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Letters to the Editor

A link between hyperlipidemia and lithium? Confirmation of a recent previous observation

To the Editor:

After a case report published in your journal [1] and the final request by the authors of the article to submit for publication similar clinical cases, we report here another suggestive link between carbolithium treatment and the appearance of combined hyperlipidemia in a young (35 years old) white man.

The outpatient was forwarded for the first time to our endocrinology unit in March 2008 from the psychiatric clinic (where he was treated for bipolar disorder and aggressiveness) for the presence of a dramatic lipid profile with total cholesterol (TC) level of 921 mg/dL (23.8 mmol/L), triglycerides (TG) level of 2112 mg/dL (23.84 mmol/L), and high-density lipoprotein (HDL) level of 26 mg/dL (0.67 mmol/L). All the other laboratory determinations such as the kidney, hepatic, and thyroid parameters; electrolytic homeostasis; and fasting glucose levels were in the reference range. He was not treated before with any agent or drug affecting lipid metabolism. When the history was taken, he denied particular clinical findings or symptoms; and the rest of the general physical examination was unremarkable. His body mass index was 30.5 kg/m^2, waist circumference was 106 cm, and blood pressure was 130/70 mm Hg. The patient denied smoking and alcohol abuse and did not report physical activity. There was no familial history of diabetes or other endocrinologic diseases, although a first-degree positive family history for overweight and hyperlipidemia was reported.

The psychiatric symptoms started in 1987; and he was treated with carbamazepine, haloperidol, and biperiden, with lipid levels in the reference range as checked on September 1989. In April 1992, after an admission to the psychiatric clinic, the patient was treated for the first time with carbolithium 300 mg twice a day in addition to the previous therapy. The first laboratory analysis in our hands is dated on August 1997 where we observed an altered lipid profile with TG of 467 mg/dL (5.27 mmol/L), TC of 215 mg/dL (5.55 mmol/L), and normal levels of other biological parameters. No significant change in body mass index at that time was observed. In July 1998, the therapy was modified to carbolithium 300 mg twice a day with a supplement of 150 mg plus citalopram, pimozide, chlorpromazine, and delorazepam. The lipid profile successive to this therapy showed TG levels of 779 mg/dL (8.79 mmol/L) and TC of 232 mg/dL (5.99 mmol/L). This therapy was continued until March 2001 when, because of the worsening of psychiatric symptoms, there was an increase of doses of carbolithium to 300 mg 3 times a day. This fact determined a dramatic increase of TG levels to 1138 mg/dL (12.84 mmol/L) and of TC to 385 mg/dL (9.95 mmol/L). With this unmodified dose of 900 mg/d of carbolithium, the patient attended the psychiatric clinic for the following 6 years before the first visit in our department in March 2008. During this period (November 2001-2007), the mean ± SD of the TG levels in the blood was 2116.8 ± 563.9 mg/dL (23.9 ± 6.36 mmol/L), that of TC was 458.0 ± 245.4 mg/dL (11.84 ± 6.34 mmol/L), and that of HDL was 45.0 ± 9.9 mg/dL (1.16 ± 0.25 mmol/L); serum lipase, amylase, and liver enzymes levels such as aspartate aminotransferase, alanine aminotransferase, and γ-glutamyltransferase were at the reference range such as serum lithium concentration with values from 0.40 to 0.70 mEq/L (reference range, 0.40-1.2 mEq/L). Despite this worsening of the lipid profile, the patient never underwent treatment with lipid-lowering drugs but received only general dietary information. Recent ultrasonography of the abdomen revealed a moderate steatosis hepatis, and the results of the carotid ultrasonographic measurements were normal.

Because there were no symptoms or laboratory findings of pancreatitis, we first decided to treat the patient with fenofibrate 200 mg/d for 3 months, reinforcing the concept of a rigorous control on total lipids intake (30% of total calories) in the diet with a weak success: TG ,1220 mg/dL (13.7 mmol/L); TC, 243 mg/dL (6.3 mmol/L); HDL, 27 mg/dL (0.69 mmol/L); low-density lipoprotein, 232 mg/dL (6.0 mmol/L) (direct measurement); creatine phosphokinase, 163 U/L; γ-glutamyltransferase, 29 U/L; ALT/AST, 26/30 U/L; fasting glucose, 87 mg/dL (4.8 mmol/L); fasting insulin, 34.3 mU/L (3-17 mU/L); apolipoprotein (apo) A-1, 1.04 mg/dL (95-194 mg/dL); and apo B, 1.24 mg/dL (47-129 mg/dL). On June 2008, the patient was prescribed a combined lipid-lowering pharmacologic therapy with fenofibrate 200 mg/d, n-3 polyunsaturated fatty acids 3 g/d, orlistat 240 mg/d, and ezetimibe 10 mg/d associated to specific hypocaloric diet (with 25% fat and less than 7% saturated fatty acids), with a weight loss of about 2.5%. This therapy determined a

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dramatic improvement of the lipid profiles (TC, 239 mg/dL [6.18 mmol/L]; HDL, 38 mg/dL [0.98 mmol/L]; TG, 272 mg/dL [3.0 mmol/L]; and low-density lipoprotein, 167 mg/dL [4.3 mmol/L]). To date, the patient maintains this complex therapy with success in terms of lipid metabolism, although the weight has not decreased furthermore.

To look at a possible explanation of this lipid phenotype in our patient, we evaluated the genetic analysis of the lipoprotein lipase gene working with genomic DNA prepared from 200 μL of peripheral whole EDTA blood. Polymerase chain reaction technical conditions and analysis for exons 1 through 9 with primers were carried out as previously reported [2]. The single nucleotide polymorphism analysis of apo B-100 (R3500Q) resulted in wild type for the patient. He showed an E4/E4 apo E genotype and a heterozygous state for the B1/B2 polymorphism of the *CETP* as well as heterozygous A-204C alleles of the *CYP7A1* gene. Thus, although the hypercholesterolemia of the patient can be coexplained by these genetic findings, the explanation for the hypertriglyceridemia remains to be elucidated.

In a previous similar psychiatric clinical case recently reported [1], the authors discussed the hyperlipidemia observed with carbolithium treatment with an interference of this drug with the sodium-lithium countertransport kinetics, as observed in overweight/obese type V hyperlipidemia subjects [3]. In fact, in psychiatric patients treated with carbolithium, a moderate lipid metabolic disorder with an increase of very low-density lipoprotein, triglycerides, and glucose together with a decrease of HDL was reported [4], markers typically observed in an insulin-resistant state. In our patient, we also observed this link between carbolithium and hyperlipidemia. It is noteworthy that linear regression showed a statistically significant correlation ($P < .01$) between the increasing doses of carbolithium during the years of treatment and the serum levels of triglycerides reached (Fig. 1). Looking at another possible mechanism affecting the lipid metabolism, we detected in our patient that the serum level of insulin-like growth factor binding protein–1 (IGFBP-1) was low when tested during the therapy with carbolithium compared with a matched obese population (n = 96 male subjects) of controls (11.8 ± 3.2 vs 23.6 ± 5.1 ng/mL, $P < .05$), although no information about this protein was available before the carbolithium therapy. It has been reported that, in in vitro experimental models, lithium can inhibit the secretion of IGFBP-1 [5] and that fibroblasts from obese patients presented an impairment of IGFBPs secretion [6], whereas in vivo studies confirmed these data because low serum levels of IGFBP-1 were observed in obese insulin-resistant subjects because of the inhibition of IGFBP-1 liver transcription by insulin [7]. Altogether, these data suggest that, in our obese patient per se affected by a well-characterized genetic lipid disorder, an additive effect of insulin and lithium on the control of IGFBP-1 levels might contribute to the worsening of the insulin-resistance state and the lipid pattern related. It is important to point out that the levels of IGFBP-1 were not significantly modified (10.2 ± 2.8 ng/mL) despite the partial weight reduction and the improvement of the lipid profile because the therapy with carbolithium was not stopped owing to the severity of psychiatric disorder.

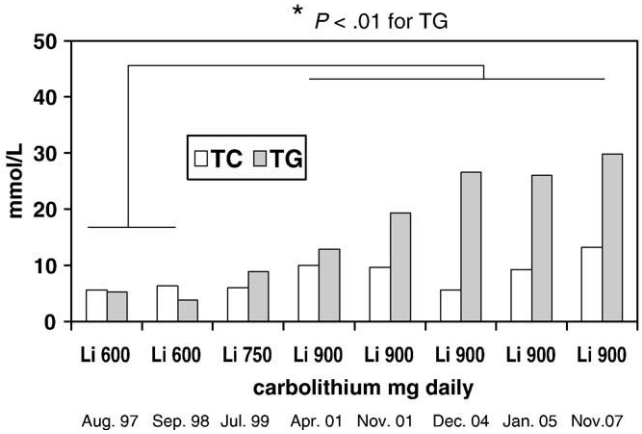

Fig. 1. Triglyceride and TC serum levels (in millimoles per liter) during treatment with increasing doses of carbolithium (in milligrams per day) from August 1997 to November 2007.

In summary, we confirm a previous report of appearance of a dramatic lipid profile in an obese psychiatric patient under treatment with high doses of carbolithium, suggesting that lipid metabolism examination should be recommended in patients chronically treated with high doses of this mood stabilizer drug. The levels of IGFBP-1 might be useful to better estimate the insulin-resistance state of the patients. The timely recognition and the first treatment with specific lipid drugs are required and recommended. A more complex therapeutic approach should be considered if the therapeutic lipid goal is not reached.

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Reply to “A link between hyperlipidemia and lithium?” by G Bardini et al

To the Editor:

In 2007, we hypothesized that the excessive hyperlipidemia of a 38-year–old woman with a peak of serum triglycerides (TG) of 9757 mg/dL (111.2 mmol/L) and of serum total cholesterol of 1178 mg/dL (30.5 mmol/L) in April 2006, making plasmapheresis mandatory, might have been caused by carbolithium treatment [1]. Other causes had been excluded in this very patient. The patient is still under our surveillance; and after withdrawal of the carbolithium treatment, her lipid values are now well controlled with gemfibrozil (600 mg bid) and nicotinic acid (500 mg). In February 2008, her serum TG were 219 mg/dL (2.5 mmol/L) and serum cholesterol was 188 mg/dL (4.9 mmol/L). The body mass index is now 30.1 kg/m^2.

Interestingly, our hypothesis is supported by the report of Bardini et al [2]. The authors describe the case of a 35-year–old man who developed dyslipidemia with a peak in TG of 2116.8 mg/dL (23.9 mmol/L) and total cholesterol of 458 mg/dL (11.8 mmol/L) in a carbolithium-dose–dependent manner.

Similarities between the 2 cases are as follows:

1. There was no history of preexisting dyslipidemia in the 2 cases (confirmed by laboratory measurement before onset of carbolithium therapy in our patient). Although the state in the Italian case is not known exactly, a preexisting dyslipidemia would very likely have been observed in a routine laboratory because the patient had been under antipsychotic therapy since 1987. Given that carbolithium is the culprit in these 2 cases, the drug seems to initiate dyslipidemia and not to aggravate a preexisting dyslipidemia.
2. The 2 patients were not only treated with carbolithium, but also with a “cocktail” of other antipsychotic drugs during the course of their disease. A possible action or an interaction together with carbolithium on the lipid metabolism should be considered.

Bardini et al observed a low level of insulin-like growth factor binding protein–1 (IGFBP-1) in their patient and speculate about a possible lithium-induced inhibition in the production of IGFBP-1 typical for an insulin-resistant state and, thus, probably contributing to dyslipidemia. In our patient, we had not measured IGFBP-1. However, calculating the homeostasis model assessment of insulin resistance score in our patient (fasting insulin, 8.6 IU/mL; fasting glucose, 96 mg/dL = 5.33 mmol/L), it is 2, suggestive of insulin resistance, too. Because insulin resistance is not uncommon and usually does not lead to excessive hyperlipidemia, it may be just one among other (unknown) pieces of the puzzle. To my knowledge, there are no more recent experimental data on the possible role of carbolithium on lipid metabolism than those described in the letters here [3-5].

What should be kept in mind is that the dyslipidemia was not that excessive in the Italian patient compared with ours. Given that lithium impacts on lipid metabolism, it remains an intriguing question whether or not there are also other carbolithium-treated patients in whom a moderate elevation of serum lipids exists. However, this may be misinterpreted as a preexisting condition; and we suggest to compare prelithium lipid levels with those under therapy.

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