Non-immune diabetes mellitus and neurodegeneration: two distinct cases of Wolfram syndrome

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Background: **Wolfram syndrome features :**

D*iabetes *I*nsipidus, *D*iabetes *M*ellitus, *O*ptic nerve *A*trophy, *D*eafness *(DIDMOAD)

We present **2 cases** of Wolfram syndrome caused by **heterozygous mutations in the WFS1 gene**: an autosomal dominant and recessive type.

Case 1

17 year old girl

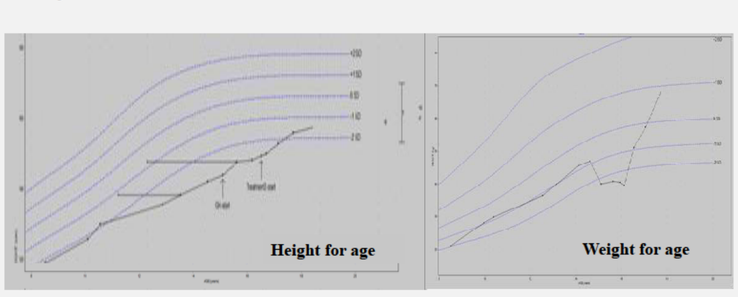
History of - **sensorineuronal hearing loss** (cochlear implants) since 2,5 years.
- **optic nerve atrophy** since age 11 years, age

Presentation with growth failure at age 13 years:
- height 138.3 cm (-3.1 SD) / weight 40 kg (-1 SD)
- Tanner stage M2P2A1
- bone age 11 years at chronological age 13 years

Endocrine work-up:
- low baseline IGF-1: 150 ng/ml (ref 212-665 ng/ml)
- glucagon test: max. growth hormone (GH) level 1.38 µg/ml
- insulin test: max. GH level 1.1 µg/ml
- CT scan: normal pituitary gland
- no other pituitary hormone deficiencies

→ diagnosis of **isolated idiopathic GH deficiency** → start rhGH treatment

Evolution: development of polyuria and polydipsia with significant weight loss and decreased height velocity after 18 months of GH treatment



Endocrine work-up: non ketotic hyperglycemia
- HbA1c: 15% (140 mmol/mol)
- C-peptide: 0.71 nmol/L (ref. 0.37-1.47 nmol/l)
- Anti-islet cell antibodies and anti-GAD65 antibodies: negative

→ diagnosis of **non-immune diabetes mellitus**

→ start multiple daily subcutaneous insulin injections

Genetic analysis:
1 pathogenic heterozygous mutation in the WFS1 gene: c.2051C>T(p.Ala684Val) in exon 8 → **autosomal dominant type of Wolfram syndrome**

Evaluation of Wolfram syndrome at age 17 years:
- no diabetes insipidus
- late start and slow evolution of puberty (thelarche at 12,5 years), normal near final height (157,5 cm -1,5 SD)
- insulin dependency remained after discontinuation of GH treatment
- no other neurological disorders
- no overt psychiatric illness, but severe diabetes coping difficulties

Case 2

13-year old boy

Presentation
- headache since 4 months
- diplopia

→ diagnosis of bilateral vision loss (50%) and **optic nerve atrophy**

Work-up: non ketotic hyperglycemia
- HbA1c: 10.2% (88 mmol/mol)
- C-peptide: 0.24 nmol/l (ref. 0.37-1.47 nmol/l)
- Anti-islet cell antibodies and anti-GAD65 antibodies: negative

→ diagnosis of **non-immune diabetes mellitus**

→ start continuous subcutaneous insulin injections

Genetic analysis:
2 heterozygous mutations in the WFS1 gene: c.631+2T>G(r.spl?) and c.1511C>G(p.(Pro504Arg)

→ **autosomal recessive type of Wolfram syndrome**

Work-up and evolution of Wolfram syndrome:
- no diabetes insipidus
- normal linear growth and evolution of puberty
- no other neurological disorders, normal hearing
- depression and suicidal thoughts after diagnosis resolved after 5 months. no other psychiatric illness, high intelligence.

Discussion

***WFS1* gene** (chromosome 4p) encodes **wolframin:**
- is a transmembrane protein of pancreatic β cells
  → loss of beta cells causes non-immune diabetes mellitus
- has a role in neural tissue survival
  → different degrees of brain atrophy → diverse neurologic and psychiatric illnesses
  → hypothalamic neurodegeneration → endocrine disease

Higly **variable clinical picture** of Wolfram syndrome

Main diagnostic criteria: combination of
- early-onset insulin-dependent non-immune diabetes mellitus
- optic nerve atrophy

However:
- case 1:
Diabetes mellitus only appeared after the occurrence of neurodegenerative disease (hearing loss and optic nerve atrophy) and pituitary dysfunction (growth hormone deficiency).
→ delayed diagnosis of Wolfram syndrome
- case 2:
Vision loss was the only presenting symptom with hyperglycemia as an incidental finding.

Conclusion

The diagnosis of Wolfram syndrome should be considered in patients without diabetes mellitus who have evidence of neurodegenerative disease.

Longitudinal follow-up is necessary for monitoring disease progression and hypothalamic-pituitary dysfunction.

No conflict of interest

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