

Clinical Analysis on 10 Patients with Permanent Neonatal Diabetes Mellitus

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Abstract

Aim: Permanent neonatal diabetes (PNDM) is a rare condition occurring within the first six months of life. The patients with PNDM showed complex clinical features. A few patients accompanied with abnormalities of other systems and formed a series of PNDM syndrome. In this study, 10 patients with PNDM were selected as research subjects, the clinical manifestations and the treatment situations of the patients were analyzed so as to improve our cognition on PNDM and PNDM syndrome.

Methods: 10 PNDM patients hospitalized during 2002-2009 to our hospital were selected as research subjects. Clinical data of the patients were retrospectively concluded, and the clinical characteristics and treatment situations of the patients were analyzed.

Results: After long time followed up, all of the 10 patients were diagnosed as PNDM. 2 patients accompanied with muscle weakness, developmental delay, which diagnosed as iDEND syndrome. One patient accompanied with multiple epiphyseal dysplasias, growth retardation, and an episode of acute liver failure and isolated central hypothyroidism, which finally diagnoses as WRS syndrome. The growth and development of other 7 patients were normal. 5 patients used Glibenclamide as a trial for 2-3 weeks immediately after the diagnosis of PNDM was made, during which 2 cases successfully switched from insulin injections to oral glibenclamide. One case had partial reaction to glibenclamide and was treated with the combination plan of insulin and glibenclamide. 2 cases had no reaction to the treatment of glibenclamide, continue with the insulin treatment.

Conclusion: PNDM have complex clinical manifestations. For the patients accompanied with abnormalities of other systems, NDM syndrome should be considered. Partial PNDM patients caused by KATP mutation have reaction to glibenclamide and could be treated with glibenclamide in long term.

Keywords: Permanent Neonatal Diabetes Mellitus; Glibenclamide; KATP channel; DEND syndrome

Introduction

Neonatal diabetes mellitus (NDM) is a rare form of diabetes with an estimated prevalence of 1 in 100,000-300,000 live births [1]. Patients with NDM can be grouped into two well-defined subgroups, permanent and transient, each accounting for approximately 50% of patients [2,3]. Approximately 20% of individuals with mutations in KCNJ11 have associated neurologic findings called the DEND syndrome (developmental delay, epilepsy, and neonatal diabetes mellitus); a milder form without seizures and with less severe developmental delay is called intermediate DEND syndrome [4]. Some PNDM patients accompanied with the abnormalities of other systems and formed various PNDM syndromes [5]. In present study, we analyzed the clinical data of 10 patients with PNDM, and the clinical characteristics of and treatment processes of the patients were concluded.

Materials and Methods

Clinical data of the patients

10 patients with neonatal diabetes were chosen as research subjects. All diagnosed as neonatal diabetes in the first 6 months of their lives. The group of patient's includes 5 boys and 5 girls. Birth weight between 2.01-3.6kg, during which 5 patients belongs to SGA. NDM onset at the age of 38-170 days, when diagnosed as NDM, their blood glucoses were between 24.9-45.0mmol/L, with the HbA1Cs during 7.4-13.7. All patients suffered DKA when diagnosed as NDM. Their insulin levels were less than 2mIU/L and their C-Peptides were less than 0.5ug/L. The autoantibodies (islet cell antibody, insulin autoantibody, IA-2 antigen, and GADA) of the 10 patients were negative. The parents of the patients are non-consanguineous and all the patients having no family history

of diabetes mellitus. The initial dose of insulin was 1.1-1.2U.kg.d. The pancreatic ultrasound results of the 10 patients were normal (Table 1).

After diagnosis of NDM, 5 patients were treated with glibenclamide, a kind of sulfonylureas, instead of insulin. The initiate dosage of glibenclamide was 0.05mg/kg/d. The dosage of glibenclamide was increased gradually according to the blood glucose monitoring results. 2 patients were responsive to glibenclamide treatment and at the dose of 0.45 mg · kg⁻¹ · day⁻¹, insulin were discontinued. 1 patient was partially reactive to glibenclamide treatment, and treated with glibenclamide and insulin combinedly. The blood glucose of the 3 patient was well controlled (6-8mmol/L). The patient's basal c-peptide levels increased after one week of glibenclamide therapy, and one month later, the insulin and c-peptide levels were in the normal ranges without any episodes of hyper or hypoglycemia, which indicated that the treatment of glibenclamide on the patient was effective. The other 2 patients have no reaction to medical treatment and continuing with insulin treatment.

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Followed-up materials showed that the NDM of the 10 patients were not recovered until they were older than 2 years old, indicating that they all suffered PNDM. The 3 patients treated with glibenclamide attained well blood glucose control, and no serious side effects were found. The 7 patients treated with insulin all attained well controlled blood sugar, no obvious side effects of insulin treatment were observed.

Case 1 showed a gradually growth retardation and a multiple epiphyseal dysplasia was diagnosed at the age of 7. At 8 years of age, he suffered of an episode of acute liver failure (ALT 2733 IU/L, AST 7908 IU/L), from which he recovered 3 weeks later, after treatments with a series of medicines. Thyroid function examination indicated that the patient suffered from an isolated central hypothyroidism. Screening for other pituitary hormone imbalances was negative in the patient and there was no radiological evidence of a hypothalamic pituitary defect. Based on these observations, a clinical diagnosis of Wolcott-Rallison syndrome was made. Besides PNDM, case 2 and case 3 also suffered moderate motor and intelligent developmental delay, muscle weakness, but having no onset of convulsions, which called iDEND syndrome (Table 2).

Discussion

Permanent neonatal diabetes mellitus (PNDM) is characterized by the onset of hyperglycemia within the first six months of life (mean age: seven weeks; range: birth to 26 weeks). It has complex genetic backgrounds, till now several genes have been found to be related to the disease, including KCNJ11, ABCC8, INS, GCK, and PDX1 etc. Compared with TNDM, the patients with PNDM usually have a relatively later onset of NDM, and relatively rare occurred incidence of IUDR. Patients with PNDM usually have more serious symptoms and be susceptible to DKA [8,9]. In our present study, the patients all suffered diabetes mellitus in the first 6 months of their lives. All accompanied with insufficiency of insulin secretion and the autoimmune antibodies of the patients were negative. The onset age of the patients were later

than neonatal period, accompanied with different degree of DKA. The initial dosage of the patients was relatively larger (1.1-1.2ukg/d). The clinical manifestations of the patients all corresponds with that of PNDM. After dismissed from our hospital, all the patients were followed-up for more than 2 and a half years, no patients recovered from DM, which indicating that the group of the patients all suffered PNDM.

Heterozygous activating mutations in the ABCC8 and KCNJ11 genes have recently been shown to be the common causes of permanent neonatal diabetes [10,11]. SUR1 and Kir6.2 are expressed in muscle, neuron and brain as well as the pancreatic beta-cell, so patients with ABCC8 or KCNJ11 mutations could have a neurological phenotype in addition to their diabetes. Researchers recently revealed that among patients with neonatal diabetes due to KCNJ11 mutations, approximately 25% have neurological findings including developmental delay, motor dysfunction, and epilepsy, known as DEND syndrome. A milder form without seizures and with less severe developmental delay and motor dysfunction is called intermediate DEND (iDEND) syndrome [12]. Case 2 and Case 3 in our study was followed up for more than two years. We found that the two patients also had neurological features including mild developmental delay, hypotonia and muscle weakness, but the patients suffered no onset of seizures, indicating that the two patients suffered iDEND syndrome. Case 2 has successfully been transferred from insulin to sulphonylureas. The patient was successfully managed by oral glibenclamide therapy at a daily dose of 0.45mg/kg, which suggested that the patient may carry a mutation in ABCC8 or KCNJ11 genes. Further genetic analysis on ABCC8 and KCNJ11 gene is necessary for making genetic diagnosis of thus patients.

Clinical researchers found that few PNDM patients can accompanied with abnormalities of other systems and formed some rare PNDM syndrome, such as IPEX syndrome, Fanconi-Bickel syndrome and Wolcott-Rallison syndrome (WRS) etc. [13]. WRS is a

case	sex	BW(kg)	onset age(d)	accompanied abnormalities	Insulin initialdosage (u/kg/d)	Glibenclamide mg/kg/d
1	male	2.5	116	multiple epiphyseal dysplasia an episode of acute liver failure isolated central hypothyroidism	1.2	
2	male	2.25	50	muscle weakness, motor and intelligent developmental delay	1.3	0.9
3	male	2.01	38	muscle weakness, motor and intelligent developmental delay	1.5	0.9
4	female	2.15	66		1.2	
5	female	2.4	135			
6	female	2.9	150		1.2	1.0,partial effective
7	female	3.2	90		1.4	unresponsive
8	male	3	170			
9	male	2.6	90		1.2	
10	female	3.5	165		1.1	unresponsive

Table1: Clinical data of 10 patients with PNDM.

Case	BG mmol/L	β-hydroxybutyric acid mmol/L	DKA	Insulin uIU/ml	C-P ng/ml	HBA1C(%)
1	42.3	2.78	+	<2	<0.2	8
2	34.6	0.70	+	<2	<0.2	8.1
3	40	1.35	+	<2	0.94	10
4	45	0.42	+	<2	<0.2	8.7
5	36.5	0.35	+	<2	<0.5	7.4
6	39.8	1.56	+	<2	<0.5	10.2
7	43.4	1.48	+	5	<0.5	14.2
8	24.9	2.98	+	<2	<0.5	10.2
9	28.2	4.86	+	<2	<0.2	13.7
10	29.4	1.3	+	<2	<0.2	9.8

Table 2: Test results of the 10 patients with PNDM.

rare autosomal recessive disease, which is associated with permanent neonatal insulin-dependent diabetes, severe multiple epiphyseal dysplasia, osteoporosis, growth retardation and other variable multisystemic clinical manifestations [14]. Researches revealed that EIF2AK3 mutation underlie the onset of WRS syndrome, most of which are recessively inherited. In non-consanguineous families, WRS accounts for only 1.4% of the cases [15]. In our research, besides PNDM, case 1 also suffered a gradually growth retardation, multiple epiphyseal dysplasia, an episode of acute liver failure and an isolated central hypothyroidism, thus a clinical diagnosis of Wolcott-Rallison syndrome was made. The patient's parents are non-consanguineous, which adds valuable information in understanding the inheritance mood of WRS. In summary, WRS is a very rare and challenging disease. The disease should be suspected in infants with PNDM and skeletal dysplasia.

Insulin has been the only way to treat PNDM in the past years since NDM has been found. Recent researches revealed that most of the patients with KCNJ11 and ABCC8 mutations are responsive to glibenclamide treatment, a closer of KATP channel [16]. In our study, 2 cases successfully switched from insulin injections to oral glibenclamide. 1 had partial reaction to glibenclamide and was treated with the combination plan of insulin and glibenclamide. After long-term followed-up, the patients treated with glibenclamide attained well glycemic control without obvious side effect, which is consistent with reported in the literatures. Genetic analysis thus should be done as earlier as possible on the patients suffered PNDM so as to make correct therapy plan. For the patients with KCNJ11 and ABCC8 mutations, glibenclamide should be used as a trial.

In general, PNDM has complex clinical characteristics. For the patients accompanied with neurologic abnormalities, the possibility of DEND and iDEND syndrome should be considered. Rare PNDM patients can showed PNDM syndrome, for the patients diagnosed as PNDM, long-term followed-up are necessary. For the patients accompanied with multiple abnormalities of other systems, PNDM syndrome should be considered. For the patients suffered PNDM, genetic analysis is necessary to make correct diagnosis, correct choice of treatment plans and future family planning.

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