Cognitive and behavioral profile of Williams Syndrome toddlers

Perfil cognitivo comportamental de crianças pré-escolares com Síndrome de Williams

ABSTRACT

Purpose: To verify indicators of cognitive development, receptive language skills and adaptive behavioral patterns in toddlers with Williams syndrome (WS). Methods: The sample comprised 8 children of both sex, aged between 48 and 72 months with WS. Instruments of data collection were Denver Developmental Screening Test II; Peabody Picture Vocabulary Test; Vineland Adaptive Behavior Scale; Child Behavior Checklist for Ages 1½-5 and 6 to 18; Columbia Mental Maturity Scale (CMMS), and Behavior Problems Inventory-01. Results: The major developmental impairments were associated with fine motor skills and personal care abilities. Deficits in receptive language and communication skills were reported according to the PPVT and Denver II, respectively. The caregivers reported behavioral and emotional problems associated to anxiety and depression, and attention problems scales of CBCL. Conclusion: The toddlers demonstrated deficits in adaptive functioning and behavioral, motor and cognitive difficulties such as inattention and hyperactivity, stereotypies and aggressive behavior.

RESUMO

Objetivo: Verificar indicadores de desenvolvimento cognitivo, habilidades de linguagem receptiva e padrões comportamentais adaptativos em pré-escolares com Síndrome de Williams (SW). Método: A amostra foi composta por 8 crianças de ambos os sexos, com idade entre 48 e 72 meses com SW. Os instrumentos de coleta de dados utilizados foram Denver Developmental Screening Test II; Peabody Picture Vocabulary Test; Escala de comportamento adaptativo Vineland; Child Behavior Checklist (CBCL) para as idades 1½-5 e 6 a 18; Inventário de Problemas de Comportamento (BPI-01) e Escala de Maturidade Mental Columbia. Resultados: Os principais prejuízos de desenvolvimento foram associados a habilidades motoras finas e habilidades de cuidados pessoais. Os déficits em linguagem receptiva e habilidades de comunicação foram relatados de acordo com o PPVT e Denver II, respectivamente. Os cuidadores relataram problemas comportamentais e emocionais associados às escalas de ansiedade e depressão e de problemas de atenção do CBCL. Conclusão: Os pré-escolares demonstraram déficits no funcionamento adaptativo e dificuldades comportamentais, motoras e cognitivas, como desatenção e hiperatividade, estereotipias e comportamento agressivo.

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INTRODUCTION

Williams Syndrome (WS) is a genetic multisystemic neurobehavioral disorder whose etiology is associated with the microdeletion of approximately 28 genes in the 7q11.23 region\(^1\). Clinical characteristic features of this disorder include facial dysmorphisms, cardiovascular problems (most commonly supravalvular aortic stenosis and other arteriopathies), connective tissue abnormalities, childhood hypercalcemia, endocrine problems, and growth failure\(^2\). The syndrome is described by a cognitive and language phenotype characterized primarily by developmental and language delay, intellectual disability, deficits in executive control, difficulty with relational/conceptual vocabulary, impairment in syntactic, pragmatic, and functional language that vary according to the level of intellectual functioning\(^3\). Standardized intelligence assessments report overall deficits in cognitive abilities indicative of mild to severe intellectual disability\(^4,14\).

The distinctive behavioral and clinical characteristics of toddlers and infants with WS compared to typical children and other individuals with neurodevelopmental disorders associated with intellectual disability (ID) are emotional and behavior problems (EBP), fears, different psychiatric conditions as specific phobias, generalized anxiety disorder, and attention-deficit/hyperactivity disorder (ADHD)\(^5\), appetitive drive toward social engagement and heightened approachability, excessive social responsiveness, and lack of selectivity in interpersonal contacts, difficulties in emotion processing with decreased recognition of negative social signals, emotional responsibility, including enhanced empathic display and reaction\(^6\). Previous studies have also demonstrated severe hyperacusis during early childhood that may decrease with age\(^7\). The behavioral phenotype is characterized by the presence of motor restlessness, impulsiveness, body, gestural and verbal stereotypies, impairment in adaptive functions of daily living, and hyperactivity\(^8\). Among speech and language, the distinctive characteristics are use of clichés, excessive pauses during the speech, perseverative speech and exaggerated prosody, pragmatic and structural difficulties in the formation of sentences, disfluencies and difficulty segmenting words\(^9\).

The cognitive profile is heterogeneous. The presence of deficits and relatively preserved abilities can result in contrasts in neurocognitive clinical evaluations\(^10\). This contrast of skills was coined by Mervis\(^11\) as the peak and valley profile. In this profile, the greatest contrasts are observed between the verbal and non-verbal reasoning skills\(^12\).

There are few Brazilian studies that evaluate indicators of cognitive development, receptive language skills and adaptive behavioral patterns in toddlers with WS. The study of Rossi and Giachetti\(^13\) with sample composed by 26 WS individuals from Brazil with ages between 8 and 17.92 years showed higher single-word receptive vocabulary (examined by the Peabody Picture Vocabulary Test-Revised/PPVT-R) and narrative vocabulary (The Cookie Theft Picture from the Boston Diagnostic Aphasia Test) were negatively associated with EBP and social problems. The authors verified that the verbal IQ was significantly positively correlated with raw scores on the receptive language measure, and significant negative correlations were found between receptive vocabulary abilities and social problems.

In Brazil the cognitive, adaptive and emotional-behavioral evidences on individuals with WS in early ages of development are scarce. Brazilian studies have focused mainly on other ages, such as children and adolescents\(^5,13\). The early identification of phenotypic indicators that can later interfere with the literacy, adaptation and socialization of the infants is crucial. The results of assessments like these can be used as basis to monitor the developmental paths of these children until they start school. This study aims to identify indicators of cognitive development, receptive language skills and adaptive behavioral patterns in preschoolers with WS, and to explore the associations between EBP, adaptive functioning and receptive language skills.

METHODS

Participants

The design of study is exploratory and correlational. The sample was composed by eight toddlers with a genetically confirmed diagnosis of WS (five females and three males, aged between 48 and 72 months; mean=60 months / SD=9.07 months), and their respective parents. The informants were responsible for the care of the child for at least 6 hours per day, and 90% of the total were the biological mother. Only half of the toddlers (4 children) received some type of mental and physical healthcare such as speech therapy, physiotherapy and occupational therapy. Participants were recruited from the Brazilian Association of Williams Syndrome (ABSW), Medical Genetics Unit at Instituto da Criança, Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo (ICr-HC-FMUSP) and the Service of Attending of Children and Adolescents at Program in Developmental disorders at Universidade Presbiteriana Mackenzie. The project was approved by the Human Research Ethics Committee of Mackenzie Presbyterian University under the CEP protocol/UPM No. 1398/09/2011 and CAAE No. 0092.0.272.000-11. Participation in the study was authorized by signing the Informed Consent Form by the caregiver.

Data collection instruments

a. Denver Developmental Screening Test-II\(^{14}\): a screening test which assesses neuropsychomotor developmental delay, suitable for children from birth to 6 years old. The areas of development assessed are personal-social, fine motor-adaptive, language and gross motor skills. The children were evaluated individually with the tests corresponding to their age group;

b. Peabody Picture Vocabulary test, computerized version (PPVT)\(^{15}\): assesses auditory receptive language. The test covers ages between 2.5 to 90 years and consists of 125 items, plus 5 training items, with four pictures on each screen. In the test, the child should point to the figure that corresponds to the word he/she hears;

c. Child Behavior Checklist for Children Ages1 ½ to 5 (CBCL/1.5-5), and Child Behavior Checklist for Children Ages6-18 (CBCL/6-18)\(^{16}\): The checklists are based on a multi-axial approach. The behavioral problem items from
both questionnaires are distributed in five scales: syndromes scales, DSM oriented scale, internalizing, externalizing and total problems scales). For example, some scales of the CBCL/1.5-5 and the CBCL/6-18 are emotional reactivity, anxiety/depression, somatic complaints, isolation, sleep problems, problems of attention and aggressive behavior, affective problems, anxiety problems, pervasive developmental disorders, deficit of attention/hyperactivity problems, and opposition and defiant behavior problems\(^{19}\).

d. Behavior Problems Inventory-01 (BPI-01)\(^{17,18}\): an inventory of specific behavioral problems associated with intellectual disability in people of all ages and levels of functioning. It evaluates different types of behavioral problems according to patterns of stereotypy, auto-aggression and aggressive/destructive behavior;

e. Vineland Adaptive Behavior Scales: The scale assesses adaptive behavior in six areas: communication (expressive, receptive and read/write); daily living skills (personal, domestic and community); socialization (interpersonal relationships, play and leisure time, coping skills); motor skills (gross and fine); adaptive behavior and inappropriate behavior\(^{19}\);

f. Columbia Mental Maturity Scale (CMMS): It is an individually administered instrument designed to assess the general reasoning ability of children among the ages of 3 years, 6 months to 9 years, 11 months. Test items require no verbal response and a minimal motor response, which is suitable for use with children who have intellectual disability. The 92 items are arranged in a series of eight overlapping scales or levels. Raw scores are converted to age deviation scores, percentile ranks, stanines, and Maturity Index scores\(^{20}\).

Data collection procedures

The analysis was conducted according normative data of the developmental, behavioral and language tests. Spearman correlation analysis was performed to identify possible associations between the results of tests of development, language, adaptive behavior and behavioral problems. The level of statistical significance was set at 95% for all tests.

As no control group was included in the sample, the test data were analyzed according to the norms of the instruments themselves. In the case of Denver II and Vineland tests, since there is no standardization for the Brazilian population, were used the American standards\(^{14,19}\).

RESULTS

Table 1 shows the results obtained from the Denver II developmental test. A comparison of means was performed using the t-test between the chronological age and the age in months, compatible with the performance in the Personal-social scales; Fine Motor; Language and Gross Engine of the Denver Test. Were observed that 100% of the children have developmental delay according to the indicators evaluated by the test. However, it is noteworthy that although developmental delay was identified in all the four scales comprising the instrument, the better results were obtained in the language scale and the gross motor scale. The language scale items in which the participants obtained corrected scores were: ‘know three objects’; ‘know four actions’; ‘understand four prepositions’, and ‘name four colors’. All participants failed in the items: ‘define five and seven words’ and ‘name two opposites’.

Table 2 presents the scores and the maturity index (MI) of each participant on Columbia Mental Maturity Scale. Three children had difficult to perform the test; in these cases, the application was interrupted, and it was not possible to calculate the mental maturity index. Regarding MI of the remaining five participants, it was below their chronological age, except for individual 4, which presents MI in accordance to real age. Differently, five children had receptive vocabulary indicators in accordance or higher than those expected for their chronological age. One participant did not perform the task of the CMMS, because he was unable to understand the instructions. On the one hand, receptive language skills measured by the PPVT are relatively preserved in five children, two present low scores, and one did not perform the test. In the Denver the results showed delay in all the neurodevelopment indicators according the American norms (Table 1).

The main problems shown by the Behavioral Problems Inventory (BPI-01) were the behavioral stereotyped (predominantly yelling and screaming objects, arm swinging, rolling head, bouncing around, whirling, turning around on spot, having bursts

| Table 1. Results of the Denver Developmental Screening Test scores, Developmental Age (months) and Classification of Child Development |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                               | Chronological Age | Denver Test II |                  |                  |                  |
|                               |                  | Personal-social |                  |                  |                  |
|                               |                  | Score           | Developmental Age |                  |                  |
|                               |                  | Fine Motor      | Score           | Developmental Age |                  |
|                               |                  | Language        | Score           | Developmental Age |                  |
|                               |                  | Gross Motor     | Score           | Developmental Age |                  |
| Mean                          | 66.75            | 20.4            | 32.37           |                  |                  |
| SD                            | 9.7              | 1.8             | 3.1             |                  |                  |
| T                             | 9.52             | 6.91            | 14.70           |                  |                  |
| df                            | 7                | 7               | 7               |                  |                  |
| Sig.                          | < 0.001          | < 0.001         | < 0.001         |                  |                  |
| Classification of Child Development | Delay           | Delay           | Delay           |                  |                  |

of running around), followed by problems of aggressive and destructive behaviors (predominantly hitting others, destroying things, pushing others, kicking others, grabbing and pulling others, spitting on others).

According with the T-scores, the greatest impairments reported in the empirically based scales of the CBCL/1.5-5 and CBCL/6-18 were Anxiety/Depressed, Somatic Complaints, Withdrawn/Depressed (Internalizing Problems), Rule-breaking Behaviour, Aggressive Behavior (Externalizing Problems), and Attention Problems. The data showed difficulties in all three higher-order factors (Internalizing Problems, Externalizing Problems, and Total Problems), and in the DSM-oriented scales (Affective Problems; Anxiety Problems; Attention Deficit/Hyperactivity Problems, and Oppositional Defiant Problems). Figure 1 shows the distribution of participants in borderline/clinical and normal ranges for each of the scales. The scales in which the largest number of children within the clinical range were concentrated in internalizing problems (Anxious/Depressed, Withdrawn/Depressed

**Table 2.** Results of the Receptive Vocabulary Age, and differences between vocabulary age and chronological age in the Peabody picture vocabulary test

<table>
<thead>
<tr>
<th>Subject</th>
<th>Chronological Age (months)</th>
<th>Columbia Mental Maturity Scale</th>
<th>Peabody Picture Vocabulary Test</th>
<th>Differences between Vocabulary Receptive Age and Chronological Age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Score</td>
<td>Maturity Index</td>
<td>Score</td>
<td>Receptive Vocabulary Age (months)</td>
</tr>
<tr>
<td>1</td>
<td>72</td>
<td>32</td>
<td>51</td>
<td>32</td>
</tr>
<tr>
<td>2</td>
<td>48</td>
<td>Not performed</td>
<td>Not performed</td>
<td>52</td>
</tr>
<tr>
<td>3</td>
<td>48</td>
<td>22</td>
<td>41</td>
<td>52</td>
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<td>4</td>
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<td>Not performed</td>
</tr>
<tr>
<td>7</td>
<td>72</td>
<td>27</td>
<td>61</td>
<td>60</td>
</tr>
<tr>
<td>8</td>
<td>60</td>
<td>Not performed</td>
<td>Not performed</td>
<td>58</td>
</tr>
</tbody>
</table>

**Percent of the children into borderline/clinical and normal range in the Child Behavior Checklist**

![Graph showing the distribution of children into different problem areas.]

**Figure 1.** Percent of the children into borderline/clinical and normal range in the Child Behavior Checklist

and Somatic Complaints), Externalizing Problems (Aggressive Behavior and Oppositional Defiant Problems), Total Problems and Attention Deficit/Hyperactivity Problems. The scale that assessed Withdrawn/Depressed had the highest number of participants in the normal range, but another 85.2% were in the clinical range on the scale of social problems.

The greatest difference between chronological age and age of adaptive performance was shown in adaptive functioning related to the execution of the activities of daily living (areas: personal, domestic and community), followed by adaptive performance in items assessing socialization (inter-personal relations, play and leisure, social skills).

The only correlations that showed statistically significant positive associations were between indicators of EBP problems (assessed by CBCL and BPI-01), the adaptive functioning (assessed by Vineland), and language skills (assessed by Denver test). The correlations were: a) Aggressive Behavior and Adaptive Functioning of Activities of Daily Living/R= -0.75; p=0.03; b) Aggressive Behavior Problems and Adaptive Functioning of Socialization/ R= -0.76; p=0.02; c) Withdrawn/Depressed and frequency of stereotyped behavior problems/R= -0.69; p=0.05; d) Oppositional Defiant Problems and frequency of auto-aggression behavior problems/R= 0.84; p=0.00; e) Language impairment of Denver Test and auto-aggression behavior problems/R=0.74; p=0.03.

DISCUSSION

The main objective of this study was to explore the associations between EBP, adaptive functioning and receptive language skills. As the study aimed to track indicators of developmental delay, it was used the Denver II test. Although Denver Test did not have precision indicators similar to Bayley Scales of Infant and Toddler Development(21), the results of delay in the group of children in all areas of the Denver test are similar to those found with Bayley, shown by a recent study(8), whose authors evaluated 16 children between 3 months and 5 years old and, according to the data, there was a delay check in all the areas evaluated by the test(8).

The Columbia test evidences also showed development delays, from the 5 children who were able to perform the test, all of them had very low scores for their age (4 of them presented results less than half of their chronological age), another indicator of developmental delay. The data from the PPVT indicated that receptive language skills are relatively preserved, and are indicative of the peaks and valley profile(11,22). Denver II reveals delay indicators in various areas of neurodevelopment. These results show a mismatch between the actual receptive vocabulary and the developmental indicators, probably related to the intellectual disability (as showed in the Table 2) that characterizes the cognitive phenotype of the syndrome(22). The group shows delays in terms of vocabulary knowledge and grammatical structures such as ‘name two opposites’. These impairments may be associated with the mental deficiency factor. Mental maturity indicators (assessed by the Columbia Mental Maturity Scale) did not show associations with indicators of language abilities, probably because three children had difficulty performing the test. However, it is likely that this delay in mental maturation contributes to difficulties in word evocation, and later these children will have other impairments in the integrity of phonological and articular components of speech as shown in the study of Rossi et al.(23). This study was carried out in a group of individuals with SW between 6.6 and 23.6 years with variable degrees of intellectual disability. The authors hypothesized that the increased frequency of word hesitations and repetitions in the speech of individuals with SW may correspond to the language strategies used by these individuals in the presence of difficulties in word evocation, reflecting a rupture in the flow of discourse.

If deficits in expressive language abilities are not mitigated by appropriate interventions, they will compromise social communication, pragmatic language, and social acceptance of these children. The Stojanovik’s study(24) explored social interaction abilities in a group of children with WS (mean age 9.1 years), compared to a group of children with language-specific disorder and a group of typically developing children, matched by receptive vocabulary. The results showed that the WS group had difficulties with exchange structure and responding appropriately to the interlocutor’s requests for information and clarification, had significant difficulties with interpreting meaning and providing enough information for the conversational partner. In our study, the language abilities development trajectory of the sample may follow the same pattern of delay as shown in Stojanovik’s study(25).

The high number of participants in the clinical range on the scale of social problems from the CBCL, typical of the behavioral phenotype of the syndrome, confirm that children with WS have excessive emotional responsiveness, which increases their sociability, although there is little selectivity in these interpersonal contacts(25-27). The Vineland scale does not evaluate the functional aspects of communication. Therefore, the high scores in the communication scale contrast with the low scores in adaptive functioning scales, in which all participants showed deficits indicators(24). In a study by Rossi et al.(28), the authors reported that a group with WS showed more facility to interact in situations of social communication compared to a control group, however, the structural and functional use of language was limited by excessive cliché use, intonation deficits, sound effects and other problems. Many also presented echolalia and repetitive speech that harm communicative performance with others. The positive correlations between language and adaptive functioning impairments with EBP reveals that, since early ages, there may be interrelations between language delay and adaptive impairment, with severe behavioral problems such as aggressiveness and self-aggressiveness, and stereotyped behavior problems in toddlers with WS.

Our results were similar to Pérez-Garcia et al.(29) study that compared EBP in WS children from Spain and the United States using the CBCL 6-18. The results showed that the distributions of T-scores for the Internalizing scales were higher for the Spanish sample than for the American sample, indicating more difficulty for Spanish children. For the Spanish sample, the only significant correlation was with Internalizing Problems (correlation coefficient=r=-.36, p=.009), indicating that internalizing problems increased as chronological age increased. Our results
emphasized the importance of assessing EBP in the Brazilian toddlers with WS. At the time of the study only half of the group was receiving mental and physical health care, which shows the need to improve early interventions for this group.

CONCLUSION

The data showed delay indicators in overall development, impairments in adaptive functioning, cognitive deficits reported by mothers in the CBCL (e.g. inattention and hyperactivity), as well as aggressive and auto-aggression behavior problems. Brazilian studies with toddlers with WS are still scarce and although this study has been realized with a small sample, there are evidences of several cognitive, neuropsychomotor and adaptive functioning impairments in the evaluated group. Our study did not record data on the insertion of the toddlers in schools or child day care center, however, the data showed that mental health and educational interventions are needed from early childhood. The correlations showed how developmental delays and behavioral problems are associated with difficulties in adaptive functioning. The main results obtained in the Vineland scale were the losses in the socialization domains (inter-personal relationships, social skills, skills to play and involvement in leisure activities) and activities of daily living. The behavioral stereotypes verified in the BPI-01 alert us to the presence of behavioral problems probably associated with intellectual disability. Future studies could be developed with larger sample to permit the outlining of cognitive and behavioral profiles that enable the development of large scale early intervention strategies in Brazilian toddlers with WS.

REFERENCES


Author contributions

ACB participated in the conception, planning and execution of the study, besides the writing and critical revision of the final version; LRRC participated in data analysis, writing and critical review of the final version; TLT participated in the writing and critical revision of the final version; NMGR participated in the writing and critical revision of the final version; MFCS participated in the writing and critical review of the final version; RSH participated in the clinical and genetic diagnosis of the participants, besides the writing and critical revision of the final version; CAK participated in the clinical and genetic diagnosis of the participants, besides the writing and critical revision of the final version; MCTVT participated in the design, planning and execution of the study, besides the data analysis, writing and critical review of the final version.