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Lipoprotein abnormalities in compound heterozygous lipoprotein lipase deficiency after treatment with a low-fat diet and orlistat

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BACKGROUND: The treatment of familial hyperchylomicronemia presenting in early childhood with episodes of pancreatitis has been ineffective, and affected patients remain at risk for pancreatitis.

OBJECTIVE: To report on the effect of orlistat in siblings with severe inherited hyperchylomicronemia and to assess posttreatment lipoprotein concentrations and composition.

METHODS: Serial observations of plasma lipid levels and hospitalizations after treatment with orlistat and lipoprotein studies on a single fasting posttreatment sample.

RESULTS: The affected siblings inherited a lipoprotein lipase gene mutation from each of their parents: a novel mutation from their father (c.542G > C, p.G181R) and a known missense mutation from their mother (c.644G > A, p.G215E). When the boy presented to us at age 9 years of age and his sister at age 7 years, we found that addition of orlistat, a pancreatic lipase inhibitor, at a dose of 120 mg given before three low-fat meals a day was effective in reducing episodes of pancreatitis in the boy and in maintaining the triglyceride at lower levels in both children. During treatment, the children were observed to have elevations in apolipoprotein (apo)B, low-density lipoprotein particle concentration, abnormal apoB-containing subclasses, and deficiencies in apoA-I and apoA-II-containing lipoproteins, changes consistent with continuing increased cardiovascular risk.

CONCLUSION: The data support the need for more effective long-term treatments that not only prevent pancreatitis but also offset cardiovascular risk. Orlistat can be considered effective in augmenting the effect of a low-fat diet and reducing risk for pancreatitis.

Familial chylomicronemia, although rare (affecting 1 in 1,000,000),[1,2] presents in patients as severe lipemia associated with triglyceride levels greater than 2000 mg/dL and recurrent pancreatitis even with stringent dietary fat restriction.[3] Conventional triglyceride-lowering agents that down-

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regulate very-low-density lipoprotein (VLDL) production and enhance lipoprotein lipase such as fibrates and omega-3 fatty acids usually have been ineffective because VLDL is seldom elevated and lipoprotein lipase remains defective.[2] Recent trials of incorporating the lipoprotein lipase gene into muscle using the adeno-associated viral vector-1 coupled to a gain-of-function lipoprotein lipase gene variant (AAV1-LPL^{S447X}) have been encouraging. Initial results showed that a single administration of multiple intramuscular injections given under spinal anesthesia transiently lowered triglyceride levels for 5 months[4]; however, postprandial chylomicron clearance was improved by 93% at 14 weeks.[5] This therapy is considered to be in a developmental phase, only achieving partial success,[4,6] and the long-term effectiveness and potential for the development of this treatment method is unclear.

We present evidence that hyperchylomicronemia can be improved and the risk for pancreatitis can be reduced by the administration of orlistat (Xenical; Genentech, South San Francisco, CA), a pancreatic lipase inhibitor given before meals in affected siblings on a fat-restricted diet. In addition to documenting reduction in fasting triglyceride, we also studied the status of the remaining lipoprotein profile to determine whether lipoproteins with atherosclerotic characteristics are present in the affected children and their carrier parents.

Subjects

Case 1

A 12-year-old boy first presented at 3 months of age. His plasma was found to be lipemic during a preoperative evaluation for perirectal abscess. Subsequently, he experienced recurrent abdominal pain, and triglyceride levels increased to >13,000 mg/dL in the first year. Fat was restricted to less than 10 g per day, and medium-chain triglycerides were added.

At age 2 years 10 months, the patient's triglyceride levels were 1264 mg/dL, cholesterol 178 mg/dl, and high-density lipoprotein cholesterol (HDL-C) 11 mg/dL. Apolipoprotein (Apo)C-II was reported to be present. Amylase was 68 (25–125) and lipase 20 U/L (10–140). He first developed pancreatitis at age 5 years and had eruptive xanthomata. He presented to our clinic at the age of 8 years and was admitted to the hospital with mild acute pancreatitis and a history of 14 previous episodes of pancreatitis requiring hospital admissions. Triglyceride levels were 2670 mg/dL, cholesterol 1370 mg/dL, and HDL-C 10 mg/dL. Magnetic resonance imaging showed that the head of the pancreas appeared large and edematous; peripancreatic fluid tracked to the right of the abdomen, a short segment of regional colon was thickened, and there were lymph nodes seen in the right upper and lower quadrants consistent with inflammation.

After restriction of all oral intake and treatment with intravenous fluids, he was placed on restricted fat intake to less than 20 g per day with supplemental vitamins A, D, E, and K; vitamin C; beta-carotene; and orlistat 120 mg before meals. During the following year, he had only one episode of pancreatitis and has been symptom-free over the past 3 years, except for occasional oily stool leakage and flatulence. Lipase and amylase activities have remained normal. The fasting triglyceride levels under home conditions has ranged from 500 to 600 mg/dL over 31 months (Table 1), but the fasting triglyceride was increased on the day of the study (at age 12 years) after they had stayed at a nearby hotel overnight (Table 2). Body mass index (BMI) was 18.9, and there were no abnormal physical findings. He had attained Tanner stage 2 for puberty. Vitamin levels (with normal ranges) while the patient was receiving supplemental treatment were as follows: vitamin A, 26 μg/dL (18–77), vitamin E, 23 mg/dL (4.6–17.8), vitamin K, 5.02 ng/dL (0.28–1.78), and 25(OH)D, 20 ng/mL (30–100). The dose of vitamin D subsequently was increased to 800 mIU per day.

Case 2

A 10-year-old girl, the younger sister of case 1, first presented in the newborn nursery with a triglyceride level of >500 mg/dL, which increased to >15,000 mg/dL after the first month while she was breastfed. She was treated

Table 1 Lipid values in the affected siblings before and after orlistat treatment given as 120 mg before meals during 17 months (girl patient) and 31 months (boy patient)

Girl					Boy				
Months	TG, mg/dL	TC, mg/dL	TG:TC	HDL-C, mg/dL	Months	TG, mg/dL	TC, mg/dL	TG:TC	HDL-C, mg/dL
0†	2820	320	8.8	10	0*,†	2670	370	7.2	10
6	570	215	2.6	13	14	960	173	5.5	14
17	504	196	2.6	17	20	549	123	4.5	16
					31	515	144	3.6	15

HDL-C, HDL-cholesterol; TC, total cholesterol; TG, fasting triglycerides; TG:TC, triglycerides to cholesterol ratio.
*Patient had acute pancreatitis.
†Orlistat treatment commenced.