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Treatment of primary hypertriglyceridemia states – General approach and the role of extracorporeal methods

Claudia Stefanutti [a,*], Ulrich Julius [b]

[a] *Extracorporeal Therapeutic Techniques Unit – Department of Molecular Medicine, University of Rome Sapienza, Umberto I Hospital, 155 Viale del Policlinico, 00161 Rome, Italy*

[b] *Department of Internal Medicine III, University Hospital Carl Gustav Carus at the Technische Universität Dresden, Fetscherstr 74, 01307 Dresden, Germany*

Abstract

Hypertriglyceridemia (HTG) is a common metabolic disorder in which the concentration of very low density lipoproteins (VLDL) and of chylomicrons (CMs) is elevated in the plasma. HTG may be caused by primary and/or secondary causes and affected subjects may express HTG when children or in adulthood. In children and adults a genetic cause may underlie HTG which can be expressed as CMs a severe clinical picture known as Familial Hyperchylomicronemia due to lipoprotein lipase (LPL) or apolipoprotein (apo) CII deficiencies. Genetically determined HTG includes Familial Dysbetalipoproteinemia due to deficiency of apolipoprotein EIII of VLDL and Familial HTG. However, recent data suggest that classical Fredrickson phenotypes describing clinically HTG, which were once considered to be distinct based on biochemical features, have a shared genetic set up. The HTG has been classified according to a recent international paper: mild HTG: 2–10 mmol/L (176–882 mg/dL); severe HTG: > 10 mmol/L (>882 mg/dL) associated to CMs remnants, or Intermediate Density lipoprotein (IDL) like particles, and/or CMs. The treatment includes limitation of dietary content of saturated fat and alcohol, fibrates and omega3 fatty acids. When TG are severely elevated and associated to CMs the risk of acute pancreatitis suggests the use of more drastic therapeutic option such as therapeutic plasma exchange. This paper summarizes the experience with conventional plasmapheresis (Plasma-Exchange, PEX) and different Lipoprotein Apheresis methods with respect to acutely lowering TG levels in patients with normal TG, with mild and severe HTG. Upcoming promising therapies are gene therapy, novel apolipoprotein CIII inhibitors and lomitapide.

Keywords: Hypertriglyceridemia; Familial hyperchylomicronemia; Lipoprotein lipase; Lifestyle; Omega3-fatty acids; Fibrates; Lipoprotein apheresis; Plasma exchange; Atherosclerotic disease; Acute pancreatitis; **Apolipoprotein CIII inhibitors**; **Lomitapide**; **Alipogene tiparvovec**

1. Background

Triglycerides (TG) are mainly carried in plasma in two forms: TG-rich very low density lipoproteins (VLDL) and chylomicrons (CMs). Consequently primary Hypertriglyceridemia (HTG) results from increased concentration of either or both of these lipoprotein classes. The commonest form of primary HTG involves endogenous TG, not directly derived from dietary fats. This form is described as type IV in the Fredrickson/WHO classification [1,2]. On the other side, Hyperchylomicronemia (HCM, type I), a rare disease, is genetically, clinically and biochemically distinct. The excess of TG in plasma is partly of exogenous origin but it is related to a deficiency of lipoprotein lipase (LPL) and/or its cofactor apolipoprotein CII (apoCII). In some patients with HTG an excess of both VLDL and CMs is demonstrable. This is consistent with the type V pattern. When CMs are elevated in plasma, independently of the phenotype considered, biochemical and genetic disorders

* Corresponding author. Tel.: +39 06499970578; fax: +39 0649970141.
E-mail address: Claudia.stefanutti@uniroma1.it (C. Stefanutti).

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appear to be closely linked. Although HTG may be itself an expression of a genetic disorder: Familial Hypertriglyceridemia.

2. Primary hyperchylomicronemia (*Burger-Grutz disease*)

This relatively rare form of hyperlipidemia is characterized by gross HTG, usually in the range 15−100 mmol/L (1500−10.000 mg/dL). The condition usually presents in childhood (Fig. 1, Table 1) [1,2]. The diagnosis is most often made in the first decade, not infrequently in the first year of life. The TG are present almost entirely in CMs. The disorder appears to be due to deficiency of LPL, leading to severe impairment of the clearance of CM and other TG-rich lipoproteins from plasma (Fig. 2) [3−7]. Acute abdominal pain may occur episodically in these patients, frequently with the features of acute pancreatitis (AP). AP frequently leads to the diagnosis. Serum lipids are elevated consistently, in particular TGs, VLDL and CMs. Total cholesterol (TC) concentration is always elevated whereas HDL-cholesterol (HDL-C) can not be measured

Table 1
Baseline characteristics and apheresis technical parameters in a 25-days old newborn (male) with Familial Hyperchylomicronemia submitted to extracorporeal treatment with PEX. *Reproduced from: Stefanutti C, Lanti A, Di Giacomo S, Mareri M, De Lorenzo F, Landolfo A, Isacchi G. Therapeutic apheresis in low weight patients: technical feasibility, tolerance, compliance, and risks. Transfus Apher Sci. 2004 Aug; 31(1):3−10.*

Case 2 ([a]): Baseline characteristics	Therapeutic plasma exchange (method)
25 days old male	Anticoagulation = Heparin (30 UI/Kg)
Weight: 3.9 Kg	ACD (1:30)
Height: 56 cm	Blood flow = 15 mL/min
Type I Hyperlipoproteinemia	Balance = 100%
Triglycerides: 38,000 mg/dL	Plasma exchange = 800 mL
Cholesterol: 1200 mg/dL	Substitution solution = Albumin 5% (600 mL)
	Fresh frozen plasma = 200 mL ACD used = 46 mL (16 mL to the patient)
	Time = 90 min

ACD: Acid Citrate Dextrose.
[a] Treated by therapeutic plasma exchange.

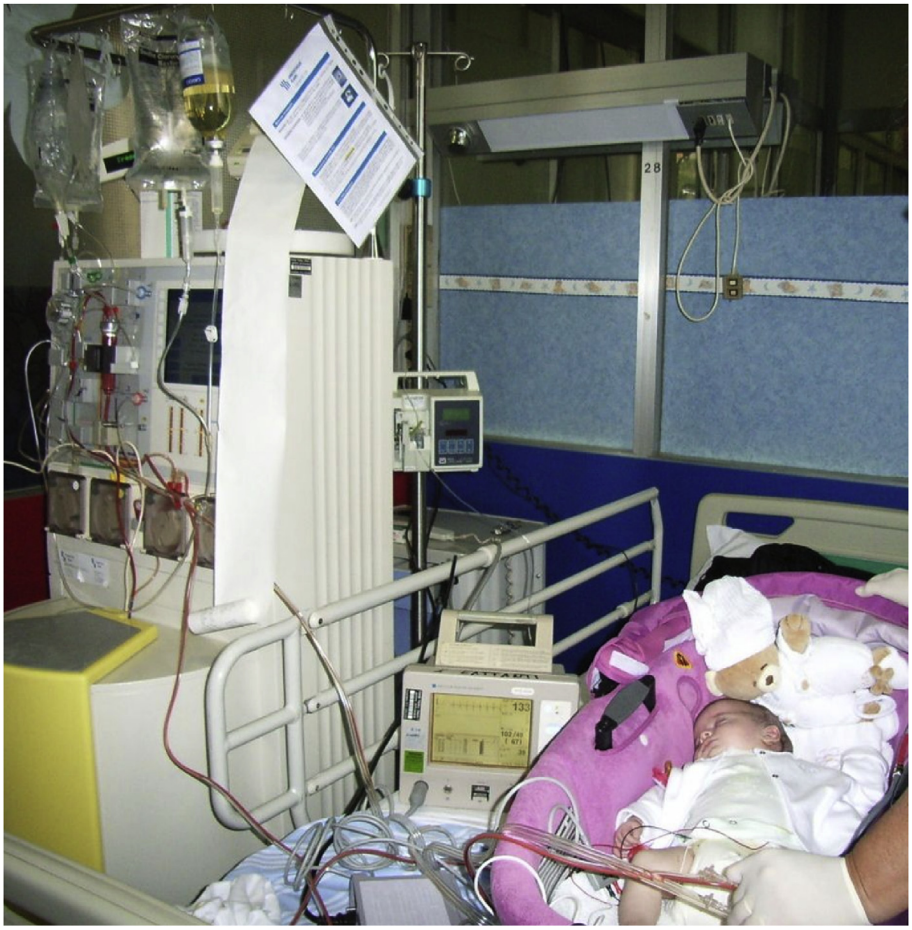

Fig. 1. Treatment of a 3-months old newborn (female) with familial hyperchylomicronemia (TG: 14.779 mg/dL; 167.00 mmol/L) by means of PEX. Details are reported in: *Stefanutti C, Gozzer M, Pisciotta L, D'Eufemia P, Bosco G, Morozzi C, Papadia F, Shafii M, Di Giacomo S, Bertolini S. A three month-old infant with severe hyperchylomicronemia: molecular diagnosis and extracorporeal treatment. Atheroscler Suppl. 2013 Jan;14(1):73−6.*