Brief Communication

Didmoad (Wolfram) Syndrome: Case Report

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Abstract

Wolfram syndrome, also known by the mnemonic DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy and deafness) is a rare progressive neurodegenerative disorder. This syndrome is further divided to WFS1 and WFS2 based on the different genetic molecular basis and clinical features. In this report, we described a known case of Wolfram syndrome requiring anesthesia for cochlear implantation. Moreover, a brief review of molecular genetics and anesthetic considerations are presented.

Keywords: Anesthesia, Cochlear Implantation, Wolfram Syndrome, Wolframin protein

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Introduction

Wolfram syndrome was first described by physician D J Wolfram and Wagener in 1938 (1-3). This autosomal recessive syndrome is also referred to as DIDMOAD syndrome, which stands for Diabetes Insipidus, Insulin Dependent Diabetes Mellitus, Optic Atrophy and Deafness (4). Wolfram is a progressive neurodegenerative disorder, mostly the first manifestation is diabetes mellitus at the age of 6 years and followed by optic atrophy at 11 years. Diabetes insipidus and deafness would arise at the second decade of life. Other manifestations could include atonic bladder, ureterohydronephrosis, myoclonus, ataxia, peripheral neuropathy, retinopathy, and cataract, neurologic dysfunction leading to sleep apnea, depression and psychotic features (1, 4). Life expectancy would vary between 25 and 49 years due to respiratory and renal failure (1, 2, 4). Its prevalence is about 1/100 000 in northern America, 1/770 000 in United Kingdom and 1/710 000 in Japanese population (1, 3, 5). Diabetes mellitus and optic atrophy occurs in all of patients. Prevalence of other symptoms are as follow: Hearing loss in 75%, Neuropsychiatric illness in 69%, Diabetes Insipidus in 55%, and renal tract involvement in 45% of patients (5).

There are two types of wolfram syndrome based on their genetic cause and clinical feature.

Wolfram syndrome type 1 is related to WFS1 Gene in the short arm of chromosome 4 (4p16). This gene spans 33.4kb of genomic DNA and consist of 8 exons (first one is non-coding, 2–7 are coding, and the 8th is 2.6kb long) that encodes an 890 amino acid polypeptide with 9 transmembrane domains and weight of 100kDa (1, 4). Wolframin protein is an endoglycosidase H-sensitive membrane glycoprotein forming a membrane Ca^{2+} channel in the endoplasmic reticulum that could protect neurons and islet β cells from premature cell death (1, 4).

Deficiency in Wolframin results in multisystem neurodegenerative process that cause atrophy of optic tracts, hypothalamus, and posterior pituitary and

cochlear nerve (2).

There are several mutations detected in this genome. All of them are located in exon 8, corresponding to the transmembrane region and carboxy tail of wolframin protein (1, 4).

Wolfram syndrome type 2 is caused by mutations in CISD2 gene located in 4q24. This gene encoded protein named ERIS (Endoplasmic Reticulum Intermembrane Small Protein). On the other hand as symptoms are restricted to energy consumptive cells, it is hypothesized that these genes could have effect on mitochondrial functions (6). This hypothesis has confirmed by studies on knockout mice (7).

In this type diabetes mellitus occurs in the first or second decade; afterwards, visual loss and optic atrophy developed in all patients. Sensorineural hearing loss could be presented afterwards. Other symptoms are urinary tract dilatation and depression and upper gastrointestinal ulceration and bleeding, but no diabetes insipidus is reported in this type (8).

In this study we present a Wolfram case that candidate for cochlear implantation, anesthetic implications and a review about geneticomolcular basis of this disease.

Brief Report

A 5-years old boy presented with history of progressive hearing loss of 3 years duration. He was adopted therefore no family history could be acquired. His past medical history was significant due to prior hyperglycemia during which he was found to be diabetic and had been on plain and Lente insulin since then. He was admitted once due to weakness with diagnosis of severe anemia during which he was transfused 1 unit of packed RBC. In these years he was under treatment with Vitamin B1 (Thiamine) and Vitamin B6 (Pyridoxine) and Vitamin B Complex under supervision of pediatric hematologist. Although from his second year of life he was using hearing aids and attended speech therapy, no significant progression was observed therefore he was candidate for cochlear implantation.

On physical examination his visual acuity was 9/10 in both eyes and esotropia in left eye. Other examinations were normal.

No Auditory Brain Response (ABR) waveforms or Distortion Product OtoAcoustic Emissions (DPOAE) were observed in audiometry of both ears.

All of his laboratory exams including Biochemistry, Complete Blood Count, and Coagulation studies were within normal range.

Midazolam 1mg/IV and Fentanyl 50µg/IV prescribed as premedication in the operating room. General anesthesia was induced with Propofol 2mg/kg and atracurium 0.5mg/kg. Anesthesia maintained with oxygen, nitrous oxide and Propofol 100 mcg/kg/min with standard monitoring in place. During 150 minutes of surgery to implant cochlea, his blood sugars measured each hour were within normal range. Meanwhile, he received 20cc/kg/hr of 0.9% sodium chloride solution and his urine output was preserved 2cc/kg/hr. At last atracurium reversed by neostigmine 0.05mg/kg and atropine 0.02mg/kg.

Discussion

Wolfram Syndrome can be diagnosed by Insulin Dependent Diabetes Mellitus and optic atrophy in the first two decades of life. This could be the simplest criteria for diagnosis of this syndrome (3, 9). Early diagnosis helps to initiate treatment sooner, therefore avoid serious complications like hyperglycemia, hypernatremia, and hyperosmolar coma (9). Unfortunately there has not been any documentation for treatment or prevention of neurodegeneration in these patients and there is no therapeutic intervention to expand their life expectancy (5, 9). However, early detection, accurate management, and prevention of complications with careful and repeated examinations of bulbar function may improve quality of life and survival of these patients(9).

Loss of islet cells in pancreas which results in insulin dependent diabetes mellitus, though to be resulted from deficiency in cellular stress response in the absence of wolframin (2).

Symptoms including deafness, blindness, diabetes insipidus, and psychotic features are due to neurodegenerative basis of this disease which is also related to wolframin and WFS1 gene (2). Hilton et al. (2) demonstrated that this disease resulted from cellular degeneration rather than developmental or congenital basis. Diffuse Neurodegeneration in

central nervous system could result in hypothyroidism, alteration in thermoregulation, and gonadal failure (9).

Death in these patients often results from brainstem atrophy, followed by hypoventilation and apneic episodes (9). On the other hand, degeneration of brainstem and lateral 2/3 of Substantia Nigra and cerebellum results in loss of protection of airway that leads to aspiration pneumonia. There are some reports that imply on correlation of this syndrome with sinus tachycardia, atrial or ventricular arrhythmias and congenital cardiac abnormalities like Tetralogy of Fallot or Pulmonary valve Stenosis (9).

Anesthetic management of this syndrome should focus on glucose control and fluid management of DI. As other uncommon neurodegenerative diseases, anesthesiologists should consider chronic use of anticonvulsant and alteration in anesthetics metabolism (10).

Conclusion

Although there has not been any documented treatment for wolfram syndrome, early detection and managing the complications could extend life expectancy of these patients. Further studies by addressing geneticomulecular basis, should aim at finding new agents which could interrupt the degeneration feature of this syndrome.

Anesthetic management of this syndrome should focus on glucose control and fluid management of DI. As other uncommon neurodegenerative diseases, anesthesiologists should consider chronic use of anticonvulsant and alteration in anesthetics metabolism (10).

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Conflicts of Interest

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript.

References

1. Eller P, Foger B, Gander R, Sauper T, Lechleitner M, Finkenstedt G, *et al.* Wolfram syndrome: a clinical and molecular genetic analysis. *Journal of medical genetics.* 2001;38(11):E37.

2. Hilson JB, Merchant SN, Adams JC, Joseph JT. Wolfram syndrome: a clinicopathologic correlation. *Acta neuropathologica.* 2009;118(3):415-28.

3. Barrett TG, Bundey SE. Wolfram (DIDMOAD) syndrome. *Journal of medical genetics.* 1997;34(10):838-41.

4. d'Annunzio G, Minuto N, D'Amato E, de Toni T, Lombardo F, Pasquali L, *et al.* Wolfram syndrome (diabetes insipidus, diabetes, optic atrophy, and deafness): clinical and genetic study. *Diabetes care.* 2008;31(9):1743-5.

5. Matsunaga K, Tanabe K, Inoue H, Okuya S, Ohta Y, Akiyama M, *et al.* Wolfram syndrome in the Japanese population; molecular analysis of WFS1 gene and characterization of clinical features. *PloS one.* 2014;9(9):e106906.

6. Kanki T, Klionsky DJ. Mitochondrial abnormalities drive cell death in Wolfram syndrome 2. *Cell research.* 2009;19(8):922-3.

7. Chen YF, Kao CH, Chen YT, Wang CH, Wu CY, Tsai CY, *et al.* Cisd2 deficiency drives premature aging and causes mitochondria-mediated defects in mice. *Genes & development.* 2009;23(10):1183-94.

8. El-Shanti H, Lidral AC, Jarrah N, Druhan L, Ajlouni K. Homozygosity mapping identifies an additional locus for Wolfram syndrome on chromosome 4q. *American journal of human genetics.* 2000;66(4):1229-36.

9. Fabbri LP, Nucera M, Grippo A, Menicucci A, De Feo ML, Becchi C, *et al.* Wolfram syndrome. How much could knowledge challenge the fate? A case report. *Medical science monitor : international medical journal of experimental and clinical research.* 2005;11(7):CS40-4.

10. Nashibi M, Tajbakhsh A, Safari F, Mottaghi.K. Anesthetic Consideration of Niemann- Pick Disease Type C. *J Cell Mol Anesth.* 2016;1(2):73-7.