Partial central diabetes insipidus after simultaneous pancreas-kidney transplantation exacerbated orthostatic hypotension in type 1 diabetes mellitus

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Abstract
A 34-year-old woman with type 1 diabetes on hemodialysis was admitted to our hospital for simultaneous pancreas-kidney transplantation received from her father. She had suffered from type 1 diabetes mellitus since age 13, and had complained of serious atomic gastroenteropathy and orthostatic hypotension. After the transplantation, she became free from hemodialysis and insulin injection. At the same time, her gastrointestinal symptoms disappeared. However, she still had orthostatic hypotension, which was improved by taking fludrocortisone. Two months after the transplantation, orthostatic hypotension with marked polyuria became obvious. By hypertonic saline challenge test, she was diagnosed as partial central diabetes insipidus. Although treatment with desmopressin was necessary for 5 months, she became free from medication afterwards. Diabetes insipidus seems to be a rare but could be an important complication after simultaneous pancreas kidney transplantation and/or or kidney transplantation.

Keywords: Pancreas-kidney transplantation, Type 1 diabetes mellitus, Diabetes insipidus, Orthostatic hypotension, Gastroparesis

Introduction
Simultaneous pancreas-kidney transplantation is a therapeutic option for concurrent recovery of pancreatic and renal function in patients with type 1 diabetes on dialysis. Since the revision of Japan’s Law for Organ Transplantation, the rate of pancreas transplantation using brain dead donors has increased.1-4

Simultaneous pancreas-kidney transplantation improves both blood glucose control and renal function, and additional benefits can be expected for diabetic complications such as neuropathy. However, their clinical courses are quite variable and co-existing disease could affect their management. We report a case of central diabetes insipidus with pancreas-kidney transplantation in a type 1 diabetes patient with dysautonomia, which was associated with orthostatic hypotension deterioration.

Case Presentation
A 34-year-old woman with type 1 diabetes with proliferative retinopathy, neuropathy and end-stage renal disease (ESRD) was admitted to our hospital for living donor pancreas-kidney transplantation. She was diagnosed with type 1 diabetes at 13 years old, and insulin therapy was initiated. She underwent surgery for cataracts and diabetes retinopathy and, at the age of 30 years, she was initiated on hemodialysis for ESRD caused by diabetic nephropathy. She received docarpamine and amezinium metilsulfate at 400 mg/day and 10 mg/day, respectively. The orthostatic hypotension was thought to be caused by dysautonomia and symptoms of light-headedness and restlessness did not improve. Her food intake was unstable, often taking approximately 2 h to eat a meal because of complaints of abdominal distention and nausea, thought to be due to a functional gastrointestinal disorder. Furthermore, her quality of life had decreased markedly owing to abdominal symptoms, for example, paralytic ileus that required repeat hospitalizations. She was receiving quick-acting insulin (5 units in the morning, 5 in the afternoon, and 3 in the evening) in addition to intermediate-acting insulin (4 units in the morning and 8 immediately before sleep). However, blood glucose levels remained unstable despite insulin therapy.

On admission, her height, weight and BMI were 165.4 cm, 48.7 kg, and 17.8 kg/m², respectively. Her blood pressure and heart rate were 130/94 mmHg and 76 bpm and quite variable. She was conscious. There was no visible pallor or jaundice. A diffuse hard goiter due to chronic thyroiditis was noted. Both heart and respiratory sounds were normal. In the abdominal region, intestinal murmurs were decreased and distention was present. A shunt for hemodialysis was present in the left forearm. Achilles tendon reflexes and vibration sense at the medial malleolus were absent bilaterally. Dorsalis pedis artery was present with good perfusion of the toes on both sides.

Laboratory data on admission (before hemodialysis) is shown in Table 1. In relation to diabetes, a random blood glucose level was markedly elevated (381 mg/dl), HbA1c level was mildly elevated (6.3%, NGSP), anti-glutamic acid decarboxylase antibodies were negative (1.1 IU/ml, reference level <1.5), and serum C-peptide levels were below measurement sensitivity (<0.3 ng/ml). No abnormal findings were noted on 12-lead electrocardiography or echocardiography. Ankle-brachial index (ABI) was normal at 1.08 on the right side and 1.13 on the left side. Pulse wave velocities (PWW) were also close to normal, at 14.8 m/s on the right side and 13.9 m/s on the
left side. Peripheral nerve conduction velocity studies of perception/motor nerves in the upper limbs (median and ulnar nerves) and lower limbs (tibial and peroneal nerves) revealed bilateral F wave latency and amplitude attenuation. The tibial nerve in particular was non-inducible. No clear abnormalities were noted on upper and lower gastrointestinal endoscopy or chest computed tomography (CT) conducted as part of the preoperative screening.

The patient underwent living donor pancreas-kidney transplantation from her father. The pancreatic tail and left kidney were used as grafts. For the graft pancreas, the edge of the parenchyma was anastomosed to the ileum and the splenic vein and artery were anastomosed to the external iliac artery and vein, respectively. Immunosuppression was initiated with 1000 mg/day of mycophenolate mofetil, 3 mg/day of tacrolimus and 12 mg/day of methylprednisolone.

Hemodialysis was discontinued immediately after surgery. A small amount of insulin was administered with fluid replacement solution. However, this was discontinued after blood glucose levels became stable at around 90 mg/dl for several days. Regarding gastrointestinal symptoms, abdominal distention and nausea quickly improved following transplantation, and meals were started from post-operative day (POD) 8. The patient was able to finish an entire meal at approximately 30 min at this time. However, as orthostatic hypotension caused continued light-headedness and restlessness, 0.1 mg/day of fludrocortisone was initiated on POD 57. Despite fludrocortisone administration, blood pressure remained unstable with significant daily variation in urine volume, ranging from 2500 to 4000 ml/day. At this time, we assumed it was because of the intentionally excessive amount of drip infusion for daily need.

Increases in urine volume were more apparent after POD 66 (approximately 3000 to 6000 ml/day). There were no obvious changes in physical findings and, despite a somewhat low serum potassium level (3.2 mEq/l), general laboratory data, such as serum calcium level (9.4 mg/dl), were within the normal range and no hyperglycemia was noted. Initially, we assumed the increased renal blood flow due to fludrocortisone had caused the change in urinary volume. However, a plasma osmolality of 295 mOsm/kg·H₂O and a urine osmolality of 239 mOsm/kg·H₂O measured from 24-h urine samples (2870 ml/day) indicated impairment of urinary concentration, leading to clinical suspicion of diabetes insipidus. A hypertonic saline challenge test was then conducted. This revealed a plasma osmolality of 288 mOsm/kg·H₂O at 1.4 μg/ml rising to a plasma osmolality of 302 mOsm/kg·H₂O at 2.1 pg/ml at 120 minutes despite normal antidiuretic hormone (ADH) levels prior to loading, leading to a diagnosis of partial central diabetes insipidus (Table 2).

Following discharge from hospital, blood pressure fluctuations improved and light-headedness and restlessness improved further. Therefore, fludrocortisone was discontinued at 6 months postoperatively and the dosage of desmopressin nose drops was reduced as polyuria decreased and eventually discontinued at 5 months postoperatively. Approximately 3 years postoperative, no symptoms had recurred. However, although transplanted kidney function had been maintained, the function of the transplanted pancreas had gradually declined to the point of necessitating insulin potentiation therapy at 10 months postoperative. Abdominal symptoms, such as abdominal distention, gradually worsened as required amounts of insulin increases.

### Discussion

We report the case of a patient who developed central diabetes insipidus following a pancreas-kidney transplantation with improvements in hemodynamic stabilization symptoms. A hypertonic saline challenge test suggested that this patient had partial ADH secretion dysfunction. During hemodialysis, patients often experience hypotension and subsequent volume overload, which may affect ADH secretion. However, ADH concentration in ESRD patients does not increase sufficiently in orthostatic hypotension especially in the presence of severe diabetic neuropathy. In addition, the kidneys in ESRD patients do not respond well to ADH. Therefore, it is difficult to diagnose...

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**Table 1. Laboratory data on admission**

<table>
<thead>
<tr>
<th>WBC</th>
<th>5500/μl</th>
<th>BUN</th>
<th>50.6 mg/dl</th>
</tr>
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<tbody>
<tr>
<td>RBC</td>
<td>425 × 10^6/μl</td>
<td>Cr</td>
<td>7.24 mg/dl</td>
</tr>
<tr>
<td>Hb</td>
<td>13.2 g/dl</td>
<td>UA</td>
<td>5.2 mg/dl</td>
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<tr>
<td>Hct</td>
<td>42.2%</td>
<td>Na</td>
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<tr>
<td>Plt</td>
<td>148 × 10^6/μl</td>
<td>K</td>
<td>6.3 mEq/l</td>
</tr>
<tr>
<td>TP</td>
<td>7.5 g/dl</td>
<td>Cl</td>
<td>99 mEq/l</td>
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<tr>
<td>Alb</td>
<td>3.9 g/dl</td>
<td>Ca</td>
<td>9.2 mg/dl</td>
</tr>
<tr>
<td>T-Bil</td>
<td>0.3 mg/dl</td>
<td>Pi</td>
<td>3.6 mg/dl</td>
</tr>
<tr>
<td>AST</td>
<td>13 IU/l</td>
<td>T-CHO</td>
<td>160 mg/dl</td>
</tr>
<tr>
<td>ALT</td>
<td>9 IU/l</td>
<td>TG</td>
<td>39 mg/dl</td>
</tr>
<tr>
<td>LDH</td>
<td>173 IU/l</td>
<td>CRP</td>
<td>3.0 mg/dl</td>
</tr>
<tr>
<td>γ-GTP</td>
<td>12 IU/l</td>
<td>Plasma glucose</td>
<td>381 mg/dl</td>
</tr>
<tr>
<td>ALP</td>
<td>211 IU/l</td>
<td>HbA1c (NGSP)</td>
<td>6.3%</td>
</tr>
<tr>
<td>Ch-E</td>
<td>188 IU/l</td>
<td>GAD antibody</td>
<td>11 U/ml</td>
</tr>
<tr>
<td>Amy</td>
<td>43 IU/l</td>
<td>Serum CPR</td>
<td>0.3 μg/ml</td>
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**Table 2. Hypertonic saline solution challenge test**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>0</th>
<th>30</th>
<th>60</th>
<th>120</th>
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<tbody>
<tr>
<td>Na (mEq/l)</td>
<td>138</td>
<td>141</td>
<td>143</td>
<td>145</td>
</tr>
<tr>
<td>Plasma Osmolarity (mOsm/kg·H₂O)</td>
<td>288</td>
<td>294</td>
<td>298</td>
<td>302</td>
</tr>
<tr>
<td>ADH (pg/ml)</td>
<td>1.4</td>
<td>1.4</td>
<td>1.8</td>
<td>2.1</td>
</tr>
</tbody>
</table>

**Legend**

central diabetes insipidus during hemodialysis. In our case study, we could not perform preoperative magnetic resonance imaging (MRI) of the brain and therefore, we were not sure if she had diabetes insipidus before the kidney transplantation.

In an investigation of posterior pituitary signal intensity on T1-weighted images from dialysis cases, Sato et al. reported that hyperintense signals that were considered normal were present in only 36% of cases, and isointense signals in 40% and hypointense signals in 24%. As hyperintense signals on T1-weighted images of the posterior pituitary reflect ADH storage volume, these findings suggest that ADH secretion was somewhat impaired in a proportion of hemodialysis patients. Thus, we suggest the following mechanisms may have been present in our patient: (1) ADH storage volume (secretory ability) decreased during chronic hemodialysis and (2) ADH-mediated regulation of free water was impaired in response to changes in circulating plasma volume following kidney transplantation, which lead to exacerbation of diabetes insipidus. Recovery of ADH secretory ability following transplantation may have led to normalization of water balance. However, we cannot exclude the possibility that this patient had diabetes insipidus with partial adrenal insufficiency, which resulted in "masked" diabetes insipidus. After the transplantation, our patient took methylprednisolone as well as fludrocortisone that might have uncovered masked diabetes insipidus, and which thereafter ceased inflammation of the pituitary posterior lobe, such as lymphocytic infundibulo-neurohypophysis. Further studies involving a greater number of similar cases are required to evaluate fully the changes in ADH secretory ability before and after kidney transplantation.

The abdominal symptoms reported by our patients appear to be caused mainly by gastrointestinal motility disorder. Possible complicating and underlying diseases include (1) systemic diseases with multiple organ failure (amyloidosis and collagen disease, etc.), (2) organic intestinal disease, (3) irritable bowel syndrome and (4) dysautonomia. No preoperative dysautonomia evaluation was performed at our hospital. However, we suggest dysautonomia due to diabetes was involved in the gastrointestinal motility disorder according to the following observations: the patient had been diagnosed with type 1 diabetes for a considerable period (approximately 20 years), nerve conduction studies had revealed marked peripheral nerve disorders, vitreous surgery had been performed for retinopathy, and nephropathy had led to a requirement for hemodialysis.

Pancreases (islets of Langerhans) transplantation and pancreas-kidney transplantation, in which physiological blood glucose levels are recreated, have been trialed as methods of treating neurological disorders, and the utility of this approach has been demonstrated by favorable clinical outcomes. We observed temporary improvements in gastrointestinal symptoms before subsequent exacerbation resulting from decreased function of the transplanted pancreas, suggesting a relationship between blood glucose variation and gastrointestinal symptoms. However, other short-term postoperative changes, such as improvement in uremia and hemodynamic stabilization, may have contributed to changes in gastrointestinal symptoms. In our case study, orthostatic hypotension required treatment with fludrocortisone following the development of hemodynamic instability postoperatively, which subsequently improved in response to the therapy. Khurana et al. reported a relationship between pancreas transplantation and orthostatic hypotension, suggesting the involvement of vasoactive substances originating from the pancreas. At physiological concentrations, insulin dilates major blood vessels causing decreased blood pressure. Furthermore, the balance of vasodilator substances and vasoconstrictor substances has been reported to have possibly changed in response to pancreas transplantation in rats. Thus, the mechanisms that we have described may also have contributed to the pathophysiology observed in this case, in addition to dysautonomia.

Conclusions

The development of diabetes insipidus, as observed in our patient, is a rare complication of pancreas-kidney transplantation. However, physicians should consider the risk of diabetes insipidus during postoperative management of kidney or pancreas-kidney transplantation.

Acknowledgements

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Conflict of Interest

There is no conflict of interest.

References