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Williams Syndrome

5820 Oberlin Drive, #202

San Diego, CA 92121

ABSTRACT

Williams syndrome (WS), also known as Williams-Beuren syndrome, is a rare genetic disorder characterized by a range of physical and developmental symptoms. One of the notable features of Williams syndrome is the presence of cardiovascular anomalies. Stenosis refers to the narrowing of blood vessels, particularly major arteries. In Williams syndrome, individuals may experience stenosis in different arteries, such as the aorta (the main artery that carries blood from the heart to the rest of the body), pulmonary arteries, or coronary arteries (which supply blood to the heart muscle).

Aortic stenosis is a common cardiovascular issue in individuals with Williams syndrome. It involves the narrowing of the aortic valve, which can obstruct the flow of blood from the heart into the aorta, leading to reduced blood flow to the body.

Pulmonary stenosis occurs when there is narrowing in the pulmonary valve or the arteries that carry blood to the lungs. This can affect the flow of blood to the lungs for oxygenation.

In some cases, individuals with Williams syndrome may develop stenosis in the coronary arteries, which can increase the risk of heart problems and cardiac events.

Treatment: The management of cardiovascular anomalies in Williams syndrome often involves regular monitoring by a cardiologist, and interventions such as medication or surgical procedures may be necessary to address specific issues like aortic stenosis.

Other Symptoms: Apart from cardiovascular issues, Williams syndrome is associated with a range of other physical and developmental characteristics, including distinctive facial features, intellectual disabilities, social and behavioral challenges, and a friendly and outgoing personality.

It's important to note that while cardiovascular anomalies, including stenosis, are a common feature of Williams syndrome, the severity and specific cardiac issues can vary from person to person. Early diagnosis, medical supervision, and appropriate interventions can help individuals with Williams syndrome manage their unique symptoms. The frequency of Williams syndrome is equal across all ethnicities and genders. Several studies have estimated the frequency of the disorder in the range of 1 in 7,500 to 1 in 75,000 children. According to

the National Organization for Rare Disorders, the prevalence of this disorder is 1 in 10,000-20,000 births in the United States. The affected infants show a failure to thrive and are physically present with short statures and supra-vascular stenosis of the aorta. Children with WS may have other defective elastin-related pathological conditions of the arteries, along with high blood pressure and peripheral pulmonary stenosis. Some distinct symptoms in childhood are middle ear infections as well as visual difficulty. All WS-affected children often exhibit distinctive facial features, sometimes referred to as "elfin features." The child also shows hypercalcemia (high levels of blood calcium), hypercalciuria (elevated urine calcium), connective tissue and endocrine abnormalities, growth abnormalities, intellectual disability, behavior deficits, and a sociable personality. The diagnosis should be made early to decide the treatment regime and improve the quality of life in childhood. This rare genetic disorder is usually the consequence of an irregular random genetic mutation in chromosome 7, meaning it most often occurs in people with no family history of this syndrome. However, in a small number of cases, the chromosome deletion in a parent with the condition may be inherited by the offspring, which is counted as a risk factor for the disease. There is no cure for the disease. Proper management of the WS among the young population, especially children, needs a multidisciplinary management approach. The team should possess experts and physicians from healthcare sectors in endocrinology, obstetrics, genetic counseling, cardiology, nephrology, gastroenterology, as well as psychiatry.

INTRODUCTION

Williams syndrome (WS) is a rare genetic disorder leading to neurodevelopmental disorders and cardiovascular anomalies. The genetic defect comprises deletions as genetic mutations on chromosome 7. The specific genetic fragment 7q11.23 is recurrently deleted, involving codes for an important gene, elastin [1]. Cardiovascular irregularities and anomalies occur in almost 80% of WS patients [2]. Williams syndrome is also known as Williams-Beuren syndrome. WS affects multiple systems of the body and results in behavioral deficits and intellectual disabilities. The typical congenital cardiological defects in WS include supravalvular aortic stenosis (the narrowing or stenosis of the large blood vessel called the aorta occurs that carries blood from the heart to the rest of the body), pulmonary stenosis (both valvular and peripheral), aortic coarctation (a birth defect where a part of the largest artery or aorta is narrower than usual), as well as mitral valvar prolapsed (improper closure of the valve between the heart's

upper and lower-left chambers). Pulmonary stenosis is the constriction or narrowing of the valve located between the lower right heart chamber (right ventricle) and the pulmonary arteries (lung arteries) [3]. This paper provides an insight into the different facets of this disease, such as the symptoms, diagnosis, treatment, and surgical outcomes, as well as emerging therapeutics for improving the quality of life in WS patients.

BACKGROUND

The eponym "Williams syndrome" was coined in honor of the cardiologist John Cyprian Phipps Williams, who identified this condition in 1961. Subsequently, a physician, A. J. Beuren, reported his valuable observations of this syndrome. Thus, the syndrome was renamed Williams-Beuren syndrome [4, 5]. Further, in 1993, the genetic basis of Williams syndrome was revealed [6].

EPIDEMIOLOGY

Williams syndrome is equally prevalent across ethnicities and genders [7]. Several studies have estimated the frequency of the disorder in the range of 1 in 7,500 to 1 in 75,000 children [1, 8]. According to the National Organization for Rare Disorders, the prevalence of this disorder is 1 in 10,000-20,000 births in the United States [9]. The prevalence of the characteristic features of Williams syndrome may vary among populations. For example, in the Hong Kong Chinese population, peripheral pulmonary stenosis is more common than supravalvular aortic stenosis [10], while the prevalence of cardiovascular anomalies is found to be comparatively lower among the Greeks [11].

SYMPTOMS

The affected infants show a failure to thrive and, physically, present with short statures and supra-vascular stenosis of the aorta [1]. Children with WS may have other defective elastin-related pathological conditions of the arteries, along with high blood pressure and peripheral pulmonary stenosis [1]. Some distinct symptoms in childhood are middle ear infections as well as visual difficulty. All WS-affected children show distinctive –elfin-like features [1]. The child also shows hypercalcemia (high levels of blood calcium), hypercalciuria (elevated urine

calcium), connective tissue and endocrine abnormalities, growth abnormalities, intellectual disability, behavior deficits, and a gregarious or sociable personality [1].

The patient may have signs of hypothyroidism (the thyroid gland fails to produce and release enough thyroid hormone into the bloodstream, slowing down metabolism with people feeling tired, weight gain occurring with intolerance to cold), features of delayed growth, or early puberty [1, 12]. The abnormalities of connective tissue often lead to hyperextensible joints or hypotonia (decrease or decline in muscle tone), resulting in delayed motor milestones, specifically toilet training for a growing child (Figure 1) [1].

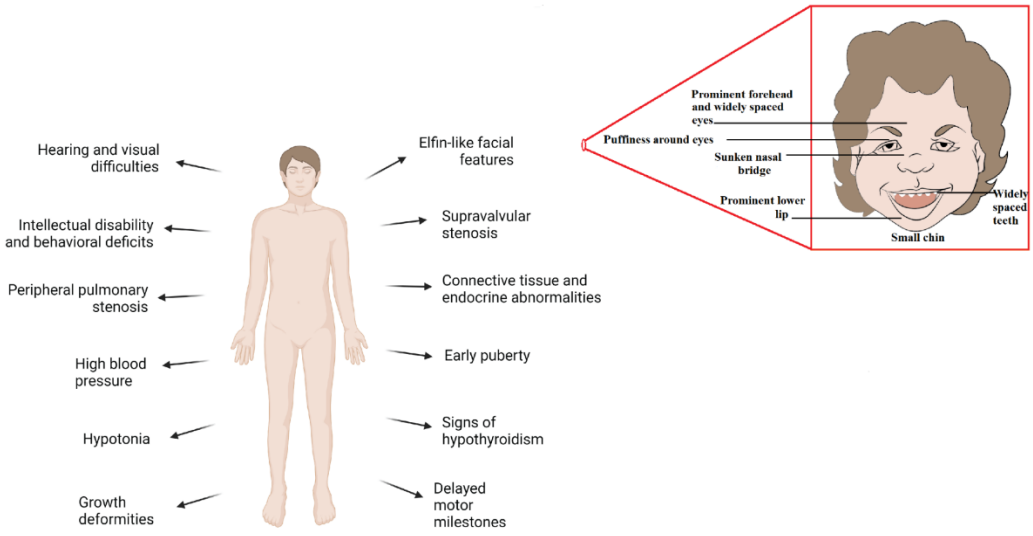

Figure 1. Major symptoms of Williams syndrome (WS) WS patients born with green or blue eyes may frequently exhibit a "starburst" or stellate pattern on the iris of their eye, with a characteristic white and lacy appearance [1].

DIAGNOSIS

The diagnosis should be early to decide the treatment regime and to improve the quality of life in childhood. The major laboratory-based tools for diagnosing WS in suspected patients are:

- Visual and hearing screening
- Body mass index (BMI) measurement
- Complete blood count (CBC) evaluation
- Complete metabolic panel (CMP) evaluation

- Calcium levels in blood evaluation, Thyroid-stimulating hormone, including free T3 as well as free T4 evaluation
- Echocardiogram and electrocardiogram of the heart
- The gene deletion in chromosome 7, consisting of 26 genes, is detected from DNA extracted from peripheral blood samples through dual-color fluorescent *in situ* hybridization (FISH) or deletion/duplication testing
- Microarray analysis of the extracted DNA, is also carried out as a diagnostic test that can identify the size of the elastin (ELN) gene deletion [6]
- In addition to the above basic tests, intellectual disability (ID) assessment in WS is another important area of diagnosis. The assessment is done using the Kaufman Brief Intelligence Test, Second Edition, or KBIT-2. The assessment measures a composite IQ in addition to verbal and non-verbal standard scores (SSs) [7]

WS-affected children often struggle with visuospatial construction (a form of cognition defining the ability to see an object or picture by a person as a set of parts and then to construct a replica of the original from these parts), which is not measured by the KBIT-2 [7]. To evaluate visuospatial construction, the Differential Ability Scale-II or DAS-II Special Nonverbal Composite assessments and Wechsler IQ tests are helpful (Figure 2) [7].

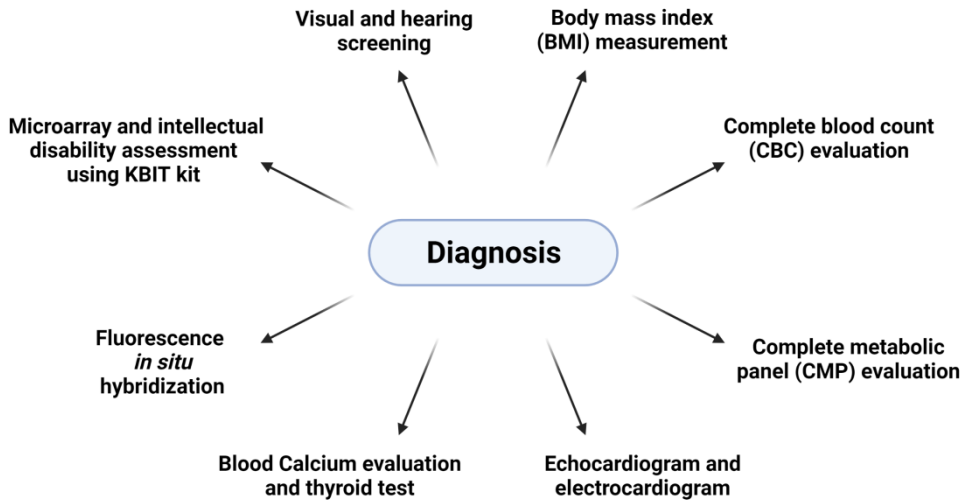

Figure 2. Diagnostic procedures for Williams syndrome (WS)

DIFFERENTIAL DIAGNOSIS

Furthermore, it is imperative to eliminate the possibility of misdiagnosis with other conditions that share similarities with Williams Syndrome (WS). In the case of the diagnosis of WS, the initial focus should be on excluding autosomal dominant supravalvular aortic stenosis, particularly in children, as its consequences closely resemble those of WS. Subsequently, attention should be directed towards ruling out Noonan syndrome, Fetal alcohol syndrome, DiGeorge syndrome (specifically, deletion 22q11.2), Kabuki syndrome, Marshall syndrome, and Smith-Magenis syndrome [6].

ETIOLOGY

The genetic defect in this rare genetic disorder is a gene mutation or specific deletion at chromosome band 7q11.23 of chromosome 7. The band deletion involves the elastin gene (ELN) in the Williams-Beuren Syndrome Critical Region (WBSCR) of the chromosome [6]. This genetic mutation with deletion of the elastin gene is evident in 96-98% of WS patients [8]. The resultant defective elastin protein is the major cause of WS disorder, which leads to arteriopathy, especially of the medium- to large-sized arteries [6].

PATHOPHYSIOLOGY

The human body has 23 pairs of homologous chromosomes. Thus, every gene has two copies, or alleles, in the cells of the body. There are several genes on each chromosome. The WS disease is a contiguous gene deletion syndrome (refers to a genetic disorder in which a person is born with a deletion of a small piece of genetic material from one of their chromosomes), as it not only involves the loss of one of two copies of the ELN gene but also involves the deletion of neighboring 28 other genes of chromosome 7 in humans [13, 14, 15]. In chromosome 7, WBSCR is a band of genes involving some major genes such as LIMK1, GTF1IRD1, GTF1IRD2, GTF21, NCF1, STX1A, BAZ1B, CLIP2, and TFII-1, along with the ELN gene [16].

A number of these other genes, including LIMK1, are thought to affect the cognitive profile of Williams syndrome patients. Some other genes in this band are implicated in hypercalcemia,

facial feature abnormalities, glucose metabolism impairment, and blood pressure (Figure 3) [16].

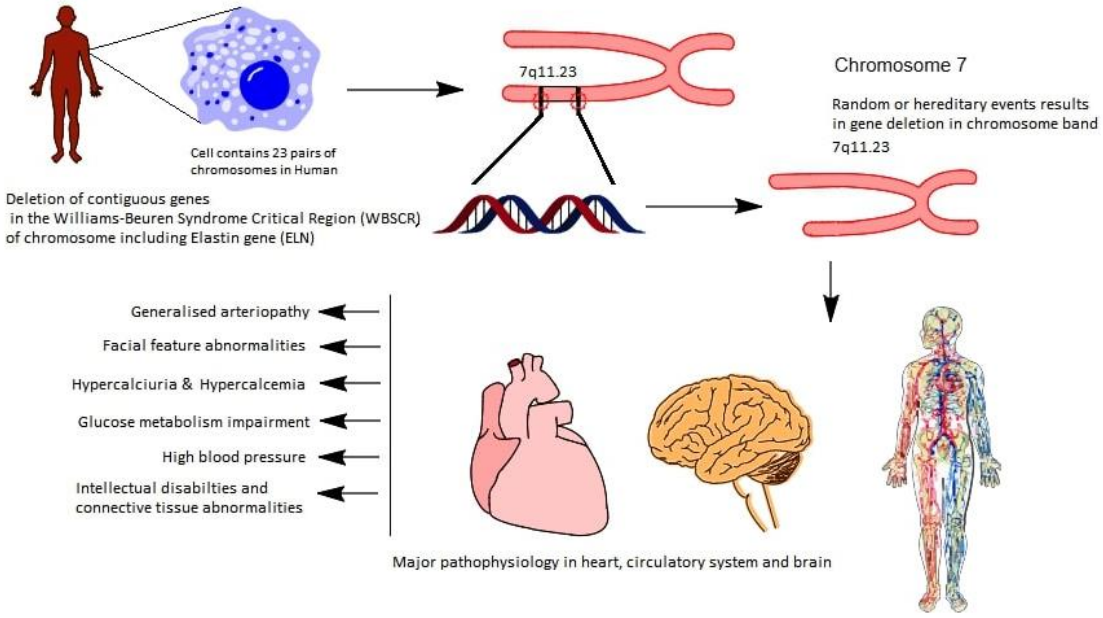

Figure 3. Pathophysiology of Williams syndrome (WS)

The specific deletion on the elastin (ELN) gene is responsible for familial supravalvular aortic stenosis. Normal elastin levels maintain the distensibility of the aorta during systole (part of the heart pumping cycle when the heart muscle contracts to pump the blood out) and its subsequent recoil during diastole (part of the heart pumping cycle when the heart muscle relaxes after contraction) [17]. During systole, the hydrodynamic energy that is stored is released during diastole, and this phenomenon is known as the Windkessel effect [2]. Loss of elastin may lead to the loss of this effect, thus resulting in a wide pulse pressure with elevated systolic and reduced diastolic blood pressures, which subsequently impair coronary blood flow [18]. The anesthetic setting before any surgery and/ or prolonged corrected QT (QTc) period on electrocardiogram (ECG) are factors associated with the sudden death of patients with Williams syndrome [19].

RISK FACTORS

Williams syndrome is usually the consequence of an irregular random genetic mutation in chromosome 7. This means that it most often occurs in people with no family history of this syndrome. However, in a small number of cases, the chromosome deletion in a parent with the

condition may be inherited by the offspring, which is counted as a risk factor for the disease [20]. In these cases, it is inherited in an autosomal dominant manner because only one changed copy of chromosome 7 in each cell is sufficient to cause signs and symptoms of the disorder. Regardless of whether the disorder is sporadic or inherited from a family history, each child (irrespective of their gender) of a person with Williams syndrome has a 50% chance of inheriting the condition [1].

Some cases of WS are also associated with a risk factor of hypercalcemia, which may occur due to abnormal sensitivity to vitamin D [9].

MANAGEMENT

There is no cure for WS. A multidisciplinary approach is needed to manage MS, especially in children. The team must comprise experts and physicians from healthcare sectors in endocrinology, obstetrics, genetic counseling, cardiology, nephrology, gastroenterology, and psychiatry. Some major management issues are highlighted, as follows [6]:

- Genetic counseling, in the form of creating awareness of the risk of developing the disease in the offspring of parents, is of utmost priority in managing and preventing this disease. It may also be employed during pregnancy when prenatal testing is available.

- All pregnant WS patients are considered high-risk due to the risk of developing arrhythmia, heart failure, as well as hypertension, or high blood pressure. Urine analysis (UA) is required due to the risk of urinary tract infections (UTI).

- Postnatal care for the newborn with WS should be considered for supra-vascular aortic stenosis, which necessitates open-heart surgery by a cardiothoracic surgeon.

- The role of an endocrinologist is crucial to managing hypercalcemia, hypothyroidism, and growth reduction in patients with WS. Diet modification, intravenous (IV) pamidronate, or oral corticosteroids are recommended under the supervision of physicians. If the child's short stature is apparent, therapeutic interventions with growth hormone are an option.

- Proper management of hypercalcinuria should be done by consulting a nephrologist, and if it occurs, lithotripsy (a medical procedure involving ultrasound shock waves

which break a kidney stone or other calculus into small particles that can be passed out by the body) may be suggested.

- Gastroenterological management is required for WS children with feeding difficulties who may need a permanent feeding tube. Infants diagnosed with such issues often need feeding therapy and nutritionist consultation to maintain a proper diet.

- Dentist and Orthodontist consultations are also required due to the risk of the development of malocclusion (a condition defining a poor bite or crooked teeth) and dental abnormalities.

- Integrative care in the form of improving the quality of life of patients with neurodevelopmental deficits and intellectual disabilities is needed. They require special education programs, physical therapy (PT), occupational therapy (OT), speech therapy (ST), and sensory integration therapies. Psychiatric management is another important aspect of management. Psychiatric evaluation is inevitable to determine the need for psychotherapeutic interventions to treat certain comorbid diseases like attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), or generalized anxiety disorder.

EMERGING THERAPEUTICS

The importance of having emerging and symptomatic therapies for prompt treatment responses cannot be overstated. Various research studies are currently underway, with a particular emphasis on the cognitive and behavioral management of patients with Williams Syndrome (WS). In one such study, the drug minoxidil's effectiveness in potentially increasing the intima-media thickness (IMT) of the carotid artery was discovered through a randomized placebo-controlled double-blind trial (NCT00876200) [21]. Furthermore, there is an ongoing phase IV trial (NCT04807517) evaluating the efficacy and tolerance of Buspirone in the symptomatic treatment of anxiety disorder in individuals with WS [22]. Additionally, research has been directed towards multilevel surgical pulmonary artery reconstruction, which has demonstrated exceptional outcomes in the treatment of pulmonary artery stenosis [2].

QUALITY OF LIFE

All patients with WS need to be checked regularly for any potential cardiovascular problems, like symptomatic narrowing of the blood vessels, high blood pressure, and heart failure. Most individuals suffering from this disorder are found to present some degree of impaired intellect. Although some adults can function relatively independently, most have to live under the supervision of a caregiver. Parents have an important role to play in this regard [23]. The self-help skills taught by parents since early childhood can increase the likelihood of their child being able to live semi-independently [24]. Similarly, early intervention and individualized educational programs that are specifically designed keeping in mind the characteristic cognitive and personality profiles of WS also help individuals maximize their potential. However, various medical complications that are associated with this disorder may shorten the lifespan of some WS patients [25].

The patient should be kept under the observation of a cardiologist after surgery to avoid the risk of hypertension (a condition of high blood pressure) and arteriopathy, as these can also lead to pulmonary artery stenosis, mitral valve insufficiency, and renal artery stenosis [1]. Children with WS are at risk of hyperopia (farsightedness) and recurrent otitis media (an impaired visual condition in a child). Thus, they must be routinely tested for hearing and vision loss [1]. A low calcium diet may lead to rickets in WS-affected individuals, and hence their calcium levels are required to be carefully monitored [26]. The blood glucose levels and thyroid function of WS patients are also routinely monitored by an endocrinologist. Children affected by WS often need thyroid hormone replacement therapy [12].

CONCLUSION

Early diagnosis and symptomatic treatment are the keys to better managing patients. The maintenance of quality of life in the form of monitoring cardiovascular complications is needed throughout life, and the dose of the medicine can be altered according to the clinical conditions of each patient. Investigations on therapeutic modalities and managing the complications of the disease are hence important.

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