Abstract: We report here a 15 year old female patient, known case of type-1 Diabetes Mellitus on insulin for the past 5 years, admitted in our hospital with complaints of reducing visual acuity and increased frequency of micturition. Further evaluation revealed her to be a case of Wolfram Syndrome.

Keyword: Diabetes Mellitus, Diabetes Insipidus, Deafness, Optic Atrophy

CASE REPORT:

PATIENT'S PHOTO

A 15 year old girl Sheela from Paramakudi, Ramnad dist., Tamilnadu, a known case of type-1 Diabetes Mellitus since the age of 10 years, who was on insulin treatment, was admitted in our hospital with complaints of blurring of vision which was progressively increasing, increased frequency of micturition associated with increased thirst for the past 3 years, with no complaints of any difficulty in hearing.

She was the second child of a second degree consanguineous marriage and there were no history of any peripartum complications. Developmental milestones were achieved normally. No history similar illness in siblings and her parents were non-Diabetics.

On physical examination, she was conscious, oriented, moderately built and poorly nourished with Ht- 142cms, Wt-28kgs and BMI-13.88kg/m2. Pallor was present, no icterus or cyanosis, no clubbing, no lymphadenopathy or pedal edema. Vitals were normal.

On CNS examination, her higher mental functions were normal. Her best-corrected visual acuity was 6/36 in both eyes, colour vision was defective in both eyes, bilateral fundus showing features of primary optic atrophy with chalky white disc and nerve fibre loss. On testing 8th cranial nerve showed features of bilateral sensorineural hearing loss with Rinne’s test positive in both ears, Weber’s test showed no lateralization and absolute bone conduction test.
revealed decreased bone conduction bilaterally compared to examiner. Other cranial nerves were normal. Rest of the CNS systems were within normal limits. Examination of other systems were within normal limits.

**Work Up:**
- **Hb:** 11.4 gm%
- **Urine:** Alb (+), Sugar (+++), Deposits: 2-4 pus cells/Hpf
- **RBS:** 479 mg%, **Bl. Urea:** 30 mg%, **S. Creatinine:** 1.1 mg%
- **FBS:** 215 mg%, **PPBS:** 479 mg%
- **S. Electrolytes-** Na+: 145 meq/L, K+: 3.8 meq/L, Cl-: 102 meq/L
- **ECG:** Normal
- **Chest X-Ray:** Normal
- **USG Abd & pelvis:** Normal study
- **USG Thyroid:** Normal.
- **FSTH & L & S.prolactin levels** were within normal limits.
- **FSH:** 5.28 μIU/ml, **LH:** 3.2 μIU/ml, **S.Prolactin:** 7.6 ng/ml
- **Thyroid profile:** Normal.
- **Free T3:** 106 μg/dl, **Free T4:** 8.6 μg/dl, **TSH:** 0.8 μIU/ml
- **Urine Sp. Gravity (Done after glycemic control):** 1010
- **Water deprivation test (Done after glycemic control):**

<table>
<thead>
<tr>
<th>Time</th>
<th>Volume of urine</th>
<th>Urine Sp. Gravity</th>
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<tbody>
<tr>
<td>9.00 am</td>
<td>60 ml</td>
<td>1010</td>
</tr>
<tr>
<td>10.00 am</td>
<td>100 ml</td>
<td>1010</td>
</tr>
<tr>
<td>11.00 am</td>
<td>100 ml</td>
<td>1010</td>
</tr>
<tr>
<td>12.00 noon</td>
<td>100 ml</td>
<td>1012</td>
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**Result:** Persistent low specific gravity inspite of water deprivation suggestive of Diabetes Insipidus.

**MRI BRAIN SHOWS** Anterior pituitary(double arrows in Figure) measures about 5.9 X 6.8 mm.

Posterior pituitary T1 bright spot not identified in sellar region or hypothalamus.

Infundibulum(single arrow head in Figure) - thin. Optic nerve, optic chiasma, optic tract(single arrow in Figure) are thinned out.

Thus, with the presence of Type-1 Diabetes Mellitus, diabetes insipidus, optic atrophy and sensorineural deafness in our patient, the diagnosis of Wolfram(DIDMOAD) syndrome was made, treated symptomatically, blood sugar controlled with proper dose adjustment of insulin and discharged. Now she is under follow up.

**DISCUSSION:**
Wolfram syndrome is a condition that affects many of the body's systems. The hallmark features of Wolfram syndrome are high blood sugar levels resulting from a shortage of the hormone insulin (diabetes mellitus) and progressive vision loss due to degeneration of the nerves that carry information from the eyes to the brain (optic atrophy). People with Wolfram syndrome often also have pituitary gland dysfunction that results in the excretion of excessive amounts of urine (diabetes insipidus), hearing loss caused by changes in the inner ear (sensorineural deafness), urinary tract problems, reduced amounts of the sex hormone testosterone in males (hypogonadism), or neurological or psychiatric disorders. Diabetes mellitus is typically the first symptom of Wolfram syndrome, usually diagnosed around age 6. Nearly everyone with Wolfram syndrome who develops diabetes mellitus requires insulin replacement therapy. Optic atrophy is often the next symptom to appear, usually around age 11. The first signs of optic atrophy are loss of color vision and peripheral (side) vision. Over time, the vision problems get worse, and people with optic atrophy are usually blind within approximately 8 years after signs of optic atrophy first begin. In diabetes insipidus, the pituitary gland does not function normally. This abnormality disrupts the release of vasopressin. Approximately 70 percent of people with Wolfram syndrome have diabetes insipidus. Pituitary gland dysfunction can also cause hypogonadism in males. The lack of testosterone that occurs with hypogonadism affects growth and sexual development. About 65 percent of people with Wolfram syndrome have sensorineural deafness that can range in severity from deafness beginning at birth to mild hearing loss beginning in adolescence that worsens over time. Sixty to 90 percent of people with Wolfram syndrome have a urinary tract problem. Urinary tract problems include obstruction of ureters, a large bladder that cannot empty normally (high-capacity atomic bladder), bladder sphincter dyssynergia, & incontinence. About 60 percent of people with Wolfram syndrome develop a neurological or psychiatric disorder, most commonly ataxia, typically beginning in early adulthood. Other neurological problems experienced by people with Wolfram syndrome include irregular breathing caused by the brain's inability to control breathing (central apnea), loss of the sense of smell, loss of the gag reflex, myoclonus, seizures, peripheral neuropathy, and intellectual impairment. Psychiatric disorders associated with Wolfram syndrome include psychosis, episodes of severe depression, and impulsive and aggressive behavior. There are two types of Wolfram syndrome with many overlapping features. The two types are differentiated by their genetic cause. In addition to the usual features of Wolfram syndrome, individuals with Wolfram syndrome type 2 have gastric or intestinal ulcers and abnormal gastrointestinal bleeding. People with Wolfram syndrome type 2 do not develop diabetes insipidus. The estimated prevalence of Wolfram syndrome type 1 is 1 in 500,000 people worldwide. Approximately 200 cases have been described in the scientific literature. Only a few families from Jordan have been found to have Wolfram syndrome type 2. Mutations in the WFS1 gene cause more than 90 percent of Wolfram syndrome type 1 cases. This gene encodes for a protein called wolframin that is thought to regulate the amount of calcium in cells. A proper calcium balance is important for many different cellular functions, including cell-to-cell communication, contraction of muscles, and protein processing. The wolframin protein is found in many different tissues, such as the pancreas, brain, heart, bones, muscles, lung, liver, and kidneys. Within cells, wolframin is located in the membrane of endoplasmic reticulum that is involved in protein production, processing, and transport. Wolframin’s function is important in the pancreas for the conversion of proinsulin to insulin.
A certain mutation in the CISD2 gene was found to cause Wolfram syndrome type 2. The CISD2 gene provides instructions for outer membrane of mitochondria. The exact function of the CISD2 protein is unknown, but it is thought to help keep mitochondria functioning normally.

The CISD2 gene mutation that causes Wolfram syndrome type 2 results in an abnormality small, nonfunctional CISD2 protein. As a result, mitochondria are not properly maintained, and they eventually break down. Since the mitochondria provide energy to cells, the loss of mitochondria results in decreased energy for cells. Cells that do not have enough energy to function will eventually die. Cells with high energy demands such as nerve cells in the brain, eye, or gastrointestinal tract are most susceptible to cell death due to reduced energy. It is unknown why people with CISD2 gene mutations have ulcers and bleeding problems in addition to the usual Wolfram syndrome features.

Some people with Wolfram syndrome do not have an identified mutation in either the WFS1 or CISD2 gene. The cause of the condition in these individuals is unknown.

When Wolfram syndrome is caused by mutations in the WFS1 gene, it is inherited as autosomal recessive pattern. Some studies have shown that people who carry one copy of a WFS1 gene mutation are at increased risk of developing individual features of Wolfram syndrome or related features, such as type 2 diabetes, hearing loss, or psychiatric illness. However, other studies have found no increased risk in these individuals.

Wolfram syndrome caused by mutations in the CISD2 gene is also inherited in an autosomal recessive pattern. As age advances, impaired sexual development, central nervous system complication such as nystagmus, ataxia, startle myoclonus, seizure disorders, mental health disorders and digestive problems are likely to appear and are not identified till now in our patient and hence to be screened periodically.

The median age of death in these patients according to Kinsley is 28 yrs and 60% of the people with Wolfram syndrome die at age 35. Death can be caused by respiratory centre failure following brain stem atrophy, complications related to urinary tract atony, bulbar dysfunction (aspirations) and in some cases suicide secondary to depression.

There has been no treatment to reverse the under lying mechanism of neuro degeneration in persons with WFS and all cases reported till now have progressed to one or more of the above discussed lifethreatening complications and premature death.

REFERENCES:
