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Case Report
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Neonatal Diabetes-From Insulin to Oral Hypoglycemic Agent: Case Report

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Introduction

Neonatal diabetes mellitus (NDM) is a monogenic form of diabetes that occurs in first 6 months of life with an incidence of 1 in 100,000 to 500,000 live births [1]. It is one of the disorders in which the role of genetic analysis is not limited to confirmation of the diagnosis, but also required for selecting the appropriate therapy. Patients with certain mutations like the ones involving *KCNJ11* and *ABCC8* genes respond to oral sulfonylurea [2]. Successful switch over from subcutaneous insulin to oral sulfonylurea has been previously reported by various authors [3,4]. In this case report, we present our experience on transferring three patients with genetic mutations from insulin to oral glibenclamide in last three years.

Case Report

The clinical characteristics of the three patients are given in Table 1. The genetic report and transfer from insulin to glibenclamide are discussed individually and follow up details are shown in Table 2.

Case 1: This boy was heterozygous for missense mutation *pA90V* in *ABCC8* gene involving SUR1 (Sulfonylurea receptor 1) subunit of pancreatic ATP sensitive potassium channel (K_{ATP}) which he had inherited from his mother, who was a carrier. He was started on glibenclamide on 197th day of life in a dose of 0.1 mg/kg/dose twice a day and the dose was increased gradually while insulin dose was decreased. His blood sugar stabilized at glibenclamide dose of 0.4 mg/kg/dose twice a day on day 7 of treatment when insulin could be omitted. On follow up, his glycemic control improved substantially without any episode of hypoglycemia.

Case 2: This boy was heterozygous for *ABCC8* missense mutation pR1380C in SUR1 subunit of K_{ATP} channel while both his parents were negative. He was transferred to oral glibenclamide on 139th day of life. The starting dose was 0.1 mg/kg/dose twice a day which was gradually escalated while decreasing the insulin dose. He maintained stable glucose levels at glibenclamide dose of 0.5 mg/kg/dose twice a day on day 8 when insulin could be omitted. Improvement in glycemic control was obvious on regular follow up.

Case 3: This girl had heterozygous KCNJ11 missense mutation pVal328Met involving Kir 6.2 subunit of K_{ATP} channel. Genetic analysis of her biological parents could not be done as she was an adopted child and her parents were untraceable. She was switched over to oral glibenclamide on 133th day of life with a starting dose of 0.1 mg/kg/dose twice a day. Her insulin dose was reduced as her glibenclamide dose was stepped up. She maintained stable glucose levels at a glibenclamide dose of 0.2 mg/kg/dose twice a day and her insulin could be omitted on day 5 of switch over. She is being followed up periodically and is showing improvement in glycemic control.

Discussion

This case report describes the clinical presentation, treatment and follow up details of three infants who presented to our center in last three years with diabetes and were found to have mutations involving K_{ATP} channel gene. Genetic testing will allow diagnosis of a specific type of monogenic diabetes in over 80% of patients who present with diabetes within six months of age [5]. K_{ATP} channels are hetero octameric complexes formed by four pore-forming Kir 6.2 subunits and four SUR1 regulatory subunits encoded by genes *KCNJ11* and *ABCC8* respectively [6]. Mutations in these genes prevent K_{ATP} channel closure and hence insulin secretion in response to hyperglycemia and are common causes of permanent neonatal diabetes mellitus [7,8]. One of our patients with *ABCC8* mutation had developmental delay suggestive of intermediate form of DEND (developmental delay, epilepsy and diabetes mellitus) syndrome as described in literature [9]. Approximately 90% of patients with mutations in K_{ATP} channel genes can be transferred from insulin onto sulfonylurea tablets [2,10]. The sulfonylurea of choice is glibenclamide in usual dose of 0.5 mg/kg/day, but doses up to 2.3 mg/kg/day have been reportedly used [11]. The only common side effect reported to date in children is transient diarrhea which was not encountered in our patients [12]. In most patients, the dose of sulfonylurea required for achieving initial glycemic control can be reduced over a period of time as evidenced in our patients [2]. As noted in our patients, the glycemic control improves substantially without increasing the risk of hypoglycemia following transfer from insulin to oral hypoglycemic agents. This improved glycemic control and absence of hypoglycemic episodes are essential pre-requisites for normal growth and development of these infants.

Hence ISPAD guidelines recommends genetic testing for all patients diagnosed with diabetes in first six months of life as the results may change the treatment modality and improve glycemic control and hence the quality of life.

Characteristic	Case 1	Case 2	Case 3
Age at presentation (days)	100	75	143
Gender	Male	Male	Female
Mode of presentation	Non- DKA	DKA	DKA
Gestational age	Pre-term	Term	Term
Birth weight (grams)	1700	2250	2560
Consanguinity	nil	nil	nil
Family history of diabetes	Maternal grandfather	Maternal grandmother	nil
HbA_1c at presentation (%)	13.1	12.5	7.2
C peptide at presentation(ng/ml)	0.51	0.04	1.4
Insulin dose prior to transfer (u/kg/day)	0.75	1.57	1

Table 1: Clinical characteristics of the patients.

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Patient	Duration of follow up	Present glibenclamide dose	HbA_1c		Growth	Development
			Before transfer	After transfer		
Case 1	22 months	0.18	6	5.1	Severe Acute Malnutrition	Global developmental delay
Case 2	14 months	0.3	8.5	5	Normal	Normal
Case 3	9 months	0.12	8.7	5.4	Normal	Normal

Table 2: Follow up details of the patients.

Key Messages

• Genetic analysis of infants presenting with diabetes within first six months of life is mandatory.

• Switching over from insulin to oral glibenclamide in patients with mutation involving K_{ATP} channel gene results in better glycemic control.

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