

Insulin-dependent diabetes mellitus as long term complication of haemolytic-uraemic syndrome

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SUMMARY

Haemolytic-uraemic syndrome (HUS) is a rare cause of insulin-dependent diabetes mellitus during the acute stage. We previously reported the case of a 3-year-old girl having presented with typical HUS with diarrhea, microangiopathic anaemia, thrombocytopenia and acute renal failure (17 days of anuria). Transient hyperglycaemia (highest level: 513 mg/dl) was observed, requiring continuous intravenous insulin infusion for 9 days. Subcutaneous insulin injections were stopped after 24 days.

Oral glucose tolerance test performed 4 months after normalization of blood glucose was normal. HLA DQ genotype (DQA1-DQB1.AZH/DQA3-DQB3.1) was not at risk for type 1 diabetes and there were no auto-antibodies (ICA and IAA).

The 3-years follow-up was marked by persistent arterial hypertension, proteinuria and slight renal insufficiency despite angiotensin-converting enzyme inhibitor treatment.

Ten years after HUS occurred (the patient had been lost to follow-up for 7 years), she came back with complaints of headache but neither polyurodipsia nor weight loss. She was found to have arterial hypertension. Chronic renal impairment had moderately progressed with decreased glomerular filtration rate (63 ml/min/1.73 m²) and proteinuria (2 g/24 hours).

Fasting blood glucose was 189 mg/dl and reached 315 mg/dl during an oral glucose tolerance test. HbA_{1c} level was 8.2% (N<6.2%) and diabetes mellitus was diagnosed without any signs of autoimmunity (IAA, ICA, GADA and IA2B were negative). Good glycaemic control was obtained with 0.5 U/kg/day of insulin.

In conclusion, transient beta-cell dysfunction complicating HUS acute stage may evolve to overt non-autoimmune diabetes mellitus (microangiopathic process?), even after a long free interval. This case emphasizes the need for a long-term follow-up of patients with HUS.

Key-words: Haemolytic-uraemic syndrome · Microangiopathic process · Non auto-immune diabetes · Diabetic children.

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RÉSUMÉ

Survenue tardive d'un diabète insulino-dépendant comme complication d'un syndrome hémolytique et urémique

Le syndrome hémolytique et urémique (SHU) peut entraîner un diabète insulino-dépendant durant la phase aiguë de la maladie. Nous avons rapporté le cas d'une fillette âgée de 3 ans qui avait présenté un SHU avec diarrhée, anémie, thrombocytopenie et insuffisance rénale aiguë (17 jours d'anurie). Une hyperglycémie transitoire était survenue (maximum 513 mg/dl), nécessitant une insulinothérapie durant 33 jours (voie intraveineuse continue durant 9 jours).

Une épreuve d'hyperglycémie provoquée par voie orale réalisée 3 mois plus tard était normale. Le génotype HLA DQ ne représentait pas un risque accru de diabète de type 1 et la recherche d'auto-anticorps (ICA et IAA) était négative.

Durant les 3 années suivantes, persistent une hypertension artérielle marquée, une protéinurie et une légère insuffisance rénale.

Dix ans après l'épisode initial de SHU, la patiente consulte pour des malaises accompagnés de céphalées, sans polyurodipsie ni perte de poids. Outre l'hypertension artérielle (193/114 mmHg), l'insuffisance rénale chronique a modérément progressé, s'accompagnant d'une protéinurie à 2 g/24 h.

La glycémie à jeun est de 189 mg/dl et atteint 315 mg/dl après charge orale en glucose. L'HbA_{1c} s'élève à 8,2% (N < 6,2%) et le diagnostic de diabète insulino-dépendant est posé. Aucune auto-immunité bêta insulaire n'est mise en évidence (IAA, ICA, GADA et IA2B négatifs). Un bon contrôle des glycémies est obtenu avec une dose quotidienne d'insuline de 0,5 U/kg/j.

En conclusion, une dysfonction transitoire des cellules bêta survenant durant la phase aiguë d'un SHU, peut entraîner un diabète insulino-dépendant non auto-immun patent (conséquence de l'atteinte microangiopathique), parfois même après un intervalle libre de plusieurs années. Ce cas souligne l'importance du suivi à long terme des patients atteints de SHU.

Mots-clés: Syndrome d'hémolyse-urémie · Processus microangiopathique · Diabète insulino-dépendant non auto-immun · Enfant diabétique.

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Haemolytic-uraemic syndrome (HUS) is a major cause of acute renal failure in childhood. Children present with a classical picture of microangiopathic haemolytic anaemia, thrombocytopenia and azotemia, usually following gastroenteritis. In fact, HUS is a multiorgan disease, potentially affecting the central nervous system, intestine, liver, heart and pancreas [1,2]. Indeed, beta cell dysfunction may develop during the acute stage [3,4]. Usually transient, it may rarely evolve to overt insulin-dependent diabetes mellitus (IDDM). There is sometimes a few months remission between the acute phase hyperglycaemia and the development of permanent IDDM [5,6]. We report an exceptional case of HUS with transient hyperglycaemia during the acute phase, having developed permanent non-autoimmune IDDM 10 years later.

History and examination

The medical story of the girl began when she was 3 years old [7]. She presented with a typical HUS picture including bloody diarrhea (without identified pathogenic verotoxin-producing organisms), microangiopathic anaemia (7.3 g haemoglobin/dl), thrombocytopenia (7,000 platelets/mm³), and acute renal failure. Moreover hyperleucocytosis was noted (34,000/mm³). Anuria lasted for 17 days, requiring 7 days of peritoneal dialysis (with mostly 1.36% dextrose dialysate) and 20 days of haemodialysis. She had high blood pressure treated by nifedipine for 15 days (no diazoxide used).

Transient hyperglycaemia was observed during 28 days (highest level: 513 mg/dl), requiring continuous intravenous insulin infusion for 9 days, followed by subcutaneous insulin injections for 24 days. Hyperglycaemia had persisted despite withdrawal of glucose overload (total parenteral nutrition and peritoneal dialysis). HLA-DQ genotype (DQA1-DQB1.AZH/DQA3-DQB3.1) was not at risk for type 1 diabetes mellitus and there were no autoantibodies (ICA, IAA).

Serum lipase (165 U/l; normal <60) and amylase (111 U/l; normal <100) were transiently slightly elevated. Abnormal ultrasonographic pancreas aspect was observed with increased volume, heterogeneous aspect, pseudomass of the head and pseudokystic aspect of the tail.

After one month, HbA_{1c} was within the normal range.

Abbreviations

BMI:	body mass index
GADA:	glutamic acid decarboxylase autoantibodies
GFR:	glomerular filtration rate
HUS:	haemolytic-uraemic syndrome
IAA:	insulin autoantibodies
IA-2A:	insulinoma-associated antigen 2 antibodies
ICA:	islet cell cytoplasmic autoantibodies
IDDM:	insulin-dependent diabetes mellitus

The 3-year follow-up was marked by normalization of blood glucose level without insulin therapy. An oral glucose tolerance test performed 4 months later was normal as well as ultrasonographic pancreas aspect. Systolo-diastolic arterial hypertension (mean of 114/70 mmHg=percentile 97.5) persisted, associated with proteinuria (2.1 g/24 h) and slight renal failure (GFR 75 ml/min/1.73 m²) despite angiotensin-converting enzyme inhibitor treatment.

Unfortunately, the girl was lost to follow-up for 7 years. She came back at the age of 13 years with complaints of headaches and faintness. There was neither polyurodipsia, nor weight loss. Physical examination was normal except for high blood pressure (193/114 mm Hg>percentile 97.5).

Investigations

Fasting blood glucose was 189 mg/dl and during an oral glucose tolerance test, glycaemia rose 315 mg/dl after 2 hours. HbA_{1c} level was 8.2% (N<6.2%; 5.6 SD above mean control levels). Diabetes mellitus was diagnosed. Islet cell autoantibodies (IAA, ICA, GADA and IA-2A) were negative. Pancreatic ultrasonography was normal as well as lipase and amylase level. Moreover, severe systolodiastolic arterial hypertension (mean of 191/122 mmHg > percentile 97.5) was associated with hypertensive retinopathy (stage I-II), proteinuria (2g/24h) and decreased GFR (64 ml/min/1.73 m²). Blood urea and creatinine were slightly elevated respectively at 54 and 0.98 mg/dl.

Good glycaemic control was obtained with a two daily insulin injection regimen, the mean daily insulin dose being 0.5 U/kg. Five months later, HbA_{1c} was normalized: 5.7%. High blood pressure was treated by losartan (75 mg/day).

Discussion

HUS may be complicated by islet cells dysfunction as a result of pancreatic involvement in the microangiopathic process. Tissue ischaemia and necrosis result from toxin-mediated endothelial cell damage with intraluminal thrombosis of small vessels supplying the islets of Langerhans (usually preserving exocrine pancreas) [2-4,8-10]. Actually, β -cell dysfunction occurs in 4 to 15% of patients affected by this disease during the acute phase [1,6,8-9]. Usually transient, it may evolve to overt IDDM. In a very recent review of 1 189 cases of HUS in children, the pooled incidence of diabetes was 3.2% [8]. This meta-analysis showed that diabetes was more likely to occur in patients with more severe disease (OR 12.0 if central nervous system symptoms – OR 5.4 if acute dialysis necessary). Moreover, mortality risk was 15 times higher if diabetes was present. Effectively, 23% of those who developed diabetes acutely died and 38% of survivors required long term insulin (mean follow-up of 32 months). Recurrence of diabetes was

possible up to 60 months after initial apparent recovery [6] but the majority recovers definitely. In our case, the free interval after initial episode of transient diabetes reached 10 years. As no sign of autoimmunity was present, the mechanism of late insulin deficiency may be progressive and continued loss of β -cells as late complication of the micro-angiopathic process. Moreover, Suri et al. [8] have proposed that a predisposition to type 2 diabetes decreased islet reserve. However, BMI of our patient was 19.6 kg/m² (+0.2 SD). Lane et al. reviewing 121 patients with HUS have identified risk factors to develop hyperglycaemia: female gender, elevated white blood cells count on admission, presence of anuria requiring dialysis or central nervous system complications [9]. All these risk factors were present in our patient. Beta cell autoantibodies, searched in some patients, were negative [2,5,10]. HLA genotype, determined in only one patient, was not at risk for type 1 diabetes mellitus [10]. Our patient had no signs of autoimmunity or genetic predisposition for type 1 diabetes as well.

In conclusion, this patient is, to our best knowledge, the first case of permanent non autoimmune insulin-dependent diabetes mellitus occurring after a 10 year free interval, as a late complication of microangiopathic process. This case emphasizes the need of a long term follow-up of patients with HUS, including a search of subclinical diabetes using an oral glucose tolerance test.

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