CASE REPORT

Hypertriglyceridaemia unresponsive to multiple treatments

James M Backes,¹ Thomas D Dayspring,² Daniel M Hoefner,³ Patrick M Moriarty⁴

¹Department of Pharmacy Practice, University of Kansas School of Pharmacy, Kansas City, Kansas, USA

²Foundation for Health Improvement and Technology, Richmond, Virginia, USA

³Health Diagnostics Laboratory Inc, Richmond, Virginia, USA

⁴Division of Clinical Pharmacology, Department of Medicine, Kansas University Medical Center, Kansas City, Kansas, USA

Correspondence to

Dr James M Backes,
jbackes@kumc.edu

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SUMMARY

A 52-year-old man with a longstanding history of hypertriglyceridaemia (approximately 7 mmol/L (600 mg/dL)), unresponsive to treatment, presented to a lipid-specialty clinic. Additional triglyceride-lowering therapies were added with no effect. It was then noted that despite the apparent hypertriglyceridaemia, his serum sample was clear. A 'glycerol blank' was then requested from an advanced lipid laboratory, which reported a triglyceride value of 0.7 mmol/L (62 mg/dL). These findings suggest isolated asymptomatic glycerol kinase deficiency (GKD) or 'pseudohypertriglyceridaemia'. The falsely elevated triglyceride values in such individuals are a result of excess serum glycerol and clinical laboratories measuring glycerol to report triglyceride concentrations. After discontinuation or modification of the patient's primary triglyceride-lowering agents, the lipid panels and triglyceride values remained comparable to previous readings. Recognition of asymptomatic GKD is important to prevent unnecessary treatment and overestimated cardiovascular risk.

BACKGROUND

Asymptomatic glycerol kinase deficiency (GKD), or 'pseudohypertriglyceridaemia', is a perplexing and frequently misdiagnosed X linked recessive enzyme disorder often discovered after routine lipid testing.¹ Owing to the suspected risk for pancreatitis and coronary heart disease, patients are often subjected to both aggressive Therapeutic Lifestyle Changes (TLC) and combination lipid-altering drug therapy, which generally prove to be ineffective. The apparent hypertriglyceridaemia is the result of nearly all clinical laboratories utilising assays that measure glycerol to report triglyceride values—as triglycerides consist of three fatty acids attached to a glycerol backbone.² Lipases are used to de-esterify the three fatty acids from the glycerol backbone of triglyceride molecules, allowing the glycerol component to be measured. Individuals with GKD have hyperglycerolaemia; thus triglyceride values are falsely reported as being elevated. Classically, the serum of patients with actual hypertriglyceridaemia is described as turbid (figure 1), or milky/creamy.

CASE PRESENTATION

A 52-year-old man was referred to a lipid-specialty clinic, for hypertriglyceridaemia (fasting range 6.24–7.85 mmol/L (552–695 mg/dL)), unresponsive to daily doses of rosuvastatin 20 mg and fenofibrate 160 mg. He reported previous therapy with simvastatin and another trial of fenofibrate, but they were

'not effective'. The individual consumed 2 beers daily, smoked 1 pack of cigarettes per day, and his diet involved limiting saturated and trans fats. Findings from the physical examination were unremarkable including an absence of xanthomas. Body mass index was measured at 28 kg/m², with a waist circumference of 100 cm (39.5 inches). His medical history was significant for hypertension and a cerebral vascular accident.

The patient was subsequently prescribed additional TLCs and ω-3 fatty acids (fish oil), up to approximately 6500 mg of eicosapentaenoic acid (EPA)+docosahexaenoic acid (DHA) daily. The three-drug regimen (rosuvastatin, fenofibrate and EPA/DHA) produced a fasting lipid profile of: total cholesterol 2.49 mmol/L (96 mg/dL), high-density lipoprotein cholesterol (HDL-C) 1.14 mmol/L (44 mg/dL) and low-density lipoprotein cholesterol (LDL-C) 0.91 mmol/L (35 mg/dL) (directly measured), yet triglycerides remained elevated at 5.85 mmol/L (518 mg/dL), despite positive medication adherence per patient self-report. Other relevant laboratory tests included a slightly elevated glycated haemoglobin (HbA1c) of 6.0%.

During sample collection in clinic, it was noted that although the patient's recent fasting triglyceride reading was elevated (5.85 mmol/L), the serum was clear (figure 1). Given the clear sample, we requested a 'glycerol blank' from an advanced lipid laboratory, which reported a markedly lower triglyceride value of 0.7 mmol/L (62 mg/dL). It was explained to the patient that his laboratory results were suggestive of asymptomatic GKD, which most often presents as a falsely elevated triglyceride value or 'pseudohypertriglyceridaemia'.

DIFFERENTIAL DIAGNOSIS

Other potential causes of hyperglycerolaemia were ruled out including critical illness, heparin infusions, intravenous lipids, propofol and peritoneal dialysis solutions.^{2–3} We then assessed certain factors and patient characteristics. Asymptomatic GKD is commonly characterised by male gender (almost exclusively), reported elevated triglyceride values (variable but usually <11.3 mmol/L (1000 mg/dL)), visibly clear serum sample, negligible response to triglyceride-lowering therapies, absence of low HDL-C (commonly observed in those with true hypertriglyceridaemia) and, frequently, glucose impairment. Also, the patient's reported total cholesterol values were markedly lower in context to triglyceride and lipoprotein (HDL-C and LDL-C) concentrations. For example, when calculating his total cholesterol from a

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Figure 1 Collection tubes with clear serum (left) and turbid hypertriglyceridaemic serum (right) with corresponding triglyceride values of approximately 0.68 mmol/L (60 mg/dL) and approximately 5.65 mmol/L (500 mg/dL), respectively. Photo courtesy of Health Diagnostics Laboratory Inc.

rearranged Friedewald formula (SI units (mmol/L)): total cholesterol = triglyceride (TG)/2.2 + HDL-C + LDL-C (*note that if calculated for mg/dL—change to TG/5*) using his reported lipid panel values ($4.71 = 5.85/2.2 + 1.14 + 0.91$); (conventional units (mg/dL)) ($183 = 518/5 + 44 + 35$), you obtain a total cholesterol that far exceeds the reported value of 2.49 mmol/L (96 mg/dL). This discrepancy created suspicion and prompted further investigation.

To obtain a more definitive diagnosis, a ‘glycerol blank’ was requested from a clinical laboratory, to account for the excess glycerol. The challenge was identifying a laboratory that could provide such testing. We contacted several local laboratories, although none were able to accommodate our request. Ultimately, we discovered four major laboratories in the USA utilising glycerol blanking. Of note, other possible measures to further support a diagnosis of pseudohypertriglyceridaemia could have been performed, including an evaluation of blood and urine glycerol concentrations. Serum glycerol does not generally exceed 0.2 mmol/L (1.8 mg/dL), while urine glycerol excretion is normally undetectable.^{1 4}

TREATMENT

Because the patient’s LDL-C goal was achieved (at the time: <2.59 mmol/L (100 mg/dL) or optional <1.81 mmol/L (70 mg/dL)),⁵ and the accurately reported triglyceride value (0.7 mmol/L (62 mg/dL)) was optimal, we discontinued the fenofibrate and reduced the EPA/DHA to approximately 1000 mg daily (for cardioprotection). The rosuvastatin and TLCs were continued, and smoking cessation was encouraged.

OUTCOME AND FOLLOW-UP

On follow-up with his primary care physician, the patient’s lipid regimen was further modified by replacing the rosuvastatin 20 mg daily with atorvastatin 40 mg daily. Overall, the

atorvastatin and low-dose fish oil produced lipid panels and triglyceride values comparable to previous reports, during the following 18 months, despite the discontinuation of fenofibrate and high-dose fish oil. Specific ranges included total cholesterol 2.87–3.44 mmol/L (111–133 mg/dL), triglycerides 4.75–6.03 mmol/L (420–534 mg/dL), LDL-C (not reported) and HDL-C of 1.22–1.35 mmol/L (47–52 mg/dL). The patient also continued to demonstrate mild glucose impairment with fasting blood glucose values ranging from 5.38 to 6.33 mmol/L (97–114 mg/dL).

DISCUSSION

Asymptomatic GKD is a relatively benign form of the disorder compared to complex and isolated symptomatic GKD.¹ The latter forms involve infantile or early childhood metabolic crises and developmental decompensation, with complex GKD having a mortality rate of approximately 20% secondary to misdiagnosis and inappropriate management in the neonatal and childhood years. Conversely, asymptomatic GKD is frequently associated with mild to moderate glucose impairment,^{6 7} but is also linked to the symptomatic forms.¹ Thus, identification is important to allow for familial awareness that male offspring are at risk for symptomatic GKD. The prevalence of asymptomatic GKD is unknown and is generally considered rare, with approximately 25 cases being reported in the literature.⁸ However, we discovered four patients in our lipid-specialty clinic during a span of 24 months.^{9 10} Given this information, and knowing that asymptomatic GKD is frequently misdiagnosed, the actual prevalence is likely higher.

Patient’s perspective

It was a great relief to learn that my triglycerides were not actually elevated. I battled this for several years and it became quite stressful and frustrating. Many times I became upset because my physician believed that I was not taking my cholesterol medicine—when in fact I really was.

Learning points

- ▶ Isolated glycerol kinase deficiency (GKD), or ‘pseudohypertriglyceridaemia’, is frequently misdiagnosed as hypertriglyceridaemia and unsuccessfully treated with aggressive triglyceride-lowering therapies.
- ▶ Recognition of asymptomatic GKD is essential to prevent unnecessary treatment and overestimated cardiovascular risk. Additionally, identification allows for familial awareness that male offspring may be at risk for symptomatic GKD.
- ▶ This case is a classic example of discontinuing potent triglyceride-lowering agents in a patient with asymptomatic GKD with minimal changes to subsequent lipid panels and triglyceride concentrations.

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Competing interests JMB: Speaker's Bureau: Kowa Pharm, Astra Zeneca; Sanofi Research grant; Kowa Pharm. TDD: Speaker's Bureau: Astra Zeneca, Merck Advisory Board; Astra Zeneca Consultant; Health Diagnostics Laboratory. DMH: Employee: Health Diagnostics Laboratory. PMM: Research grants: Amgen, Kowa, Lilly, Novartis, Sanofi, Regeneron, Genzyme, Pfizer, Catabasis, Espirion, B Braun, Kaneka; Consultant: Regeneron, Duke Clinical Research Institute, Lilly, Catabasis, B Braun, Kaneka, Genzyme; Honoraria: Amarin, Kowa, Aegerion.

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