Patient report

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Three cases of Wolfram syndrome with different clinical aspects

Abstract

Background: Wolfram syndrome is an autosomal recessive disorder caused by mutations in the WFS1 gene. Clinical heterogeneity has been reported both within and between families with WFS1 mutations.

Subjects: The first case was diagnosed with insulin-dependent diabetes mellitus with positive for pancreatic autoantibodies and had a ketoacidotic attack in the follow-up period. The second case presented initially with optic atrophy and was diagnosed with behavioral and psychiatric problems at an early age. The third case had early onset insulin-dependent diabetes with multiple anomalies and congenital hypothyroidism. Many of these features have not been reported previously in patients with Wolfram syndrome. In all three patients homozygous mutations in WFS1 were identified.

Conclusion: Wolfram syndrome is a disease where the characteristic features may present at different times. A diagnosis of Wolfram syndrome should therefore be considered even in the absence of the full spectrum of clinical features.

Keywords: clinic; mutation; Wolfram syndrome.

Introduction

Wolfram syndrome (WS), which is inherited in an autosomal recessive pattern, is a rare cause of monogenic diabetes mellitus. The most commonly reported features of the syndrome are diabetes insipidus (DI), diabetes mellitus (DM), optic atrophy (OA), and deafness. Consequently, the syndrome has also been termed the DIDMOAD syndrome (1). Other symptoms include urogenital pathologies (neurogenic bladder, hydronephrosis, hypogonadism), progressive neurodegenerative disease (ataxia, peripheral neuropathy, dementia) and psychiatric problems. The estimated prevalence of the disease is 1 in 500,000 children. In countries like ours, in which consanguineous marriage is common, the prevalence increases to approximately 1 in 68,000. The prevalence of WS in patients with insulin-dependent diabetes diagnosed in childhood is estimated to be 4.8% in countries with high rates of consanguinity (1, 2).

The WFS1 gene is located on chromosome 4p16.1 and encodes the transmembrane protein Wolframin. WFS1 consists of eight exons with the majority of previously reported mutations residing in the last exon.

While the disease results from mutations in a single gene, it can be clinically heterogeneous. Patients can present with a range of symptoms which may in turn result in a delay in the genetic diagnosis. In this paper, our aim is to raise awareness of the disease and to emphasize the clinical heterogeneity of this disorder by reporting three cases with a genetic diagnosis of WS.

Cases

Case 1

A female patient, born at term by vaginal delivery weighing 3500 g with an unremarkable neonatal period, presented to our clinic at the age of 3 years with the complaint of increased urination and water intake which had...
progressively worsened over the previous 4 weeks. Ten
days prior to presentation, the patient had recovered from
varicella infection and had a fever a day before hospital
admission. Her grandmother and paternal aunt had type
2 DM.

During physical examination, she was found to have
a slight tachycardia (heart rate: 120/min). She was well
hydrated, and on her skin there were sloughed varicella
lesions. Ophthalmological examination was found to
be normal. Laboratory examinations demonstrated that
serum glucose was 351 mg/dL, and urinary ketones were
positive; blood gas analysis showed pH was 7.43, HCO₃
was 18.7, pCO₂ was 28.5, and base deficit was detected as
positive; blood gas analysis showed pH was 7.43, HCO₃
was 18.7, pCO₂ was 28.5, and base deficit was detected as
−5.5. Fasting and postprandial c-peptide levels were low at
0.16 (0.78–5.19) ng/mL and 1.5 ng/mL, respectively. Other
biochemical tests were normal. She was diagnosed with
diabetic ketosis, and appropriate treatment was started.
Pancreatic autoantibodies including antiglutamic acid
decarboxylase antibody (anti-GAD), anti-insulin antibody
(AIA), and anti-islet cell antibody (ICA) were all nega-
tive. Thyroid and celiac auto-antibodies were also tested
and found to be negative. In the euglycemic period, urine
density was determined as 1033 g/cm³ with a refractom-
eter; there was no DI.

Pubertal signs first developed when she was 9 years
of age. During the same period, mild polyneuropathy was
detected following a routine electromyography for evalua-
tion of diabetic complications. There were no clinical
neurological symptoms. Polyneuropathy did not improve
during patient follow-up. When she was 9.7 years old, a
mild arthropathy was detected on examination.

While her blood glucose levels were more regulated for the
first years of her treatment, this regulation had worsened
with time. When her average glycated hemoglobin (HbA1c)
reached >9% at 10.8 years of age, the insulin regimen was
changed to an intensive basal-bolus regimen from neutral
protamine Hagedorn (NPH-regular) insulin treatment. Dia-
betes autoantibodies were reevaluated and were found to
be positive, (anti-GAD 2.9 U/L (N: <1) AIA 52.4% (N: 4–10)).
Thyroid and celiac auto-antibodies were reevaluated but
were negative. Ophthalmological examination was normal.

Due to an incompatibility of treatment, the patient’s
HbA1c level was raised from 7.8% to 10%, and she was
hospitalized for diabetic ketoacidosis (DKA) during the
follow-up period.

At the age of 15.5 years the patient started to complain
of low vision, and the possibility of bilateral OA was inves-
tigated. Brain and hypophysis were examined by magnetic
resonance, and it was found that her bilateral optic nerves
were thin and there was a 3-mm-diameter lesion, micro-
adenoma at the hypophysis. Thyroid function tests, serum
prolactin, cortisol, and adrenocorticotropic hormone
( ACTH) levels were normal. Bilateral mild to moderate
sensorial hearing loss was detected by audiometry. Bilat-
eral mild distension was found in caliceal structures in
renal ultrasound (US). During the same time, the patient
complained of frequent urination at which stage the urine
density was found to be 1002 g/cm³, urinate osmolarity
was 97 mosm/kg, serum osmolarity was 297 mosm/kg,
and urine-serum osmolarity was 0.32 (<0.7). On the basis
of these results, central DI was diagnosed, and the patient
was started on intranasal desamino arginin vasopressin
dAVP treatment with good response. When the audi-
ometry and renal US were repeated at the age of 16.5 years,
they were found to be normal. The patient was also diag-
nosed with minor depression after a psychiatric examina-
tion at the age of 17 years for which antidepressant therapy
was prescribed. The patient is currently 17.25 years of age
and is treated with basal-bolus insulin, dDAVP 5 μg/day,
and antidepressant medication.

Genetic analysis identified a homozygous mutation
(p.462_464del) c.1385_1393del in WFS1.

Case 2

A female aged 9.56 years presented to the pediatric endo-
crine department after her blood glucose level was found
high (337 mg/dL) following an examination for flank pain
and nocturnal enuresis which had started over the previ-
ous week. The patient had been diagnosed with asthma
at the age of 3 years. Bilateral OA was detected at the age
of 7 years. At 9 years of age following recurrent urinary
system infections and urination dysfunction, she was
referred to the pediatric nephrology clinic. Renal US was
undertaken, but no abnormalities were detected. Physical
examination was normal except for bilateral costoverte-
bral angle sensitivity and amblyopia. Laboratory exami-
nations showed serum glucose was 337 mg/dL, blood
ketones were at 0.1 mmol/L, and blood gas readings were
as follows: pH was 7.35, HCO₃ was 25 mmol/L, and pCO₂
was 45.3 mm Hg. Serum electrolytes were normal. HbA1c
was 8.4%, fasting c-peptide was 1.43 ng/mL (N: 0.78–5.19),
and postprandial c-peptide was 0.84 ng/mL (low). Urinary
density was 1023 g/cm³. She was diagnosed with insulin-
dependent diabetes, and a basal-bolus insulin regimen
was initiated. In further examinations, pancreatic (anti-
GAD, AIA, ICA), thyroid, and celiac antibodies were found
to be negative. There was significant vision loss associ-
ated with bilateral OA, but audiometry was normal. Due
to a crying fit, the patient was examined by the pediatric
psychiatry department and was subsequently diagnosed
with minor depression and obsessive compulsive disorder (OCD). The patient underwent an electroencephalography following complaints of chronic headaches; however, no abnormalities were detected. At 11 years of age the patient was examined by the urology department for the complaint of urinary incontinence. Urinary drainage with clean intermittent catheterization was undertaken, and a diagnosis of neurogenic bladder was made. The patient is currently 11.5 years of age and has an average HbA1c of 6.5% while on an intensive insulin regimen. Genetic analysis identified a novel homozygous mutation p.R177C (c.529C>T) in the patient’s WFS1 gene. Both unaffected parents were heterozygous for the mutation, and in silico analysis using SIFT (http://sift.jcvi.org/) and Mutation Taster predicted the mutation to be disease causing.

Case 3

A male aged 1 month was referred to our clinic following the detection of elevated thyroid-stimulating hormone (TSH) on a congenital hypothyroidism screen. He was born weighing 2960 g at 37 weeks’ gestation following a pregnancy established by in vitro fertilization. At the age of 3 days he had undergone surgery for duodenal atresia. His mother and father were first-degree relatives. His maternal grandfather had type 2 DM, and his two cousins have DM and DI. Following physical examination, hydrocephalus, oxycephaly, and a wide back fontanel were noted. Laboratory examinations during admission demonstrated that free T4 was 12 pmol/L (N: 10–22), TSH was 140.8 µIU/mL (N: 0.3–4.5), thyroglobulin was 617.3 ng/mL (N: 1.4–78), urinary iodine was 246 µg/L (N: 100–200), and thyroid receptor antibodies were negative. An iodine uptake was observed outside of the thyroid region in the upper cervical area (sublingual thyroglossal canal) in the thyroid scintigraphy. This was interpreted as ectopic thyroid tissue. On US a hypoplastic thyroid gland was observed. Nuclear medicine indicated that because there was no iodine uptake in the thyroid region, the gland did not function. The patient was initiated on 10 µg/kg/day levothyroxine (LT4) treatment. A ventriculoperitoneal shunt for the congenital hydrocephalus was placed when he was 2 months of age. Visual evoked potential and brainstem auditory evoked response tests were normal. Cardiologic examination and echocardiography were normal. He was operated on for right inguinal hernia at the age of 3.5 months and for left inguinal hernia at the age of 21 months. Free T4, TSH and thyroglobulin levels were measured by electrochemiluminescence immunoassay using Roche® (Switzerland) Elecsys reagent. Urinary iodine was measured by “calorimetric ceric ion arsenous acid wet ash method based on Sandell Kolthoff reaction. Serum thyroid receptor antibodies were measured by “radioceptor assay” by using Zen Tech® (Belgium) reagent.

At the age of 21 months, the patient was examined for complaints of cough, anorexia, and frequent urination and fluid intake. Laboratory findings showed blood glucose to be 447 mg/dL. Blood gas analysis demonstrated the following: pH was 7.31, HCO₃ was 14.7 mmol/L, pCO₂ was 24.3 mm Hg, and base deficit was –14. Urinary ketones were positive. HbA1c and c-peptide were 9.4% and 0.09 ng/mL (N: 0.78–5.19), respectively. Hemogram and serum biochemistry were within the normal limits. The patient was diagnosed with DM, and insulin treatment (short-acting and basal insulin) was started. Anti-GAD and ICA antibodies were negative.

On neurological examination, motor retardation was detected. Cranial and hypophysis magnetic resonance scanning demonstrated asymmetric and oxycephalic calvarium, dysgenetic corpus callosum, cortical defect in anterior (similar to schizencephaly), and bilateral parietal chronic subdural collection. Additionally, the lateral and third ventricles were in the form of one common ventricle; the hypophysis was normal. Septooptic dysplasia and hypophyseal insufficiency were suspected due to a lack of the interventricular septum. While serum insulin like growth factor (IGF1) at 19.1 ng/mL (–3 SD) and insulin like growth factor binding protein (IGF BP3) at 715 ng/mL (<–3 SD) levels were very low, serum ACTH, cortisol, and prolactin levels were normal. The growth rate was sufficient in the follow-up period, and no optic OA, hearing deficits, or renal involvement was identified following intensive investigations. Urinary densities were normal (1013 g/cm³) during normoglycemia. While on insulin treatment, the average HbA1c was 8.42%. Chronic serious otitis media and adenoid vegetation problems were seen. The patient is currently 4 years of age and receives insulin and LT4 treatments.

Due to the association of early-onset DM, congenital hypothyroidism (hypoplasia and ectopia), and intestinal atresia, it was considered that the patient might have a mutation in the GLIS3 gene which encodes a pancreatic transcription factor (3). However, owing to the fact that his two cousins have DM+DI sequence, analysis of the WFS1 gene was undertaken, and a homozygous p.V412fs (c.1230_1233del) mutation was identified. Mutation testing confirmed that both parents were heterozygous for the mutation and the two cousins were also homozygous.

Clinical features, treatment, and genetic analysis results of our cases are given in Table 1. Informed consent was given by all patients and/or family.
Table 1  Clinical features, treatment, and genetic analysis results of our cases.

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>17.25 years</td>
<td>10.9 years</td>
<td>4 years</td>
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<tr>
<td>Age at admission</td>
<td>3 years</td>
<td>9.5 years</td>
<td>1 month</td>
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<td>Sex</td>
<td>Female</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Consanguineous marriage</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Family history</td>
<td>Paternal aunt has type 2 DM</td>
<td>–</td>
<td>Maternal grandfather has type 2 DM, two cousins have DM+DI</td>
</tr>
<tr>
<td>Age at diagnosis of DM</td>
<td>3 years</td>
<td>9.5 years</td>
<td>1.75 years</td>
</tr>
<tr>
<td>Diabetes autoantibodies</td>
<td>Anti-GAD, AIA, ICA (–) at admission. Anti-GAD, AIA (+) at 11 years old</td>
<td>Anti-GAD, AIA, ICA (–)</td>
<td>Anti-GAD, ICA (–)</td>
</tr>
<tr>
<td>Age at diagnosis of DI</td>
<td>15.5 years</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Age at diagnosis of OA</td>
<td>15.5 years</td>
<td>7 years</td>
<td>–</td>
</tr>
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<td>Audiometry</td>
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<td>Normal</td>
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<td>Urinary tract problems</td>
<td>–</td>
<td>Voiding dysfunction, enuresis, recurrent urinary tract infection, and neurogenic bladder</td>
<td>–</td>
</tr>
<tr>
<td>Neuropsychiatric symptoms/age of detection</td>
<td>Depression/17 years</td>
<td>Minor depression, obsessive-compulsive disorder/9.5 years</td>
<td>Motor/mental retardation, congenital hydrocephalus, oxycephalia, dysgenesis of the corpus callosum, single ventricle, and cortical defect/1.75 years</td>
</tr>
<tr>
<td>Other findings</td>
<td>Nonsecretory pituitary microadenoma</td>
<td>Asthma</td>
<td>Duodenal atresia, ectopic and hypoplastic thyroid, bilateral inguinal hernia</td>
</tr>
<tr>
<td>Treatment</td>
<td>Insulin</td>
<td>Insulin</td>
<td>Insulin</td>
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<td></td>
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<td>Clean intermittent catheterization</td>
<td>Levothyroxine</td>
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<tr>
<td>Genetic mutation in WFS1 gene</td>
<td>p.462_464delEVT (c.1385–1393 del 9bp) homozygous mutation</td>
<td>p.R177C (c.529C&gt;T) homozygous novel mutation</td>
<td>p.V412fs (c.1230_1233del) homozygous mutation</td>
</tr>
<tr>
<td>Domain</td>
<td>Transmembrane region</td>
<td>N terminal domain</td>
<td>Transmembrane region</td>
</tr>
</tbody>
</table>

Discussion

WS is a rare cause of recessively inherited monogenic DM (4). According to two different studies the classic presentation of the syndrome is DM followed by OA, central DI, and sensorineural deafness. These four findings are reported together in between 13% and 54% of cases (5).

It has been observed that urinary system dysfunction/anomalies and neuropsychiatric problems are frequent in this syndrome. Gastrointestinal dysmotility (constipation and chronic diarrhea), peptic ulcer, hypogonadism, hypopituitarism, and heart malformations have also been reported (1, 4–6). The age of onset and frequency of symptoms reported in the literature are provided in Table 2 (5–7).

DM which is insulin dependent but not immune mediated is often the first finding in WS. It is seen at an average age of 6 years; however, patients with diabetes diagnosed as early as 3 weeks and as late as 16 years have been reported (1, 5–7). For these patients, insulinopenia secondary to degeneration of the beta cells is a causative factor in DM. Some studies have also suggested that patients probably have a defect in insulin secretion in addition to β-cell loss (1, 7). When compared to type 1 DM, DKA is rare with daily insulin requirements and HbA1c levels lower for WS patients (1). In a study by Barrett et al., just 3/45 cases with WS had presented with DKA (5). In addition, the majority of cases are islet autoantibody negative suggesting that this is not immune-mediated diabetes. Nakamura et al. reported a 47-year-old case with WS and positivity for anti-GAD and insulinoma-associated antigen 2 antibodies (8). Case 1 was diagnosed with insulin-dependent DM when she was 3 years of age at which stage autoantibodies were negative. However, when she was 11 years old, anti-GAD and AIA were...
positive. Although this patient was on a full-replacement dose of insulin (>1 U/kg/day), her HbA1c levels were high (10%), and DKA was observed. Contrary to previous reports, DM did not show a moderate course in this patient. Case 3 was admitted with DKA but showed a moderate course of diabetes when on treatment. Co-occurrence of WS and type 1 diabetes in this patient is another possibility.

OA has been observed in the majority of cases reported to date and is generally the second emerging feature. It has been shown that the age at diagnosis of OA is very variable ranging from 6 weeks to 30 years with the median age at diagnosis of 11–12 years (1, 4–7). In our first case similar to the literature, OA developed in the second decade; however, in our second case, OA was the first feature to present at the age of 7 years, which results in a near full loss of vision 4 years later. In the third patient, OA was not detected, but this could be due to the young age of our patient (4 years). Close observation will be required for this patient.

D1 is one of the late findings; generally it occurs in the second decade of life. The median age of diagnosis is between 9 and 14 years but ranges from the third month of life to 41 years (1, 5–7). In our first case similar to the literature, D1 was detected at the age of 11 years for the patient received clean intermittent catheterization treatment. In our other cases, D1 has not been detected; however, they are being observed in this respect.

Hearing loss is one of the most frequent characteristics of the syndrome and is in the form of slow progressive high-frequency sensorineural hearing loss. It is diagnosed generally in the second or third decades of life (1). During audiometric evaluation, partial hearing loss was determined in case 1. However, her control test was normal. In the other two cases, hearing loss has not been detected, and they are being followed up in this respect.

Urinary system anomalies (neurogenic bladder, hydronephrosis, repetitive urinary system infections) are frequently seen features of the syndrome, and it has been suggested that they are added to the DIDMOAD acronym as urinary dysfunction or urinary tract atony (1, 6). When the disease is not diagnosed early and the urinary system is not evaluated, acute or chronic renal insufficiency can develop (1). The long-term prognosis of a patient with WS is determined by complications of DM and renal failure as a consequence of urinary system anomalies associated with repeated urinary infections (6). In our second case, the patient was referred to the Pediatric Nephrology team at the age of 9 years following urinary dysfunction, enuresis diurna, and repetitive urinary tract infection. Neurogenic bladder was determined at the age of 11 years for which the patient received clean intermittent catheterization treatment. Urinary anomalies have not been detected in the other two cases.

Although the most frequently seen neurological sign of WS is truncal ataxia, other signs such as areflexia, myoclonus, epilepsy, nystagmus, loss of gag reflex, loss of sense of taste/smell, brain-brain stem atrophy, and central apnea can occur. Neurological deficit and urinary system complications are the most frequent causes of morbidity and mortality in this disease (1). In review by Barrett et al., the median age at death is 30 years (between 25 and 49 years), with the most frequent cause being central respiratory insufficiency based on brain stem atrophy (5). In our third case, motor and mental retardation, congenital hydrocephalus, cortical defect (similar to schizencephaly), corpus callosum dysgenesis, and one ventricle were identified. The patient also had thyroid hypoplasia and ectopia, duodenal atresia, and bilateral inguinal hernia. None of these features have been reported previously in patients with WS. The only feature in keeping with WS was early onset insulin-dependent DM. A diagnosis of WS was confirmed in this patient following the identification of a homozygous WFS1 frameshift mutation. It is possible that these are novel features of the disease or that they reflect a second undetermined syndrome caused by a concomitant genetic disorder.

Psychiatric problems are also a part of the syndrome and have been reported with different frequencies. Swift et al. identified psychiatric or behavioral disorders in 41 of 68 cases (60%). In 17 cases, the symptoms were serious with 11 patients having attempted suicide (9). Barrett et al.
defined depressive symptoms in 3 of 45 cases, of which 1 had committed suicide (5). In our first case, depression was diagnosed at the age of 17 years. The second case was diagnosed with minor depression and OCD which has not been reported previously.

It is known that there is no clear genotype/phenotype correlation of WS patients. It is very hard to say anything about potential impacts of detected mutations on clinical heterogeneity in this report. To clarify the genotype/phenotype correlation or the effect of detected mutation on clinical heterogeneity, we should compare clinical manifestations of the subjects showing the same mutations. One of the cases had novel mutation, and the clinical findings of the other two mutations were not reported clearly.

**Conclusion**

Our first case was diagnosed with insulin-dependent DM and unlike the majority of previously reported cases was positive for pancreatic autoantibodies. She also had a ketoacidosis attack in the follow-up period, and her HbA1c levels were higher than expected considering her insulin dose.

In our second case, OA was detected at an early age and was the presenting feature. Behavioral problems, depression, and OCD were also diagnosed early.

In our third case, although the only clinical finding of WS was early onset insulin-dependent DM, a family history of consanguinity and DM and DI in two cousins prompted genetic testing. The patient had multiple features which have not been reported in patients with WS.

We have shown that WS is a clinically heterogeneous disease, and as the clinical features can present at different times, all the classic signs may not be seen at referral. We therefore recommend that genetic testing be undertaken on any patient born to consanguineous parents where WS is suspected as an early diagnosis will provide important information on the additional features likely to develop, and precautions can then be taken before complications occur.

**References**

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