Management of Wolfram Syndrome

A Clinical Guideline

Wolfram Syndrome Guideline Development Group
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Introduction...

... to Wolfram Syndrome

Wolfram syndrome (WS), also known as DIDMOAD (Diabetes Insipidus, Diabetes Mellitus (DM), Optic Atrophy (OA), and Deafness) is a rare autosomal recessive disorder. The estimated prevalence of WS is 1 in 770,000. The minimal criteria for diagnosis are juvenile-onset DM and OA but patients may also develop diabetes insipidus, sensorineural deafness, renal tract abnormalities, and neuropsychiatric disorders; and variants exist with only partial features. The prognosis is mainly linked to the severity of the neurological symptoms.

WS is a genetically heterogeneous disease. Most patients carry mutations in the WFS1 gene, encoding an endoplasmic reticulum membrane embedded protein called Wolframin. CISD2 is a second causative gene associated with WS. It encodes a mitochondrial and endoplasmic reticulum protein. In addition, mutations in the WFS1 gene are also associated with the poorly defined ‘Wolfram-Like Syndrome (WS-like) disorders’ including DM, OA, or deafness in dominant or recessive families, and in dominantly-inherited low-frequency sensorineural hearing loss (LFSNHL).

... to the Wolfram syndrome guideline project

These guidelines have been developed by referring physicians involved in the EURO-WABB project, according to the DYSCERNE guideline development process (www.dyscerne.org.dysc.home/). The experts who participated in the guideline development are listed on page 15.

... to the Wolfram syndrome clinical management guidelines

What are the aims of the guidelines?

The guidelines aim to provide recommendations for the diagnosis, management and the follow-up of patients with WS. As it is a multisystemic disorder, WS patients may require various tests, screening and multidisciplinary interventions at different stages of their lives. These recommendations aim to support high quality care for people with WS in a format that is accessible to anybody who is involved in the care of these patients. Note that transition is a process which includes the event of transfer from childrens’ to adult services and needs to attend to the medical, psychosocial, and educational/vocational needs of the young person and his/her parents/carers. Care needs to be provided that includes attention to transition needs.

How are they organised?

The guidelines are divided into
- clinical features and diagnostic criteria
- baseline investigations
- recommended tests, that are listed and organised into specific groups corresponding to the different symptoms and affected organs. Any recommendations that are specifically addressed either to children or to adult patients are specified.

A list of references starts on page 14, organised according to the different sections of the guidelines.

Additionally, there is a list of useful contacts for patients and families affected by WS, on page 16.

Note: ABNL=abnormal or symptomatic
## Diagnosis and clinical features of Wolfram Syndrome

### Diagnostic criteria of WS

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Minor criteria</th>
<th>Minimum required</th>
<th>Other variable suggestive evidence:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Diabetes mellitus &lt;16 yrs (87%)</td>
<td>- Diabetes insipidus (42%)</td>
<td>-2 major OR</td>
<td>- Hypogonadism (males) (6%)</td>
</tr>
<tr>
<td>- Optic atrophy &lt;16 yrs (80%)</td>
<td>- Diabetes mellitus &gt;16 yrs (4%)</td>
<td>OR</td>
<td>- Absence of type 1 diabetes auto-antibodies</td>
</tr>
<tr>
<td></td>
<td>- Optic atrophy &gt;16 yrs (7%)</td>
<td>-1 major plus 2 minor criteria OR</td>
<td>- Bilateral cataracts (1%)</td>
</tr>
<tr>
<td></td>
<td>- Sensorineural deafness (48%)</td>
<td>-2 pathological WFS1 or CISD2 mutations are identified</td>
<td>- Psychiatric disorder (26%)</td>
</tr>
<tr>
<td></td>
<td>- Neurological signs (ataxia, epilepsy, cognitive impairment) (29%)</td>
<td></td>
<td>- Gastrointestinal disorders (5%)</td>
</tr>
<tr>
<td></td>
<td>- Renal tract abnormalities (structural or functional) (33%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- 1 loss of function mutation in WFS1/CISD2 AND/OR family history of Wolfram syndrome</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Diagnostic criteria. Percentages in parentheses refer to prevalence of feature in EURO-WABB Registry (121 participants with genetically confirmed diagnosis)

### Wolfram Syndrome-like disorders: variable mode of inheritance

One criterion among diabetes mellitus (or glucose intolerance), optic atrophy or deafness AND At least one loss of function WFS1 or CISD2 mutation

### The differential diagnoses of Wolfram syndrome and Wolfram syndrome-like disorders include:

- Mitochondrial disorders: Maternally Inherited Diabetes mellitus and Deafness, Leber Hereditary Optic Neuropathy
- Thiamine-responsive megaloblastic anemia, diabetes and deafness
- Autosomal Dominant Optic Atrophy
- X-linked Charcot-Marie-Tooth disease type 5
- Deafness, Dystonia, Optic Neuronopathy syndrome
- Friedreich ataxia
- Bardet-Biedl syndrome
- Alstrom syndrome
**Recommended baseline investigations in Wolfram Syndrome**

<table>
<thead>
<tr>
<th>Clinical Features of WS</th>
<th>Baseline investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endocrine system</strong></td>
<td>Fasting plasma glucose and HbA1c. Type 1 diabetes associated auto-antibodies most often absent: mainly glutamate decarboxylase (GAD), tyrosin phosphatase (IA-2) and insulin antibodies, if available islet cell Ab (ICA) or ZnT8 Ab. Low insulin reserve assessed by basal and/or post standard meal stimulated C-Peptide measurements. <em>Note that Wolfram patients present rarely with diabetic ketoacidosis and diabetes often characterized by prolonged remission phase compared to T1D.</em></td>
</tr>
<tr>
<td>... Diabetes Mellitus</td>
<td>Morning paired urine and fasting plasma for osmolarity and sodium concentration after nocturnal and morning euglycaemia.</td>
</tr>
<tr>
<td>... Diabetes Insipidus</td>
<td>Testosterone, FSH and LH, inhibin B</td>
</tr>
<tr>
<td>... Hypogonadism (male)</td>
<td>Visual acuity, fundus examination, visual field, OCT scan, visual evoked potentials, colour vision testing</td>
</tr>
<tr>
<td><strong>Sensory involvement</strong></td>
<td>Audiogram, auditory evoked potentials</td>
</tr>
<tr>
<td>... Optic Atrophy</td>
<td>Neurological examination with brain MRI and cognitive assessment. Other specific investigations according to the results of clinical examination. Mental health assessment. Consider test of olfaction</td>
</tr>
<tr>
<td>... Hearing Loss</td>
<td>Questionnaire regarding urinary symptoms with voiding diary. Assessment of renal function (blood electrolytes, urea, creatinine, GFR), ultrasound renal tract and urodynamic testing.</td>
</tr>
<tr>
<td><strong>Neurological signs</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Urological signs</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Confirmation of WS diagnosis**

**Molecular Analysis**

*WFS1. Analysis of CISD2 only if negative WFS1 sequencing and MLPA analysis; characteristic phenotype; or middle eastern origin.*
### Recommendations for the management of Wolfram Syndrome

#### Endocrine System – Diabetes Mellitus (I)

#### Diagnostic criteria of diabetes

- Fasting (at least 8 hours) Plasma Glucose (FPG) $\geq 7.0$ mmol/L
- Casual PG $\geq 11.1$ mmol/L + symptoms of diabetes (polyuria, polydipsia and unexplained weight loss)
- 2 hour PG $\geq 11.1$ mmol/L in a 75-g oral glucose tolerance test

*If there are no osmotic symptoms or ketone production, then a confirmatory glucose test must be done on another day. In a child, raised glucose measurement should lead to same day referral to a hospital specialist experienced in management of childhood diabetes and should not delay initiation of treatment to avoid rapid deterioration (diabetic ketoacidosis : DKA)*

#### Management of DM for children by an interdisciplinary pediatric diabetes healthcare team

<table>
<thead>
<tr>
<th>Intensive education</th>
<th>Insulin injection, dosage adjustment, blood glucose and ketone testing, exercise, nutrition, formal smoking avoidance, prevention and management of DKA and hypoglycemia.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycemic targets</td>
<td>Improve metabolic control to reduce diabetes-related complications with strategies tailored to each child, according to individual risk factors and vulnerability to severe hypoglycemia. HbA1c goals should be $&lt;7.5%$. Less stringent A1C goals may be appropriate for patients with a history of severe hypoglycemia, hypoglycemia unawareness, limited life expectancy, advanced microvascular or macrovascular complications, or extensive comorbid conditions.</td>
</tr>
<tr>
<td>Insulin therapy</td>
<td>Insulin regimen chosen according on age, duration of diabetes, lifestyle, socioeconomic factors, and family, patient and physician preferences. Intensive management is usually required: continuous subcutaneous insulin infusion or multiple daily injection regimens using basal insulin analogues.</td>
</tr>
<tr>
<td>Glucose monitoring</td>
<td>Self-monitoring of blood glucose (adapted devices for vision impaired people), glucose diary, and quarterly HbA1c measurement. If necessary and available, Continuous Glucose Monitoring System (CGMS) can be used</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Regular evaluation (at least annually) with nutrition counseling (based on the nutritional needs, eating habits, lifestyle, ability and interest) ensuring normal growth and development with optimal glycaemic control</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Significant risk of hypoglycemia often necessitates less stringent glycemic goals or the use of a continuous glucose monitoring system. Severe hypoglycemia should be treated with intravenous dextrose (hospital) or subcutaneous glucagon (at home) followed by buccal glucose syrup. Hypoglycemia awareness may be severely disturbed.</td>
</tr>
</tbody>
</table>
Recommendations for the management of Wolfram Syndrome  
*Endocrine System – Diabetes Mellitus (II)*

<table>
<thead>
<tr>
<th>Management of DM for children by an interdisciplinary pediatric diabetes healthcare team</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chronic poor metabolic control</strong></td>
</tr>
</tbody>
</table>
| **DKA**                                | Is rare at the time of manifestation of diabetes in Wolfram syndrome, although possible at an advanced stage of diabetes. Education and family support.  
As risk for cerebral edema is increased in child during DKA, standard pediatric diabetes protocols should be followed. |
| **Psychological issues**                  | Regular evaluation for symptoms of psychological distress (cause or consequence of diabetes)  
Consider eating disorders and/or insulin misuse if adolescents unable to achieve and maintain metabolic targets. |
Recommendations for the management of Wolfram Syndrome

*Endocrine System – Diabetes Mellitus (III)*

<table>
<thead>
<tr>
<th>Management of diabetes complications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nephropathy</strong></td>
</tr>
<tr>
<td>- Yearly screening, starting at 12 years of age, in patients with duration of diabetes &gt;5 years</td>
</tr>
<tr>
<td>- First morning or random urine albumin to creatinine ratio, and microalbuminuria demonstrated.</td>
</tr>
<tr>
<td>- Introduce renoprotection with angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) as soon as microalbuminuria is confirmed.</td>
</tr>
<tr>
<td><strong>Retinopathy</strong></td>
</tr>
<tr>
<td>- Yearly screening with retinal photography in patients with duration of diabetes more than 5 years</td>
</tr>
<tr>
<td>- Fundoscopy, OCT scan and fluorescein angiography if signs of diabetic retinopathy are present</td>
</tr>
<tr>
<td><strong>Neuropathy</strong></td>
</tr>
<tr>
<td>- Yearly neurological exam to look for numbness, pain, cramps and paresthesia (cf. neurological section)</td>
</tr>
<tr>
<td>- Nerve conduction studies and dysautonomia assessment in presence of clinical signs or symptoms</td>
</tr>
<tr>
<td>- Treat symptoms</td>
</tr>
<tr>
<td><strong>Dyslipidemia</strong></td>
</tr>
<tr>
<td>- Screen at 12 and 17y (when stabilized), or &lt;12y if risk factors exist (obesity, familial hypercholesterolaemia)</td>
</tr>
<tr>
<td>- Fasting total cholesterol, high-density and low-density lipoprotein cholesterol, triglycerides</td>
</tr>
<tr>
<td>- Lipid lowering drug therapy</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
</tr>
<tr>
<td>- Screen at least annually, use appropriate cuff size, +/- 24 hour ambulatory blood pressure monitoring</td>
</tr>
<tr>
<td>- Lifestyle modification and anti-hypertensive drug therapy</td>
</tr>
</tbody>
</table>
Symptoms to seek: polyuria and polydipsia (could be masked by the polyuria induced by poor glycemic control). Note these symptoms also caused by bladder dysfunction. Disturbance of night sleep (by voiding and necessity to drink during nighttime).

Assessment of concentrating ability of the urine: morning paired urine and fasting plasma for osmolarity and sodium concentration – even if the patient denies symptoms. Prerequisite for the evaluation of morning urine osmolarity: nocturnal and morning euglycaemia (blood glucose levels beneath the renal threshold)

Follow up and management in standard way (according to criteria for desmopressin administration). Always consider bladder dysfunction before dose escalation of Desmopressin, as desmopressin carries a risk of hyponatraemia.

Symptoms to seek:
- Boys and girls: delayed puberty or pubertal arrest
- Male adolescents and men: impaired fertility, oligo/azoospermia, erectile dysfunction, reduced libido, testicular hypotrophy
- Women: a/oligomenorrhea, infertility, loss of libido, dyspareunia

Hormone levels: testosterone (or oestradiol), FSH and LH, inhibin B

Management in standard way (i.e. testosterone replacement in male patients with testosterone enanthate gradually increasing 50-250mg i.m. every 3-4 weeks at age less than 18 years; alternatively testosterone undecanoate i.m.every 3 months or testosterone gel 50mg/day at age over 18 years. Oestrogen-gestagen replacement in female patients)

Free-T3, free-T4 and TSH if presence of symptoms
Thyroid substitution therapy with L-Thyroxine (starting dose 25μg/day)

Monitoring of linear growth in children using standard growth charts
Recommendations for the management of Wolfram Syndrome

**Sensory involvement**

### Visual assessment

- **At diagnosis**
  - Eye examination, including refraction and visual acuity, slit-lamp examination, color vision testing, visual field (Goldman perimetry), funduscropy, OCT scan of the retinal nerve fiber layer, visual evoked potentials, systematic retinography. Fundoscopy and OCT scan if signs of diabetes retinopathy are present. Fundus autofluorescence testing, fluorescein angiography and electroretinogram may be required in case of retinal involvement.
  - Correction of refractive error (myopia, hyperopia, astigmatism).
- **Follow up**
  - Yearly eye examination: visual acuity, funduscopy, visual field and OCT scan are mandatory. Other tests as described at diagnosis, depending on the course of the disease.
  - Cataract surgery if needed. Magnifying glasses, digital systems, voice systems depending on the level of visual acuity. Loss of visual acuity requires support from vision impairment specialists.

### Hearing assessment

- **At diagnosis**
  - Audiogram
  - Auditory evoked potentials
  - Test every 2 years
- **Follow up**
  - Hearing Loss
    - Management with hearing aids. Consider cochlear implant.
Recommendations for the management of Wolfram Syndrome

**Neuro-psychiatric involvement**

Management of neurological involvement by adult or paediatric neurologists

<table>
<thead>
<tr>
<th>Neurologic examination yearly for asymptomatic patients and twice a year for symptomatic patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain MRI to repeat if acute aggravation of central disorders or at adult age</td>
</tr>
</tbody>
</table>

**Cerebellar ataxia assessment**
- Use of validated ataxia-specific rating scales for measuring progression (E.g. SARA: [http://www.neurology.org/content/suppl/2006/06/07/66.11.1717.DC1/E1.doc](http://www.neurology.org/content/suppl/2006/06/07/66.11.1717.DC1/E1.doc))
- Therapy or rehabilitation for:
  - Nystagmus (if disability),
  - Cerebellar intention tremor (drug, physiotherapist, intervention),
  - Dysarthria and swallowing disorder (swallowing therapy by speech therapist), prevention of pulmonary aspiration disease (pulmonary infection)

**Brainstem involvement assessment: Central respiratory failure**
- Screening by polysomnography or overnight oximetry (every 2 years)
- Assessment of sense of smell; decline may be associated with progression of disease.
- If symptoms: bronchoscopy (vocal cord mobility, obstructive cause), spirometry, morning blood gases
- Management in standard way by respiratory physician (tracheostomy, optimal ventilation)

**Peripheral neuropathy assessment**
- Symptoms to seek (numbness, tingling, burning, jabbing or electric-like pain) or arreflexia
- Consider cardiovascular and gastrointestinal autonomic neuropathy
- Electromyography, tilt-test in presence of symptoms, then if acute aggravation:
  - Treatment for relieve the pain (Anti-epileptic, antidepressants, lidocaine patch, TENS) or hypotension

**Epilepsia assessment**
- Electroencephalography (EEG) if seizures occur
- Anti-epileptic drugs

**Cognitive assessment**
- Neuropsychological testing adapted to age (Children: WISC-IV) and to low vision
- Review yearly if cognitively impaired. Rehabilitation, special education

**Mental health assessment**
- Screening: anxiety, depression, abnormal behavior (compulsive aggression, eating disorders) or psychosis
- Examine: complete history, appearance, behaviour, speech, mood, thinking, abnormal perceptions
- Management in standard way by psychiatric expert

SARA: Scale for the assessment and rating of ataxia ;
WISC-IV: Wechsler Intelligence Scale for Children, Fourth Edition ; MMSE :Mini Mental State Examination; FAB: Frontal Assessment Battery
## Recommendations for the management of Wolfram Syndrome

### Urological involvement

#### Management of urological involvement by urologists, rehabilitation physicians and neurologists

| Baseline investigations | Standardised questionnaire regarding urinary symptoms and voiding diary, clinical examination  
Assessment of renal function (blood electrolytes, urea, creatinine, glomerular filtration rate (GFR))  
Bladder and renal ultrasound (residual urine), urodynamic testing |
|-------------------------|-------------------------------------------------------------------------------------------------------------------|
|                         | Yearly assessment :  
- Questionnaire regarding urinary symptoms and voiding diary  
- Assessment of renal function (urea, creatinine, GFR)  
- Bladder and renal ultrasound (PVR) |
|                         | Urodynamic testing : yearly  
Clinical exam, questionnaire regarding urinary symptoms and quality of life scale twice a year  
Management in standard way according expert’s decision:  
+/- Intra-venous urography, retrograde urethrocystography (voiding), renal scintigraphy  
+/- treatment (anticholinergic drugs, botulinum toxin, intermittent self-catheterization) …  
Electrical stimulation and physiotherapy, surgical intervention when needed |
| Screening urinary infections | Urine culture if fever or other symptoms |
| Intermittent self-catheterization | Preliminary assessment of the ability to self-catheterize, taking into account ataxia, low vision or cognitive deficiency |
| Indwelling urinary catheter | Risk factors for infection |
Recommendations for the management of Wolfram Syndrome

**Genetics**

- **Genetic testing**
  - Index case: $WFS1 \pm/- CISD2$ screening if desired by patient or parents
  - 1 or 2 mutated alleles: perform mutation screening in parents of index case

- **Genetic counselling**
  - Information about recurrence risk to parents (25%), to adult patients and extended family members.

- **Prenatal Diagnosis (PN)**
  - Available only for families in which the disease-causing mutation has been identified
  - For 25% recurrence risk (example: parents of an index case)

- **Preimplantation Genetic Diagnosis (PGD)**
  - To discuss with referral centres (may be available for families in which the disease-causing mutation has been identified).
Management of Wolfram Syndrome

Bibliography

1. INTRODUCTION

2. DIABETES

3. NEUROLOGICAL SIGNS

4. GENETICS
Acknowledgements

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Information for patients

Sources of information and support

The groups listed below are useful sources of support and information

• **Association du syndrome de Wolfram** ([http://asso.orpha.net/ASW/](http://asso.orpha.net/ASW/))
  Contact: Tél. +33.2.97.61.42.37  Email: nolwenn.jaffre@voila.fr

• **EURO-WABB project** – [www.euro-wabb.org](http://www.euro-wabb.org)
The general objective of this project is to support efficient diagnosis, treatment, and research for Wolfram, Alström, Bardet-Biedl (WABB) and other rare syndromes. The project is managed by a collaboration of scientists, clinicians, and patient groups. The website contains useful information about these rare diseases, some of it in several European languages.

• **Orphanet** ([www.orpha.net](http://www.orpha.net))
Orphanet is an online database of rare diseases and related services provided through Europe. It contains information on over 5,000 conditions and lists specialised clinics, diagnostic tests, patient and organizations, research projects and clinical trials.

• **OMIM** ([http://www.omim.org/](http://www.omim.org/))
OMIM is a comprehensive, authoritative compendium of human genes and genetic phenotypes that is freely available and updated daily. The full-text, referenced overviews in OMIM contain information on all known mendelian disorders and over 12,000 genes. OMIM focuses on the relationship between phenotype and the entries contain copious links to other genetics resources.

• **RareConnect** ([https://www.rareconnect.org/en](https://www.rareconnect.org/en))
RareConnect was created by EURORDIS (European Rare Disease Organisation) and NORD (National Organization for Rare Disorders) to provide a safe space where individuals and families affected by rare diseases can connect with each other, share vital experiences, and find helpful information and resources.

• **Wolfram Syndrome UK: www.wolframsyndrome.co.uk**
This is a UK registered charity (No 1152445). The website is run by families affected by this rare genetic disorder and the aim is to raise as much awareness of the syndrome as possible. Contact details: Tel: 01903 211358. Email: families@wolfram.co.uk or admin@wolfram.co.uk