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SHORT REPORT

Additional Distinct Findings in Three Cases with Wolfram Syndrome

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Wolfram syndrome (WS) is a rare dysmorphogenetic recessive disorder characterized by early-onset, non-autoimmune diabetes mellitus (DM), progressive optic atrophy and further neurological and endocrinological abnormalities. It was identified in 4 patients in 1938 by an American physician, DJ Wolfram (1-3). Its prevalence is reported as 1/770,000-1/100,000 (2-5). DM and optic atrophy are requisites for diagnosis. Signs that are most frequently associated with the syndrome are diabetes insipidus (DI), sensorineural deafness, urinary system anomalies, ataxia, peripheral neuropathy, mental retardation and psychiatric problems (3,4).

WS has been attributed to mutations in the WFS1 gene, which codes for a protein predicted to possess 9-10 transmembrane segments. Little is known concerning the function of the WFS1 protein (wolframin). Endoglycosidase H digestion, immunocytochemistry, and subcellular fractionation studies all indicate that wolframin is localized to the endoplasmic reticulum in rat brain hippocampus and rat pancreatic islet beta-cells, and after ectopic expression in Xenopus oocytes. Expression of wolframin also increased cytosolic calcium levels in oocytes. Wolframin thus appears to be important in the regulation of intracellular Ca2+ homeostasis. Disruption of this function may place cells at risk of inappropriate death decisions, thus accounting for the progressive beta-cell loss and neuronal degeneration associated with the disease.

Peripheral neuropathy and neurogenic bladder in WS may result from this mechanism as well as increased polyol activity (5).

Peculiar findings (hydronephrosis, neurogenic bladder, short stature, anemia and depression) in 3 patients, 2 of whom were brothers, diagnosed with WS are presented. The aim of the present report is to alert physicians about the association between DM and monogenic syndromes, such as WS, and to address the necessity of monitoring these patients in terms of multifaceted problems.

Case Reports

Case 1

An 11-year-old male patient who presented with poor metabolic control was being followed for DM diagnosed at 5 years of age, DI and bilateral sensorineural lack of hearing diagnosed at 8 years of age and depression diagnosed 1 month previously. His parents were second-degree cousins and his 8-year-old brother was also being monitored due to WS diagnosis. The patient was regularly using insulin and vasopressin. Physical examination of the patient showed introversion, pallor, short stature (height: 110 cm, below the 3 third percentile), optic atrophy (Figure 1), bilateral sensorineural hearing loss and truncal ataxia. Laboratory analyses demonstrated that Hb was

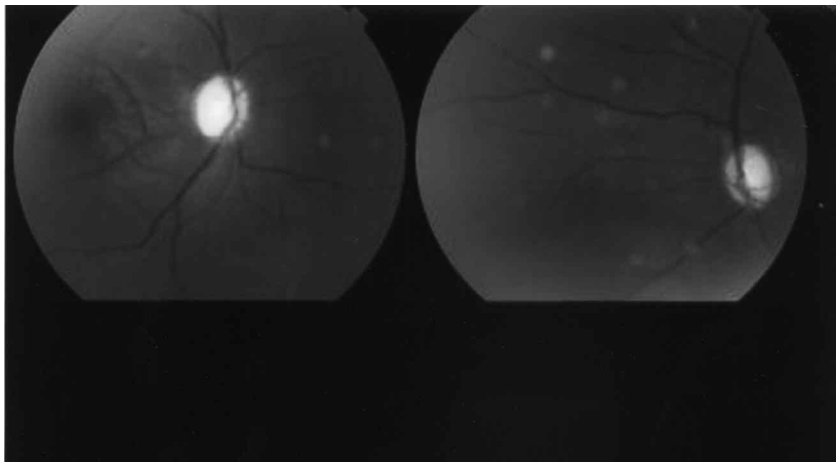


Figure 1. Optic disk examination of patient 1 showed bilateral optic atrophy.

11.1 g/dl, HbA1c was 12% and fasting blood sugar was 346 mg/dl. It was also found that the patient's basal and stimulated growth hormone levels were low (basal growth hormone: 3 ng/ml, L-Dopa, clonidine-stimulated growth hormone: 3.2 ng/ml, 3.6 ng/ml hypophyseal-origin growth hormone deficiency). Wide-scan metabolic tests were normal. Repeated audiological examination revealed that the patient had sensorineural hearing loss at medium-high frequencies. Bilateral grade 1-2 hydronephrosis was observed in renal ultrasonography and cerebral and hypophyseal magnetic resonance imaging (MRI) showed cerebellar atrophy as well as signal loss in neuro-hypophysis (Figures 2a, b). An antipsychotic agent (risperidone) was added to the systemic follow-up and treatment of the patient.

Case 2

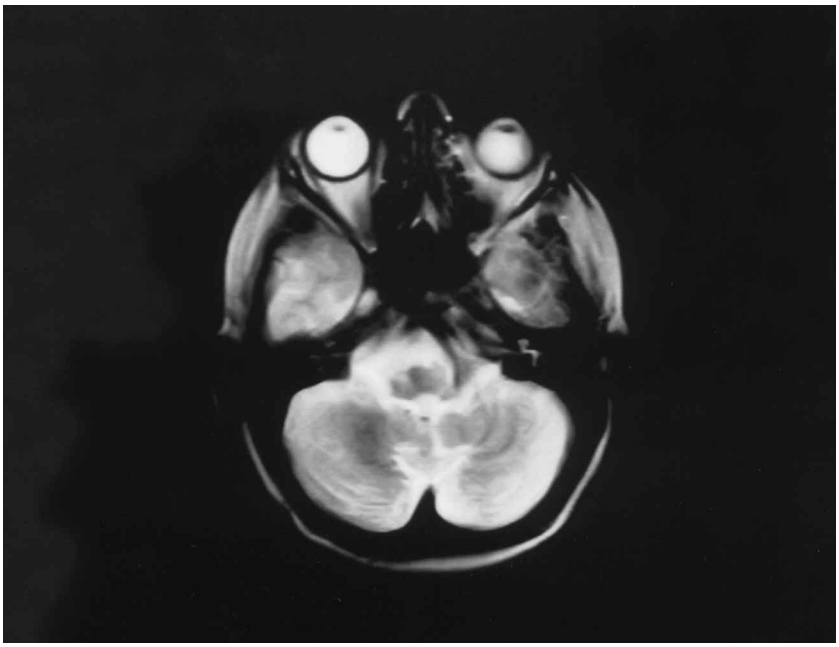
The patient, who was the brother of patient 1, was found to have DM and bilateral optic atrophy at 6 years of age and DI and bilateral sensorineural hearing loss at 7. He was being treated for these conditions (crystallized insulin and vasopressin) and his blood sugars were in the targeted limit during follow-up. His physical examination showed, in addition to the above-mentioned findings, that his gait was wide-based and lurching, and that he had explosive speech. HbA1c was 7.1% and fasting blood sugar was 102 mg/dl in the laboratory tests and other findings were normal. Renal ultrasonography showed bilateral grade 2 hydronephrosis and cerebral MRI demonstrated cerebellar atrophy.

Case 3

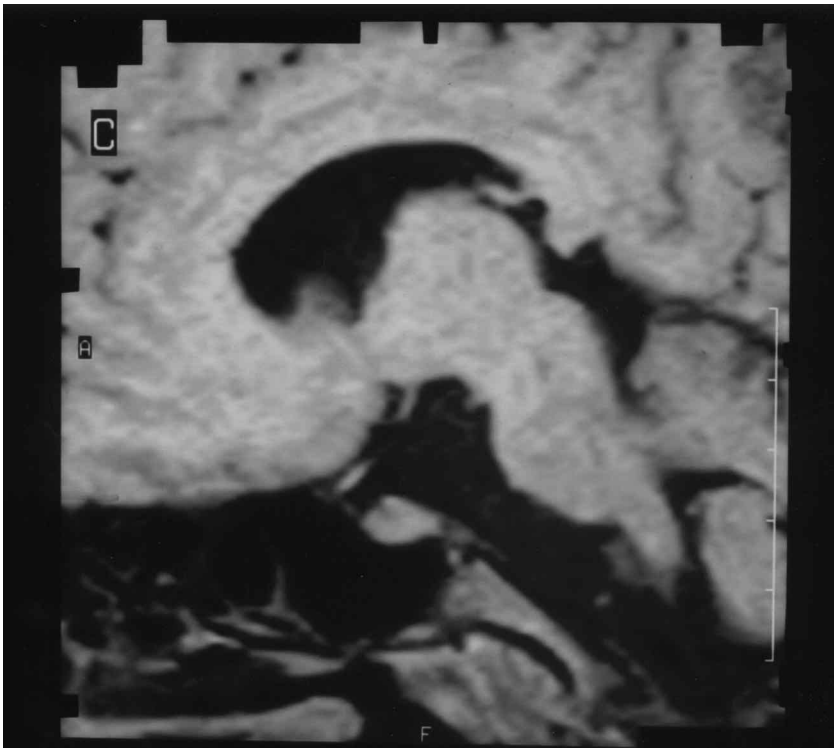
A 14-year-old girl, who had bilateral sensorineural loss of hearing at age 9, bilateral optic atrophy at 11 and DI at 12 came for routine checks. She complained of recent urinary frequency. Her mother and father were second-degree relatives and her 3 sisters and 2 brothers were healthy. In addition to previous findings, short stature was determined at physical examination (height: 140 cm, below the 3 third percentile). Laboratory tests showed HbA1c at 8.4% and fasting blood sugar at 128 mg/dl. Her basal and stimulated growth hormone levels were low (basal growth hormone: 4 ng/ml, L-Dopa, clonidine-stimulated growth hormone: 4.9 ng/ml, 5.1 ng/ml. hypophyseal-origin growth hormone deficiency). Urologic examination revealed that she had neurogenic bladder and treatment was started for this condition. Her cerebral MRI was normal.

Clinical characteristics of all 3 patients are presented in the Table.

More than 20 syndromes including WS among the significant and increasing number of degenerative diseases of neuronal tissues are known to be associated with DM. WS is highly variable in its clinical manifestations, which include DI, DM, optic atrophy, and deafness. It may affect the central nervous system, peripheral nerves, and neuroendocrine tissues (5,6). WS mutations are spread over the entire coding region, and are typically inactivating, suggesting that a loss of function causes the disease phenotype. It is established that WS is a mitochondrial disease, inherited as an



(A)



(B)

Figure 2. T2 W magnetic resonance imaging showed cerebellar atrophy (A) as well as signal loss in neuro-hypophysis (B).

Table. Clinical characteristics of all patients.

Case	Age / DM* / DI* / OA* / Deafness* (years)	Sex	Relatives	Renal anomalies	Brain MRI	Other findings
1	11 / 5 / 8 / 10 / 8	M	+	Bilateral hydronephrosis	Cerebellar atrophy Signal loss in neuro-hypophysis	Depression Anemia (Megaloblastic) Short stature
2	8 / 6 / 7 / 6 / 7	F	+	Bilateral hydronephrosis	Cerebellar atrophy	-
3	14 / 8 / 12 / 11 / 9	F	+	Neurogenic bladder	-	Short stature

M: Male F: Female DM: Diabetes mellitus DI: Diabetes Insipidus OA: Optic Atrophy MRI: Magnetic Resonance Imaging
* Diagnosed age

autosomal recessive trait and the gene responsible for the disease is located on the shorter branch of 4p16.1 (6, 7). A new locus for WS has been located on 4q22-24, providing evidence for the genetic heterogeneity of this syndrome.The hypothesis that heterozygous carriers of the gene for WS are predisposed to psychiatric illness was supported previously by the finding of an excess of psychiatric hospitalizations and suicides in WS blood relatives compared to spouse controls (9).

DM is generally the first symptom in WS and it is reported that DM develops in the second half of the first decade and optic atrophy develops in the second half of the second decade. WS patients may also have DI, loss of hearing, urinary tract dilatation, ataxia, peripheral neuropathy, mental retardation, brain stem/cerebral/cerebellar/olivopontal atrophy, color blindness, vertigo, anosmia and psychiatric illness (10-12). It is reported in the literature that all signs, except for DM, DI and optic atrophy, are seen between 16 and 30 years of age on average (2,3). Optic atrophy, loss of hearing and renal anomalies found in all 3 patients developed much earlier than the ages reported in the literature, and pathological cerebellar findings in the brothers also developed at a much lower age than the mean age in the literature (mean age 30 years, 8 and 11 years in our patients). This suggests that the emergence of the components of WS may be influenced by environmental and hereditary factors, in addition to controlled follow-up of the disease.

Short stature is a common feature in WS. Several types of hormonal abnormalities are associated with it, including a deficiency in the somatotropic axis. Induction of early and adequate hormonal substitution requires endocrinological diagnosis. The short stature determined in patients 1 and 3 may essentially be due to hypophyseal-origin growth hormone deficiency.

Neurogenic bladder in children with WS can result from sphincteric dyssynergia, from bladder hyper-reflexia, from autonomic nerve dysfunction or from a combination of factors. Dilatation of the urinary tract was considered to be either a consequence of high diuresis associated with DI or a degenerative process affecting the central and peripheral nervous system (3). Since all 3 patients have urinary tract problems, they need to be closely monitored.

Optic atrophy in case 2 was determined concurrently with DM. This indicates that optic atrophy in WS can emerge as early as DM. Another important finding in our cases was the depression that our first patient had been experiencing for 1 month. It is reported that depression may be one of the primary signs of WS and that WS patients can have a variety of psychiatric problems (5,9,13). The genetic mutation (4p16.1) responsible for WS and the capacity of this mutation to create a disposition towards psychiatric disorders in heterozygote carriers are well known (9). It has been suggested that there is a relation between cerebellar atrophy and bipolar disorders (14). Early manifestation of depression in our patient may be accounted for by the chronic disease process, as well as cerebellar involvement.

Parents and siblings of WS patients should be examined in terms of pathological findings; problems that tend to become chronic should be noticed early and specific follow-up/treatment of these should be started as early as possible. In this way, patients' quality of life can be improved and their lifespans can be prolonged.

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