

**Neuropsychological Remediation Program in Teenager with
22Q11 Deletion Syndrome**

**Programa de Remediação Neuropsicológica em Adolescente com
Síndrome de Deleção 22q11**

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Abstract

Currently the 22q11 deletion syndrome is considered one of the most common genetic diseases in humans, with an estimated prevalence of 1 in every 2.000 births. Individuals with 22q11 deletion syndrome have learning difficulties, with several neuropsychological impairments, such as in global skills (e.g, delay in refined motor skills, expressive language delay and difficulties in sustaining attention). Objective: This study aims to present the results of a remediation program implemented with a teenager with 22q11 deletion syndrome. Method: the program had three stages: pre-testing, application of neuropsychological remediation program and post-testing. Results: the remediation procedure adopted was effective, there was increased the interest and motivation of the teenager due to the successes, improving the assimilation and in the stimulated functions.

Keywords: 22q11 Syndrome, neuropsychology, remediation program

Resumo

Atualmente, a síndrome de deleção 22q11 é considerado uma das doenças genéticas mais comuns em seres humanos, com uma prevalência estimada de 1 em cada 2.000 nascimentos. Indivíduos com 22q11 síndrome de deleção têm dificuldades de aprendizagem, com vários prejuízos neuropsicológicos, tais como, em competências globais, (e.g., motricidade refinada, atraso na linguagem expressiva e dificuldades em manter a atenção). Objetivo: Este estudo tem como objetivo Presente os resultados de um programa de remediação implementado juntamente junto de um adolescente com síndrome de deleção 22q11. Método: O programa tinha três fases: pré-teste, aplicação de programa de remediação neuropsicológica e pós-teste. Resultados: O procedimento de remediação adotado foi eficaz, foi observado aumento no interesse e motivação do adolescente devido aos sucessos, melhorando na assimilação e nas funções estimuladas.

Palavras-Chave: síndrome 22q11, neuropsicologia, programa de remediação.

Introduction

The 22q11 deletion syndrome is considered today one of the most common genetic diseases in humans, with a estimated prevalence of 1 in every 2,000 births (Robin & Shprintzen, 2005; Shprintzen & Golding-Kushner, 2008).

The etiology is associated with a deletion in the chromosome 22q11.2 region, however, the presence or size of this deletion does not predict phenotypic expressivity. The clinical manifestations are highly variable. However, patients with different deletions in the 22q11 region may exhibit similar phenotypes, and deletion not compromise the same set of genes (Kokitsu-Nakata, Guion-Almeida, & Richieri-Costa, 2008).

The main clinical signs are facial dimorphisms, palate anomalies such as cracks or velopharyngeal dysfunction, cardiac anomalies, early hypotonia, delayed speech acquisition and psychomotor development. Individuals

with 22q11 deletion syndrome have Velocardiofacial (VCFS) and are at higher risk for developing attention deficit hyperactivity disorder and obsessive-compulsive disorder (Antshel *et al.*, 2006; Campbell *et al.*, 2006; Sandri, 2011). It is estimated that 90 to 100% have learning difficulties, with several neuropsychological impairments, and delays in global refined motor skills, expressive language delays and difficulties in sustaining attention (Lipson *et al.*, 1991; Shprintzen *et al.*, 1981).

Faced with specific learning problems in the 22q11 deletion syndrome, should be considered the presence of neuropsychological dysfunctions that affect the gnosis - interpretative and praxis - productive functions that cause failure in decoding processing, programming and implementation of language/learning (Gerdes, 1999; Capelline, 2001).

The research for strategies that facilitate the acquisition and development

of learning is central to the development of intervention programs in clinical and educational fields, such as neuropsychological rehabilitation through cognitive remediation. The intervention is a concept that is related to the broader work of stimulation, involving all the necessary skills for the development of learning. Unlike remediation is related to diagnostic scanning and limited the number of skills focused in the exercise of the child's cognitive skills. The planning of individual remediation programs requires analysis of what must be taught and how this information can be stimulated by identifying the potential, losses and tasks components. Therefore, the diagnosis will be the basis for the identification of learning problems guiding the course of intervention (Capelline, 2001).

The interest of this study was to determine the effectiveness of a program

of neuropsychological remediation in a teenager with 22q11 deletion syndrome.

Case description

The study was approved by the Research Ethics Committee of Craniofacial Anomalies Rehabilitation of the São Paulo University (HRAC - USP), with protocol number 387/2012. The responsible person signed the disclaimer Informed Consent Form, The head of the patient in the study signed the Accession Agreement, HRAC-USP, consenting this way, with the release of data for scientific purposes. consenting with the data divulgation for scientific purpose. The A.S.C. patient, with 12 years and 2 months, male, was referred for neuropsychological and phonoaudiological assessment due to poor academic performance complaints. In medical history, reports being an only child, non-consanguineous parents, born preterm cesarean. During pregnancy, the mother had hypertension, and reported bleeding

and contractions throughout pregnancy. The patient reported developmental delay (ADNPM) because he started walking at 1 year and 8 months, with the issuance of the first words only at 3 years old, which is considered delayed development of speech and language. The diagnostic velocardiocardiofacial syndrome was carried out at six by genotypic analysis based on polymerase chain reaction (PCR) in the Human Genome Research Center (CEGH-HRAC / USP).

Materials and Method

The study was composed by three phases: pre-testing, application of neuropsychological remediation program and post-testing.

Preview testing

The following assessment instruments were used: BANI-T¹, RAVEN², BENDER³, WISC III⁴, WCST⁵.

¹ Simplified neuropsychological examination (BANI-T)

² Testing Matrices adult colored Progressive (RAVEN)

The first instrument BANI-T is a tool for cognitive evaluation to analysis of cortical functions Tool for cognitive evaluation to analysis of cortical functions such as motor functions of the hands, driving acoustic organization of rhythmic structures, upper skin sensations and kinesthetic functions, higher visual functions, receptiva language, expressive language, linguistic cognitive function, mnemonic processes, reading activities writing and arithmetic skill activities. The Raven - General Scale aims to assess the immediate ability to observe and think clearly, assess the intellectual development, learning ability and mental disabilities. Bender, objectively evaluate the perceptual-motor maturity, by distorting its shape. Bender is associated with measures of intelligence (g factor as) and also shows respect to learning (writing acquisition and series of differentiation).

³ Gestalt Test Visuo-motor (BENDER)

⁴ Wechsler Intelligence Scale for Children - 3rd edition (WISCIII)

⁵ Test Wisconsin Card Classification (WCST)

The WISC-3 is a clinical instrument, individual application, to assess the intellectual capacity of children and adolescents (6-16 years). It consists of several subtests, each measuring a different aspect of intelligence. The performance in these subtests is summed up in three composite measures: Verbal IQ, Execution and Total providing estimates of the intellectual capacities of individuals. Finally, the Wisconsin Card Sorting Test is another tool for psychological and neuropsychological evaluation, adapted and standardized for use in Brazil. Although it was originally developed and used as a measure of mental flexibility, executive functions, among others, has been increasingly used as a neuropsychological test. Age range: 6-18 years. The investigation of the subject's resources and limitations were analyzed and were elected as the fundamental neuropsychological functions to compose the remediation program.

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Remediation Program

This type of program is defined by the methodological organization with defined strategies and limited number of skills focused on improving the impaired neuropsychological functions. It is proposed that the elected functions are systematically and intensively stimulated during the proposed period. Thus, in this study, ten 40-minute sessions were held for five consecutive days, in two periods (morning and afternoon) with the purpose to increase the attentional-executive and visuospatial functions. Reinforcing and motivational strategies were adopted in order to minimize fatigue and stimulate the cognitive skills.

The method involved the systematic training of teaching and learning visuo-constructive activities, based on behavioral design and the saturation of clues progressively reduced, in order to enable the conceptual accommodation. The program emphasized

different strategies in task performance, which trained executive functions in order to improve the functional repertoire of attention, visual-logical reasoning, organization and visual-spatial perception. The resources used in the training were manipulated objects of wood, plastic and paper used to adjust the administered stimulus.

The training of visuo-constructive activities included two strategies: "Arrangement of Figures" and "Cubes Building". During the five days of sessions, the patient was encouraged to develop the proposed activities. The activity "Arrangement Figures" aims to encourage the development of visual logical reasoning and the understanding, in which is required that the patient arranges the pieces according to the order of events. The "Cubes Building" task proposes to develop the organization of spatial perception, through the construction of cube models, similar to that built by the

examiner. In "Arrangement Figures" task it was explained to the patient how to proceed with the pieces. The method included the description of the detailed parts and organizing them according to the order of events, and the subsequent description of the story as a whole. Initially, sequences composed by three pieces were presented. The same procedure was clarified at the beginning of each new sequence. Following positive responses was possible to introduce sequences with greater number of pieces.

Throughout the sessions were implemented new sequences with assimilation of learning made in previous sessions. At the end of the five sessions were presented 12 sequences of stories and A.S.C. patient solved them accurately and quickly. In the "Cube Building" activity, cubes composed by two colors with two blue sides, two white sides and two sides half blue and half white were presented.

The first combinations were

composed of four cubes and models were presented by the combination made by the examiner, with a low level of difficulty. Subsequent combinations gradually increased difficulty degree, with models presented in print. In the first combination, the patient obtained a good performance at executing them quickly. The combinations models presented in print represented a considerable difficulty for the patient with a high degree of disorganization. Strategies to build models and systematic guidance were presented. After five sessions, A.S.C. built ten models of cubes in an organized and accurated way, with improvement in time, yet, using the strategies presented by the examiner.

In post testing remediation program were reapplied the same instruments of the pre-assessment phase.

Results and Discussion

Pre testing

The teenager underwent neuropsychological assessment of cognitive abilities related to the initial complaint of difficulties in school and sustaining attention impairments.

The neuropsychological research about 22q11 deletion syndrome is relatively new, the reports are still inconsistent and the profile is incomplete. The most significant change was observed in visuospatial memory function, but studies do not agree that the performance in this field is low among children with 22q11 deletion syndrome (Sobin, 2005).

Conversely, Azuma *et al.* (2009) argues that children and adults with 22q11 deletion syndrome usually have mild learning disabilities and a specific cognitive profile with deficits in visuospatial function, working memory, attention and executive function.

In this study, RAVEN instrument was applied to, which assesses intellectual abilities. The results indicated classification level below of what was expected for their age (V Classification), which indicated limited spatiotemporal logical reasoning, with a decline in problem solving and in understanding and organizing ideas, fundamental to learning.

The IQ (Intelligence Quotients) detected in individuals with 22q11 has demonstrated variability from moderate to normal levels (Jacobson *et al.*, 2010; Vicari *et al.*, 2012). In this study, the research evidence of intellectual abilities indicated classification level lowered to age with percentile V indicative of intellectual disability, limited spatiotemporal logical reasoning, impaired problem solving, difficulties in understanding and organizing ideas, critical to school performance.

Some neuropsychological features have been identified as being impaired in

this population, such as verbal quotients (Jacobson *et al.*, 2010; Niklasson & Gilberg, 2010; Vicari *et al.*, 2012), visuospatial abilities (Goldberg *et al.*, 1993; Jacobson *et al.*, 2010) and short and long term visuo-spatial memory (Majerus *et al.*, 2006; Campbell *et al.*, 2010; Jacobson *et al.*, 2010). In the present study, satisfactory results were identified about the evidence relating to motor functions of the hands, skin and kinesthetic sensations, higher visual functions and numerical skills.

There have been discrepancies in findings that compare receptive and expressive language. Glaser *et al.* (2001) reported poorer performance in verbal comprehension. The difficulties highlighted in this study related to the rhythmic organization, receptive and expressive cognitive-linguistic functions and reading and writing skills were the most impaired neuropsychological functions in the subject, confirming the findings of Gerdes *et al.* (1999) and

Jacobson et al. (2010) who found lower performance in verbal production. The short and long term memory processes were also identified with impaired scores.

In the graphic-perceptual-motor assessment, investigated by BENDER, results obtained under the age of 6 years, i.e., its maturity to perform graphics tasks, such as writing, did not correspond to their chronological age, with losses mainly in the construction of angles and spatial orientation. Motor function in school-aged children with 22q11 deletion syndrome is rarely discussed or evaluated, despite children present early hypotonia and motor changes before the age of 3 years. The extent of motor deficits for school years is relatively unexplored in the literature (Sobin, 2005).

One of the clinical features of 22q11.2 SD is the cognitive profile, which shows great variability at injury level (Thomas & Graham, 1997; Sandrin-

Garcia, 2007; Jacobson *et al.*, 2010; Vicari *et al.*, 2012).

In this study, the tests of cognitive abilities (intellectual resources for learning) showed better results in verbal tasks (VIQ = 91), with weighting on average, compared to realization tests (IQ = 71), borderline weighting. The factorial indices of verbal comprehension were associated to middle-lower levels (compatible to the VIQ average). The attentional and information processing indices indicated neighboring profiles for the development and perceptual organization deficitary. Many children with 22q11 deletion syndrome perform at a significantly lower than their peers of the same age at the executive domain. Often the executive function is poorer than the operation in verbal domain. It seems clear, however, that the losses are very common in the following areas: attention, particularly visuospatial attention, spatial cognition, including spatial memory,

quantitative cognition, involving the temporal and numeric domain and, later, arithmetic procedures and concepts (Simon, 2008). Attentional indices and information processing indices indicated neighboring profiles for the development and the perceptual organization indices appeared deficitary. According to Sobin *et al.* (2005), the application of the WISC in subjects with 22q11 deletion syndrome showed that IQ scores indicated lower scores than normal, a factor attributed to the strong dispersion in the subtests scores. Instead of global impairment, these results indicate marked variability in cognitive functioning of children with 22q11 deletion syndrome. The WCST instrument showed the features of abstract reasoning and the ability to modify the cognitive strategies in response to changing environmental contingencies, corresponding to executive functions. Such skills were shown to be impaired in identifying the error, in sustaining attention and in productivity of the task.

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These findings were also found in Sobin and colleagues (2005) research that administered the NEPSY and Intelligence Scale Stanford-Binet in 40 children with 22q11 deletion syndrome and showed impaired performance on tests of visual attention, sensorimotor motor ability and executive function.

In the sphere of social and moral understanding, showed satisfactory resources for the age group, with intentional and reasonably collaborative behaviours during the testing. Studies regarding social skills among children with 22q11 deletion syndrome are scarce and current reports are predominantly descriptive (Bradeck & Sobin, 2006). The first social traits observed by the researchers were poor social competence, concrete thinking and difficulty to generalize new situations with previous experience (Furst, Dool, & Rourke, 1995). The children were also described as having poor social interactions with disabilities in

decision-making ability and global social immaturity (Shprintzen, 2008).

Considering the results obtained in the assessment, related to execution skills, particularly in attention, perceptual organization and speed of information processing, we proposed a neuropsychological remediation program with emphasis in these affected areas.

Post testing

In this post-remediation neuropsychological program reassessment the same instruments of the initial assessment were used, such as BANI-T, RAVEN, BENDER, WISC III and WCST.

The research tools of intellectual abilities continued to indicate classifications below to that expected for age (Raven - V), but with improvement in scores, demonstrating progress in the ability to understand the visuo-spatial

information and solve problems, as shown in the following chart.

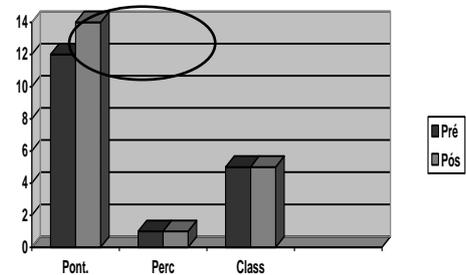


Figure 1 – Graph about representations of points (Pont.), score (Perc) and classifications (Class).

Although the systematic training has been focused on perceptual visuospatial and attentional abilities, there was significant gains in several functions, representing intra-program gains. Results were maintained at cutaneous and kinesthetic sensations and higher visual functions. Lowered scores on expressive language also maintained the same rates.

The functions of working memory, manual motor coordination, rhythmic organization, semantic language, copy of words and understanding stories showed increased rates, with the rhythmic

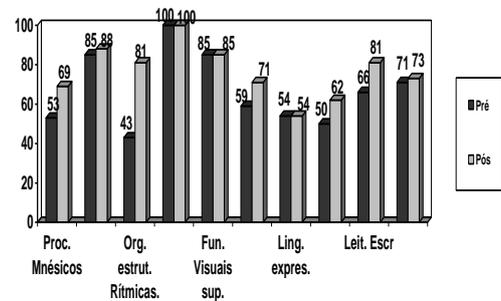
organization, receptive language and writing activities mastery showing scores on average level. These data represent significant gains post-remediation program, as shown in the figure 2.

In tests of cognitive abilities for learning, A.S.C showed higher levels compared to the initial assessment. In the verbal (VIQ) and performance (LL) activity results were within the expected range for age, increasing score by 77% and reaching the average. Although scores have risen in 75 % of the factorial indices, the verbal comprehension scores (lower middle), attention and processing speed (borderline) were maintained; perceptual organization, with deficitary rate, increased to medium-low level.

Figure 2 – Graph about representations of score (percents) in the memory process (Proc. Mnésicos), rhythmic structure organization (Org.Estrut.Ritimicas), High Vision Functions (Fun Visuais Sup),

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Expressive Language (Ling. Expres) and Write and Reading (Leitura e Esc).



In the graphic-perceptual-motor reassessment, the results showed increased scores in all modalities, changing the age group classification of 06 years to a median of 07 years, which represents maturity for writing in literacy. The pre-assessment and post-assessment results are shown in the following table.

Table 1

Representations of points (pont.) and classifications.

	<i>Angles</i>	<i>Spatial Orientationl</i>	<i>Relative Position</i>	<i>Global Score</i>	<i>Classification</i>
<i>PRÉ</i>	3	5	6	19	- 6a
<i>PÓS</i>	6	7	11	28	Md 7a

It is a case study which we used descriptive statistics in order to represent the performance of the subject of the study.

Final Thoughts

The difficulties encountered in the early implementation of the remediation program, related to the patient's engagement to the proposed tasks were redirected in each meeting for greater participation, whose activities were challenging and stimulating to execute. Thus, A.S.C. showed greater interest and motivation resulting from hits, from assimilation improvements and mastery in functions stimulated, so the remediation procedures adopted were effective.

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However, for the accommodation of abilities and skills developed, it is necessary to maintain the stimulation focused in the function, so that assimilated resources are not lost and learning is consolidated.

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