Radiological findings in Wolfram syndrome

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ABSTRACT

Objective: To determine the precise radiologic findings in Wolfram syndrome (WFS) patients using objective techniques in order to better define the reference population for the clinical evaluation.

Methods: Sixteen patients (6 males and 10 females) with WFS found in 4 families were included in this study. Fourteen patients with WFS-2 came from 3 families while 2 patients with WFS-1 from one family. All patients were studied at Jordan University Hospital, Amman, Jordan, from January 2001 through to January 2003 by definite radiologic techniques as part of a thorough clinical comprehensive assessment. These include intravenous urography, abdominal and pelvic ultrasonography, barium meal, upper gastrointestinal endoscopy and magnetic resonance imaging with and without contrast to the brain and the pituitary glands.

Results: Five of the female patients had a small uterus. Spina bifida was found in 7, hydronephrosis in 9 and hydroureter in 5 patients. Peptic ulcer was detected in 10 out of 14 available patients and helicobacter pylori in 7 out of 16 patients. Atrophy was detected in all brains, 9 brain stems, 12 cerebellums and 14 optic tracts of all patients. The size of the pituitary glands was variable.

Conclusion: The particular radiologic assessment of patients with WFS proofed that, urinary tract dilatation was detected in WFS-1 and WFS-2 patients though all WFS-2 patients have no diabetes insipidus. Peptic ulcer was frequently higher in WFS-2 patients. No significant radiologic difference was found between patients with WFS-1 and WFS-2.

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Wolfram syndrome [MIM # 222300 and MIM # 604928], also known as "DIDMOAD" show signs of diabetes insipidus (DI), diabetes mellitus (DM), optic atrophy (OA), and deafness, is associated with high morbidity and mortality.[1] It is a progressive neurodegenerative condition, in which only insulin dependent diabetes mellitus (IDDM) and progressive OA are necessary to make the diagnosis.[2] Wolfram syndrome is an autosomal recessive disorder with demonstrable clinical and genetic heterogeneity.[3-13] There are at least 2 genes involved in Wolfram syndrome, WFS-1 and WFS-2. Although the WFS-1 has already been cloned and WFS-2 is waiting of identification, the pathogenesis of Wolfram syndrome is not very clear.[8-9] The literature contains numerous comprehensive clinical reviews.[2,3,12,14-17] Most case reports contain descriptive radiologic findings; however, few discussed the specific aspects of the radiologic findings with considerable depth.[18-21] The present study, illustrated the detailed radiologic findings in 16 individuals diagnosed as Wolfram syndrome patients.

Methods. Sixteen patients obtained from 4 inbred Jordanian families, who carry the clinical diagnosis of Wolfram syndrome, were approved to participate in this study. They include 6 males, age range 10-37-years; mean 19.7 ± 9.8, and 10 females, age range 7-35-years; mean 14.7 ± 5 **(Table 1).** One family (family 1) is linked to WFS-1 while the other

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Table 1 - Radiologic findings in patients with Wolfram syndrome.

Number	Family	Sex	Age	SB	HN	HU	PU	HP	GBA	CA	BSA	CNS deg	OTA	ONHS	ASPPL	PS
1	1	M	37	+	+	+	-		+	+	+	+	+	+	+	N
2	1	F	35	+	+	+	NA		+	+	+	+	+	+	+	N
3	2	M	24	-	-	-	+		+	+	+	-	-	-	-	S
4	2	F	22	-	+	-	+	+	+	+	+	-	+	+	+	N
5	2	M	19	-	+	-	+		+	+	+	+	+	-	+	L
6	2	F	14	-	-	-	+		+	-	-	+	+	-	+	N
7	2	M	14	-	-	-	+	+	+	+	+	+	+	-	+	N
8	2	F	14	-	-	-	+		+	-	-	+	+	-	+	S
9	3	M	14	+	+	-	+	+	+	-	-	-	-	-	+	L
10	3	F	20	+	+	+	+	+	+	+	+	+	+	+	+	L
11	3	F	20	+	+	-	+	+	+	-	-	-	+	-	+	N
12	3	M	10	+	+	+	-		+	+	-	+	+	-	+	L
13	4	F	13	-	+	+	-	+	+	+	-	-	+	-	+	N
14	4	F	11	-	-	-	+	+	+	+	-	-	+	-	+	S
15	4	F	11	-	-	-	-		+	+	+	-	+	-	+	S
16	4	F	7	+	-	-	NA		+	+	+	-	+	-	+	S
Frequency (%)				44	56	31	70	44	100	75	56	50	87.5	25	94	N=44 L=25 S=31

SB - spina bifida, HN - hydronephrosis, HU - hydroureter, PU - peptic ulcer, HP - *helicobacter pylori*, GBA - generalized brain atropy, CA - cerebellar atrophy, BSA - brain stem atrophy, CNS Deg - CNS degeneration, OTA - optic tract atrophy, ONHS - optic nerve high signal, ASPPL, absent signal posterior pituitary lobe, PS - pituitary size, N - normal, L - large S - small

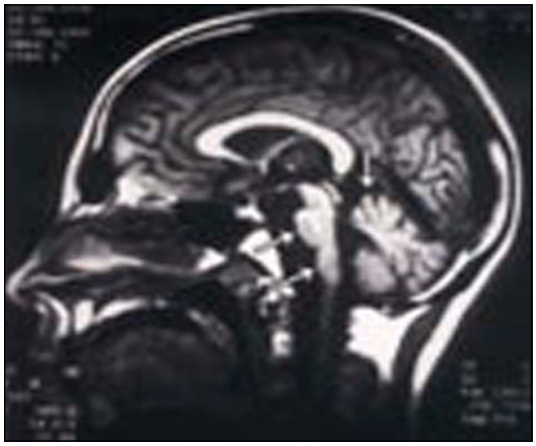

Figure 1

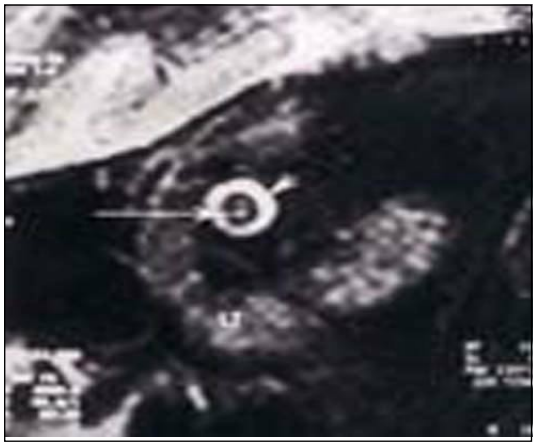

Figure 2

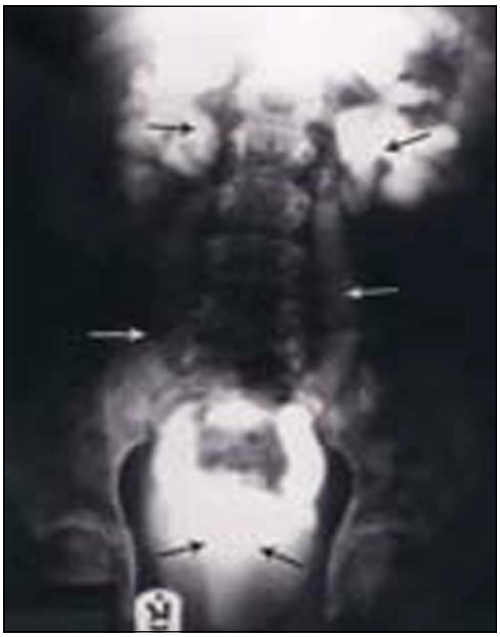

Figure 3

Figure 1 - Sagittal T1 - weighted magnetic resonance image of the brain with intravenous contrast showing cerebellar and brain stem atrophy.

Figure 2 - Coronal T2 - weighted magnetic resonance image of the left orbit showing high signal and atrophy of the optic nerve.

Figure 3 - Full length intravenous urography film showing bilateral dilatation in the pelvicalyceal systems and both ureters in a patient without high urinary output.

3 are linked to WFS-2.[10] The same 16 patients were focus of a linkage study.[10] The radiologic study was part of a comprehensive clinical and investigational work up carried out for each individual at Jordan University hospital, Amman, Jordan, from January 2001 through to January 2003. The protocol consisted of a standard intravenous urography, abdominal and pelvic ultrasonography, barium meal, upper gastrointestinal endoscopy. The brains of all patients were studied by using axial and sagittal T1 with and without contrast (Gadilinium), axial T2 and coronal flair. The pituitary glands and anterior optic tract in all patients were examined by using coronal and sagittal T1- with and without contrast and T2-coronal weighted images. All images were performed on MRI vision plus (Siemens, Erlangen, Germany). The definitions mentioned below were followed for all objective findings. The images were reviewed independently by 2 radiologists to outline the subjective findings such as atrophy. In case of discrepancy in the radiologists' evaluation, a third opinion was sought.

Definitions and parameters. The size of the adult kidney was determined by the standard measurements (length 10-12 cm; width 4-6 cm) whereas, of children the published measurements were employed.[22] The uterus length of 5-8 cm and width of 1.5-3 cm were considered as the normal limit, independent of age. The published methods were used to assess the pituitary gland size.[23]

Results. Two patients from one sibship (family 1) have WFS-1 (No.1 and 2) **Table 1**. The remainder 14 patients have WFS-2.[10] Five of 10 females found to have a small uterus, while only one male with small testicles. Spina bifida was present in 7 patients coming mainly from 2 families (family 1 and family 3). Hydronephrosis and hydroureter **(Figure 3)** were found in 9 and 5 patients. Peptic ulcer was discovered in 10 of 14 examined patients where all related to WFS-2 families, while *Helicobacter pylori (H.pylori)* was only detected in 7 patients. Brain atrophy was dominant in all patients **(Figure 1)** with variable degrees. Cerebellar atrophy was distinguished in 12 patients and brain stem atrophy in 9 patients with manifested signal increase on T2- weighted images from the cochlear nucleus. There was evidence of CNS degeneration in half of the patients. The majority of patients showed optic tract atrophy while only 4 showed evidence of optic nerve degeneration detected by high signal on T2-weighted images. **(Figure 2)** Almost all patients showed absence of high signal of the posterior lobe of the pituitary gland. The size of the pituitary gland was found to be normal in 7, small in 5 and large in 4 patients.

Discussion. This report revealed the radiologic findings in patients with Wolfram syndrome. One of the extraordinary findings is the presence of peptic ulcers with high frequency in families with WFS-2. The presence of peptic ulcer is probably related to the bleeding disorder reported in WFS-2.[11] The frequency of genitourinary abnormalities in our study is not different from previous observations.[1,2] The dilated urinary tract was mostly attributed to the high urinary output,[1] that was observed in only 3 individuals of our cohort. Barrett et al[1,2] declared that, treatment of the DI improved the urinary tract dilatation in some of their patients, which was not the case in our group. Although neuroimaging findings have been previously reported, here we point particularly, the atrophic degenerative changes in the optic tract and cerebellum that were clearly detected on the MR images.[1,16,18] Magnetic resonance imaging is a reliable technique in evaluating patients with Wolfram syndrome as it demonstrates the degenerative changes with extreme sensitivity.[1,16,18] The present study showed increased signal in the T2-weighted images of the vestibulocochlear nuclei in 4 individuals, indicating degeneration of the cochlear nucleus. The absence of high signal in the posterior lobe of the pituitary gland was noticed in almost all of our patients despite the fact that only 2 patients had diabetes insipidus DI. This finding was coined to the presence of DI.[18] There does not seem to be any significant difference in the radiological findings between patients with WFS-1 and WFS-2. The urinary tract findings and the neuroimaging findings in the posterior pituitary lobe are consistent despite the absence of DI in patients with WFS-2. It is of note that the peptic ulcer disease is more prevalent in WFS-2, which probably related to the bleeding disorder. However, it is of interest to study carefully the relation between peptic ulcer, presence of *H.pylori* and the severity of bleeding abnormalities in both types of Wolfram syndrome, which will be the essential topic of our next investigation.

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References

1. Barrett TG, Bundey SE, Macleod AF. Neurodegeneration and diabetes: UK nationwide study of Wolfram (DIDMOAD) syndrome. ***Lancet*** 1995; 346: 1458-1463.
2. Barrett TG, Bundey SE. Wolfram (DIDMOAD) syndrome. ***J Med Genet*** 1997; 34: 838- 841.
3. Rose FC, Fraser GR, Friedmann AI, Kohner EM. The association juvenile diabetes mellitus and optic atrophy: clinical and genetical aspects. ***Q J Med*** 1966; 35: 385-405.
4. Cremers CW, Wijdeveld PG, Pinckers AJ. Juvenile diabetes mellitus, optic and other abnormalities (Wolfram syndrome). A review of 88 cases from the literature with personal observations on 3 new patients. ***Acta Paediatr Scand Suppl*** 1977; 264: 1-16.

5. Swift RG, Sadler DB, Swift M Psychiatric findings in Wolfram syndrome homozygotes. ***Lancet*** 1990; 336: 667-669.
6. Salih MA, Tuvemo T. Diabetes insipidus, diabetes mellitus, optic atrophy and deafness (DIDMOAD syndrome). A clinical study in two Sudanese families. ***Acta Paediatr Scand*** 1991; 80: 567-572.
7. 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: 95-97.
8. Inoue H, Tanizawa Y, Wasson J, Behn P, Kalidas K, Bernal-Mizrachi E et al. A gene encoding a transmembrane protein is mutated in patients with diabetes mellitus and optic atrophy (Wolfram syndrome). ***Nat Genet*** 1998; 20: 143-148.
9. Strom TM, Hortnagel K, Hofmann S, Gekeler F, Scharfe C, Rabl W et al. Diabetes insipidus, diabetes mellitus, optic atrophy and deafness (DIDMOAD) caused by mutations in a novel gene (wolframin) coding for a predicted transmembrane protein. ***Hum Mol Genet*** 1998; 7: 2021-2028.
10. 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: 1229-1236.
11. Al-Sheyyab M, Jarrah N, Younis E, Shennak MM, Hadidi A, Awidi A et al. Bleeding tendency in Wolfram syndrome: a newly identified feature with phenotype genotype correlation. ***Eur J Pediatr*** 2001; 160: 243-246.
12. Ajlouni K, Jarrah N, El-Khateeb M, El-Zaheri M, El-Shanti H, Lidral A. Wolfram syndrome: identification of a phenotypic and genotypic variant from Jordan. ***Am J Med Genet*** 2002; 115: 61-65.
13. Al-Till M, Jarrah NS, Ajlouni KM. Ophthalmologic findings in fifteen patients with Wolfram syndrome. ***Eur J Ophthalmol*** 2002; 12: 84-88.
14. Bretz GW, Baghdassarian A, Graber JD, Zacherle BJ, Norum RA, Blizzard RM. Coexistence of diabetes mellitus and insipidus and optic atrophy in two male siblings: studies and review of literature. ***Am J Med*** 1970; 48: 398-403.
15. Blasi C, Pierelli F, Rispoli E, Saponara M, Vingolo E, Andreani D. Wolfram's syndrome: a clinical, diagnostic, and interpretative contribution. ***Diabetes Care*** 1986; 9: 521-528.
16. Kinsley BT, Swift M, Dumont RH, Swift RG. Morbidity and mortality in the Wolfram syndrome. ***Diabetes Care*** 1995; 18: 1566-1570.
17. JA, Rainbow LA, Ricketts C, Barrett TG. Wolfram syndrome. ***Rev Endocr Metab Disord*** 2003; 4: 53-59.
18. Rando TA, Horton JC, Layzer RB. Wolfram syndrome: evidence of a diffuse neurodegenerative disease by magnetic resonance imaging. ***Neurology*** 1992; 42: 1220-1224.
19. Saiz A, Vila N, Munoz JE, Marti MJ, Graus F, Tolosa E. Wolfram's syndrome: correlation of clinical signs and neurological images. ***Neurologia*** 1995; 10: 107-109.
20. 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: 352-360.
21. Galluzzi P, Filosomi G, Vallone IM, Bardelli AM, Venturi C. MRI of Wolfram syndrome (DIDMOAD). ***Neuroradiology*** 1999; 41: 729-731.
22. Dinkel E, Ertel M, Dittrich M, Peters H, Berres M, Schulte-Wissermann H. Kidney size in childhood. Sonographical growth charts for kidney length and volume. ***Pediatr Radiol*** 1985; 15: 38-43.
23. Lurie SN, Doraiswamy PM, Husain MM, Boyko OB, Ellinwood EH Jr, Figiel GS et al. In vivo assessment of pituitary gland volume with magnetic resonance imaging: the effect of age. ***J Clin Endocrinol Metab*** 1990; 71: 505-508.