Case Report: Wolfram to Alstrom: Analysis of a Diagnostic Error

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Abstract: Wolfram syndrome (DIDMOAD) and Alstrom syndrome are two rare, clinically similar diseases inherited in an autosomal recessive pattern. We report the case of a 19 year old male who presented with left upper abdominal mass and two episodes of high coloured urine. He was a diagnosed case of Wolfram syndrome and exhibited classical features such as juvenile onset diabetes mellitus, vision difficulties and hearing loss. The patient’s new symptoms were irreconcilable with the previous diagnosis and after a thorough workup, the diagnosis was revised to Alstrom syndrome. In this paper, we hope to explore the challenges faced in making a clinical diagnosis of this syndrome in a step by step analysis of the path to rectifying a misdiagnosis. This disease is often not identified due to its rarity, lack of information on the natural history and presentation of the disease and financial constraints of the patient. We also aim to highlight the lack of accessible diagnosis and management infrastructure for people with rare diseases.

Key Words: Wolfram Syndrome, Alstrom Syndrome, DIDMOAD, Diabetes Mellitus

Introduction:
Wolfram Syndrome or DIDMOAD is a very rare, autosomal recessive disease with a prevalence of 1 in 100,000-700,000 depending on the clinical features[1]. It is characterized by diabetes insipidus(DI), juvenile onset Type 1 diabetes mellitus (DM), optic atrophy(OA), deafness(D). It is caused by mutations in WSF1 or WSF2 gene. Type 1 DM and optic atrophy are sufficient for diagnosis[2].

Alstrom Syndrome is an autosomal recessive disorder characterized by type 2 diabetes mellitus, cone-rod atrophy and hearing loss. This is caused due to a mutation in the ALMS1 gene on chromosome 2p 13 which codes for a ciliary protein[3]. This leads to multi organ pathologies due to ciliopathy.

Ciliopathy in Alstrom syndrome also makes its symptoms similar to Bardet-Biedl syndrome, which is caused due to a mutation in BBS gene, and presents later in life. The EURO-WABB (Wolfram, Alstrom, Bardet-Biedl) Project was started to document these cases to study their natural history and to prevent misdiagnosis and mismanagement[4].

Case Report
A 19 year old male, known case of Wolfram Syndrome was referred to the hospital with a mass in the left upper quadrant of the abdomen which appeared insidiously and progressively increased in size over 3 months. He also reported two episodes of dark colored urine starting two days before admission to the hospital.

Past history revealed that the patient had had delays in reaching developmental milestones in gross motor, personal-social and language domains. He was evaluated for hearing deficits at age 3 and was diagnosed with sensorineural hearing loss after a brainstem evoked response audiometry (BERA) test. Around the same age he also started to have vision problems for which he was not evaluated. At age 13 he was diagnosed with Type 1 diabetes mellitus (DM) and started on insulin therapy which he continued for the last 5 years. During the same visit, in light of his vision and hearing loss, coupled with Type 1 DM, a diagnosis of Wolfram Syndrome was made. At age 19, the patient presented to a clinic with his current symptoms and was subsequently referred to our hospital.

On examination, he was found to have gross splenomegaly, spleen was felt 16 cm below the costal margin, soft and non-tender. Cardiovascular examination was unremarkable except for the presence of a loud P2 heart sound. The patient was of short stature (149cm) and weighed 49 kg putting his BMI in the normal range (22.07). His head circumference was lower than normal (48.5cm). Fundoscopy revealed diffuse retinal pigment epithelial (RPE) atrophy and attenuation of retinal vasculature.

Blood investigations showed low hemoglobin (5.3g/dL) and hematocrit (18%), decreased RBC indices and increased red cell distribution width, low platelet count (3.2x10^11/microliter), low total WBC count (2.8x10^9/microliter). In addition the patient had high fasting blood glucose (362g/dL) and HbA1c (9.1%), hypertriglycerideremia (319mg/dL) and elevated total and direct bilirubin levels. Urine examination showed glycosuria. Ultrasonography revealed chronic hepatic parenchymal changes and features of portal hypertension with dilated splenic vein (13mm) and gross splenomegaly (21cm along the anteroposterior axis). Chest X-Ray (Fig.1) showed...
prominent main pulmonary artery, loss of pulmonary conus and biatrial enlargement as evidenced by the double contour within the right atrial shadow. Cardiac apex is round and elevated above the diaphragm suggesting right ventricular hypertrophy.

The clinical evidence of ineffective glycemic control with insulin, dyslipidemia and multiorgan involvement led to revision of the diagnosis to Alström syndrome.

**Discussion**

Overlap in the clinical presentation of these two syndromes reveals important challenges in the diagnosis of rare diseases. DM is a feature of both conditions but early age of presentation led to the patient being misdiagnosed with Type 1 DM. This along with loss of vision and sensorineural hearing loss led to the diagnosis of Wolfram Syndrome without confirmatory genetic testing due to lack of resources. But when patient presented at age 19, with uncontrolled diabetes despite five years of insulin therapy, the diagnostic error was identified and corrected. The treatment plan was revised for Type 2 DM by adding oral hypoglycemics as well as rapid acting insulin after which blood glucose levels were controlled [5]. Clinical evidence for insulin resistance such as acanthosis nigricans is usually the key to detecting Type 2 DM in juvenile presentation[6]. Therefore, in young children presenting with syndromic features and symptoms of diabetes, it is important to perform a thorough clinical examination to avoid mismanagement. Sensorineural hearing loss is also seen in both conditions, and apart from subtle differences in age of presentation, does not aid in differentiation. Similarly, growth retardation and developmental delay are features of both Alström and Wolfram syndrome and cannot be used in this case to support one diagnosis over the other. Vision loss in this patient due to retinal pigment epithelium atrophy more closely resembles the cone-rod atrophy found in Alström syndrome than the optic atrophy characteristic of Wolfram. Childhood truncal obesity is a characteristic feature of Alström syndrome which was absent in this patient. This could be explained by the presence of uncontrolled Type 2 DM leading to weight loss. Juvenile hypertriglyceridemia is a characteristic feature of Alström syndrome. The patient was advised a low fat diet and prescribed statins in order to reduce triglyceride levels and prevent further complications like pancreatitis. Liver parenchymal coarsening on USG is caused due to ciliopathic effect of mutation in the ALSM1 gene which in turn leads to features of portal hypertension. Splenomegaly results from portal hypertension leading to hypersplenism. This explains the low platelet and red cell counts. Iron supplementation was initiated as he had low serum iron, ferritin and TIBC. Splenectomy was advised after surgical consultation, but the patient was not willing to undergo surgery. Loud P2 heart sound and chest X-ray findings are due to pulmonary hypertension caused by lung fibrosis ultimately leading to right ventricular hypertrophy. This is a serious complication which could not have been predicted with the diagnosis of Wolfram syndrome and has therefore increased morbidity in this patient. Dilated cardiomyopathy is another feared complication of Alström syndrome and it is important to be on the lookout for impaired cardiac function in long term care.

In further management, renal involvement was ruled out; abdominal ultrasound showed normal kidneys and renal function tests were within normal limits. Genetic testing was advised to confirm diagnosis which the patient declined due to financial constraints.

**Conclusion**

The only way to definitively diagnose Wolfram or Alström syndrome is through gene testing. There are few medical centers in India that offer such facilities and many patients are unable to afford these tests. This case is an eye opener regarding the dearth of affordable diagnostic resources for rare genetic diseases, therefore it is important that we focus on diagnosing such conditions by correctly interpreting the clinical features. The diagnosis of Type 2 diabetes in the paediatric age-group was a particularly tricky aspect of the case. Even though the management of such diseases is primarily dependent on monitoring and treating the symptoms as and when they present [7], gene testing and a definitive diagnosis will help us predict the inheritance of the disease in future generations leading to early diagnosis and treatment and a better quality of life for the patient.

**Conflict of Interest:** None

**References**