Type V hypertriglyceridemia in children, a therapeutic challenge in pediatrics
A case report and a review of the literature

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Abstract
Rationale: Hypertriglyceridemia is defined as a level of triglycerides above 150 mg/dL. The complex causes and classification of hypertriglyceridemia lead to difficulties in the diagnosis and management of this condition.

Patient concerns: We present the case of a 15 years and 6 months old female teenager, admitted in our clinic for the following complaints: severe abdominal pain predominantly in the lateral left quadrant, nausea, vomiting, and the lack of stools for 2 days. The clinical exam showed: impaired general status, painful abdomen at superficial and deep palpation in the left and upper abdominal quadrants, the absence of stools for 2 days.

Diagnoses: The laboratory parameters revealed leucocytosis with neutrophilia, thrombocytopenia, high level of serum amylase and triglycerides, and increased inflammatory biomarkers. The imagistic investigations showed ascites and paralytic ileus.

Interventions: The management was burdened by the side-effects of hypolipidemic drugs impairing the liver function and leading to rhabdomyolysis, but eventually the patient’s outcome was good.

Outcomes: Type V hyperlipoproteinemia is a rare condition accounting for approximately 5% of the cases. The risk for acute pancreatitis is well-known to be associated with hypertriglyceridemia, even though in rare cases.

Lessons: The prognosis of hypertriglyceridemia is pediatrics is burdened not only by the long-term risk factors associated to the diseases itself, but also by the negative effects of long-term hypolipidemic treatment.

Abbreviations: Chol = total cholesterol, CRP = C-reactive protein, CT = computer tomography, ESR = erythrocyte sedimentation rate, HDL = high-density lipoproteins, HTg = hypertriglyceridemia, Leu = leukocytes, Na = natrium, Neu = neutrophils, Plt = platelets, Tg = triglycerides.

Keywords: children, hepatic cytolysis, hypertriglyceridemia, rhabdomyolysis

1. Introduction
The definition of hypertriglyceridemia consists in a fasting (10–12 hours) plasma triglycerides (Tg) concentration above 150 mg/dL, while severe hypertriglyceridemia (HTg) is defined as a level of Tg above 885 mg/dL, or, according to other authors, above 500 mg/dL.1,2 For example, in the United States, the prevalence of Tg above 885 mg/dL, or, according to other authors, above 500 mg/dL, is approximately 30%.3,4 HTg is divided into primary and secondary types, and even though most of the patients encountered with HTg have at least 1 secondary factor, not everyone with the same risk factor develops equally severe HTg suggesting that the endogenous primary monogenic or polygenic susceptibility carries and important role.5,6 According to Friedrichson’s classification of hyperlipoproteinemias, the only 2 types that suppose the presence of chylomicrons in plasma are types I and V.6 The differences between types I and V consist in the level of cholesterol and frequency. Therefore, type I hyperlipoproteinemia is defined by the presence of chylomicrons, a normal level of total Chol, a very high level of Tg, and a relative frequency below 1%; whereas type V hyperlipoproteinemia is characterized by the presence of chylomicrons and very low density lipoproteins, an increased level of cholesterol, a very high level of Tg, and a slightly higher relative frequency, of approximately 5%.6,8 These 2 types are also called familial chylomiconemia, and primary mixed hyperlipidemia, respectively. Their clinical picture includes: eruptive xanthomata, lipemia retinalis, hepatosplenomegaly, focal neurologic symptoms (e.g., irritability), and recurrent abdominal pain with high risk for pancreatitis, but these are not mandatory to be found in all patients. In certain cases, extremely high levels of chylomicrons can cause the so-called chylomiconemia syndrome characterized by recurrent abdominal pain, nausea, vomiting, and pancreatitis, and it supposes a level of Tg above 2000 mg/dL.2,2

Type V hyperlipoproteinemia carries the severest hypertriglyceridemia and it is classically caused by 2 rare genetic conditions, familial lipoprotein lipase deficiency, and familial
lipoprotein C-II deficiency. In contrast to this condition, type V hyperlipoproteinemia is much more complex, it rarely expresses familial occurrence, and its inheritance pattern is variable. Therefore, type V hyperlipoproteinemia is considered to develop in genetic susceptible individuals triggered by acquired environmental factors.

Besides these primary types of HTg, there were described multiple secondary causes that can lead to HTg. Among these we recall different medical conditions such as diabetes mellitus, hypothyroidism, obesity, and nephrotic syndrome, but also certain drugs, high carbohydrate diets, and alcohol consumption. Nevertheless, most commonly HTg is a result of a complex of factors in individuals with genetic susceptibility.

HTg is a well-known risk factor for pancreatitis, and it can represent a leading cause in 1 to 4% of cases diagnosed with this condition. The risk for pancreatitis is significantly clinically when the Tg level exceeds 1 000mg/dL, but it was also encountered in patients with Tg levels above 500mg/dL. Patients diagnosed with types I and V hyperlipoproteinemia experience frequent episodes of abdominal suggesting recurrent episodes of acute pancreatitis.

We report this case with the aim of underlining a rare case of type V hyperlipoproteinemia diagnosed in a female teenager associated with the impairment of pancreas, and the challenges associated to the management.

Informed consent was obtained from the patient's father (legal guardian) for the publication of this case report.

2. Case report

2.1. Presenting concerns

We present the case of a 15 years and 6-month-old female teenager, admitted in our clinic for the following complaints: severe abdominal pain predominantly in the lateral left quadrant, nausea, vomiting, and the lack of stools for 2 days. The familial history revealed both parents with obesity. The personal history did not show anything pathological.

2.2. Clinical findings

The clinical exam at the moment of admission showed: impaired general status, painful abdomen at superficial and deep palpation in the left and upper abdominal quadrants, the absence of stools for 2 days. The patient's weight was 60kg, and her height was 150cm.

2.3. Diagnostic focus and assessment

We performed a CBC count at the moment of admission, which revealed leukocytosis (Leu 15,300/µL) with neutrophilia (Neu 12,500/µL), and thrombocytopenia (Plt 81,000/µL). The inflammatory biomarkers were elevated: erythrocyte sedimentation rate (ESR) 88mm/h, and C-reactive protein (CRP) was 175.34mg/L. We also found an increased level of serum amylase (174U/L), hyponatremia (Na 135mmol/L), and increased level of triglycerides (Tg 555.1mg/dL) with a normal level of total cholesterol (Chol 180.5mg/dL). The electrophoresis of lipoproteins revealed a low level of alpha-lipoproteins (7.6%), an increased level of pre-beta lipoproteins (71.2%), did not identify any beta-lipoproteins, but showed the presence of chylomicrons (21.2%). We also found a low level of apolipoprotein A (0.82g/L), and a normal level of apolipoprotein B. The level of high-density lipoproteins (HDL) was severely decreased, 16.8mg/dL.

We performed also other tests, such as thyroid hormones, antinuclear antibodies, serology for viral hepatitis and HIV, but they were all negative. The urinary exam was also within the normal ranges. The abdominal ultrasound revealed a medium quantity of free abdominal fluid surrounding the spleen (of approximately 5cm), and also in the Douglas pouch. Therefore, we performed an abdominal CT scan that confirmed the ultrasound findings and also showed the descending colon with filiform caliber associated with severe stasis of feces above this segment (up to the cecum), and multiple small adenopathies surrounding the abdominal aorta and inferior vena cava. We also performed an echocardiography and a carotid Doppler ultrasound, but they did not reveal anything pathological. Both parents tested for a potential dyslipidemia, but their values were within the normal ranges. We also performed genetic tests targeting potential genetic defects in triglycerides metabolism (e.g., lipoprotein lipase deficiency), but they were normal. Therefore, our final diagnoses were type V hyperlipoproteinemia, ascites, and paralytic ileus.

2.4. Therapeutic focus and assessment

We initiated antibiotic therapy with a 3rd generation cephalosporin, analgesics, and electrolytes by vein. We also recommended a hypocaloric, hypolipidemic diet. Clinically, her evolution improved, but on the 5th day of admission, the level of Tg was 2 589.7mg/dL and Chol 303mg/dL, and therefore, according to the endocrinologist's recommendations, we initiated the therapy with statins and omega 3, but without any improvement within the next 2 weeks, the level of Tg remaining above 1000mg/dL. Therefore, we associated a fibrate compound to the therapy regimen. After approximately 2 weeks, the Tg decreased considerably (393.7mg/L), but the patient developed hepatic cytolysis (AST 240.8U/L, ALT 96.9U/L, LDH 393.7U/L) and rhabdomyolysis (creatine kinase 6 484U/L), with a normal level of creatinine. We stopped both hypolipidemic drugs and we initiated steroids for 3 days and liver protector drugs, and after the normalization of the formerly mentioned parameters, we initiated treatment only with fenofibrate and omega 3, with the normalization of Tg value (50.5mg/dL) after approximately 1 month.

2.5. Follow-up and outcome

The follow-up during the next 3 months showed the persistence of Tg values within the normal ranges, and therefore we decreased progressively the fenofibrate dose accordingly, without any associated side-effects.

3. Discussions

The diversity of causes that can lead to HTg and its complex classification make diagnosis and management a challenge for many clinicians, especially the pediatrician. Traditionally, the classifications used for HTg imply terms such as familial HTg or familial combined HTg involving a single gene or monogenic defects. Nevertheless, most causes of HTg involve usually multiple genetic factors, being defined as multigenic or polygenic. Therefore, HTg in individuals that carry a genetic susceptibility is further exacerbated by exposure to nongenetic secondary factors, such as overweight/obesity or alcohol abuse. Similarly, we consider that in our case, HTg was exacerbated by the fact that our patient was overweight, with a
body mass index of 26.6. Also, we did not identify any common genetic cause, therefore considering this case as a result of a polygenic cause. Multigenic HTg is a result of a complex cause represented by the association between an excess burden of common small-effect variants and rare heterozygous large-effect variants related or not with plasma Tg concentration. Nevertheless, many carriers of heterozygous mutations have normal Tg concentrations. Therefore, it is very clear that these types of mutations are not enough to lead to HTg, and that these carriers need an associated exposure to different environmental triggers. On the other hand, monogenic HTg expresses autosomal recessive inheritance, with a prevalence of approximately 1 in 1 million individuals, and it develops usually during childhood or adolescence. It is also true that monogenic HTg is usually more severe than polygenic, and it requires early diagnosis and management. Pugni et al described the case of newborn presenting severe hypertriglyceridemia who was diagnosed with monogenic lipoprotein lipase deficiency, and benefited by exchange transfusion, as a safe alternative to plasmapheresis, in order to prevent acute pancreatitis in young infants diagnosed with this condition.

It is well documented that high levels of Tg are strongly associated with low levels of HDL cholesterol, and that HDL owns a very important antiatherogenic function together with others cardioprotective functions like antioxidative, anti-inflammatory, and endothelium-dependent vasodilatory effects. Also, in a study performed on mice, it was proved that the overexpression of the major HDL protein, apolipoprotein A-I is a protective factor for atherosclerosis, and that it can even lead to the regression of the pre-existing atherosclerotic lesions. Our patient also presented a decreased level of HDL cholesterol and a low level of apolipoprotein A with multiple cardiovascular implications and an increased risk for long-term atherosclerotic disease. Based on the facts mentioned above, HDL can be studied as a major target for novel therapeutic approaches to decrease atherosclerosis.

HTg is a well-known cause of acute and recurrent acute pancreatitis, and the decreased awareness regarding this cause or contributing factor for acute pancreatitis is in many cases delayed or completely missed. Patients with pancreatitis caused by HTg often express recurrent attacks of abdominal pain and may require repeated hospital admissions. Therefore, an optimum control of Tg concentrations can prevent recurrences of pancreatitis. It is also true that mild to moderate elevated values of serum Tg are encountered in up to one third of all cases of acute pancreatitis, independently by the etiology hindering even more the identification of HTg as a leading cause for pancreatitis. In contrast, severely increased levels of Tg are considered uncommon, but well-established cause of acute pancreatitis, encountered in up to 4% of cases. Our patient also presented severe abdominal pain and mildly elevated level of amylase suggesting the development of a possible episode of acute pancreatitis.

The management of HTg consists in both nonpharmacological and pharmacological treatment. The nonpharmacological measures include weight reduction, dietary modifications and exercise. Also, a daily consumption of 4 grams of omega-3 fatty acids associated with restricted energy and saturated-fat intakes can decrease the concentrations of Tg by as much as 20%, but they are rarely effective as single therapy. Pharmacological therapy consists in fibrates, statins, niacin, and other emerging treatments, such as rimonabant, glitazar drugs or lipoprotein lipase gene therapy. Fibrates, i.e. gemfibrozil, bezafibrate and fenofibrate represent the mainstay of HTg treatment, and they can reduce the plasma concentrations of Tg up to 50%, raising the HDL cholesterol levels as much as 20%. The first step in the management of HTg consists in monotherapy alone with dietary adjustments. In contrast, combined therapy should be considered in cases of refractory severe hypertriglyceridemia, but it requires close monitoring of creatine kinase, transaminase and creatinine serum concentration. In our case we also initiated monotherapy, but due to the persistence of high levels of Tg, we were forced to initiate combined therapy. The patients developed hepatic cytolysis and rhabdomyolysis requiring steroids, with afterwards favorable evolution under monotherapy with fenofibrate.

4. Conclusions

Type V hyperlipoproteinaemia is a rare condition accounting for approximately 5% of the cases. The risk for acute pancreatitis is well-known to be associated with hypertriglyceridemia, even though in rare cases. The management of hypertriglyceridemia in children can be hindered by the potential side-effects of hypolipidemic drugs. The prognosis of hypertriglyceridemia is pediatrics is burdened not only by the long-term risk factors associated to the diseases itself, but also by the negative effects of long-term hypolipidemic treatment.

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