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Wolfram Syndrome Clinical Guidelines

1. Diagnosis by genetic testing (WES or WGS-based panels)

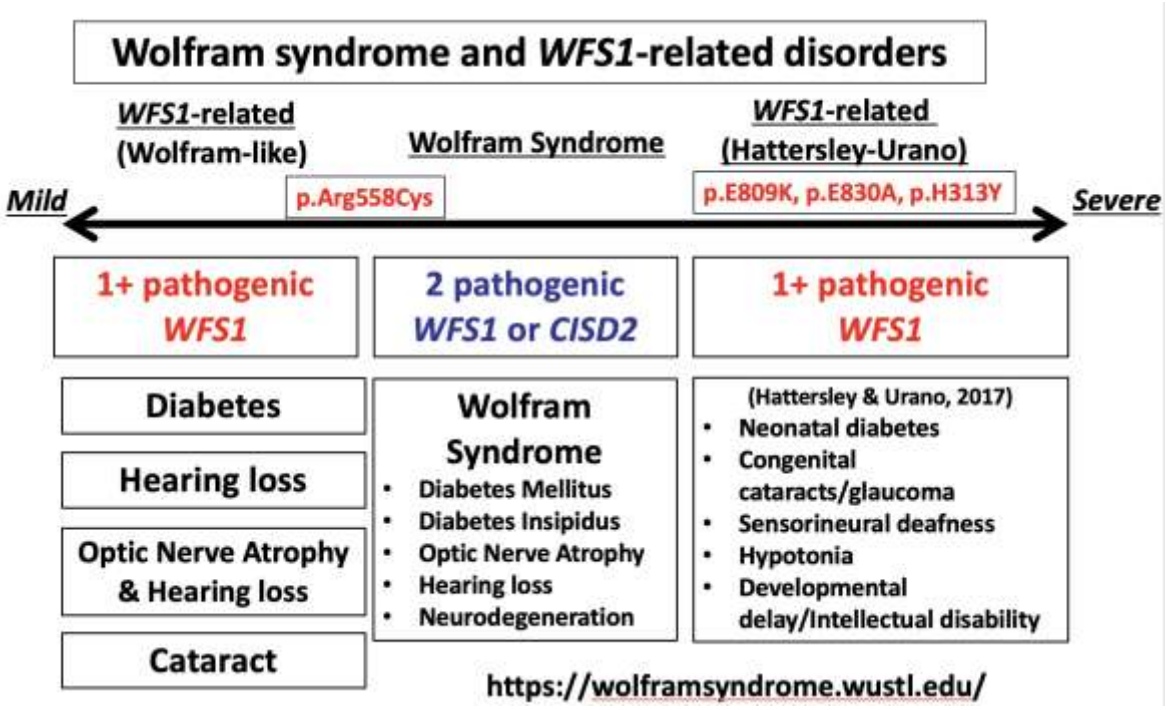
Patients of any age with lean, antibody-negative (GAD65, IA-2, ZnT8), C-peptide positive diabetes: Consider the **Monogenic Diabetes Panel**, which includes WFS1 and CISD2 genes.

Optic nerve atrophy of unknown etiology: Consider the **Optic Nerve Atrophy Panel**, which includes WFS1 and CISD2 genes.

Cases of early-onset hearing loss: Consider the **Hearing Loss Panel**, which includes WFS1 and CISD2 genes.

Rule out mitochondrial disorders.

For Wolfram syndrome, confirm two pathogenic variants are in trans via careful evaluation of the NGS data or sequence biological parents.



2. Initial Evaluations

A. Endocrine System

a. Diabetes Mellitus

Conduct tests for fasting plasma glucose and HbA1c. Auto-antibodies commonly associated with Type 1 diabetes, such as glutamate decarboxylase (GAD), tyrosin phosphatase (IA-2), and ZnT8 are usually absent. Assess insulin reserve through basal and/or random C-peptide levels together with glucose measurements.

*Note: Wolfram syndrome patients rarely present with diabetic ketoacidosis, and their diabetes is often characterized by a prolonged remission phase compared to Type 1 Diabetes.

b. Diabetes Insipidus

Collect morning paired urine and fasting plasma for osmolarity and sodium concentration after nocturnal and morning euglycemia.

c. Hypogonadism

Monitor for delayed puberty or a halt in pubertal progression.

Test for Testosterone, FSH, LH, and inhibin B.

B. Optic Nerve Atrophy

Assess visual acuity, perform fundus examination, visual field test, OCT scan, visual evoked potentials, and color vision testing.

C. Hearing Loss

Conduct an audiogram
Consider auditory evoked potentials test (auditory brain response).

D. Neurological Symptoms

Conduct a neurological examination with a brain MRI and cognitive assessment. Carry out other specific investigations based on the results of the clinical examination. Mental health assessment should also be done. Consider a test of olfaction and taste.

E. Urological Symptoms

Assess renal function (blood electrolytes, urea, creatinine, GFR), perform ultrasound renal tract and urodynamic testing.

3. Management

A. Endocrine system

a. Diabetes Mellitus

The continuous glucose monitoring system, coupled with an insulin pump, is a preferred method for diabetes management.

It is advisable to assess insulin reserves by measuring both random C-peptide and glucose levels.

If appropriate, consider the use of GLP-1 receptor agonists if C-peptide positive (liraglutide, semaglutide etc), biguanides (metformin), and SGLT2 inhibitors.

b. Diabetes Insipidus

Symptoms to Look For: Look out for polyuria and polydipsia. These symptoms may be masked by the increased urination caused by poor glycemic control. Also, be aware that these symptoms can be caused by bladder dysfunction. Disturbed nighttime sleep could also be a sign, as it may be caused by frequent voiding and the need to drink during the night.

Assessment of Urine Concentration Ability: In order to evaluate the urine's ability to concentrate, a morning paired urine and fasting plasma test for osmolarity and sodium concentration should be done. This is necessary even if the patient does not report any symptoms. As a prerequisite for evaluating morning urine osmolarity, nocturnal and morning euglycemia (blood glucose levels below the renal threshold) must be established.

Follow-Up and Management: These should be conducted in the standard manner, in accordance with the criteria for desmopressin administration. Prior to escalating the dosage of Desmopressin, bladder dysfunction should always be considered as a possibility, as Desmopressin carries a risk of hyponatremia.

c. Hypogonadism

Signs to Watch For:
In both boys and girls: Monitor for delayed puberty or a halt in pubertal progression.

In male adolescents and adult men: Look for signs of impaired fertility, such as oligospermia or azoospermia. Erectile dysfunction, reduced libido, and testicular hypotrophy could also indicate hypogonadism.

In women: A reduced frequency of menstruation (oligomenorrhea) or its absence (amenorrhea), infertility, loss of libido, and discomfort during intercourse (dyspareunia) are all symptoms to watch out for.

Hormone Levels to Monitor:

Testosterone (or estradiol), Follicle-Stimulating Hormone (FSH) and Luteinizing Hormone (LH), and inhibin B.

Standard Management:

For male patients: Testosterone replacement therapy is recommended. Testosterone enanthate may be administered in gradually increasing doses of 50-250mg intramuscularly every 3-4 weeks for patients under 18 years of age. For those over 18, alternatives include testosterone undecanoate administered intramuscularly every 3 months, or a daily dose of testosterone gel at 50mg.

For female patients: Consider estrogen-progestin replacement therapy.

d. Hypothyroidism

Free-T3, free-T4 and TSH if presence of symptoms

Thyroid substitution therapy with L-Thyroxine (starting dose 25 ug/day)

e. Growth retardation

Monitoring of linear growth in children using standard growth charts.

Consider growth hormone therapy if necessary.

B. Ophthalmological Assessment

An eye examination, which includes refraction and visual acuity, slit-lamp examination, color vision testing, Goldman perimetry for visual fields, fundoscopy, Optical Coherence Tomography (OCT) scan of the retinal nerve fiber layer, visual evoked potentials, and systematic retinography is recommended. Both fundoscopy and an OCT scan should be undertaken if signs of diabetic retinopathy are detected. In cases of retinal involvement, further tests such as fundus autofluorescence testing, fluorescein angiography, and an electroretinogram may be required.

The correction of refractive errors such as myopia, hyperopia, and astigmatism is important.

A yearly eye examination, which includes assessments of visual acuity, fundoscopy, visual fields, and an OCT scan, is mandatory. Depending on the course of the disease, other tests as described at diagnosis might be needed.

Cataract surgery should be considered if necessary. Depending on the level of visual acuity, magnifying glasses, digital systems, or voice systems may be beneficial. Any loss of visual acuity should be managed with the support of vision impairment specialists.

If appropriate, consider/discuss the use of idebenone (https://idebenone.net/) (300 mg, TID, adults) or CoQ10/Ubiquinol (200 mg per day). Also, TUDCA (500 mg per day). Don't take both idebenone and CoQ10/Ubiquinol. Just take one of them.

C. Hearing Assessment

Audiogram

Assessment of Auditory Evoked Potentials

Recommended Testing Interval: Every 2 Years

Management of Hearing Loss:
The use of hearing aids is advised. A cochlear implant may also be considered, depending on the individual's condition.

D. Neurological Assessment

Assessment of cerebellar functions

Utilize validated ataxia-specific rating scales, such as SARA (Scale for the Assessment and Rating of Ataxia), to measure disease progression. You can access SARA at this link: http://www.neurology.org/content/suppl/2006/06/07/66.11.1717.DC1/E1.doc.

Implement therapies or rehabilitation for the following conditions:

- Nystagmus, if it results in disability.
- Cerebellar intention tremor, through methods such as pharmacological interventions, physiotherapy, or other medical interventions.
- Dysarthria and swallowing disorders, via swallowing therapy provided by a speech therapist, and prevention of pulmonary aspiration disease to reduce the risk of pulmonary infections.

Assessment of brainstem functions, including central respiratory drive

Schedule screenings by polysomnography (**a sleep study**) or overnight oximetry every 2 years.

Conduct assessments of the sense of smell and taste, as a decline might be associated with disease progression.

If symptoms are present, consider bronchoscopy for checking vocal cord mobility and possible obstructive causes. Other useful tests might include spirometry and morning blood gas analysis.

Standard respiratory management should be performed by a respiratory physician. This could involve procedures like tracheostomy, providing optimal ventilation and positive pressure.

Headaches

Trigeminal Neuralgia is common in patients with Wolfram syndrome. There are medications available for its management. It's essential to consult with your local neurologist for appropriate treatment recommendations. If there is acute aggravation, consider treatment options for relieving pain, such as anti-epileptics, antidepressants, lidocaine patches, or Transcutaneous Electrical Nerve Stimulation (TENS).

Ketorolac (Toradol)
Sumatriptan (Imitrex)
Carbamazepine (Tegretol)
Gabapentin
Propranolol
Valproic acid (Caution is needed as valproic acid may cause cortical atrophy and liver toxicity. If a patient is pregnant or has mitochondrial dysfunction, valproic acid is contraindicated.)

Neuropathy, including autonomic neuropathy

Look out for symptoms such as numbness, tingling, burning, jabbing, or electric-like pain, or areflexia. Also consider the possibility of cardiovascular and gastrointestinal autonomic neuropathy.

Employ techniques like electromyography and tilt-testing when symptoms are present. If there is acute aggravation, consider treatment options for relieving pain, such as anti-epileptics, antidepressants, lidocaine patches, or Transcutaneous Electrical Nerve Stimulation (TENS).

Treatments for hypotension should also be considered.

Epilepsy

If seizures occur, electroencephalography (EEG) might be necessary, alongside the prescription of anti-epileptic drugs.

Cognitive Assessment
Adapt neuropsychological testing to the age and vision abilities of the patient. For children, the WISC-IV scale can be used. In cases of cognitive impairment, review should be conducted annually and include interventions such as rehabilitation and special education.

E. Mental Health Assessment

Screening: anxiety, depression, abnormal behavior (compulsive aggression, eating disorders) or psychosis Examine: complete history, appearance, behavior, speech, mood, thinking, abnormal perceptions

Management in standard way by psychiatric expert

F. Urological Assessment

Baseline investigations

- Standardized Questionnaire Regarding Urinary Symptoms and Voiding Diary
- Clinical Examination and Assessment of Renal Function
- Blood electrolytes, urea, creatinine, and glomerular filtration rate (GFR) assessments
- Bladder and renal ultrasound
- Urodynamic testing

Annual Assessment

- Questionnaire regarding urinary symptoms and voiding diary
- Evaluation of renal function, including urea, creatinine, and GFR levels
- Bladder and renal ultrasound to determine post-void residual volume (PVR)

Management of abnormal bladder functions

Urodynamic Testing: Conducted annually.

Clinical Exam and Quality of Life Assessment:
Conducted twice annually, incorporating a questionnaire on urinary symptoms.

Managed as per expert's decision, which may include:

- Optional procedures such as intravenous urography, retrograde urethrocystography during voiding, and renal scintigraphy.
- Potential treatment approaches including anticholinergic drugs, botulinum toxin injections (Botox injections).

Anticholinergic drugs

- Oxybutynin (Ditropan XL, Oxytrol, Gelnique)
- Tolterodine (Detrol, Detrol LA)
- Darifenacin
- Solifenacin (Vesicare, Vesicare LS)
- Trospium
- Fesoterodine (Toviaz)

Complementary interventions such as electrical stimulation (Neurostimulator implant) and physiotherapy, along with surgical interventions as necessary.

Intermittent Self-Catheterization:
Initial evaluation of the ability to self-catheterize, considering potential barriers such as ataxia, impaired vision, or cognitive deficiencies.

Indwelling Urinary Catheter:
Assessment of risk factors for infection

Urinary Tract Infection:
Urine culture to be conducted in case of fever or other associated symptoms

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