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Case Report

Co-occurrence of heterozygous *CREB3L3* and *APOA5* nonsense variants and polygenic risk in a patient with severe hypertriglyceridemia exacerbated by estrogen administration

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Abstract: We describe a case of a 36-year-old woman with severe hypertriglyceridemia likely caused by double heterozygosity of a known pathogenic *APOA5* nonsense variant (p.Q275X) and a novel *CREB3L3* nonsense variant (p.C296X) on a background of very strong polygenic susceptibility. Her clinical course worsened with development of eruptive xanthomata after oral administration of 2 mg estradiol twice daily for 2 weeks as part of a medical protocol for intrauterine embryo transfer following in vitro fertilization. Her triglyceride levels decreased to baseline and xanthomata resolved without treatment after discontinuation of hormonal therapy, which also resulted in termination of pregnancy. Before undergoing a second embryo transfer using her natural cycle and no exogenous hormones, the patient started combination therapy with eicosapentaenoic acid ethyl ester and gemfibrozil, leading to an ∼80% decrease in triglyceride levels. She continued treatment throughout pregnancy, which progressed to term with the delivery of healthy twins.

Introduction

Hypertriglyceridemia (HTG) with fasting triglycerides (TGs) 150–500 mg/dL is a very common polygenic condition (1:20), inherited in a complex fashion resulting from the interaction of many genes with different penetrance and exacerbated by unhealthy lifestyle choices such as obesity, sedentary lifestyle, carbohydrate-rich diet, excessive alcohol consumption, and the use of medications needed for other conditions.[1–3] It is often associated with decreased high-density lipoprotein cholesterol (HDL-C) levels and increased concentrations of small, dense low-density lipoprotein (LDL) particles, both components of the metabolic syndrome. Epidemiologic evidence indicates that plasma TG concentration is an independent risk factor for cardiovascular disease, at least in the moderate range.[4,5]

Hypertriglyceridemia with TG levels >500 mg/dL is sometimes monogenic, occasionally resulting from homozygosity or compound/double heterozygosity for pathogenic variants in 1 of 6 known genes: lipoprotein lipase (*LPL*), apolipoprotein (apo) C-II (*APOC2*) apo A-V (*APOA5*),

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glycosylphosphatidylinositol anchored HDL-binding protein 1 (*GPIHBP1*), lipase maturation factor 1 (*LMF1*), and glycerol-3-phosphate dehydrogenase 1 (*GPD1*).[1] Another reported case involved compound heterozygous rare variants of the glucokinase regulator gene (*GCKR*), which are associated with induction of de novo hepatic lipogenesis associated with unopposed effects of glucokinase.[6] Heterozygosity for rare *CREB3L3* variants, encoding the transcription factor cAMP-responsive element-binding protein H (CREB-H), has also been associated with heritable HTG.[7,8] Severe acquired HTG can also result from autoantibodies interfering with activity of LPL or GPIHBP1.[9,10] Hypertriglyceridemia with TG levels >500 mg/dL and especially >1000 mg/dL is associated with increased risk of acute pancreatitis requiring hospitalization. Other clinical manifestations of severe HTG include eruptive xanthomata and lipemia retinalis.[11] Patients with TG levels above 1000 mg/dL usually have at least some chylomicrons, and the rare inherited typically monogenic subtype of this condition is referred to as familial chylomicronemia syndrome.[11,12]

Treatment of HTG involves fibrates, niacin, omega-3-PUFAs, and statins. However, these medications often fail to bring TG levels close to normal in cases of chylomicronemia, which frequently require the adoption of a drastic very-low–fat diet to avoid repeated episodes of pancreatitis.[12] Novel therapies of severe HTG include antisense oligonucleotides targeting apo C-III and angiopoietin-like protein type 3, currently in development.[3,4]

Estrogen administration is an infrequent cause of elevated TGs, most likely via a dual effect with increased hepatic production (reduced proteasomal degradation of apo B) and decreased clearance (inhibition of LPL).[13–15] Several cases of pancreatitis caused by HTG induced by estrogen treatment during cycles of in vitro fertilization and preparation for embryo transfer have been previously described.[16–18] In the current report, we present a case of severe HTG with eruptive xanthomata but without pancreatitis, which has been successfully managed by a combination of gemfibrozil and eicosapentaenoic acid (EPA) ethyl ester. We hypothesize that this condition has been caused by double heterozygosity of a known pathogenic variant of *APOA5* and a novel, likely, pathogenic *CREB3L3* variant.

Case report

A 36-year-old white female, G2P1011, was referred to our clinic by her primary care provider after she developed eruptive xanthomata with TG > 3000 mg/dL, following intrauterine embryo transfer after IVF.

The patient prepared for embryo implantation with daily injections of 20 U of leuprolide acetate for 3 weeks before an ultrasound was performed to confirm suppression of follicular growth. At that point, she was started on 2 mg of estradiol p.o. BID and daily i.m. injections of 100 mg progesterone. Embryo transfer was performed 1 week later, and administration of estradiol and progesterone was continued.

Eleven days after embryo transfer, implantation was confirmed by positive beta human chorionic gonadotropin testing. At the same time, the patient contacted the fertility clinic via phone to report the development of a nonpruritic rash described as "raised bumps over lower portions of buttocks (not at injection sites), back of legs, and abdominal area". She was told to see an urgent care clinic, where she was diagnosed with a suspected allergic reaction to administered hormones and instructed to take diphenhydramine for the relief of symptoms. Because the antihistamine was not helping and the rash spread and became painful, 2 days later, the patient discontinued hormonal therapy and spontaneous abortion ensued. She was referred to dermatology, where eruptive xanthomata were diagnosed. Four weeks after discontinuation of hormonal therapy, a lipid panel was obtained showing TGs of 3223 mg/dL, with HDL-C of 24 mg/dL, direct LDL-C of 32 mg/dL, and total cholesterol of 211 mg/dL. Her complete metabolic profile, glycated hemoglobin and thyroid stimulating hormone levels were all normal at the same time.

The patient reported to have been told in the past about having high cholesterol and TGs, although she did not remember specific values and was never prescribed any treatment. She never had eruptive skin rash before the reported episode. Her previous natural pregnancy was uneventful, except that the newborn was large for gestational age and she was tested for gestational diabetes with negative results. The patient was not diagnosed with pancreatitis and never experienced unexplained abdominal pain or nausea/vomiting. The rest of medical and surgical history was unremarkable. She did not report taking any diet supplements or herbal preparations.

Family history was significant for her paternal grandmother having high TGs, without reported pancreatitis or heart disease. Her father had a myocardial infarction in his 60s but did not have a clear history of dyslipidemia. Her mother reports high cholesterol without TG elevation. Two paternal half-sisters are apparently healthy but have not been tested for lipid levels. Social history was unremarkable: the patient has never smoked, does not drink alcohol, exercises regularly, and follows a healthy diet plan rich in whole grains, fruits, vegetables, fish, and white meat. She works as an executive in a technology company and perceives her job to be stressful.

Patient vitals included heart rate of 52, respiratory rate of 16, and blood pressure of 112/72. Her body mass index was 24.78 kg/m^2. Physical examination was unremarkable, except very discrete palmar xanthomata, while her eruptive xanthomata have already been resolved. Specifically, there was no hepatosplenomegaly or abdominal tenderness.

After the initial visit, the patient has been advised to start a very-low–fat diet and was referred to a dietician in our lipid clinic. The patient was also advised to start EPA ethyl ester 4 g daily, with instructions to continue it during possible planned pregnancy despite it being a category C, because benefits were deemed to outweigh the risk. For future embryo transfer, the use of natural cycle and