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Altered mental status caused by hypertriglyceridemia in an adolescent

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Keypoints

1. Several diseases and disorders can result in altered mental status in pediatric-aged patients including accidental or intentional toxicological exposure or ingestion of over-the-counter medications, prescription medications or psychotropics as well as neurologic, infectious, psychiatric, and metabolic causes.
2. Although uncommon, anecdotal reports have noted the association of hypertriglyceridemia with central nervous effects including altered mental status, seizures, and stroke.
3. Hypertriglyceridemia can occur with excessive circulating triglyceride-rich lipoproteins either from increased production or decreased peripheral clearance.
4. The management of symptomatic hypertriglyceridemia in acute settings includes restriction of oral fat intake, hyperhydration with intravenous fluids, insulin therapy, and plasmapheresis for refractory cases or those associated with severe end-organ effects including coma.

Abstract

A long list of diseases and disorders can result in altered mental status in pediatric-aged patients including neurologic, infectious, toxicological, traumatic, metabolic, and psychiatric etiologies. Laboratory testing and radiologic imaging is frequently necessary to further narrow the differential diagnosis. We present a 13-year-old adolescent who presented with altered mental status that was originally attributed to metabolic derangements associated with diabetic ketoacidosis. The subsequent laboratory work-up demonstrated lipemic serum with profound hypertriglyceridemia, which was eventually thought to be the etiology of his altered mental status. As treatment resulted in correction of the hypertriglyceridemia, his mental status improved and returned to baseline. The pathophysiology of lipid metabolism is reviewed, etiology of hypertriglyceridemia presented, and mechanisms for its role in altered mental status discussed.

Keywords

altered mental status; hypertriglyceridemia; lipid metabolism; cerebral blood flow.

Introduction

A myriad of diseases and disorders can result in altered mental status in pediatric-aged patients.[1,2] This clinical presentation is commonly encountered in the emergency department, and reaching a definitive diagnosis can be difficult as etiologies range from neurologic, infectious, toxicological, traumatic, metabolic and even psychiatric.[3,4] In adolescents, the most common etiologies of alterations in mental status are the accidental exposure to

or intentional ingestion of medications as well as neurologic, infectious or psychiatric etiologies. Metabolic etiologies may include diabetes ketoacidosis (DKA), electrolyte derangements, hyperammonemia, and uremia.[1-3] During the initial presentation and evaluation, the history and physical examination may offer specific clues as to the etiology. However, laboratory testing and radiologic imaging is frequently necessary to further narrow the differential diagnosis.

Hypertriglyceridemia is defined as a fasting serum triglyceride (TG) above the 95th percentile for age and gender, which generally includes fasting serum values ≥130 mg/dl in adolescents and ≥100 mg/dl in children aged 0-9 years.[5] Risk factors such as primary hypertriglyceridemia and the rising incidence of childhood obesity have led to the increased occurrence of hypertriglyceridemia, with an estimated incidence of 10% of children and adolescents in the United States. While the majority of focus has been on long term consequences of hypertriglyceridemia including the progression of atherosclerotic disease, acute complications have been reported including pancreatitis and ischemic stroke due to triglyceride-induced plasma hyperviscosity.[6,7] We present a 13-year-old adolescent who presented with altered mental status that was originally attributed to DKA. The subsequent work-up demonstrated hypertriglyceridemia, which was eventually thought to be the etiology of his altered mental status. The pathophysiology of lipid metabolism is reviewed, etiology of hypertriglyceridemia presented, and mechanisms for its role in altered mental status discussed.

Case report

Review of this case and presentation in this format followed the guidelines of the Institutional Review Board of Nationwide Children's Hospital. A 13-year-old, 104.2-kilogram (body mass index 32.8 kg/M^2) African American male adolescent presented to the Emergency Department (ED) with a 24-hour history of nausea, vomiting, and abdominal pain that progressed to altered mental status. He had a past medical history of obesity, moderate persistent asthma, pre-diabetic HbA1C levels, dyslipidemia, and a strong family history of type 1 diabetes mellitus. On examination, he was disoriented and agitated with a Glasgow coma scale (GCS) of 11 (E3V3M5). His body temperature was 37.6°C, pulse rate 146 beats/minute, respiratory rate 30 breaths/minute with Kussmaul breathing, and oxygen saturation 97%. His cardiac, respiratory, and abdominal examination were unremarkable.

The remainder of his neurologic examination was non-focal. Point-of-care glucose test in the ED was 552 mg/dL (60-115 mg/dL). He received 3% hypertonic saline (5 mL/kg) to treat suspected cerebral edema and an insulin infusion was started at 0.1 units/kg/hour. A non-contrast computed tomography (CT) scan of the head was negative for cerebral edema, bleeding or space occupying lesions.

A venous blood gas revealed pH 7.14 (7.32-7.42), pCO2 34 mmHg (40-50 mmHg), pO2 <30 mmHg (25-47 mmHg), $HCO3^-$ 11 mmol/L (21-30 mmol/L), and base deficit -16.6 mmol/L. Urinalysis showed glucosuria ≥ 500 mg/dL, ketones 80 mg/dL, proteinuria 30 mg/dL, and moderate occult blood. Other chemistries and basic laboratory values were not able to be obtained due to difficulties in securing venipuncture related to the patient's agitation. While in the ED, the patient developed a fever (38.6°C) and received rectal acetaminophen. Broad spectrum antibiotics (ceftriaxone and vancomycin) were started, and he was admitted to the Pediatric Intensive Care Unit (PICU) for further management. The patient was held *nil per os*, maintenance intravenous fluids were administered, and hourly neurologic assessments were started. Hyperglycemia was treated with an insulin infusion per the standard protocol for DKA. Due to the fever and altered mental status that were thought to be out of line with the metabolic derangements, a lumbar puncture was performed which revealed white blood cell count 1/mm^3 (0-5/mm^3), glucose 351 mg/dL (40-70 mg/dL), and protein 40 mg/dL (15-45 mg/dL). Intravenous

acyclovir was added to the antibiotic regimen. Dexmedetomidine was started to control agitation.

Blood samples drawn were noted to be grossly lipemic and subsequent laboratory results revealed an elevated serum glycohemoglobin (HbA1C) 13.7% (4.0-5.6%), markedly high serum lipid profile with a lipase 1450 U/L (<202 U/L), triglyceride (TG) 2984 mg/dL (60-134 mg/dL), total cholesterol 321 mg/dL (95-195 mg/dL), and reduced high density lipoprotein (HDL) cholesterol 23 mg/dL (44-62 mg/dL). Serum electrolytes revealed hyperkalemia 7.0 mmol/L (3.6-4.9 mmol/L), hypermagnesemia 2.7 mg/dL (1.5-2.4 mg/dL), hypophosphatemia 2.7 mg/dL (3.3-5.4 mg/dL), HCO_3^- 7 mmol/L (21-30 mmol/L), and a high anion gap metabolic acidosis with an anion gap of 23 mmol/L. Renal function was impaired with an elevated creatinine 1.3 mg/dL (0.6-0.8 mg/dL) and blood urea nitrogen 41 mg/dL (5-18 mg/dL). Inflammatory markers including C-reactive protein 7.0 mg/dL (<1.0 mg/dL), erythrocyte sedimentation rate 76 mm/hr (<13 mm/hr) and procalcitonin 34.5 ng/mL (<0.5 ng/mL) were elevated. The serum β-hydroxy butyrate 8.96 mmol/L (<0.30 mmol/L) and lactate 2.6 mmol/L (0.5-2.2 mmol/L) were also elevated. Hepatic function, hemoglobin/hematocrit, white blood cells count, serum ammonia, and creatinine kinase were normal. Islet antigen 2 autoantibody, insulin antibodies, thyroid function test, anti-TPO antibody were negative. Toxicology and drug screening were negative. Cerebrospinal fluid (CSF) culture, blood culture, rapid SARS-COV-2, herpes simplex virus PCR, meningitis, encephalitis, and respiratory infection array were negative. Electrocardiography (ECG) showed sinus tachycardia, with non-specific ST changes and T wave inversion in the inferolateral leads. Initial echocardiography revealed left ventricular hypertrophy and dynamic obstruction secondary to a hyperdynamic left ventricle with decreased intravascular volume. Abdominal ultrasound revealed diffuse fatty infiltration of the liver; however, the pancreas could not be visualized. Abdominal MRI showed hepatic steatosis and interstitial edema of the pancreatitis with moderate peripancreatic fluid. Neurological assessment in the PICU showed persistence of the altered mental status in the presence of hypertriglyceridemia, despite resolving acidosis and improving hyperglycemia. Magnetic resonance imaging (MRI) of the head showed no evidence of acute infarction or bleed. There were punctuate foci of increased susceptibility in the right lateral frontal subcortical white matter, representing microhemorrhage of no clinical significance and a grossly negative contrast enhanced MRI. Twice maintenance IV fluids were continued, and an insulin infusion titrated with supplemental glucose until the TG level was <800 mg/dL. Serum triglyceride levels were monitored every 12 hours (Table 1 and Figure 1). Approximately 36 hours after admission with resolution of the profound hypertriglyceridemia, the patient's neurologic status abruptly returned to normal. The patient was transferred out of the PICU on hospital day 3. The serum triglyceride level at transfer was 1105 mg/dL. The insulin infusion and intravenous fluids were continued until hospital day 5 to treat the hypertriglyceridemia. Therapy was then transitioned to subcutaneous insulin. The patient was eventually discharged home on hospital day 7 with a TG level of 384 mg/dL on low-fat-diabetic diet and intermittent subcutaneous insulin. His serum triglyceride at his 6-month follow-up was 122 mg/dL.

Discussion

Hypertriglyceridemia is defined as a fasting serum triglyceride level ≥130 mg/dL in the adolescent age group.[8] Triglyceride is obtained from dietary fat and synthesized endogenously by the liver. The process of digestion and absorption of fat begins with the intraluminal hydrolysis of fat followed by digestion by brush border enzymes and lymphatic transport into the circulation. Dietary fat is commonly consumed as triacylglycerol (TAG). Digestion begins in the oral cavity with lingual lipase followed by gastric lipase that is secreted from chief cells in the fundus to begin the breakdown of TAG into diglycerides and fatty acids. The stomach contents enter the small

intestine where pancreatic enzymes (lipase and colipase) further breakdown fats into free fatty acids and monoglycerides.[9] These fatty acids then combine with bile salts that are released from the gallbladder to form micelles that facilitate lipid transportation across the intestinal membrane.[10] Once absorbed into the intestinal lumen, lipoproteins travel as chylomicrons into the lymphatic system for release into the bloodstream throughout the body to provide energy for various cellular functions. Circulating chylomicrons are cleared by the enzyme lipoprotein lipase (LPL). LPL facilitates the lipolysis of triglycerides in triglyceride-rich lipoproteins into free fatty acids.[6] Fatty acids are then taken up as an active fuel-source by the muscle cells and stored in the adipose tissue as inactive fuel. Excess fat is stored as cytoplasmic lipid droplets. The activity of LPL is regulated by the interaction of several proteins involved in its promotion and suppression.[6,8] Mutations in LPL and these regulatory proteins genes play key roles in the pathophysiology of hypertriglyceridemia.

Hypertriglyceridemia can occur due to excessive circulating triglyceride-rich lipoproteins either from increased production or decreased peripheral clearance.[6,8,10] The underlying etiology can be primary or secondary. Primary causes include genetic syndromes such as; familial hyperchylomicronemia (type I), familial combined hyperlipidemia (types IIb), dysbetalipoproteinemia (type III), multifactorial hypertriglyceridemia (type IV) and multifactorial chylomicronemia (type V). Secondary causes include obesity, diabetes mellitus, metabolic syndrome, excessive alcohol intake, autoimmune diseases, hypothyroidism, renal disease, and medications.[6,8,11] The etiology of our patient's hypertriglyceridemia was proposed to be due to secondary causes including obesity, prediabetes, sedentary lifestyle, and a diet high in carbohydrate and fat. During his admission, he was noted to have some degree of insulin resistance with radiographic evidence of fatty liver. Genetic factors were likely involved as there was a parental history of hypertriglyceridemia.

Although the main focus remains on the potential long term sequelae of hypertriglyceridemia including accelerated atherosclerotic disease, acute manifestations have also been reported. Our patient presented with severe hypertriglyceridemia associated with altered mental. With correction of the TG value, there was a prompt resolution of the altered mental status. Additionally, exhaustive work-up failed to reveal another etiology for the altered mental status thereby suggesting that the altered mental status was the result of alterations in cerebral blood flow due to the high TG level and hyperviscosity.

Previous anecdotal reports have noted the association of hypertriglyceridemia and various neurological manifestations.[7,12,13] Inokuchi et al. reported a 56 year-old man who presented with acute onset of coma.[7] Laboratory investigations showed profound hypertriglyceridemia, hyperglycemia, and elevated plasma viscosity. CNS imaging (CT and MRI) was normal. Treatment resulted in correction of the hypertriglyceridemia and return of normal consciousness as serum triglyceride levels decreased over the course of 3 days. The authors documented hyperviscosity on laboratory analysis and suggested that the alteration in consciousness was related to triglyceride-mediated hyperviscosity. Others have demonstrated the effect of hypertriglyceridemia on plasma viscosity as well as the impact of increased plasma viscosity on cerebral blood flow.[12-15] Lee et al reported a 14-year-old adolescent who presented with a 3-day history of headaches and an initial work-up demonstrating DKA.[12] Over the initial course of her hospitalization, she developed a depressed level of consciousness that did not improve despite therapy and correction of the DKA. Further evaluation revealed lipemic serum samples with severe hypertriglyceridemia. Thirty-six hours into management, the encephalopathy persisted with an increasing serum lipase levels. After the initial cycle of plasmapheresis, aimed at preventing hypertriglyceridemia-induced pancreatitis, they noted an immediate resolution of encephalopathy and marked reduction is serum triglyceride. Onal et reported resolution of coma, encephalopathy, and seizures

following exchange transfusion in a 6-month-old with severe hypertriglyceridemia (serum TG level 51,300 mg/dL) related to type I hyperlipoproteinemia).[13] In these three cases, the neurologic symptoms were attributed to alterations in cerebral blood flow related to hyperviscosity caused by the hypertriglyceridemia.[14-16] These cases highlight that neurologic symptoms induced by hypertriglyceridemia may be otherwise be overlooked or attributed to other causes.

The management of symptomatic hypertriglyceridemia in acute settings includes restriction of oral fat intake, hyperhydration with intravenous fluids, insulin therapy, and plasmapheresis or exchange transfusion for refractory cases or those associated with severe end-organ effects including coma.[13,17,18] Insulin acts as a potent activator of the enzyme lipoprotein lipase which removes triglycerides from the circulation. It is likewise effective in the setting of co-existing diabetes. Plasmapheresis has been shown to be a rapid and effective therapy in decreasing serum triglyceride levels and reducing blood viscosity.[17,18] Long-term management includes non-pharmacological therapies such as dietary modifications and weight loss.[19] Dietary therapy includes decreased caloric intake, fat restrictions, substitution of refined carbohydrates for complex carbohydrates, and increased consumption of dietary fiber and fish oils (omega-3 fatty acids). Daily moderate-to-vigorous physical activity and weight loss are also encouraged to reduce triglyceride levels and improve insulin sensitivity. Pharmacologic therapy includes fibrates, statins, niacin, and prescription fish oils to reduce TG and LDL cholesterol levels. Our patient was successfully managed with insulin and intravenous fluids. Atorvastatin was instituted as a long term therapy to reduce LDL cholesterol.

In summary, altered mental status can be a presentation of hypertriglyceridemia with alterations in plasma viscosity and cerebral blood flow. Acute neurological manifestation in association with severe hypertriglyceridemia may be the result of triglyceride-induced hyperviscosity with alterations in cerebral blood flow and/or thrombosis. Treatment options for the acute lowering of triglyceride levels includes hyperhydration, insulin-glucose therapy, plasmapheresis or exchange transfusion. Hypertriglyceridemia may be seen in the setting of diabetes (type 1 or 2) as a result of the deficiency of insulin. Insulin deficiency promotes lipolysis in adipose tissue followed by the release of free fatty acids which are eventually converted to very low density lipoproteins. This coupled with the inhibition of lipoprotein lipase in peripheral tissues, results in hypertriglyceridemia.

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