

National Diagnostic and Care Protocol (NDCP)

Text of the PNDS

Wolfram Syndrome

**Reference Centre for Rare Diseases in Ophthalmology
(OPHTARA)**

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SUMMARY FOR GENERAL PRACTITIONERS

1- General information on Wolfram syndrome

Wolfram Syndrome (WS) is a rare, autosomal recessive neurodegenerative disorder with an estimated prevalence of 1/830,000 people (1/55,000 to 1/700,000 for Barrett)¹. It is still known as DIDMOAD syndrome, an acronym for Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, and Deafness. WS is characterised by the combination of insulin dependent diabetes and optic atrophy, both of which occur early, most often before the second decade. Other conditions may develop, such as diabetes insipidus, sensorineural hearing loss, urinary tract abnormalities and neurological or psychiatric impairment. *WFS1* is the main gene involved, responsible for type 1 WS (MIM #222300) while *CISD2* is responsible for the rare cases of type 2 WS (MIM #604928)²⁻⁴. These 2 genes code for proteins located in the endoplasmic reticulum but do not interact with each other. No mutation is found in 10% of people with WS.

Its clinical diagnosis is based on the combination of either two major criteria or one major criterion and two minor criteria, **which will be developed further below**. The diagnosis is confirmed by the detection of two pathogenic variants in *WFS1* or *CISD2*.

The first manifestations of type 1 WS usually occur within the first decade and are found in more than 80% of patients⁵⁻⁷: insulin dependent diabetes and bilateral optic neuropathy progressing to optic atrophy. The other manifestations are inconsistent and appear from the middle of the second decade. Hearing disorders and diabetes insipidus are found in almost half of all patients. Urinary tract abnormalities, which have long been neglected, are responsible for functional impairment in one in three patients. Some authors have even proposed to rename it to DIDMOADUA syndrome because of the frequency of urinary dysfunctions (neurogenic bladder, hydrouretera, hydronephrosis). Neurological disorders, mainly cerebellar syndrome, are noted in 29% of all patients, but their frequency increases with age⁶. In addition, cerebral abnormalities predominating on the brain stem and cerebellum are found early on MRI 8-10. These neurological disorders can affect patient's vital prognosis when they are responsible for swallowing disorders with the risk of asphyxia or central inhalation and apnea pneumonia due to brainstem damage and reduce their life expectancy. Other causes of death are due to acute complications of diabetes, end-stage renal disease and suicide. The WS type 2 differs from the previous one in that

the absence of diabetes insipidus and the presence of gastrointestinal disorders and digestive bleeding.

2- Diagnostic criteria

The main criteria are:

- Insulin dependent diabetes that appeared before the age of 16;
- Bilateral optic neuropathy progressing to optic atrophy that appeared before the age of 16;

The minor criteria are suggestive of this syndrome but do not, on their own, allow it to be retained:

- Insulin dependent diabetes that appeared after the age of 16;
- Bilateral optic neuropathy progressing to optic atrophy that appeared after the age of 16;
- Diabetes insipidus;
- Sensorineural hearing loss;
- Neurological manifestations;
- Abnormalities of the upper or lower urinary tract;
- Family history of Wolfram Syndrome

The clinical diagnosis of WS is discussed before the association of either two major criteria or one major criterion and two minor criteria. The diagnosis of WS will be confirmed by the identification of 2 biallelic pathogenic mutations in the *WFS1* or *CISD2* gene.

Other rarer symptoms may lead to the diagnosis of WS, but are not minor criteria:

- The absence of autoantibodies in insulin dependent diabetes;
- Bilateral cataract of the young subject;
- Nystagmus;
- Psychiatric disorders with depression type; -
- Hypogonadism or puberty delay
- Hypothyroidism
- Gastric disorders and digestive bleeding in WS type 2;
- Platelet deficiency in WS type 2.

3 - Diagnostic and therapeutic care and the role of the attending physician

Diagnosis is often difficult and delayed due to the rarity of WS. The attending physician should discuss it in a child who develops insulin dependent diabetes and bilateral optic neuropathy with no known cause. The diagnosis will be confirmed by the identification of bi-allelic mutations of the *WFS1* gene. If this search is negative, mutations in the *CISD2* gene can be searched for. Nevertheless, this research can be done simultaneously on panels containing these two genes.

When the diagnosis is confirmed, the patient's management is based on:

- Insulin dependent diabetes monitoring (blood sugar, search for complications)
- Monitoring and compensation for visual impairment (visual aids, low vision rehabilitation, etc.);
- The regular search for other WS related ailments and their specific treatment or compensation;
- The request for exemption from user fees and recognition of disability by the MDPH or the MDA depending on the department.

The general practitioner must ensure that this care is optimised in conjunction with the various specialists concerned. It must also inform families of any benefits and assistance to which they may be entitled in connection with the CDM to ensure optimal educational integration and vocational guidance.

4- Special cases

The clinical spectrum of phenotypes associated with mutations in the *WFS1* gene is not limited to the classical WS.

1.4.1 - Some phenotypes are transmitted in autosomal recessive mode, and are linked to the presence of 2 "recessive" mutations in *WFS1*. These are incomplete forms of WS, in which there is only one major criterion (in particular an optical neuropathia without diabetes) and one or more minor criteria. The transmission mode is autosomal recessive, identical to that of WS.

1.4.2- Other phenotypes are autosomal dominant transmission, associated with the presence of a single "dominant" mutation in *WFS1*. These entities are not WS, and their specific support will not be detailed in this PNDS.

1.4.2.2.1- Some syndromic forms may mimic WS, by combining several disorders, including at least two of the following abnormalities: optic neuropathy, deafness or insulin-dependent diabetes. Neurological disorders are reported to be less common in these forms.

1.4.2.2 Progressive deafness with optic neuropathy and/or dysregulation of blood sugar is sometimes referred to as Wolfram like Syndrome (OMIM #614296). Faced with these syndromic forms of dominant transmission, the question of differential diagnosis with forms of dominant optical atrophy and deafness with a heterozygous mutation in the *OPA1* gene (*OPA1* plus form, *OPA3* gene...) arises.

1.4.2.2.3- Other non-syndromic forms correspond to attacks on isolated organs

- Non-syndromic low-frequency hearing loss DFNA6/14/38 (MIM#600965)
- Isolated insulin-dependent diabetes (MIM#125853)
- - Congenital cataract (MIM#116400).

1.4.2.2.3- Finally, there are congenital forms with a very severe prognosis that are due to de novo "dominant" mutations (not inherited from the parents) of *WFS1*. The diagnostic triad consists of neonatal or very early onset diabetes, cataracts and congenital or very early onset deafness, combined with psychomotor delay and feeding difficulties.

1- INTRODUCTION

1.1- Theme and objectives of the National Diagnostic and Care Protocol (NDCP)

The objective of this PNDS is to explain to health professionals the optimal management and care path for people with WS.

This PNDS and the attached List of Procedures and Benefits (LAP) may be used as a reference by the attending physician (doctor appointed by the patient to the health insurance fund), in consultation with the specialist physician, in particular when establishing the care protocol jointly with the medical officer and the patient, in the case of a request for exemption from the co-payment for an unlisted condition.

The purpose of this PNDS is to homogenize the management and follow-up of the disease, in order to improve the quality of life for patients and their families. However, the PNDS cannot consider all specific cases, all co-morbidities, all therapeutic features, hospital care protocols, etc. It can not claim the exhaustiveness of the possible treatments nor can it claim the exhaustiveness of the possible treatments or replace the individual responsibility of the physician towards his patient. However, this protocol reflects the essential structure for the management of a patient with WS, and will be updated based on the validation of new data.

This work answers the following questions:

- What are the signs to suggest the diagnosis of WS?
- What are the associated manifestations and complications of WS, how to identify them?
- How to confirm the diagnosis of WS?
- What are the manifestations and methods of diagnosis of Wolfram like syndrome?
- What are the modalities of information on the disease and its management?

1.2- Methodology

The National Diagnostic and Care Protocol (NDCP) for Wolfram Syndrome (WS) was developed by professionals from the Reference Centre for Rare Diseases in Ophthalmology (OPHTARA) and the Reference Centre for Sensory Diseases of Genetic Origin (MAOLYA), both belonging to the Sensgène sector and the Reference Centre of Mitochondrial Diseases (CALISSON) of the FILNEMUS sector, in collaboration with the Haute Autorité de Santé (HAS), in accordance with the provisions of the national rare disease plan 2005-2008.

This PNDS has taken into account the European recommendations for the diagnosis and management of WS. After reviewing the international literature, the PNDS was developed according to the method published by the HAS (March 2006) and discussed by a multidisciplinary group of experts. The text of this PNDS was submitted to a review group which evaluated it and proposed corrections. The corrected document was discussed and validated by the multidisciplinary expert Reference Centre for Rare Diseases in Ophthalmology (OPHTARA) / October 2019

group.

1.3- Aspects not covered in this PNDS

This text does not address the particular case of non-syndromic disorders (isolated optical atrophies, isolated deafness and isolated diabetes) or atypical syndromic disorders due to mutations in the *WFS1* gene.

2- DISEASE DEFINITION AND EPIDEMIOLOGY

2.1- Definition

WS is an autosomal recessive neurodegenerative disease combining insulin dependent diabetes, optic neuropathy, progressive cerebral atrophy predominant on the brain stem and cerebellum, leading to various neurological signs: cerebellar ataxia, peripheral neuropathy, dysautonomy, central apnea, hypersomnia, sensory disorders (smell and taste), epilepsy attacks, cognitive and/or psychiatric disorders^{1, 4}.

⁷. Neurological damage and its consequences (motor disability, swallowing disorders.

Its clinical diagnosis is based on the combination of either two major criteria or one major criterion and two minor criteria:

These major criteria are:

- Insulin dependent diabetes that appeared before the age of 16;
- Bilateral optic neuropathy progressing to optic atrophy that appeared before the age of 16;

The minor criteria are:

- Insulin dependent diabetes that appeared after the age of 16;
- Bilateral optic neuropathy progressing to optic atrophy that appeared after the age of 16;
- Diabetes insipidus;
- Sensorineural hearing loss;
- Neurological manifestations;
- Abnormalities of the upper or lower urinary tract;
- WS family history;

Other anomalies may be found that are not part of the minor criteria. These are the absence of autoantibodies for insulin-dependent diabetes, the existence of cataracts, nystagmus, psychiatric disorders, hypogonadism or puberty delay.

In case of type 2 WS, there may be gastric disorders, digestive bleeding, and platelet dysfunction¹².

The diagnosis is confirmed by the detection of two pathogenic mutations of the *WFS1* gene (WS type 1) or *CISD2* (WS type 2)²⁻⁴.

There are incomplete forms of Wolfram syndrome requiring an initial assessment and follow-up identical to the search for the appearance of new symptoms, sometimes sub-clinical.

2.2- Evolution and prognosis:

Insulin dependent diabetes is usually the first manifestation of WS on average at age 7, followed by optic neuropathy discovered at age 9 or 10. Nevertheless, WS can start with damage to the optic nerve.

Hearing disorders are found, depending on the series, in 62 to 72% of patients, related to an inner ear injury, therefore endocochlear^{13 - 16}. There is also a loss of cochlear nerve fibres, cochlear nucleus neurons and lower colliculus¹⁷.

Patients may have balance disorders but these are more frequently related to neurological damage than to vestibular damage.

Diabetes insipidus is found in about 42% of patients and also occurs in the second decade. It can aggravate urinary disorders that may exist as early as adolescence. They combine urinary tract malformations and bladder innervation disorders due to neurological impairment of the disease.

These neurological disorders begin clinically in late adolescence and become more pronounced with age. Neuro-radiological abnormalities are sometimes found very early in the course of the disease. Cerebellar syndrome with ataxia, dysarthria and dysphagia is the most common disease (54%). Epilepsy, cognitive disorders, peripheral neuropathy or dysautonomy may also be observed. Neurological disorders can be complicated by respiratory distress or inhalation syndrome due to swallowing disorders that can lead to death. As a result, life expectancy is reduced without it being possible to determine the precise duration.

2.3- Genetics :

Two genes are responsible for WS:

- *the WFS1* gene, located in 4p16.1, is responsible for type 1 WS corresponding to the majority of cases^{2, 18, 19}. patients with type 1 WS may carry homozygous biallelic mutations or composite heterozygotes.
- *the CISD2* gene, located in 4q22.24, is responsible for type 2 WS whose prevalence is lower and which mainly affects populations of Jordanian origin^{20, 21}.

2.4- Epidemiology:

The prevalence of WS is between 1/550,000 and 1/830,000 people¹.

2.5- Special forms :

The phenotypic spectrum associated with mutations in the WFS1 gene is not limited to the classical WS.

2.5.1 - Some phenotypes associated with WFS1 mutations are transmitted autosomally recessively with the identification of biallic mutations in the WFS1 gene. These are incomplete forms of WS, in which there is only one major criterion (in particular optic atrophy without diabetes) and one or more minor criteria.

2.5.2- Certain phenotypes transmitted in the autosomal dominant mode, **due to** the presence of a single "dominant" mutation in WFS1. These entities are not WS, and their specific support will not be detailed in this PNDS.

2.5.2.2.1- Some syndromic forms may mimic a WS, by combining several disorders, including at least two of the following abnormalities: optic neuropathy, deafness or insulin-dependent diabetes. Neurological disorders are less common in these forms. Progressive deafness with optic atrophy and sometimes deregulation of blood sugar is sometimes called Wolfram like Syndrome (MIM #614296).

2.5.2.2.2- Other non-syndromic forms correspond to isolated disorders:

- Non-syndromic low frequency deafness DFNA6/14/38 (MIM #600965)
- Insulin dependent diabetes (MIM #125853) █
- Congenital cataract (MIM#116400).

2.5.2.2.3- Finally, there are congenital forms with a very severe prognosis that are due to de novo "dominant" mutations (not inherited from the parents) of WFS1. The diagnostic triad consists of neonatal or very early onset diabetes, congenital or very early onset cataract and deafness, combined with psychomotor delay and feeding difficulties.

MAJOR CRITERIA	MINOR CRITERIA	OTHER EVENTS	MUTATION
Insulin dependent diabetes that appeared before the age of 16	Insulin dependent diabetes that appeared after the age of 16	Absence of auto antibodies for insulin dependent diabetes	<i>WFS1</i> (WS type 1) or <i>CISD2</i> (WS type 2)
	Optical neuropathy bilateral progressing to optic atrophy that appeared after the age of 16	Cataract	
	Diabetes insipidus	Nystagmus	
	Deafness neurosensory	Psychiatric disorders	
Bilateral optic neuropathy progressing to optic atrophy that appeared before the age of 16	Neurological demonstrations	Hypogonadism	
	Upper or lower urinary tract anomalies	Pubertal delay	
	Family history of WS		
		Gastric disorders	<i>CISD2</i> (WS type 2)
		Digestive bleeding	
		Platelet dysfunction	

Major and minor WS criteria and other manifestations according to the mutated genes

3- DIAGNOSIS AND INITIAL ASSESSMENT

3.1- Main objectives: There are five of them:

- Detect the disease;
- Confirm the diagnosis;
- Look for possible damage to the different **target organs**;
- Provide genetic counselling;
- Define therapeutic management.

3.2- Professionals involved :

The detection of WS concerns both the attending physician (diabetes) and the various specialists (diabetologist, endocrinologist, ophthalmologist, paediatrician, ENT specialist, nephrologist, neurologist).

Confirmation of WS and the search for possible damage to other **devices** or organs require multidisciplinary medical collaboration involving the geneticist, diabetologist, endocrinologist, ophthalmologist, ENT specialist, nephrologist, neurologist, radiologist and urologist. A Reference or Competence Centre involved in the management of this pathology may be called upon.

3.3- Circumstance of discovery: WS is usually mentioned in a child under 16 years of age in the presence of insulin dependent diabetes associated with a decrease in vision reported with damage to the optic nerve due to the absence of retinal abnormalities and/or a decrease in hearing. The occurrence of such a picture must lead to a clinical and paraclinical assessment which aims to:

- on the one hand to confirm the diagnosis;
- on the other hand, to seek sub-clinical or patent damage to other **target devices** or organs: endocrinological, ENT, neurological, neuroradiological, urological, psychiatric.

The appearance of different clinical manifestations is correlated with the age of the patient. However, some anomalies, particularly neuroradiological ones, can be detected at an infra-clinical stage.

3.4- Clinical diagnosis and initial assessment: The diagnosis of WS is based on the combination of either two major criteria or one major criterion and two minor criteria. It's definitely

established by the detection of two pathogenic biallelic mutations of the *WFS1* genes or *CISD2*.

The assessment specifies:

- any family history,
- the age of onset of the first anomalies, as diagnosis is often delayed.

Different systemic violations can be found or must be investigated.

3.4.1- Insulin dependent diabetes: Diabetes is often the first manifestation of WS. Diabetes is associated with a functional defect and a decrease (in function and number) in beta pancreatic cells. Beta cell loss is a constant feature of the disease. However, there is still very long and often residual insulin secretion, so patients will not experience acute complications such as ketoacidosis.

The initial diagnostic assessment must:

- check the negativity of autoimmunity markers in type 1 diabetes (antibodies against insulin, GAD, IA2, ZnT8)
- look for rare associations with HLA DR3 and DR4 groups with a predisposition to type I diabetes²².

3.4.2- Optical neuropathy :

The most common **occurrence** is a decrease in bilateral visual acuity in a middle-aged child of 9 years of age.

The initial diagnostic assessment must include:

- an ophthalmological examination with:
 - A measurement of refraction under cycloplegic;
 - A measurement of visual acuity at the Monoyer scale or preferably with the international EDTRS scale;
 - A measure of eye tone;
 - An examination of the fundus that reveals a pale optic papilla, bilateral and symmetrical;

- Papillary retinography showing optic atrophy (decrease in optic nerve fibres) main sign of optic neuropathy;
- An assessment of colour vision with the 15-tone (Hue) saturated or desaturated test or the 28-tone (Hue) Lanthony test based on the level of visual acuity looking for dyschromatopsia along a red/green axis of confusion;
- A Goldmann manual visual field that allows better control of the fixation that will reveal a central or caecocentral scotoma;
- Multimodal imaging:
 - colour shots of the papilla,
 - autofluorescent cliches to remove drusen from the papilla and hereditary retinal dystrophy,
 - an OCT measurement of the thickness of the optical fibres around the optic disc and the thickness of the layer of ganglion cells in the macular region ²³;
 - a macular section in OCT;
- Electrophysiological investigations:
 - electroretinogram and
 - potential evoked visual flashes (generally normal) and checkers (decrease in amplitude and increase in latency depending on the size of the checkers).

-Other ***circumstances of occurrence and other signs***.

Decreased visual acuity may precede the diagnosis of diabetes, or on the contrary occur later in adolescence. In both cases, it is the systematic search for mutations in the *WFS1* gene, which must be done before any isolated optical neuropathy, that will allow diagnosis. The achievement of colour vision may take precedence over the decrease in visual acuity and should lead to a search for an optic nerve defect as a matter of principle in order to make a diagnosis ⁷.

There may be a certain degree of intolerance to light (photophobia), but this is still limited.

The decrease in visual acuity is related to the loss of optical fibres, but it can also be related to a cataract, willingly of the dusty or sub-capsular type, which can be congenital ²⁴. This cataract may be present before the onset of diabetes and optic neuropathy, and may require phakoexeresis ^{25 26}. Associated congenital glaucoma cases have been reported ²⁷. Finally, very rare cases of retinal pigment rework, particularly macular, moderate, without dysfunction from the retina to the electroretinogram, were mentioned (lesions similar to those noted in cases of MIDD syndrome) ²⁸.

3.4.3- Neurological abnormalities:

The age of onset of neurological disorders is variable; with a median age of 15 years but which actually reflects 2 age peaks of onset ⁶; they are rarer or absent in the case of CISD2 mutation.

NEUROLOGICAL EVENTS	SYMPTOMS	COMMENTS
Neurodevelopmental	Epilepsy Sometimes psychomotor retardation and/or learning disabilities Rarely a mild intellectual disability	Rare scene from childhood
Cerebellar Ataxia ⁸⁻⁹	Unstable walking, Dysmetry, Coordination disorders, dysarthria, Sometimes nystagmus	Most common symptom
Paresthesias and dysesthesia ⁸⁻¹¹	Deep sensitivity disorders	By peripheral neuropathy
Dysautonomy syndrome ⁸⁻⁹	Hypotension, Abnormalities of sweating (hypo/hyper/anhydrosis), digestive motility disorders (gastroparesis, constipation), Thermal regulation disorders	
Brainstem Disease ⁸⁻⁹ .	Bulbar dysfunction leading to <ul style="list-style-type: none"> • Ventilatory insufficiency, and apnoeas that may be associated with daytime hypersomnolence • Pronicpalement of swallowing disorders. 	Inhalation pneumonitis and apnoea are the frequent causes of death in patients.
Anosmia or hyposmia (loss of sense of smell) ⁸⁻⁹	Affected by other pairs of cranial nerves	From the second or third decade onwards
Sleep disorders ²⁹ .	Frequent awakenings, Snoring, Enuresis	Often linked to nocturnal urination due to neuropathic disorders

	Hyper-sleepiness,	bladder emptying and bladder disorders concentration of urine from diabetes insipidus
Epileptic seizures ⁶	Generalized (myoclonias, tonic-clonic seizures) More rarely focal seizures	Advanced neurological impairment
Cognitive impairment ⁶ .	Memory disorders, Dementia with a memory disorder executive functions (problem solving, planning, anticipation, reasoning, decision making) and apraxia.	Most often late, insidious
	Learning disabilities or delayed learning, Decreased verbal performance	From childhood onwards
Psychiatric disorders ^{8,9,30}	Anxiety, depression, Oppositional disorders, Eating disorders	Frequent

The consequences of these clinical and paraclinical manifestations are marked by a progressive motor disability, which can compromise patients' walking autonomy. Kinetic ataxia is associated with clumsiness, which can limit the independence of patients in performing the usual fine movements (dressing, preparing meals, cutting). Digestive and urological disorders of neurological origin are sometimes very significant, and penalise the comfort of life. Neurological disorders are aggravated by sensory deficits (vision, hearing), sometimes compounded by psychiatric or cognitive comorbidity, gradually impacting patients' quality of life, autonomy and socialisation.

The initial diagnostic assessment must include :

- A neurological examination
- A brain MRI that can show various abnormalities that appear and gradually worsen. The earliest signs are cerebral atrophy, cerebellar atrophy, cerebral stem atrophy, especially of the ventral part of the bridge and middle cerebellar peduncles ^{8 9 10}. It may also show atrophy of the optic pathways, thinning of the hypothalamus and infundibulum, abnormalities of the black substance ³¹. In diabetes insipidus, the physiological hypersignal of the post-hypophysis is lost in sequence T1 ^{8,9}.

- A neuropsychological assessment according to the patient's situation and age
- Further investigations based on clinical examination data (EMG, EEG)

3.4.4- Urological disorders are related to neurodegeneration, which also affects the urological system, and are probably secondary to damage to the autonomic nervous system. Urinary manifestations are frequent, occurring in about 90% of patients and early with a median age of onset close to 15 years, previously described in the third decade ^{1, 32}.

Clinical signs are linked to different diseases:

UROLOGICAL EVENTS	SYMPTOMS	COMMENTS
Dysfunction vesicosphincter ^{33 34}	Stress urinary incontinence, OAB Dysuria, Storage phase disorders (detrusorian hyperactivities or hypoactivities and vesicosphincterial dyssynergies)	Polymorphic symptoms of the lower urinary tract
Reaching the top of the device, ^{33. 35}	Expansion (uretero - hydronephrosis) rarely isolated	Partner <ul style="list-style-type: none"> • Neurodegenerative damage (central and/or peripheral somatic and autonomous) • To vesicosphincterial dysfunctions
Impaired renal function ³⁶		Mixed linked: <ul style="list-style-type: none"> • To diabetic nephropathy • To the expansion of the upper device

Severity is related to uro-nephrological complications (20% of patients) and impact on quality of life, reported in half of patients with urological symptoms. The Reference Centre for Rare Diseases

vesicosphincter dysfunction is therefore a major concern during type 1 WS. Systematic screening from childhood would prevent progression to serious uro- nephrological complications that could impact patients' vital prognosis.

The initial diagnostic assessment must include:

- The search for functional signs using validated questionnaires (USP and ICIQ-FLUTS).
 - Determination of creatinine and blood urea with an estimate of the glomerular filtration rate
 - A bladder and kidney ultrasound with post-void residual search (PVD)
- A urodynamic check-up.

3.4.5- ENT damage can affect hearing, balance and swallowing.

3.4.5.1- Hearing disorders having an average age of onset between 10 and 16 years, deafness is then post-lingual and allows normal oral language development. However, much earlier onset, before the age of 2 years, has been noted, although deafness would not usually be congenital ^{7 37}. The degree of deafness is variable, medium to deep, with a preferential effect on high frequencies. This hearing loss can be slowly progressive.

The initial diagnostic assessment must include:

- An otoscopy with growing material more or less associated with a tympanometry
- Subjective audiometry
 - Tone audiometry in a soundproof audiometry booth with air conduction to the helmet (or less frequently with inserts) and bone. For children, conditioning techniques must be adapted to the child's age (behavioural test, conditioned orientation reflex, TV show...). Depending on the child's age and cooperation abilities, if the headset test is not feasible, a free-field test can be performed, testing the best of both ears.

- Voice audiometry in silence in a soundproof audiometry booth (see for usable voice equipment). The technique must be adapted to the child's age (image designation, intelligibility test with word recognition, etc.)³⁸.
- A vocal audiometry in noise can be added (Hirsch test, Hint test... in adults, to be adapted for children according to age).
- An electrophysiological evaluation
 - Potentials evoked with study of latencies and search for auditory thresholds, in air conduction (+/- bone if in doubt about associated conductive hearing loss, especially in children of otitis seromucosa age). The stimuli used are usual to the examiner's choice (clicks, tone burst, chirp...).
 - Search for acoustic oto-emissions or distortion products
- Frequency stationary auditory evoked potentials or ASSR (Auditory Steady State Response) can complete the assessment of hearing thresholds.

● Cochleo-vestibular imaging (in particular MRI that will be able to couple neurological and cochleo-vestibular exploration). The age at which cochleo vestibular MRI is performed will vary in children and may be performed during follow-up if hearing rehabilitation does not require surgery, to allow MRI to be performed without general anesthesia.

+/- a speech and language therapy assessment

- An assessment of speech comprehension (in silence and noise). In children and adults, an evaluation of the spontaneous use of visual aids such as lip reading is interesting because of the double sensory impairment of hearing and sight (test performed with and without lip reading).
- An assessment of articulation and phoneme acquisition (to be checked before word recognition tests in children).
- An assessment of speech and language, particularly in children in the event of pre-lingual or peri-lingual deafness.

3.4.5.5.2- Balance disorders with ataxia are reported in WS, related to neurological disorders, around the age of 30 years^{5 39}. However, an earlier start was also

described⁴⁰. Studies have also shown abnormalities in the vestibular check-up, which may contribute to the balance difficulties encountered by patients^{7,37}. The vestibular check-up is therefore recommended and must be adapted to the visual impairment. Ideally, an overall assessment of root canal and saccular function can be performed

:

The initial diagnostic assessment could include :

- A videonystagmoscopy with search for an induced nystagmus (head shaking test, vibrations, positional manoeuvres)
- High-frequency tests of the six vestibular channels, video-head-impulse-test (VHIT) type
- A video-nystagmography (VNG) with rotating and caloric tests. Geometric calibration may be necessary depending on the visual impairment
- Myogenic evoked potentials (MEPs)
- A global equilibrium test (posturography), type MiniBest

The tests are to be adapted to the child's age⁴¹.

3.4.5.3- Neurological olfactory and taste disorders have been described. A precise assessment can make it possible to identify them.

The initial diagnostic assessment could include:

- discrimination and identification tests for odours and primary tastes

3.4.5.5.4- Swallowing disorders, accompanied by chewing difficulties, and of neurological origin can be responsible for false routes.

The initial diagnostic assessment could include:

- In addition to the neurological examination (especially of cranial pairs),
 - a swallowing nasofibroscope
 - a videoradiology of the swallowing can be proposed.
 - A speech and language assessment of swallowing ability may also be helpful.

3.4.6- Endocrine status: Endocrine involvement of type 1 WS can have an impact on the progression of neurodegenerative disease. A good management of these endocrine disorders,

with a "tailor-made" substitution, slows down the progression of certain neurological symptoms.

Endocrine Deficit		Clinical signs	Commentary
Hypothyroidism		Fatigue, Constipation, Bradycardia, Dry skin Elevated TSH and decreased thyroid hormones (T3 and T4)	Can start in adolescence
Hypogonadism	Boy => gonadal insufficiency	Cessation of puberty between 12 and 16 years of age +/- Incomplete virilization ³⁴ ; Stops the growth of the testicles; Fertility could be impaired ⁴² ; Blood concentration of testosterone does not increase during puberty; Significant increase in blood levels of LH and FSH.	Found in 50% of adolescents with WS. Affects boys and girls equally
	Girl	Delayed onset of menstruation or irregularity in the menstrual cycle.	
<p>The initial diagnostic assessment must include:</p> <ul style="list-style-type: none"> • A blood test for TSH and thyroid hormones • A dosage of FSH, LH, testosterone, Inhibin B 			

3.4.7- Diabetes insipidus assessment: During type 1 WS, classically, diabetes insipidus appears in the 2nd decade, after optic atrophy and diabetes mellitus and before ataxia and deafness ¹: it is considered central ⁴³, probably due to an alteration in the synthesis pathway of the antidiuretic hormone ⁴⁴.

Clinical sign	Biology	Differential diagnosis
Polyuria (diuresis volume > 3 L/day) Hypernatremia if lack of thirsty feeling or limited access to water	Natremia (and/or plasma osmolality) => high values of normal AND Urinary osmolality (on	Glycosuria (related to hyperglycemia) => osmotic polyuria: Urinary osmolality # of the value measured in plasma

	Sample) < to the value measured in plasma	
Origin	Mechanism	DDAVP test
Power plant	Lack of secretion of antidiuretic hormone	Urinary osmolality increases
Nephrogenic	Failure of renal response to the antidiuretic hormone	
The distinction between these two origins can only be made after studying the response to the administration of dDAVP during day hospitalization		

It is not present in all patients (38 to 75% of patients) and diabetes mellitus can complicate phenotypic analysis ^{7 45 46}. In case of diagnostic doubt, do not hesitate to use a specialized centre used to explore and manage patients with polyuria.

3.4.8- Coagulation and digestive assessment: During type 2 WS, there is a classic risk of digestive bleeding, particularly by gastric ulcer. The risk of bleeding is increased by platelet coagulation abnormalities due to the *CISD2* mutation.

However, no systematic assessment is recommended.

3.4.9- Diagnostic genetic assessment: The clinical diagnosis is confirmed by molecular analysis which consists of research, from a blood sample, of the mutations responsible for the disease. Genetic diagnosis is only made after a medical genetics consultation and informed consent from the patient or his or her parents. Obtaining consent for adults with a disability (persons with cognitive disorders or serious psychiatric cases, persons under guardianship) must be the subject of a special procedure that requires the signature of the legal representative.

The diagnosis of WS, an autosomal recessive disease, can be confirmed by the implementation of evidence of 2 biallelic mutations in the *WFS1* gene encoding Wolframase or in the *CISD2* ^{2 3 3 20 47} gene. These mutations can be identical (homozygous) or different (composite heterozygous in the most frequent case).

3.5- Different clinical forms: At the end of this assessment, it is possible to differentiate between several clinical forms related to WS

- Depending on the mutated gene: type 1 WS is due to the presence of mutations in the *WFS1* gene while type 2 WS is associated with mutations in the *CISD2* gene.
- Depending on the diffusion of the achievement: Some patients have damage to all the different organs and **devices**. Others have limited impairment in diabetes and optic neuropathy. However, these incomplete forms of WS require an initial assessment and follow-up identical to the search for the appearance of new symptoms, sometimes sub-clinical. In addition, some symptoms have a delayed onset with age.
- Depending on the mode of transmission: The particular form transmitted in an autosomal dominant mode produces a WS like syndrome that should benefit from the same initial assessment. The care and subsequent follow-up must be adapted to these particular forms, which are not developed in this PNDS.

4- GIVING THE DIAGNOSIS AND GENETIC COUNSELLING

4.1- Giving the diagnosis: Giving the diagnosis must be the subject of a dedicated consultation to allow time to :

- explain the disease, its natural history and prognosis for this disabling chronic multisystemic disease;
- explain the medical care and subsequent follow-up;
 - discuss social and medico-social care and to present the patients' association on this occasion;
- to consider genetic counselling for the family.

It is desirable that the diagnosis be made in the presence of both parents in the case of children or adolescents. If possible, it may involve the various members of the multidisciplinary team, including a psychologist, social worker and specialists depending on the clinical manifestations.

It is advisable to see the patient and their family again in a second step to answer their questions again.

4.2- Genetic counselling: This must be carried out during a medical genetic consultation, the purpose of which is to inform the patient or parents of the risk of passing on the disease, the potential clinical consequences of passing it on, and the possible indication of a prenatal diagnosis (PND) or pre-implantation diagnosis (PID). As soon as the diagnostic suspicion is raised, the geneticist must explain the bases of the autosomal recessive heredity of the WS, which will be repeated during the consultation of the results of the molecular study ⁵.

For a couple who have had a child with WS, the risk of recurrence in future pregnancies is 1 in 4 (25%) with each pregnancy, regardless of the sex of the expected child.

For people with WS, genetic counselling is reassuring with a low risk of passing it to their offspring. Nevertheless, some teams recommend looking for the mutation identified in the family in the spouse of a heterozygous person. Indeed, the risk that her partner may also carry a mutation in the same gene varies from 1/230 to 1/900, given the low prevalence of heterozygotes in the general population. Similarly, in the case of a request for genetic counselling from a healthy relative, a low risk of recurrence is given, given the low prevalence of heterozygotes in the general population, provided that the 2 spouses are not related ⁴⁸. In this situation, some teams recommend testing the healthy relative first to determine whether or not he is heterozygous for the mutated gene. If it is not heterozygous, the risk of the couple is zero or very close to zero. If he is a heterozygous carrier of the mutation, the risk of the couple varies according to the prevalence of heterozygotes in the general population, from 1/460 to 1/800.

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Prevalence of WS according to different references	Prevalence of heterozygotes	Risk for a union between an affected person and a person from the general population	Risk for a union between a heterozygous subject and a person from the general population
1/50 000	1/115	1/230 RR : 240	1/460 RR : 120
1/700 000	1/420	1/840 RR : 830	1/680 RR : 415
1/830 000	1/450	1/900 RR : 900	1/800 RR : 450

RR : Relative risk, i.e. the factor that increases the risk relative to the general population

PND or PGD is only possible if the mutations in the index case have been identified and the segregation of the mutations has been confirmed in both parents. The indication must be carefully discussed. A consultation of specific medical genetics must be proposed and the indication must be discussed within the framework of a multidisciplinary centre for prenatal diagnosis (CPDPN). If the couple opts for a PND, the SCOD may propose medical termination of pregnancy in the event of a recurrence, taking into account the severity and incurability of WS. PND is performed by determining the genotype of foetal cells obtained either by chorionic villus biopsy (between 11 and 14 weeks of amenorrhea) or by amniocentesis (from 16 weeks of amenorrhea). The main complication of these methods is the risk of miscarriage, estimated at 1% and 0.5% respectively.

PGD is also available for a couple at risk of passing on the disease to their offspring. It consists in searching for the genetic anomaly on embryos obtained by in vitro fertilization. Only embryos, which do not carry both mutations, will be transferred to the uterus.

In the absence of curative treatment of the disease, PND and PGD are the only procedures to date that can prevent the recurrence of the disease for a couple at risk. The latter must be informed of the possibility of using them and of their practical arrangements.

5- THERAPEUTIC MANAGEMENT

5.1- General objectives: They are multiple:

- early control of diabetes and prevention of its complications;
- treat endocrine, urological and neurological complications;
- Slow down or compensate for sensory disabilities and balance disorders;
- provide comprehensive care for patients and their families and adapt their lifestyles. In particular, it is necessary to promote the person's academic or socio-professional integration.

5.2- Staff involved: The overall management of the patient's illness is based on multidisciplinary cooperation, coordinated by one of the doctors at the referral or competence centre.

Comprehensive patient care involves many professionals in the city and in the hospital who work jointly with the attending physician (see Appendix 1). Paramedical professionals (speech therapists, speech therapists, dieticians, occupational therapists, etc.) and professionals in the medico-social sector participate in assessments, adapt care according to needs and carry out actions within their competence.

Coordination with a specialised facility for the visually impaired, hearing-impaired or people with reduced mobility may be useful in the course of the disease's progression.

5.3- Therapeutic education and lifestyle adaptation: Information given to the patient and his family is not a substitute for therapeutic education. This information includes:

- Symptoms that may occur during WS, specifying that any modification or aggravation of the symptomatology must justify a consultation;
- Prescribed treatments, their monitoring and possible side effects;
- Organising regular follow-up and planning the necessary examinations to detect possible complications.

5.3.1- Therapeutic education and sensory compensation: Therapeutic education is mainly focused on blood glucose control education and teaching about the use of rehabilitation equipment for vision and hearing disorders.

It is essential to ensure that the patient's and possibly his or her family's knowledge is learned and evaluated, that blood glucose controls are managed and that doses of insulin are adjusted and diet. The involvement of a dietician is often necessary from the first visit, and reinforced at each consultation.

Knowing that we are willing to find ourselves in a context of multiple disabilities, with rapidly significant visual impairment and deafness in 50% of patients, an assessment of visual and auditory function is required before any rehabilitation.

Deficit	Techniques	Means
Visual impairment	Fixing refraction errors	Glasses, Filter glasses in case of photophobia
	Optical aids	Magnifying glasses, magnifying glasses, telescopes, telemagnifiers. Large computer screen, tablet
	Non-optical aids	Large print books,...
	For schooling	School life assistance => help with reading and learning; Additional time for checks and exams; Electronic devices: tablet, electronic magnifying glass, tele-enlarger, large computer screen.
	Rehabilitation: <ul style="list-style-type: none"> • In case of degradation of visual acuity and visual field • In a specialized centre with integrated care • Or on an outpatient basis 	Mobility course (handling a cane), Learning Braille, Occupational therapy (identification in the environment), Psychological assistance, Computers, Voice software
	In the blindness stage	Preserving social integration
Hearing loss	Significant hearing loss at early onset in children	In collaboration with parents Audiophonic or bilingual (sign language) approach rather than exclusive visuo-gesture approach <ul style="list-style-type: none"> • due to the double sensory impairment and possible neurological disorders, there are foreseeable difficulties in the long term use of sign language
	Hearing rehabilitation	Hearing aids : <ul style="list-style-type: none"> • conventional, • cochlear implant if audiological indication; Technical aids associated with hearing aids: <ul style="list-style-type: none"> • remote microphones and HF system, • interfaces for television and smartphones • magnetic curl
	Aids to understanding	Lip reading, completed spoken language or signed English may be used But autonomous communication test via the ear canal alone makes dual sensory impairment auditory and visual

	socio-educational charge/help school enrolment	
Vestibular damage	re-education focusing on proprioception, which itself can be damaged in the event of neurological damage	
Swallowing disorders	speech therapy	adapting food textures

5.3.2- Lifestyle adaptation: The socio-educational care will have to be adapted to all the patient's problems, and may require care as a Rare Handicap. Rare Disability Relay Teams (ERHR) can support coordination with the different care teams and provide the necessary support to build a life course that meets the patient's expectations and needs. This may require multiple support services and sometimes multiple notifications to the MDPH/MDA, as rare disability places are not available or even existing in each department. The development of an Individualised Reception Protocol (IAP) may be justified based on the patient's symptomatology when the balance of diabetes or sensory disorders makes integration in the school environment difficult. Within the framework of a personalised schooling project (PPS), it may be useful, depending on the case, to use support to facilitate the child's schooling, education and academic progress through CAMSPs (Early Medical and Social Action Centres for children aged 0 to 6), Specialised Education and Home Care Services such as Family Support and Early Childhood Education (SAFEP) for children under 3 years of age, or to use specialised S3AS structures, Support Services for the Family Education and Schooling (SSEFS) or to support persons accompanying pupils with disabilities (AESH). Lifestyle adaptation must anticipate the use of adult-style structures.

5.3.3- Patient associations: Health professionals and patients should be informed of the existence of patient associations through referral and competency centres. See Appendix III. They contribute to better overall management of the disease by promoting cooperation between patients and caregivers. They can help to inform, advise and guide patients in lifestyle planning.

5.4- Pharmacological treatments:

To date, there is no specific drug treatment for optic neuropathy or deafness. Gene therapy remains a field of research.

5.4.1- The initial treatment of diabetes is insulin, with conventional treatment regimens given the young age of the patients. The glycemic target seems easier to achieve at the beginning of the disease, related to the persistence of residual insulin secretion by the pancreas. With age, residual secretion appears to decrease and glycemic variations are less predictable⁴⁶⁻⁴⁹. Over time, however, the psychological component and cognitive alterations make insulin treatment more difficult to manage. Neurological disorders make new treatment technologies (insulin pumps, sensors) less accessible to the patient and require even more help from those around them. The treatment regimens used are basal insulins combined with prandial insulins and insulin pumps. Because Wolfram syndrome diabetes, as a completely insulin-deprived diabetes, for many years, raises the question of the possible use of anti-diabetic treatments.

Some therapies seem promising:

- the use of a GLP1 receptor agonist (exenatide, liraglutide) interferes with protein plicaturation in the endoplasmic reticulum, resulting in decreased apoptotic signalling and increased cell survival⁵⁰⁻⁵². The use of exenatide in one WS1 case resulted in a 70% reduction in insulin requirements, improved glycemic control and a 7-fold increase in basal insulin secretion⁵³. Due to its mechanism of action, with increased survival of beta cells in the pancreas, treatment with GLP1 analogue should be initiated early in the disease course. GLP1 analogues do not have MA in children in France.
- Another promising strategy would also be the use of DPP4 inhibitors, the enzyme that degrades natural GLP1 and extends its lifespan. These are oral treatments (unlike GLP1 analogues which remain injectable). However, in type 2 diabetes, their effectiveness is less.
- Not all treatments stimulating pancreatic insulin secretion have shown beneficial effects on murine WS models. A study on gliclazide, a potent hypoglycemic sulfonamide, was ineffective.

Due to the complexity and constraints of insulin treatment, all new therapies to reduce insulin and preserve the pancreatic cell are very promising and need to be developed.

In 2014, Lu and colleagues demonstrated that dantrolene could prevent apoptosis of neural progenitor cells derived from iPS54 cells. Unfortunately, hepatotoxicity, even with sporadic and short-term use, is a known side effect of this drug. It can range from asymptomatic elevation of transaminases to fulminant hepatic failure. Cases of fatal hepatotoxicity related to dantrolene have been associated with daily doses greater than 300 mg / day 54 55 56. More recently, it has been suggested that lower daily doses (<200 mg/day) can be safely used in patients without coexisting hepatic dysfunction or other associated hepatotoxic drugs.

In 2009, pioglitazone (a thiazolidinedione) was also studied with a beneficial effect on glycemic control and the survival of beta cells in the pancreas 58. However, pioglitazone was withdrawn from the market in France in 2011 due to the risk of bladder cancer and osteoporosis.

In practice the treatment of diabetes:

- The initial treatment for diabetes is insulin
- The treatment regimens used are basal insulins combined with prandial insulins and insulin pumps.
- The use of some diabetes treatments seems promising since this diabetes is not completely insulin deprived for many years.
 - GLP1 receptor agonists and GLP1 analogues could reduce insulin requirements, improve glycemic control and increase the basal insulin secretion 53

5.4.2- There is no curative treatment for optic neuropathy, but the decrease in visual acuity can be compensated for by different procedures. Idebenone prescription has been tried on three patients with results that do not support a conclusion on the efficacy of such a treatment that does not dispose AMM in this indication 59. Clinical trials, based on different pharmacological agents, are underway but it is too early to mention them in this PNDS.

5.4.3- The management of the neurological impairment will be personalised to the patient according to the observed disorders. This support is not specific to WS type 1.

In practice:

- There is no causal treatment for optic neuropathy
- The management of neurological impairment depends on the disorders observed.

5.4.4- The management of vesicosphincterial disorders during WS is multidisciplinary, involving urologist, neurologist and rehabilitation physician.

Therapeutic proposals must be adapted to the authenticated condition: anticholinergics, botulinum toxin, physiotherapy, neurostimulation, intermittent self-sounding with a prior assessment of the ability to self-sound taking into account neurological disorders (ataxia and cognitive disorders) and low vision, and if necessary surgical alternatives: urinary diversion (permanent surgical or temporary by suprapubic catheter or indwelling urethrovesical catheter), transiléal skin ureterostomies of the Bricker type for bladder acontractility with complications...^{60 32}.

Screening for urinary tract infections by performing ECBU in case of fever or suggestive symptoms should be systematic. Risk factors for urinary tract infection should be investigated if the person has an indwelling urinary catheter.

In practice:

- Different treatments may be adapted to observed and confirmed vesicosphincterial disorders
- Before prescribing self-tests, assess the ability to perform them, taking into account neurological disorders and low vision
- There are surgical alternatives to vesicosphincterial disorders
- Screening for urinary tract infections should be systematic.

5.4.5-The pharmacological treatment of ENT disorders is purely symptomatic and based on the compensation of the disorders.

In practice:

- The treatment of ENT disorders is purely symptomatic

5.4.6- Endocrine management: The search for signs of endocrine deficiencies as part of an annual follow-up is recommended, particularly in type 1 WS.

5.4.6.6.1- The management of hypothyroidism is based on hormone replacement therapy to compensate for Levo-thyroxine deficiency. This oral treatment should be taken in the morning on an empty stomach. The dosage is adjusted according to the level of TSH in the blood.

5.4.6.6.2- The management of hypogonadism in boys is based on hormone replacement therapy with testosterone. The purpose of this is to allow pubertal virilization to resume. This treatment has positive effects on the well-being of adolescents.

In practice:

- Annual search for signs of endocrine deficits
- Hormone replacement therapy for hypothyroidism adapted to serum TSH levels
- Hormone replacement therapy with testosterone to restore virilization pubertal

5.4.7- Specific treatment of diabetes insipidus should preferably be implemented during hospitalisation, as it is important to measure weight and natremia (and/or plasma osmolality) regularly (several times a day).

The treatment of central diabetes insipidus depends on the intensity of the functional impact: if polyuria (and/or nocturnal +/- pollakiuria) is tolerable, it is not necessary to implement specific treatment and monitoring alone may be sufficient. When the functional impact is too great, it is possible to use in the long term a synthetic analogue of the antidiuretic hormone, dDAVP (Minirin®): in France, it is available in 2 forms, as a nasal spray (Minirin Spray® 10 µg/spray) or as orodispersible tablets (Minirinmelt® tablet at 60, 120 or 240 µg). Dosage should be adapted to each patient, dividing administration according to need into several doses per day: at the beginning of treatment, needs are often low (the response is quickly effective) and two daily doses (60 µg morning and evening to begin with) may be sufficient but, during follow-up and evolution, needs may be significantly increased and dosage should be adjusted either by increasing the dosage per tablet or by increasing the number of doses to 3 to 4 per day. It is also possible to combine oral form and nasal sprays.

In any case, as long as the feeling of thirst and free access to water are respected, the polydipsia induced by the tendency towards plasma hyperosmolality due to renal water loss allows each patient to adapt his water supply to his own needs. It is important to note that WS patients with diabetes insipidus may have difficulty accessing water freely in order to satisfy their sense of thirst due to their neurosensory disability.

This point must be sought during the assessment and it is essential to facilitate access to water for these patients. In the particular case of school children and adolescents, it is important to give them free access to both water and toilets so that they do not limit themselves.

In practice:

- The treatment of central diabetes insipidus depends on the intensity of the functional impact
 - If the impact is tolerable => simple monitoring
 - If the functional impact is too high => start specific treatment for diabetes insipidus, preferably during hospitalisation
 - Rest on the ddavp (minirin available in 2 forms, as a nasal spray or as orodispersible tablets, the dosage of which is adapted on a case-by-case basis in several doses per day.
 - It is essential to facilitate access to water for these patients, in particular in a school environment.

5.4.8- Psychological care should be systematically offered when the diagnosis is given. Indeed, a psychological interview would be an opportunity to allow the patient to elaborate on the diagnosis, to resume with him his understanding of the elements provided by the medical profession and to offer him information on existing associations. It may also be justified in detecting possible behavioural or psychiatric disorders (anxiety disorder, mood disorder, depression, behavioural disorders, etc).

It is also advisable to provide psychological care over time, as the evolutionary nature of the syndrome can reactivate the traumatic elements of the diagnosis. Psychological follow-up would make it possible to support the patient in adjusting his or her life course according to his or her abilities, needs and desires. In addition, since people with WS are at greater risk of discrimination or harassment (in their private or professional lives), psychological care would be an opportunity for the patient to develop appropriate coping strategies in response to the situations encountered. Psychological care based on the ACT method (Therapy of acceptance and commitment) could be adopted. This method has been shown to be effective in improving self-determination and self-esteem in patients with other chronic diseases. This method could be combined with mindfulness-based psychotherapy to reduce anxiety and depressive movements due to unpredictability of symptom onset or progression.

Finally, it would be important to take a close look at close family members (parents, children, siblings). Research has shown that family members of people with rare disabilities often experience strong feelings of guilt, helplessness and exhaustion (generally being direct caregivers).⁶² Family psychological care should be recommended in order to maintain dialogue between family members and thus ensure that family functioning is supportive and adapted to everyone's possibilities and needs.

6- PATIENT FOLLOW-UP

6.1- Monitoring objective:

- Establish a comparative assessment of the achievement of the various **devices or organs** in relation to the initial assessment or the previous assessment:
- Specify the evolution of these **different attacks**;
- Detecting the damage caused by **new devices or organs**;
- Detect the development of complications related to insulin dependent diabetes or neurological disorders;
- Evaluate the efficacy, tolerance and compliance of treatments;
- Evaluate the academic, socio-professional and psychological impact of WS.

6.2- Professionals involved: Follow-up is the domain of the specialist doctor within the Reference or Competence Centre. It brings together the various specialists of the multidisciplinary team in coordination with local health professionals, including the attending physician as well as paramedical professionals and professionals in the medical and social sector. Depending on the age of the patient, it is necessary to involve the school doctor in the PPS or the occupational doctor.

6.3- Monitoring content: The pace and content of monitoring is summarised in Appendix II. It must include:

6.3.1- The follow-up of insulin-dependent diabetes has no specificity in the context of WS.

We have already discussed the glycemetic target to be achieved.

Typical complications of diabetes are rather rare, including typical diabetic retinopathy (7%), diabetic neuropathy and nephropathy (in 9% of cases) and macrovascular complications with coronary artery disease ^{7.46}. However, this should not neglect regular monitoring of microalbuminuria and creatinine levels and the initiation of nephroprotective treatment if necessary.

6.3.2- Ophthalmological follow-up of patients is obviously important in the case of a **progressive disease**. The frequency of this follow-up may be one to two years depending on the evolution of the disease, but also according to age since the deterioration in visual performance is felt more markedly in adolescents and young adults than in adults.

During follow-up, the **evolution of symptoms** will be recorded. A difficulty in reading or seeing details in distance vision is usually related to a decrease in visual acuity. Colour vision anomalies progress with difficulties in recognising light colours and then bright colours. Discomfort in walking movements may be related to an absolute central scotoma but especially to the appearance of scotomas in the peripheral visual field. The appearance of nystagmus can be observed when the visual acuity is 1/10 or less.

If there is an associated cataract, the degree of visual discomfort due to cataract (visual veil, photophobia) should be assessed in relation to optical neuropathy and, if necessary, phakoexeresis

²⁵ should be performed.

6.3.3- Neurological follow-up should be annual, or biannual if the patients are neurologically symptomatic ¹³. Brain MRI is controlled according to clinical signs

Cerebellar ataxia: it is clinically assessed using validated scales (SARA scale, mini-Best)

³⁹

Brainstem damage: the search for sleep apnoea, or excessive daytime sleepiness, can be carried out by questioning the patient or his or her family and friends. **Peripheral neuropathy/Dysautonomic dysautonomic syndrome:** Pharmacological management of neuropathic pain may be considered. Swallowing disorders may require the use of a gastrostomy. Dysautonomic digestive disorders may also require follow-up by a gastroenterologist: medical treatment of constipation, surgical management with stoma placement.

Epileptic seizures: Anti-epileptic treatment may be necessary.

Cognitive/psychiatric/disability consequences: a specific assessment can be proposed, adapted to the age. Accommodations must be proposed depending on the situation.

6.3.4- A urological evaluation must be carried out every year

6.3.5- The frequency of ENT follow-up will vary according to the patient, his age, the degree of deafness and the proposed hearing rehabilitation. It will be closer together when the hearing aid is inserted and in the case of cochlear implantation, the frequency of adjustments varying according to the teams.

Once the diagnosis has been made and the auditory rehabilitation has been carried out, the frequency of ENT and audiophonological follow-up could be:

- Every 6 months before the age of 6 years (verification of hearing stability and absence of fluctuation by seromucosal otitis media)
- Once a year for children from 6 years old
- Once every two years in adults

Speech therapy may be necessary for both children and adults.

In children, socio-educational care will also have to be adapted according to the child's abilities (age, effectiveness of auditory rehabilitation, comprehension skills, degree of associated visual, endocrine, neurological disorders, etc.).

6.3.6- The monitoring of diabetes insipidus requires, when the treatment is balanced, a multi-year measurement of the natremia. The patient should be advised to monitor their weight regularly (especially when growth is complete). In the event of a recurrence of polyuria and/or new symptoms (such as headaches), natremia should not be hesitated to be measured: it is possible that the progression of the disease (whether diabetes insipidus, renal impairment and/or diabetes mellitus) may favour the occurrence of an overdose of dDAVP and require a dosage adjustment.

In addition, diabetes mellitus associated with WS can in itself stimulate the sensation of thirst without this being part of diabetes insipidus: it is therefore important to distinguish the two cases by close self-monitoring of blood glucose levels in the event of an increase in the sensation of thirst.

6.4- Therapeutic management during follow-up

Organ	Type of damage	Treatment
Diabetes		Insulin therapy cf Initial management Nephroprotective treatment if necessary.
Ophthalmological damage	Optical neuropathy	No treatment
	Other problems	Cataract removal
Neurological impairment	Cerebellar ataxia:	Kinesitherapy and speech therapy Specific aids can be offered (walkers, orthoses, wheelchairs).
	Brainstem damage	In case of sleep apnoea, discuss the implementation of non-invasive ventilation with Respiratory team

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	Peripheral neuropathy	Pharmacological management of neuropathic pain
	Dysautonomic syndrome:	In case of swallowing disorders, discuss the implementation of a gastrostomy. In case of dysautonomic digestive disorders, followed by a gastroenterologist: <ul style="list-style-type: none"> • Medical treatment of constipation, • Surgical management with stoma placement.
	Epileptic seizures:	Introduce anti-epileptic treatment.
	Consequences of disability:	Accommodations must be proposed according to the situation: <ul style="list-style-type: none"> • AHV, • Computer, • School guidance for young patients, • Support for professional integration, • Workstation layout, • Professional reorientation for adults.
Urological		See Initial management
ENT	Speech and language therapy rehabilitation for children,	Focuses on auditory training and phoneme, speech and language acquisition.
	Speech and language therapy rehabilitation in adults	Focuses on auditory training, memory with particular emphasis on mental substitution; Visual aids (especially lip reading) are not to be encouraged. In the case of mobility difficulties, offer home rehabilitation sessions. The duration and intensity of work should be adapted to the patient's ability to concentrate and fatigue, particularly because of the associated neurological damage.
	Socio-educational care	In children, adapt to the child's capacities (age, effectiveness of auditory rehabilitation, comprehension skills, degree of visual,

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		endocrine, neurological associated impairments, etc.
	Swallowing	Enteral feeding may be necessary In case of an associated respiratory problem, night ventilation assistance more or less associated with a tracheostomy can be discussed as part of the multidisciplinary care project, with the help of palliative care units if necessary
Diabetes insipidus		dDAVP adapted to the natremia

APPENDIX I

List of professionals involved in the management of patients with Wolfram syndrome

- Diabetologist
- Ophthalmologist
- ENT
- Neuropediatrician/Neurologist
- Neuroradiologist
- Gastroenterologist
- Pneumologist/Respiratory
- Electrophysiologist
- Rehabilitation doctor
- CAMSP or Socialisation or schooling service
- Physiotherapist
- Nutritionist
- Orthoptist
- Speech-Language (SaLT) Team
- Psychologist.
- Psychomotor therapist
- Occupational therapist
- Social worker.
- Gov.UK Benefits Department (DLA: disabled child allowance, PIP: disabled adult's allowance, Carer's Allowance, Disabled Facilities Grant etc).
- Multi-disability support networks.

APPENDIX II

Follow-up rate and content of the assessment during the management of patients with Wolfram syndrome

Systemic impairment	Follow-up rate	Content
Diabetology	6 months	<p>Glycemic balance</p> <p>Search for:</p> <ul style="list-style-type: none"> • Diabetic retinopathy, • Diabetic neuropathy, • Diabetic nephropathy (microalbuminuria and creatininemia) • Macrovascular complications
Ophthalmology	<p>12 to 24 months depending on scalability and age</p> <p>24 months for adults</p>	<p>Assessment of symptoms and functional discomfort (walking,...);</p> <p>Measurement of refraction and visual acuity at a distance (preferably on the ETDRS scale) and at close range (Parinaud scale);</p> <p>Reading speed test and contrast vision test;</p> <p>Slit lamp examination (cataract search) with tonometry;</p> <p>Orthoptic check-up (nystagmus if visual acuity < 1/10, strabismus, often divergent, oculomotor paralysis);</p> <p>Retinophotographs of the optic disc</p> <p>OCT with measurement of RNFL and macular ganglion cell layer and macular study ⁶³ ;</p> <p>Colour vision test; Visual field analysis;</p> <p>Fluorescein angiography if diabetic retinopathy</p>
Neurology	<p>12 months or 6 months in case of neurological symptomatology</p>	<p>Cerebral MRI according to clinical signs, especially in cases of acute aggravation.</p> <p>Cerebellar Ataxia => validated scales (SARA scale, mini-Best) 39;</p> <p>Peripheral neuropathy => EMG, tilt test;</p> <p>Dysautonomic syndrome => tests adapted to functional complaints (false roads, digestive disorders,...).</p> <p>Epileptic seizures => if necessary EEG</p>
	every 2 years	<p>Night-time sleep recording (ventilatory polygraphy, polysomnography and possibly night oximetry) in case of sleep apnoea, or excessive daytime sleepiness.</p>

PNDS - Wolfram Syndrome

	Depending on age and need	Cognitive/psychiatric/disability consequences => IQ assessment, school assessment, speech therapy assessment, anxiety assessment, social integration skills. Regular evaluation of learning and vocational adaptation; Followed up by a psychologist, child psychiatrist or psychiatrist is legitimate or recommended
Urology	12 months	Search for functional signs using validated questionnaires (USP and ICIQ-FLUTS). Determination of creatinine and blood urea with estimation of glomerular filtration rate ³⁶ . Bladder and kidney ultrasound with post-void residual search (PVD) ³² An additional check-up may be considered in the event of an abnormality: IV urography, retrograde and voiding urethrocytography, renal scintigraphy ³² .
ENT	6 months before the age of 6 years 12 months between 6 and 16 years 24 months after that	Essentially subjective audiophonological follow-up : • Tone Audiometry ; • Voice audiometry in silence; Voice audiometry in noise.
	According to age:	• regular speech and language therapy check-ups with a frequency that varies according to the patient's age. ○ Annual in children, for the understanding of speech in silence and noise, use of visual aids to understanding, articulation, speech, oral and written language. ○ In adults, speech and language therapy assessments may also be interesting, but may be spaced more widely. The assessment will focus on speech comprehension in silence and noise, the use of visual aids to comprehension (lip reading), cognitive and memory skills.
	According to the evolution of the disorders	Classic hearing aid monitoring. In adults, it is necessary to request a functional check of the hearing aids (earmolds, impressions, tube...) at the patient's place of residence (home, reception centre...). The repetition of vestibular explorations (VHIT, VNG, PEM) will be proposed according to their feasibility The frequency of assessment of the ability to rehabilitate swallowing disorders is adapted to the evolution of neurological disorders.

PNDS - Wolfram Syndrome

Endocrinology	6 months	Control of TSH data
Diabetes insipidus	Annual Plurality	Natremia measurement Regular monitoring of weight In case of recurrence of polyuria and/or new symptoms (such as headaches), => measure the natremia

These assessments must be adapted to each patient according to the symptomatology.

APPENDIX III:

Useful addresses

- Reference centres: Complete postal addresses on the Sensgène site.
 - Reference centre for sensory disorders of genetic origin (MAOLYA, Montpellier University Hospital)
 - Centre de référence des affections ophtalmologiques of genetic origin (CARGO, Strasbourg University Hospital): cargo@chru-strasbourg.fr
 - Reference Centre for Mitochondrial Diseases (CALISSON, Nice University Hospital): www.mito-calisson.fr
 - Centre de référence des surdités congénitales d'origine génétique (Hôpital Necker Enfants Sick, Paris)
 - Reference Centre for Rare Diseases in Ophthalmology (OPHTARA. Necker Enfants Malades, Paris and Hôpital Européen Georges Pompidou, Paris)
 - Reference centre for retinal dystrophies (Hôpital des 15/20, Paris)
 - Service d'Explorations de la Vision, Lille University Hospital
- Wolfram Syndrome UK: www.wolframsyndrome.co.uk
- WellChild : www.wellchild.org.uk
- Orphanet: www.orpha.net
- EURO-WAAB: www.euro-wabb.org
- VICTA: www.victaparents.org.uk

Rare Relay Team for Disabled People in your region: <https://www.qnchr.fr/reseau-acteurs-national-regional-local/relative-teams-for-disabled-people>

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