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A Rare Case of Wolfram Syndrome Presenting With Tuberculous Meningitis: A Case Report

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ABSTRACT

Wolfram syndrome is an extremely rare condition composed of a tetrad of diabetes insipidus, diabetes mellitus, optic atrophy, and deafness. When concurrently presenting with another condition, such as tuberculous meningitis, the widespread range of resulting symptoms delays the establishment of diagnosis and treatment, which results in increased patient morbidity.

1 | Introduction

Wolfram syndrome is a rare autosomal recessive neurodegenerative disorder with about 160,000–770,000 cases worldwide. In 1938, Wolfram and Wegner discovered it in four siblings who presented with complaints of juvenile-onset diabetes mellitus and optic atrophy. These are the two most common complaints in Wolfram syndrome patients [1].

It is also known as DIDMOAD syndrome, a tetrad of diabetes insipidus (DI), diabetes mellitus (DM), optic atrophy(OA), and deafness(D). Many other abnormalities occur in association with Wolfram syndrome. These include urinary tract abnormalities, atonic bladder, and renal functional changes. Neurological abnormalities like cerebellar ataxia, brainstem dysfunction, and epilepsy occur in Wolfram patients [1].

Previous studies have shown that fluctuating glucose levels and poorly controlled diabetes mellitus lead to increased oxidative stress and increased production of reactive oxygen species, which adversely affect neurocognitive functions [2].

Tuberculous meningitis is the most lethal form of tuberculosis and affects approximately 100,000 people worldwide [3]. Immunosuppression due to diabetes mellitus increases the risk of tuberculous infections in endemic regions such as Pakistan [4]. Tuberculous meningitis and Wolfram syndrome tend to present with overlapping neurological complications, such as neurocognitive deficits, cranial nerve palsies, and seizures [5]. Early diagnosis and treatment of tuberculous meningitis are necessary as delayed diagnosis and lack of a multidisciplinary approach in treatment of tuberculous meningitis lead to high morbidity and high mortality [6].

This case report aims to examine the co-occurrence of Wolfram syndrome and tuberculous meningitis, highlighting the diagnostic and therapeutic challenges involved in managing these two complex conditions.

2 | Case History/Examination

A 17-year-old male, a known case of type 1 diabetes mellitus for 6 years (poorly controlled), presented to the neurology ward with complaints of progressive bilateral vision loss for 4 years; progressive bilateral hearing loss for 3 years; and walking difficulty, confusion, and headache for 2 months. He was born full term, and there were no complications during or after birth. He had no developmental delays. He was the only affected child of nonconsanguineous parents. His other two siblings were normal. His father had tuberculosis and was getting treated with ATT (anti-tuberculous therapy).

The patient was first diagnosed with DM 6 years ago when he had recurrent UTI (urinary tract infections) along with polydipsia and polyuria. Urine examination was done, and it showed glycosuria and proteinuria along with pus cells. HBA1c was 10.8 at that time.

Patient had progressive vision loss in both eyes for 4 years. Examination showed the patient had complete vision loss in both eyes with no light perception bilaterally. Pupils were mid dilated, and direct and indirect reflexes were absent. Pupils reacted to miotic and mydriatic drugs. Fundoscopy showed a pale optic disk (Figure 1A,B). There was optic nerve thinning on MRI scan of the orbit. The patient had complete vision loss, and B-scan (Figure 1C,D) was done as a part of the assessment to rule out other causes of complete vision loss, such as retinal detachment and vitreous hemorrhage, as the patient was diabetic.

The patient had progressive bilateral hearing loss for 3 years. Eventually, he became unresponsive to verbal commands. Hence, the Rinne test was done, and it showed AC (air conduction) was more than BC (bone conduction) in both ears, while Weber test was not lateralized to either side. Audiometry was done, and it showed moderate to severe bilateral sensorineural hearing loss. Tympanometry showed a type A tympanogram.

Patient had difficulty walking and holding objects for 2 months. He also had complaints of frequent headaches and confusion. By the time he presented to the ward, he was unable to hold his limbs against gravity. On examination, he had poor speech, conjugated gaze movements, and delayed processing of information. Tone and bulk were normal. Power was 3/5 in all limbs. He had generalized hyperreflexia. He had positive clonus, a positive Hoffmann sign, and upgoing plantars bilaterally. Mild nuchal rigidity was present, and the Kernig's sign was positive. Lumbar puncture was done, which showed a turbid appearance of the CSF. CSF analysis demonstrated the picture of tuberculous meningitis in the patient. Genexpert for MTB was consistent with TBM.

The patient had no meningitic or paralytic symptoms until 2 months ago, when his father developed pulmonary tuberculosis, and this made him susceptible to TBM. This was further supported by a CT scan of the brain, which was normal with no findings 2 years ago.

3 | Methods (Differential Diagnosis, Investigations and Treatment)

24-h urine volume osmolality was measured to rule out vasopressin deficiency (central diabetes insipidus). 24-h urine volume was 1200 mL, with a urine osmolality of 720 mOsm/Kg and a plasma osmolality of 288 mOsm/Kg.

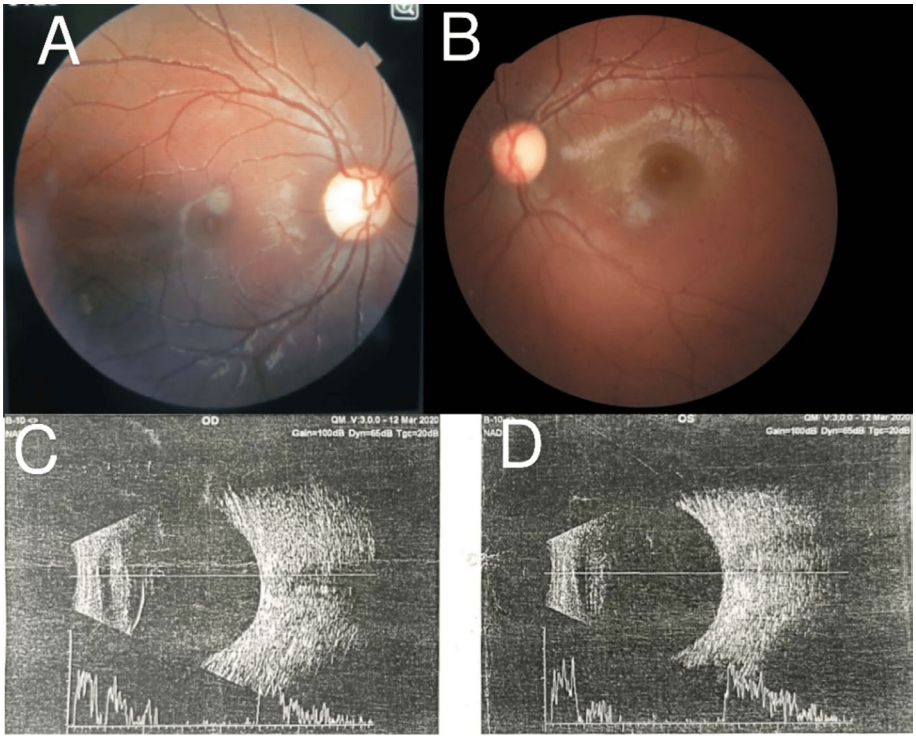

FIGURE 1 | (A, B) Fundoscopy findings of the patient supporting optic atrophy. (C, D) B-scan ruling out any other cause of vision loss, such as retinal detachment and vitreous hemorrhage.

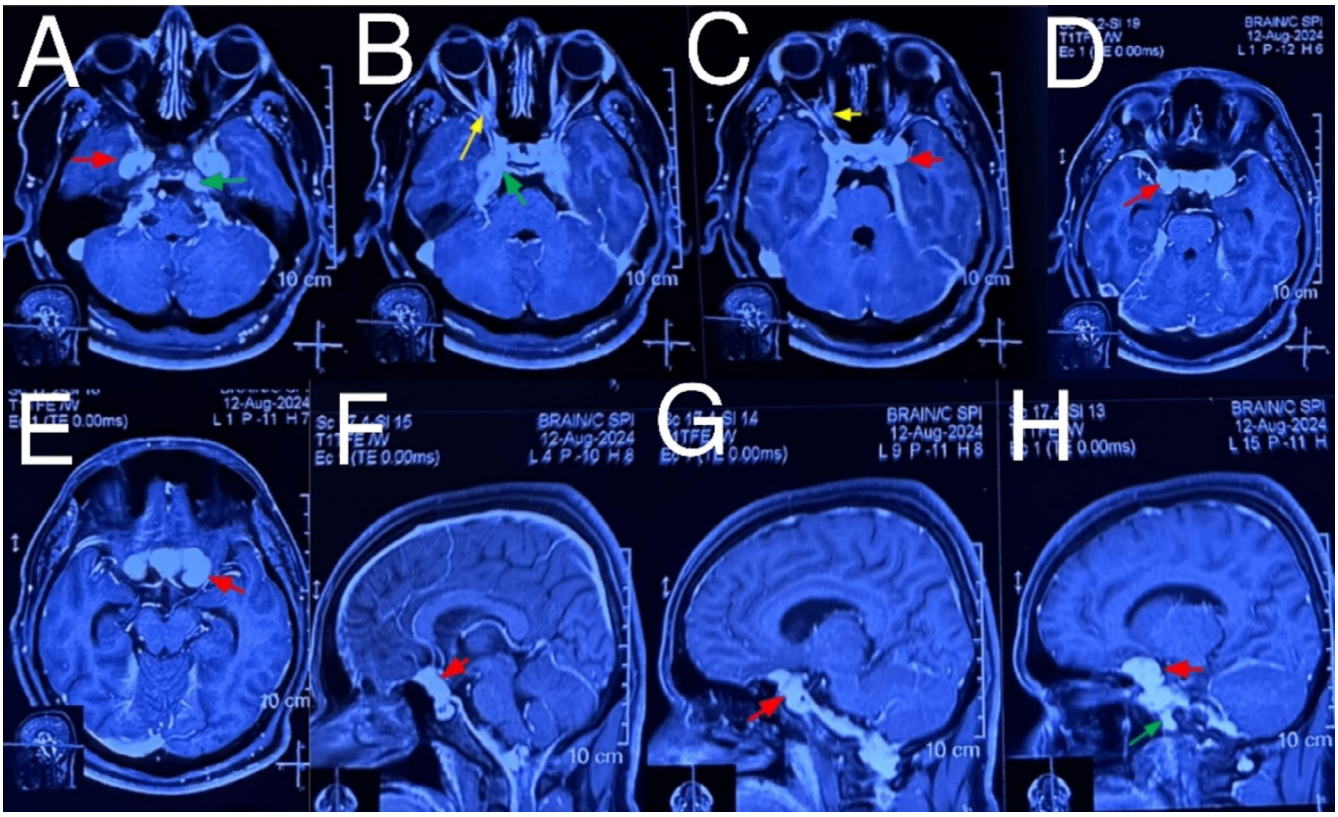

FIGURE 2 | (A–E) (axial post-contrasT1W) and (F–H) (sagittal post-contrast T1W) images showing significant nodular leptomeningeal thickening and enhancement along the base of the skull (red arrows) forming confluent nodular masses, encasing the optic nerve sheaths (yellow arrow), involving multiple cranial nerve complexes, and extending into the carotid canals bilaterally (green arrows).

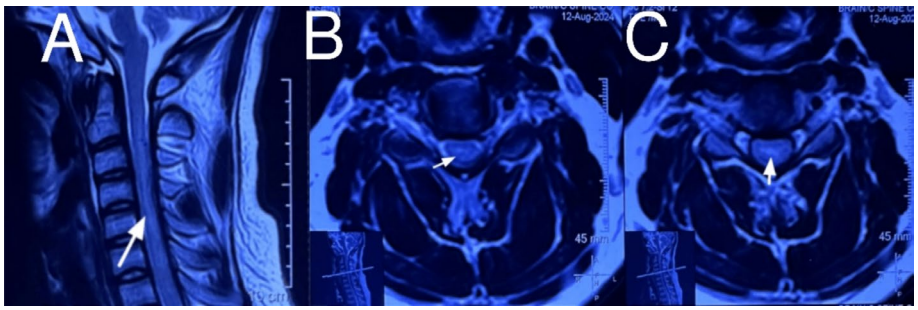

FIGURE 3 | MRI cervical spine: A (mid-sagittal T2W) and B,C (axial T2W) showing diffuse signal changes (T2 hyperintensities) in the visualized cervical spinal cord (white arrows).

For further evaluation, MRI of the brain (Figure 2A–E (axial post-contrast T1W) and 2F–H (sagittal post-contrast T1W)) and of the spinal cord (Figure 3A (midsagittal T2W) and 3B,C (axial T2W)) was done. MRI displayed significant nodular thickening of the leptomeninges in the entire visualized cervical spine, insinuating along the skull base and forming large, confluent nodular masses in the frontal region. These masses completely encased the optic nerve and extended along the optic nerve sheaths into the orbit. Mild leptomeningeal thickening was seen in the brain without significant parenchymal changes. Suspicion of sarcoidosis was ruled out as serum ACE levels, serum calcium, and HRCT chest findings were normal. HIV serology was also negative.

Other laboratory investigations, including ultrasound of the abdomen and kidney, ureter, and bladder, and renal function tests, were normal.

Differential diagnoses include leber hereditary optic neuropathy, thiamine-responsive anemia with DM and SNHL, Friedreich ataxia, and Alstrom syndrome. The latter was ruled out by a normal echocardiography report.

During hospital stay, the patient was given 1 g of methylprednisolone for 5 days, along with insulin therapy to maintain strict glucose control. He was given ATT, proton pump inhibitors, and

other broad-spectrum antibiotics to prevent hospital-acquired infections.

4 | Conclusions and Results (Outcome and Follow-Up)

After the treatment of TBM was started, the patient showed improvement in terms of the frequency and intensity of headache, cognition, and weakness. Power was 4/5 in upper limbs, 4/5 in lower limbs, and deep tendon reflexes were 2+ in 2–3 weeks. No improvement was seen in his vision or hearing, even after being treated for TBM.

His consciousness level improved, and he was able to move his limbs against slight resistance. The patient was discharged with a 9-month course of ATT and insulin therapy. A digital hearing aid was advised. His family was counseled about the patient's diagnosis and prognosis.

5 | Discussion

Wolfram syndrome, also known as DIDMOAD (diabetes Insipidus, diabetes mellitus, optic atrophy, and deafness) syndrome, is a rare autosomal recessive disorder characterized by juvenile-onset insulin-dependent diabetes and progressive vision loss due to optic nerve atrophy [7].

Wolfram syndrome is primarily associated with mutations in the WFS1 or CISD2 genes [8, 9]. The primary form, WS1, is caused by mutations in the WFS1 gene located on chromosome 4p, encoding wolframin, a protein involved in endoplasmic reticulum (ER) function [7]. WS2 is caused by mutations in the CISD2 gene and is differentiated from WS1 by the presence of bleeding, upper intestinal ulcers, and defective platelet aggregation, and it does not include diabetes insipidus or psychiatric conditions [1, 10].

Wolfram syndrome is often diagnosed through a patient's history and clinical signs, such as optic nerve atrophy following early-onset diabetes mellitus [1]. Genetic testing, especially Sanger sequencing of the WFS1 gene, can be used to confirm the diagnosis of Wolfram syndrome by identifying WFS1 as the main mutated locus in most patients [8].

The diagnosis of TB meningitis in a patient with Wolfram syndrome (WS) can be difficult due to overlapping neurological symptoms, such as optic atrophy, hearing loss, and cognitive decline, complicating the distinction between WS progression and a superimposed TB infection. Diagnosing TB meningitis in a laboratory setting is similarly difficult. The diagnosis is confirmed by detecting *Mycobacterium tuberculosis* (MTB) in the cerebrospinal fluid (CSF) [11]. While MTB culture provides definitive confirmation, it has variable sensitivity, and results take 6–8 weeks. PCR testing also offers high specificity but has lower sensitivity, while smear microscopy is quick and has very low sensitivity [11]. CSF analysis shows lymphocytic pleocytosis, increased protein levels, and decreased glucose levels in TB meningitis (TBM). Distinguishing TBM from viral meningitis remains difficult due to their similar CSF findings [12].

A thorough treatment plan is essential for effectively managing the diverse symptoms of Wolfram syndrome. Management of WS involves regular assessments of neurological, renal, and bladder functions, with treatment including anticholinergic medications, intermittent catheterization, and hearing aids or cochlear implants [1]. Effective control of diabetes mellitus and insipidus, along with careful monitoring for hyponatremia, is essential [1]. Treatment for tuberculous (TB) meningitis in a patient with WS is complicated by the possibility of therapeutic interactions and side effects, such as exacerbated hyperglycemia from corticosteroids and worsened visual neuropathy from ethambutol. The complex interactions between TB treatment and WS symptoms make overall management especially difficult.

Given the severity of both illnesses, patients with both Wolfram syndrome and TB meningitis typically have a poor prognosis. Tuberculous meningitis (TBM) is the most lethal form of *Mycobacterium tuberculosis* (MTB) infection, with a mortality rate of 20% to 67% even with treatment [11]. The patient's neurological state at the time of diagnosis and the quick initiation of anti-tuberculous medication play a major role in the outcome of TBM [13]. The prognosis for WS is already poor; the majority of patients die prematurely from severe neurological complications such as respiratory failure brought on by brainstem atrophy, with a median age of death of about 30 years [14]. The prognosis is further complicated by the combination of WS and TBM, which increases the chance of fatal consequences and makes management exceedingly difficult.

In summary, the co-occurrence of TB meningitis with Wolfram syndrome presents a difficult clinical situation with serious consequences for diagnosis, treatment, and prognosis.

6 | Conclusion

This case illustrates a rare manifestation of Wolfram syndrome in combination with tuberculous meningitis (TBM), occurring secondary to poorly controlled juvenile type 1 diabetes mellitus. The progressive nature of the vision and hearing loss and neurological deficits that characterize Wolfram syndrome emphasize the multisystem involvement of this syndrome. Such patients are highly susceptible to opportunistic infections, since TBM develops concurrently with household exposure.

Timely diagnosis and initiation of anti-tuberculous therapy (ATT) were associated with significant improvement in neurological symptoms, but vision and hearing impairments were irreversible, analogous to the requirement for early diagnosis and treatment for Wolfram syndrome and TBM. The case calls for multidisciplinary management of complex cases with combinations of genetic disorders and infectious diseases and monitoring for complications in patients with chronic diseases.

Author Contributions

Nabiha Khan: conceptualization, data curation, investigation, methodology, project administration, visualization, writing – original draft. **Muhammad Usama Ashraf:** formal analysis, project administration, resources, validation, writing – original draft. **Sadia Khan:**

conceptualization, methodology, project administration, validation, visualization, writing – original draft. **Allahdad Khan:** conceptualization, methodology, project administration, visualization, writing – original draft, writing – review and editing. **Humna Shahzad:** conceptualization, data curation, formal analysis, project administration, writing – original draft. **Mudasira Habib:** conceptualization, data curation, investigation, project administration, writing – original draft. **Aseel Kamal:** project administration, software, validation, visualization, writing – original draft.

Consent

Written consent was obtained from the father of the patient.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data available on request from the authors.

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