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CASE REPORT

Not All Diabetes in Infants is Type 1: A Case Report

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ABSTRACT

Neonatal diabetes mellitus (NDM), defined as persistent hyperglycemia occurring in the first months of life, is a rare cause of hyperglycemia and is often misdiagnosed as type 1 diabetes mellitus (T1DM). Numerous reports have shown that the successful transition from insulin to sulfonylurea agents can be achieved in up to 90% of patients with NDM. However, most of the reports pertain to infants; the literature is limited regarding treatment of adults with NDM. We present our experience with a patient with permanent NDM, initially misdiagnosed as T1DM, who subsequently was successfully transitioned to oral sulfonylurea therapy after 37 years of insulin dependence.

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INTRODUCTION

Neonatal diabetes mellitus (NDM), defined as persistent hyperglycemia occurring in the first six months of life, is a rare cause of hyperglycemia with an estimated incidence of 1 in 100,000 to 1 in 260,000 live births [1–3]. Almost all cases of NDM have monogenic etiology in contrast to the autoimmune diabetes presenting in children beyond 6 months of age [4]. There are 22 known genetic causes of NDM (mutations in 21 genes and methylation abnormalities at the 6q24 locus) that identify different clinical subtypes of the disease [1]. This includes transient NDM (TNDM), permanent NDM (PNDM), and complex syndromes in which NDM is often the presenting feature (i.e., Wolcott–Rallison syndrome) [1]. The most common cause of NDM are mutations in the adenosine triphosphate (ATP)-sensitive potassium channel (K-ATP channel) subunit genes ABCC8 and KCNJ11 which regulate the release

of insulin from pancreatic β cells [1, 5–8]. The pancreatic β-cell K-ATP channels are hetero-octamers assembled by four Kir6.2 subunits and four high-affinity sulfonylurea receptor 1 (SUR1) subunits encoded by the genes KCNJ11and ABCC8, respectively [9–11]. *KCNJ11* mutations are more frequent in patients with PNDM, whereas mutations in *ABCC8* cause TNDM more frequently [8]. The majority of infants with NDM are small for gestational age, which may be related to decreased insulin secretion in the fetus and exhibit postnatal catch-up growth with insulin therapy [12]. The most severe defect includes marked developmental delay and early onset epilepsy, also known as DEND syndrome [8, 10].

Subcutaneous insulin was routinely used in the past to treat patients with this disorder; however, studies have shown that the successful transition from insulin to sulfonylurea (SU) agents can be achieved in up to 90% of patients with NDM [11]. We report a case of PNDM whose treatment was successfully transitioned from insulin to oral SU therapy after 37 years of insulin dependence.

CLINICAL CASE

A 37-year-old man with history of poorly controlled diabetes with multiple microvascular complications of proliferative diabetic retinopathy, stage 3 chronic kidney disease (CKD) and peripheral neuropathy, presented to our institution for further evaluation. The patient reported frequent hypoglycemia and blood glucose (BG) excursions with BG ranging from 48–330 mg/dL. Review of his medical records demonstrated previous hemoglobin A1c (HbA1c) measures as high as 12.9%. He was diagnosed with "type 1 diabetes mellitus" (T1DM) when he was 2 weeks old and multiple daily injections of insulin (MDI) were initiated to control glycemia. He reported a strong family history of early-onset insulin-dependent diabetes in both of his siblings, and his mother had insulin-dependent diabetes mellitus (unknown type). The patient's medical and family history warranted further investigation and consideration of other forms of diabetes. HbA1c was 7.7%, C-peptide <0.2 ng/mL (range 0.8–3.2 ng/mL) with corresponding BG of 80 mg/dL (65–100 mg/dL; Table 1). Testing for pancreatic islet cell and glutamic acid decarboxylase antibodies was negative. The patient's physical exam, and specifically the patient's neurological status, was otherwise normal. As genetic testing could not be afforded by the patient, a trial of SU therapy was offered. Glimepiride 2 mg daily (QD) was initiated and slowly titrated up to 8 mg twice daily (BID) over a 3-month period with an observed increase in C-peptide from undetectable to 0.7 ng/dL (BG 176 mg/dL). Glimepiride was then increased to 12 mg BID with further improvement in glycemic control. Insulin detemir and insulin lispro were slowly decreased as the dose of SU therapy was increased. In an attempt to increase the patient's own endogenous insulin production and achieve further insulin independence, a 7-day trial of sitagliptin 100 mg QD was initiated with a subsequent increase in C-peptide to 0.9 ng/dL (BG 252 mg/dL). However, glycemic control did not improve so the sitagliptin was discontinued and a trial of dapagliflozin 5 mg QD was initiated (despite his CKD stage 3). Glycemic control significantly improved, and after dapagliflozin was increased to 10 mg QD, insulin therapy was completely discontinued (his original total daily dose of insulin was 64 units). The patient follows a carbohydrate-controlled diet of approximately 45 g per meal and occasionally takes 3 units of

Table 1 C-peptide, glucose, and HbA1c values with corresponding insulin and SU regimen

Date	C-peptide (0.8–3.2 ng/mL)	Glucose (65–100 mg/dL)	HbA1c, %	Insulin regimen + dose of SU
7/28/14	<0.2	80	7.3	Det 27 units + Lis 7-15-15 and GLIM 2 mg QD was added after labs obtained
7/30/14	0.3	291		
7/31/14				Increased GLIM 4 mg QD
8/4/14	0.4	263		Det 22 units + Lis 7-15-15 + GLIM 4 mg QD
8/12/14	0.5	306		Changed Det to 18 units + Lis 7-14-12 + increased GLIM to 4 mg BID
8/29/14	0.7	321		
9/17/14				Increased GLIM to 8 mg BID, decreased Lis to 3-6-5
9/24/14	0.7	178		Det 18 units + Lis 3-6-5 + GLIM 8 mg BID
9/25/14				Decreased Lis to 3 units with meals
10/6/14				Stopped mealtime Lis, increased GLIM 12 mg BID
10/20/14	0.7	175	7.0	Det 15 units + GLIM 12 mg BID, Lis PRN, add sitagliptin 100 mg QD
10/28/14	0.9	252		Det 15 units + GLIM 12 mg BID, stop sitagliptin, start dapagliflozin 5 mg QD
2/23/15	0.6	219	6.6	Det 10 units + GLIM 12 mg BID + dapagliflozin 10 mg QD + Lis PRN, 45 g of CHO per meal
2/25/15				Decreased Det to 6 units
3/4/15				GLIM 12 mg BID and dapagliflozin 10 mg QD, stopped Det
7/15/15		168	6.9%	GLIM 12 mg BID and dapagliflozin 10 mg QD + Lis 3 units PRN for "high CHO" meal
11/16/15		148	6.8	

BID twice daily, *CHO* carbohydrate, *Det* insulin detemir, *GLIM* glimepiride, *HbA1c* hemoglobin A1c, *Lis* insulin lispro, *PRN* pro re nata (as needed), *QD* daily, *SU* sulfonylurea

insulin lispro when planning to eat a high carbohydrate containing meal, particularly when eating out at restaurants. The addition of the sodium-glucose cotransporter-2 (SGLT2) inhibitor has helped tremendously with postprandial glucose control and the patient has not had any episodes of diabetic ketoacidosis. Repeat HbA1c after 3 months of oral anti-diabetic therapy was 6.6%, with average BG in the 70–130 mg/dL range. Over the last year since the initiation of SU therapy, his HbA1c has remained below 7% without any episodes of hypoglycemia (Table 2). Multiple attempts to evaluate and test his parents and siblings for NDM have been unsuccessful thus far.

Informed consent was obtained from the patient for publication of this case report.

Table 2 HbA1c% trend

Year	2008	2009	2010	2011	2014	2015
HbA1c%	12.9	11.7	11.2	9.4	7.7	6.6

HbA1c hemoglobin A1c

DISCUSSION

NDM is a monogenic form of diabetes that presents within the first six months of life. In approximately half of patients, the diabetes will be permanent, and in the remaining cases the diabetes will remit within a few weeks or months although it might relapse later in life [10]. Approximately, two-thirds of TNDM cases are caused by abnormalities in an imprinted region on chromosome 6q24 [13, 14] with activating mutations in either of the genes encoding the two subunits of the K-ATP channel of the β-cell membrane (KCNJ11 or ABCC8) causing the majority of the remaining cases [15].

In contrast, the genetic abnormality responsible for up to 30% of PNDM cases remains unknown although the commonest known cause in outbred populations is mutations in the K-ATP channel or INS genes [10].

Heterozygous activating mutations in the KCNJ11 or ABCC8 gene, which encodes the Kir6.2 subunits and SUR1 regulatory subunits of the K-ATP channel, respectively, have been implicated and account for 30% to 58% of cases of PNDM diagnosed in patients less than 6 months of age [6, 11]. Mutations in the K-ATP channels lead to decreased sensitivity to ATP inhibition; consequently, the channels remain open in the presence of glucose, thereby reducing insulin secretion [11]. SUs close K-ATP channels by an ATP-independent route thereby causing insulin secretion. Studies have shown that many patients with diabetes caused by KCNJ11 or ABCC8 mutations can successfully switch from treatment with insulin to oral SU therapy [11]. The dose of SU therapy that is required to manage glycemia in patients with NDM, particularly to achieve insulin independence, is often higher than the maximum recommended dose for the treatment of type 2 diabetes mellitus [11], typically needing around 0.5 mg/kg/day of glibenclamide [11, 16]. In our case, glimepiride was chosen instead of glibenclamide (glyburide) because of the ever-evolving literature reporting a lower risk of hypoglycemia [17] and lower risk of all-cause and cardiovascular-related mortality with the other readily available SUs compared to glibenclamide [18, 19].

A report by Thurber et al. [20] found that, in patients with NDM, earlier age at initiation of SU treatment was associated with an improved response to SU therapy. This led the authors to appropriately hypothesize that perhaps the declining sensitivity to SU therapy observed with more advanced age may be due to the loss of β-cell mass over time in those treated with insulin therapy, thereby highlighting the importance of early recognition and initiation of SU therapy.

In our patient, we were able to demonstrate a rise in C-peptide as the SU dosage was increased. While it is certainly possible that the original C-peptide may have been undetectable because the patient did not follow directions (drink orange juice prior to laboratory assessment to ensure BG is over 200 mg/dL) the observed gradual rise in C-peptide, in the setting of hyperglycemia, as the SU dose was increased, demonstrates a slow increase in endogenous insulin secretion in response to the therapy. The patient did follow the directions to raise serum glucose >200 mg/dL at the time of subsequent C-peptide measures, as demonstrated in Table 1.

While the lack of genetic testing is a significant limitation of our report, this

limitation does not take away from the main point of this report, that being the importance of performing a very thorough personal and family history in patients who present with a prior diagnosis of diabetes, particularly T1DM very early in life, as a near-miraculous transformation in management may be possible in a minority of patients, as was the case in our patient, even if genetic testing is not available/feasible. Other means to obtain genetic testing on this patient are actively being pursued. Genetic testing for some conditions is available free of charge on a research basis in certain academic institutions in patients diagnosed with diabetes before 6 months of age (e.g., [21–23]) [10].

To the best of our knowledge, we are the first to report the effective and safe use of SGLT2 inhibitors in a patient with NDM. While the HbA1c did not appear to improve significantly after the addition of dapagliflozin, the therapy did help to lower postprandial glycemic excursions, not adequately addressed by the SU therapy, and helped to reduce the frequency at which the patient took a correction dose of bolus insulin, or a dose of bolus insulin to assist with glycemic control when he consumed higher carbohydrate containing meals.

CONCLUSIONS

We report the case of a patient with long-standing poorly controlled NDM initially misdiagnosed and treated as having T1DM. Many patients with NDM treated with insulin-only therapy behave as brittle diabetics, with difficult to control glycemia leading to complications. The addition or transition to SU therapy may help some of these patients achieve better glycemic control, while requiring less dependence on insulin therapy. Our case highlights the importance of history taking in the management of patients with diabetes, especially the need to conduct a thorough family history, as recognition of NDM can profoundly impact the diabetes-related management of both the patient and their family members.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies, and does not involve any new studies of human or animal subjects conducted by the authors. Informed consent was obtained from the patient for the publication of this case report.

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