CASE REPORT

WOLFRAM SYNDROME – CLINICAL AND DIAGNOSTIC DETAILS

Rohith Valsalan, Hazel gonsalves**, Maneesh Mailankot***, Navin Mulamani* and Shubha Sheshadri

Departments of Medicine and *Radiodiagnosis, Kasturba Medical College, Manipal-576104, Karnataka

Department of Obstetrics and Gynaecology, Academy of Medical Sciences, Pariyaram Medical College, Kannur-670502, Kerala and *Department of Biochemistry, Melaka Manipal Medical College, Manipal-576104, Karnataka

ABSTRACT

Wolfram syndrome, a rare genetic disorder is characterized by juvenile onset diabetes mellitus and optic atrophy. We describe two cases of wolfram syndrome belonging to same family; 25 year old female and her only 15 year old brother. In female, diabetes mellitus and optic atrophy were manifested in 1st decade, diabetes insipidus in 2nd decade and hypoacusis at the age of 25 years. Her ophthalmic evaluation revealed bilateral optic atrophy, decreased vision and peripheral constriction of visual field. However she didn't have any renal dysfunction which is also considered to be one of the features of the syndrome. Though associated psychiatric features are later manifestations of the syndrome she was admitted with alleged suicidal consumption at the age of 25 years. The brother was asymptomatic except for the diabetes mellitus and insipidus.

KEY WORDS

Wolfram syndrome, Diabetes Mellitus, Optic atrophy.

INTRODUCTION

Wolfram syndrome an autosomal recessive disorder (1, 2), is characterized by non-inflammatory atrophic changes in the brain and in pancreatic islets resulting in diabetes insipidus, diabetes mellitus, optic atrophy, and deafness (DIDMOAD). Genetic analysis has demonstrated mutations in the wolfram gene (WFS1) that encodes a 100-kDa tetrameric protein (wolframin) possessing 9–10 predicted transmembrane segments (3) are clearly associated with DIDMOAD syndrome (1). This progressive, neurodegenerative disorder presents diabetes mellitus and optic atrophy in the first decade and cranial diabetes insipidus and sensorineural deafness in second decade. Sometimes the four cardinal features of WFS will be accompanied by anomalies of urinary tract and endocrine glands.

Address for Correspondence :

Dr. Rohith Valsalan,
Department of Medicine,
Kasturba Medical College,
Manipal- 576104, Karnataka
E-mail: drrohithv@gmail.com

CASE REPORT

A 25 year old female postgraduate engineering student presented to the emergency department with alleged consumption of 30 tablets of Levocetizine. She was a known diabetic since age of 5 years and was born of consanguineous marriage. Her parents were first degree cousins. Her only 15 year old brother was also diabetic since age of 6 years. Physical examination of the female revealed a conscious, well built and nourished individual. Neurological, cardio respiratory and abdominal examination were essentially normal at the time of admission. Preliminary investigations including electrolytes were also normal. On the 2nd day of admission she went into coma. Investigations revealed polyuria (800ml/hr) and hypernatremia (189meq/dl). Urinary sodium and osmolality were 75mEq/L and 510mEq/L respectively. However the blood sugar level was normal and urinary ketones were negative.

MRI scanning showed central pontine myelinolysis, bilateral optic atrophy, brain stem atrophy with prominent prepontine cistern and loss of normal hypersensitivity of posterior pituitary (figure I). Mild dilatation of the ventricles was detected. On desmopresin, her level of consciousness and sensorium

Fig 1: MRI Images: A. T2-weighted axial & B. Flair axial MRI showing central pontine myelinolysis (arrow head). C. T1-weighted sagittal showing loss of normal hyperintensity of posterior pituitary (arrow head). D. T1-weighted axial showing brain stem atrophy (black arrow head) and prominent preoptine cistern (white arrow head). E. T2-weighted coronal showing optic atrophy (arrow heads). F. T1-weighted axial showing ventricular dilatation.

improved and serum sodium and urine output became normal. During follow up visits pure tone audiometry showed loss of auditory acuity in both the ears. Ophthalmologic evaluation showed decrease in field of vision, visual acuity and evidence of optic atrophy with normal retina.

The brother was asymptomatic except for the diabetes mellitus and insipidus. His MRI brain showed loss of normal hyperintensity of posterior pituitary (data not included).

DISCUSSION

The incidence of WFS is reported to be greater in consanguineous parents, but the possibility that same clinical form may also appear in relatives of heterozygote subjects cannot be excluded. Table 1 compares the most common period of clinical manifestations in WFS (4) with the above described female patient. Diabetes mellitus and optic atrophy were manifested in 1st decade and diabetes insipidus was manifested in 2nd decade. Hypoacusis was present at the age of 25 years. However there was no renal dysfunction probably due to early age of presentation. Though associated neurological features are later manifestations of the syndrome our patient was admitted with alleged suicidal consumption at the age of 25 years.

Table 1: Clinical manifestation of Wolfram's syndrome (+; present, -; absent)

	Most common period of manifestation (4)	In the described case
Type-1 Diabetes Mellitus	1 st decade	+
Optic atrophy	2 nd decade	+
Diabetes Insipidus	2 nd decade	+
Hypoacusis	2 nd decade	+
Renal tract disorder	3 rd decade	-
Neurological disorder	4 th decade	+/-

The protein wolframin, 890 aminoacid glycoprotein is coded by WFS1 or wolframin gene and is localized to the endoplasmic reticulum in rat brain hippocampus and rat pancreatic islet β -cells (5) and studies (6) have demonstrated that the wolframin protein induced a large cation-selective ion channel that was blocked by Mg^{2+} or Ca^{2+} . Expression of wolframin increased cytosolic calcium levels in oocytes. Wolframin thus appears to be important in the regulation of intracellular Ca^{2+} homeostasis. Disruption of this function may place cells at risk to suffer inappropriate death decisions, thus accounting for the progressive β -cell loss and neuronal degeneration associated with the disease. Among its many activities, the endoplasmic reticulum folds and modifies newly formed proteins so they have the correct 3-dimensional shape to

function properly. The endoplasmic reticulum also helps to transport proteins, fats, and other materials to specific sites within the cell or to the cell surface. Based on its location in the endoplasmic reticulum, wolframin may play a role in protein folding or cellular transport. In the pancreas, wolframin may help to fold protein precursor of insulin (called proinsulin) into the mature hormone that controls blood glucose levels. WFS1 mutations results in highly unstable wolframin proteins which undergoes proteasomal degradation. Absence of wolframin aggregates in patient cells suggest wolfram syndrome is not protein aggregation disease rather it is due to loss-of-function by cellular depletion of wolframin (7). WFS-1 mutations leads to sensorineural hearing loss (8) and mostly non-inactivating mutations are responsible for hearing impairment (9). WFS1 gene is likely to play role in inner ear ion homeostasis as maintained by the canalicular reticulum (10) and it may help to maintain the correct cellular levels of calcium ions.

Not all patients with juvenile onset diabetes mellitus and optic atrophy have this syndrome. Other diagnoses include congenital rubella syndrome, hereditary optic neuropathy, Friedricks ataxia, Refsums syndrome, Lawrence –moon-beidl syndrome and Alstrom syndrome. Although these diseases share some major and minor neurological features of wolframs syndrome, it can be easily distinguished from others by clinical criteria. The recognition of clinical differences is important for correct therapy. The earlier the treatment better will be the outcome considering the high mortality index (about 65% at the age of 35 years) of patients with wolfram syndrome.

REFERENCES

- Hardy C, Khanim F, Torres R, Scott-Brown M, Seller A, Poulton J, et al. Clinical and molecular genetic analysis of 19 Wolfram syndrome kindreds demonstrating a wide spectrum of mutations in WFS1. *Am J Hum Genet* 1999; 65: 1279–90.
- Rando TA, Horton JC, Layzer RC. Wolfram syndrome: evidence of a diffuse neurodegenerative disease by magnetic resonance imaging. *Neurol* 1992; 42: 1220–4.
- Hofmann S, Philbrook C, Gerbitz KD, Bauer MF. Wolfram syndrome: structural and functional analyses of mutant and wild-type wolframin, the *WFS1* gene product. *Hum Mol Genet* 2003; 12: 2003–12.
- Barrett TG, Bunday SE, Macleod AF. Neurodegeneration and diabetes: UK nationwide study of Wolfram (DIDMOAD) syndrome. *Lancet* 1995; 346: 1458–63.
- Cryns K, Sivakumaran TA, Van den Ouweland JM, Pennings RJ, Cremers CW, Flothmann K, et al. Mutational spectrum of the *WFS1* gene in Wolfram syndrome, nonsyndromic hearing impairment, diabetes mellitus, and psychiatric disease. *Hum Mutat* 2003; 22(4): 275–87.
- Osman AA, Saito M, Makepeace C, Permutt MA, Schlesinger P, Mueckler M. Wolframin expression induces novel ion channel activity in endoplasmic reticulum membranes and increases intracellular calcium. *J Biol Chem* 2003; 278 (52): 52755–62.
- Hofmann S, Bauer MF. Wolfram syndrome-associated mutations lead to instability and proteasomal degradation of wolframin. *FEBS Lett* 2006; 580(16): 4000–4.
- Bespalova IN, Van Camp G, Bom SJ, Brown DJ, Cryns K, DeWan AT, et al. Mutations in the Wolfram syndrome 1 gene (*WFS1*) are a common cause of low frequency sensorineural hearing loss. *Hum Mol Genet* 2001; 10(22): 2501–8.
- Cryns K, Pfister M, Pennings RJ, Bom SJ, Flothmann K, Caethoven G, et al. Mutations in the *WFS1* gene that cause low-frequency sensorineural hearing loss are small non-inactivating mutations. *Hum Genet* 2002; 110(5): 389–94.
- Cryns K, Thys S, Van Laer L, Oka Y, Pfister M, Van Nassauw L, et al. The *WFS1* gene, responsible for low frequency sensorineural hearing loss and Wolfram syndrome, is expressed in a variety of inner ear cells. *Histochem Cell Biol* 2003; 119(3): 247–56.