Case report

Persistent neonatal diabetes mellitus and primary congenital hypothyroidism: a hitherto unknown association

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Abstract: We describe a 4-year-old boy who has persistent neonatal insulin dependent diabetes mellitus (IDDM) with a documented decrease in endogenous insulin secretory capacity. He also has athyreotic primary congenital hypothyroidism. To our knowledge such an association has never been reported before. A brief review of the literature on the subject is presented.

Introduction: Primary congenital hypothyroidism (CH) is among the most common endocrine disorders, with a worldwide incidence of 1:2,500–5,500 [1–4]. A high percentage of infants with CH have additional anomalities [3–11].

Here we report a child who, in addition to primary CH, has persistent neonatal insulin-dependent diabetes mellitus (IDDM). To our knowledge such an association has not been reported before.

Case report: A 36-week-gestation male infant was born by normal vaginal delivery to a gravida 3, para 2, 30-year-old mother. Apgar scores were 5 and 9 at 1 and 5 min respectively. The birth weight was 1,650 g, below the fifth centile, length was 43 cm at the tenth centile, and the head circumference was 32 cm, at the twenty-fifth centile. He was small and emaciated, with no palpable thyroid gland. Dubowitz neonatal assessment was in agreement with the mother's dates. The pregnancy was normal and the mother did not receive any medication, apart from ferrous sulfate. She had no goitre and was clinically euthyroid. The parents are consanguinous, with no family history of thyroid dysfunctions or diabetes.

The infant was started on frequent feeding of Similac 20. His blood glucose was 3.9 mmol L^{-1} at 4 of age. On day 3, a routine urinalysis showed glycosuria, and random Dextrostix (Chemstrip bG, Bohreinger, Ingelheim, Germany) determinations were elevated to 11–17 mmol L^{-1} which were confirmed by laboratory measurements. At 5 days of age, he remained hyperglycaemic, which necessatated referral to Riyadh Medical Complex for further evaluation and management.

On arrival, the infant was found to be mildly dehydrated, but not acidotic. After appropriate blood samples were taken for blood sugar, insulin and C-peptide (radioimmuno assay, RIA kits, CIS, Gif-Sur-Yvette, France) (Table 1), he was started on subcutaneous regular insulin (Novo Nordisk A/S, Bagsvaerd, Denmark) (0.5 U kg^{-1} q 6–8h) which was later changed to intermediate acting insulin (NPH) Novo Nordisk) adjusted at 2–3 U day^{-1} given in two divided doses.

On day 7, the results of blood cord screening test for congenital hypothyroidism revealed thyroid stimulating hormone (TSH) (Delfia immuno fluorescent, Pharmacia Diagnostic, Wallac Oy, Finland) of 596 mU $l.^{-1}$ (normal range; <30), and thyroxine (T4) (Delfia Kits) of 29 nmol L^{-1} (normal range, 85–225). Confirmatory thyroid function test revealed TSH of 668 mU L^{-1} and T4 15 nmol L^{-1}, and serum thyroglobulin (Tg) <5 µg L^{-1} (normal, 10–240). Technetium 99m pertechnetate (^{99m}Tc) scanning failed to show any thyroid tissue, with normal uptake by salivary glands.

On day 9, the infant was started on L-thyroxine (Glaxo Laboratories Ltd, Greenford, England) 25 µg daily. He continued to improve and was discharged on day 35 with a weight of 2.7 kg. Serum autoantibodies, including islet cell antibodies (commercial kits, Bioscientia Laboratory, Ingelheim, Germany), thyroid microsomal and thyroglobulin antibodies (haemagglutination method) were negative in both the patient and his mother. At the age of 3 years and while off L-thyroxine for 6 weeks, a ^{99m}Tc thyroid scan failed to show any thyroid tissue.

At his current age of 5 years, the boy requires L-thyroxine 100 µg day^{-1} to keep him clinically and biochemically euthyroid. He continues to have frequent hyperglycaemic episodes and is being managed with twice daily subcutaneous NPH insulin injections at a dose of 10-14 U day^{-1}. The patient's physical growth continues to be normal and his neurological and psychological development have been normal except for a mild delay in language skills. HbA1c (high pressure liquid chromatography method) levels have fluctuated between 7.8 and 13.8%.

Table 1: Biochemical profile during the course of illness.

Age (days)	Preprandial serum glucose (mmol L^{-1})	C-peptide (pmol mL^{-1})	IRI (µU mL^{-1})	Hb A1c (%)
5	11.5	<0.1	<5	–
	13.9	<0.1	<5	–
42	7.9	0.15	ND	12.9
390	8.9	0.16	ND	8.2
756*	20.9	0.11	ND	11.7
Normal value	4–6	0.2–1.3	5–21	4–7.8

IRI, Immunoreactive insulin; HbA1c, Haemoglobin A1c; ND, Not done.
**Patient had upper respiratory tract infection (URTI)*

Discussion: Primary congenital hypothyroidism is among the most common endocrine disorders with a world wide incidence of 1:2,500–5,500 [1–4]. The majority of cases are due

to thyroid gland dysgenesis [3, 4, 8, 11], the aetiology of which remains unknown [1, 2, 4]. Some investigators suggest an association with the production of maternal thyroid growth-blocking antibodies, which cross the placenta and may produce fetal hypothyroidism [12, 13]. However, their role in the pathogenesis has not yet been established. Recent studies [3–11] have shown that a high percentage of patients with CH have additional extrathyroidal anomalies. To our knowledge, the association of CH with neonatal diabetes mellitus has never been reported.

Insulin-dependent diabetes mellitus (IDDM) during the neonatal period is a rare event; the majority of reported cases are transient [14–18] Many infants show only a transient delay in insulin release, while fewer babies have a permanent insulin-deficiency [15–19]. Permanent and transient neonatal diabetes may have a common aetiology: genetic or autoimmune [15, 16, 20, 21]. The transient diabetic state may recur or become permanent due to unrecognised factors [22, 23]. Furthermore, intrauterine growth retardation [15, 18], microcephaly [20], and macroglossia [14] have been reported with neonatal diabetes.

Our patient appears to have a unique association. He has persistent neonatal IDDM with a documented decrease in endogenous insulin secretory capacity, indicated by diminished plasma C-peptide and insulin levels on serial measurements. There is also, persistent hyperglycaemia with an increasing insulin requirement (Table 1). The patient was small for gestational age, which might indicate insulin deficiency *in utero* [15, 18]. He has also the classical biochemical, and radiological features of athyreotic primary congenital hypothyroidism [24].

It is tempting to postulate that this observed association could be due to a common factor such as autoimmunity. Insulin-dependent diabetes mellitus and Hashimato's thyroiditis (a well known association), have common pathophysiology, namely autoimmunity [13]. This, however, is unlikely to be the case in our patient as serum autoantibodies against islet cells, thyroglobulin and thyroid microsomal antibodies were absent in the patient and his mother, with no history of diabetes or thyroid disorder in the family.

Finally, although the association of persistent neonatal IDDM and CH in this patient might represent a coincidental finding, it still appears to be unique and can be added to the extrathyroidal anomalies in patients with CH. If such an association is confirmed in other cases this might contribute to our understanding of the pathogenesis of thyroid dysgenesis and neonatal diabetes.

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