**Introduction**

Wolfram syndrome (WFS) is a rare progressive neuroendocrine disease that shows autosomal recessive inheritance characterized by diabetes insipidus, diabetes mellitus (DM), optic nerve atrophy and deafness. WFS is a gene encoding a protein, wolframin, which is essential to the function of the endoplasmic reticulum, is identified as main causative gene of the disease. We report here a sibling case suspected WFS with insulin-dependent DM and optic atrophy in early childhood.

**Case 1: The proband**

**[Case] 7 year and 8 month old boy**

**[Chief complaint]** positive glucose urine test in elementary school

**[Family history]** nonconsanguineous parents, No DM and eye disease

**[Delivery/Past medical history]** He was born in spontaneous delivery at 39 weeks with a birth weight of 2.886 kg and a length of 48.0 cm.

**[Present illness]**

He was referred to our hospital for a positive glucose urine test in elementary school and hyperglycemia. He did not show thirst, polydipsia, and polyuria, but feel Capillary refilling: prompt, No obvious neurological findings

**[Laboratory findings]**

<table>
<thead>
<tr>
<th>Chemistry</th>
<th>Normal range</th>
<th>Value</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma glucose</td>
<td>11.8 mmol/l</td>
<td>7.449</td>
<td>increased</td>
</tr>
<tr>
<td>GA</td>
<td>108.5 mmol/l</td>
<td>10.7</td>
<td>increased</td>
</tr>
<tr>
<td>β-Hba (NGSP)</td>
<td>10.5 %</td>
<td>9.5</td>
<td>increased</td>
</tr>
<tr>
<td>Bil</td>
<td>&lt; 0.5 mg/dl</td>
<td>0.5</td>
<td>normal</td>
</tr>
<tr>
<td>SCR</td>
<td>0.8 mg/dl</td>
<td>1.4</td>
<td>increased</td>
</tr>
<tr>
<td>B–Ketone</td>
<td>0.2 mmol/l</td>
<td>0.5</td>
<td>increased</td>
</tr>
</tbody>
</table>

**Clinical findings**

Height 112.0 cm (-0.73SD), Weight 17.4kg (-2.8SD, no weight loss), BMI 13.9 BT 36.4℃, PR 90/min, BP 107/62 mmHg, RR 16/min, SpO2 100%. Level of consciousness: clear, Chest: no rales, no murmurs, Abd: soft and flat, Skin: dry

**[Clinical course]**

He was cared as type 1B DM because all islet-associated autoantibodies were all negative. He was treated with multiple daily injection of insulin. The glycomic control is good and Hba1c is gradually improved and maintains 6%. level.

He pointed out the decrease of visual acuity by medical examination at school one month before the diagnosis of DM, and was noted enlargement of optic disc cupping in ophthalmology. He showed a marked reduction in the retinal nerve fiber layer thickness at 7 months after DM onset, and notable visual disturbance at 9 months after DM onset. His visual acuity was 0.3 for both eyes.

**[Onset clinical signs in WFS]**

- Diabetes mellitus: DM
- Diabetes insipidus: DI
- Optic atrophy
- Hearing impairment
- Renal tract abnormalities
- Psychiatric symptoms

**[Diagnosis]** WFS1 gene encoding a protein, wolframin, which is essential to the function of the endoplasmic reticulum, is identified as main causative gene of the disease (Nat Genet. 1995; 1: 770-779). WFS1 mutation is identified in the Japanese patients in approximately 70%, and genetic heterogeneity exists. Second WFS2 gene, also known as CISO2, is identified in Jordanian families (Am J Hum Genet, 2007).

**[Estimation of prevalence]** 1: 770,000 in the UK (Lancet, 1995), 1: 710,000 in Japan (PLoS one, 2014) 

**[Treatment/Progression]** Only symptomatic treatment or supportive care. Decreased visual acuity, hearing loss, neurological symptoms reduce the quality of the patients. The main reason of death are respiratory disorder and aspiration due to brainstem atrophy, urinary tract complications. Average age at death is 35 years old and the vital prognosis are poor.

**[Conclusions]**

- In a typical case, DM due to insulin hyposecretion in 3-8 years old occurs first, and OA occurs subsequently. But there are varieties in the order symptoms appear. Both our brothers showed OA prior to DM onset.
- In some cases, DI was manifested before OA was manifested after the DM onset. In other cases, OA or DI occurred at first before the DM onset. Our cases also developed OA prior to DM.
- Moreover, there are some cases that neuropsychiatric symptoms relatively develop from an early stage, and that the brainstem atrophy is present before neuropsychiatric symptoms develop (PLoS one, 2014; 9(8): e102990).
- Japanese cases of 30% are not identified WFS1 mutation even if diagnosed as WFS clinically. Disease course and prognostic difference due to presence or absence of WFS1 abnormally are not found. The hereditarily clinical condition of the patients is unknown at this point in time. The exome analysis will be considered in the future.

**Gene analysis**

- In the analysis by PCR direct sequence method, gene mutation to produce amino acid alterations to both WFS1, WFS2 gene was not identified.
- The genetic polymorphism (SNP) was not identified, too.
- The known mitochondrial gene point mutation analysis of older brother show no abnormalities.

**Diabetes and insulin**

Dai Suzuki

**Post presented at:**

Poster presented at: P15-P3 Diabetes and insulin Dai Suzuki

**Acknowledgement**

I thank the members of Division of Endocrinology, Metabolism, Hematological Science and Therapeutics, Yamaguchi University for analyzing WFS1 and WFS2 mutation.

---

**Case 2: younger brother of Case 1**

**[Case] 6 year and 1 month old boy**

**[Chief complaint]** nocturnal enuresis

**[Delivery/Past medical history]** He was born at 38 weeks with a birth weight of 3.108 kg and a length of 49.3 cm.

**[Present illness]**

After 1 month episode of nocturnal enuresis, he showed hyperglycemia of almost 10-20 mmol/l measured by his mother using his brother’s blood glucose meter. He was also referred to our hospital on suspicion of DM (10 months after his brother’s diagnosis of DM).

**[Clinical findings]**

Height 108.5 cm (-0.44SD), Weight 18.4kg (-1.2SD, no weight loss), BMI 15.6 BT 36.5℃, PR 90/min, BP 102/71 mmHg, RR 16/min, SpO2 98%, Abd: flat and soft, Capillary refilling: prompt, No obvious neurological findings

**[Laboratory findings]**

<table>
<thead>
<tr>
<th>Chemistry</th>
<th>Normal range</th>
<th>Value</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma glucose</td>
<td>11.8 mmol/l</td>
<td>7.437</td>
<td>normal</td>
</tr>
<tr>
<td>GA</td>
<td>108.5 mmol/l</td>
<td>10.7</td>
<td>normal</td>
</tr>
<tr>
<td>β-Hba (NGSP)</td>
<td>10.5 %</td>
<td>9.5</td>
<td>normal</td>
</tr>
<tr>
<td>Bil</td>
<td>&lt; 0.5 mg/dl</td>
<td>0.5</td>
<td>normal</td>
</tr>
<tr>
<td>SCR</td>
<td>0.8 mg/dl</td>
<td>1.0</td>
<td>normal</td>
</tr>
<tr>
<td>B–Ketone</td>
<td>0.2 mmol/l</td>
<td>0.0</td>
<td>normal</td>
</tr>
</tbody>
</table>

**[Clinical course]**

Young boy was also diagnosed with DM and treated with multiple daily injection of insulin. The adjustments such as insulin sensitivity factor, insulin carbo ratio, the quantity of insulin degludec are good, Hba1c level improved to 6.5% at 5 months after DM onset.

Since hereditary eye disease was suspected from the findings of older brother, he received an ophthalmic examination one month prior to DM onset. He was also pointed out enlargement of optic disc cupping and mild thinning of the optic nerve fiber similarly.

**[Onset clinical signs in WFS]**

- Diabetes mellitus: DM
- Diabetes insipidus: DI
- Optic atrophy
- Hearing impairment
- Renal tract abnormalities
- Psychiatric symptoms

**[Diagnosis]**

We experienced a sibling case diagnosed as WFS clinically with juvenile-onset insulin-dependent DM and optic atrophy.

Identification of WFS patients among all DM patients presenting in childhood or adolescence is important because the management of patients with this syndrome is different from that of patients with classic T1DM.

At the moment, they do not show diabetes insipidus, deafness and other neurological or psychiatric symptoms. But since WFS is a poor prognosis disease that various clinical manifestations develop.

**[Acknowledgement]**

I thank the members of Division of Endocrinology, Metabolism, Hematological Science and Therapeutics, Yamaguchi University for analyzing WFS1 and WFS2 mutation.

---

**An additional clinical feature include the following:**

- Diabetes mellitus (classical form)
- Diabetes mellitus (insulin dependent, non-insulin dependent)
- Neurological disease (CNS, peripheral nervous system, gastrointestinal symptoms)
- Psychiatric disease (insomnia, affective disorder etc.)

---

**Wolfram syndrome diagnostic criteria**

[1] In the analysis by PCR direct sequence method, gene mutation to produce amino acid alterations to both WFS1, WFS2 gene was not identified.

[2] The genetic polymorphism (SNP) was not identified, too.