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CASE REPORT

Coexistence of type 2 diabetes mellitus, arginine vasopressin deficiency, and Marfan syndrome: A case report

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ABSTRACT

Diabetes mellitus (DM) and arginine vasopressin deficiency (AVP-D) are characterized by polyuria. Marfan syndrome is an autosomal dominant disorder caused by pathogenetic variants in *FBN1*. Here, we report a patient with type 2 diabetes mellitus, AVP-D, and Marfan syndrome. Although the coexistence of type 2 diabetes mellitus and AVP-D is rare, for those patients with type 2 diabetes mellitus, the existence of AVP-D should be considered when polyuria is not in accordance with the blood glucose levels, especially for those with a low urine specific gravity. Specific symptoms or signs help to identify Marfan syndrome early, and genetic testing of the *FBN1* pathogenetic variant helps to make a definitive diagnosis.

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease characterized by hyperglycemia and the symptoms of polydipsia and polyuria[1]. Diabetes insipidus (DI) is one of the main causes of polyuria polydipsia syndrome and is characterized by prominently increased urine production[2]. Arginine vasopressin deficiency (AVP-D), a subtype of DI, is caused by inadequate secretion or deficient synthesis of AVP from the hypothalamic–neurohypophyseal axis in response to osmotic stimulation[2]. It is important and challenging to diagnose the coexistence of AVP-D and diabetes mellitus because of their similar symptoms. Marfan syndrome is an autosomal dominant, age-related disease and is caused by pathogenetic variants in *FBN1*[3]. Several case reports have demonstrated the coexistence of type 2 diabetes mellitus and Marfan syndrome, but the association between Marfan syndrome and type 2 diabetes mellitus is obscure. Until now, no case report has reported the combination of type 2 diabetes mellitus, AVP-D, and Marfan syndrome in a patient. Here, we present the first case of a patient with coexisting type 2 diabetes mellitus, AVP-D, and Marfan syndrome.

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CASE PRESENTATION

A 32-year-old woman presented to the Department of Endocrinology and Metabolism with thirst, polydipsia, and polyuria for 3 years and hyperglycemia for 1 year. Her fasting blood glucose (FBG), 2 h postprandial blood glucose (2 h PBG), and hemoglobin A1c (HbA1c) were 21.7 mmol/L, 30.6 mmol/L, and 14.6%, respectively, 1 month before. She had a medical history of thyroid nodules, Hashimoto's thyroiditis, subclinical hypothyroidism, fatty liver, ovarian cysts, and ectopia lentis. She is a married woman with a child, and no family history of hereditary disease was reported. On physical examination, she was 166 cm tall and weighed 76.7 kg, with a body mass index of 27.8 kg/m^2. She had abnormally long fingers and toes and was positive for the thumb and wrist signs (Figure 1). No significant abnormalities in the head and neck, chest, cardiopulmonary, or abdominal examination were found, and her skin was not dry.

The results revealed an HbA1c of 13.8%, C-peptide of 314 pmol/L, hyperlipidemia, and negativity for diabetes-associated autoantibodies, suggesting the diagnosis of type 2 diabetes mellitus (Table 1). No diabetic complications were found. After treatment with insulin and blood glucose in the range of 7–10 mmol/L, the urine volume was more than 10 liters a day, and the urine specific gravity was 1.002. Further, urine osmolality was

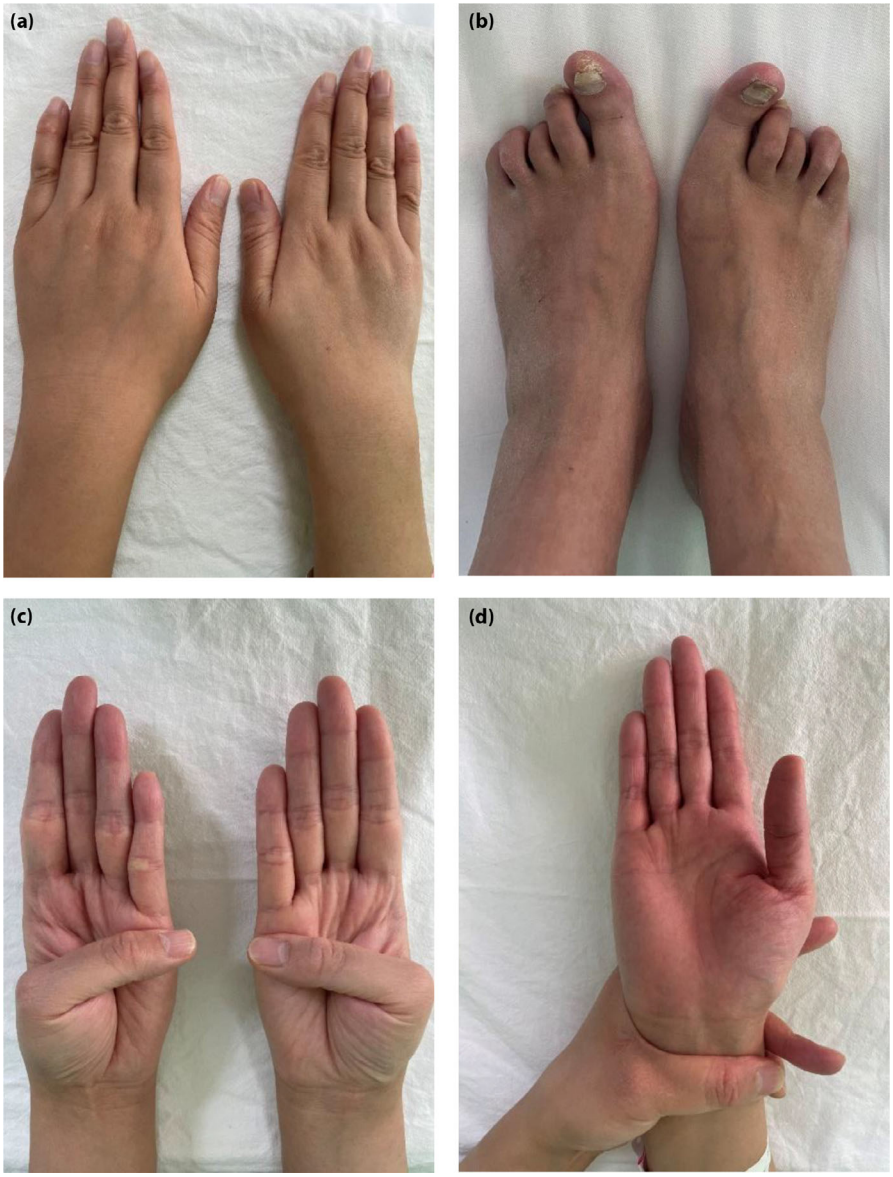

Figure 1 | Abnormal physical examination of the patient.

98 mOsm/kg H_2O (600–1,000), and serum osmolality was 309 mOsm/kg H_2O (285–305). The results showed an initial urine gravity of 1.006 and a urine osmolality of 152 mOsm/kg H_2O and the diagnosis of AVP-D was definite in the water deprivation test and vasopressin administration test (Table 2). No other pituitary damage or space-occupying lesion were found in brain magnetic resonance imaging (MRI) (Figure 2), except for the loss of posterior pituitary bright spot on T1 weighted imaging under well-controlled blood glucose. This imaging feature further indicated AVP-D but not caused by diabetes mellitus, considering the bright spot will appear in patients with controlled diabetes mellitus[4]. Other causes of AVP-D were all excluded, and these results were consistent with idiopathic AVP-D. As the patient was positive for the thumb sign and wrist sign without a family history of Marfan syndrome, genetic testing was obtained. Whole-exome sequencing revealed a c.7871A>G (p. Asn2624Ser) heterozygous mutation in the *FNB1* gene. There were no cardiovascular system manifestations, as evaluated by transthoracic echocardiography and aortic computed tomography angiography, but ectopia lentis was found.

During hospitalization, insulin and metformin were used to achieve good and mild fluctuation glycemic control at FBG levels of 5–7 mmol/L and 2 h PBG levels of 8–9 mmol/L. Upon treatment with the AVP-D, she was prescribed oral desmopressin at a dosage of 0.025 mg twice daily and 0.05 mg at bedtime. Her thirst, polydipsia, and polyuria were relieved, and

Table 1 | Laboratory data

Variable	On admission	Reference range
Blood		
White blood cells ($\times 10^9$/L)	6.17	3.5–9.5
Hemoglobin (g/L)	135	115–150
Sodium (mmol/L)	147	137–147
Potassium (mmol/L)	3.6	3.5–5.3
Urea nitrogen (mmol/L)	3.1	2.6–7.5
Creatinine (mmol/L)	64	53–97
Total cholesterol (mmol/L)	5.21	<5.18
Glucose (mmol/L)	9.5	3.9–6.1
C-peptide (pmol/L)	314	270–1,282
Hemoglobin A1c (%)	13.8	4.0–6.0
Osmolality (mOsm/kg H_2O)	309	285–305
Cortisol (μg/dL)	7.7	5–25
Thyroid stimulating hormone (μIU/mL)	4.01	0.55–4.78
Free triiodothyronine (pg/mL)	3.23	2.3–4.2
Free thyroxine (ng/mL)	1.10	0.89–1.80
Prolactin (ng/mL)	5.7	1.9–25
Luteinizing hormone (mIU/mL)	1.31	0.8–7.6
Follicle stimulating hormone (mIU/mL)	3.89	0.7–11.1
Progesterone (nmol/L)	1.18	0.86–2.9
Estradiol (pmol/L)	95	<143
Growth hormone (ng/mL)	1.31	<8
Insulin-like growth factor 1 (ng/mL)	86.4	71–234
Alpha fetoprotein (ng/mL)	3.06	≤20
Human chorionic gonadotropin (mIU/mL)	0.08	0–3.1
Urine		
Glucose	Negative	Negative
Ketones	Negative	Negative
Protein	Negative	Negative
Specific gravity	1.002	1.015–1.025
Osmolality (mOsm/kg H_2O)	98	600–1,000

her volume of urine decreased to <2 L. In addition, her urine specific gravity increased to 1.018 and urine osmolality to 420 mOsm/kg H_2O. The follow-up of manifestations of Marfan syndrome, especially aortic disease, is still ongoing.

DISCUSSION

Type 2 diabetes mellitus and AVP-D coexistence is a rare condition, and the possible intrinsic connection between the two diseases is still obscure. The pathogenesis of type 2 diabetes mellitus is multifactorial and involves insulin resistance and impaired insulin secretion, without autoimmunity, which is supposed to be a possible etiology for AVP-D[5]. Whether the damage to the hypophyseal portal system derived from diabetic vascular complications contributes to the occurrence of AVP-D needs to be further determined. In addition, further efforts are warranted to identify whether other diseases, such as asthma, Albright's hereditary osteodystrophy-like syndrome, and Klinefelter's syndrome, might be considered plausible causes for their coexistence[6].

Marfan syndrome is a predominantly autosomal dominant condition and the major manifestations of Marfan syndrome are aortic root aneurysm, acute aortic dissection, disproportionate long bone overgrowth, and ectopia lentis. Several case reports have reported the concomitant occurrence of Marfan syndrome and type 2 diabetes mellitus. Although it is a rare condition, the coexistence of Marfan syndrome and type 1 diabetes mellitus has also been reported in some cases. Abnormal *TGFB* genes, matrix metalloproteinases (MMPs), and adipose tissues might play critical roles in the coexistence of Marfan syndrome and type 2 diabetes mellitus[7]. Moreover, *TGFB* and fibrillin-1 also participate in the development and progression of diabetic nephropathy and retinopathy, making *TGFB* responsible for the diabetic vascular complications in individuals with Marfan syndrome[8]. MMPs are proteases that play an important role in the degradation of extracellular matrix proteins. It has been reported that in both type 2 diabetes mellitus and Marfan syndrome, the expression of MMPs is increased, and MMPs may be the link between type 2 diabetes mellitus and Marfan syndrome[9]. Moreover, patients with Marfan syndrome exhibit alterations in adipose tissues, leading to lipodystrophy and obesity in some individuals. The abnormal adipose tissue deposition in patients with Marfan syndrome is responsible for metabolic abnormalities such as insulin resistance and type 2 diabetes mellitus[10].

In summary, to our knowledge, this case is the first case of the coexistence of type 2 diabetes mellitus, AVP-D, and Marfan syndrome. For those patients with type 2 diabetes mellitus, the existence of AVP-D should be considered when polyuria is not

Table 2 | Results of the water deprivation test and vasopressin administration test

Test time (h)	Heart rate (bpm)	Weight (kg)	Blood pressure (mmHg)	Urine volume (mL)	Urine specific gravity	Urine osmolality (mOsm/kg H_2O)	Blood osmolality (mOsm/kg H_2O)	Sodium (mmol/L)
0	79	71.9	108/64	0	1.005	165	306	145
1	77	71.5	120/64	300	1.005	174	308	146
2	82	71.4	109/63	300	1.006	170	312	148
3[†]	83	71.1	110/65	350	1.006	152	311	148
4	82	70.9	104/61	100	1.015	411	311	148
5	90	70.4	107/62	100	1.018	499	311	148

[†]5 U vasopressin was administered at 3 h.

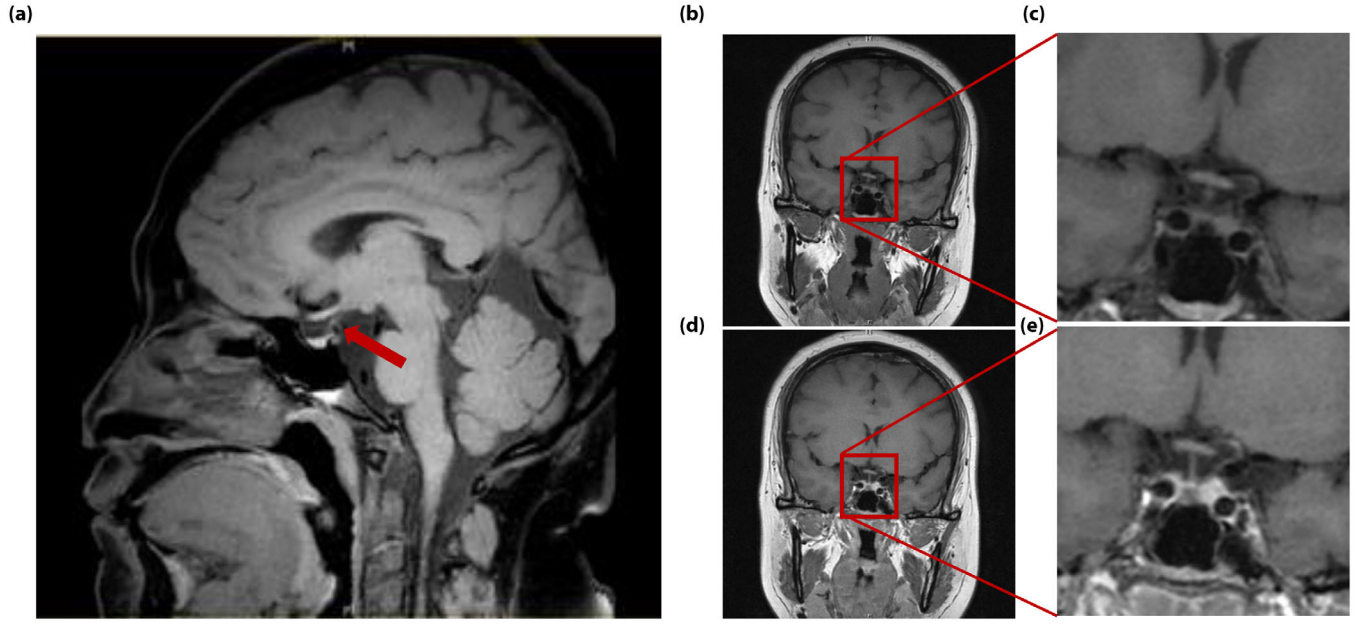

Figure 2 | Representative images of brain magnetic resonance imaging (MRI) focused on the pituitary region.

in accordance with the blood glucose levels, especially for those with low urine specific gravity. Specific symptoms or signs help to identify Marfan syndrome early, and genetic testing of the *FBN1* pathogenetic variant helps to make a definitive diagnosis. The correlation between type 2 diabetes mellitus, AVP-D, and Marfan syndrome is still obscure, and further studies are needed to obtain a deeper understanding of these diseases.

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DISCLOSURE

Tianpei Hong is an Editorial Board member of *Journal of Diabetes Investigation* and a co-author of this article. To minimize bias, he was excluded from all editorial decision-making related to the acceptance of this article for publication. The other authors declare that they have no competing interests.
Approval of the research protocol: N/A.
Informed consent: Written informed consent was obtained from the patient.
Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.

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