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A Case of Wolfram Syndrome

Mithat Bahçeci* **Alpaslan Tuzcu*** **Kadim Bayan**** **Metin Çelik****

Dicle University Medical School, Diyarbakır, Turkey
** Department of Endocrinology and Metabolism*
*** Department of Internal Medicine*

Wolfram syndrome (WS) is the inherited association of juvenile-onset insulin-dependent diabetes mellitus and progressive bilateral optic atrophy. We have identified a complete DIDMOAD syndrome. Bilateral papillary atrophy was found in optic fundoscopic examination. The diagnosis of diabetes insipidus was determined after a water deprivation test. Fasting serum insulin levels was 0.4uU/ml and serum C-peptide level was 0.2 ng/ml. Antibodies to islet cell (ICA) and anti-insulin antibodies were negative. In MRI of the patient the posterior pituitary bright spot was absent. Deafness was found in odiometric examination. The disease is believed to account for 1/150 patients with young-onset insulin-requiring diabetes mellitus. Interestingly we follow- up almost 450 patients with type 1 diabetes mellitus per year, but we determined a Wolfram syndrome at first time. In the literature WS were found 27 patients in 589 type 1 diabetic patients. Whereas in UK population syndrome is rare and its prevalence is estimated to be 1/ 770 000 people. As a result we can say that frequency of syndrome may show ethnic differences and may be rare in our region.

Key words: **Wolfram syndrome, optic atrophy, diabetes mellitus, diebetes insipidus and deafness**

Introduction

Wolfram syndrome (WFS) was first described in 1938 as a combination of familial juvenile-onset diabetes mellitus and optic atrophy. Insulin-requiring diabetes mellitus occurs with mean age of onset at 6 years (1). When examined, pancreatic islets were atrophic and insulin-producing (beta)-cells selectively absent. The disease is believed to account for 1/150 patients with young-onset insulin-requiring diabetes mellitus (1). The pathogenesis of Wolfram syndrome is unknown. Linkage of the gene to markers on chromosome 4p was reported in 1994 and recently were determined successful in the positional cloning of the WFS gene (WFS1) (2). But in a recent study Tanizawa (3) has shown the gene within a region less than 250 kb on chromosome 6p. In the region, it was identified a novel gene (WFS1) encoding a putative trans-membrane protein. Comparison of the cDNA sequence of WFS1 with those in public databases revealed no related genes.

Report of Case

(File no: 517178 and protocol no: 1996063981), HB, A 16-year-old girl (height, 138 cm (-4 SD) body weight, 27 kg, BMI: 14 kg/m^2) was presented with diabetes mellitus and optic atrophy (Figure 1). Her parents and siblings did not have diabetes mellitus. Diabetes mellitus had appeared who she was 8 year old. Before admitted to our department she has been treated with diet and insulin since 1993. At first her fasting serum insulin levels was 0.4 µU/ml (normal: 3-17 µU/ml) and serum C-peptide level was 0.2 ng/ml (reference range <3.5 ng/ml). After strict glycemic control for three months, we performed an oral glucose tolerance

Correspondence address:

Mithat Bahçeci
Department of Endocrinology and Metabolism, Medical School of Dicle University 21280 Diyarbakır, Turkey
E-mail: mbahceci@dicle.edu.tr
Telephone: +90 (412) 248 80 01

test with 48-gram glucose (1.75 gr/per body weight). Insulin concentrations at basal, 30th, 60th, 90th, 120th minutes were 0.4 µU/ml, 0.5 µU/ml, 0.6µU/ml, 0.5 µU/ml, 0.4 µU/ml respectively. After glucose loading, C-peptide levels were found to be 0.2 ng/ml, 0.3 ng/ml, 0.2 ng/ml, 0.2 ng/ml, 0.3 ng/ml respectively. The results of laboratory investigations, including liver and renal function tests and measurement of serum lactate and pyruvate levels, were within normal ranges. Islet cell antibodies (ICA) was 1.8 JDF unit (reference range <5 unit) and anti-insulin antibodies was 0.2 KronusU/ml (reference range <1.0 s U/ml) detected as negative. In optic fundoscopic examination, bilateral papillary atrophy, diffuse narrowing in retinal arteries, and grade-1 hypertensive retinopathy were found. The patient has been suffering from blurred vision and polyuria. The diagnosis of diabetes insipidus was determined after a water deprivation test. Before water deprivation test plasma osmolality of the patient was 314 mosm/ kg and urine osmolality was 200 mosm/L. During the test tension arterial, urine volume, body weight, plasma and urine osmolality were measured. Water deprivation test was terminated at end of 6th hour, because of the fact that body weight falls by more than 3%. At the end of the test plasma osmolality was 319 mosm/ kg and urine osmolality was 205 mosm/L. Vasopressin levels was 1 pg/ml (reference range 0-14 pg/ml). Then, desmopressin acetate was administrated subcutaneously, after one-hour, urine osmolality increased to 325 mosm/L. As a result, patient was accepted as central type diabetes insipitus. Other basal hypophyseal hormone levels were within normal limits. In MRI of the patient the posterior pituitary bright spot, which is normally visualized by MRI, was absent in the patient. Urinary tract dilatation and bladder dysfunction are coexisting features of this syndrome (4). However no signs of urinary tract dilatation was revealed by ultrasonography. Diverse and serious psychiatric manifestations frequently have been observed in wolfram syndrome (1,5). But, our patient was found as normal by psychiatric evaluation. HLA-DR2 haplotype has been reported to be associated with wolfram syndrome. But, we could not studied HLA subgroups because of technical failure (6). Neurosensory hearing lost was found in odiometric examination of the patient. Other coexisting features of DIDMOAD syndrome, such as cerebellar atrophy, were not found. The patient's diabetes mellitus was not well controlled (glycosylated hemoglobin (HbA1c: 12.4 %) [Reference range, 4-6%]). Three-daily administration of regular insulin and bedtime NPH insulin were given for the treatment of diabetes mellitus. For the treatment of diabetes insipidus, Desmopressin acetate was given at the dose of 20 µg/day by nasal route. She was not ketosis prone.

Comment

We have identified a complete DIDMOAD syndrome. Wolfram syndrome (WS) is the inherited association of juvenile-onset insulin-dependent diabetes mellitus and progressive bilateral optic atrophy. The onset of diabetes mellitus was defined at she was 8 year old. Optic atrophy and deafness were determined relatively later when she was 16 year old. In general, DIDMOAD syndrome occurs in childhood or adolescence. This syndrome is inherited as autosomal recessive, implying that both the copies of the gene in any individual need to be defective to show the symptoms associated with this disease. It has also been noted that carriers of this syndrome, i.e. those who have only one defective copy of the gene, are estimated to represent 1% of the US population and are predisposed to psychiatric illness (1). A nuclear gene, WFS1/wolframin, was identified that segregated with disease status and demonstrated an autosomal recessive mode of inheritance. Mutation analysis of the WFS1 gene in WS patients has identified mutations in 90% of patients. Most were compound heterozygotes with private mutations distributed throughout the gene with no obvious hotspots. Mutation screening in patients with psychiatric disorders or diabetes mellitus has also been performed to test the hypothesis that heterozygous carriers of WFS1 gene mutations are at an increased risk following the observation that WS first-degree relatives have a higher frequency of these disorders. Most studies showed no association, however two missense mutations were identified that demonstrated significant association with psychiatric disorders and diabetes mellitus (7). WS can be differentiated from type 1 diabetes mellitus by a lack of serum autoimmune markers, such as antibodies to glutamic acid decarboxylase, and by higher morbidity and mortality rates than those of typical type1 diabetes. This patient had typical features of WS. The disease is believed to account for 1/150 patients with young-onset insulin-requiring

diabetes mellitus (1). Interestingly in our clinic we follow up almost 450 patients with type 1 diabetes mellitus per year but we determined a Wolfram syndrome at first time. Frequency of this syndrome may show ethnic difference. Baz (8) et al found 27 patients with WS in 589 type 1 diabetic patients. On the contrary in UK population syndrome is rare and its prevalence is estimated to be 1/770 000 people (9). As a result we can say that frequency of syndrome may show ethnic differences and may be rare in our region. In a study 4 novel mutations (1387delCTCT, S443I, 1519del16, and IVS6+16g->a) were identified (10). In addition, in this study were also found two new, probably neutral changes (A684V and R708C). The present case is unusual because in her family history there is no any subjects who suffer from Wolfram syndrome. There is no any familial linkage in our patient. Then this patient may be a result of a new mutation. Since we have not genetic technical support in terms of to determine mutations for WFS1 gene, we did not make any genetic study in our patient.

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