CASE REPORT

Transient chylomicronemia preceding the onset of insulin-dependent diabetes in a young girl with no humoral markers of islet autoimmunity

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Abstract

Objective: We investigated the possible causes of diabetes in a young child who presented with hyperglycemia associated with severe hypertriglyceridemia (>166 mmol/l), hypercholesterolemia (>38 mmol/l) and fasting chylomicrons.

Results: The patient did not have any of the HLA and autoantibody markers typically associated with type 1 diabetes. A glucose clamp failed to demonstrate insulin resistance (peripheral glucose utilization rate (M) = 4.3 mg/kg per min) and there was no family history of type 2 diabetes or maturity onset diabetes in youth. Both fasting and stimulated C-peptide levels, including those in response to i.v. glucagon, were below the limit of detection. This is consistent with loss of β -cell function. The family history did not reveal the existence of relatives with lipid abnormalities, coronary heart disease, and pancreatitis. We did not find any abnormality of plasma apoC_{II}, lipoprotein lipase and hepatic lipase activities. The patients had a $\epsilon 3/\epsilon 3$ apoE genotype and she rapidly cleared an oral fat load after normalization of plasma lipids.

Conclusions: The mild hyperglycemia seems an unlikely explanation for both the severe hypertriglyceridemia and chylomicronemia. A more plausible explanation is transient lipoprotein lipase deficiency. This rare condition, occasionally associated with a high-fat diet, could have caused the rapid and dramatic hypertriglyceridemia observed in this patient, which in turn might have led to the β -cell destruction by direct lipid toxicity.

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Introduction

Type 1 diabetes mellitus occurs in genetically predisposed persons as a consequence of the immune-mediated destruction of pancreatic islet β -cells that secrete insulin. The onset of clinically overt diabetes represents the end point of an insidious, progressive decline in the function of β -cells after the majority of β -cells have been damaged or destroyed (1). This asymptomatic preclinical phase, which may last from a few months to several years, is characterized by the appearance of autoantibodies against islet cell molecules such as insulin, glutamic acid decarboxylase (GAD), and a tyrosine-phosphatase-like protein known as anti-islet antigen 2 (IA-2). The presence of these antibodies is highly predictive of impending diabetes development and is considered a diagnostic marker of type 1 diabetes (2). Environmental factors may contribute to the possible development of the disease, but there is no evidence of a role for hyperlipidemia (3).

The chylomicronemic syndrome is a rare disorder characterized by massive hypertriglyceridemia and fasting chylomicronemia (4). At least two different genetic forms, lipoprotein lipase (LPL) or apoC_{II} deficiency, may be responsible for the disease. The former is relatively more frequent whereas the latter seems to have some peculiar clusters in Sicily (5, 6). A possible cause of the chylomicronemic syndrome may also be diabetes. Lack of LPL activity due to the insulin deficiency and consequent hyperglycemia has been postulated to cause fasting chylomicronemia (7). Finally, a condition of transient LPL deficiency has been described, but the prevalence of this form has not been investigated (8).

We report the onset of diabetes in a young child in whom the chylomicronemic syndrome was the main feature of her clinical presentation. Since we were able to exclude all of the most common causes of both disorders, we hypothesize that the rapid and massive hypertriglyceridemia, due to a possible transient LPL deficiency, may have led to β -cell destruction by a mechanism of

direct lipid toxicity and finally to the development of an unusual form of insulin-dependent diabetes.

Case report

A 9-year-old girl developed symptoms of mild diabetes (polyuria, polydipsia, weight loss). She was hospitalized 2 weeks later. At that time she had fasting glucose levels >11 mmol/l and urinary ketones. Plasma

triglyceride and cholesterol levels were dramatically elevated (triglyceride >166 mmol/l and cholesterol >38 mmol/l) and fasting chylomicronemia was present (Table 1). Her parents reported that she had been fed a high-fat diet to compensate for her progressive weight loss, but this diet did not result in weight gain (see Fig. 1). Secondary causes of hyperlipidemia were excluded (e.g. hypothyroidism or kidney disease). A fundus oculi exam revealed a lipemia retinalis, and eruptive xanthomatosis was noted on the arm and head skin (Fig. 1). The patient also had elevated amylase levels and a CT scan showed signs of a mild pancreatitis. Infusion with saline and glucose solutions was instituted together with i.v. insulin therapy. This approach positively affected both glucose and lipid levels (Tables 2 and 3). Pancreatic enzymes fell into normal range within 3 days (data not shown). After 4 weeks, lipid levels were normalized and have remained so for up to 24 months. The lipemia retinalis as well as the eruptive xanthomatosis lesions also resolved. The exocrine pancreatic function was normal during

Table 1 Lipoprotein parameters in the proband and relatives.

	CHO (mmol/l)	TG (mmol/l)	HDL C (mmol/l)	apoE	apoC _{II}	PvuII	HindIII
Proband	38.5	166.2	NM	$\epsilon 3/\epsilon 3$	Present	-/-	-/-
Father	4.6	1.1	1.0	$\epsilon 3/\epsilon 3$	NM	+/-	-/-
Mother	4.2	0.4	1.2	$\epsilon 3/\epsilon 3$	NM	+/-	-/-
Brother	4.5	0.5	1.1	$\epsilon 3/\epsilon 3$	NM	-/-	-/-

CHO, total cholesterol; TG, triglycerides; HDL C, HDL cholesterol; NM, not measured.

Figure 1 The proband at admittance (a), fasting chylomicronemia (b), and eruptive xanthomatosis on the head (c) and arm skin (d) with magnifications of two representative lesions.

Table 2 Plasma lipids in a 9-year-old girl with severe triglyceride elevation and fasting chylomicronemia at admittance to hospital (day 1) and during the first 5 months.

Time	CHO (mmol/l)	TG (mmol/l)	HDL C (mmol/l)	Chylo
Day 1	38.5	166.2	NM	+
Day 2	33.8	102.1	NM	+
Day 3	21.7	63.2	NM	+
Day 5	21.9	21.5	NM	+
Day 6	21.4	16.1	NM	+
Day 8	12.9	6.7	NM	–
Day 9: enteral feeding				
Week 2	10.3	6.9	0.4	–
Week 3	9.0	3.0	0.7	–
Week 4	4.8	0.6	1.3	–
Month 3	3.1	0.4	1.4	–
Month 5	3.4	0.3	1.7	–
Month 6	3.2	0.3	1.8	–

CHO, total cholesterol; TG, triglycerides; HDL C, HDL cholesterol; Chylo, presence of fasting chylomicrons; NM, not measured.

the entire period of observation. The patient has diabetes and requires insulin injections, both short and long acting, four times a day.

Materials and methods

Blood samples were collected in the morning into EDTA-containing tubes after a 12–14 h overnight fast. Total cholesterol, triglyceride, high-density lipoprotein (HDL) cholesterol, glycemia and urinary ketones were quantified by standard laboratory procedures. C-peptide levels were measured after i.v. glucagon (1 mg, bolus) using an ELISA method (Arnika, Milan, Italy). Glycated hemoglobin (HbA_{1c}) was measured by HPLC with a HA8121 Analyzer (Menarini, Florence, Italy).

Lipoprotein metabolism studies

Chylomicrons were detected after isolation from plasma by preparative ultracentrifugation under standard conditions. apoC_{II} was determined by isoelectric focusing of very low density lipoproteins (VLDL) in polyacrylamide gels as previously described (6). An oral fat load test was performed during the fourth week (day 22) using a protocol already reported using retinyl palmitate as a marker of the metabolism of chylomicrons and 'remnants' (9, 10). LPL and hepatic lipase (HL) were determined according to the method described by Krauss *et al.* (11). Samples were collected after an overnight fasting before and after 10 min after rapid i.v. administration of sodium heparin (10 units of heparin/kg). Plasma was immediately separated by a refrigerated centrifuge and stored at –80 °C until determination. In this method a normal serum is added to the emulsion as an external source of apoC_{II}. In an additional set of experiments, the sample of the proband was used in the assay of normal plasma to evaluate its own influence on lipolytic enzymes. These experiments were performed by MR at the Lawrence Berkeley National Laboratory, Berkeley, CA, USA, courtesy of Dr R. M. Krauss. The apoE genotypes were determined using the PCR method described by Hixson and Vernier (12). For the analysis of LPL gene single nucleotide polymorphisms (SNPs), genomic DNA was isolated from whole blood by standard methods. PCR was performed using the PvuII and HindIII enzymes (13).

Glucose metabolism studies

Venous blood samples for anti-islet autoantibodies were collected and refrigerated at –70 °C until assayed in two independent laboratories (CG, Palermo, Italy and

Table 3 Metabolic and immunologic parameters in a 9-year-old girl with a massive triglyceride elevation and fasting chylomicronemia at admittance to hospital (day 1) and during the first 5 months. Antibodies were measured in two independent laboratories using specific radioimmunoassays.

Time	DMG (mmol/l)	UK (mmol/l)	HbA _{1c} (%)	IR (U/kg BW)	ICA (JDF IU) (<2.5)*	GAD65 (IU/ml) (<24.6)*	IA-2 (IU/ml) (<2.74)*	IAA (nU/ml) (<39)*
Day 1	12.1	+		1.65	NA	NA	NA	NA
Day 2	8.1	+		1.72	NA	NA	NA	NA
Day 3	5.8	–		1.75	NA	NA	NA	NA
Day 5	6.5	–		1.60	NA	NA	NA	NA
Day 6	7.2	–		1.03	NA	NA	NA	NA
Day 8	9.5	–	6.9	1.05	Neg.	Neg.	Neg.	12
Day 9: enteral feeding								
Week 2	6.2	–		0.32	NA	NA	NA	NA
Week 3		–		0.35	Neg.	Neg.	Neg.	NA
Week 4	7.4	–	6.9	0.50	NA	NA	NA	NA
Month 3	9.8	–	7.8	0.62	Neg.	Neg.	Neg.	NA
Month 5	11.3	–	9.6	0.82	Neg.	Neg.	Neg.	NA
Month 6	6.1	–	7.2	1.08	Neg.	Neg.	Neg.	NA

DMG, daily mean glycemia; UK, urinary ketones; HbA_{1c}, glycated hemoglobin; IR, insulin requirement; BW, body weight; ICA, islet cells antibodies; GAD65, anti-glutamic acid decarboxylase antibodies; IA-2, anti-islet antigen 2 antibodies; IAA, insulin autoantibodies; Neg., absence of antibodies; NA, not analyzed.

* Normal values.

AP, Miami, FL, USA). Cytoplasmatic islet cells antibodies (ICA) were measured on frozen sections of human pancreas by indirect immunofluorescence. This ICA assay had a sensitivity of 100%, with a specificity of 74.4% in new onset patients younger than 30 years. The values are considered positive >2.5 Juvenile Diabetes Foundation IU. Antibodies to glutamic acid decarboxylase (GAD65) and the tyrosine phosphatase-like antigen IA-2 were measured in triplicate using specific radioimmunoassays. For GAD65 antibodies the GAD65 clone was used, kindly provided by A Lernmark (14, 15); for IA-2 antibodies two IA-2 clones were used together to maximize sensitivity, kindly provided by G S Eisenbarth (14, 16, 17) and E Bonifacio (18–20). The upper limit of normal for GAD65 antibody levels is an index of 24.6. The upper limit of normal for IA-2 antibody levels is 2.74. In the 2002 Diabetes Autoantibody Standardization Program the sensitivity and specificity for the GAD65 and IA-2 antibody tests combined were 92% and 88% (GAD65: 80% sensitivity, 93% specificity; IA-2: 68% sensitivity, 85% specificity). Insulin autoantibodies were determined with a fluid phase radioassay using polyethylene glycol precipitation with a method with assayed specificity of 100% and sensitivity of 85%. Normal values were <39 nU/ml. C-peptide levels were measured after i.v. glucagon (1 mg, bolus) at the following times –15, 0, 1, 3 and 6 min every 3 months for the entire period of follow-up. The hyperinsulinemic–euglycemic glucose clamp was performed under standard conditions and the rate of glucose metabolism (M) was calculated by dividing the glucose infused during the last 40 min of the clamp by the body weight in kilograms (mg/kg per min) (21).

Results

The lipoprotein parameters of the proband (at admittance) and her relatives are shown in Table 1. The proband's plasma triglyceride levels were extremely high whereas her parents and brothers had normal lipid levels. apoE genotypes were not informative and SNPs for LPL revealed no linkage with the LPL gene. A normal apoC_{II} was demonstrated in the proband.

Table 2 shows the plasma lipids of the proband at admittance and during the following 6 months. Plasma lipid levels fell rapidly following the institution of parenteral nutrition. After a few weeks, triglyceride levels normalized and remained normal afterwards. Insulin therapy was started with a significant improvement of glucose metabolism and a rapid disappearance of urinary ketones (Table 3). Glucose control was obtained by insulin therapy; insulin requirement was low after the discharge and then was stable around 1 U/kg body weight with a fair metabolic control. Humoral markers associated with type 1 diabetes were consistently negative at onset and during the first 6 months after diabetes onset. C-peptide measurements, both fasting and stimulated, including a glucagon test (at week 2 and during the entire follow-up, every 3 months) were consistent with lack of insulin secretion (<0.045 μ g/l) for the entire period of follow-up (2 years). A hyperinsulinemic–euglycemic clamp (week 6, $M = 4.3$ mg/kg per min) demonstrated that she was insulin deficient and had no insulin resistance, with C-peptide levels (at 0, 30, 60, 90 and 120 min) under the detection limit for the entire test.

LPL and HL were in the normal range (respectively 14.9 ± 1.1 μ mol free fatty acids (FFA)/ml per h and

Figure 2 LPL and HL in the proband (a), in controls plus a normal serum (b) and in controls plus proband serum (c). Data shown in (a) and (c) are the mean of three different determinations; control sera in (b) and (c) represent pooled sera from normal subjects selected at the Lawrence Berkeley National Laboratory, Berkeley, CA, USA. Vertical bars represent s.d.

Figure 3 Triglyceride (TG) levels and retinyl palmitate in chylomicrons (Chylo RP) after oral fat load in the proband.

$9.7 \pm 0.4 \mu\text{mol FFA/ml per h}$, Fig. 2). The serum of the proband normally activated control plasma and LPL and HL activities were similar to those detected when a normal sample was added.

After an oral fat load the proband had a triglyceride peak at the first hour and then rapidly cleared triglyceride levels. A similar behavior was observed for chylomicrons' retinyl palmitate as a marker of the metabolism of these lipoprotein particles (Fig. 3). This experiment was even conducted in conditions of insulin deficiency. Since the results were completely normal, we avoided repeating the test while on insulin therapy.

Discussion

Type 1 diabetes is an autoimmune disease. About 80–90% of patients have autoantibodies against islet cell molecules in their serum at the time of clinical onset. The HLA locus accounts for approximately 50% of the familial aggregation and both susceptible and protective HLA haplotypes have been defined (22). Three islet antigens, insulin, GAD65 and IA-2 are the most common targets of autoimmune responses (1, 22). The synergistic action of CD4^+ and CD8^+ T cells is thought to mediate β -cell destruction (23, 24). Environmental factors have also been associated with type 1 diabetes. To date, environmental risk determinants can be classified into three groups: viral infections (e.g. Coxsackie virus and cytomegalovirus), early infant diet (e.g. breast feeding vs early introduction of cow's milk components) and toxins (e.g. nitroso derivatives) (3). No data exist showing that the chylomicronemic syndrome may cause β -cell destruction.

Chylomicrons are large, buoyant, triglyceride-rich lipoproteins of intestinal origin (25). In the fasting state, chylomicrons are absent in human plasma; their presence, together with a massive hypertriglyceridemia,

is the feature of the chylomicronemic syndrome (4). This rare syndrome may be the consequence of genetic disorders as well as of secondary conditions, including diabetes (7). There is also some evidence for transient forms of this lipoprotein abnormality (8, 26).

At admission we hypothesized that the severe hypertriglyceridemia was the consequence of the onset of the diabetes (7). However, mild hyperglycemia such as the one observed is unlikely to be the explanation for such severe chylomicronemia. We therefore investigated the presence of an associated defect in the lipoprotein metabolism. Personal and familial history did not show evidence of lipid disorders (including a low HDL phenotype), no linkage with LPL gene was found and apoE genotypes were found to be $\epsilon 3/\epsilon 3$. Furthermore, we were not able to find any apoCII abnormalities and lipolytic enzymes (assayed after normalization of plasma triglyceride since pancreatitis discouraged us from using infusion of heparin for these tests) were in the normal range. The proband's chylomicronemic sample activated LPL in a normal plasma: these experiments demonstrate that there is no inhibitor of LPL in the serum of the proband and that apoCII of the proband is able to activate a normal LPL (25). After a few months the patient rapidly cleared an oral fat load test in conditions of insulin deficiency, with a triglyceride peak of 2.6 mmol/l after 1 h. In addition, data regarding retinyl palmitate metabolism confirmed no delay in the clearance of chylomicron particles. Therefore, the only plausible explanation for the high lipid levels observed transiently at the time of onset remains a transient LPL deficiency, a rare condition indistinguishable from genetic forms of LPL deficiency (8, 26), occasionally associated with a high-fat diet, which was a documented factor in this patient.

The patient did not have any of the HLA and autoantibody markers typical of type 1 diabetes. She carried the DR1 and DR6 HLA antigens and several serum samples

were consistently negative for type 1 diabetes-associated autoantibodies (Table 3) (1, 24). A glucose clamp failed to demonstrate insulin resistance and there was no family history of type 2 diabetes or maturity onset diabetes in youth (data not shown). Repetitive assays of both fasting and stimulated C-peptide levels, also obtained after i.v. glucagon stimulus, showed deficient β -cell function soon after the first 2 weeks when a normalization of blood glycemic levels was achieved by daily insulin therapy (Table 3). The causes of the observed β -cell secretory defect remain unknown, and a viral infection cannot be excluded (27). However, since lipid toxicity has been demonstrated in β -cells *in vitro*, the sudden and massive elevation of chylomicrons may have contributed to diabetes development (28). Although diabetes is rarely a consequence of pancreatitis, the possible toxicity of high lipid levels and perhaps a viral infection may have heightened the pronounced sensitivity of β -cells to inflammation and may help to explain the onset of diabetes in this child. In conclusion, we have identified a rare young patient in whom a severe and transient hyperlipidemia may contribute to explain the onset of diabetes in the absence of typical markers of autoimmune diabetes.

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