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CASE REPORT

Phenotypic differences and similarities of monozygotic twins with maturity-onset diabetes of the young type 5

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ABSTRACT

Here, we report phenotypic differences and similarities of monozygotic twins with maturity-onset diabetes of the young type 5 harboring a partial deletion of chromosome 17q12. The proband and her twin sister manifested complete aplasia and marked hypoplasia, respectively, of the body and tail of the pancreas. Whereas both twins showed marked hypoplasia of the right kidney and multiple cysts in both kidneys, only the proband's sister showed hydronephrosis in the left kidney. The proband had profound defects in insulin and glucagon secretion, as well as mild renal dysfunction, whereas her sister had pronounced renal dysfunction accompanied by mild defects in insulin and glucagon secretion. Both twins manifested hypomagnesemia and hyperuricemia, but no apparent liver dysfunction or intellectual disability. The severity of renal and pancreatic defects differed between monozygotic twins with maturity-onset diabetes of the young type 5, suggesting that the phenotypes of this condition are determined not solely by genetic factors.

INTRODUCTION

Mutations in the gene for hepatocyte nuclear factor 1β (*HNF1β*) give rise to maturity-onset diabetes of the young type 5 (MODY5)[1,2]. Individuals with MODY5 manifest not only early-onset diabetes mellitus, but also various disorders including pancreatic, renal and genital tract malformations; liver dysfunction; hypomagnesemia; and hyperuricemia, as well as intellectual disability[2]. The severity of diabetes and its associated disorders in MODY5 can vary even among individuals with the same mutation in *HNF1β*[2,3]. It is likely that environmental factors, as well as genetic factors other than mutations of *HNF1β*, influence the manifestations of this condition, although the relative contributions of these two types of factors are unknown. Information on the phenotypes of monozygotic twins with MODY5 would be expected to shed light on this issue. Here, we describe phenotypic differences and similarities for a set of monozygotic twins with MODY5.

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CASE REPORT

A 30-year-old woman (twin 1) who had not previously been diagnosed with diabetes mellitus presented at a clinic of Kobe University Hospital, Kobe, Japan, because of the recent onset of thirst and polyuria. She had a plasma glucose concentration of 739 mg/dL, glycosylated hemoglobin level of 16.9% and ketonuria of ≥3, and she was admitted to the hospital. On admission, her height was 152.3 cm and bodyweight 41.8 kg. After her blood glucose level had been lowered sufficiently, various examinations were carried out. Glucagon challenge and meal challenge tests showed that her insulin secretion was markedly impaired (Table 1). Her estimated glomerular filtration rate was within normal range (Table 2). She showed hypomagnesemia and hyperuricemia, but her liver function was normal (Table 2). Computed tomography and magnetic resonance imaging showed complete aplasia of the body and tail of the pancreas, as well as marked aplasia of the right kidney and multiple cysts in both kidneys (Figure 1). Pancreatic volume calculated by a method described previously[4] was 5.2 mL. A diagnosis of MODY5 was suspected on the basis of the clinical features.

Given that the proband had an identical twin sister, twin 2 was also examined for MODY5. Her height was 151.9 cm and bodyweight 40.3 kg. Although her glycosylated hemoglobin level was 5.8%, the results of a 75-g oral glucose tolerance test (fasting plasma glucose 135 mg/dL; 2-h postload 337 mg/dL) met the criteria for diabetes mellitus. She manifested renal dysfunction, hypomagnesemia, hyperuricemia and normal liver function (Table 2). Her glucagon challenge and meal challenge test results showed preservation of insulin secretion (Table 1). Computed tomography and magnetic resonance imaging showed hypoplasia of the body and tail of the pancreas, with a pancreatic volume of 14.6 mL, as well as marked aplasia of the right kidney, multiple cysts in both kidneys and hydronephrosis in the left kidney. Serum glucagon levels during an arginine challenge test of twin 1 and twin 2 were smaller and greater, respectively, than those observed with type 2 diabetes patients (Figure 2).

The bodyweights of twin 1 and twin 2 at birth were 2,250 and 2,550 g, respectively, and those at 2 years and 20 years were 13.0 and 12.0 kg, as well as 40.1 and 40.4 kg, respectively. Although twin 2 underwent surgery for hydronephrosis immediately after birth, there was no other notable event in their medical history until this presentation. They had no family history of diabetes mellitus, multiple kidney cysts and aplasia of kidneys (Figure S1).

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national), and with the Helsinki Declaration of 1964 and later versions. Written informed consent was obtained from all patients before they were included in the report.

Array-based comparative genomic hybridization showed a heterozygous 857-kb deletion of a region at chromosome 17q12 (arr[GRCh37] 17q12 (34817422_36079369) x1) that contains

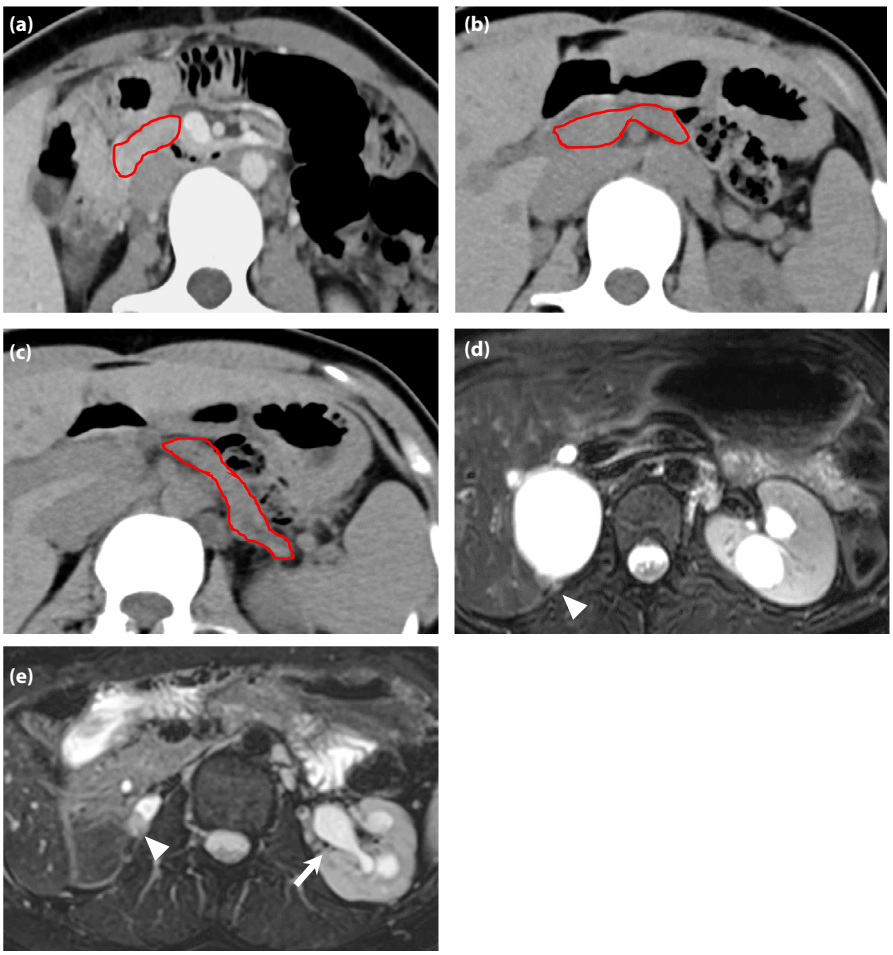

Figure 1 | Abdominal computed tomography (a-c) and T2-weighted magnetic resonance imaging (d,e) for twin 1 (a,d) and twin 2 (b,c,e). The boundary of the pancreas is outlined in red (a-c). Computed tomography shows a small pancreatic head and complete deficiency of the pancreatic body and tail in twin 1 (a) as well as hypoplasia of the pancreatic body and tail in twin 2 (b,c). Arrowheads indicate marked aplasia of the right kidney and multiple bilateral renal cysts in both patients (d,e), and the arrow indicates hydronephrosis of the left kidney in twin 2 (e).

Table 1 | Glucagon and meal challenge tests

	Twin 1	Twin 2
Glucagon challenge test		
Preload plasma glucose (mg/dL)	140	100
Postload plasma glucose (mg/dL)	151	122
Preload serum CPR (ng/mL)	0.5	1.8
Postload serum CPR (ng/mL)	1.4	3.5
Difference between post- and preload CPR	0.9	1.7
Meal challenge test		
Preload plasma glucose (mg/dL)	154	114
Postload plasma glucose (mg/dL)	315	136
Preload serum CPR (ng/dL)	0.2	3.0
Postload serum CPR (ng/dL)	0.8	7.0

For the glucagon challenge test, 1 mg of glucagon was injected intravenously after an overnight fast, and plasma glucose and serum C-peptide immunoreactivity (CPR) before (pre) and 6 min after (post) the injection were measured. For the meal challenge test, a standardized meal of 500 kcal (60% carbohydrate, 16% protein and 24% fat) was provided after an overnight fast. Plasma glucose and serum CPR before (pre) and 2 h after (post) the meal were measured.

Table 2 | Comparison of characteristics of identical twin

	Twin 1	Twin 2	Reference range
Birthweight (g)	2,250	2,550	
Height (cm)	152.3	151.9	
Weight (kg)	41.8	40.3	
BMI (kg/m^2)	18	17.5	
Blood biochemistry			
Aspartate aminotransferase (U/L)	31	14	13–30
Alanine aminotransferase (U/L)	22	14	7–23
γ-Glutamyl transpeptidase (U/L)	17	26	9–32
Total protein (g/dL)	6.5	6.0	6.6–8.1
Albumin (g/dL)	4.0	3.6	4.1–5.1
Total bilirubin (mg/dL)	0.8	0.5	0.4–1.5
Creatinine (mg/dL)	0.81	1.58	0.46–0.79
eGFR (mL/min/1.73 m^2)	68.0	32.7	≧60
Magnesium (mg/dL)	1.3	1.3	1.7–2.3
Uric acid (mg/dL)	7.2	7.9	2.6–5.5
Urine biochemistry			
C-peptide (μg/day)	1.4	52.9	
Albumin (mg/day)	11.8	123.3	

BMI, body mass index; eGFR, estimated glomerular filtration.

the *HNF1β* locus, as well as *LHX1*, in both twins. They were therefore diagnosed with MODY5 associated with a deletion of 17q12 containing *HNF1β* (known as 17q12 deletion syndrome).

DISCUSSION

This is the first study to examine the differences and similarities in constitutional manifestations of monozygotic twins with MODY5. Twin 1 showed a profound defect in insulin secretion and mild renal dysfunction, whereas twin 2 manifested pronounced renal dysfunction and a mild defect in insulin secretion. Although both twins showed hypoplasia of the pancreas, the pancreatic volume was reduced to a greater extent in twin 1 than in twin 2. The secretion of glucagon was also severely impaired in twin 1, consistent with the notion that impairment of insulin secretion in MODY5 is due not to a functional defect specific to pancreatic β-cells, but rather to hypoplasia of the pancreas. Only one report of monozygotic twins with MODY5 has been published[5]. Although detailed phenotypes of the patients were not described, the severity in renal and pancreatic defects appeared to be similar between the twins[5]. The current report is thus unique in that the severity of renal and pancreatic dysfunction of the twins markedly differed.

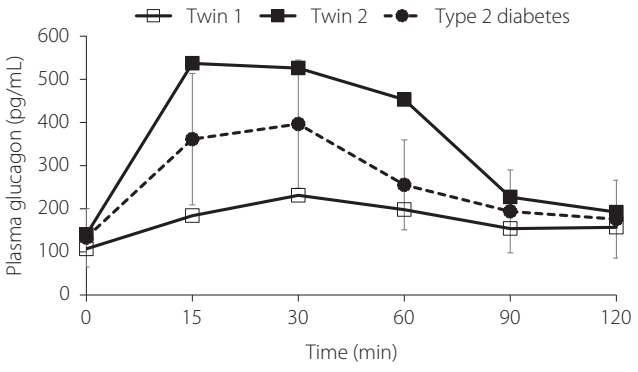

Figure 2 | Arginine challenge test results. Arginine (10% L-arginine hydrochloride) was administered intravenously at a dose of 0.5 g/kg over 30 min. Plasma glucagon concentration measured before, as well as 15, 30, 60, 90 and 120 min after completion of the onset of arginine loading with the use of a radioimmunoassay (Glucagon RIA SML; Sceti Medical Laboratory, Tokyo, Japan) for twin 1 (open square), twin 2 (closed square) and mean ± standard deviation of type 2 diabetes patients (n = 40; closed circle) are shown. Detailed characteristics of the type 2 diabetes patients were previously reported[12].

Whereas malformation of and the presence of multiple cysts in the kidneys are often associated with *HNF1β* mutations, hydronephrosis is less common[6]. As far as we are aware, six cases of hydronephrosis or obstruction of the ureteropelvic junction associated with *HNF1β* mutations have been reported to date, including four cases with large deletions at 17q12[4,7], one case with a duplication of 17q12 and one case with a point mutation in *HNF1β* [6]. In addition to loss of *HNF1β*, 17q12 deletion syndrome is often associated with the deletion of *LHX*, which plays an important role in morphogenesis of the nephric duct and ureteric bud. It is thus possible that 17q12 deletion is more likely to give rise to the development of hydronephrosis compared with other types of mutation underlying MODY5.

The phenotypes of monozygotic twins with monogenic diseases, such as Rett syndrome[8] and Huntington's disease[9], have

been found to differ both in severity and mode of development. Given that nucleotide variants rarely differ between monozygotic twins[10], differences in the phenotypes for such disease are likely attributable to non-genetic factors.

The phenotypic differences in the present cases, including those in the severity of renal and pancreatic dysfunction, might thus also be attributable at least partly to non-genetic factors. However, even between monozygotic twins, a small number of genomic sequences might differ. Furthermore, copy number variations, as well as mitochondrial DNA variations and heteroplasmy, are often observed in monozygotic twins[11]. It is also possible that such factors affected the phenotypes of the twins.

In conclusion, we showed that the severity of renal and pancreatic defects differed between monozygotic twins with MODY5. The present findings thus suggest that constitutional manifestations of this condition are determined not solely by genetic factors.

DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1 | Pedigree of the family.