

WOLFRAM SYNDROME, CLINICAL AND GENETIC ASPECTS. CASE REPORT

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Keywords: Wolfram Syndrome, diabetes mellitus, optic atrophy, deafness, wolframin gene, CISD2 gene

Abstract: Wolfram's Syndrome (WS) is a genetic disorder that is frequently seen in affected individuals as juvenile onset diabetes and optic atrophy, along with diabetes insipidus and deafness. It affects one in 20 million people from the United States, about one in 770 000 inhabitants or 1 in 500 000 children in the United Kingdom. Wolfram's Syndrome, also called DIDMOAD (DI-diabetes insipidus, DM-diabetes mellitus, OA-optic atrophy, D- deafness) registered only 3 cases in Romania in the past 12 years. The purpose of this presentation is to reveal the diagnostic difficulties in a case of suspected DIDMOAD syndrome, no family history of WS, diabetes or deafness.

INTRODUCTION

Wolfram syndrome (WS) was first described in 1938, by Dr. Don J. Wolfram, who discovered that the disease affects the brain and central nervous system. More than 90 individuals from more than 60 families have been described worldwide.(1) It is a genetic disorder that is frequently seen in affected individuals as juvenile onset diabetes and optic atrophy, along with diabetes insipidus and deafness. It is very rare, so a consultant pediatrician may only see one affected child in a professional lifetime. Most patients with this progressive, neurodegenerative disorder eventually develop all four symptoms and die prematurely. Complications arise in this disease such as: ataxia, dementia/ mental retardation, deterioration in speech recognition, cardiomyopathy, other ophthalmologic findings, hypothyroidism, growth retardation, neurogenic bladder.(2)

Wolfram syndrome is an autosomal recessive disorder characterized by juvenile diabetes and neurodegeneration, and is considered a prototype of human endoplasmic reticulum (ER) disease.(3) Wolfram syndrome is caused by loss of function mutations of Wolfram syndrome 1 or Wolfram syndrome 2 genes, which encode transmembrane proteins localized to the ER. Identification of that gene could provide important information about several disorders, but the investigators are particularly excited about how it might affect the understanding and treatment of the more common forms of diabetes.(1,2,3,4) In terms of genetic aspects, three genetic forms have been described: Wolfram Syndrome 1- WFS1 gene is involved, on chromosome 4p16.1 Wolfram Syndrome 2- CISD2 gene is involved, on chromosome 4q24;

Mitochondrial Syndrome.

Wolfram syndrome 1 - The WS1 or wolframin gene provides instructions for making the wolframin protein. It is active in the cells throughout the body with strong activity in the heart, brain, inner ear and pancreas. In the pancreas, wolframin helps fold the proinsulin (a protein precursor of insulin) into the mature hormone that controls blood glucose level (the loss of wolframin disrupts the production of insulin which leads to poor glucose control and diabetes mellitus). Wolframin also maintains the correct cellular level of charged calcium ions by controlling how much is stored in endoplasmic reticulum.(5)

In the inner ear, wolframin may help maintaining the proper levels of calcium ions or other charged particles that are essential for hearing. Researchers have identified more than 100 WFS1 mutations that cause Wolfram syndrome. Some of these mutations delete or insert DNA from the WFS1 gene, so as a result little or no wolframin is present in cells. Other mutations replace one of the protein building blocks (amino acids) used to make wolframin with an incorrect amino acid. These mutations appear to reduce wolframin dramatically, but it is still unclear how WFS1 mutations lead to other features of Wolfram syndrome.(4) WFS1/wolframin was identified that segregated with disease status and demonstrated an autosomal recessive mode of inheritance.(3,6) Wolfram syndrome 2 is caused by mutation in the CISD2 gene, which encodes an endoplasmic reticulum intermembrane small protein. The protein encoded by this gene is a zinc finger protein that localizes to the endoplasmic reticulum.(7) The encoded protein binds an iron/sulfur cluster and may be involved in calcium homeostasis. There is no interaction between wolframin 1 and endoplasmic reticulum intermembrane small protein (ERIS) encoded by WFS2, the gene that causes WFS2.(8)

Mitochondrial form of Wolfram syndrome.

Researchers suggested that some cases of the syndrome of early-onset diabetes mellitus, optic atrophy and deafness may have their basis in a mitochondrial mutation. It was found that they carried the 11778 mitochondrial mutation, which is the most common cause of Leber hereditary optic neuropathy; so the DIDMOAD phenotype may have been the result of a combination of the 11778 mutation (inherited from the mother) with an as yet undetected mutation elsewhere in the mitochondrial genome or with a mutation in the nuclear genome (Hardy et al 1999). A mutation in a gene in the 4p16 region predisposes to multiple mitochondrial DNA deletions in families.

PURPOSE

The purpose of this presentation is to reveal the particularities of a case with juvenile diabetes, diabetic retinopathy and neurological abnormalities, as well the diagnostic difficulties in a case of suspected DIDMOAD syndrome, no family history of WS, diabetes or deafness.

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Article received on .08.10.2015 and accepted for publication on 27.11.2015
ACTA MEDICA TRANSILVANICA December 2015;20(4):35-37

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CASE REPORT

We present the case of a 13-year old Romanian girl who lives in urban environment. She was born from healthy, unrelated parents and the family history was negative. The patient's complains upon the admission in the Ophthalmology Pediatric Clinic of Sibiu were: blurred vision and decreased visual acuity. Personal history of the patient revealed that she was repeatedly hospitalized for fatigue, frequent urination, fruity breath, repeated urinary tract and loss of consciousness.

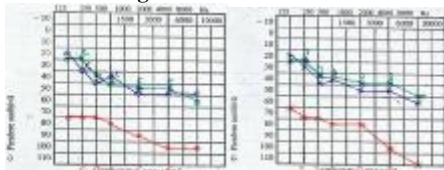
Figure no. 1. Patient, T.R., 9 years old



The biological samples have indicated high levels of blood sugar and the glucose tolerance test was positive. The girl was diagnosed with juvenile diabetes, onset at 9 years old, with dependence on exogenous insulin. In evolution she had accused vision problems. The ophthalmic examination evaluated visual acuity, colour vision, and visual fields and indicated a diabetic retinopathy. Other investigations were made in evolution:

- Audiologic examination: audiometry revealed a medium bilateral sensorineural high frequency hearing impairment (figure no. 1).

Figure no. 1. Audiologic evaluation



- Neuroimaging with magnetic resonance imaging scans showed reduced signal from the optic nerve.
- Baseline psychological assessment: developmental assessment in young children was normal; the assessment of cognitive abilities in late childhood were delayed.
- Neurologic examination: affected coordination of muscle movements.
- Test of the concentrating urine (to evaluate for diabetes insipidus) - normal.

Based on the medical history with early onset juveniles diabetes, vision disturbance, on the clinical findings with hearing loss, some lack of coordination of muscle movements the following diagnose was suspected: Wolfram's Syndrome type1. There was established insulin therapy, diet food and correcting refractive disorders. In evolution, education and lifestyle of the patient were influenced. Differential diagnosis had to exclude mitochondrial disorders as maternally congenital diabetes and deafness, autosomal optic atrophy, Leber optic neuropathy, Wolfram Syndrome type 2 (no diabetes insipidus), Alstrom syndrome and imposed genetic testing. In our case, molecular genetic analysis (performed with the support of Worldwide Society of Wolfram Syndrome Families) did not identify the wolframin gene mutations on chromosome 4p16.1. The family investigation did not reveal other cases with diabetes, deafness or neurological disorders. In this case, a mutation de novo was suspected and genetic investigation must continue. The therapeutic plan follows the multidisciplinary team assessment of this case: pediatrician, nutritionist, audiologist, ophthalmologist, physiotherapist, genetic and

psychological support to the patient and family. Patient management has included: the following initial diagnosis, treatment of manifestations, surveillance, testing of relatives at risk and genetic counseling. Unfortunately, there were no material conditions for continue testing the patient and the other family members, but these data require further efforts for molecular genetic testing.

DISCUSSIONS

Wolfram's syndrome comprises a group of genetic disorders that are characterized by a heterogeneous spectrum of clinical features. Wolfram's syndrome, also known as DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy and deafness), is a rare, autosomal recessive disorder of the central and peripheral nervous system. Multiple complications are associated with this disorder, but only optic atrophy and diabetes mellitus are compulsory for diagnosis. Optic atrophy usually develops in the first decade of life, but can be present as late as the age of 16-18. Other complications, such as renal outflow tracts and various neurological disorders, may develop later. Unfortunately, about 60% of patients with Wolfram's syndrome die by the age of 35. The genetic complexity of its molecular bases, new mutations that have been described and the variation of the clinical manifestations led to discussions regarding Wolfram's syndrome and Wolfram-like disease.(2)

Wolfram syndrome is inherited in an autosomal recessive manner. Individuals with typical Wolfram syndrome (WFS) who have apparently only one, and in some cases, de novo mutations have been reported [Hansen et al 2005]. Wolfram syndrome-like disease is inherited in an autosomal dominant manner.

Molecular Genetic Testing. Tests used: Sequence Analysis and a variety of methods including quantitative polymerase chain reaction (PCR), long-range PCR, multiplex ligation-dependent probe amplification (MLPA), or array CGH may be used for deletion/ duplication testing. GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information. Current research estimates that mutation analysis of the WFS1 gene in WS patients has identified mutations in 90% of patients.(4)

Genotype-Phenotype Correlations

Wolfram syndrome. The clinical course of WFS is highly variable, even within a family, and is not predictable from the type or location of the mutation. Cano et al. (2007) found that two WFS1 alleles, both with inactivating mutations, predisposed to an earlier age of onset of both diabetes mellitus and optic atrophy. Moreover, the clinical expression of WFS was more complete and occurred earlier in individuals harboring no missense mutation.(2,9)

Wolfram-like syndrome. Two families have been identified with WS-like features that are inherited in an autosomal dominant manner (Eiberg et al. 2006); in another family the same missense mutation was associated with co-segregation of hearing impairment and diabetes mellitus, but no optic atrophy (Valéro et al, 2008). Using combined linkage and candidate gene study, the research selected ALMS1, responsible for Alström syndrome, as a candidate gene.(10) They identified a novel splice mutation in intron 18 located 3 bp before the intron-exon junction (IVS18-3T>G), resulting in exon 19 skipping and consequent frameshift generating a truncated protein (V3958fs3964X in a Lebanese patient diagnosed with juvenile-onset insulin-dependent diabetes presenting

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ketoacidosis, early-onset retinopathy with optic atrophy, hearing loss, diabetes insipidus, epilepsy, and normal weight and stature, who later developed insulin resistance.(11) This observation broadens the clinical spectrum of Alström syndrome and suggests that ALMS1 mutations may be considered in patients who initially present with an acute onset of insulin-dependent diabetes.(10)

Genetic counselling. Genetic counselling may be of benefit for Wolfram syndrome patients and their families, by providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. Family genetic counselling grant allows the family to find out their risk of recurrence and attitude of family planning. A correct diagnosis is important for correct related genetic counselling issues: family planning and prenatal testing.

Risk to Family Members – for parents of a proband: A proband with WFS-like disease may have the disorder as the result of a new gene mutation. The proportion of cases caused by de novo mutations is unknown. If the disease-causing mutation found in the proband cannot be detected in the DNA of either parent, two possible explanations can be given: germline mosaicism in a parent or a de novo mutation in the proband. Although no instances of germline mosaicism have been documented, it remains a possibility, as there are reports of apparently de novo mutations in individuals with WFS. The family history may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. If the parent is the individual in whom the mutation first occurred, s/he may have somatic mosaicism for the mutation and may be mildly/minimally affected.(2) Recommendations for the evaluation of parents of a proband with an apparent de novo mutation include hearing evaluation, physical examination, and molecular genetic testing of WFS1 if the mutation has been identified in the proband. Evaluation of parents may determine that one is affected but has escaped previous diagnosis because of failure by health care professionals to recognize the syndrome and/or a milder phenotypic presentation. Therefore, an apparently negative family history cannot be confirmed until appropriate evaluations have been performed.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents. In our case, when the parents are clinically unaffected and neither has a WFS1 mutation, the risk to the sibs of a proband appears to be low. Attention: the sibs of a proband with clinically unaffected parents are still at increased risk (for the disorder) because of the possibility of reduced penetrance in a parent.

Family planning. The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy. It is appropriate to offer genetic counselling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant when the sensitivity of currently available testing is less than 100%. Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis or chorionic villus sampling (CVS). The disease-causing allele(s) of an affected family member must be

identified before prenatal testing can be performed.

CONCLUSIONS

- Juvenile Diabetes Mellitus and optic atrophy is the first sign that we should look for in Wolfram Syndrome.
- Molecular genetic analysis is useful for confirming the clinical signs and differential diagnosis.
- The genetic analysis of the WFS1 gene in WS patients has identified mutations in 90% of patients.
- Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions.

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