

Title page

Wolfram syndrome: report of three siblings with early vision loss and documented lesion of the entire visual pathway

Brunella Maria Pavan Taffner¹

Patricia Grativol Costa Saraiva²

Fábio Petersen Saraiva³

1 – Second Year Resident of Ophthalmology - Federal University of Espírito Santo.

Specialized Medicine Department - Federal University of Espírito Santo.

Address: Departamento de Medicina Especializada/CCS/UFES. Av. Marechal Campos, 1468, Maruípe, Vitória-ES, Brazil.

Email: brunellapavan@hotmail.com

2 – Ph.D, Professor of Empresa Brasileira de Ensino, Pesquisa e Extensão AS – Multivix

Address: Rua José Alves, 301, Goiabeiras, Vitória-ES, Brazil. 29075-080

Email: patriciagrativol@yahoo.com.br

3 – Ph.D, Professor of Specialized Medicine Department - Federal University of Espírito Santo.

Address: Departamento de Medicina Especializada/CCS/UFES. Av. Marechal Campos, 1468, Maruípe, Vitória-ES, Brazil.

Email: fabiopetersen@yahoo.com.br

Mailing Address:

Departamento de Medicina Especializada/CCS/UFES.

Av. Marechal Campos, 1468, Maruípe, Vitória-ES, Brazil

Abstract

Objective: Report and document in images the presence of WFS1 in three of four siblings, with loss of visual acuity as the initial clinical presentation. **Design:** Case series study. **Participants:** Three of four siblings with WFS born to consanguineous parents. **Methods:** All patients had diagnostic imaging with contrast-enhanced brain magnetic resonance imaging (MRI) and digital retinography. **Results:** The patients and their father reported vision loss since before the age of seven, backed up by reports of multiple unsuccessful prescriptions for glasses and poor first-grade school performance due to visual deficit. Diabetes mellitus was diagnosed at seven years of age. All patients presented bilateral neurosensory deafness, atrophy of the posterior pituitary lobe, cerebellum, nerve, chiasma, optic tract and optic disc (bilateral), as well as urological changes and gait and balance disorders. One patient is epileptic and another suffers from a combination of anxiety and depression. **Conclusion:** Three unique cases of WFS due to early loss of visual acuity, lesion of the entire visual pathway documented in images, and an unusually high level of familial penetrance.

Main Text

Aims

Wolfram syndrome (WFS) is a rare, progressive, neurodegenerative autosomal recessive disorder with incomplete penetrance characterized by the association of non-autoimmune insulin-dependent juvenile diabetes mellitus and optic atrophy.¹⁻³ The prevalence of WFS has been estimated at 1/100,000 pop in the US [1] and 1/770,000 pop in the UK²

WFS was first described by Dr. D. J. Wolfram in a report of four siblings from 1938.³ Later reports added diabetes insipidus (observed in 73%) and deafness (observed in 62%) to the syndrome^{2,4}, leading to the adoption of the acronym DIDMOAD (Dibetes Insipidus, Dibetes Mellitus, Optic Atrophy, Deafness).² Approximately 50% express the complete phenotype.⁵ Insulin deficiency, the classic initial manifestation of WFS, tends to occur at about seven years of age, followed by optic atrophy at eleven.² In the second decade of life, many patients develop central diabetes insipidus and neurosensory deafness.⁶ Manifestations may also include atonal bladder, ataxia, myoclonia, peripheral neuropathy, hypogonadism, depression and WFS-related psychotic behavior.^{6,7} Death occurs between 25 and 49 years of age (median: 30), usually due to central respiratory failure.⁸

Wolfram syndrome is usually caused by mutations in the WFS1 gene. The recent discovery WFS2, a phenotypical and genotypical variant of the syndrome, requires diabetes mellitus and optic atrophy as minimum criteria for diagnosis. WFS2 is caused by a dysfunction of the CISD2 gene. The clinical phenotype of WFS2 differs from that of WFS1 by the absence of diabetes insipidus and psychiatric disorders and by the presence of bleeding from upper intestinal ulcers and platelet aggregation defects.⁹

To our knowledge, this is the first report of WFS with anterior visual pathway dysfunction manifesting well before the onset of diabetes symptoms. The familial penetrance is also unusually high. The purpose of the study was to report and document in images the presence of WFS1 in three of four siblings, with loss of visual acuity as the initial clinical presentation.

Presentation of Case

Our three patients (A=42 years, male; B=40 years, male; C=32 years, female) were born to consanguineous parents (third cousins) from Southeastern Brazil. The family history included a grandfather with type II diabetes mellitus, but no reports of genetic disorders.

The first consultations were conducted at another service. The father and the three patients reported vision loss since before the age of seven. These statements were backed up by reports of multiple unsuccessful prescriptions for glasses and poor first-grade school performance due to visual deficit. At the time, visual acuity was <20/400 in both eyes. Patient A has proliferative diabetic retinopathy and Patient B has nonproliferative diabetic retinopathy, both of which diagnosed in their twenties.

Type I diabetes mellitus was diagnosed at seven years of age after which the patients were started on insulin. Bilateral sensorineural deafness with a downward curve in the audiometry forums was evidenced in the second decade of life in all three brothers.

All patients presented bilateral atrophy of the posterior pituitary lobe, cerebellum, nerve, chiasma, optic tract and optic disc documented by cranial magnetic resonance and retinography (Figures 1, 2, 3 and 4) in addition to urological changes (A=hyperactive bladder; B&C=pyelocalyceal dilation) and gait and balance disorders. Patient A has been epileptic since age 22, with EEG-confirmed complex partial and absence seizures and upward ocular deviation lasting 10-30 seconds. Patient B suffers from a combination of anxiety and depression diagnosed at age 38.

Table 1 provides additional information on the patients' WFS 1 phenotype. However, our hospital laboratory is not presently equipped to carry out the genetic tests required to sequence the WFS1 from this family.

Discussion

The gene for WFS was identified on the short arm of chromosome 4 (4p16) by linkage analysis.⁵ The primary genetic defect was attributed to the WFS1 gene, which accounts for symptoms in 90% of cases.¹⁰ The gene encodes a transmembrane protein (wolframin) in the endoplasmic reticulum found in neurons, pancreatic β -cells and other tissues, such as the heart, placenta, inner ear, lung and liver. The function of wolframin is not known, but wolframin deficiency is believed to increase the tension inside the endoplasmic reticulum, with negative impacts on the cell cycle and calcium homeostasis.^{4,11}

In 2000, a second locus, WFS2, was mapped in chromosome 4q22-q24 after linkage analysis of four consanguineous Jordanian families. The ZCD2-encoded protein ERIS (endoplasmic reticulum intermembrane small protein) is also located in the endoplasmic reticulum but does not interact directly with wolframin.¹²

The incidence of WFS is reported to be higher in children of consanguineous parents.¹ In the three cases reported here, the time of diagnosis of diabetes mellitus was compatible with the literature, but WFS-related reduced visual acuity in early childhood, prior to the onset of diabetes symptoms, to the extent of interfering

with the acquisition of literacy, has to our knowledge not been described before. Likewise, The high familial penetrance of WFS (three out of four siblings), with more severe ophthalmological and neurological symptoms in the male siblings, is very unusual.

Neurological symptoms tend to occur later in the evolution of WFS.² However, Patient A started having epileptic seizures in the first decade of life, and Patient B presented a combination of anxiety and depression as early as the second decade.

The MRI changes observed in our patients match descriptions of WFS patients with atrophy of the brainstem, visual pathways, hypothalamus and posterior pituitary gland.¹³⁻¹⁵

Conclusion

The occurrence of WFS in 3 of 4 brothers born to consanguineous parents represents an unusually high level of familial penetrance. WFS is a rare syndrome, with few well described and image-documented cases in the literature. In addition, visual complaints preceding the manifestation of diabetes mellitus had not been described before.

Acknowledgments/disclosure

The authors have no competing interests to disclose.

All authors contributed substantially to the development of the study.

The authors declare that they have no additional contributions.

The authors received no financial support.

References

- 1 - Fraser FC, Gunn T. **Diabetes mellitus, diabetes insipidus, and optic atrophy. An autosomal recessive syndrome?** *J Med Genet* 1977;14(3):190–3
- 2 - Barrett TG, Bunday SE, Macleod AF. **Neurodegeneration and diabetes: UK nationwide study of Wolfram (DIDMOAD) syndrome.** *Lancet* 1995;346(8988):1458-63.
- 3 - Wolfram DJ. **Diabetes mellitus and simple optic atrophy among siblings: report of four cases.** *Mayo Clin Proc* 1938;13:715-18.
- 4 - Shannon P, Becker L, Deck J. **Evidence of widespread axonal pathology in Wolfram syndrome.** *Acta Neuropathol* 1999;98(3):304–8.
- 5 - Polymeropoulos MH, Swift RG, Swift M. **Linkage of the gene for Wolfram syndrome to markers on the short arm of chromosome 4.** *Nat Genet* 1994;8(1):95-7.
- 6 - Scolding NJ, Kellar-Wood HF, Shaw C, Shneerson JM, Antoun N. **Wolfram syndrome: hereditary diabetes mellitus with brainstem and optic atrophy.** *Ann Neurol* 1996;39(3):352-60.
- 7 - Swift RG, Sadler DB, Swift M. **Psychiatric findings in Wolfram syndrome homozygotes.** *Lancet* 1990;336(8716):667-9.
- 8 - Domenech E, Gomez-Zaera M, Nunes V. **Wolfram/DIDMOAD syndrome, a heterogenic and molecularly complex neurodegenerative disease.** *Pediatr Endocrinol Rev* 2006;3(3):249–257.
- 9 - Ajlouni K, Jarrah N, El-Khateeb M, El-Zaheri M, El Shanti H, Lidral A. **A Wolfram syndrome: identification of a phenotypic and genotypic variant from Jordan.** *Am J Med Genet* 2002;115(1):61–65.
- 10 - Inoue H, Tanizawa Y, Wasson J, et al. **A gene encoding a transmembrane protein is mutated in patients with diabetes mellitus and optic atrophy (Wolfram syndrome).** *Nat Genet* 1998;20(2):143-8.
- 11 - Zatyka M, RickMinton J, Fenton S, et al. **Sodium–potassium ATPase 1 subunit is a molecular partner of Wolframin, an endoplasmic reticulum protein involved in ER stress.** *Hum Mol Genet* 2008;17(2):190–200.
- 12 - El-Shanti H, Lidral AC, Jarrah N, Druhan L, Ajlouni K. **Homozygosity mapping identifies an additional locus for Wolfram syndrome on chromosome 4q.** *Am J Hum Genet* 2000;66(4):1229–1236.
- 13 - Ganie MA, et al. **Presentation and clinical course of Wolfram (DIDMOAD) syndrome from North India.** *Diabet Med* 2011;28(11):1337–42.
- 14 - Hershey T, et al. **Early Brain Vulnerability in Wolfram Syndrome.** *PLoS One* 2012;7(7):e40604.

15 - Galluzzi P, Filosomi G, Vallone IM, Bardelli AM, Venturi C. **MRI of Wolfram syndrome (DIDMOAD).**
Neuroradiology 1999;41(10):729–731.

Keywords

Wolfram Syndrom; Optic Atrophy; Rare diseases

Figure and table legends

Figure 1: Cranial magnetic resonance imaging scan of patient A. T2-weighted saggital sequence showing accentuated atrophy of the optic nerve on the right (white arrow) and left (red arrow) side.

Figure 2: Cranial magnetic resonance imaging scan of patient B. T1-weighted saggital sequence with absence of the hypersignal of the posterior pituitary lobe habitually observed in patients with diabetes insipidus (white arrow). Note hyperechoic area posterior to the pituitary gland representing the dorsum sellae, with hyperechoic fatty bone marrow in T1. Note mild atrophy of pontina anterior portion characterized by reduction of the protuberance (red arrow). Note atrophy of vermis and cerebellar hemispheres (green arrow).

Figure 3: Cranial magnetic resonance imaging scan of patient C. Axial FLAIR sequence showing an attenuated hypersignal in the white matter adjacent to the trigone of the lateral ventricles, and optic tracts (red arrows).

Figure 4: Digital angiography of patient C. Optic atrophy in the right eye.

Table 1: Clinical findings of patients A, B and C.



Figure 1

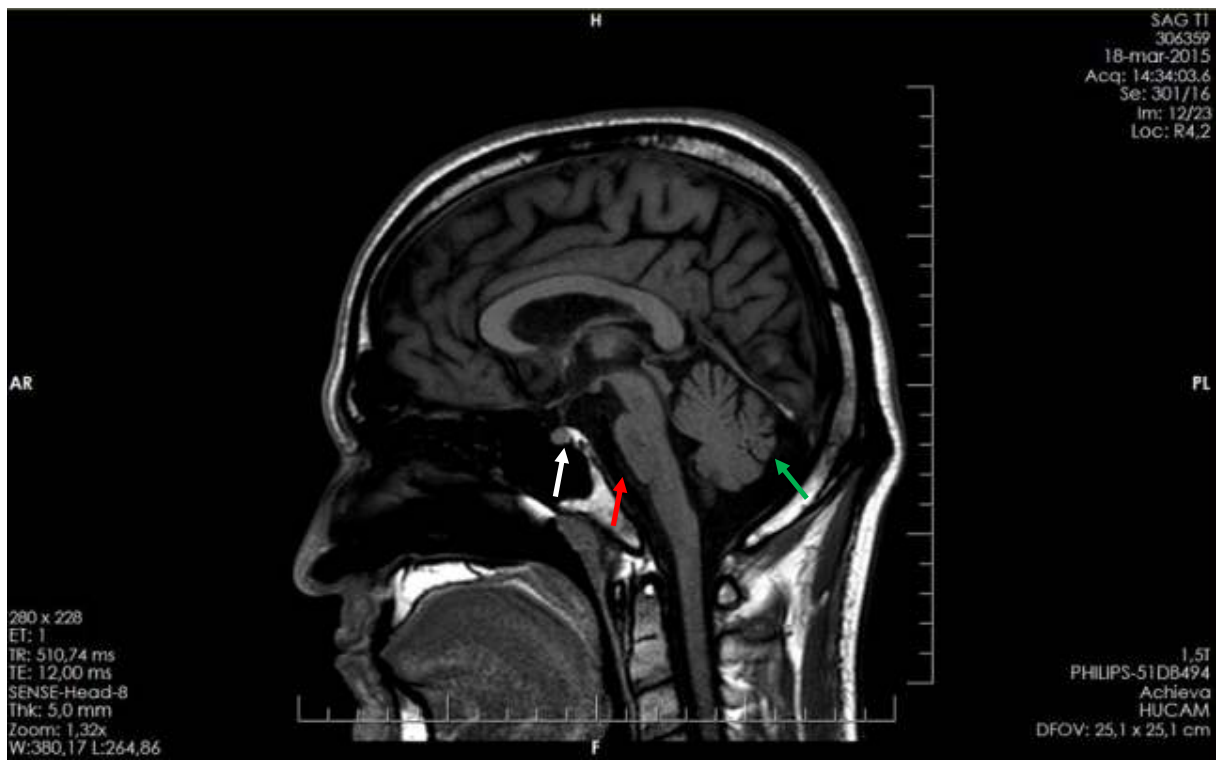


Figure 2

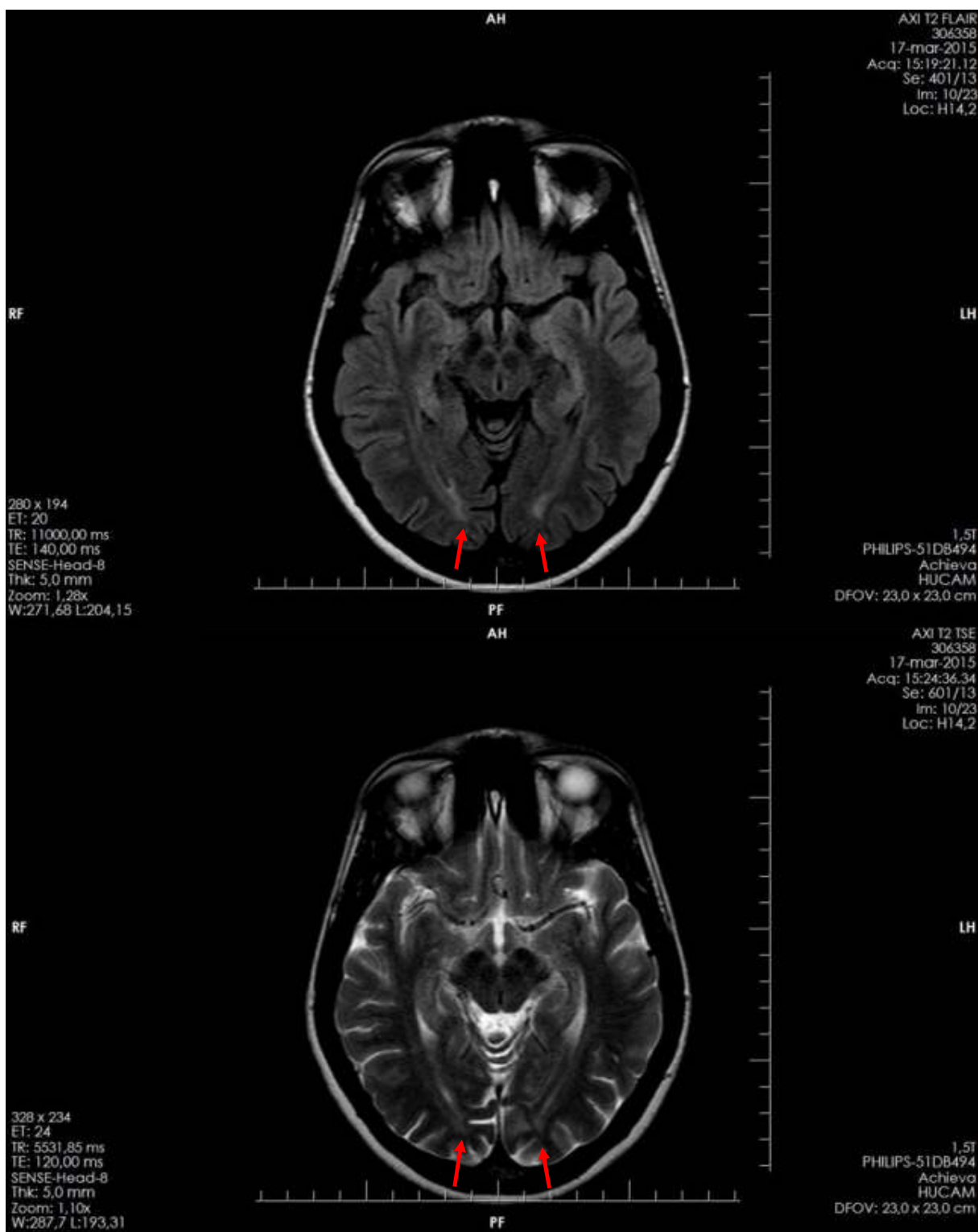


Figure 3

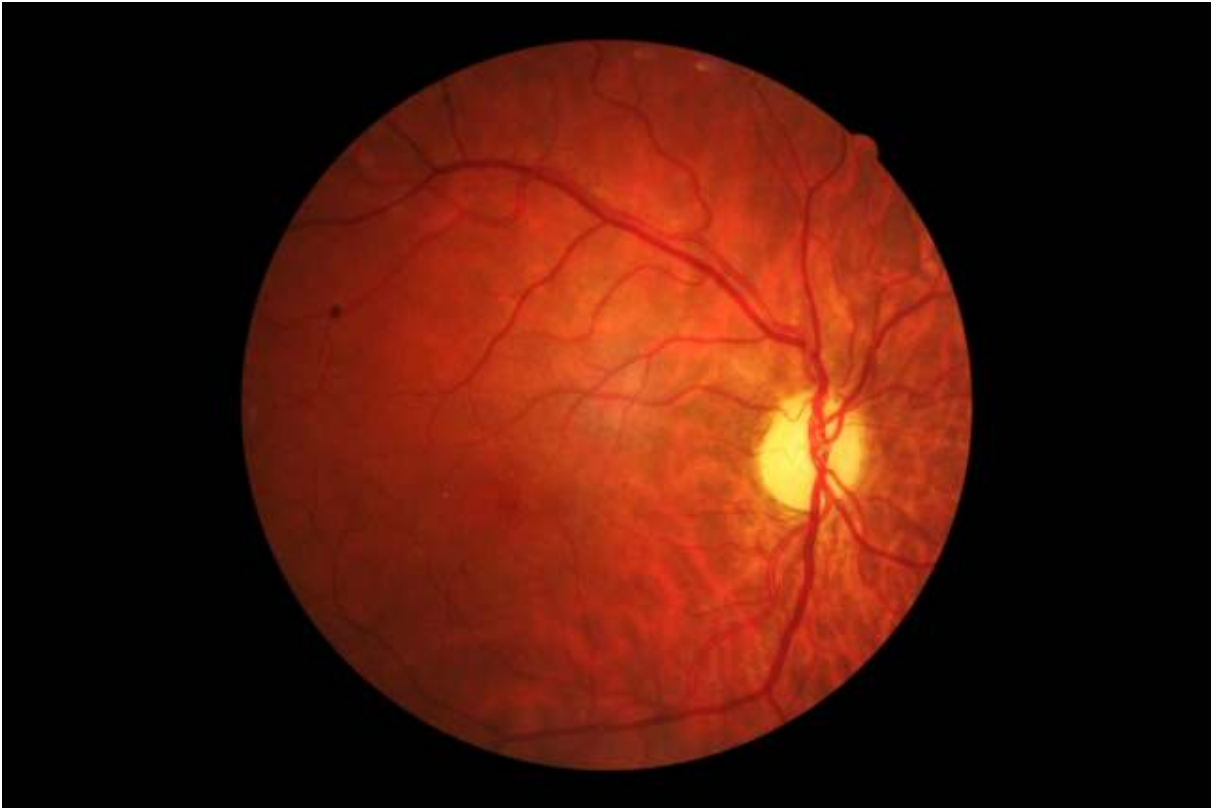


Figure 4

Patient	A	B	C
Birth date	20/12/1972	31/05/1975	22/09/1983
Weight	70 Kg	71 kg	56 Kg
Height	1.68 m	1.73 m	1.66 m
Skin color	White	White	White
Diagnosis type I diabetes mellitus	At 7 years of age	At 7 years of age	At 7 years of age
Symptoms of vision loss	Before 7 years of age	Before 7 years of age	At 6 years of age
Otological changes	Audiometry: bilateral sensorineural hearing loss.	Audiometry: bilateral sensorineural hearing loss.	Audiometry: bilateral sensorineural hearing loss.
Urological changes	Complaints of incontinence. Urodynamic study: detrusor overactivity (overactive bladder).	Ultrasound of the urinary tract: pyelocaliceal dilation and bilateral ureteral ectasia.	Ultrasound of the urinary tract: mild dilation of the right pyelocaliceal system.
Best-corrected visual acuity in 1994	Counting fingers: 2 meters in both eyes.	Counting fingers: 3 meters in both eyes.	20/100 in both eyes.
Best-corrected visual acuity in January 2015	<20/400	<20/400	<20/400
Eye examination in January 2015	Bilateral papillary atrophy. Proliferative diabetic retinopathy stabilized with laser panretinal photocoagulation.	Bilateral papillary atrophy. Nonproliferative diabetic retinopathy. Mild bilateral cortical cataracts.	Bilateral papillary atrophy. Absence of diabetic retinopathy.
Neurological disorders	Epileptic absence and complex partial seizures confirmed by EEG. Trunk ataxia with unstable gait and falls. Mild muscular hypertension. Diminished patellar and Achilles reflexes.	Mixed anxiety and depression disorder. Trunk ataxia with unstable gait and falls.	Trunk ataxia with unstable gait and falls.
Diagnosis diabetes insipidus	Absence of diabetes insipidus.	At 40 years of age	At 32 years of age
Medication	Insulin + Simvastatin 50mg/day + Losartan 50 mg/day + Lamotrigine 300 mg/day + Carbamazepine 1200 mg/day	Insulin + Desmopressin + Losartan 50 mg/day + Fluoxetine 20 mg/day + Clonazepam 2mg/night	Insulin + Desmopressin

Table 1.