

Genética e linguagem na síndrome de Williams-Beuren: uma condição neuro-cognitiva peculiar****

Genetics and Language in Williams-Beuren Syndrome: a distinct neurobehavioral disorder

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****Parte da Dissertação de Mestrado do Primeiro Autor, Apresentada ao Programa de Pós-Graduação em Ciências Biológicas - Área de Concentração: Genética do Instituto de Biociências da Universidade Estadual Paulista - Campus de Botucatu. Trabalho Realizado no Ambulatório de Fono-Genética do Serviço de Aconselhamento Genético do Instituto de Biociência da Universidade Estadual Paulista - Campus Botucatu, com Auxílio Financeiro do CNPq (Processo nº 481111/04-2).

Revisão de Literatura

Artigo Submetido a Avaliação por Pares

Conflito de Interesse: não

Recebido em 16.11.2005.

Revisado em 28.12.2005; 21.06.2006; 27.09.2006.

Aceito para Publicação 26.10.2006.

Abstract

Background: genetic, cognitive and language aspects of the Williams-Beuren Syndrome (WBS). Aim: to present a review of the literature about WBS, highlighting its genetic, cognitive and language characteristics. Conclusion: the literature indicates that although the etiology of WBS is known, early diagnosis is difficult due to the great variability of its clinical characteristics. This great phenotypic variability has been associated to a deletion of several genes in region 7q11.23 which includes the elastin gene. The deletion of this gene is identified by the Fluorescent in situ Hybridization test (FISH). The incidence of this syndrome is 1 in every 20,000 birth and is the result of a "de novo" genetic alteration. The syndrome is characterized by an elfin type face, cardiac alterations, cognitive deficits and behavioral aspects that include language. A peculiar cognitive profile has often been described as consisting of outstanding social and verbal skills associated to visuo-spatial impairments. Cognitive deficits are variable and may not be present. Studies that describe language abilities indicate that syntax might be intact or partially intact; speech can be precise and intelligible indicating that the phonological system is preserved. The receptive vocabulary is mentioned in a few studies as being adequate and in others as being impaired according to mental age. Researches have produced incongruent findings regarding the cognitive and linguistic abilities. The correlation between the language and cognitive abilities and the divergent findings presented in the literature will be discussed in this article.

Key Words: Williams-Beuren Syndrome; Genetics; Cognition; Language.

Resumo

Tema: aspectos genéticos, cognitivos e de linguagem na Síndrome de Williams-Beuren (SWB). Objetivo: revisar a literatura sobre a SWB, destacando aspectos genéticos, cognitivos e de linguagem. Conclusões: a literatura mostrou que a etiologia da SWB é conhecida, embora o diagnóstico precoce pode ser difícil pela variabilidade de manifestações clínicas dessa condição. O fenótipo variável tem sido atribuído a deleção de vários genes na região 7q11.23, que inclui o gene da elastina. A deleção desse gene é identificada pelo estudo citogenético molecular denominado Hibridização in situ por Fluorescência (FISH). A frequência populacional desta síndrome é de 1 em 20,000 nascimentos e é resultante de uma alteração genética "de novo". O quadro da SWB é caracterizado principalmente por fácies típica conhecida como face de duende, alterações cardíacas, prejuízos cognitivos e aspectos comportamentais que incluem a linguagem. A característica falante e sociável associada as dificuldades viso-construtivas conferem a esta síndrome um quadro neuro-cognitivo peculiar. A deficiência mental é variável e pode ou não estar presente. Estudos que descreveram as habilidades de linguagem nesta síndrome destacaram que a habilidade sintática pode estar íntegra ou parcialmente íntegra, a produção verbal pode ser precisa e inteligível, mostrando a integridade do sistema fonológico. O vocabulário receptivo-auditivo é citado em alguns estudos como adequado e em outros como prejudicado para a idade mental. Pesquisas na área têm produzido, resultados incongruentes com respeito ao perfil de habilidades cognitivas e lingüísticas nos portadores dessa condição. A correlação entre as habilidades de linguagem e a cognição e a divergência de achados na literatura serão abordadas neste artigo.

Palavras-Chave: Síndrome de Williams-Beuren; Genética; Cognição; Linguagem.

Referenciar este material como:



ROSSI, N. F.; MORETTI-FERREIRA, D.; GIACHETI, C. M. Genetics and Language in Williams-Beuren Syndrome: a distinct neurobehavioral disorder (original title: Genética e linguagem na síndrome de Williams-Beuren: uma condição neuro-cognitiva peculiar). *Pró-Fono Revista de Atualização Científica*, Barueri (SP), v. 18, n. 3, p.331-338, set.-dez. 2006.

Introduction

Williams-Beuren syndrome (OMIM: 194050), first described by Williams et al. (1961) and Beuren et al. (1962), is a rare genetic disorder caused by a microdeletion of chromosome 7. The clinical diagnosis is usually made on the basis of a distinctive face, cardiovascular malformations, idiopathic hypercalcemia, peculiar cognitive profile and language skills resultant from unusual personality and behavioral characteristics.

In Williams-Beuren syndrome (WBS), facial features include full cheeks, flat nasal bridge, long philtrum, periorbital fullness, wide mouth, full lips and anteverted ears. The most frequent cardiovascular abnormalities are supravalvular aortic stenosis and pulmonary arterial stenosis. Individuals with WBS frequently show mental retardation with impaired visuospatial skills and difficulties in language development/learning associated with an outgoing and expressive personality (Montgolfier-Aubron et al., 2000). The Williams Syndrome Cognitive Profile (WSCP) involves a clear strength in auditory rote memory, strength in language, and an extreme weakness in visuospatial construction relative to the overall level of intellectual ability, supporting the hypothesis that language and cognitive skills are dissociated in this syndrome (Pagon et al., 1987; Mervis and Klein-Tasman, 2000).

The purpose of this work was to review the literature on WBS with an emphasis on the genetic aspects of cognition and language.

Etiology and diagnosis

WBS is frequently of "de novo" origin and affects 1:20,000 livebirths (Borg et al., 1995). The term "de novo" is used to describe this syndrome as sporadic and of low risk of familial recurrence.

WBS is caused by the hemizygous microdeletion of approximately 20-25 genes on chromosome 7q11.23 (Figure 1A). Over 95% of the individuals with WBS have deletion of the elastin gene (ELN) (Ewart et al., 1993) detectable by fluorescence in situ hybridization (FISH) (Figure 1B). Therefore, chromosome analysis and the Williams Syndrome Chromosome Region Fish Test are recommended for confirmation of the diagnosis.

However, a negative FISH result should not rule out WBS. The assessment of clinical signs and the use of molecular techniques more specific for the identification of other genes involved should also be taken into account when establishing the diagnosis.

In Brazil, the use of the FISH has been divulged, as associated diagnostic resource to the study of the clinical characteristics of the WBS, with the purpose to establish parameters for the request of this examination for the geneticist (Sugayama 2001; Souza, 2003).

Clinical characteristics

The WBS phenotype is characterized by cardiovascular abnormalities, typical facial features, unique cognitive profile, unusual personality, and language abilities. Very frequently, the presence of cardiac problems is the clinical sign that allows the early diagnosis of WBS because they can be identified at an early age. Approximately 75 to 80% of the individuals with WBS display cardiovascular disorders, particularly supravalvular aortic stenosis (65% of the cases) and pulmonary artery sclerosis (38% of the cases) (Sugayama et al., 2001).

The facial features typically observed in WBS individuals have given rise to different denominations to this disorder. One of them is Elfin Facies syndrome (Joseph and Parrot, 1958), given the presence of facial dysmorphisms such as upturned nose, flat nasal bridge, periorbital fullness, wide mouth, full lower lip, full cheeks, and long nasal philtrum

Other clinical characteristics could be found as: inguinal and umbilical hernia; stellate iris; harsh and hoarse voice; chronic otitis media; dental abnormalities; prenatal growth and weight deficiency and short stature. The poor weight gain is common in the first years of life and is likely due to the severe difficulties with feeding and gastrointestinal problems (Pankau et al. 1994; Souza, 2003).

The literature reviewed included WBS clinical characteristics in patients with and without microdeletion of the ELN gene (Chart 1). The variation in the total number of cases shown in Table 1 is due to the fact that not all studies reviewed included all the characteristics below.

Visuospatial construction and verbal abilities: cognitive studies

Psychometric tests have revealed that, in WBS, Intelligence Quotient (IQ) ranges from 50 to 70, i.e., mild to moderate mental retardation (Udwin et al., 1987; Bellugi et al., 1999) with poor visuospatial construction when compared to

verbal ability, providing evidence for dissociation between these tasks (Udwin and Yule, 1991; Jarrold et al., 1999). However, some studies have shown that verbal and executive skills are equally impaired (Carrasco et al., 2005; Porter and Coltheart, 2005). The study of visuospatial processing has shown that WBS individuals have a preference to process the parts of an image at the expense of attending to the global form, suggesting that the ability to group visual stimuli may be affected (Jordan et al., 2002; Farran et al., 2003). The investigation of visual and spatial memory skills, either isolated or associated, showed that this weakness in perceptual grouping is a result of spatial impairment because visual abilities when dissociated from spatial relations, is preserved (Vicari et al., 2003; Farran, 2005). Other findings regarding visual abilities include strength in face recognition and judgment of emotional expressions (Bellugi et al., 2000). The ease in performing musical tasks favors learning as it increases attention span, which is frequently reduced in WBS individuals (Levitin et al., 2004).

Oral language and reading abilities

Studies of language abilities in WBS have yielded conflicting results (Chart 2). The so called dissociation between abilities (execution x verbal) has been questioned. According to some authors, different methods could yield variable performance patterns depending on the complexity of the task (Gosch et al., 1994; Karmiloff-Smith et al., 1998).

Receptive vocabulary in WBS, as assessed by the Peabody Test, has been considered to be adequate for mental age (Ewart et al., 1993; Mervis et al., 1999). However, others advocate that a good receptive vocabulary is not enough for a good semantic performance. The difficulty in lexical selection during linguistic tasks, such as narratives, has been pointed out, and characterizes loss of verbal fluency (Bellugi et al., 2001; Karmiloff-Smith et al., 2003; Reilly et al., 2004). Oral narratives frequently display prosodic strength amid sound effects and exclamative phrases (Gonçalves et al., 2004).

Pragmatic skills have been poorly addressed in studies of WBS, although they seem to be of significant importance in the understanding of the language difficulties experienced by affected individuals. WBS individuals very frequently produce narratives that, although grammatically correct, lack coherence. The amount of speech, or number of communication acts used by WBS

individuals do not respond for the social use of language (Laws and Bishop, 2004). Sociability and verbosity may be better related to the use of oral language as a communication resource rather than to competence in language abilities (Carrasco et al., 2005). Rossi et al. (2005) found deficits in semantic coherence and logic/chronologic organization of events in WBS.

Some studies have shown that WBS individuals had an adequate performance in the Digit Span test (Mervis et al., 1999) and point out that children with WBS display slightly impaired lexical-semantic and morphosyntactic abilities (Wang and Bellugi, 1994; Karmiloff-Smith et al., 1998), though with a significant difficulty in the long-term storage of information.

The visuomotor difficulties experienced by WBS individuals are associated with weakness in writing, which is frequently more affected than reading (Udwin et al., 1987). A longitudinal study of cognitive abilities and educational attainment indicated that the development of reading, spelling and arithmetic skills is quite compromised, being more favorable over the first school years and making little progress beyond that (Udwin et al., 1996).

Investigations of the contribution of phonological and semantic processes to verbal span in WBS children have suggested an impaired contribution of the lexical semantic resources to verbal span, that is, a reduced frequency effect. In fact, in tasks calling for reproducing lists of words of different frequency, normal children repeated much better the high-frequency than the low-frequency word list (Vicari et al., 1996). In a study of phonological awareness, Majerus et al., (2001) found that WBS children were more impaired than their controls in rhyme detection and phoneme manipulation. Levy et al., (2003) found no correlation between reading and rhyme tasks, whereas word segmentation significantly correlated with the ability to read non-words. In addition, they reported that the ability to judge separate phonemes of a given word and non-word, and performance on measures of letters and word decoding were especially correlated.

Studies of language skills have yielded conflicting results. The oral language abilities in WBS have been more frequently described than writing skills. Even the studies focusing on oral language have poorly addressed pragmatic abilities and the use of communicative resources by WBS individuals within several communicative contexts.

FIGURE 1A. Chromosome 7 ideogram showing the 7q11.23 region deleted in WBS

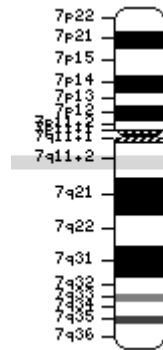


FIGURE 1B. FISH test used in the cytogenetic-molecular diagnosis of WBS. Notice the absence of the red sign (arrow) in one of the chromosomes 7, confirming the deletion of the ELN gene.

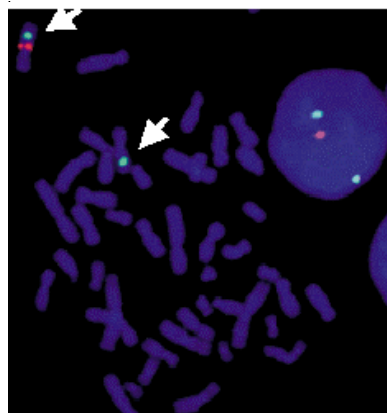


FIGURE 2. Facial aspect of 4 WBS individuals with deletion of the ELN gene detected by FISH at the Genetic Counseling Service, Institute of Biosciences/UNESP-Botucatu, SP.



CHART 1. Frequency of clinical signs in the literature reviewed (Borg et al., 1995; Kotzot et al., 1995; Lowery et al., 1995; Nickerson et al., 1995; Joyce et al., 1996; Perez-Jurado et al., 1996; Elçoglu et al., 1998; Beust et al., 2000; Mila et al., 2000; Sugayama, 2001; Souza, 2003).

Clinical Manifestations	with microdeletion	Without microdeletion
	Np / Ni (%)	Np / Ni (%)
At birth/ early childhood		
Failure to thrive	202/218 (92,6)	45/58 (77,5)
Low birthweight	42/61 (68,8)	8/44 (18,1)
Difficulty in gaining weight	40/70 (57,1)	16/37 (43,2)
Low stature	37/94 (39,3)	6/22 (27,2)
Intestinal constipation	39/60 (65,0)	10/37 (20,0)
Recurrent otitis	4/14 (28,5)	0/3 (0,0)
Hypercalcemia	44/197 (22,3)	9/41 (21,9)
Inguinal/ umbilical hernia	65/179 (36,3)	5/14 (35,7)
Facial characteristics		
Periorbital fullness	241/260 (92,6)	22/56 (39,2)
Full cheeks	236/274 (86,1)	27/57 (47,3)
Low nasal bridge	156/175 (89,1)	21/23 (91,3)
Anteverted nostrils	216/235 (91,9)	18/47 (38,2)
Long nasal philtrum	228/252 (90,4)	18/50 (36)
Wide mouth	253/271 (93,3)	25/58 (43,1)
Full lips	218/227 (96,0)	21/43 (48,8)
Dental anomalies	60/93 (64,5)	18/53 (33,9)
Big anteverted ears	7/15 (46,6)	1/3 (33,3)
Cardiovascular characteristics		
Cardiovascular disorders (supravalvular aortic stenosis and pulmonary artery sclerosis)	306/470 (65,1)	22/167 (13,1)
Systemic hypertension	16/128 (12,5)	0/42 (0,0)
Ophthalmological characteristics		
Strabismus	39/76 (51,3)	2/17 (11,7)
Stellate íris	25/72 (34,7)	3/16 (18,7)
Muscle-skeleton characteristics		
Clinodactyly of the 5th finger	35/65 (53,8)	22/42 (52,3)
Renal disorders		
	18/91 (19,7)	1/16 (6,5)
Personality, cognition, language and hearing characteristics		
Mental retardation	187/210 (89,0)	51/77 (66,3)
Friendliness	78/93 (83,8)	29/78 (37,1)
Anxiety	24/37 (64,8)	5/8 (62,5)
Hyperactivity	35/51 (68,3)	7/12 (58,3)
Loquacity	29/52 (55,7)	1/10 (10,0)
Hyperacusia	27/55 (49,0)	2/13 (15,3)
Hoarse voice	25/32 (78,1)	21/77 (27,2)

Legend: Np =number of subjects with clinical sign present; Ni = number of subjects investigated for the clinical sign.

CHART 2. Reviewed studies that focused on aspects related to cognition and language/learning abilities.

Strengths and Weaknesses in Language/Learning		
Oral Language	Syntax / Semantic	Strengths: Adequate reception and emission (Bellugi et al. 1988), adequate (Jones and Smith, 1975) or relatively adequate (Jarrold et al. 1998; Mervis et al. 1999; Freitas et al. 2003) morphology and syntax Weaknesses: Reception and expression (Udwin e Yule 1990; Gosch et al, 1994), lexical-semantic and morphosyntactic (Volterra et. al 1996; Karmiloff-Smith et al. 1997, 1998)
	Phonology	Strengths: adequate phonetic-phonological with intelligibility (Karmiloff-Smith et al. 1997, 1998) preservation of the phonoarticulatory (Wang e Bellugi, 1994) over the lexical-semantic circuit (Karmiloff-Smith et al. 1998). Weaknesses: phonemes and rhyming (Laing et al. 2001)
	Pragmatic	Strengths: Initiates conversations (Carrasco et al. 2005). Cocktail Party Speech Phenotype – articulatory fluency, verbosity (Udwin e Yule, 1990). Weaknesses: Cocktail Party Speech Phenotype – stereotyped phrases, cliches, perseverative speech and habit of introducing personal experiences in irrelevant and inappropriate contexts (Udwin e Yule, 1990). Difficulty in using oral language for social purposes and communicative contexts (Laws e Bishop, 2004; Carrasco et al. 2005) and TDAH (Gosch e Pankau, 1996).
Reading	Cognitive aspects related to reading abilities	Strengths: Reading and writing superior to cognitive level (Pagon et al. 1987). Reading comparable to verbal IQ (Laing et al. 2001) and oral reading favored by auditory memory (Mervis et al. 1999). Weaknesses: Cognitive level comparable to reading/writing level (Udwin et al. 1987). IQ correlated with decoding ability (Levy et al. 2003). Writing perceptual-motor impairment (Mervis et al. 1999).
	Phoneme-to-grapheme Decoding	Strengths: Predominant phonological process (Bohning et al. 2002). Weaknesses: Failure in auditory-visual integration resulting from impaired visual process (Bohning et al. 2002). Difficulty in decoding non-words and understanding oral reading (Laing et al. 2001).
Logical thinking		Strengths: in the performance of arithmetical operations due to abstraction deficits (Udwin e Yule, 1991)

Conclusion

Studies of language abilities in WBS are still scarce considering the number of genetic and cognitive studies conducted over the past 5 years.

The literature reviewed about the genetic aspects of cognition and language in WBS showed that the etiology of this genetic condition is known, but early diagnosis may be hindered by the variability in clinical manifestations, especially in the absence of cardiac abnormalities or symptoms. The clinical phenotype includes remarkable characteristics of personality, compromised cognition and language, which associated with physical features, could allow the clinical diagnosis of this condition and indicate the performance of the FISH test by a geneticist.

The studies reviewed reported interesting results that justify the recognition of a peculiar neuron-cognitive profile phenotype of WBS and point out to the hypothesis of dissociation between cognition and language abilities. This hypothesis was supported by the studies that reported

relatively preserved language abilities and weakness in cognition. This was not corroborated by all investigators, who demonstrated linguistic deficits in oral narrative tasks that allowed the identification of pragmatic impairment. Unfortunately, the national literature reviewed revealed a shortage of studies focusing cognition and language problems in WBS.

Studies devoted to the characterization of the neuron-cognitive and linguistic phenotype in this syndrome, associated with molecular studies, may bring, in a near future, benefits to the patients and their families, given that the information obtained may be helpful for the conduction of genetic counseling and interventions for these clinical manifestations, including communication aspects.

These findings might also improve the understanding of mechanisms related to the personality traits, cognition and language from the standpoint of genetics not only in WBS individuals, but in the whole humankind.

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