A sibling case of Wolfram syndrome with diabetes mellitus diagnosed within 10 months in early childhood

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Introduction

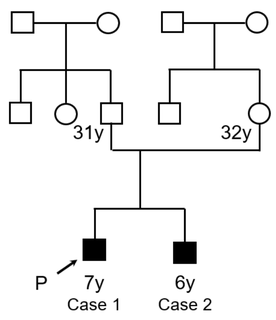
Wolfram syndrome (WFS) is a rare progressive neurodegenerative disease that shows autosomal recessive inheritance characterized by diabetes insipidus, diabetes mellitus (DM), optic nerve atrophy and deafness. WFS1 gene encoding a protein, wolframin, which is essential to the function of the endoplasmic reticulum, is identified as main causative gene of the disease. 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】 Non 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 g 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 fatigability.

【Clinical findings】

Height 112.0 cm (-0.73SD), Weight 17.4kg (-1.28SD, no weight loss), BMI 13.9
BT 36.4℃, PR 96/min, BP 107/62 mmHg, RR 16/min, SpO_2 100%
Level of consciousness: clear, Chest: no rales, no murmurs, Abd: soft and flat, Skin: dry
Capillary refilling: prompt, No obvious neurological findings

【Laboratory findings】

Chemistry			BGA (vein, room air)			Urinalysis	
Plasma glucose	11.8	mmol/l	pH	7.464		pH	5.5
GA	32.2	%	pCO_2	36.9	mmHg	Pro	(-)
HbA1c (NGSP)	10.7	%	HCO_3^-	26.1	mmol/l	Glu	(4+)
IRI	0.5	μIU/ml	BE	2.9	mmol/l	Ket	(-)
S-CPR	0.55	ng/ml	AG	7.4	mmol/l	O.B	(-)
β-Ketone	0.2	mmol/l	Lac	1.0	mmol/l	Bil	(-)

■ Glucagon stimulation test (Hospital day2)
peak C-peptide (CPR) level : 1.32 ng/mL（<3.0 ng/mL）

■ Islet-associated Autoantibodies to GAD/Insulin/IA-2/ZnT8 : all negative

【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 glycemic control is good and HbA1c is gradually improved and maintains 6% level.
- He was 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.

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 g 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 (-0.12SD, no weight loss), BMI 15.6
BT 36.5℃, PR 90/min, BP 102/71 mmHg, RR 16/min, SpO_2 100%
Level of consciousness: clear, Chest: no rales, no murmurs, Abd: soft and flat
Capillary refilling: prompt, No obvious neurological findings

【Laboratory findings】

Chemistry			BGA (vein, room air)			Urinalysis	
Plasma glucose	10.1	mmol/l	pH	7.437		S.G	1.021
GA	30.7	%	pCO_2	37.4	mmHg	pH	6.5
HbA1c (NGSP)	19.5	%	HCO_3^-	24.7	mmol/l	Pro	(-)
IRI	2.1	μIU/ml	BE	1.2	mmol/l	Glu	(3+)
S-CPR	0.89	ng/ml	AG	8.4	mmol/l	Ket	(-)
β-Ketone	0.2	mmol/l	Lac	15	mg/dl	O.B	(-)
						Bil	(-)

■ Glucagon stimulation test (2 wks after starting medication)
peak C-peptide (CPR) level : 2.73 ng/mL（<3.0 ng/mL）

■ Islet-associated Autoantibodies to GAD/Insulin/IA-2/ZnT8 : all negative

【Clinical course】

- Young brother 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 ophthalmologic examination one month before DM onset. He was also pointed out enlargement of optic disc cupping and mild thinning of the optic nerve fiber layer similarly.
- At the moment, brothers do not show other WFS related manifestations such as diabetes insipidus, hearing impairment, renal tract abnormalities, neuropsychiatric symptoms.

WFS was not suspected at first when Case 1 developed insulin-dependent DM. But only after 10 months, his younger brother also presented insulin-dependent DM without autoimmune response in addition to optic atrophy, so WFS was strongly suspected.

Both brothers were complicated with juvenile insulin-dependent DM and optic atrophy, and WFS was clinically diagnosed.

Wolfram syndrome diagnostic criteria

Mandatory feature
1. Juvenile-onset (age < 16 years) diabetes mellitus
2. Optic atrophy

Additional clinical feature include the following:
1. Sensorineural hearing impairment
2. Central diabetes insipidus
3. Renal tract abnormalities (Hydronephrosis, bladder dyssynergia etc.)
4. Neurologic dysfunction (brain stem/cerebellar ataxia, myoclonus etc.)
5. Psychiatric disease (depression, affective disorder etc.)

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.

Discussion

Wolfram syndrome (WFS)

【Concept】

WFS is a recessive neurologic and endocrinologic degenerative disorder defined by the association of early onset insulin dependent DM and progressive bilateral optic atrophy. WFS was first described by Wolfram and Wagener in 1938 as the association of childhood-onset diabetes and optic atrophy. Affected indivisuals may also have other clinical manifestations, particularly diabetes insipidus and sensory nerve deafness such that disease sometimes referred as **DIDMOAD** (diabetes insipidus:DI, diabetes mellitus:DM, optic atrophy:OA, and deafness:D) syndrome.

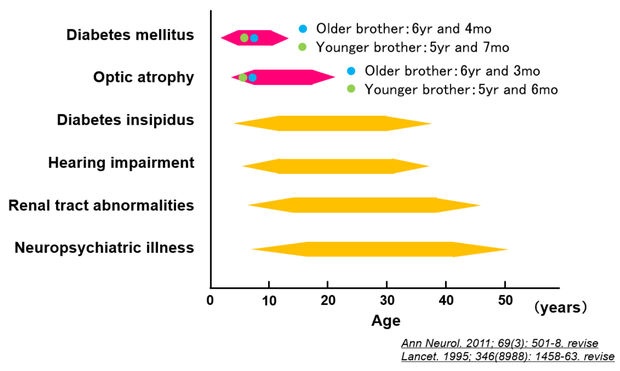
【Etiology】

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, 1998*). *WFS1* mutation is identified in the Japanese patients in approximately 70%, and genetic heterogeneity exists. Second WFS2 gene, also known as *CISD2,* 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/Prognosis】 Only symptomatic treatment or supportive care. Decreased visual acuity, hearing loss, neurologic 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.

Onset summary of clinical signs in WFS



Ann Neurol. 2011; 69(3): 501-8. revise
Lancet. 1995; 346(8988): 1458-63. revise

Prevalence of complications in Japanese 67 patients with WFS

Manifestation	Precvalence
Diabetes mellitus	67 (100%)
Optic atrophy	67 (100%)
Diabetes insipidus	37 (55%)
Hearing impairment	50 (75%)
Renal tract abnormalities	31 (46%)
Neuropsychiatric illness	46 (69%)
4 components of DIDMOAD	33 (49%)
All 6 components	22 (33%)

PLoS one. 2014; 9(9): e106906. revise

- 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 the DM onset.
- In some cases, DI was manifested before OA was manifested after the DM onset. In another 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 neurologic symptoms develop. *PLoS one. 2014; 9(9): e106906.*
- 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* abnormality are not found. The heredity clinical condition of the patients is unknown at this point in time. The exome analysis will be considered in the future.

Conclusions

- 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 characteristics pass progressively, careful observation and continuous inclusive follow-up of the patients are needed with associated department in future.

Acknowledgement

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