Management of Wolfram Syndrome

A Clinical Guideline

Wolfram Syndrome Guideline Development Group

www.euro-wabb.org

European Commission

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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

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

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 *WFS*1 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

Clinical Features of WS	Baseline investigations
Endocrine system … Diabetes Mellitus	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 ** Note that Wolfram patients present rarely with diabetic ketoacidosis and diabetes often characterized by prolonged remission phase compared to T1D.*
… Diabetes Insipidus	Morning paired urine and fasting plasma for osmolarity and sodium concentration after nocturnal and morning euglycaemia.
… Hypogonadism (male)	Testosterone, FSH and LH, inhibin B
Sensory involvement … Optic Atrophy	Visual acuity, fundus examination, visual field, OCT scan, visual evoked potentials, colour vision testing
… Hearing Loss	Audiogram, auditory evoked potentials
Neurological signs	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
Urological signs	Questionnaire regarding urinary symptoms with voiding diary, Assessment of renal function (blood electrolytes, urea, creatinine, GFR), ultrasound renal tract and urodynamic testing.

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) ≥ 7.0 mmol/L
Or
Casual PG ≥ 11.1 mmol/L + symptoms of diabetes (polyuria, polydipsia and unexplained weight loss)
Or
2 hour PG ≥ 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

Intensive education	Insulin injection, dosage adjustment, blood glucose and ketone testing, exercise, nutrition, formal smoking avoidance, prevention and management of DKA and hypoglycemia.
Glycemic targets	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 <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.
Insulin therapy	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.
Glucose monitoring	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
Nutrition	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
Hypoglycemia	Significant risk of hypoglycemia often necessitates less stringent glycemic goals or the use of a continous 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.

Recommendations for the management of Wolfram Syndrome
Endocrine System – Diabetes Mellitus (II)

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

Chronic poor metabolic control	Hb A1C >7.5% (frequent during adolescence): identification of potential causative factors
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)

Management of diabetes complications

Nephropathy	ABNL	- Yearly screening, starting at 12 years of age, in patients with duration of diabetes >5 years - First morning or random urine albumin to creatinine ratio, and microalbuminuria demonstrated. - Introduce renoprotection with angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) as soon as microalbuminuria is confirmed.
Retinopathy	ABNL	- Yearly screening with retinal photography in patients with duration of diabetes more than 5 years - Fundoscopy, OCT scan and fluorescein angiography if signs of diabetic retinopathy are present
Neuropathy	ABNL	- Yearly neurological exam to look for numbness, pain, cramps and paresthesia (cf. neurological section) - Nerve conduction studies and dysautonomia assessment in presence of clinical signs or symptoms - Treat symptoms
Dyslipidemia	ABNL	- Screen at 12 and 17y (when stabilized), or <12y if risk factors exist (obesity, familial hypercholesterolaemia) - Fasting total cholesterol, high-density and low-density lipoprotein cholesterol, triglycerides - Lipid lowering drug therapy
Hypertension	ABNL	- Screen at least annually, use appropriate cuff size, +/- 24 hour ambulatory blood pressure monitoring - Lifestyle modification and anti-hypertensive drug therapy

Recommendations for the management of Wolfram Syndrome
Endocrine System – Others

Diabetes insipidus

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. Distrubance of night sleep (by voiding and necessity to drink during nighttime).

ABNL

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.

Hypo or hyper gonodatropic hypogonadism

Symptoms to seek :

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

ABNL

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)

Hypothyroidism

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

ABNL

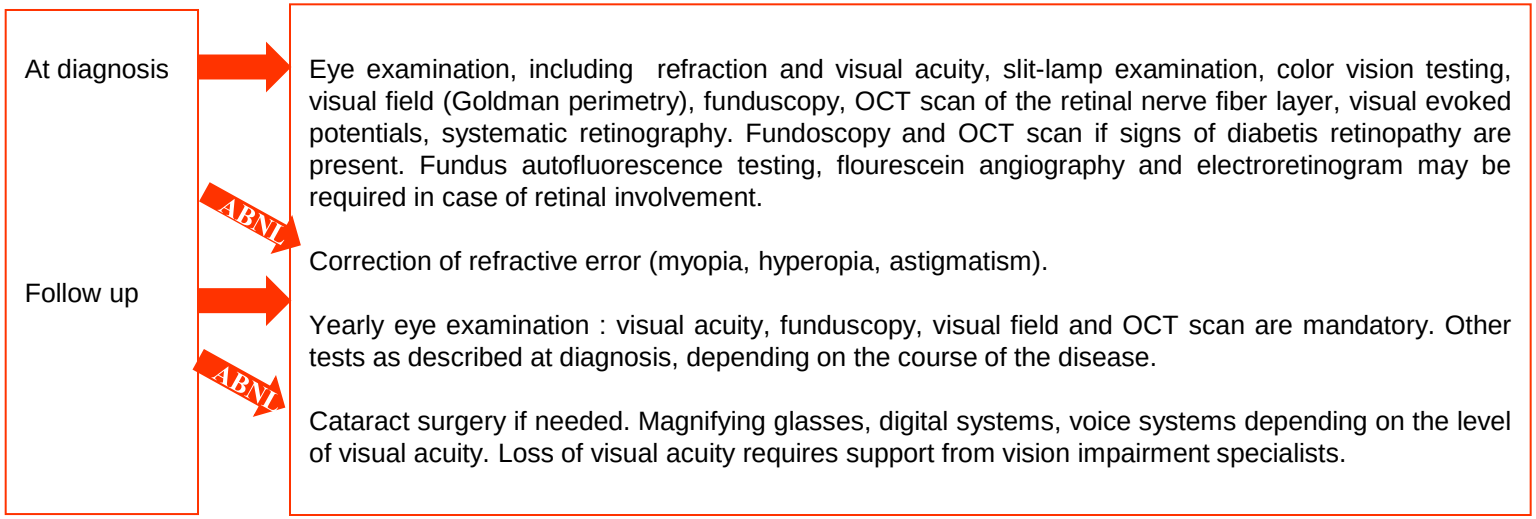
Thyroid substitution therapy with L-Thyroxine (starting dose 25μg/day)

Growth retardation

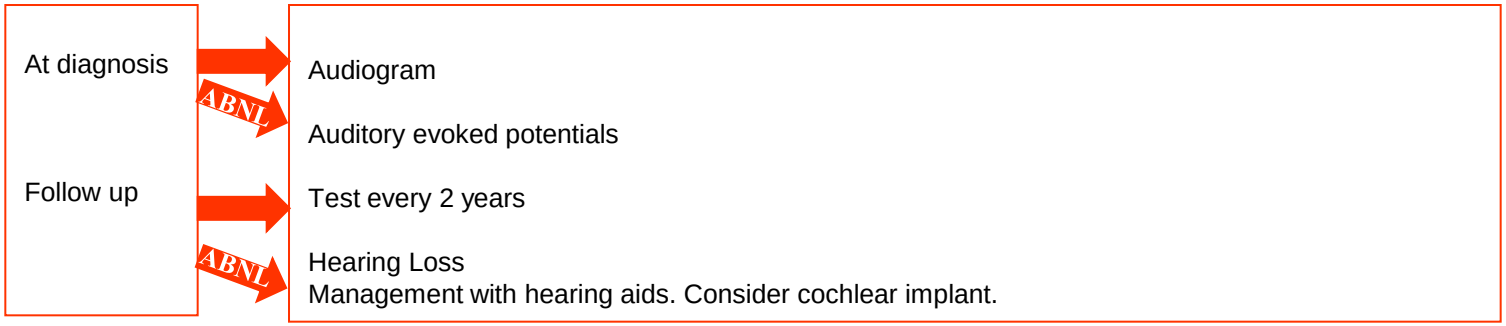
Monitoring of linear growth in children using standard growth charts

Recommendations for the management of Wolfram Syndrome
Sensory involvement

Visual assessment



Hearing assessment



Wolfram Syndrome Clinical Management Guidelines

Recommendations for the management of Wolfram Syndrome
Neuro-psychiatric involvement

Management of neurological involvement by adult or paediatric neurologists

Neurologic examination yearly for asymptomatic patients and twice a year for symptomatic patients
Brain MRI to repeat if acute aggravation of central disorders or at adult age

Cerebellar ataxia assessment	ABNL	- 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 - 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 involvment assessment : Central respiratory failure	ABNL	- 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, obstrutive cause), spirometry, morning blood gases - Management in standard way by respiratory physician (tracheostomy, optimal ventilation)
Peripheral neuropathy assessment	ABNL	- 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	ABNL	- Electroencephalography (EEG) if seizures occur - Anti-epileptic drugs
Cognitive assessment	ABNL	- Neuropsychological testing adapted to age (Children: WISC-IV) and to low vision - Review yearly if cognitively impaired. Rehabilitation, special education
Mental health assessment	ABNL	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)
ABNL	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 +/- 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
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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/)**
Contact : Tél. +33.2.97.61.42.37 Email. nolwenn.jaffre@voila.fr

•**EURO-WABB project – 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)**
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/)**
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)
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