Clinical Pediatric Endocrinoligy (2005.12) vol.14 suppl.24:81～84.

Permanent Neonatal Diabetes Mellitus with Growth Disturbance,Developmental Delay,Epilepsy and Dysmorphic Features～成長異常,発育遅延,てんかん,奇異な顔貌を伴った永続型(恒久的)新生児糖尿病～

Suzuki Shigeru, Mukai Tokuo, Uetake Kimiaki, Sageshima Syun-ichi, Matsuo Kumihiro, Ueda Osamu, Ito Yoshiya, Fujieda Kenji

Clin Pediatr Endocrinol 2005; 14(Suppl 24), 81-84

Permanent Neonatal Diabetes Mellitus with Growth Disturbance, Developmental Delay, Epilepsy and Dysmorphic Features

Shigeru Suzuki[1], Tokuo Mukai[1], Kimiaki Uetake[2], Syun-ichi Sageshima[2], Kumihiro Matsuo[1], Osamu Ueda[1], Yoshiya Ito[1] and Kenji Fujieda[1]

[1]*Department of Pediatrics, Asahikawa Medical College, Asahikawa, Japan*

[2]*Obihiro Kosei General Hospital, Obihiro, Japan*

Abstract. We report the case of 15-mo-old girl who manifested neonatal diabetes mellitus associated with IUGR, developmental delay, epilepsy dysmorphic features and growth disturbance. She was born at 38 wk of gestation after normal pregnancy. Her birth weight was 2262 g (<10%tile) and height 45.0 cm (<10%tile). Since birth she gradually presented failure to thrive and presented hyperglycemia (glucose 692 mg/dl), ketoacidosis and elevated HbA1c level (7.7%) at 3 mo of age. The anti-GAD antibody was negative and the serum CPR level was 0.5 ng/ml. The girl was treated with intensive insulin therapy from 3 mo of age, however, her weight did not improve and was only 3305 g (−4.6 SD) at 5 mo of age. When admitted to our hospital, she was recognized as having dysmorphic features such as prominent forehead, downturned mouth, bilateral ptosis, arthrogryposis, hypertonia and umbilical hernia. Because she presented frequent hypoglycemic episodes under the intensive insulin injection regimen, treatment was changed to a twice a day injection schedule. Subsequently, the patient did not show any hypoglycemic episodes and she gradually gained a weight. However, at 7 mo of age, seizures developed and her EEG was hypsarrhythmic. She is now 15 mo of age but she cannot sit without support. She is still short and her height is 64.8 cm (−3.9 SD).

Key words: permanent neonatal diabetes, growth disturbance, developmental delay, epilepsy, dysmorphic feature

Introduction

Neonatal diabetes mellitus (NDM) is a rare disorder defined as insulin-requiring hyperglycemia that manifests in the first 3 mo of life (1). This NDM is classified into two subtypes: a transient form and a permanent form. Intrauterine growth retardation is a typical clinical feature (2), presenting with hyperglycemia in the first 6 wk of life in the transient form of NDM (TNDM). Such cases manifest open-alert face, subcutaneous fat wasting, macroglossia, and rarely have umbilical hernia. Furthermore a significant number of patients with TNDM manifest type II diabetes later in life. In most of patients with TNDM, abnormalities in an imprinting region of chromosome 6 are identified (3). On the other hand, there are no reports about complications of permanent NDM (PNDM) of unknown cause, but such cases are likely to be older when diagnosed and have ketoacidosis more frequently (2). Moreover, most of the causes of PNDM remain

Correspondence: Dr. Kenji Fujieda, Department of Pediatrics, Asahikawa Medical College, 2-1-1-1 Midorigaoka Higashi, Asahikawa 078-8510, Japan
E-mail: ken-fuji@asahikaw-med.ac.jp

unknown although several molecular bases of PNDM have been identified (4–7).

We present here the case of 15-mo-old girl who manifested neonatal diabetes with intrauterine growth retardation (IUGR), developmental delay, epilepsy, dysmorphic features, umbilical hernia and growth disturbance.

Case Report

The female patient was born at 38 wk of gestation by Cesarean section because of breech presentation. Pregnancy was uneventful. She is the second child of unrelated parents. Her parents and sister are healthy. Her maternal grandmother (I:2) was diagnosed as type 2 diabetes and her paternal grandmother (I:4) suffered from multiple sclerosis. The child was born as an intrauterine growth retarded baby. Her birth weight was 2262 g (<10%tile) and her height was 45.0 cm (<10%tile). Because of poor weight gain of 23 g/day, formula was added to breast milk at 1 mo of age. After that, her weight increased 28 g/day from 1 to 2 mo of age. At 3 mo of age, she was hospitalized in Obihiro Kyoukai Hospital because she manifested poor sucking and vomiting. She was diagnosed as having diabetic ketoacidosis based on elevated blood glucose of 692 mg/dl, blood pH 7.332, HCO_3^- 14.0 mmol/L and HbA1c 7.7%. The anti-GAD antibody was negative. Insulin therapy was started at that time. At 5 mo of age, she was admitted to our hospital because of failure to thrive and poor control of diabetes. On admission, her height was 55.0 cm (−2.8 SD) and her weight was 3305 g (−4.6 SD). She was recognized as having dysmorphic features such as prominent forehead, downturned mouth and bilateral ptosis. She also had umbilical hernia, arthrogryposis and hypertonia, and she could not hold her head steady while in the sitting position. Her liver function, renal function and thyroid function were normal. Blood analysis of amino acid was normal and there were no elevations of organic acids in the urine. Her karyotype was 46,XX. Serum CK and lactate level

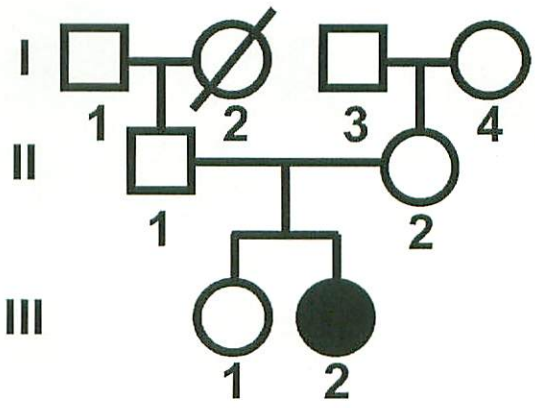

Fig. 1 Pedigree of the patient. The black circle indicates the patient.

were high (Table 1), but they were not continuously high. Lactate and the lactate/pyruvate ratio in cerebro-spinal fluid was not high. The IGF-1 level was 60.7 ng/ml under insulin therapy. Abdominal examinations by ultrasonography and magnetic resonance imaging (MRI) showed a normal pancreas. Brain MRI, and auditory brainstem response (ABR) showed no abnormalities. Electroencephalogram (EEG) showed multifocal spike waves though seizure was not observed. Electrocardiogram (ECG) showed incomplete right bundle branch block although cardiac ultrasonography (UCG) detected no abnormalities.

No abnormality in an imprinting region of chromosome 6 was detected and no mutation at both 3243 and 8344 in mitochondrial DNA was present. Because she presented frequent hypoglycemic episodes under the intensive insulin injection regimen, the insulin injection regimen was changed to a twice a day injection schedule. Subsequently, she did not show hypoglycemic episodes and she gradually gained weight.

At 7 mo of age, tonic seizures developed, and her EEG showed hypsarrhythmic pattern (Fig. 2). Clobazam was administered and the seizures were suppressed until 14 mo of age when her seizure changed to tonic spasm. The girl's developmental quotient (DQ) was 18 at that time, thus West

Table 1 Laboratory findings at admission to our hospital

WBC	14,900 /ml	Na	139 mEq/l	IGF-1	11.1 ng/ml
RBC	532 × 10^4 /ml	K	5.5 mEq/l	IGFBP-3	0.59 μg/ml
Hb	13.6 g/dl	Cl	98 mEq/l		
Plt	81.5 × 10^4 /ml	Ca	10.2 mg/dl	NH_3	93 mmol/l
		IP	5.0 mg/dl	Lactate	39.8 mg/dl
TP	6.5 g/dl			Pyruvate	1.6 mg/dl
Alb	4.3 g/dl	FBS	117 mg/dl		
T-cho	210 mg/dl	HbA1c	7.0%	Karyotye	46,XX
TG	101 mg/dl	s-CPR	0.5 μg/ml		
ALP	480 IU/l	u-CPR	1.2 μg/day	<Blood gas> (venous)	
AST	68 IU/l	GAD-Ab	0.4 U/ml	pH	7.331 mmol/l
ALT	64 IU/l			HCO_3	28.1 mmol/l
LDH	492 IU/l	Leptin	2.9 ng/ml	B.E.	1.5
CK	243 IU/l			<Cerebrospinal fluid>	
AMY	14 IU/l	F-T3	3.11 pg/ml	Lactate	6.2 mg/dl
BUN	8 mg/dl	F-T4	1.12 ng/dl	Pyruvate	1.2 mg/dl
Cre	0.16 mg/dl	TSH	4.26 mIU/l	L/P ratio	5.2

syndrome was diagnosed. Zonisamide was initiated and the seizure has been well controlled with a frequency of 1–2 times a day. The patient is now 15 mo of age but she cannot sit without support. She is still short and her height is 64.8 cm (−3.9 SD) and her weight is 6950 g (−2.6 SD). She is taking insulin injection with a diluted NPH insulin regimen twice a day (0.55 unit per kg) and her HbA1c is 7.5%.

Discussion

We present a complicated case of neonatal diabetes mellitus with a variety of clinical manifestations. The patient's NDM seems to be permanent because she required insulin therapy since 3 mo of age although insulin secretion usually recovers within a median of 3 mo in TNDM patients (3). Although IUGR and ketoacidosis are one of the manifestations of PNDM, our patient also has umbilical hernia and dysmorphic face. She also manifests a further variety of unusual symptoms such as poor postnatal growth, developmental delay, hypertonia and epilepsy. All of these manifestations have not been reported

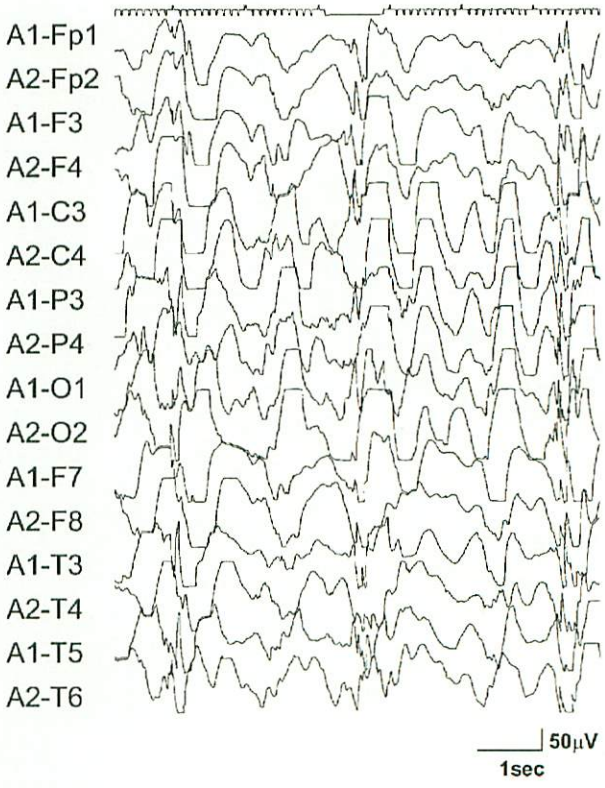

Fig. 2 Electroencephalogram in the patient at 7 mo of age.

previously in PNDM of unknown cause (2, 8–10). The girl's epilepsy seems not to be related to hypoglycemia because there was no evidence of seizure induced by hypoglycemia and the seizures developed after normoglycemia. These broad ranges of clinical presentation may suggest that some common factor in the brain, muscle and pancreas plays a role in the disease manifestation.

An abnormal imprinting region of chromosome 6 is indicated as a cause of TNDM. However, our case did not harbor any abnormality in the imprinting region such as uniparental disomy, duplication of paternal origin and a loss of methylation (3). Also, we could not identify any mutation at positions 3243 and 8344, thus ruling out mitochondrial abnormality (11). Metabolic abnormality may also be absent, because no abnormality of serum aminoacid and lactate level was noted. Postnatal growth retardation was not attributed to abnormality of GH and the thyroid axis.

Some of the molecular bases of PNDM recently have been identified. Of these, glucokinase deficiency presents severe intrauterine growth retardation and hyperglycemia within 10 days of life (4). Pancreatic agenesis manifests clinical exocrine pancreatic insufficiency at few days of life with neonatal diabetes (5). IPEX syndrome is known to manifest immunodysregulation, polyendocrinopathy, enteropathy (6). Wolcott-Rallison syndrome presents multiple epiphyseal dysplasia with insulin-dependent diabetes (7). All of these forms result in PNDM, however, our case is not compatible with these cases. Thus, the present case may be a new syndrome of PNDM. We are now searching for the candidate genes for this complicated case. Kir6.2 (12) is one of the candidates and additional complicated PNDM cases would be helpful for elucidating the pathophysiology.

References

1. Polak M, Sield J. Neonatal and very-early-onset diabetes mellitus. Semin Neonatal 2004;9:59–65.
2. Metz C, Cave H, Bertrand AM, Deffert C, Gueguen-Giroux B, Czernichow P, *et al.* Neonatal diabetes mellitus: chromosomal analysis in transient and permanent cases. J Pediatr 2002;41:483–9.
3. Temple IK, Gardner RJ, Mackay DJ, Barber JC, Robinson DO, Shield JP. Transient neonatal diabetes: widening the understanding of the etiopathogenesis of diabetes. Diabetes 2000;49:1359–66.
4. Njolstad PR, Sovik O, Cuesta-Munoz A, Bjorkhaug L, Massa O, Barbetti F, *et al.* Neonatal diabetes mellitus due to complete glucokinase deficiency. N Engl J Med 2001;344:1588–92.
5. Stoffers DA, Zinkin NT, Stanojevic V, Clarke WL, Habener JF. Pancreatic agenesis attributable to a single nucleotide deletion in the human IPF1 gene coding sequence. Nat Genet 1997;15:106–10.
6. Wildin RS, Smyk-Pearson S, Filipovich AH. Clinical and molecular features of the immunodysregulation, polyendocrinopathy, enteropathy, X linked (IPEX) syndrome. J Med Genet 2002;39:537–45.
7. Senee V, Vattem KM, Delepine M, Rainbow LA, Haton C, Lecoq A, *et al.* Wolcott-Rallison Syndrome: clinical, genetic, and functional study of EIF2AK3 mutations and suggestion of genetic heterogeneity. Diabetes 2004;53:1876–83.
8. Shield JP. Neonatal diabetes: new insights into aetiology and implications. Horm Res 2000;53 Suppl 1:7–11.
9. Iafusco D, Stazi MA, Cotichini R, Cotellessa M, Martinucci ME, Mazzella M, *et al.* Permanent diabetes mellitus in the first year of life. Diabetologia 2002;45:798–804.
10. Marquis E, Robert JJ, Bouvattier C, Bellanne-Chantelot C, Junien C, Diatloff-Zito C. Major difference in aetiology and phenotypic abnormalities between transient and permanent neonatal diabetes. J Med Genet 2002;39:370–4.
11. Finsterer J. Mitochondriopathies. Eur J Neurol 2004;11:163–86.
12. Gloyn AL, Pearson ER, Antcliff JF, Proks P, Bruining GJ, Slingerland AS, *et al.* Activating mutations in the gene encoding the ATP-sensitive potassium-channel subunit Kir6.2 and permanent neonatal diabetes. N Engl J Med 2004;350:1838–49.