Maia M, et al., J Neonatol Clin Pediatr 2019, 6: 037
DOI: 10.24966/NCP-878X/100037

HSOA Journal of Neonatology and Clinical Pediatrics

Case Report

A Case of Severe Hypertriglyceridemia and Omega-3 Fatty Acids

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Abstract

A 4-year-old boy was referred to a Paediatric Endocrinologist due to severe obesity, global developmental delay and family history of diabetes and severe hypertriglyceridemia. At that time, serum Triglycerides (TG) levels were 137 mg/dL, but at 7 years of age they were considerably higher (410 mg/dL). Despite attempting lifestyle modifications, TG levels increased further, reaching 2312 mg/dL, and idiopathic nephropathy with paucialbuminuria also developed. Fish oil supplementation with Omega-3 Fatty Acids (OM3FA) was then prescribed and after two months TG levels dropped to 400 mg/dL and after a year they were considerably lower. The authors present this case once it represents a therapeutic challenge due to the coexistence of severe familial Hypertriglyceridemia with childhood manifestations, obesity and global developmental delay, as well as nephropathy with paucialbuminuria, which limited greatly the choices of treatment.

Keywords: Dyslipidemia; Familial; Hypertriglyceridemia; Obesity, Omega-3 fatty acids

Introduction

Hypertriglyceridemia in children means an increased plasma fasting TG concentration above the 95th percentile for age and sex [1,2]. A TG level greater than or equal to 100 mg/dL for children of ages 0 to 9 years and a level greater than or equal to 130 mg/dL for children of ages 10 to 19 years are considered above the 95th percentile [3-6]. Hypertriglyceridemia can be classified as mild to borderline high (150-199 mg/dL), moderate to high (200-499 mg/dL), very high (500-999 mg/dL), severe (1000-1999 mg/dL) and very severe (> 2000 mg/dL) [5,7,8].

Hypertriglyceridemia is a common disorder and polygenic and lifestyle factors are its main etiologic factors; monogenic etiology is much rarer [9]. It can result from either increased TG production or reduced clearance. The Fredrickson classification describes primary causes of hypertriglyceridemia according to the pattern of increased lipoproteins as shown in table 1 [10]. All except type II a exhibit increased serum TG levels. Familial hypertriglyceridemia is caused by excessive TG synthesis, which can manifest as type IV or type V hyperlipoproteinemia and is thought to affect 1 % of the population.

Diagnosis	Fredrickson phenotype	Lipoprotein (s) elevated	Serum cholesterol concentration	Serum triglyceride concentration	Relative frequency (%)
Familial Hyperchylomicronemia	I	Chylomicrons	Normal to ↑	↑↑↑↑	<1
Familial Hypercholesterolemia	IIa	LDL	↑↑	Normal	10
Familial Combined Hyperlipoproteinemia	IIb	LDL and VLDL	↑↑	↑↑	40
Dysbetalipoproteinemia	III	IDL	↑↑	↑↑↑	<1
Primary Hypertriglyceridemia	IV	VLDL	Normal to ↑	↑↑	45
Mixed Hypertriglyceridemia	V	VLDL and chylomicrons	↑ to ↑↑	↑↑↑↑	6

Table 1: Fredrickson classification.

Secondary hypertriglyceridemia is frequently caused by interplay of combinations of hormonal and environmental conditions, as well as genetic causes. Obesity, metabolic syndrome, insulin resistance and uncontrolled diabetes play a central role in secondary hypertriglyceridemia, but other causes have been described as shown in table 2 [7,11-13].

Primary hypertriglyceridemia diagnosis is based on increased fasting TG concentration in association with family history of dyslipidemia, pancreatitis and cardiovascular disease, along with associated risk factors and clinical features. It is important to exclude secondary causes of hypertriglyceridemia in all patients [8]. It is believed that moderate hypertriglyceridemia may enhance the risk of cardiovascular disease [9,14] while severe hypertriglyceridemia is strongly associated with an increased risk of acute pancreatitis [8,14,15]. Ideally, serum TG concentration should be less than 500 mg/dL to prevent pancreatitis.

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Citation: Maia M, Castro C, Santos AL, Afonso I, Santos P, et al. (2019) A Case of Severe Hypertriglyceridemia and Omega-3 Fatty Acids. J Neonatol Clin Pediatr 6: 037.

Received: October 23, 2019; **Accepted:** November 06, 2019; **Published:** November 13, 2019

Causes of secondary hypertriglyceridemia
Metabolic syndrome
Obesity
Diabetes
Hypercortisolemia
Hypothyroidism
Liver disease (including non-alcoholic fatty liver disease)
Glycogen storage disorders
Renal disease
Lipodystrophy
Infections
Autoimmune diseases
Cancer
Medication (such as steroid, glucocorticoids, estrogen, diuretics ans B-blockers, cytostatics)

Table 2: Causes of secondary hypertriglyceridemia.

There is a paucity of data on a systematic approach to management of hypertriglyceridemia in Paediatric patients and therefore the approach is mostly based on current adult guidelines that are tailored for the Paediatric population. Management is challenging due to the interplay of genetic and secondary causes and lack of evidence-based guidelines [4,8,13,16].

Case Presentation and Investigation

A 4 year-old boy with obesity (body mass index - BMI 26.1 kg/m^2, > P97) and global developmental delay was referred to a Paediatric Endocrinology consultation.

Past medical history: 38-week gestation, complicated with gestational diabetes, c-section delivery. Birth somatometry was appropriate for gestational age: Weight: 3310 g, Length: 47.5 cm, head circumference: 34 cm. During the neonatal period the newborn was admitted to the Neonatal Intensive Care Unit due to suspected neonatal sepsis, thrombocytopenia, hypoglycaemia, jaundice and small interventricular communication (fully shut at 6 months of age). Right orchidopexy was performed at 3 years of age, in order to correct cryptorchidy. Comorbidities: Global developmental delay, Obstructive Sleep Apnoea (OSA), lactose intolerance, nystagmus and hypermetropy (under ophthalmologic follow-up).

Family diseases: Father has severe primary hypertriglyceridemia (TG ~2450 mg/dL, under medication with fibrates); mother has type 2 diabetes (under medication with insulin and oral anti-diabetics).

Given the setting of severe familial hypertriglyceridemia with childhood manifestations, obesity and global developmental delay, an initial approach with an extensive blood panel was performed, including insulin levels, liver and renal function, uric acid, lipid panel (at this time TG serum levels were 137 mg/dL), hemogram and abdominal ultrasound in order to exclude related comorbidities.

Further etiological investigation was then carried out: Karyotype was normal (46 XY) and a comparative genomic hybridization array found a deletion in 15q26.1 and the patient was referred to Genetic consultation. Serum levels of amino acids, long chain fatty acids, organic acids, cortisol and thyroid hormones were normal. Glycosylation defects diseases and mucopolisacaridosis were excluded, as well as X-fragile mutations. Cerebral magnetic resonance imaging was also normal.

The lipid panel revealed, at 7 years of age, considerably high serum TG levels: 410 mg/dL (normal age-adjusted range: 28-129 mg/dL). Therefore, diet and exercise were strongly recommended, although compliance was very poor and the patient was referred to a clinical nutritionist. Nevertheless, at 8 years of age weight increased (BMI 33.9 kg/m^2, > P97) and TG levels were also significantly higher (2312 mg/dL - serum levels confirmed in laboratory through dilution and titration methods). Shortly after, nephropathy of unknown origin developed, with paucialbuminuria (urinary albumin/creatinine ratio 55.3 mg/g).

Treatment

In this particular case, considering the Paediatric setting and the coexistence of hypertriglyceridemia, obesity, OSA, nephropathy with paucialbuminuria and the risk of acute pancreatitis, the following approach was implemented:

- Moderate to intense daily physical activity for 30 to 60 minutes.
- Restricted diet with less than 25 % to 30 % of calories from fat, less than 7 % of calories from saturated fat and less than 200 mg per day of cholesterol.
- Fish oil supplementation with OM3FA (Equazen liquid®: EPA and DHA content per 15 mL: 556 mg and 174 mg, respectively).
- Non-Invasive Ventilation (NIV) during sleep: In this patient NIV may play a role in treatment and hold potential benefit until weight loss is sufficient to restore adequate ventilation, since inadequate ventilation promotes obesity and is associated with abnormal lipid profile [17,18].

After two months of fish oil supplementation, TG levels dropped to 400 mg/dL and after a year they were considerably lower (168 mg/dL - table 3).

	4 year-old	7 year-old	8 year-old	After 2 months of OM3FA	After 1 year of OM3FA
Triglyceride serum levels (mg/dL)	137	410	2312	400	168

Table 3: Evolution of triglyceride serum levels.

Outcome and Follow-Up

A multidisciplinary team composed by Paediatric Endocrinology, Nephrology, Genetic, Pneumology, Nutrition and Ophtalmology was established in order to achieve appropriate management. At 10 years of age, TG levels increased to 500 mg/dL after suspending OM3FA supplementation (despite attempting dietary measures) and returned to previous levels after resuming supplementation. Currently at 12 years of age, the child maintains sustained TG levels between 150 and 300 mg/dL, paucialbuminuria and elevated BMI (37.6 kg/m2, > P95), which still meets the criteria of obesity. To this date no other complications were recorded, namely acute pancreatitis, which was the greatest risk in this particular case.

Discussion

Pharmacotherapeutic options for children with elevated TG are limited. The main interventions remain diet modification (including increased intake of fish or dietary supplementation with fish oil) and increased physical activity and weight loss [6,19].

Regarding lifestyle modification, children and adolescents with both primary and secondary hypertriglyceridemia should be advised to follow a restricted diet: Less than 25 % to 30 % of calories from fat, less than 7 % of calories from saturated fat, less than 200 mg per day of cholesterol, and avoidance of trans fats consumption [19]. The replacement of simple carbohydrates with complex carbohydrates is also recommended, as well as limiting intake of sugar and sugar-sweetened beverages, and increasing the dietary intake of fish (to increase OM3FA consumption). Performing moderate to intense physical activity for 30 to 60 minutes daily can also reduce TG level. Weight loss is expected to improve insulin sensitivity and lead to better clearance of TG [4,19].

There is evidence that shortened sleep duration or sleep fragmentation and consequent inadequate ventilation promotes obesity and is associated with abnormal lipid profile and decreased insulin sensitivity [17,18]. The underlying mechanism for this association may include alterations in serum leptin and ghrelin levels, both of which have been implicated in the regulation of appetite. Sleep deprivation is also associated with increased neural reward processing, which may lead to increased food intake in susceptible individuals [17,20]. Therefore, weight loss can improve ventilation and general health [21,22].

Regarding pharmacological management, there are no FDA-approved TG level-lowering medications for use under 18 years of age, and there are no established indications for their use in children [7,19]. Nevertheless, extrapolation of adult guidelines may be judiciously applied in this scenario [7,8,13]. Indications for pharmacologic treatment include [4,6]: Primary hypertriglyceridemia with average TG levels > 500 mg/dL [6,12,23,24] or a single TG level > 1000 mg/dL; children with TG levels between 200 mg/dL and 499 mg/dL and a non-HDL-C ≥ 145 mg/dL may warrant pharmacologic intervention if lifestyle changes are unsuccessful [3,6,8,24] . There are several pharmacological options available.

Omega-3 Fatty Acids (OM3FA) has a TG-lowering effect entirely dependent on the content of Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA) and limited data are available on the effectiveness of this treatment [6]. The main effects of both EPA and DHA are decreased fasting and postprandial serum TG levels, through reduction of hepatic Very Low Density Lipoproteins (VLDL) and TG production. The exact mechanism for reduced VLDL production is not clear but does not include retention of lipids in the liver; rather, increased hepatic fatty acid oxidation is likely [9]. It is important to notice that when compared to prescription fish oil products that contain specific amounts of EPA, over-the-counter unregulated fish oil supplements vary in concentration of EPA and DHA. A low- dose over-the-counter fish oil trial was carried out [25] and it was verified that in patients with TG levels greater than 140 mg/dL there was no effectiveness. Fish oil supplements may be used after confirming that a patient has severe hypertriglyceridemia and a failure to control TG levels by means of lifestyle modification [19]. A trial of OM3FA supplementation (dose of 2 to 4 g per day) for patients with extremely elevated serum TG (600 to 1000 mg/dL) may be recommended. OM-3FA can be given in conjunction with fibrate therapy or as a substitute if fibrates are not tolerated [6].

Fibrates are usually reserved for children with severe TG elevations (most useful for TG levels > 1000 mg/dL, but may be considered for TG levels 600 to 1000 mg/dL and are most often used in older adolescents) [6]. They must be carefully used in patients with mild to moderate renal disease and are contraindicated in severe renal impairment [19].

Niacin (nicotinic acid) reduces plasma TG levels by 5 % to 40 % [26]. Niacin can only be used in children with at least 10 years of age and is rarely used because of high rates of side effects [6,26]. Adjustments for renal impairments in children have not been studied.

Statins are not considered a primary agent for hypertriglyceridemia treatment.

Insulin is a therapeutic option in hypertriglyceridemia-induced acute pancreatitis and was considered in this case if OM3FA were unsuccessful, since it can lower TG levels to less than 500 mg/dL over 3 to 4 days. The use of insulin promotes intracellular TG generation within adipocytes and the fatty acid metabolism in insulin sensitive cells, which reverts the stress-associated to the release of fatty acid from adipocytes [27].

In selected cases, plasmapheresis reduces serum TG levels rapidly and can be used in symptomatic patients with severe hypertriglyceridemia and pancreatitis [19]. It should also be mentioned that currently there are genetic tests capable of detecting mutations that may predispose to hypertriglyceridemia [28], but in this case in particular they were not performed. To this day, and as far as the authors are concerned, evidence suggests that such testing does not alter management or outcome in these patients.

In this case, the treatment of choice was attempting lifestyle modification and OM3FA. Fibrates were contra-indicated, since paucialbuminuria had developed and renal impairment was suspected, which is a contraindication to its use. Niacin was also not the treatment of choice, given its incidence of side- effects. Currently there are a few reported cases in which this approach was found to be effective and, therefore it is yet to be thoroughly investigated.

Take Home Messages:

- The lack of Paediatric-specific guidelines and FDA-approved TG level-lowering drugs makes the management of hypertriglyceridemia in the Paediatric setting a difficult challenge.
- Dietary restriction and physical exercise remains the main pillar of management supplemented by TG level-lowering medications.
- Limited data are available on the effectiveness of OM3FA, but in this case they have shown to be effective reducing TG levels.
- Fibrates are recommended as first-line pharmacologic therapy in patients with severe hypertriglyceridemia in order to prevent acute pancreatitis.
- A multidisciplinary team approach is essential in order to optimize treatment and achieve appropriate management.

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