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Lithium—a role in hyperlipidemia?

To the Editor:

We report the case of a 38-year-old Caucasian woman who was admitted to our department in March 2006 because of a fasting cholesterol level of 600 mg/dL (15.52 mmol/L) and fasting triglyceride level of 4354 mg/dL (49.63 mmol/L). Other measurements of hepatic and renal function, pancreatic enzymes, sodium, and potassium as well as the blood count were normal. She has been pretreated with 80 mg of fluvastatin and 375 mg nicotinic acid since February 2006. This treatment was started because of elevated values for total cholesterol (524 mg/dL [13.55 mmol/L]) and serum triglycerides (2520 mg/dL [28.45 mmol/L]). At presentation, the patient was free of symptoms. Physical examination showed a body mass index of 31 kg/m^2; otherwise, there were no pathologic findings, especially of xanthoma or xanthelasma. The patient was not hypertensive. There was no family history of hyperlipidemia.

The patient had endogenous depression in 2004 and was treated with risperidone, lorazepam, pipamperone, and zopiclon from June to July 2004. In addition, she received biperiden to prevent extrapyramidal symptoms. To prevent a recurrence of depression, the patient had then been treated with lithium carbonate from July 2004 until February 2006. It is worth mentioning that her cholesterol and triglyceride levels were reported normal in July 2004. At this time, total cholesterol was 198 mg/dL (5.12 mmol/L) and triglycerides were 175 mg/dL (1.98 mmol/L). Cholesterol and triglycerides were found elevated for the first time in August 2005. Total cholesterol was only slightly elevated at 255 mg/dL (6.59 mmol/L) and triglycerides were measured at 1690 mg/dL (19.08 mmol/L) (Fig. 1). Unfortunately, between July 2004 and August 2005, no other measurements of total cholesterol or triglycerides were performed.

Thyroid dysfunction, elevated alcohol intake, hormonal contraceptive therapy, paraproteinemia, renal insufficiency, as well as overt diabetes mellitus were excluded in our laboratory. The only pathologic finding was an impaired fasting glucose concentration of 115 mg/dL (6.44 mmol/L) according to American Diabetes Association criteria. Controls of the fasting glucose levels were within the same range; furthermore, a pathologic glucose tolerance had been confirmed by oral glucose tolerance test. Ultrasonography showed signs of steatosis hepatis. It is not known if she had lipemia retinalis. Under the assumption that the therapy with statin and nictonic acid was ineffective, the treatment was withdrawn. The indices of hyperlipidemia remained stable

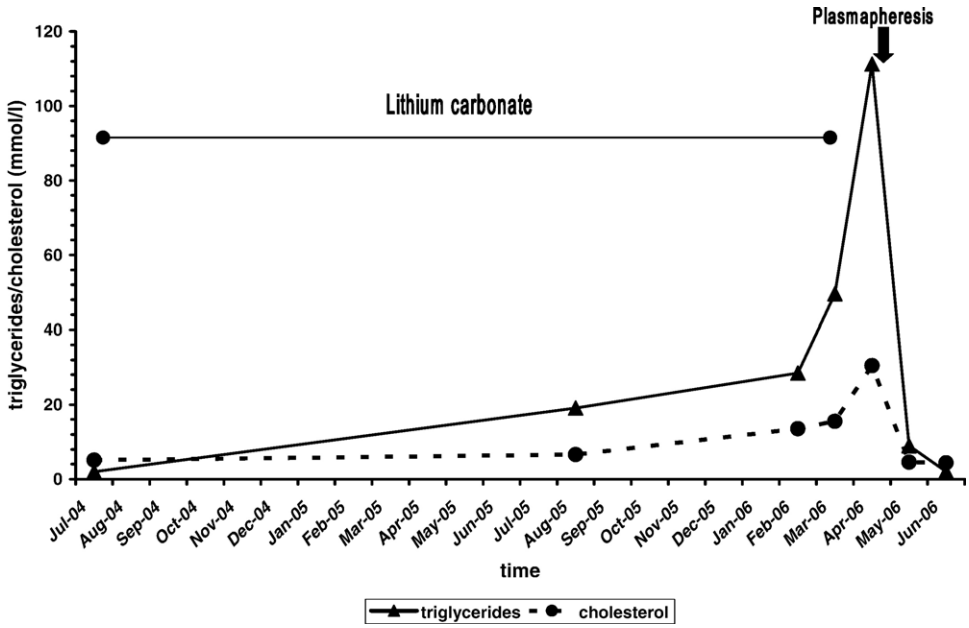

Fig. 1. Course of serum cholesterol and triglycerides (mmol/L) in the patient.

for approximately 3 weeks, but increased to a total cholesterol of 1178 mg/dL (30.46 mmol/L) and triglycerides of 9757 mg/dL (111.23 mmol/L) in January 2006. At this time, the pancreatic lipase was elevated to 428 U/L (reference range 0-59 U/L). The patient remained free of any symptoms. Because of this excessive hyperlipidemia and the high risk of pancreatitis, we decided to initiate plasmapheresis treatment, which was performed 7 times and eventually led to a decrease of the triglycerides to 787 mg/dL (8.97 mmol/L) and the cholesterol to 176 mg/dL (4.55 mmol/L). After initiation of a treatment with 600 mg gemfibrocil twice daily and 375 mg of nicotinic acid supported by a low-fat diet, we achieved a decrease of the triglycerides to 179 mg/dL (2.04 mmol/L) and total cholesterol to 169 mg/dL (4.37 mmol/L) in June 2006 with no clinical signs or laboratory findings of myopathia. To date, the patient has achieved a weight loss of 3 kg.

Apart from evaluating the above-mentioned and not present risk factors for hyperlipidemia besides pathologic glucose tolerance, genetic analysis of the LPL gene was performed as follows: Genomic DNA was prepared from 200 μL of peripheral whole blood. Polymerase chain reaction (PCR) was carried out for exons 1 through 9 with the following primers:

F1-hLPL	ATAgCCAATAggTgATgAgg
R1-hLPL	ATCCTCAgTTCgggTggC
F2-hLPL	CTCCAgTTAACCTCATATCC
R2-hLPL	ggAgATCCACgTgAgATgT
F3-hLPL	gTgTATTgggCTgATgTATC
R3-hLPL	TATCCACgCTgATTCTgAAg
F4/5hLPL	TggCAgAACTgTAAgCACC
R4/5hLPL	gggTTAAggATAAgAgTCAC
F6-hLPL	TgCCgAgATACAATCTTg
R6-hLPL	TCAgTACATgTgATgCAgTg
F7-hLPL	TCTgAATTgCCTgACTATTTg
R7-hLPL	TCTAggCATCgCTCTCTgC
F8-hLPL	gCAgggAgAgCTgATCTC
R8-hLPL	TATgTTTTCCTTACATgAAATAC
F9-hLPL	AACAgTCCTgACAgAACTg
R9-hLPL	TCACATgAgTCAgggCAAg

The amplification reactions for every single exon were performed in a thermocycler (GeneAmp PCR System 9600 from Applied Biosystems/Perkin Elmer, Weiterstadt, Germany) using approximately 50 ng of genomic DNA and 10×10^{-3} nmol of each primer (TibMolbiol, Berlin, Germany). The PCR conditions were the same as previously described [1]. Sequencing analysis of the PCR products was carried out on a CEQ 8800 capillary sequencer (Beckman Coulter, Krefeld, Germany). Neither a known nor a novel mutation could be detected when comparing the results to the published sequence of clone NC_000008 from GenBank.

Single nucleotide polymorphism analysis of apolipoprotein B-100 (R3500Q) and CETP genes (B1/B2) resulted in wild types for the patient. She showed an E3/E4 apolipoprotein E genotype and homozygosity for CYP7A1 −204C alleles.

To summarize, we found no adequate explanation for the excessive hyperlipidemia observed in this patient; the pathologic glucose tolerance was unlikely to be able to cause such an increase especially in triglycerides. Referring to the pharmaceutical information, none of the drugs the patient received initially (June 2004 to July 2004) as primary treatment of her depression has hypertriglyceridemia as known side effect. In the medical literature, cases of hypertriglyceridemia during treatment with atypical neuroleptic drugs such as risperidone have been described [2-5]. However, the study of these articles reveals that the hypertriglyceridemia described is moderate in most cases. Some cases with higher triglyceride levels were described in patients treated with neuroleptic drugs other than risperidone [3,4]. It has to be mentioned that metabolic changes are reported to improve after switching treatment to risperidone [5]. In conclusion, we do not regard the initial therapy as a cause of the extensive hypertriglyceridemia, especially because the treatment with those drugs was stopped in July 2004 with the onset of the treatment with lithium carbonate. So far, no case of hypertriglyceridemia has been described during or after treatment with lithium carbonate. Interestingly, a relation between sodium-lithium countertransport and hypertriglyceridemia has been described [6,7]. Although according to the pharmaceutical company that produces lithium carbonate, no other cases of elevated lipids during treatment with lithium carbonate have been reported, and to our knowledge, none have been reported in the medical literature, an explanation in our case for these surprisingly high lipid levels seems to be the pretreatment with lithium carbonate. It would be highly interesting if such an observation has also been made by other readers of this journal.

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