Clinical Manifestations of Wolfram Syndrome 1

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Wolfram syndrome 1 (WS1) is a rare neurodegenerative disease transmitted in an autosomal recessive mode. It is characterized by diabetes insipidus (DI), diabetes mellitus (DM), optic atrophy (OA), and sensorineural hearing loss (D) (DIDMOAD). The clinical picture may be complicated by other symptoms, such as urinary tract, endocrinological, psychiatric, and neurological abnormalities.

Keywords: Wolfram syndrome 1 ; Urological Abnormalities ; Sensorineural Deafness ; DIDMOAD ; Optic atrophy ; Diabetes insipidus

1. Introduction

Wolfram syndrome 1 (WS1; MIM 222300) is a rare autosomal recessive neurodegenerative disease first described in 1938 by Wolfram and Wagener [1]. The main clinical features are diabetes insipidus (DI), diabetes mellitus (DM), optic atrophy (OA), and deafness (D), hence the acronym DIDMOAD. However, WS1 is frequently complicated by other symptoms, such as urinary tract, endocrinological, psychiatric, and neurological abnormalities [2][3]. Early-onset non-autoimmune insulin-dependent DM and bilateral OA are key clinical criteria for the diagnosis of WS1 [1]. WS1 is a rare type of DM and has been included in subcategory 5A16.1 of the International Classification of Disease (ICD-11) [4]. Prognosis is poor, as the clinical course of WS1 is rapidly progressive and leads to a premature death of patients at the mean age of 30 years (25–49 years). The main cause of death is respiratory failure due to brainstem atrophy [5][6]. There are currently no therapies for WS1. However, careful clinical follow-up and supportive care can be helpful for relieving severe and progressive symptoms of WS1.

2. Natural History and Clinical Manifestations

The clinical diagnosis of WS1 requires the coexistence of two main criteria: early onset of insulin-dependent non-autoimmune DM (DM) (usually during the first decade of life) and bilateral optic atrophy (OA) before age 15 [2]. Diabetes insipidus (DI) and sensorineural hearing loss (D) are usually associated with DM and OA. Thus, WS1 has also been defined with the acronym DIDMOAD. Other clinical manifestations of WS1 are renal tract abnormalities or neuropsychiatric disorders [7][8]. Many studies have shown that renal anomalies are very frequent in WS1. Thus, the acronym DIDMOADUD has been suggested [2][9]. Other symptoms include cognitive problems and mood disorders [5][10]. As WS1 is characterized by many clinical features, it has been suggested that WS1 can be diagnosed in the following cases: (1) coexistence of the two major criteria (DM + OA); (2) one main criterion together with two minor criteria; and (3) two of any of the DIDMOAD manifestations [2][9][7]. Many studies have attempted to establish the order in which symptoms of WS1 start [9][11]. However, it is hard to establish an accurate order of the WS1 clinical manifestations and therefore, the number of patients that may be studied is small. De Heredia et al. analyzed the clinical and genetic features of 412 published WS1 patients with age specified for any clinical symptom. They found that DM (98.21%) and OA (82.14%) were the most frequent clinical features. D and DI were shown in 48.21% and 37.76% of cases, respectively. Other clinical manifestations, such as renal anomalies (19.39%) and neurological symptoms (17.09%), were found in a smaller number of WS1 patients. The mean age of death was about 30 (range 25–49) years. Interestingly, the mean age of death showed two peaks of higher frequency, one at 24 years and the other at 45 years. Respiratory failure was the most frequent cause of death [7].

3. Insulin-Dependent and Non-Autoimmune Diabetes Mellitus

DM is typically the first clinical feature of WS1, with onset at the mean of 6 years (3 weeks–16 years). Insulin-dependent DM of WS1 differs from common type 1 DM (T1D) in the following features: earlier diagnosis, rarely positive autoantibodies, rare ketoacidosis, longer remission periods, lower daily requirement of insulin, mean values of HbA1c lower than T1D, and frequent episodes of hypoglycemia [9][7][12]. Moreover, slowly progressing microvascular

complications, such as microvascular retinopathy, are less common than T1D. It has been suggested that the impaired carbohydrate metabolism is a consequence of neurological alterations caused by ER stress. [12][13][14]. Therefore, clinicians must consider these clinical differences between WS1 DM and T1D to avoid a misdiagnosis of WS1 because such a mistake would have very severe health repercussions on the patient.

4. Optic Atrophy

In WS1 patients, OA is diagnosed in the first decade of life, usually before 15 years of age. The first clinical manifestation of OA is the progressive decrease of visual acuity with loss of color vision. The blindness develops after a few years [7][14][15]. Ophthalmological anomalies, such as cataract (29.6–66.6%), alterations in pupillary reflexes to light, nystagmus, maculopathy, and glaucoma, have been found in rare cases [15]. Pigmentary retinopathy is very rare, and few cases have been reported [6][16][17][18][19]. Pigmentary maculopathy in WS1 patients, although rare, may be due to the severe alterations of mitochondrial dynamics that have been described in WS1 [20]. Microspherophakia was found in two sisters who were also affected by congenital cataract, glaucoma, and OA [21]. Many ophthalmic alterations, which also include abnormalities of the retinal nerve fiber layer thickness, were found in 15 WS1 patients at relatively early stages [18]. However, Zmyslowska et al. showed that alterations of retinal nerve fiber layer thickness are less frequent in WS1 subjects than in T1D patients or healthy subjects [13]. Waszczykowska et al. found a significant reduction of corneal sensitivity in patients with WS1. Indeed, the corneal nerve fiber, branch density, and nerve fiber length were low in WS1, suggesting corneal nerve degeneration. In addition, the variability of corneal sensitivity was found to correlate with the degree of disease progression [22].

Full eye examination by assessing of visual acuity and color vision, fundoscopy, visual field, and optical coherence tomography (OCT) scan should be done early. The visual evoked potential test allows to evaluate the therapeutic efficacy. Other expedients are increase in the size of the image and writing on mobile devices, such as computers, notebooks, smartphones, and tablets, and the use of voice systems. Unfortunately, there are no drugs available to treat OA. Attempts have been made to slow the progression of OA using drugs, such as idebenone or docosahexaenoic acid, but there are few data about the efficacy of therapy [23][24].

5. Diabetes Insipidus

Central DI is frequent, affecting approximatively 70% of WS1 patients [5]. It occurs at a mean age of 14 years (3 months–40 years). However, a high variability in age of onset was found, as DI is often diagnosed with delay. Assessment of DI should be done by urine concentration test, which is recommended for all patients with DM; color vision impairment; deafness; and neurological symptoms. In most cases, intranasal or oral administration of desmopressin improves the clinical picture of DI [25].

6. Sensorineural Deafness

Sensorineural deafness (D) occurs at a mean age of 12.5 years (range 5–39 years) in 62% of WS1 patients [5]. The clinical spectrum is broad as the severity of hearing impairments varies between patients. The progression of D is relatively slow and first affects the high frequencies [5]. In WS1 patients, D is more severe than in other patients with hearing loss due to degenerative impairments in the central nervous system [5]. Annual or two-year audiometric testing and brain stem auditory response (ABR) assessment are useful for monitoring D in WS1 patients. Therapeutic tools, such as hearing aids and cochlear implants, are very helpful for WS1 patients [26]. Hearing symptoms in WS1 must be carefully evaluated as low-frequency sensorineural D caused by dominant mutations of WFS1 has been described [27]. However, patients suffering from this dominant type of genetic deafness have a different clinical picture than WS1.

7. Neurological and Psychiatric Manifestations

Most WS1 patients (>60%) have been shown to exhibit neurological symptoms at a mean age of 40 years (range 5–44 years) [5], but in some cases, onset is earlier [9][28]. De Heredia et al. found the onset of neurological complications at the mean age of 23 years, with two peaks of greater frequency, one at 13 years and the other at 30 years [7]. Cerebellar ataxia of the trunk is the most common manifestation (45%), and a neurological counseling one or two times a year is recommended [11]. Other neurological abnormalities are peripheral neuropathy (39%), cognitive impairment (32%), epilepsy (26%), and lastly, dysarthria, dysphagia, and nystagmus (10%) [11]. Severe complications, such as aspiration pneumonia, can be prevented by swallowing therapy. Esophageal dilatation and esophagomyotomy are useful in some cases. Neurological symptoms, such as loss of the gag reflex, decreased ability to taste and smell, orthostatic hypotension, anhidrosis, hypohidrosis or hyperhidrosis, constipation, gastroparesis, hypothermia, or hyperpyrexia, may

often be reported [11]. Atrophy of the brain, cerebellum, and brainstem are abnormalities found by nuclear magnetic resonance imaging (MRI) in 54% of WS1 patients [11]. Respiratory failure or dysphagia are common causes of mortality [5] [11]. Thus far, the progression of neurological manifestations cannot be slowed down, as there is no therapy. Psychiatric disorders, such as severe depression with suicide attempts, psychosis, sleep abnormalities, verbal impulsivity, and physical aggression, can complicate the clinical picture in WS1 patients. Moreover, a predisposition to psychiatric diseases was found in *WFS1* heterozygotes [29]. Cognitive performance is generally normal. However, Chaussenot et al. found that 32% of 59 studied WS1 patients had cognitive impairment [11]. It has been suggested that the smell and sleep alterations can be used as indicators to follow-up WS1 patients with psychiatric manifestations [30].

8. Urological Abnormalities

Neurogenic bladder, which causes hydroureteronephrosis, urinary incontinence, and recurrent infections, has frequently been found in WS1 patients [11]. Urinary tract abnormalities have been found in up to 90% of patients. The average age of onset is 20 years old, and specifically, three high-frequency peaks were found: one at 13 years, the second at 21, and the third at 33 years [7].

Neurogenic bladder and upper urinary tract dilation are the main urological abnormalities. Anticholinergic drugs and clean intermittent catheterization are therapeutic tools for neurogenic bladder [7]. Some WS1 patients also undergo electrical stimulation and physiotherapy [2]. Follow-up is carried out through clinical, instrumental, and laboratory checks of renal function. Moreover, the measurement of the residual urinary volume after voiding by ultrasound and urodynamic tests are needed. Urinary tract infections at a very early age are the first manifestations of WS1 only in rare cases [31]. Urine culture is required in WS1 patients suffering from fever or other symptoms, such as headache. Yuca et al. described a Turkish family in which the course of chronic renal failure was rapidly progressive in some WS1-affected members [32].

9. Endocrinology and Reproductive Biology

Primary and secondary hypogonadism, more frequent in males, are the main manifestations of endocrine function impairment in WS1 patients. Delayed menarche and menstrual cycle alterations are frequent in WS1 females, but ovarian function is normal, and some pregnant patients have been described [15]. Short stature, growth hormone (GH) deficiency, and impaired corticotrophin secretion were found in WS1 patients [5] due to anterior pituitary hypofunction of hypothalamic origin [15]. Growth rate and pubertal development must be closely monitored for GH therapy, and steroid supplementation should be considered during stressful periods, such as severe infections [33].

10. Additional Anomalies

Gastrointestinal disorders include gastroparesis (29%), bowel dysmotility (24%), and bowel incontinence [28]. Congenital heart diseases, such as Fallot's tetralogy and pulmonary valve stenosis, have been reported in rare cases of WS1 [15][34] [35], and hence, heart monitoring is recommended.

11. Diagnosis of WS1

A careful and accurate diagnosis of WS1 allows for early identification of patients so that appropriate interventions can be initiated. History and clinical manifestations, such as the diagnosis of OA after that of DM under the age of 16, should lead to suspicion of WS1. Visual abnormalities and insulin-dependent DM must be carefully evaluated in WS1 patients, as they may be misdiagnosed as T1D with diabetic retinopathy. This mistake would cause a delay in diagnosis of WS1 [2][36]. Given the clinical complexity of WS1, alterations such as DI, sensorineural D, and neurological and urological symptoms together with non-auto-immune insulin-dependent DM or OA, allow to suspect WS1. Differential diagnosis should be made with mitochondrial diseases, deafness caused by *WFS1* mutations, autosomal dominant OA, Bardet–Biedl syndrome, Alström syndrome, and Friedreich ataxia [15]. Genetic tests, such as exome sequencing and genome sequencing-based diagnostic methods, are valuable tools to confirm or rule out the diagnosis of WS1. Sequencing of the entire *WFS1* with all eight exons and their flanking intronic regions is recommended [9][37]. Early diagnosis of WS1 is imperative to enable successful follow-up that includes specialist consultations and appropriate instrumental and laboratory tests. If WS1 is suspected, thorough genetic counseling should be done to study family members even if they are asymptomatic.

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