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ARTICLE

Nationwide questionnaire data of 229 Williams-Beuren syndrome patients using WhatsApp tool

Resultados de um questionário nacional de 229 pacientes com síndrome de Williams-Beuren obtidos por WhatsApp

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ABSTRACT

Background: Williams-Beuren syndrome is a multisystemic disorder caused by a microdeletion of the 7q11.23 region. Although familial cases with autosomal dominant inheritance have been reported, the vast majority are sporadic. **Objective:** To investigate the main complaints and clinical findings of patients with Williams-Beuren syndrome. **Methods:** A total of 757 parents of patients registered in the Brazilian Association of Williams-Beuren Syndrome (ABSW) received a questionnaire via WhatsApp from March to July 2017. **Results:** In total, 229 parents answered the survey. Age of diagnosis ranged from 2 days to 34 years (median: 3 years). The main clinical findings reported by the parents were abdominal colic (83.3%), failure to thrive (71.5%), feeding difficulty in the first year (68.9%), otitis (56.6%), urinary tract infections (31.9%), precocious puberty (27.1%) and scoliosis (15.9%). Cardiac defects were present in 66% of patients, and the most frequent defect was supravalvular aortic stenosis (36%). Arterial hypertension was reported in 23%. Hypercalcemia was reported in 10.5% of patients, mainly during the first year of life. Hyperacusis and hypersociability were common complaints (both present in 89%). Other behavioral and neuropsychiatric symptoms reported by the parents included attention deficit (89%), anger crises (83%), excessive fear (66%), depression (64%), anxiety (67%) and hypersexuality (33%). The most common complaints were hypersensitivity to sounds, talkative personality, emotional dependence and learning difficulties. In 98.3%, the parents denied family history. **Conclusions:** Williams-Beuren syndrome requires close follow-up with different medical specialties due to their variable clinical comorbidities, including language and school learning difficulties, behavioral and psychiatric problems.

Keywords: Williams Syndrome; Medical, Genetics; Behavior; Mental Disorders; Phenotype.

RESUMO

Antecedentes: A síndrome de Williams-Beauren é doença de acometimento multisistêmico causado pela microdeleção da região 7q11.23. Apesar de haver casos familiares com herança autossômica dominante, a grande maioria dos casos é esporádica. **Objetivo:** Investigar as principais queixas e achados clínicos da síndrome. **Métodos:** 757 pais de pacientes inscritos na Associação Brasileira de Síndrome de Williams-Beuren (ABSW) receberam um questionário pelo WhatsApp, entre março e julho de 2017. **Resultados:** 229 pais de pacientes responderam à pesquisa. A idade de diagnóstico variou de 2 dias até 34 anos (mediana: 3 anos). Os principais achados reportados pelos pais: cólicas abdominais (83,3%), deficiência ponderoestatural (71,5%), dificuldade de alimentação no primeiro ano (68,9%), otite (56,6%), infecções do trato urinário (31,9%), puberdade precoce (27,1%) e escoliose (15,9%). Cardiopatias estavam presentes em 66%, sendo que a mais frequente era a estenose pulmonar supravalvar (36%). Hipertensão arterial foi reportada em 23%. Hipercalcemia foi reportada em 10,5%, principalmente no primeiro ano de vida. Hiperacusia e hiperssociabilidade foram achados comuns (89%). Os principais achados comportamentais e psiquiátricos reportados pelos pais foram: déficit de atenção (89%), crises de raiva (83%), medo excessivo (66%),

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depressão (64%), ansiedade (67%) e hiperssexualidade (33%). As queixas principais referidas foram hipersensibilidade a sons, personalidade excessivamente amigável, dependência emocional e dificuldades escolares. Em 98,3% dos casos os pais negaram história familial.
Conclusões: A síndrome de Williams-Beuren é requer um seguimento e manejo estritos, com diferentes especialidades médicas devido às comorbidades clínicas variadas, que incluem dificuldades de linguagem e aprendizagem escolar, além de dificuldades comportamentais e psiquiátricas.

Palavras-chave: Síndrome de Williams; Genética Médica; Comportamento; Transtornos Mentais; Fenótipo.

INTRODUCTION

Williams-Beuren syndrome (WBS) is a multisystemic disorder caused by microdeletion of chromosome 7 in the critical region q11.23. The microdeletion is between 1.5 to 1.8 Mb in size and comprises 28 genes[1–4]. WBS is typically caused by spontaneous ***de novo*** mutations; however, some familial cases have been described[2]. The estimated prevalence is 1 to 10.000 live births[5].

Originally described as two distinct health conditions[6,7], WBS is now referred to as a single genetic disease[8,9] characterized by a congenital heart defect, usually supravalvular aortic stenosis (SVAS) (80%)[10]; mild short stature; facial dysmorphism; and variable abnormalities of genitourinary, ocular, endocrine, and skeletal systems[3].

Typical facial dysmorphisms in WBS include a high forehead, medial broadening of the eyebrows, periorbital puffiness, depressed nasal bridge, short upturned nose, malar hypoplasia, flat midface, thick lips, wide mouth, long nasolabial philtrum, dental malocclusion with small and spaced teeth, and mild micrognathia[1,3,11,12]. In childhood, affected individuals often have classic phenotypic facial dysmorphisms. As patients age, these characteristics become more subtle, giving them a gaunt appearance with a prominent supraorbital ridge, a long narrow face and a long neck. Patients with light eyes may also a star shaped iris pattern[11,12].

Individuals with WBS also have unique cognitive and behavior profiles[3], such as high skills in languages and music[2,3,13]. They also have a hypersocial personality, including excessive friendliness, lack of fear of strangers, strong prosocial urge, excessive talkativeness, fluency with extensive and expressive vocabulary, but with little discursive coherence and no mastery of the discourse topic, especially in adulthood[3,11].

It is a consensus among WBS experts that a multidisciplinary approach for evaluation and intervention is the best practice to maintain satisfactory physical and mental health in individuals with WBS[14,15]. Parents can be excellent informants for health teams in reporting their children's physical and mental health problems when complaints are not spontaneously identified by education and health professionals[16]. Furthermore, questionnaires are an important methodological tool to explore education needs and mental and physical health complaints through oral reports from parents. In Brazil, there are no studies based on parent reports to capture their perceptions about clinical characteristics, school difficulties and emotional and behavioral profiles of children with WBS. Parents can help to target the needs of individuals with this syndrome.

This study was a pioneering initiative in the WBS support association, and its results can improve education and health care for these patients. The aim of the present study was to investigate the main clinical, physical, educational, and psychological complaints of Brazilian children, adolescents, and adults with WBS according to their parents and to compare the parents' perceptions with the findings of previous studies.

METHODS

This was an exploratory study. Therefore, a non-probabilistic sample selection was used. The eligible sample comprised 757 parents of children, adolescents and adults with WBS who were registered as members of the Brazilian Association of Williams-Beuren Syndrome (ABSW). All parents were invited to participate in the study. Of these 757 parents, 229 agreed to participate (30.25%). The sample included parents from 24 of Brazil's 27 states, including the Federal District. The most represented states were São Paulo (37.11%), Minas Gerais (11.79%), Rio Grande do Sul (10.48%) and Rio de Janeiro (9.60%). The inclusion criterion was WBS diagnosis. The study was approved by the Ethics Committee for Analysis of Research Project HCFMUSP/CAPPesq, and patients or legal guardians provided consent for participation in this study.

Instrument

The questionnaire was developed by a multidisciplinary team composed of geneticists, psychologists and speech therapists. The questionnaire contained items about the patient's life, starting with the mother's obstetric history, including previous pregnancies and abortions, pregnancy complications, delivery conditions, birth conditions, early complications, age of WBS diagnosis and genetic test used. In addition, many health conditions described in the syndrome phenotype were investigated: calcium levels, cardiac defects, multiple systemic abnormalities, presence of arterial hypertension or stenosis, behavioral problems, learning difficulties, psychiatric disorders and neuropsychomotor development, and use of mental health services, such as psychiatrists and psychologists. To capture the main complaints, the survey had a specific field where parents could report other health conditions. The questionnaire was written in a Microsoft Word document and sent to participants via the WhatsApp application.

Procedures

Initially, the ABSW provided the parents' cell phone numbers to invite them to participate in the study. The questionnaire was sent to the 757 parents and answers from 229 were received for 4 months (March to July 2017). The agreement between the present results and those of previous studies was calculated for the percentage of clinical, educational and psychological features and complaints.

RESULTS

All data were collected based on verbal parents' reports about their children. In total, 229 (30.25%) parents answered the survey, including 122 males and 107 females. The age of diagnosis ranged from 2 days to 34 years (median=3 years/average=4.3 years), and the age of the patients at the time of the survey ranged from 9 months to 44 years (median=12.3 years/average=13.6 years). The WBS diagnosis was confirmed in 201 (87.7%) patients using several methods, including array analysis (12 patients=5.4%), fluorescent in situ hybridization (FISH) (139 patients=60.7%), multiplex ligation-dependent probe amplification (MLPA) (18 patients=7.8%) and polymorphic marker studies (32 patients=13.97%). The remaining 28 patients never underwent genetic testing, and their diagnosis was based exclusively on clinical features. Almost all cases (98.3%) were sporadic and had no positive family history; however, one family reported affected twins.

The study sample was composed of 133 (54%) firstborns. Maternal age at conception varied from 14 to 49 years old (median=27.5 years/average=27.4 years). Pregnancy complications were reported by 74 (32.5%) parents, and were mainly intrauterine growth retardation, gestational bleeding and gestational diabetes. When asked about delivery methods, 64 (27.52%) reported vaginal delivery, whereas 166 (72.48%) underwent caesarean surgery. Prematurity occurred in 20.2% of patients. The average body weight of the newborns was 2647 g, and 179 (78%) cried early at birth. The mean hospital discharge was 5.5 days.

Several medical health conditions were reported by the parents during growth and development, including abdominal colic (83.3%), failure to thrive (71.5%), feeding difficulty in the first year (68.9%), otitis (56.6%), urinary tract infections (31.9%), precocious puberty (27.1%) and scoliosis (15.9%). Other common WBS-related pathologies were also reported. Congenital heart diseases were present in 66% of patients, and SVAS represented 36% of all cardiopathies. Multiple arterial stenosis was reported by 33%, arterial hypertension by 23%, cerebral malformations by 8.8%, renal anomalies by 8.3%, and seizures by 7.5%.

Table 1 shows cardinal WBS clinical features and their frequencies reported by parents and the expected frequency.

Hypercalcaemia was not a common finding and was only reported in 24 individuals (10.5%). The age of onset varied between the first year of life (39.7%), childhood and adolescence (58.3%) and adulthood (4.1%), with a mean of 5 years and median of 2 years. Two most common features of WBS reported in our sample were feeling uncomfortable with loud-strident sounds, reported by 203 (89%) individuals, and hypersocial behavior, reported by 203 (89%) individuals.

Table 1. Main clinical, educational, psychological and psychiatric findings of the Williams-Beuren syndrome children, adolescents and adults reported by parents.

Clinical findings	n	%	Expected frequency
Cardiac disease	151/229	66	80-83%[15]
SVAS	54/151	36	65%[15]
Development delay			
Motor	165/229	72	70%[15]
Speech	168/229	73	91%[15]
Cognitive	77/229	34	65%[15]
Behavioral problems			
Hypersociability	203/229	83	93%[23]
Excessive Fear	152/229	66	22%[23]
Anger	190/229	85	22%[23]
Emotional and behavioral problems and psychiatric findings			
Hypersexuality	76/229	33	5-10%[22,27]
Anxiety	153/229	67	65%[15,23]
Depression	146/229	64	10-14%[15,23]
Inattention problems	203/229	89	37%[15,23]
Hyperacusis	203/229	89	37%[15,26]
Hypercalcemia	24/229	10	15%[30,31]

SVAS: supravalvular aortic stenosis.

Other common problems referred by parents in the survey included emotional and behavior problems and symptoms of neurodevelopmental and psychiatric disorders. Specifically, attention deficit was reported by 203 (89%) individuals. According to parents, 190 (83%) reported anger crises, anxiety was mentioned by 153 (67%), excessive fear by 152 (66%), depression by 146 (64%), and hypersexuality by 76 (33%) individuals. Despite the high frequency of emotional and behavioral problems, only 34.1% of patients received psychological intervention, and 2.6 % receive psychiatric treatment.

Many characteristics of neuropsychomotor development delay were reported by patients' parents: 73.2% reported motor delay, 73.4% reported speech delay, and 33.8% reported learning difficulties. Of the total sample (229 patients), 47 were 7 years old or older, of whom 59.6% were not literate. Parents' main complaints about their children with WBS were sound hypersensitivity (86%), followed by talkative personality (77%), emotional dependence (52%), inattention to problems (89%), and school and learning difficulties and illiteracy (40%).

DISCUSSION

Hypercalcemia severely affects newborn mortality, whereas congenital heart defects represent the major cause of infant morbidity and mortality[3,17]. Therefore, neonatologists and pediatricians should consider WBS as a differential diagnosis when faced with neonatal hypercalcemia and congenital heart defects, such as SVAS. If such features are present, further detailed investigation by a geneticist may be necessary. Additionally, other key features commonly found in WBS should also be investigated.

Cardiovascular abnormalities are not only a common comorbidity in patients with WBS but also the main cause of mortality[17]. A review of 108 case reports demonstrated that cardiopathies were present in 50/108 (42.3%) affected individuals[18]; on the other hand, other studies estimated an 80-83% prevalence of cardiopathies in patients with WBS[2,10]. SVAS is the most common WBS cardiopathy, and it is described as an elastin-dependent arteriopathy. Even though SVAS is reported in approximately 65% of WBS patients, it is not considered a pathognomonic sign[2,3,10].

The *ELN* gene is located at 7q11.23 and encodes the elastin protein. *ELN* deletion is responsible for several cardiac and vascular abnormalities in WBS, including multiple arterial stenosis. Special attention should be paid to renal artery stenosis, which can lead to early onset arterial hypertension in affected patients[2,19,20]. In our study, parents reported a similar incidence of congenital heart diseases as cited in the literature, and the same correlation between SVAS and WBS was also found. However, the percentage was lower than that described. The prevalence of arterial hypertension reported in the literature varies and was present in 23% of our sample. Additionally, arterial hypertension can be an early complication with a diagnosis age ranging from early infancy to adulthood and has a lifetime risk of approximately 50%. Therefore, regular screening for arterial hypertension through recurrent blood pressure measurements, which should start as soon as possible after the diagnosis of WBS[21,22] is strongly recommended.

Parents might not be fully aware of their children's cardiovascular health indicators. This knowledge depends on different factors, such as parents' educational level, access to information and quality of health services that the children receive[23]. Although these variables were not controlled in this study, the data can alert health professionals to the need to involve parents and caregivers in monitoring their children's health. Parents should be educated regarding the severity of symptoms and diseases, e.g., cardiovascular abnormalities secondary to elastin arteriopathy, like SVAS or hypercalcemia. In Brazil, there is no official guidelines for WBS[24] and specific publications for parents and caregivers with scientific information about the syndrome are scarce[25].

Individuals with WBS typically have higher plasma calcium levels than unaffected controls, but values do not exceed the normal limit[26]. Hypercalcemia has been often described in people with WBS since it was first described[8]. However, recent research demonstrates that it is not as common as previously thought, with an of only 15% incidence among infants and children with WBS[27,28]. Primary hypercalcemia is typically present in early infancy, especially in the neonatal period, and is less common in adolescence and adulthood, where it is frequently found secondary to other health conditions (e.g., hyperparathyroidism)[26–28]. For pediatricians, it is especially important to consider WBS in neonates and infants when facing idiopathic hypercalcemia either with or without associated congenital heart defects[3,28,29]. Hypercalcemia was found in 10.5% of the patients in the study sample, and this value is lower than that described in the literature. The mean manifestation age of hypercalcemia was approximately 5 years, and 37.5% reported it in the first year of life, which is consistent with the literature.

WBS is associated with a cognitive behavioral profile including mild to moderate intellectual disability, greater, although atypical, verbal than spatial abilities, anxiety, and high sociability; these patients are generally described as unusually sociable, friendly and empathic individuals[14,30,31]. Individuals with WBS are often described as more anxious, distractible, and hyperactive and are more likely to experience difficulties with peer relationships than either chronological age-matched children or those with similar levels of intellectual disability[14].

As a comparison, hypersocial behavior was not only the major finding in the studied sample but also a common complaint of parents. Another important factor is how WBS children frequently approach and interact inconsequentially with strangers. As these children grow and become adults, their parents have less control, which can eventually lead to a social vulnerability[31,32] with an increased risk of social exclusion, either sexual or verbal abuse, and victimization in assaults and robbery[33,34]. Another factor that increases the risk of abuse is enhanced sexuality, which appears to be associated with this

condition. Individuals with WBS seem to have an accelerated sexual maturation with puberty occurring 1-2 years earlier than unaffected individuals[31]. Additionally, these patients are more vulnerable to compulsive behavior and, in some cases, obsessive sexual thoughts and impulsivity[35]. This behavior was reported by 33% of parents, and only one parent complained about it. Although it is not the most common feature, it affects 1 in 3 patients, making it an important feature to consider in patient management and family approach.

Persistent and excessive fear has been reported[14], caused by altered fear processing, as these patients are less fear-sensitive in social settings but generally more fearful in nonsocial situations[14,31]. According to parents, there was a high percentages of mental health problems or emotional-behavioral problems (Table 1); however, the parents reported low use of mental health service, including psychological and psychiatric interventions. A previous epidemiological survey of four Brazilian regions showed different gaps in mental health care among typical children and adolescents (6 to 16 years old) of public elementary schools between[36]. For instance, lack of financial investment, difficult access to mental health services, untrained professionals to identify and refer children with mental health problems or stigmatization regarding their treatment were identified. In case of WBS patients, it is likely that the demands are more complex and difficult to recognize, as professionals need to be aware not only of the mental health problem but also of the specific characteristics of the behavioral phenotype of these individuals[14,30,31].

Individuals with WBS tend to present mental health problems and psychiatric conditions, such as anxiety, depression, specific phobias, excessive fear and attention-deficit/hyperactivity disorder[14,31,33,34,37]. The same neural activity and brain structural integrity were found in both anxiety disorders and WBS[37]. Similarly, they also have difficulty interpreting sociability, maintaining social relationships, and converting empathy into helpful behavior or other types of socially appropriate responses. This idea might explain the high prevalence of anxiety disorders (such as fears, phobias, panic, etc.) in people with WBS and the reported sense of isolation despite their attempts to connect with other people[14,31].

Individuals with WBS are expected to have certain degrees of neurodevelopmental delay and mild to moderate intellectual disability. Many of the characteristics associated with WBS in childhood (high sociability and expressive language) may have a negative impact later on, given that the development of other areas does not follow the same rhythm, becoming progressively deficient[15,33]. Children with WBS typically have difficulties in visuospatial skills, sensory motor processing and executive function. In contrast, they show better auditory memory, face recognition abilities and speech skills (even when language is delayed). Therefore, these patients benefit greatly from a specific and targeted educational approach with exclusive support from professionals who have sufficient knowledge of the syndrome instead of being submitted to regular school[33,38].

Children and adolescents with WBS and intellectual disabilities have learning difficulties, and need special support to acquire a minimum level of skills at school[39]. Previous studies have shown that parents of WBS individuals are dissatisfied with the education provision, but few studies have examined the educational needs of children with WBS[38]. Other problems that overlap with learning difficulties include emotional and behavioral problems, such as anxiety and inattention. In our study, parents reported a high percentage of anxiety (67%) and inattention problems (89%), which are common problems of the syndrome and exacerbate learning difficulties[40]. The results of the study showed how parents can help target the needs of individuals with the syndrome.

One important limitation of this study was that data were based on parental reports without assessment of patients, and the results may not accurately reflect the actual signs and symptoms, underestimating the percentage of cognitive impairment, because of a lack of systematic analysis. However, the study showed that the health problems of the group were similar to those reported in previous research. Another limitation is that the parents were recruited from the ABSW, the main parent organization for this syndrome in Brazil. It is possible that the parents' reports reflect a collective perception resulting from participation in the organization, despite the high representativeness of the states in the study (89% of states were represented).

In conclusion, WBS is a well-known syndrome among geneticists and other medical specialists with very specific clinical features. An important note is that physicians should look for individuals with congenital heart defects associated with distinctive facial features and behavior abnormalities when WBS is suspected.

It is also important to pay attention to the follow-up routines of these patients. Due to a highly variable spectrum of health conditions that may co-occur with WBS, a thorough clinical examination is required at the time of diagnosis to look for possible comorbidities. In addition, a surveillance protocol should be instituted with regular medical evaluations to monitor the patient's heart, renal system, blood pressure, calcium levels, and any other conditions. Psychiatric and behavioral disorders have also been found to play an important role in the WBS phenotype and should be evaluated and addressed during follow-up.

Finally, it is important to promote a better quality of life for WBS patients and therefore to encourage improvements in the education system. Trained professionals who can properly stimulate WBS patients are needed, so that these individuals can increase their skills and improve their adaptive behavior.

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