General, verbal, and non-verbal cognitive functioning of children and adolescents with 22q11.2 Deletion Syndrome

Funcionamento cognitivo geral, verbal e não verbal de crianças e adolescentes com Síndrome de Deleção 22q11.2

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ABSTRACT

Background: Cognitive dysfunctions are frequently found in the 22q11.2 Deletion Syndrome, being an aggravating factor in the impairment of social relationships and communication, strongly impacting the functionality of the individual. Increasing the knowledge regarding cognitive skills may provide contributions to the diagnostic process and the intervention planning.

Objectives: To estimate the general, verbal, and non-verbal cognitive functioning of children and adolescents with 22q11.2 Deletion Syndrome.

Methods: This is a cross-sectional, descriptive, and case series study regarding 15 individuals between 7-18 years-old diagnosed with 22q11.2 Deletion Syndrome. An assessment of the cognitive functions was performed using the Wechsler Abbreviated Scale of Intelligence (WASI). For data analysis we used a descriptive statistics analysis, having absolute frequencies for variables, and mean, median, standard deviation, minimum and maximum values for numerical variables.

Results: In the group analysis, we observed an important cognitive impairment degree. Most of the sampling (n=8; 53.33%) presented a considerably low total intelligence quotient score. Cases showing lower performances also presented greater difficulties regarding Visual Motor and Visuospatial coordination. Regarding the intelligence quotient representative punctuation in the WASI scale, the sample showed a large variability in the results (between 40 and 92 points), with the median total of 83.

Conclusions: We observed important dysfunctions, cognitive difficulties, and intellectual, verbal, and non-verbal disabilities in the population studied. These findings indicate the need for an early intervention to assist not only the cognitive aspect, but also the socio-emotional development of children with the 22q11.2 Deletion Syndrome, aiming at their participation in society.

Keywords: DiGeorge Syndrome; Velocardiofacial Syndrome; Cognition; Neuropsychology; Wechsler Scales

RESUMO

Fundamento: Disfunções cognitivas são frequentemente encontradas na Síndrome de Deleção 22q11.2, sendo um agravante no comprometimento das relações sociais e da comunicação, impactando fortemente na funcionalidade do indivíduo. O aumento do conhecimento sobre as habilidades cognitivas pode trazer contribuições no processo diagnóstico e no planejamento da intervenção.

Objetivo: Estimar o funcionamento cognitivo geral, verbal e não verbal de crianças e adolescentes com Síndrome de Deleção 22q11.2.

Métodos: Estudo transversal, descritivo, tipo série de casos, com 15 indivíduos entre 7-18 anos com diagnóstico da Síndrome de Deleção 22q11.2. A avaliação das habilidades cognitivas foi realizada com a Escala Wechsler Abreviada de Inteligência (WASI). Para análise dos dados, foi utilizada análise estatística descritiva, com frequências absolutas para variáveis, e média, mediana, desvio padrão, mínima e máximo para variáveis numéricas.

Resultados: Na análise do grupo, observou-se um importante grau de comprometimento cognitivo. A maior parte da amostra (n=8; 53,33%) mostrou quociente de inteligência total extremamente baixo. Os casos com desempenhos mais baixos apresentaram maiores dificuldades em relação às habilidades de coordenação visuomotora e visuoespacial. Em relação à pontuação representativa do quociente de inteligência na escala WASI, a amostra apresentou uma grande variabilidade de resultados (entre 40 a 92 pontos), com mediana total de 83 pontos.

Conclusões: As dificuldades cognitivas encontradas indicam a necessidade de uma intervenção precoce para auxiliar não só no desenvolvimento cognitivo, mas socioemocional de crianças com a Síndrome de Deleção 22q11.2 visando sua participação na sociedade.

Palavras-chave: Síndrome de DiGeorge; Síndrome Velocardiofacial; Cognição; Neuropsicologia; Escalas de Wechsler.

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INTRODUCTION

22q11.2 Deletion Syndrome (22q11.2del), also known as DiGeorge Syndrome or Velocardiofacial Syndrome, is the most common microdeletion identified in humans, and its populational prevalence is approximately 1:4000 born alive.[1] This syndrome possesses more than 180 clinical manifestations, both physical and behavioral, highlighting language and communication alterations, intellectual disability and learning difficulties.[2]

In general, cognitive dysfunctions are frequently found in 22q11.2del patients and tend to increase during adolescence[3, 4], being on several occasions, a case of late diagnosis. These cognitive problems are described in the literature as aggravating factors in the impairment of social relationships and communication, strongly impacting the functionality of the individual.[5,6,7]

Increasing the knowledge regarding cognitive skills in 22q11.2del children and adolescents may provide relevant contributions to the diagnostic process and the intervention planning, which is crucial for reducing secondary conditions to the inherent alterations of the genetic condition, thereby promoting an improvement to the quality of life and health of this population.[8,9]

Therefore, this study aims at estimating the general, verbal, and non-verbal cognitive functioning of 22q11.2del children and adolescents, thus contributing to the understanding of this population cognitive phenotype.

METHODS

Cross-sectional, descriptive and case series study, regarding 15 individuals between 7-18 years-old with confirmed diagnosis for 22q11.2del by means of positive result in the Fluorescent in Situ Hybridization (FISH) technique and/or CGH-array. Children and adolescents presenting severe degrees of speech intelligibility alterations or associated neurological dysfunction were excluded. The total number of participants was established by convenience sampling, where participants were selected by consulting the database of the Medical Genetics Center of a landmark hospital of the Rio de Janeiro State, and by indication of medical geneticists from Rio de Janeiro municipality.

The study was approved by the Ethic in Research Committee of the Instituto Nacional de Saúde da Mulher, da Criança e do Adolescente Fernandes Figueira (IFF/Fiocruz) under the number 3.557.676 and CAAE nº 99733418.0.0000.5269. All the children and adolescents' guardians signed the Information Consent Form and the children and adolescents themselves, the Informed Assent.

The assessment of the cognitive functioning was performed at a pre-scheduled time at the outpatient clinic of a Rio de Janeiro State landmark hospital, with an average duration of 90 minutes each session, which started by interviewing the guardians, where we collected: clinic data, education level and therapy realization. Subsequently, the Wechsler Abbreviated Scale of Intelligence (WASI)[10] evaluation was conducted with the participating children and adolescents.

The WASI aims to meet the need for a brief intelligence measurement in ages ranging from 6 years-old children to 89 years-old elders. The test was applied individually in a reserved environment with the sole presence of the examiner and the child. Application timewas around fifty minutes for the four subtests. The WASI test provides the Verbal Intelligence Quotient (VIQ), Performance Intelligence Quotient (PIQ) and Full-Scale Intelligence Quotient (FSQI) scores. This scale comprises four subtests: Vocabulary, Block Design, Similarities and Matrix Reasoning. Administration of these four subtests is a quick way to estimate the individual's general cognitive, verbal, and non-verbal functioning. The WASI also allows the assessment of several cognitive aspects, such as verbal knowledge, visual information processing, spatial and non-verbal reasoning, fluid, and crystalized intelligence in diverse contexts.[10] The application of this test was performed in agreement to the instructions of the scale manual, following all recommendations made by the authors.

IQ classification was carried out according to the Wechsler Intelligence Scale for Children - Fourth Edition (WISC IV), since the Brazilian WASI Manual does not contain a qualitative description corresponding to the IQ scores. Thus, the classification used was "extremely low" (standard scores <70); "very low" (standard scores 70-80); "low average" (standard scores 80-90); "average" (standard scores 90-110); "high average" (standard scores 110-120); "very high" (standard scores 120-130); "extremely high" (standard scores> 130).

After application, the data was plotted in an Excel spreadsheet and transported to the EPIINFO data bank for the proper treatment of the data. For the data analysis, we performed a descriptive statistics analysis with absolute frequencies for variables, and mean, median, standard deviation, minimum and maximum values for numerical variables.

RESULTS

Our sample comprised of 15 children/ adolescents with an average (mean) age of 12.13 years-old (standard deviation = 3.42), varying from 7 to 18 years-old, and a median of 13.

All children/adolescents attended school, and 13 (86.7%) reported having school difficulty. Still on the school issue, little more than half of the sample (9; 60%) is not in the school year expected for their age.

In relation to the presence of other comorbidities, 13 children/adolescents possessed associated comorbidities, the most frequent being: heart (10; 76.9 %) and respiratory (2; 15.3%) problems, and other alterations (cataract or Noonan Syndrome) (2; 15.3%).

Most part of the sample (13; 86.67%) was undergoing some kind of therapy in the time of the interview, especially psychotherapy and speech therapy.

Table 1 presents the classification of the sample performance regarding Verbal Intelligence Quotient (VIQ), Performance Intelligence Quotient (PIQ) and Full-Scale Intelligence Quotient (FSQI). Regarding the representative IQ score on the WASI scale, the sample presented a large variability of results.

Table 1. Sample distribution regarding the IQ classification obtained from the WASI test.

	Verbal IQ	Performance IQ	Full Scale IQ
Classification			
Average	1 (6.67%)	3 (20.00%)	1 (6.67%)
Low Average	5 (33.33%)	2 (13.33%)	4 (26.67%)
Very Low	4 (26.67%)	5 (33.33%)	2 (13.33%)
Extremely Low	5 (33.33%)	5 (33.33%)	8 (53.33%)
Representative Score			
Variation (Min – Max)	45-91	45-101	40-92
Mean (Standard Deviation)	72.8 (15.23)	73.93 (15.06)	70 (15.12)
Median	78	78	83

Source: Authors' own elaboration
Note: IQ = intelligence quotient; categorical result expressed by the absolute number and frequency in parentheses.

Table 2 presents the sample results in each WASI subtest. This analysis was performed through weighted scores presented by children and adolescents in each subtest. The abilities measured were knowledge and understanding of the word's meanings (Vocabulary subtests); verbal and logical analogy (Similarities subtest); visual motor and visuospatial coordination (Block Design subtest); non-verbal reasoning and general intellectual skill (Matrix Reasoning subtest).

Table 2. Sample distribution regarding the weighted score on the WASI subtests.

	Vocabulary	Similarities	Block Design	Matrix Reasoning
Variation (Min – Max)	1 - 9	1 - 11	1 - 8	1 - 13
Mean (Standard Deviation)	5.27 (2.23)	5.3 (2.98)	4.3 (2.09)	6.53 (3.20)
Median	6	5	4	6

Source: Authors' own elaboration

In the group analysis, in general, an important degree of cognitive impairment was observed. The case with the best performance compared to the entire sample, with a FSQI of 92 and classified as average, presented cognitive performance adequate to what was expected for his age, highlighting the non-verbal reasoning and general intellectual skills, assessed by Matrix Reasoning subtest, in which obtained higher average as result. On the other hand, the cases with lower performances, generally presented greater difficulties in relation to the Visual Motor and Visuospatial skills, evaluated from the Block Design subtest.

DISCUSSION

Despite our small sampling size, given this disease incidence within the population, it is possible to observe important issues regarding cognitive functioning. The results mostly showed an extremely low general cognitive functioning, with some variation of results in the intelligence quotient among the sample of children and adolescents with 22q11.2del. These findings corroborate with previous reports that indicated a great variation of cognitive alterations related to 22q11.2del.[11,12,13] From a meta-analysis with cross-sectional studies, Moberg et al.[14] highlighted robust findings concerning cognitive deficits in the intellectual functioning of individuals with 22q11.2del, being influenced by factors such as the comparison group; age; sex and clinical status. Studies describe this alteration with disparities, ranging from the presence of intellectual deficiency to moderate,[15,16,17] or within the normality parameters.[18,19] According to Fiksinski[3] in order to understand the phenotypic variability found, it is worth reflecting on additional factors that influence it – as the gene-environment interaction; variability in the assessment; age-depending phenotypes; and standardization of the diagnostic criteria.

It is important to consider that the cognitive disturbances constitute one of the most difficult psychosocial aspects for patients and their families.[20] Moreover, early cognitive decline in 22q11.2del children is a robust indicator of the risk of developing a psychotic illness,[9] [17]and there is a discussion of the possibility of both phenotypes presenting the same pathological process in different development stages;[11] highlighting the importance of monitoring the cognitive development of children and adolescents.

Results regarding the representative IQ score in the total index of the WASI[10] scale presented variation between 40 and 92 and mean of 70. These data corroborate the study of Pimenta et al.[21] also conducted with Brazilian children and adolescents with 22q11.2del, which pointed out IQ variation from 42 to 104 and mean of 73.0 following Wechsler Scale of Intelligence for Children – Fourth Edition (WISC-IV). Results from international studies also presented similar variation concerning IQ, as the one conducted by De Smedt et al. [19] with a large sample of children from Belgium, indicating variation between 50-109 and mean of 73.48 in IQ following the third edition of Wechsler Scale (WISC-III). Similar to the results of these studies, the qualitative descriptions of Full-Scale IQ of the present sample varied between 'extremely low' to 'average', whereas Jacobson et al.,[22] assessing children and adolescents from United Kingdom, found an average IQ of 65.4 and varying from 44 to 80, indicating a slightly inferior classification.

Despite the variability referent to the Intelligence Quotient, the sample classification regarding Full Scale IQ was mostly extremely low (53.33%). This result may be

related to school difficulties, presented by most of the sample, considering the cognitive functioning as a key factor for a school life and, therefore, must be taken in consideration when planning the development of individuals with 22q11.2del.[23] 23 Learning difficulties are also reported in this genetic condition, [24] and may be related to the school delay seen in this study. In this sense, we emphasize the importance of the educational intervention, covering the training of verbal and non-verbal skills.[13]

Discrepancies between verbal and non-verbal skills of individuals with 22q11.2 Deletion Syndrome are discussed in the literature. Moberg et al.[14] did not find significative differences between the verbal and non-verbal intellectual functioning in the cross-sectional studies analyzed in the review, whereas Jacobson et al.[22] and Pimenta et al.[21] pointed out superiority of the verbal intelligence over non-verbal one as an apparent characteristic of the cognitive phenotype of 22q11.2del. In the present study, the children and adolescents' performances in verbal and non-verbal tasks did not present great discrepancy, with average Verbal IQ of 72.8 and average Performance IQ of 73.9. Variation in the qualitative descriptions, in both, was from 'extremely low' to 'average', however, with higher frequency of 'average' classifications in the Performance IQ (20%) in comparison to the Verbal IQ results (6.67%).Another finding of this research was the presence of comorbidities, all consistent with the 22q11.2 Deletion Syndrome, especially the heart problems. According to the literature, 22q11.2del is the second biggest cause in the developmental delay and of congenital heart defects, behind only to Down Syndrome.[25]

Our small sample was a limitation of this research and can be explained by the diagnostic commonly being realized just after birth due to the associated comorbidities, mostly heart problems, or during adolescence when the psychological problems appear,[3,4] and there is no segment flow of this population in public services. Thus, it is understandable to face difficulties finding and convening children for this research, because many phone numbers and addresses were outdated in the health service. Still, we emphasize the importance of descriptive statistics, such as those performed here, to evaluate the needs and health trends of the population, and for the planning and allocation of resources and interventions.[26,27]

Cognitive and communication problems have a significative impact on the disability and functionality of individuals, being those of great social and economic relevance for most countries and of dramatic proportions considering the existence of millions of disabled people in the world. Thus, considering the cognitive and adaptive functioning as key factors in the school and professional life of individuals with 22q11.2del,[23] studies that discuss the impact of the cognitive functioning on the functionality of the individuals are necessary.

CONCLUSION

In conclusion, this study highlights that the presence of cognitive dysfunction and intellectual, verbal, and non-verbal disabilities are predominant in the 22q11.2 Deletion Syndrome, which reinforces the importance of its investigation. It is also essential to discuss the results found in the WASI related to functionality, aiming to guarantee the children and adolescents greater coverage in health care.

Also, the cognitive impairments found indicate the need for an early intervention to assist not only the cognitive development, but also the socioemotional development of children with 22q11.2 Deletion Syndrome aiming towards its participation in the society.

Key Messages:
- 22q11.2 Deletion Syndrome (22q11.2del) possesses more than 180 clinical manifestations, both physical and behavioral, highlighting language and communication alterations, intellectual disability and learning difficulties
- Presence of cognitive dysfunction and intellectual, verbal, and non-verbal disabilities are predominant in the 22q11.2del
- The cases with lower performances generally presented greater difficulties concerning Visual Motor and Visuospatial coordination
- Cognitive and communication problems have a significative impact on the disability and functionality of individuals, being those of great social and economic relevance for most countries
- The cognitive and adaptive functioning are key factors in the school life and professional career of individuals with 22q11.2del

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