis. Patients with Cholesterol Ester Storage Disease usually present with atypical complaints including abdominal pain from altered gut motility. Blood analysis typically reveals abnormal liver function tests with coincident dyslipidemia.

We present a case of a young woman with Cholesterol Ester Storage Disease who was followed over two decades. We discuss issues common to her initial protracted diagnosis with management options over time.

Key Words:
Cholesterol Ester Storage Disease (CESD), Lysosomal acid lipase (LAL) deficiency, Low density lipoprotein (LDL), High density lipoprotein (HDL), Triglycerides (TG), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline phosphatase (ALP).

Introduction

Cholesterol Ester Storage Disease (CESD) is an exceptionally rare dyslipidemia with less than 150 cases reported in the medical literature[1]. Patients with CESD often present with atypical complaints including abdominal pain, altered gut motility, and colitis, and blood analysis usually shows abnormal liver function testing with coincident dyslipidemia. CESD has a prevalence of around 0.5% in the United States though this is likely an under-estimate since it masquerades as many disorders including fatty liver disease, glycogen storage disease, and gastrointestinal (GI) pathology. Nonalcoholic fatty liver disease (NAFLD) and hepatic steatosis have a prevalence of around 3% in the United States and often become 'wastebasket diagnoses' when the true underlying etiology of disease is unclear. Many patients with CESD are misdiagnosed based on how the disease manifests clinically and biochemically. The time to accurate diagnosis of CESD is usually delayed, leading to undue patient suffering and the risk of irreversible hepatic impairment. Clear, evidence-based guidelines for diagnosing and managing CESD are lacking. This report will aid clinicians on the front line as well as clinical laboratorians in identifying potential patients with CESD, making a swift diagnosis with the appropriate testing. We also suggest treatment regimens based on our experience treating a patient with this disorder.

Patient Presentation

The patient is a 35-year-old Caucasian female who first presented in 1988 at the age of 11 with cramping abdominal pain associated with watery, non-bloody diarrhea during a trip to the southern United States. Her mother experienced similar symptoms at that time, and so a self-limited infectious etiology was presumed. The patient at that time had a personal history of bacterial upper respiratory infections and scarlet fever. Her family history is significant for hypertension and dyslipidemia (father) and myocardial infarction at age 52 (paternal grandfather). The patient's abdominal pain led to an extensive GI work-up in 1989 revealing normal upper and lower endoscopic biopsies, a normal hepatobiliary iminodiacetic acid (HIDA) scan, normal fecal cultures for bacteria, ova, and parasites, a negative study

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for lactase deficiency, and unrevealing serology for auto-immune disease. An HIV test and screen for cystic fibrosis were negative. Laboratory screening for thyroid function, copper, ceruloplasmin, gastrin, and porphyrin levels was also unrevealing. The patient did have significant dyslipidemia in 1989 as follows: total cholesterol 406, LDL 356, HDL 16, VLDL 41, and triglyceride 206. Additional lab work indicated ApoA1 was 63 mg/dL (normal > 140) and ApoB was 162 mg/dL (normal < 130). Liver function tests in 1989 were also abnormal as follows: AST 74, ALT 134, ALP 196. The patient continued to suffer from frequent GI upset and increased bowel motions with pediatric growth charts indicating a failure to thrive. A decision was made to start the patient on cholestyramine with a low-fat diet which showed some improvement in her lipid profile as indicated in Figure 1A. When hepatomegaly was appreciated in 1990, a liver biopsy led to a suspected diagnosis of a glycogen storage disease, and she was started on cornstarch. Cholestyramine was discontinued, but then re-started shortly after it was discovered she still had marked dyslipidemia. A second liver wedge biopsy performed in 1990 showed a non-specific storage disease of a lipid nature and, ultimately, deficiency of lysosomal acid lipase (LAL) confirmed the disorder to be CESD.

The patient was managed initially by a pediatric gastroenterologist until it was believed that her GI symptoms were unrelated to her dyslipidemia, and then a pediatric cardiologist assumed care for the patient. A modified Bruce exercise stress test was completed in 1992 (age 15), which was negative for inducible ischemia, and carotid duplex imaging showed only mild, non-obstructive disease. The patient was, then, started on atorvastatin 20 mg daily and aspirin 325 mg daily, which remained her treatment regimen for years, until it was changed to rosuvastatin 40 mg in 2009. The patient's lipid profile (Figure 1A) and liver function tests (Figure 1B) are indicated graphically at the time of diagnosis and throughout the evolution of her treatment regimen.

Discussion

The patient presented in this case has CESD which is an inborn metabolic disorder inherited in an autosomal recessive manner as a consequence of mutations on the long arm of chromosome 10. Such mutations result in reduced LAL concentration and an accumulation of unhydrolyzed lysosmal triglycerides and cholesterol ester within the liver[2]. A more severe manifestation of these mutations resulting in congenital absence of LAL is Wolman's disease which typically manifests as diarrhea, malabsorption, failure to thrive, and death in the first few months of life[3,4]. CESD presents clinically with milder symptoms consistent with a GI disorder, though atherosclerosis in patients in the first few decades of life was reported[5,6]. The diagnosis of CESD is challenging by virtue of the fact that the clinical presentation is variable, often manifesting as non-specific symptoms such as abdominal discomfort and altered gut motility. The diagnosis of CESD in our patient was likely further delayed by the patient moving many times throughout the U.S. Her medical records were fragmented, causing each new clinical counter to effectively be a *tabula rasa* evaluation which seemed to perplex her clinicians, and may have forced them to adopt a 'shot-gun' approach in the diagnostic workup. If clinicians are not attuned to the key manifestations of CESD, patients may undergo unnecessary tests and procedures which can be frustrating for both the patient and the clinician, hampering a therapeutic relationship as the correct diagnosis and treatment are delayed. The diagnosis in our patient was ultimately made invasively via liver biopsy and the discovery of reduced LAL. CESD can be swiftly diagnosed following liver biopsy only if an astute pathologist looks for reduced LAL expression upon noting fatty steatosis in which birefringent cholesterol ester crystals are said to be pathognomonic for the disease[1]. It is worth emphasizing that liver biopsy and histology alone are highly non-specific in diagnosing CESD. In this case, the second liver biopsy only lead to the diagnosis of CESD upon noting reduced tissue LAL.

The diagnosis of CESD is also possible non-invasively via commercially-available molecular assays for some of the known mutations in the LAL gene[7], though a report in patients with CESD suggests a discrepancy between the extrapolated frequency of CESD mutations in the population and reported clinical cases[8]. This report is striking since it suggests under-recognition or misdiagnosis of CESD, and so a fairly high clinical index of suspicion for the disorder rather than reliance on a genetic screen may allow diagnosis to be congruent with true disease prevalence in the general population. CESD is often, as occurred early in our patient's life, mis-

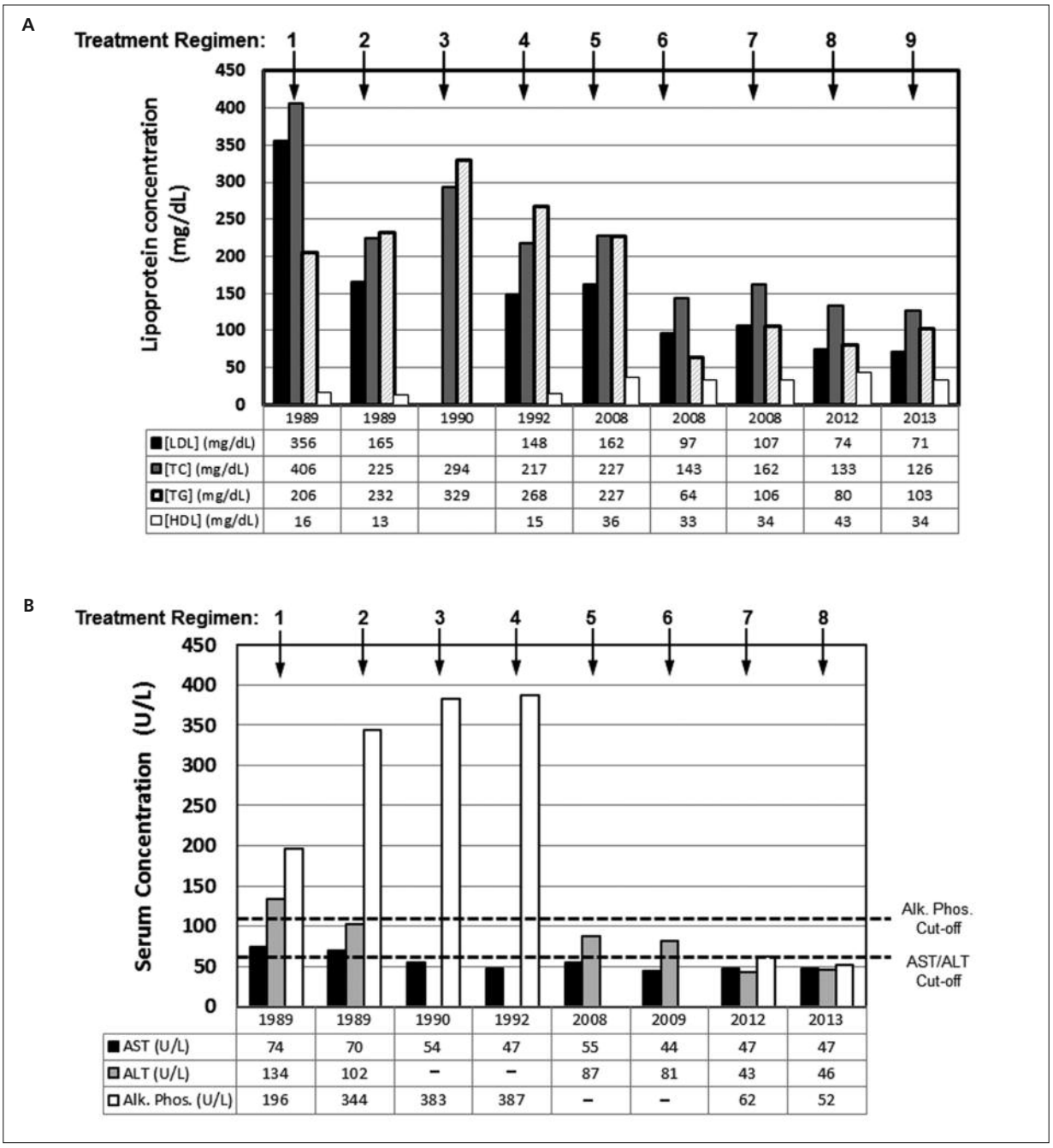

Figure 1. ***A,*** Serum concentration of lipids at the time of CESD diagnosis until medical optimization of the patient's dyslipidemia. (1) baseline (2) cholestyramine/low-fat diet (3) cornstarch/low-fat diet (4) cholestyramine/low-fat diet (5) atorvastatin 20 mg (6) atorvastatin 40 mg (7) rosuvastatin 40 mg (8) atorvastatin 40 mg + ezetimibe 10 mg (9) atorvastatin 40 mg + ezetimibe 10 mg. ***B,*** Serum concentration of liver aminotransferases and alkaline phosphatase at the time of CESD diagnosis until medical optimization of the patient's dyslipidemia. (1) baseline (2) cholestyramine (3) cornstarch/low-fat diet (4) cholestyramine/low-fat diet (5) atorvastatin 40 mg (6) rosuvastatin 40 mg (7) atorvastatin 40 mg + ezetimibe 10 mg (8) atorvastatin 40 mg + ezetimibe 10 mg.

diagnosed as a glycogen storage disease and so she was temporarily treated with cornstarch[5]. The first clue to the diagnosis of CESD is the presence of a mixed dyslipidemia with low HDL[1] (Figure 1A). The second clue is abnormal deposition of lipids in visceral organs, usually with steatosis of the liver noted on imaging studies in patients with unexplained abdominal pain, he-

patomegaly, or abnormal liver function tests[6,8]. Our patient also had episodes of profound and unexplained diarrhea which, in retrospect, may have been as an early feature of her disease as diarrhea is often reported as the single chief complaint resulting in the diagnosis of CESD in the paediatric population[9]. Abnormal liver function testing, consistent with our patient's initial presentation, is another dominant feature in every reported case of CESD[1]. The GI disturbances in our patient dissipated once her dyslipidemia was under control.

Unfortunately, there are no official guidelines for the treatment of CESD. As in our case, primary treatment focuses on normalizing the patient's lipid abnormalities. Early diagnosis is critical to avoid systemic manifestations of the disease such as nodular liver fibrosis and atherosclerosis – both common to CESD if untreated[1]. If CESD is detected in childhood, prior case reports note complete normalization of patients' lipid profile using only HMG-CoA reductase inhibitors or cholestyramine[10]. More often than not, the diagnosis of CESD is made in adulthood at which point compromise of hepatic synthetic function may leave the patient with residually low HDL even though other lipids are controlled with a low fat diet and medications[10,11]. HDL remained low in our patient which raises her risk of future adverse cardiovascular events. Thus, it seems that early identification and treatment of CESD is important to prevent the development of co-morbidities associated with the disease. Once the diagnosis of CESD was clear, a low fat diet was recommended, and our patient was initially treated with cholestyramine, escalating doses of atorvastatin alone, then rosuvastatin alone, and finally with a combination of atorvastatin and ezetimibe, similar to other cases of CESD[10-12]. Her regimen was supplemented with ezetimibe to minimize off-target statin effects and to employ the benefit of another mechanism of regulating plasma lipid content. This is not a guideline-based strategy. Improvement in both her lipid profile and liver function tests was observed with combination therapy and her symptoms dissipated. Unlike the HMG-CoA Reductase inhibitors, there is a lack of clear outcome data with respect to cholestyramine or ezetimibe on cardiovascular mortality reduction and on vascular remodeling in spite of improved lipid profiles. In patients who experienced acute coronary syndromes (ACS), dual treatment with statins and ezetimibe relative to statins alone had a similar effect on chronic vascular remodeling in spite of improved plasma LDL concentration, though the much vaunted IMPROVE-IT trial is pending publication and should address whether long-term statin therapy combined with ezetimibe shows mortality benefit over statin therapy alone[13]. For the purposes of primary prevention, however, the 2013 American Heart Association and American College of Cardiology updated guidelines do not support the use of ezetimibe or cholestryramine are first-line therapy[13-15].

Enzyme replacement therapy was first reported as a possibility for CESD since fibroblasts from a patient with CESD were reconstituted by forced LAL expression *in vitro*[16]. Early phase clinical trials focusing on LAL replacement have taken place utilizing Sebelipase Alfa by intravenous infusion, and the compound appears to be well-tolerated[17,18]. In an extreme case of CESD which caused end-stage liver disease in an adult patient, the clinical syndrome and abnormal lipid profile were rectified following orthotopic liver transplantation. This emphasizes the patient's advanced vascular disease and clinical deterioration requiring liver transplantation are direct results of the patient being lost to follow-up for many years[19]. It is interesting that some of the metabolic derangements in CESD (hypertriglyceridemia, hepatic steatosis) resemble those seen in morbidly obese patients and one may surmise that bariatric surgical procedures used to correct those metabolic derangements in the obese population may have some efficacy in metabolic disease such as CESD[20]. This, however, is speculative.

Conclusions

In summary, the key points to recognizing CESD are a combination of: 1. elevated LDL and triglycerides, 2. low HDL, and 3. unexplained hepatomegaly with or without hepatic steatosis in the context of non-specific GI complaints. The diagnosis can be made invasively via liver biopsy by detecting reduced LAL with the presence of birifrangent cholesterol ester crystals in hepatocytes[21], non-invasively using a specific magnetic resonance imaging protocol[18], by peripheral blood genomic DNA analysis, and by enzymatic testing of peripheral blood lymphocytes[22]. If detected early, the treatment for CESD is usually successful with HMG Co-A reductase inhibitors

alone or in conjunction with inhibitors of cholesterol uptake such as bile resins or cholesterol transport inhibitors. If CESD is detected late and hepatic impairment ensues the treatment is less clear though enzyme replacement therapy shows some promise, and hepatic transplant in severe cases has also been reported.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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