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Case Report

A Rare Case of William Beuren Syndrome Revealed by Arterial Hypertension: Case Report

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Abstract

William-Beuren syndrome (WBS) has been defined as a rare multisystem disorder with a serious phenotype. It affects about 1 in 7,500 newborns and has marked genotypic and phenotypic variations. Its endocrinological, mental, and behavioral characteristics force the collaboration of several medical and non-medical professionals. Consequently, a huge amount of fundamental clinical, anatomical, and experimental data has shown the close relationship between genetic constitution and the phenotype of children with WBS. In 1961, three children with supravalvular aortic stenosis were described. Approximately 15 years later, four patients with the same heart condition, mental and distinctive facial appearance were reported.

Keywords: *William-Beuren syndrome; Arterial Hypertension; Coarctation of the Aorta*

Introduction

Williams-Beuren syndrome (WBS) represents the first etiological group of genetic mental retardation and the first cardiac disease-associated genetic syndrome mapped to chromosome 7q11.23. This insight bent the clinical approach towards developmental delay in search of the dysmorphic syndrome. The 2-Mb length of the Williams-deletion chromosomal region was a record during three decades in terms of contribution to the genetic human phenotype; it was characterized as: 'hypersociability, that is, elfin facial expression, low LE, hoarse voice, mental retardation with hyperactivity that disappears after a short nap, hyperacusis, dilated veins under the skin not variant of veins varix,' increasing the characteristic sign to 29 parameters. WBS is one of the relatively few monogenic inherited forms of cardiomyopathy [1].

Case Report

A 6-year-old child, hospitalized for arterial hypertension. Born from a pregnancy carried to term, with vaginal delivery. There is no notion of fetal distress, and 2nd degree consanguinity, the child suffered from education difficulties. The history of the disease goes back 2 years with the appearance of headache and dizziness with difficulty of concentrating. The clinical examination finds a conscious child with facial dysmorphism (short nose, everted and fleshy lower lip) (Figure 1), no failure to thrive. Blood pressure measured on the 4 limbs: Upper left 17/12 mmHg greater than the 95th percentile, lower left 13/10 mmHg, lower right 12/6 mmHg, upper right 14/10 mmHg. The heart rate is 110 bpm, the O_2 saturation is 97%, and no proteinuria was found in urine strip test. The cardiac exam showed S1 and S2 well heard, with maximum systolic murmur at mitral area, no murmur near the umbilicus, and absence of femoral pulse. The rest of the examination found no abnormalities.

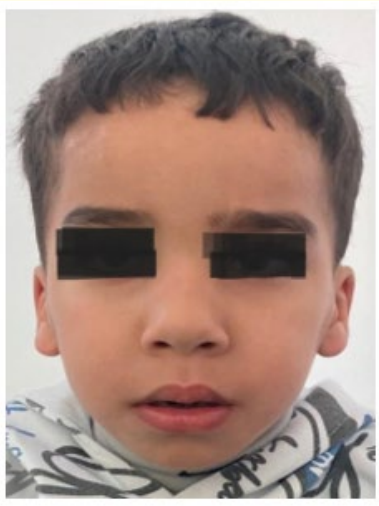

Figure 1: *Picture of the patient showing facial dysmorphism.*

The transthoracic ultrasound showed a coarctation of the aorta (Figure 2), confirmed ulteriorly by thoracic CT angiography (Figure 3). Renal doppler ultrasound is normal, so are thyroid hormones and cortisolemia. The patient was treated by angiotensin converting enzyme (ACE) inhibitor 0.5 mg/kg/day, and was transferred to a cardiovascular surgery department for surgical treatment (operated with good progress). The FISH technique showed a deletion in a gene on chromosome 7 in favor of William Beuren syndrome.

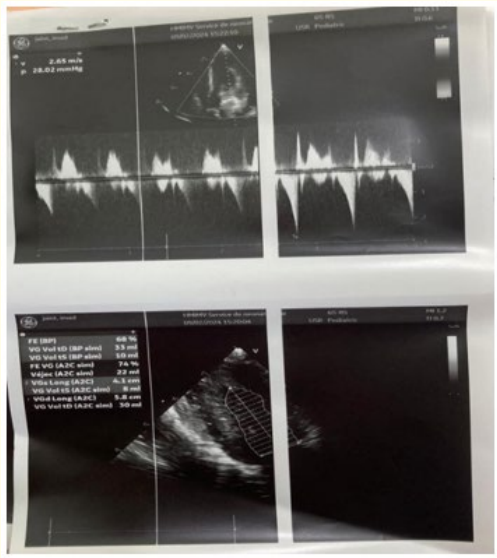

Figure 2: *Transthoracic ultrasound showing coarctation of the aorta.*

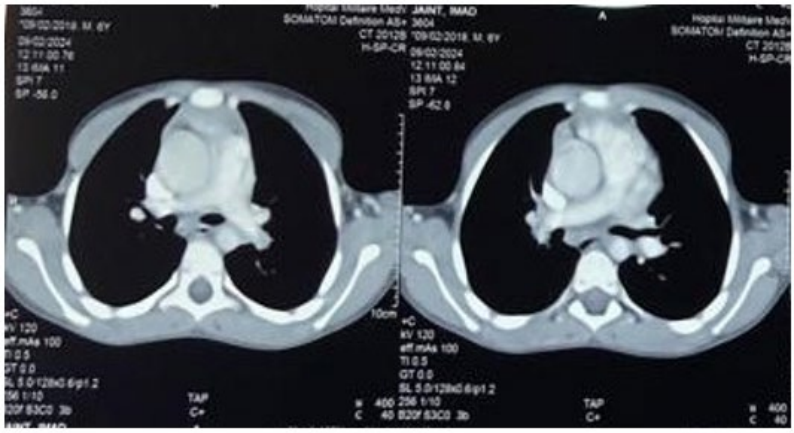

Figure 3: *Thoracic Angio CT confirming the coarctation of aorta.*

Discussion

Williams-Beuren syndrome (WBS) is a rare multisystem disorder affecting about 1 in 7,500 newborns, characterized by significant genotypic and phenotypic variations. Its complex endocrinological, mental, and behavioral traits require cooperation among various medical and non-medical professionals. Extensive clinical and experimental data highlight the link between genetic makeup and the phenotype of affected children. In 1961, three cases with supravalvular aortic stenosis were noted, followed by four patients with similar heart issues, mental challenges, and unique facial features reported 15 years later [2].

In a common approach seen in some medical literature until the late 1800s, authors aimed to showcase unusual clinical cases without delving into the underlying issues. Nonetheless, cardiac patients with an IQ under 85 attracted interest from researchers in pediatrics, pediatric cardiology, psychology, and orthopedics over the subsequent two decades in North America and Northern Europe. Notably, parents of children treated for stenotic aortic supravalvular adhered to strict parenting methods. Current WBS diagnostic definitions incorporate contributions from various authors who monitored the initial patient in the family [3].

WBS results from a submicroscopic deletion of up to 27 genes on chromosome 7, especially at 7q11.23. The important factor is the loss of contiguous genes rather than a specific gene deletion. The extent of deletion varies; some patients have only the two genes at WBSCR deleted, while others may show atypical deletions limited to LIMK1. Molecular tools indicate that 20% of cases have deletions spanning 28 genes. Other mechanisms, including atypical deletions and microdeletions/duplications, have been observed, and gene location within the WBSCR does not correlate with clinical presentation, making phenotype prediction based on deletions unreliable [4].

WBS is an autosomal dominant disorder with a 50% recurrence risk for parents, frequently arising de novo. It's crucial for diagnosing newborns in families without a history of WBS. Carriers of the 7q11.23 deletion show varied phenotypic symptoms, complicating diagnosis. Brain imaging is essential for confirming WBS in young children. Genetic counseling varies by sex, with about one-third of affected males having carrier fathers. Evaluation may change if a parental mosaic condition is present [5].

WBS has an "elfin" look with a broad forehead, full cheeks, and a wide mouth. Facial features include a full face, upturned nose, small chin, and short philtrum. Adults frequently smile excessively, maintain eye contact, possess cognitive reserve, and are well-liked. Despite mild to moderate intellectual disabilities, many individuals exhibit strong memory and verbal skills, which are rare in complex neurodevelopmental disorders [6].

The prevalence of autism spectrum disorder and social communication disorder in Williams-Beuren syndrome (WBS) is under investigation. Children with WBS often face feeding challenges and slow weight gain, leading to obesity later. Premature aging can result in health issues such as hypercalcemia, diabetes, and cardiovascular problems. A genetic diagnosis is crucial for WBS confirmation, with noted delays in psychomotor skills. A subtle "mother instinct" may be observed by parents within the first year. Current prevalence of WBS appears lower than previous studies, indicating a need for continued research [7].

Williams-Beuren Syndrome (WBS) is a genetic condition characterized by a distinctive physical phenotype that aids in diagnosis. This phenotype is influenced by genetic and environmental factors and includes facial dysmorphism, short stature, and health issues. Key facial traits of WBS are full cheeks, cherubism, a small beaked nose, thick septum, anteverted comma-shaped nostrils, long philtrum, prominent lips, wide mouth with large red upper vermilion, and malocclusion [8].

Individuals with WBS have cranial abnormalities that can cause discomfort and fear in unfamiliar situations. It's unclear if these issues stem from craniosynostosis or related craniofacial malformations, contributing to excess facial soft tissue and a cubed shape. At birth, they are around the 40th percentile for weight and height, and this continues into adulthood, leading to below-average stature—females aged 18-53 at about the 23rd percentile and males aged 21-49 at the 18th percentile. Height-weight ratios indicate obesity issues among both genders, which relate to heart disease linked to body weight and fat accumulation [9].

Major cognitive traits in Williams-Beuren syndrome (WBS) include heightened musical skills and social engagement, significantly influencing their lives. Hyperacusis is noted in animal models and hypersensitive autistic children, while musical and absolute pitch abilities in WBS may relate to auditory discrimination. Children with WBS follow slow developmental paths, leading to diverse achievements across domains. This pervasive developmental trajectory results in general cognitive delays, with specific difficulties impacting daily life. Studies underline social and behavioral aspects in WBS, with hyperacusis and hypersociability as key features. Elevated oxytocin levels may influence fear conditioning. High learning disability rates, such as visuospatial construction issues and variable auditory-verbal skills, align with overall developmental delays. Musically trained older adolescents with WBS demonstrate improved language skills. Their exceptional empathy and early musical exposure may enhance learning. A cognitive developmental algorithm has been adjusted to study the relationship between WBS traits and musical affinity [10].

Williams-Beuren syndrome (WBS) is caused by a deletion at chromosome 7q11.23. Diagnosis involves genetic testing for a 1.5-1.8 Mb deletion or clinical evaluation. A multidisciplinary team is essential for assessing organ systems and genetic issues. Early dental evaluations should start in the first year, as symptoms often overlap with other disorders, leading to late diagnosis [11].

Medical management for WBS involves a multidisciplinary approach due to significant cardiovascular complications impacting morbidity and mortality. A structural echocardiogram is advised at diagnosis for infants and children in specialized pediatric facilities. Consultations with pediatric cardiologists and geneticists may be needed. Pediatric patients might present with a heart murmur and lack typical signs, complicating diagnosis. Identified cardiac issues require further evaluations for proper interventions [12].

Most patients achieve learning and language milestones in their first year, but early support enhances outcomes and establishes literacy and social skills. Therapeutic interventions should tackle cognitive and behavioral challenges in WBS. Regular specialist check-ups are vital for managing speech loss, tics, mood disorders, and fears. Parents and educators must assist in language development, as WBS patients often struggle with vocabulary. Continued pediatric care is crucial for monitoring cardiac, renal, orthopedic, endocrine, and ocular health [13].

This sub-section addresses cardiovascular complications in Williams-Beuren Syndrome, highlighting prevalent heart conditions and the need for intervention. It details defects like supravalvular aortic stenosis and emphasizes early detection and continuous monitoring via

echocardiographic assessments. Treatment options, both surgical and medical, are reviewed, noting potential progressive complications that require lifelong care. Additionally, it discusses the impact of these issues on quality of life, stressing the need for awareness among caregivers and medical professionals involved with affected individuals [14].

The incidence of heart problems in children with WBS is around 80%, mainly congenital and hereditary, worsening with age. The primary defect, supravalvular aortic stenosis, is present in 70% of cases. Other issues include altered valve morphology, right aortic arch, and coronary artery stenosis. Early diagnosis and regular monitoring are crucial [15].

Identified defects require strict monitoring and treatment, either surgically or via medications like angiotensin-receptor antagonists for artery widening. Follow-ups in older individuals indicate no vascular aging issues. WBS individuals often encounter vascular stiffness, increasing aortic disease risk. Adults over 40 show no primary stenosis. Ongoing heart evaluations are essential, as the cardiovascular impacts on quality of life remain unclear. Caregivers and healthcare providers must understand risk factors for effective intervention [16].

Most individuals with WBS attend mainstream schools with support for processing speed, visuo-spatial learning, and dyscalculia. Techniques like visual organization inform methods. Early programming benefits milestone focus. Strategies enhance detection, parent involvement, and achievements in language and motor skills, while therapies improve communication. Individualized behavior therapies leverage strengths [17].

Recent advancements have deepened our understanding of the genomic structures and genetic factors linked to Williams-Beuren Syndrome (WBS). Three genome-wide association studies (GWAS) have identified WBS phenotypes and genetic variations, discussing issues like “non-expression” and the impact of copy number variations on the syndrome’s phenotype. Methodologies now include advanced micro single-cell RNA expression profiling. Research suggests that therapeutic approaches could change WBS’s progression, enhancing developmental, cognitive, psychological, and physical outcomes. Clinical trials targeting pathways show promise, indicating mTOR-inhibitors may offer cognitive benefits, emphasizing the need for multidisciplinary studies on rare genetic syndromes [17].

A new research direction links chromosomal syndromes from over 20 years ago with single-gene syndromes and diseases with high SNP heritability. Some chromosomal syndromes share genes with Williams Beuren syndrome (WBS), which has rare non-coding variants potentially affecting gene expression. This research emphasizes similarities, integrating various conditions, including autosomal recessive syndromes and developmental delays. The approach to WBS has shifted, focusing on genetic and micro-neuro-developmental studies. Standardizing WBS phenotypes across health programs is crucial for future advancements, indicating critical next steps are needed for the field [18].

Conclusion

Williams-Beuren syndrome (WBS) is a complex genetic and developmental condition requiring a comprehensive understanding for effective treatment. Interdisciplinary care enhances quality of life and hinges on collaboration among specialists. Early diagnosis and medical care, along with strong educational and social support, are crucial for individuals with WBS. Research progress is significant but challenges persist, necessitating evaluation of new therapeutic strategies. Future efforts will target managing accompanying diseases and improving developmental processes for patient benefit.

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