WOLFRAM SYNDROME UK
Inform, Support, CURE

Thank you for reading this information pack about Wolfram Syndrome. Wolfram Syndrome is a rare progressive neuro degenerative condition with limited life expectancy and no cure. It affects 1 in 770,000 in the UK. There are currently about 100 people (adults and children) diagnosed with WS and it is thought that there are at least another 50 people either undiagnosed or misdiagnosed. The aim of this pack is to inform medical professionals that may see a child or adult with WS, what to be aware of to aid a quicker diagnosis and so prevent years of uncomfortable and intrusive testing. Please share the information amongst the staff in your department.

Inside this pack you will find the following:

Information sheets regarding:

Urology
Neurology
Ophthalmology
Paediatricians and Healthcare Professionals
Endocrinologists
Diabetologists
Wolfram Syndrome MDT Clinical Guidelines
WSUK Charity leaflet

If you would like any further information about Wolfram Syndrome then please contact the office either by phone or email.

Yours sincerely

Tracy

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Chief Executive & Co-Founder
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n Partnership with PENFOLD VERRALL

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Wolfram syndrome guide for diabetologists

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The combination of diabetes mellitus presenting under 15 years and progressive optic atrophy is pathognomonic for Wolfram syndrome (Barrett et al 1995).

Diagnostic criteria for diabetes mellitus are based on plasma blood glucose measurements and the presence or absence of symptoms. Diabetes is diagnosed when:

- A fasting plasma glucose (FPG) is ≥ 7.0mmol/L (126mg/dl) (on two occasions if there are no symptoms of diabetes).
- OR the post challenge plasma glucose is >11.1mmol/L (200mg/dl) 2 hours after a glucose load containing the equivalent of 1.75mg/kg (max 75g) of anhydrous glucose dissolved in water
- OR there are symptoms of diabetes and a random plasma glucose ≥11.1mmol/L (300mg/dl). The symptoms may include polyuria, polydipsia, and unexplained weight loss.

The diagnosis of diabetes mellitus is usually confirmed quickly in symptomatic children by measurement of an elevated blood glucose level. In this situation, if ketones are present in the blood or urine, treatment is urgent.

This is a form of secondary diabetes mellitus. Type 1 diabetes associated auto-antibodies are most often absent (glutamate decarboxylase (GAD), tyrosine phosphatase (IA-2) and insulin antibodies, if available islet cell Ab (ICA) or ZnT8 Ab). Absolute insulin deficiency can occur, with ketosis, but insulopaenia is common, and may be assessed by basal and/or post stimulated C- Peptide measurements.

Management of diabetes mellitus

Intensive education

The principles are similar to management of type 1 diabetes. Intensive education is needed regarding insulin injection techniques, dosage adjustment, blood glucose and ketone testing, exercise, nutrition, formal smoking prevention and cessation, prevention and management of DKA and hypoglycaemia.

Glycemic targets

The aim is to improve metabolic control to reduce diabetes-related complications with strategies tailored to each individual, according to individual risk factors and vulnerability to severe hypoglycemia. HbA1c goals are to achieve an A1c equal to or ess than 48mmol/mol (6.5%). Less stringent A1C goals may be appropriate for patients with a history of severe hypoglycemia, advanced microvascular or macrovascular complications, and/or extensive comorbid conditions.

Insulin therapy

Insulin regimen is chosen according to age, duration of diabetes, lifestyle, socioeconomic factors, and family, patient and physician preferences. Intensive management is frequently required: continuous subcutaneous insulin infusion (CSII) or multiple daily injection regimens using basal insulin analogues. Many patients are now benefitting from hybrid pumps with sensors and inbuilt hypoglycaemia alarms.

There have been individual case studies of GLP-1 agonists, but it is not yet clear that these agents offer advantages over insulin treatment, particularly in the long term.

Glucose monitoring

Self-monitoring of blood glucose (adapted devices for blind people) and quarterly HbA1c measurement. If available, Continuous Glucose Monitoring System (CGMS) using a sensor system, is really helpful, and many of these now have alarms for when glucose levels fall out of range.

Nutrition
Regular evaluation is recommended (at least annually) with dietetic advice (based on the nutritional needs, eating habits, lifestyle, ability and interest) ensuring normal growth and development without disturbing glycemia.

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) according to local protocols for type 1 diabetes.

Management of diabetes complications

Nephropathy
- Annual screening, starting at 12 years of age, or in patients with duration of diabetes 5 years or more.
    - First morning urine albumin to creatinine ratio, and persistence of elevation demonstrated.

Retinopathy
- Annual screening in patients with duration of diabetes more than 5 years
    - Fundoscopy, OCT scan and fluorescein angiography if signs of diabetic retinopathy are present

Neuropathy
-Annual neurological exam to identify numbness, pain, cramps and paresthesia
    - Nerve conduction studies and dysautonomia assessment in presence of clinical signs or symptoms

Dyslipidemia
Screen at 12 and 17years (when stabilized), or below 12 years if risk factors exist (obesity, familial hyperlipidemia)
    - Fasting total cholesterol, high-density and low-density lipoprotein cholesterol, triglycerides

Hypertension
Screen at least twice a year, use appropriate cuff size, +/- 24 hour ambulatory blood pressure monitoring
    - Lifestyle modification and anti-hypertensive drug therapy

REFERENCES:

ISPAD Clinical Practice Consensus Guidelines 2018: The Diagnosis and management of monogenic diabetes in children and adolescents. Hattersley A, Greeley S, Polak M, Rubio-Cabenzas O, Nolstad P, Mlynarski W, Castano L, Carlsson A, Raile K, Chi D, Ellard S, Craig M. DOI: 10.1111/pedi.12772. https://www.ispad.org/resource/resmgr/consensus_guidelines_2018_/4.the_diagnosis_and_manageme.pdf

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https://www.ispad.org/resource/resmgr/consensus_guidelines_2018_/8.glycemic_control_targets_a.pdf

Wolfram syndrome guide for endocrinologists

Apart from diabetes mellitus, other common endocrine findings in Wolfram syndrome include:

Diabetes insipidus.
Diabetes insipidus of central origin occurred in 72% with a median age of onset of 15.5 years (Barrett et al 1995). The range in age of onset is broad, possibly because of delays in establishing the correct diagnosis. Common symptoms include polyuria and polydipsia; the differential diagnosis includes polyuria secondary to poor glycemic control, and neuropathic bladder.

Useful investigations include 24 hour urine collection to assess volume, particularly if the patient denies symptoms. To make the diagnosis of cranial diabetes insipidus, an assessment of the concentrating ability of the urine is required. It is easiest to collect morning paired fasting urine and fasting plasma for osmolarity and sodium concentration. Water deprivation tests are best avoided as they can be dangerous. A urine osmolarity > 500mOsmol/L with normal serum sodium (up to 145mmol/L) and serum osmolarity (up to 295mOsmol/L) in the presence of normal serum glucose effectively excludes diabetes insipidus. A confirmation of diabetes insipidus would by a urine osmolarity <150mOsmol/L, with serum Na > 145, and serum osmo > 295mOsmol/L.

Management is with desmopressin replacement according to local practices. The options are usually intranasal, buccal or oral. The intranasal preparations are about 20 times more potent than the oral, and about 15 times more potent than the buccal preparations. A safe starting dose in a child over 5 years would be 2.5 micrograms intranasal at night; and for an adult, 5-10 micrograms intranasal. The dose needs to be titrated according to symptoms, and by blood and urine biochemistry. As with diagnosis optimising management can be difficult due to polyuria secondary to poor glycemic control, and neuropathic bladder.

Hypogonadism.
Hypogonadism is more prevalent in males than in females. It can be either hypogonodatrophic (i.e., central) or hypergonadotrophic (i.e., secondary to gonadal failure). The underlying pathology of either type is not understood. Females usually retain their ability to become pregnant; about six successful pregnancies are described in the literature. One female had absence of the uterus [Tranebjærg, unpublished].

Symptoms to enquire about include for children, delayed puberty (the absence of secondary sexual characteristics by 14 years in a girl or 16 years in a boy), pubertal arrest. In adult men, ask about erectile impotence, reduced libido, and any history of impaired fertility or oligo/azoospermia. On examination, small, soft testes have been reported. For women, ask about amenorrhoea or oligomenorrhea, infertility loss of libido, and dyspareunia. Helpful investigations include assessment of sex hormone levels (testosterone and SHBG (or oestradiol), FSH and LH, and inhibin B in males.
Management involves hormone replacement in the standard way (*i.e* testosterone substitution in male patients, estradiol-progestagen (HRT) substitution in female patients).

Hypothyroidism
The frequency of thyroid dysfunction in Wolfram syndrome is not known. It is prudent to include an assessment of TSH in annual review investigations; and in the presence of symptoms, to measure free-T3, free-T4 and TSH. Thyroid substitution therapy can be given if required with L-Thyroxine (starting dose 25micrograms/day in children, 50 micrograms/day in adults)

Growth retardation. Most adults have normal height, but growth retardation is not infrequent. This may relate to pubertal disturbance in those with hypogonadism. Linear growth should be monitored in children using standard growth charts.

Wolfram Syndrome guide for neurologists

Management of neurological involvement by neurologists or neuro-paediatricians

In Wolfram Syndrome almost every organ/body system may be affected. Wolfram Syndrome is typically associated with sensorineural hearing loss, and other progressive neurological abnormalities. The natural history of Wolfram Syndrome was described in 45 individuals studied (mean age 16 years, range 5-32 years) from 29 families in the UK (Barrett et al 1995). Hearing impairment was present in 64%. Sixty percent of all individuals had one or more of the following signs and/or symptoms: ataxia, peripheral neuropathy, mental retardation, early onset dementia (disinhibition and/or short term memory loss), psychiatric illness (most commonly depression), and central sleep apnoea. MRI scans in individuals with this syndrome may show generalised brain atrophy with loss of the posterior pituitary bright spot, thinning of the optic nerves, and loss of volume of the cerebellum and brainstem.

<u>Suggested management</u>

Annual neurological examination for asymptomatic patients and bi-annually for symptomatic patients

Brain MRI scan at diagnosis and to be repeated if acute deterioration of neurological signs and/or symptoms or at adult age

Cerebellar ataxia assessment:

- Use of validated ataxia-specific rating scales for measuring progression : SARA (see supplementary data)
- Washington unified rating scale (WURS)

Management – Multidisciplinary team input and rehabilitation including:

- Ophthalmology services and visual impairment team input to optimise visual functioning
- Physiotherapy and occupational therapy team input with regards physical (gross motor and fine motor / coordination) difficulties
- Speech and language therapy input with regards dysarthria (speech difficulties) and swallowing difficulties (which may lead to recurrent chest infections due to aspiration)
- Drug treatments for spasticity (oral anti-spasticity medications such as baclofen, and/or botulinum toxin injections)

Brainstem (respiratory drive) involvement assessment:

- Screening by polysomnography or nocturnal oximetry (every 2 years)
- If symptoms: bronchoscopy (vocal cord mobility, obstructive cause), spirometry and morning blood gases

Management – as per respiratory / ventilation experts (tracheostomy and ventilatory support if needed)

Peripheral neuropathy assessment:

- Presence of symptoms such as numbness, tingling, burning, jabbing or electric-like pain or absence of deep tendon reflexes
- Presence of signs and / or symptoms of cardiovascular and / or gastrointestinal autonomic neuropathy
- Nerve conduction studies, Tilt-test in presence of autonomic cardiovascular symptoms, other investigations as per advice of cardiology and / or gastroenterology specialists

If neuropathic pain is present consider starting treatment for this – eg. Gabapentin, Pregablin, Carbamazepine, Amitriptyline, Lidocaine patch and / or transcutaneous electrical nerve stimulation (TENS)

Epilepsy assessment:

Electroencephalography if seizures occur

Treatment - Anti-epileptic drugs and counselling

Cognitive assessment:
Neuropsychological testing adapted to age (Children: WISC-IV; Adult: MMSE, FAB) and to vision difficulties

Management - Rehabilitation, special education

Mental health assessment:
Assessment includes taking a complete history and performing a detailed examination. Consider patient's appearance, behaviour, speech, mood, thinking and any abnormal perceptions

Screening for anxiety, depression, abnormal behaviour (obsessive-compulsive behaviours, aggression, eating disorders etc.) or psychosis

Management – consider referral for expert psychiatric input

Wolfram syndrome guide for ophthalmologists

Wolfram syndrome is an ultra-rare neurodegenerative disorder, due to mutations in the WFS1 gene that encodes wolframin, a protein located within the endoplasmic reticulum. Wolfram syndrome is also known by the acronym 'DIDMOAD' (diabetes insipidus, diabetes mellitus, optic atrophy, and sensorineural deafness), but not all patients will exhibit the full phenotype and other manifestations have been recognised including neurological, psychiatric, endocrine, and urinary tract abnormalities. The combination of insulin-dependent diabetes mellitus presenting under 15 years and progressive optic atrophy is a defining clinical feature, and historically the "minimum criteria" for the clinical diagnosis of Wolfram syndrome.

Progressive loss of retinal ganglion cells results in bilateral optic atrophy and irreversible visual failure. Optic atrophy is diagnosed on average age around the age of 15 years old and it is associated with reduced visual acuity, marked impairment of colour vision, and a central or caecocentral scotoma on visual field testing. Retinal ganglion cell loss can be detected on optical coherence tomography (OCT), with diffuse thinning of the retinal nerve fibre layer (RNFL) on peripapillary OCT and generalised loss of the ganglion cell layer on macular OCT. In the early stages of disease, thinning of the RNFL preferentially involves the papillomacular bundle with marked involvement of the retinal nerve fibres in the temporal quadrant. There is evidence that macular OCT could prove useful in differentiating between patients with dominant and recessive mutations of the WFS1 gene that leads to the development of Wolfram syndrome. Optic atrophy with or without sensorineural hearing loss are frequent manifestations of the dominant form of the disease.

Other ophthalmologic findings reported in WFS include congenital cataracts (rare; described in families with dominant WFS1 mutations) and nystagmus. Diabetic retinopathy is uncommon, despite co-occurrence of diabetes mellitus.

Management:

• Assessment by an ophthalmologist with expertise in neuro-ophthalmology or ocular genetics can be helpful to distinguish Wolfram syndrome from other inherited optic neuropathies, such as Leber hereditary optic neuropathy (LHON) and autosomal dominant optic atrophy (DOA), and guide investigations for optic atrophy and genetic testing.

• The initial ophthalmologic assessment should include: refraction to determine best-corrected visual acuity, colour vision testing, funduscopy, ideally with a slit-lamp examination, visual field perimetry, and OCT imaging of the optic nerves and macula.

• Correction of refractive error (if significant).

• Early involvement of low vision services, occupational therapy, and input from patient organisations and RNIB.

• Genetic counselling for family members and carrier testing when indicated.

• Annual eye examination to measure visual acuity and for funduscopy, and if possible, visual field perimetry and OCT imaging.

Consider Wolfram Syndrome

Does a child under the age of 16 years complain of:

- Decreasing visual acuity
- Loss of colour vision
- Central or caecocentral scotoma on visual field testing
- Optic Atrophy on testing

Does the child have any of these diagnostic / supportive features?

- Diabetes Mellitus
- Progressive Optic Atrophy
- Diabetes insipidus
- Sensorineural deafness
- Neurological signs (ataxia, epilepsy, neuropathy, cognitive impairment)

Look for additional features

- Family history of Wolfram Syndrome
- Cataracts
- Nystagmus
- Poor papillary reflexes
- Hypogonadism (males)
- Psychiatric disorders

Investigations:

- Visual fields: Central or caecocentral scotomas
- OCT - RNFL analysis
- Genetic tests WFS1 / CISD2
- Consider other genetic causes of ocular atrophy including LHON and DOA

Management:

- Correct refractive error
- Filtration glasses if photosensitive
- Rehabilitation
- Vision support: Magnifying glasses, digital systems, voice systems

Further information Wolfram Multidisciplinary Services

Birmingham Children's Hospital NHS Foundation Trust

University Hospitals Birmingham NHS Foundation Trust

Version 3 June 2021– Miss Archana Kulkarni, Mr John Ainsworth, Dr, Benson

Wolfram syndrome guide for geneticists

Wolfram syndrome (WS) (OMIM 222300) is the inherited association of childhood onset diabetes mellitus (usually before 15 years) with progressive optic atrophy (Wolfram and Wagener 1938), also known as DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness). It is a progressive neurodegenerative disorder, and many patients also develop urinary tract atony, ataxia, peripheral neuropathy, dementia and other psychiatric illnesses. Although the median age at death is 30 years, some patients have been known to survive into their 6th decade. This is an autosomal recessive monogenic disease, and most affected patients have mutations in the *wfs1* gene (ref). Several families of Jordanian origin have been described with mutations in a second gene, *ZCD2*(ref). These children had a subtly different phenotype without diabetes insipidus but with gastrointestinal bleeding.

Wolfram syndrome-like disorder has been proposed as a name for two families who were characterised by older onset diabetes mellitus, sensorineural hearing loss, psychiatric illness and variable optic atrophy. Both families had a missense mutation in the *wfs1* gene, apparently dominantly inherited.

Finally, *wfs1*-related Low Frequency Sensorineural Hearing Loss (LFSHL) is also caused by mutations in the *wfs1* gene. It is characterised by the autosomal dominant inheritance of congenital, non-syndromic, slowly progressive, low-frequency (<2,000Hz) sensorineural hearing loss.

WS occurs:

- In children presenting most often during the first decade of life, with a mean age of diagnosis of ~ 11 years. This coincides with the development of optic atrophy in addition to diabetes mellitus.
- In all races, but at a greater prevalence in those where first cousin marriages are common, reflecting the autosomal recessive inheritance of the syndrome
- Usually without a family history of diabetes; but there may be a greater risk for psychiatric illness such as depression in first or second degree relatives (Swift 1998).
- In the presence of ketosis or ketoacidosis in a minority of patients (ref). This presentation is responsible for the misclassification of WS patients as Type 1 diabetes mellitus (T1DM).
- Without T1DM associated HLA haplotypes, and without associated islet cell autoimmunity. The underlying pathology is progressive beta cell loss probably through apoptosis.

Other conditions that may be confused with WS include:

- **Wolfram syndrome-like disorder.** There are a small number of patients who have been described with onset of diabetes mellitus and / or progressive optic atrophy in adulthood (ref Nunes, Diabetic Med paper). In the family reported by Valéro et al [2008], the 60-year-old male proband had non-insulin-dependent diabetes mellitus and congenital moderate hearing impairment (50-60 dB HL over all frequencies) that had required use of a hearing aid since childhood. His 81-year-old mother had non-insulin-dependent diabetes mellitus, mild hearing impairment (no hearing aid needed), and bilateral optic atrophy since age 60 years (i.e., WFS). No other signs of WFS were present in mother and son [Valéro et al 2008].

  In the family reported by Eiberg et al [2006], autosomal dominant optic atrophy, hearing impairment, and impaired glucose regulation were observed. One individual had undiagnosed diabetes mellitus, one had impaired glucose tolerance by oral glucose tolerance test (OGTT), and others had poor pancreatic b-cell function as demonstrated by the insulinogenic index (calculated as: [the 30 minute post-OGTT serum insulin concentration minus the fasting serum insulin concentration] divided by the 30 minute post-OGTT plasma glucose concentration).

  The occurrence of (milder) optic atrophy in patients/families with dominantly inherited WFS-like disorder [Eiberg et al 2006] suggests that diabetes mellitus and congenital moderate hearing

impairment in the absence of optic atrophy may be an under-recognized presentation of heterozygosity for *WFS1* mutations, behaving in a dominant fashion.

- **Wolfram syndrome type 2** (WFS2) (OMIM 604928), diagnosed in four Jordanian families and caused by mutations in *ZCD2* on 4q22, is characterized by juvenile-onset diabetes mellitus, optic atrophy, high-frequency sensorineural hearing impairment, urinary tract dilatation, impaired renal function, hypogonadism, and severe gastrointestinal ulcer and bleeding, but not diabetes insipidus [El-Shanti et al 2000, Al-Sheyyab et al 2001, Amr et al 2007]. In one family the facial features were abnormal [Amr et al 2007]. The disorder is apparently very rare and may be confined to a certain ethnic background. Of note, molecular genetic testing of 377 hearing impaired probands did not reveal additional individuals with *ZCD2* mutations, indicating that mutation of *ZCD2* does not explain a substantial fraction of nonsyndromic hearing impairment.

- **WFS1-related Low Frequency Sensorineural Hearing Loss *(WFS1*-related LFSNHL)** Approximately 20% of genetic hearing impairment is inherited in an autosomal dominant manner, a small fraction of which is LFSNHL. Mutations in *WFS1* were identified in ten families out of 13 families with autosomal dominant LFSNHL in whom linkage studies either showed linkage or were compatible with linkage to chromosome 4p [Bespalova et al 2001, Young et al 2001, Cryns et al 2002]. In five of 30 Danish families [Tranebjærg et al 2004] and three of nine Japanese families [Fukuoka et al 2007] with characteristic findings on audiogram and/or a positive family history that were unsuitable for linkage analysis, molecular genetic testing showed *WFS1* mutations.

- **Mitochondrial diabetes.** Maternal transmission of mutated or deleted mitochondrial DNA can result in diabetes. The commonest (albeit rare) form is a point substitution at nucleotide position 3243 (A to G) in the mitochondrial tRNA (leu UUR) gene (van Den Ouweland 1992).This form of mitochondrial diabetes is associated with high tone sensorineural deafness and occasionally short stature. The diabetes is characterised by progressive non-autoimmine beta cell loss and insulin dependence.

- **Thiamine responsive megaloblastic anaemia syndrome** (Roger's syndrome). This is the triad of early onset (under 5 years of age) diabetes mellitus, sensorineural deafness and megaloblastic anaemia (Rogers 1969). This is due to mutations in the SLC19A2 gene (ref Labay). The diabetes is insulin dependent, but may respond to pharmacologic doses of vitamin B1 (Thiamin). Most patients develop an insulin requirement by puberty (Ozdemir Ped Diabetes 2002).
- **Alström syndrome** is characterized by infancy onset cone-rod dystrophy and obesity. Other features include progressive sensorineural hearing impairment, dilated cardiomyopathy, severe insulin resistance, and developmental delay. Cone-rod dystrophy presents as progressive visual impairment, photophobia, and nystagmus starting between birth and age 15 months. Affected individuals have no light perception by age 20 years. Children usually have normal birth weight but become obese during their first year. Progressive sensorineural hearing loss begins in the first decade in as many as 70% of individuals. Severe insulin resistant diabetes often presents by puberty. Other endocrine abnormalities can include hypothyroidism and male hypogonadotrophic hypogonadism. Over 60% of individuals with Alström syndrome develop cardiac failure as a result of dilated cardiomyopathy at some stage of their lives. Approximately 50% of individuals have delay in early developmental milestones. Urologic disorders of varying severity, characterized by detrusor-urethral dyssynergia, appear in females in their late teens. Severe renal disease is usually a late finding. This is a monogenic, recessively inherited form of diabetes, due to mutations in the *ALMS1* gene.

- **Bardet-Biedl syndrome** (BBS) is characterized by cone-rod dystrophy, truncal obesity, postaxial polydactyl, cognitive impairment, male hypo gonadotrophic hypogonadism, complex female

genitourinary malformations, and renal dysfunction. Birth weight is usually normal, but significant weight gain begins within the first year. Insulin resistant diabetes manifests in adolescence or adulthood. A majority of individuals have significant learning difficulties. Renal disease is a major cause of morbidity and mortality. Mutations have been found in at least twelve genes, and inheritance is autosomal recessive.

- **Friedreich ataxia** (FRDA) is characterized by slowly progressive ataxia with mean age of onset between ten and 15 years and usually before age 25 years. FRDA is typically associated with depressed tendon reflexes, dysarthria, muscle weakness, spasticity in the lower limbs, optic nerve atrophy, scoliosis, bladder dysfunction, and loss of position and vibration senses. About two thirds of individuals with FRDA have cardiomyopathy, 30% have diabetes mellitus, and approximately 25% have an "atypical" presentation with later onset, retained tendon reflexes, or unusually slow progression of disease. Mutations in *FXN* are causative. Inheritance is autosomal recessive.
- Kearns-Sayre syndrome (see **Mitochondrial DNA Deletion Syndromes**). Mitochondrial DNA (mtDNA) deletion syndromes comprise three overlapping phenotypes that may be observed in different members of the same family or may evolve in a given individual over time: Kearns-Sayre syndrome (KSS), Pearson syndrome, and progressive external ophthalmoplegia (PEO). Individuals with KSS have the onset of pigmentary retinopathy and PEO before age 20 years and at least one of the following: cardiac conduction block, cerebrospinal fluid protein concentration greater than 100 mg/dL, or cerebellar ataxia. Other frequent but not invariable clinical manifestations include short stature, hearing loss, dementia, limb weakness, diabetes mellitus, hypoparathyroidism, and growth hormone deficiency. Approximately 90% of individuals with KSS have a large-scale (i.e., 1.3-10 kb) mtDNA deletion that is usually present in all tissues; however, mutant mtDNA is often undetectable in blood cells, necessitating examination of muscle. When inherited, mtDNA deletion syndromes are transmitted by maternal inheritance.

- **Optic atrophy type 1** (OPA1, or Kjer type optic atrophy) (OMIM 605290, OMIM 165500) is characterized by bilateral and symmetric optic nerve pallor associated with insidious decrease in visual acuity usually between ages four and six years, visual field defects, and colour vision defects. Visual impairment is usually moderate (6/10 to 2/10), but ranges from mild or even insignificant to severe (legal blindness with acuity <1/20). Other findings can include auditory neuropathy resulting in sensorineural hearing loss that ranges from severe and congenital to subclinical (i.e., identified by specific audiologic testing only). Mutations in *OPA1* are causative. Inheritance is autosomal dominant [Payne et al 2004, Amati-Bonneau et al 2005].

- **Deafness-dystonia-optic neuronopathy syndrome** (DDON, or Mohr-Tranebjærg syndrome) (OMIM 304700). Males with DDON have a progressive auditory neuropathy with prelingual or postlingual sensorineural hearing impairment, slowly progressive dystonia or ataxia in the teens, slowly progressive decreased visual acuity from optic atrophy beginning at about age 20 years, and dementia beginning at about age 40 years. Psychiatric symptoms such as personality change and paranoia may appear in childhood and progress. The neurologic, visual, and neuropsychiatric signs vary in degree of severity and rate of progression. Females may have mild hearing impairment and focal dystonia. Mutations in *TIMM8A* are causative. Inheritance is X-linked.

Genetic testing
Index case : *WFS1 +/- CISD2* screening
1 or 2 mutated alleles : perform mutation screening in parents of index case
Genetic counseling
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).

My name is Denise Williams and I am a doctor specialising in genetic conditions. My role in the Wolfram syndrome clinics is to help individuals and their families by providing understandable information about the condition, explaining the way in which Wolfram syndrome is inherited and arranging genetic testing if this has not already been done. If appropriate I take the opportunity to discuss the risks to future children and / or other family members. The questions I am asked are very varied – I normally suggest you write them down before you attend the clinic as it is a long day and very busy, so important things are easily forgotten. I hope to provide the information necessary to allow families to make informed medical and personal choices.

The first time I meet a family I expect to spend about three quarters of an hour with them, but some people need more and some less. Subsequent appointments are usually shorter and sometimes I am not needed. I always think that people will want to 'dip in and out' of genetics services at different points of their lives. What's really important is that I offer to see the young people affected by Wolfram syndrome in their own right. Genetics is taught really well in school, most commonly in year 10 and year 11, so I like to start discussions at this time. The teenagers pick it up really easily and often ask me challenging questions!

I work closely with the genetic counsellors, Shagufta Khan in the paediatric clinics at Birmingham Children's Hospital and Chris Platt in the adult clinics at the Queen Elizabeth Hospital in Birmingham. Both Shagufta and Chris have specialist training in genetics and counselling skills. Before your first appointment, either Shagufta or Chris will try to telephone you to obtain some basic information before you attend the clinic. They may ask about your family, so that a family tree can be drawn. They may also ask your permission to obtain relevant medical information, including the results of any genetic investigations already carried out. Having this information ahead of the clinic allows us to make the best use of the time available in clinic.

Individuals and families attending the clinic have different knowledge, depending upon their previous experiences. I nearly always go 'back to basics' and discuss the way in which the condition is inherited assuming no previous knowledge. I feel more comfortable doing this as I know I haven't missed anything out and the concepts involved are quite complicated – many people find going over the same thing a second or third time is quite helpful. I use visual aids to help me; I have photographs of chromosomes and I draw diagrams illustrating the way in which genes are passed from the parents to their children. I also have some embossed charts to help me communicate effectively with individuals who have a severe visual impairment.

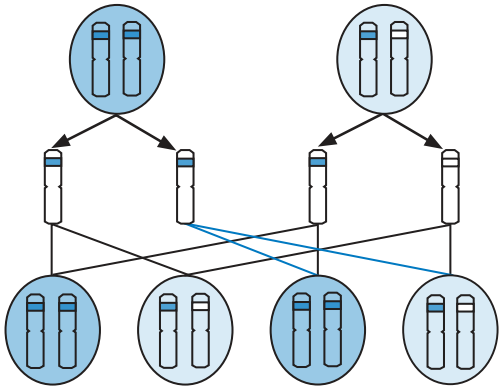
If I have been able to obtain the results of any genetics tests, then I will be able to discuss these in detail in clinic. If not then testing can be initiated using a small sample of blood. Genetic tests are often complex and the results can take several weeks or months. We confirm the diagnosis of Wolfram syndrome when we are able to find 2 misprints, a bit like spelling mistakes, in the 'Wolfram syndrome' gene. This gene is known as WFS1. In the majority of families we have been able to confirm the diagnosis, but this is certainly not true for everyone. Like many rare conditions, Wolfram syndrome is not always straightforward so it is really important that everyone is assessed individually and regular evaluation and surveillance put in place according to that individual's needs. For example, we are starting to see some

individuals with a few of the clinical problems we expect in Wolfram syndrome, but the pattern of these features is a bit different to those we recognise in the classic form of the condition. Some of these individuals have a 'misprint' in only one copy of their WFS1 gene and we say they have Wolfram syndrome-like disease. This seems to be very uncommon, but is important because it is inherited in a different way to the classic form of the condition. When this is important for a family I always discuss this carefully.

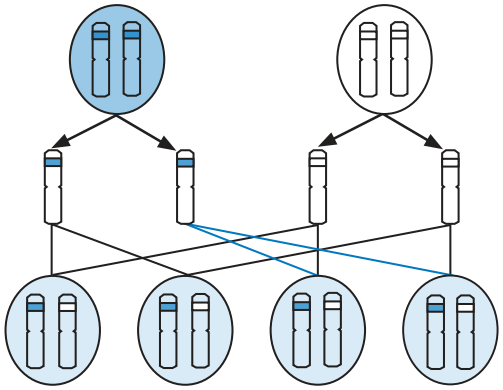
As mentioned already, part of my role in clinic is to discuss the 'risks' to other family members. From a practical point of view, finding the specific misprints responsible for causing the Wolfram syndrome in an individual means that we can use this information to test other family members who may be at risk of the condition or wish to know if they are carriers. I normally suggest this is arranged with the advice and support of the local clinical genetics service and I am in a position to liaise with my colleagues around the country and facilitate this.

Although there is currently no cure for Wolfram syndrome and this may still be a long way off, Professor Barrett who leads the multidisciplinary team in Birmingham is working closely with research doctors across Europe and America. There is no doubt that a greater understanding about the different misprints in the gene and the different ways in which people are affected by the condition, may lead to novel treatments for different aspects of it in the future. This is something we are all hoping to discuss with you in time.

Autosomal recessive inheritance: one parent affected one parent carrier



Autosomal recessive inheritance: one parent is affected one parent not a carrier



Birmingham Women's NHS Foundation Trust is not responsible for the third-party information and does not endorse any product, view or process or opinion from such sources.

Acknowledgements to Guy's and St Thomas' Genetics Department

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Reference Number: GG 12
Author: P. Preece, Genetic Counsellor
Reviewed: June 2014 Next review: June 2017

Birmingham Women's NHS
NHS Foundation Trust

Recessive Inheritance

An information leaflet for patients and families

local care: global impact

This is a no smoking hospital

What is Recessive Inheritance?

What are genes?

Genes are the unique set of instructions in every cell which make each of us an individual. There are many thousands of genes, each carrying a different instruction. If a gene is altered, it can cause a genetic condition or disease. This gene alteration is known as a mutation.

We have two copies of each gene. One copy is inherited from our mother and one copy from our father. When we have children, we pass on only one copy of each of our genes.

What does recessive inheritance mean?

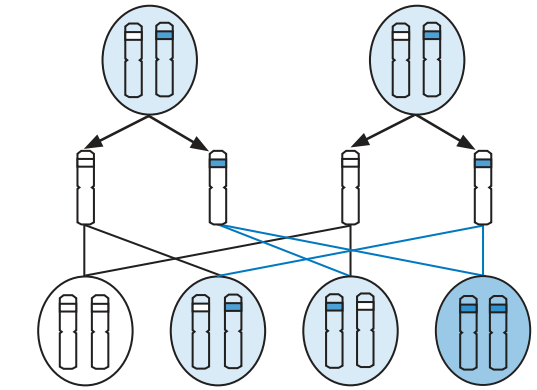
Some conditions are inherited in a way that is called recessive. Individuals who have two altered copies of a gene are affected with the condition. Individuals who have only one altered copy of a gene are usually completely healthy. They are known as carriers, because they carry one altered copy of a gene. Their normal copy of the gene keeps them healthy and compensates for the altered copy.

Having children

If both healthy parents carry the same altered recessive gene, then there are four possible outcomes for each pregnancy they have regardless of the sex of the child they have:
(see diagrams)

- A 1 in 4 (25%) chance of inheriting the altered gene from both parents and being affected
- A 1 in 2 (50%) chance of inheriting the altered gene from one parent and therefore being a healthy carrier
- A 1 in 4 (25%) chance of inheriting the normal gene from both parents and being neither a carrier nor affected

Autosomal recessive inheritance: both parents are carriers

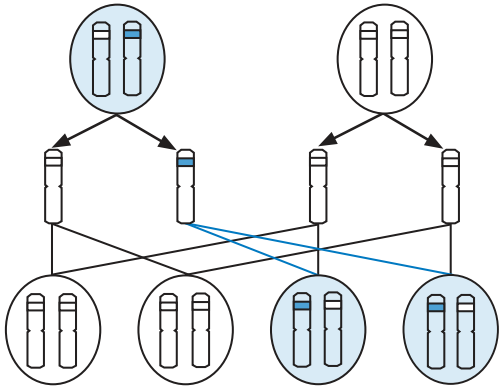


Non-carrier Carriers Affected

If only one parent is a carrier of the altered gene, then each of their children has a 1 in 2 (50%) chance of being a healthy carrier, but will not be affected.

Couples who are closely related to each other (e.g. first cousins) are more likely to share a copy of the same altered gene thereby increasing the likelihood of having a child with a recessively inherited condition.

Autosomal recessive inheritance: one parent is a carrier



Non-carriers Carriers

Wolfram syndrome guide for urologists

Management of urological involvement by urologists, rehabilitation physicians and neurologists

Urge incontinence due to bladder sysynnergia or neuropathic bladder has been reported in up to about 60% of affected people. These features can present during childhood. The pathology is not well understood, but it is thought that there is a loss of upper motor neurone control over the detrusor muscle; in addition, autonomic nervous system dysfunction may lead to altered bladder sensation. Reports from case series show pelviureteric dilatation on ultrasound scans. The part played by cranial diabetes insipidus is unclear.

Baseline investigations

- Ask about urinary symptoms, complete a voiding diary, undertake a clinical examination for evidence of neurological involvement.
- Check renal function (blood electrolytes, urea, creatinine, glomerular filtration rate (GFR))
- Bladder and renal ultrasound (residual urine)
- Urodynamic testing to include flow rates on emptying the bladder, and residual bladder volume.

Management may involve:

Treatment options include advice about double voiding technique ; electrical stimulation; anticholinergic drugs to stabilise the detrusor muscle; botulinum toxin; clean intermittent self-catheterization; permanent indwelling catheter; ileal conduit surgery.

Screening urinary infections

Urine culture if fever or other symptoms

Intermittent self-catheterization

Preliminary assessment of the ability to self-catheterization, taking into account ataxia, low vision or cognitive deficiency (PP-Test)

Indwelling urinary catheter

Risk factors for bladder tumors

Sexual dysfunction

Management in standard way

Wolfram syndrome guide for paediatricians and other health care professionals

Version 2.

Last Reviewed August 2014.

Authors: Dr Denise Williams, Prof Timothy Barrett, Birmingham Women's Hospital and Birmingham Children's Hospital.

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Wolfram syndrome (WS) (OMIM 222300) is the inherited association of childhood onset diabetes mellitus (usually before 15 years) with progressive optic atrophy (Wolfram and Wagener 1938), also known as DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness). It is a progressive neurodegenerative disorder, and many patients also develop urinary tract atony, ataxia, peripheral neuropathy, dementia and other psychiatric illnesses. Although associated with a shorter life span, some patients have been known to survive into their 6th decade. This is an autosomal recessive monogenic disease, and most affected patients have mutations in the *WFS1* gene.

Wolfram syndrome-like disorder has been proposed as a name for two families who were characterised by older onset diabetes mellitus, sensorineural hearing loss, psychiatric illness and variable optic atrophy. Both families had a missense mutation in the *WFS1* gene, apparently dominantly inherited.

Finally, *WFS1*-related Low Frequency Sensorineural Hearing Loss (LFSHL) is also caused by mutations in the *WFFS1* gene. It is characterised by the autosomal dominant inheritance of congenital, non-syndromic, slowly progressive, low-frequency (<2,000Hz) sensorineural hearing loss.

WS occurs:

- In children presenting most often during the first decade of life, with a mean age of diagnosis of ~ 11 years. This coincides with the development of optic atrophy in addition to diabetes mellitus.
- In all races, but at a greater prevalence in those where first cousin marriages are common, reflecting the autosomal recessive inheritance of the syndrome
- Usually without a family history of diabetes; but there may be a greater risk for psychiatric illness such as depression in first or second degree relatives.
- In the presence of ketosis or ketoacidosis in a minority of patients. This presentation is responsible for the misclassification of WS patients as Type 1 diabetes mellitus (T1DM).
- Without T1DM associated HLA-haplotypes, and without associated islet cell autoimmunity. The underlying pathology is progressive beta cell loss probably through apoptosis.

Other conditions that may be confused with WS include:

- ***WFS1*-related Low Frequency SensoriNeural Hearing Loss *(WFS1*-related LFSNHL)** Approximately 20% of genetic hearing impairment is inherited in an autosomal dominant manner, a small fraction of which is LFSNHL. Mutations in *WFS1* were identified in ten out of 13 families with autosomal dominant LFSNHL in whom linkage studies either showed linkage or were compatible with linkage to chromosome 4p. In five of 30 Danish families and three of nine Japanese families with characteristic findings on audiogram and/or a positive family history that were unsuitable for linkage analysis, molecular genetic testing showed heterozygous *WFS1* mutations.

- **Wolfram syndrome-like disorder.** There are a small number of patients who have been described with onset of diabetes mellitus and / or progressive optic atrophy in adulthood. In the family

reported by Eiberg et al [2006], autosomal dominant optic atrophy, hearing impairment, and impaired glucose regulation were observed. The occurrence of (milder) optic atrophy in patients/families with dominantly inherited WFS-like disorder suggests that diabetes mellitus and congenital moderate hearing impairment in the absence of optic atrophy may be an under-recognized presentation of heterozygosity for *WFS1* mutations, behaving in a dominant fashion.

- **Wolfram syndrome type 2** (WFS2) (OMIM 604928), diagnosed in four Jordanian families and caused by mutations in *CISD2* on chromosome 4q22, is characterized by juvenile-onset diabetes mellitus, optic atrophy, high-frequency sensorineural hearing impairment, urinary tract dilatation, impaired renal function, hypogonadism, and severe gastrointestinal ulcer and bleeding, but not diabetes insipidus. The disorder is apparently very rare and may be confined to a certain ethnic background. Of note, molecular genetic testing of 377 hearing impaired people did not reveal additional individuals with *CISD2* mutations, indicating mutations in this gene not explain a substantial fraction of nonsyndromic hearing impairment.

- **Mitochondrial diabetes.** Maternal transmission of mutated or deleted mitochondrial DNA can result in diabetes. The commonest (albeit rare) form is a point substitution at nucleotide position 3243 (A to G) in the mitochondrial tRNA (leu UUR) gene. This form of mitochondrial diabetes is associated with high tone sensorineural deafness and occasionally short stature. The diabetes is characterised by progressive non-autoimmine beta cell loss and insulin dependence.

- **Thiamine responsive megaloblastic anaemia syndrome** (Roger's syndrome). This is the triad of early onset (under 5 years of age) diabetes mellitus, sensorineural deafness and megaloblastic anaemia (Rogers 1969). This is due to mutations in the SLC19A2 gene. The diabetes is insulin dependent, but may respond to pharmacologic doses of vitamin B1 (Thiamin). Most patients develop an insulin requirement by puberty.

- **Alström syndrome** is characterized by infancy onset cone-rod dystrophy and obesity. Other features include progressive sensorineural hearing impairment, dilated cardiomyopathy, severe insulin resistance, and developmental delay. Cone-rod dystrophy presents as progressive visual impairment, photophobia, and nystagmus starting between birth and age 15 months. Affected individuals have no light perception by age 20 years. Children usually have normal birth weight but become obese during their first year. Progressive sensorineural hearing loss begins in the first decade in as many as 70% of individuals. Severe insulin resistant diabetes often presents by puberty. Other endocrine abnormalities can include hypothyroidism and male hypogonadotrophic hypogonadism. Over 60% of individuals with Alström syndrome develop cardiac failure as a result of dilated cardiomyopathy at some stage of their lives. Approximately 50% of individuals have delay in early developmental milestones. Urologic disorders of varying severity, characterized by detrusor-urethral dyssynergia, appear in females in their late teens. Severe renal disease is usually a late finding. This is a monogenic, recessively inherited form of diabetes, due to mutations in the *ALMS1* gene.

- **Bardet-Biedl syndrome** (BBS) is characterized by rod-cone dystrophy, truncal obesity, postaxial polydactyly, cognitive impairment, male hypogonadotrophic hypogonadism, complex female genitourinary malformations, and renal dysfunction. Birth weight is usually normal, but significant weight gain begins within the first year. Insulin resistant diabetes manifests in adolescence or adulthood. A majority of individuals have significant learning difficulties. Renal disease is a major cause of morbidity and mortality. Mutations have been found in at least nineteen genes, and inheritance is autosomal recessive.

- **Friedreich ataxia** (FRDA) is characterized by slowly progressive ataxia with mean age of onset between ten and 15 years and usually before age 25 years. FRDA is typically associated with depressed tendon reflexes, dysarthria, muscle weakness, spasticity in the lower limbs, optic nerve atrophy, scoliosis, bladder dysfunction, and loss of position and vibration senses. About two thirds

of individuals with FRDA have cardiomyopathy, 30% have diabetes mellitus, and approximately 25% have an "atypical" presentation with later onset, retained tendon reflexes, or unusually slow progression of disease. Mutations in *FXN* are causative. Inheritance is autosomal recessive.

- **Kearns-Sayre syndrome** (see **Mitochondrial DNA Deletion Syndromes**). Mitochondrial DNA (mtDNA) deletion syndromes comprise three overlapping phenotypes that may be observed in different members of the same family or may evolve in a given individual over time: Kearns-Sayre syndrome (KSS), Pearson syndrome, and progressive external ophthalmoplegia (PEO). Individuals with KSS have the onset of pigmentary retinopathy and PEO before age 20 years and at least one of the following: cardiac conduction block, cerebrospinal fluid protein concentration greater than 100 mg/dL, or cerebellar ataxia. Other frequent but not invariable clinical manifestations include short stature, hearing loss, dementia, limb weakness, diabetes mellitus, hypoparathyroidism, and growth hormone deficiency. Approximately 90% of individuals with KSS have a large-scale (i.e., 1.3-10 kb) mtDNA deletion that is usually present in all tissues; however, mutant mtDNA is often undetectable in blood cells, necessitating examination of muscle. When inherited, mtDNA deletion syndromes are transmitted by maternal inheritance.

- **Optic Atrophy type 1** (OPA1, or Kjer type optic atrophy) (OMIM 605290, OMIM 165500) is characterized by bilateral and symmetric optic nerve pallor associated with insidious decrease in visual acuity usually between ages four and six years, visual field defects, and color vision defects. Visual impairment is usually moderate (6/10 to 2/10), but ranges from mild or even insignificant to severe (legal blindness with acuity <1/20). Other findings can include auditory neuropathy resulting in sensorineural hearing loss that ranges from severe and congenital to subclinical (i.e., identified by specific audiologic testing only). Mutations in *OPA1* are causative. Inheritance is autosomal dominant.

- **Deafness-dystonia-optic neuronopathy syndrome** (DDON, or Mohr-Tranebjærg syndrome) (OMIM 304700). Males with DDON have a progressive auditory neuropathy with prelingual or postlingual sensorineural hearing impairment, slowly progressive dystonia or ataxia in the teens, slowly progressive decreased visual acuity from optic atrophy beginning at about age 20 years, and dementia beginning at about age 40 years. Psychiatric symptoms such as personality change and paranoia may appear in childhood and progress. The neurologic, visual, and neuropsychiatric signs vary in degree of severity and rate of progression. Females may have mild hearing impairment and focal dystonia. Mutations in *TIMM8A* are causative. Inheritance is X-linked.

Genetic testing
Index case : *WFS1 +/- CISD2* screening
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).

Washington University School of Medicine has a long history of pioneering medical research, including the discovery of the Wolfram syndrome gene (WFS1) and its function, led by the late Alan Permutt, MD, and his team of researchers. Today, a collaborative effort by Washington University School of Medicine faculty, led by Fumihiko (Fumi) Urano, MD, the Samuel E. Schechter Professor of Medicine, is advancing the understanding of the progression of Wolfram syndrome with the goal of identifying targets for therapeutic interventions and treatments for Wolfram syndrome.

AT WASHINGTON UNIVERSITY MEDICAL CENTER IN ST. LOUIS, USA

- Identified an enzyme implicated in endoplasmic reticulum stress as a molecular target for Wolfram syndrome treatment.
- Uncovered FDA-Approved drugs that block activation this enzyme and cell death by induced pluripotent stem cells (iPSCs) derived from patient skin cells. These pluripotent stem cells will help in the identification of therapeutics to treat Wolfram syndrome and may eventually be used to replace damaged tissues, including pancreatic β cells, brain cells, and eye cells, resulting from this monogenic disorder.
- Identified potential biomarkers reflecting the progression of the disease using blood samples from patients and their siblings.
- Several biotech and pharmaceutical companies have been identified with overlapping interests in advancing drugs of potential benefit to patients with Wolfram syndrome. With the aid of the Jack and JT Snow Scientific Research Foundation, Dr. Urano and Dr. Timothy Barrett are planning joint clinical trials.

These translational discoveries utilized an important pediatric patient population, combining multiple assessment methods and resources drawn from a dedicated basic science and clinical community working collaboratively to understand the molecular mechanism and identify actionable targets for the treatment of Wolfram Syndrome.

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http://www.erstress.com/
http://wolframsyndrome.blogspot.com/

WSUK are always pleased to hear from families and those affected by the condition.

Donations and contributions of support are always gratefully received so that we may continue to provide information, support and help fund research into trying to find medication to provide the best treatment.

Donations can be made via post or online by going to our website and following one of the links there.

Wolfram Syndrome UK (WSUK)

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www.wolframsyndrome.co.uk

Reg Charity No: 1152445

WOLFRAM SYNDROME UK
Inform, Support, CURE

June 2016 saw co-founders Tracy & Paul receive the Prime Minister's Points of Light Award.

Prime Minister David Cameron said:

Since Jennifer's diagnosis, Paul and Tracy have taken phenomenal steps to raise awareness and find a cure for Wolfram Syndrome. Their work is having an impact in the medical community and has the potential to transform the lives of those living with this rare condition. I'm pleased to name Paul and Tracy the 555th and 556th UK Points of Light."

Tracy and Paul's local MP, Sir Peter Bottomley MP said:

"Paul and Tracy have built a charity in Worthing that is supporting people across the country living with this rare condition. I'm delighted that their achievements are being recognised by the Prime Minister with this Point of Light award."

https://www.pointsoflight.gov.uk/working-wolfram-syndrome/

In Partnership with

PENFOLD VERRALL

Tracy Lynch
CEO & Co-Founder
WSUK

Prof T Barrett
Birmingham Children's Hospital

Support Group & Charity Information Leaflet

WOLFRAM SYNDROME UK
Inform, Support, CURE

Registered Charity :1152445.
Registered in England & Wales

How it all started

WOLFRAM SYNDROME UK
Inform, Support, CURE

Wolfram Syndrome is a rare, progressive neurodegenerative condition, which is life shortening.

Wolfram Syndrome UK (WSUK) is the only national charity and support group to help fund research and provide support to those affected by the condition as well as their families in the UK.

The support group and website were started in 2010 by Paul & Tracy Lynch from Worthing, West Sussex after their daughter, then aged eight, was diagnosed with WS. The only website associated with WS then was a worldwide site. There was no easy to read information available and no real support, as many medical professionals had or still have never heard or come across the syndrome.

WSUK became a registered charity in June 2013. Prior to that we had been raising funds for research via WellChild, the national charity for sick children, and our fundraising group 'The Charity Roadtrip'.

About Wolfram Syndrome……

The first signs of someone being affected by WS are juvenile onset Diabetes Mellitus and Optic Atrophy (reduced vision). Some patients go on to develop hearing loss and Diabetes Insipidus (water diabetes).

These four conditions are the main features of WS, also known as DIDMOAD. There are also other health problems for those with WS which can include irregular breathing, loss of the sense of smell, depression, loss of the gag reflex and impulsive and aggressive behaviour to name but a few. Not everyone is affected the same or develops all the features. WS affects 1 in 770,000 people in the UK.

What we are doing

There is a dedicated UK telephone line and website giving up to date information on events, research, trials, along with links to other helpful sites, multi disciplinary clinics and Social Media pages for anyone linked to WS to post on. We hold an annual conference for families and doctors to receive useful information and to just meet up. We have a quarterly newsletter with news of fundraising events and other useful information which is emailed out as well as posted on our website with an audio version.

WSUK are working in alliance with Birmingham Children's Hospital and Queen Elizabeth Hospital, Birmingham to raise awareness, bring support to patients and families and to advance research into trying to find a way of halting or slowing down the progression of this syndrome.

Research

Research is being carried out at Birmingham Children's Hospital and The Queen Elizabeth Hospital in Birmingham, as well as at other hospitals and universities around the world. We help to provide funding towards research projects and have helped to fund travel and accommodation costs for UK participants of the TREATWolfram clinical drug trial currently being run.

WSUK keeps up to date with the medical research and is in contact with medical experts who can offer advice.

We maintain the only UK database of those affected by this disorder.

We are endeavouring to get information to hospitals and GP practices around the UK.

Wolfram Syndrome UK

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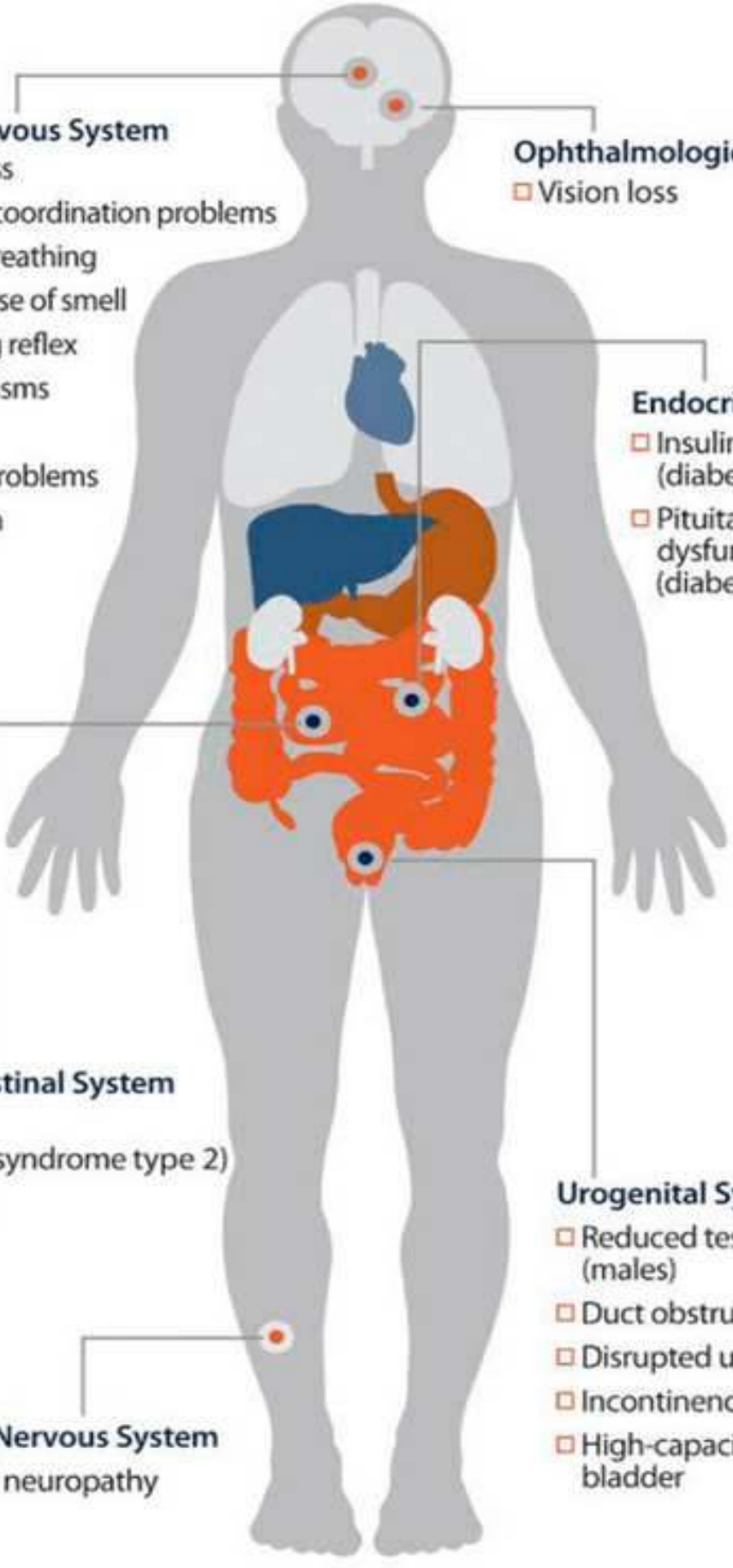
The Effects of Wolfram Syndrome



Central Nervous System
- Hearing loss
- Balance & coordination problems
- Irregular breathing
- Loss of sense of smell
- Loss of gag reflex
- Muscle spasms
- Seizures
- Behavior problems
- Depression

Ophthalmologic System
- Vision loss

Endocrine System
- Insulin shortage (diabetes mellitus)
- Pituitary gland dysfunction (diabetes Insipidus)

Gastrointestinal System
- Ulcers (Wolfram syndrome type 2)
- Bleeding

Urogenital System
- Reduced testosterone (males)
- Duct obstruction
- Disrupted urination
- Incontinence
- High-capacity atonal bladder

Peripheral Nervous System
- Peripheral neuropathy

SNOW FOUNDATION
FOR WOLFRAM SYNDROME RESEARCH

Management of Wolfram Syndrome

A Clinical Guideline

Wolfram Syndrome Guideline Development Group

EURO-WABB is supported by The European Commission under the Health Programme Framework (Agreement number 2010 12 05)

Version 15 March 4th 2015

Contents

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

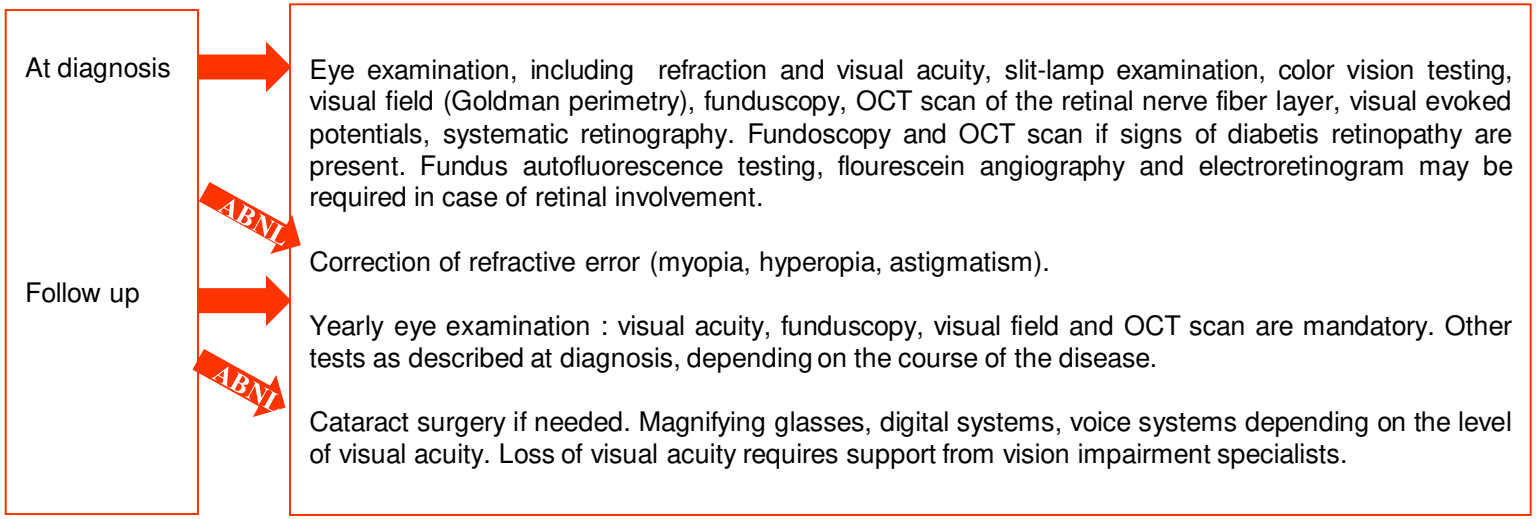
Thyroid substitution therapy with L-Thyroxine (starting dose 25μg/day)

Growth retardation

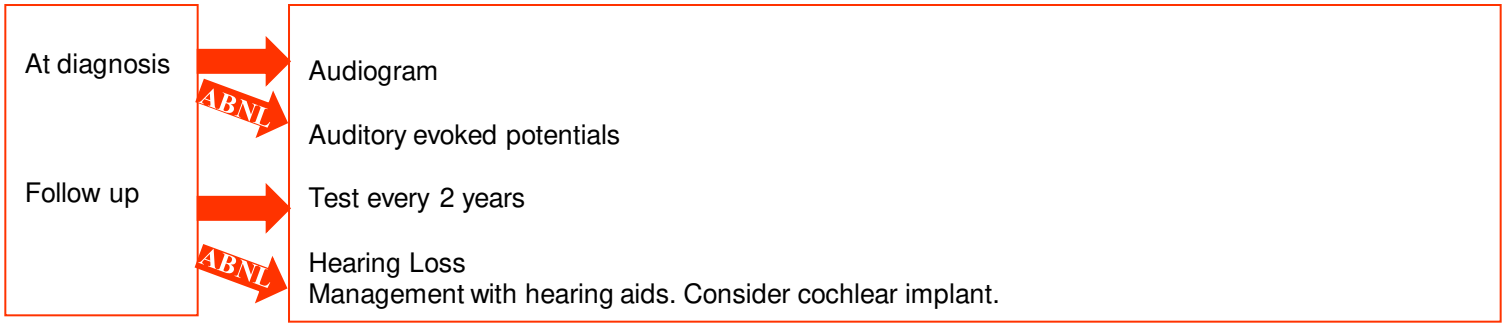
Monitoring of linear growth in children using standard growth charts

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