Graziela Jorge Polido

**Desempenho visual, cognitivo e motor de crianças com atrofia
muscular espinhal**

Dissertação apresentada à Faculdade de
Medicina da Universidade de São Paulo
para obtenção do título de Mestre em
Ciências

Programa de Ciências da Reabilitação

Orientadora: Prof. Dra. Mariana Callil Voos

SÃO PAULO

2018

Graziela Jorge Polido

**Desempenho visual, cognitivo e motor de crianças com atrofia
muscular espínhal**

Dissertação apresentada à Faculdade de
Medicina da Universidade de São Paulo
para obtenção do título de Mestre em
Ciências

Programa de Ciências da Reabilitação

Orientadora: Prof. Dra. Mariana Callil Voos

SÃO PAULO

2018

Dados Internacionais de Catalogação na Publicação (CIP)

Preparada pela Biblioteca da
Faculdade de Medicina da Universidade de São Paulo

©reprodução autorizada pelo autor

Polido, Graziela Jorge

Desempenho visual, cognitivo e motor de crianças
com atrofia muscular espinhal / Graziela Jorge
Polido. -- São Paulo, 2018.

Dissertação (mestrado) -- Faculdade de Medicina da
Universidade de São Paulo.

Programa de Ciências da Reabilitação.

Orientadora: Mariana Callil Voos.

Descritores: 1.Atrofia muscular espinhal
2.Atenção 3.Visão ocular 4.Percepção 5.Cognição
6.Reabilitação

USP/FM/DBD-2013/18

Responsável: Kátia Maria Bruno Ferreira - CRB-8/6008

DEDICATÓRIA

Dedico esta pesquisa à minha mãe, um exemplo de mulher e profissional competente, ética e humana, em quem eu sempre me espelho.

AGRADECIMENTOS

Agradeço a minha família, base de tudo.

Agradeço a minha orientadora, Mariana Voos, por ter sido tão presente, paciente e pelos momentos compartilhados.

Agradeço aos amigos que o mestrado me trouxe: Alessandra Barbosa, Joyce Martini, Mariana Artilheiro, Janini Chen, Mariene Simões e Mariana Voos.

Agradeço à Patrícia Jatobá, pela parceria, cores, incentivo e amor.

Agradeço ao casal, Juliana e Helton, por me confiarem seu bem maior, o Arthur Messias (Tuco).

Por último, mas não menos importante, agradeço ao Tuco, por ter me ensinado tanto. Por ter mudado minha visão sobre o significado de ganhar. Pelo laço que criamos e estreitamos. Por me inspirar sempre, na vida pessoal e profissional.

“Feliz aquele que transfere o que sabe e aprende o que ensina”

(Cora Coralina)

NORMALIZAÇÃO ADOTADA

Esta dissertação está de acordo com as seguintes normas, em vigor no momento da publicação:

Referências: adaptadas de *International Committee of Medical Journals Editors* (Vancouver).

Universidade de São Paulo. Faculdade de Medicina. Divisão de Biblioteca e Documentação. *Guia de apresentação de dissertações, teses e monografias*. Elaborado por Anneliese Carneiro da Cunha, Maria Julia de A. L. Freddi, Maria F. Crestana, Marinalva de Souza Aragão, Suely Campos Cardoso, Valéria Vilhena. 3a ed. São Paulo: Divisão de Biblioteca e Documentação; 2011.

Abreviaturas dos títulos dos periódicos de acordo com *List of Journals Indexed in Index Medicus*.

SUMÁRIO

Lista de abreviaturas e siglas

Resumo

Abstract

Apresentação

1 Introduction	1
2 Primeiro artigo – <i>Cognitive performance of children with spinal muscular atrophy: a systematic review</i>	7
3 Segundo artigo – <i>Matching pairs difficulty in children with spinal muscular atrophy type I</i>	23
4 General Discussion	33
5 Conclusion	36
6 Referências Bibliográficas	37

Apêndices

Apêndice A – Projeto de Pesquisa

Apêndice B – Aprovação do Projeto de Pesquisa

Apêndice C – Resumo apresentado no Congresso da World Muscle Society (WMS) 2015

Apêndice D – Resumo apresentado no XXVII Congresso Brasileiro de Neurologia 2016

Lista de abreviaturas e siglas

AME	Atrofia Muscular Espinhal
AME-I	Atrofia Muscular Espinhal do tipo I
AME-II	Atrofia Muscular Espinhal do tipo II
AME-III	Atrofia Muscular Espinhal do tipo III
SMA	Spinal Muscular Atrophy
PEDI	Pediatric Evaluation of Disability Inventory/ Inventário de Avaliação Pediátrica de Incapacidade
PedsQL	Pediatric Quality of Life Inventory/ Inventário Pediátrico de Qualidade de Vida
CHOP INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
ROBINS-I	Risk of Bias in Non-Randomized Studies of Interventions
WISC	Wechsler Intelligence Scale for Children
HFMSE	Hammersmith functional motor escale expanded
IQ	Intelligence quotient
SMN	Survival motoneuron

RESUMO

Polido GJ. *Desempenho visual, cognitivo e motor de crianças com atrofia muscular espinhal* [dissertação]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2018.

A atrofia muscular espinhal (AME) é uma doença rara e neurodegenerativa, que afeta crianças e adultos. Gera atrofia muscular, prejudica os movimentos voluntários e, em muitos casos, dificulta a comunicação oral. Esta dissertação é composta por dois artigos. O Estudo 1 objetivou revisar a literatura sobre o desenvolvimento cognitivo de pessoas com AME. O Estudo 2 objetivou avaliar o desempenho visual, cognitivo e motor de crianças com AME tipo 1 (AME-I). O primeiro estudo foi uma revisão sistemática, com levantamento dos últimos 25 anos (de 1992 a 2017) nas bases de dados PUBMED/Medline, Web of Science e Scielo. Os descritores utilizados foram: *spinal muscular atrophy* e *cognition*. O estudo 2 consistiu na avaliação de 24 crianças, divididas em dois grupos: 12 crianças com AME-I (3 a 9 anos, 9 meninos e 3 meninas) e 12 crianças saudáveis, pareadas por idade e sexo. As 24 crianças responderam a quatro tarefas de associação de figuras, com dificuldade crescente. As respostas foram detectadas por meio de um rastreador de olhar. Para o primeiro estudo foram localizados 43 artigos, desses, nove foram selecionados, de acordo com os critérios de inclusão e exclusão. O estudo apontou que o desempenho cognitivo de crianças com AME é heterogêneo. Três artigos indicaram que

essas crianças têm desempenho cognitivo normal, três artigos indicaram que há atraso e outros três estudos relataram desempenho acima da média. De modo geral, as crianças com maior fraqueza muscular (AME-I) apresentaram maior comprometimento e estudos mais recentes detectaram esse atraso. O segundo estudo descreveu pior desempenho do grupo AME-I, em relação ao grupo controle (maior número de erros e maior tempo para execução das tarefas). Concluimos que, até o momento, poucos estudos investigaram aspectos cognitivos em crianças e adolescentes com AME. O desenvolvimento cognitivo de crianças com AME deve ser acompanhado, principalmente em crianças com AME-I. É necessário avaliar o desempenho cognitivo e, se necessário, propor intervenções para pessoas com AME. O desenvolvimento cognitivo adequado facilita a autonomia e interação. Os rastreadores de olhar podem estimular e aprimorar esse repertório.

Descritores: atrofia muscular espinhal; atenção; visão ocular; percepção; cognição; reabilitação.

ABSTRACT

Polido GJ. *Visual, cognitive and motor performance of children with spinal muscular atrophy* [dissertation]. São Paulo: “Faculdade de Medicina, Universidade de São Paulo”; 2018.

Spinal muscular atrophy (SMA) is a rare and neurodegenerative disease, affecting children and adults. SMA causes muscular atrophy and weakness, and, in many cases, impairs the development of oral communication. This dissertation is composed of two articles. Study 1 aimed to review the literature about the cognitive development of people with SMA. Study 2 aimed to evaluate the visual, cognitive and motor performance of children with SMA type 1 (SMA-I). Study 1 reviewed the findings of the last 25 years (1992 to 2017), in PUBMED/Medline, Web of Science and Scielo databases. The descriptors were: spinal muscular atrophy and cognition. Study 2 consisted of the evaluation of 24 children divided into two groups: 12 children with SMA-I (3 to 9 years of age, 9 boys and 3 girls) and 12 healthy children, matched by age and sex. The 24 children performed four figure-association tasks, with increasing difficulty. Responses were detected by an eye tracking device. For the first study, 43 articles were identified and nine were selected because they met the inclusion and exclusion criteria. The study pointed out that the cognitive performance of children with SMA is heterogeneous. Three articles indicated that children with SMA had normal cognitive performance, three observed

delayed performance and three studies described cognitive performance as above average. In general, samples with children with more severe muscular weakness (SMA-I) showed some cognitive impairment and more recent studies detected this delay. The second study described poorer performance of the SMA-I group, compared to the control group (more errors and longer times). In conclusion, few studies investigated cognitive outcomes in children and adolescents with SMA. The cognitive development of children with SMA should be followed, especially children with SMA-I. More studies should evaluate and, if necessary, intervene to prevent cognitive impairment in people with SMA. The proper cognitive development facilitates autonomy and interaction. The eye tracker can stimulate and improve their repertoire.

Descriptors: muscular atrophy, spinal; attention; vision, ocular; perception; cognition; rehabilitation.

APRESENTAÇÃO

Desde que me graduei em Fisioterapia e decidi me dedicar apenas à área da neurologia infantil, o que mais me honra é o ganho: um sorriso, o controle da cervical, um alcance, o sentar sem apoio, o andar... Com o passar dos anos, fui me deparando com doenças diversas, mas sempre atingia um, alguns ou todos esses objetivos. Até que um dia eu conheci uma criança com atrofia muscular espinhal, o Arthur. Eu não tinha conhecimento sobre essa doença rara.

Naquele meu primeiro atendimento com o Arthur, eu não tinha a menor ideia do mundo que se abria... Eu não imaginava que mesmo sabendo trabalhar com prevenção, trabalhar com uma doença progressiva seria tão significativa para mim. O Arthur é uma criança com pouquíssimo movimento ativo, ele não pisca, mas conseguimos desenvolver interação e comunicação efetivas e afetivas. Depois do Arthur, conheci outras crianças com atrofia muscular espinhal, muitas delas acompanhadas por mim até hoje.

Por causa do contato diário com o Arthur e com todas as crianças com atrofia muscular espinhal, resolvi fazer esse trabalho. Eu precisava ajudá-las na independência, ao menos para brincar, porque brincar é extremamente importante. Por meio do brincar, as crianças exploram o ambiente e desenvolvem seus sistemas sensorial, motor e cognitivo.

Uma tarde, finalizei o atendimento do Arthur deixando-o posicionado para jogar videogame. Ele estava sentado em sua cadeira de rodas e em seu pé esquerdo foi colocado um acionador. Um intermediário, neste dia eu,

colocava o mouse no local onde deveria ocorrer o clique e o Arthur fazia o clique com o acionador. Alguém me chamou para dizer algo, não mudei o mouse de lugar, Arthur não conseguiu clicar, perdeu o jogo! Inúmeras outras vezes presenciei isso acontecer, quando eu ou outras pessoas eram o intermediário entre o Arthur e o jogo.

Foi então, durante as férias de julho de 2013, que decidi que deveria fazer o mestrado sobre a interação das crianças com atrofia muscular espinhal com o ambiente. Para que essa interação ocorresse, era necessário processamento sensorial, motor e cognitivo. Mas era importante que houvesse algum tipo de tecnologia que pudesse dar autonomia a essas crianças, sem intermediários na interação.

Entrei em contato com o IME (Instituto de Matemática e Estatística, Departamento de Computação). Contei a minha ideia de desenvolver um jogo para que crianças com grave incapacidade motora pudessem ter independência para jogar. Paralelamente, poderíamos avaliar o desempenho cognitivo das crianças, que, na maioria dos casos, não possuem comunicação verbal e têm poucos movimentos ativos. O professor Dr. Carlos Hitoshi Morimoto, do IME, ajudou e desenvolvemos algumas ideias, juntamente com um aluno, Celso Shimabukuro. Quando as coisas estavam se encaminhando, o professor Hitoshi me alertou que eu não poderia fazer o mestrado no IME, devido à especificidade da prova e da seleção.

Em novembro de 2013, localizei a Profa. Dra. Mariana Voos, quando procurava linhas de pesquisa de pessoas que pudessem me orientar. Foi ela quem, não só acreditou no meu projeto, como me ajudou a enxergar muitas

outras questões para melhorá-lo. Pensamos em maneiras de proporcionar liberdade para brincar e se comunicar de forma que, ao mesmo tempo, fosse possível avaliar o desempenho cognitivo das crianças. Fomos conversar com a CIVIAM, sobre o Tobii PcEye. Conseguimos o empréstimo do equipamento para nosso primeiro estudo clínico.

Em 2015, fomos à casa de doze crianças com atrofia muscular espinhal e coletamos os dados. Essa pesquisa trouxe informações essenciais sobre as habilidades sensoriais, motoras e cognitivas. Antigamente, essas crianças tinham como expectativa de vida os dois anos de idade. Atualmente, algumas crianças, como o Arthur, já estão caminhando para adolescência e não podemos continuar melhorando a expectativa de vida sem melhorarmos a qualidade de vida. Essas crianças recebem alta hospitalar acompanhadas de equipe de atendimento domiciliar, respirador, aspirador, traqueostomia e gastrostomia (estes últimos dois, em alguns casos), mas também devem receber suporte para comunicação e interação social. É fundamental que as crianças com AME não somente recebam informações passivamente, mas também possam interagir de forma efetiva, com respostas, opiniões, escolhas.

A pesquisa, intitulada “Desempenho Visual, Motor e Cognitivo em Crianças com Atrofia Muscular Espinhal Tipo I”, protocolada sob o número 1223, é apresentada nesse exemplar de qualificação de mestrado do Programa Ciências da Reabilitação do Departamento de Fisioterapia Fonoaudiologia e Terapia Ocupacional da Faculdade de Medicina da Universidade de São Paulo. A análise e discussão dos dados contaram também com a contribuição da Dra. Umbertina Conti Reed e Dr. Edmar Zanoteli (médicos do ambulatório de

Neurologia do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo), da Profa. Dra. Francis Meire Favero (Departamento de Neurologia/Neurocirurgia da Universidade Federal de São Paulo), da Profa. Dra. Fátima Aparecida Caromano e da mestrande Alessandra Ferreira Barbosa (Departamento de Fisioterapia, Fonoaudiologia e Terapia Ocupacional da Faculdade de Medicina da Universidade de São Paulo) e do Dr. Carlos Hitoshi Morimoto (Departamento de Ciências da Computação do Instituto de Matemática e Estatística da Universidade de São Paulo).

Os pacientes que compuseram voluntariamente a amostra dessa pesquisa foram recrutados pela ONG AMEVIVER e em duas escolas regulares de São Paulo/SP (Escola Florescer e EE Prof. Clorinda Danti). A avaliação ocorreu no domicílio das crianças com atrofia muscular espinhal e nas escolas regulares das crianças saudáveis. O estudo investigou o desempenho cognitivo de crianças com AME tipo I em tarefas de associação de pares. O artigo foi submetido em 12/08/2016 à revista Neuromuscular Disorders. Em 18 de janeiro de 2017 foi aceito e em maio de 2017 foi publicado.

Resultados parciais foram apresentados em forma de pôster em dois eventos científicos: “Visual-Cognitive and Motor Skills in Children with Type I Spinal Muscle Atrophy” no 20th International Congress of the World Muscle Society (WMS), que ocorreu de 01 a 04 de outubro de 2015 em Brighton, no Reino Unido (Apêndice C) e “Matching Pairs Difficulty in Children with Spinal Muscular Atrophy Type I Suggest Cognitive Impairment” no XXVII Congresso Brasileiro de Neurologia, que ocorreu de 27 a 31 de agosto de 2016 em Belo Horizonte/MG (Apêndice D).

Paralelamente ao nosso estudo experimental, realizamos uma revisão sistemática sobre cognição de pessoas com atrofia muscular espinhal, em processo de submissão, que também é apresentada nesse exemplar. Foram localizados 43 artigos e nove foram selecionados por atenderem aos critérios de inclusão/exclusão. O estudo apontou que a cognição de crianças com AME é heterogênea. Três artigos indicaram que essas crianças têm desempenho cognitivo normal, três artigos indicaram que há atraso e outros três estudos relataram desempenho acima do normal. De modo geral, as crianças com maior fraqueza muscular (AME-I) apresentaram maior comprometimento e estudos mais recentes detectaram esse atraso. Com essas duas pesquisas, visamos ampliar o conhecimento sobre desempenho cognitivo de crianças com AME. Com maior embasamento teórico sobre o desenvolvimento cognitivo, há melhor adequação dos protocolos de avaliação e tratamento. Mesmo que a doença não cause um déficit cognitivo de base, crianças sem estímulos adequados para comunicação e exploração do ambiente podem desenvolver alterações cognitivas. Não basta aumentar a expectativa de vida, é preciso melhorar a qualidade de vida.

1 INTRODUCTION

Spinal muscular atrophy (SMA) is a genetic, neurodegenerative disease linked to the SMN1 gene (survival motoneuron), which causes weakness and muscular atrophy. It is a rare disease that affects approximately 1 in 10,000 people worldwide and causes the highest infant mortality^{1,2}. Proximal weakness is more severe than distal weakness. Feeding, swallowing and breathing may be impaired, leading to increased risk of pneumonia and other infections¹.

The classification of SMA is based on the achieved milestones. Type I is diagnosed before six months of age and there is no acquisition of cervical control. In type II, children cannot sit without support, and the diagnosis is given before 18 months of age. In types III and IV, independent gait acquisition occurs. SMA progression is heterogeneous^{1,3}, but includes progressive loss of strength, contractures and scoliosis in most cases. In most cases, SMA caused by a homozygous mutation in the SMN1 gene, the clinical variability is, in part, related to the SMN2 copy number.

The main scales used to evaluate the motor performance of children with SMA are The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) and the Hammersmith functional motor escale expanded (HFMSE). CHOP INTEND evaluates children with SMA-I or children who cannot sit without support. It consists of 16 items, scored from 0 to 4. Zero is given for children who cannot perform the task and 4 is attributed to normal movement against gravity. Both sides are tested, and scores are summed. The

maximum possible score is 64⁴.

HFMSE evaluates children diagnosed with SMA-II or SMA-III, or children who can sit without support. HFMSE has 33 items, scored from 0 to 2. Zero denotes insufficient motor control to assume the initial position or the movement. One is given when the movement is partially performed or performed in association with other compensatory movements. Two is attributed to normal movements. The maximum possible score is 66⁵.

The expected benefits of therapies in patients with SMA may be greater if they are treated as early as possible^{6,7}. Intrathecal antisense oligonucleotides that prevent the skipping of exon 7 during SMN2 transcription, and intravenous SMN1 insertion using viral vector are being developed, based on different mechanisms to increase the level of SMN protein⁶. A phase 2 study followed 20 children with SMA-I, who started taking the spinraza medication between three weeks and seven months. Children showed functional improvement (assessed by CHOP INTEND). They also took longer times to depend on mechanical ventilation, compared to the natural history of the disease^{8,9}. A phase 3 double-blind trial followed 122 infants with SMA-I (aged seven months or less) in 31 centers. In the group treated with spinraza, 22% gained total cervical control, 10% were able to roll, 8 % were able to sit and 1% were able to stand. In the control group, no infants reached these milestones^{8,10}. Therefore, phenotypic characteristics are likely to change, and cognitive screening and assessment will be viable for a higher number of children with SMA-I^{8,9,10}.

In this context, it is necessary to reinforce the importance of rehabilitation, to preserve respiratory and motor functions and to avoid cognitive

delay due to environmental restriction. Respiratory care is required, such as mechanical ventilation and coughing techniques for bronchial hygiene, as well as nutritional and education management⁷.

Children with SMA require respiratory, motor or cognitive rehabilitation. In general, respiratory therapy aims to maintain bronchial hygiene and to keep the airways expanded. Motor physiotherapy acts to maintain the length of the muscle fibers, by means of stretching exercises and positioning orientations. Orthoses play an important role in providing adequate positioning. Active and active-assisted and passive movements as well as postural changes intend to let the children maintain and gain postural control and functional independence. The cognitive development must be stimulated by all health professionals, by ludic activities, such as storytelling and games.

The eye tracker can be useful for these purposes, but the visual control must be assessed prior to starting this approach and in follow-up sessions¹¹. The extraocular muscles are responsible for strabismus¹² and may be impaired in people with SMA. This fact is observed in clinical practice, although it has not been systematically assessed in any study.

The coordination of eye movements is influenced by the environment. Many babies have strabismus, which is considered normal up to 4 months of age¹³. However, some children with SMA have divergent strabismus even after this age. The visual control develops rapidly in the first year of life, as a combination of maturation and environmental stimuli¹⁴. Children with SMA have difficulty interacting with the environment, due to muscular weakness. Therefore, vision becomes the most important sensory system for the interaction and exploration, especially in children with SMA-I.

Vision is also important in non-verbal communication. The visual control contributes with the establishment of relationships and, as a consequence, it may influence the quality of life¹⁵.

Although many studies have been exploring therapeutic strategies for children with SMA, very few measure their participation and quality of life¹⁶. The intellectual development must be assured in appropriate environment (e.g. school), including the building, the furniture and the devices (assistive technology). An example of assistive technology is the eye tracker, a device for people who cannot communicate verbally and have poor voluntary muscle contraction. These people can use assistive technology to communicate and interact by lip, eyeballs or eyelids movements^{11,16}. The eye tracker evaluates cognition even in patients with minimal voluntary movements, e.g. children who cannot speak^{17,18}.

There are several scales to evaluate cognition in children and adolescents, but there is no specific scale for children with SMA. Some studies evaluated children with SMA with the following scales: The Raven Colored and Standard Progressive Matrices evaluate abstract reasoning and spatial perception¹⁹. The Kaufman Assessment Battery for Children evaluates counting, sequential processing, spatial perception and motor planning¹⁹. The *Test of Vocabulaire Actif et Passif* consists of choosing images to illustrate words²⁰. The scale *La pipe et le rat* or *Batterie D'évaluation du Langage* evaluates reading ability²⁰. The MacCarthy Intelligence Scale for Children evaluates verbal ability, spatial perception, counting and verbal/ non-verbal memory²¹. The North Syntactic Screening Test evaluates comprehension and expression (language)²¹. The Alouette Test evaluates automaticity in reading

out loud²¹. The *Batterie D'efficience Mnésique* evaluates immediate and late recalling²¹. The object localization test²²⁻²⁴ evaluates spatial memory and attention.

There are studies that investigated the functional independence and the quality of life of children with SMA. The Functional Independence Measure scale was used to evaluate self-care, mobility and cognition. In cognition domain, comprehension, expression, social interaction, problem solving, and memory were evaluated²⁵.

The quality of life was evaluated by PedsQL (Pediatric Quality of Life Inventory). PedsQL evaluates children and adolescents aged 2 to 18 years. It has a version for children and adolescents from five to 18 years and another for the parents of children and adolescents between two and 18 years. The scale addresses four dimensions: physical (8 items), emotional (5 items), social (5 items) and school routines (5 items). Zero is given when no problem is reported, and 4 when there are always problems in daily life in the item. The questions are inversely normalized on a scale from zero to one hundred. Therefore, higher scores denote better the quality of life²⁶.

One of the main findings of PedsQL was that the higher the quality of life was associated with better cognitive performance. Children with SMA-I who attended school regularly, visited friends, participated in outdoor community activities, obtained higher scores¹⁶. These children also showed better cognitive performance, as evidenced by executive function test¹⁶. In functional evaluation, not only the injury, but also daily life activities and social participation must be addressed. Children with neuromuscular diseases and/or severe motor

impairment cannot explore the environment adequately and must be properly stimulated¹³.

The present study favors interdisciplinary work, contributing to clinical practice guidelines, establishing a cognitive evaluation protocol that can be used by health professionals. This cognitive evaluation protocol can be applied regularly, to detect cognitive impairment and to monitor development.

2 PRIMEIRO ARTIGO

Cognitive performance of children with spinal muscular atrophy: a systematic review

Revista: Developmental Medicine & Child Neurology

Fator de impacto (2016): 3,116

Qualis (2015): A2 – Educação Física

Data da submissão: maio/2018

Cognitive performance of children with spinal muscular atrophy: a systematic review

Graziela Jorge Polido¹, Mariana Mangini Vaz de Miranda¹, Nelson Carvas Junior³, Rodrigo de Holanda Mendonça², Fátima Aparecida Caromano¹, Umbertina Conti Reed², Edmar Zanoteli², Mariana Callil Voos¹

¹Programa de Pós-Graduação em Ciências da Reabilitação, Faculdade de Medicina, Universidade de São Paulo, Brasil.

²Departamento de Neurologia, Departamento de Neurologia Clínica, Universidade Federal de São Paulo, Brasil.

³Programa de Pós-Graduação em Ciências da Saúde do Instituto de Assistência Médica ao Servidor Público Estadual de São Paulo, Brasil.

Corresponding author: Mariana Voos

Rua Cipotânea, 51 – Cidade Universitária

CEP 05360-000 – São Paulo – SP, Brazil

Telephone: Office: +5511 30917451

Email: marivoos@usp.br

Keywords: spinal muscular atrophy; cognition; systematic review

Short title: Cognitive performance in spinal muscular atrophy

Abstract

Aim: To evaluate the evidence about cognitive outcomes in spinal muscular atrophy (SMA). **Methods:** Searches in PUBMED/Medline, Web of Knowledge and Scielo datasources found 26 studies (1992 to 2017, descriptors “spinal muscular atrophy” and “cognition”). Nine studies were selected according to the eligibility criteria: (1) tested cognition in people with SMA; (2) written in English/ Spanish. The Risk of Bias in Non-Randomized Studies of Interventions was used to describe design, bias, participants, evaluation protocol and main findings. This study was registered in the International prospective register of systematic reviews. **Results:** In three studies, normal cognition was described. In three studies cognitive outcomes were above average. Cognitive impairment was found in three studies. Poor cognitive performance was more frequently reported in recent studies, studies that included children with SMA type I and studies that included visual/ auditory attention and executive function tests. Protocols and cognitive domains varied, therefore metanalysis was not possible. **Interpretation:** The severity of motor impairment may be related to cognitive outcomes: studies that included a higher number/ percentage of children with SMA type I found cognitive impairment. The establishment of gold-standard protocols is necessary. Further studies should compare the cognitive outcomes of SMA types I to IV.

Whats this paper adds:

This is a systematic review about cognitive outcomes of children with SMA.

Children with SMA type I showed cognitive impairment (compared to controls).

Some children with SMA may need cognitive intervention and/or rehabilitation.

The eye-tracker can avoid bias in the assessment of children with SMA.

Severe environmental restriction may be associated to cognitive impairment.

Background

Spinal muscular atrophy (SMA) is genetic and progressive, caused by the homozygous mutation in SMN1 gene that leads to degeneration of the anterior horn motor neurons and the motor nuclei of some cranial nerves. The most common form is caused by mutations in the survival motor neuron 1 (*SMN1*) gene (5q11.2) and SMA is transmitted in an autosomal recessive fashion.

SMA has been clinically classified into at least four types, based on the age of onset and the maximal function attained^{1,2}. Children who do not acquire sitting are classified as type I (non-sitter), with onset in the first semester of life (Werdnig-Hoffmann disease). Type II (sitter) usually begins before age of 18 months and includes children who can sit without support. Type III (walker) is considered a juvenile and more benign form of SMA with standing and gait acquisition. Type IV begins in adulthood. In all types of SMA, sensory function is normal^{1,2}.

For many years, researchers focused on motor and respiratory outcomes of children with SMA and the cognitive performance was not investigated. In 2006, D'Angelo and Bresolin³ stated that the cognitive development of affected children had not received much attention and that most studies relied on anecdotal clinical reports and did not follow gold-standard neuropsychology guidelines. More than ten years after that, cognitive outcomes of children with SMA must be reviewed.

SMA (mainly types I and II) is associated to severe weakness, which impacts on hand coordination and speech acquisition^{1,2}. Restricted verbal and

sensorimotor interaction can cause cognitive impairment⁴. In a previous study, we evaluated children with SMA type I and age- and sex-matched controls with an eye tracking device on pair-matching tasks. We found that pair-matching performance was poorer in children with SMA than in controls. We also found a relationship between the pair-matching performance and the social function, scored by the Pediatric Evaluation Disability Inventory⁴. However, cognitive outcomes in SMA are contradictory in the literature. For instance, the study by von Gontard (2002)⁵ reported normal intelligence coefficients in children and even above normal cognitive performance in adolescents with SMA types I-III.⁵

The present study aimed to describe and discuss the evidence about cognitive outcomes in children with SMA. The difficulties in objects and environmental exploration and the poor oral communication may impair cognitive development. Therefore, we hypothesized that there would be differences between the performance in cognitive tests of children and adolescents with SMA types I, II, III and controls. We performed a systematic review to assess the cognitive performance of children with SMA and possible differences between the cognitive performance of types I, II and III. There were no restrictions on the types of study design.

Method

Search strategy and selection criteria

This study was registered in International prospective register of systematic reviews (PROSPERO) and followed the checklist of the Preferred

Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)⁶. A search of the last 25 years (1992 to 2017) was carried out and included studies from PUBMED/Medline, Web of Knowledge and Scielo (Scientific Electronic Library Online) databases. The searches were performed from July 11th, 2015 to March 07th, 2018.

The search with the descriptors “cognition” and “spinal muscular atrophy” resulted in 36 studies in PUBMED/Medline and in 17 studies in Web of Science/ Web of Knowledge. The search with the same descriptors resulted in no studies in Scielo datasource. From the 53 studies identified, 10 were eliminated because they were duplicates.

The titles and abstracts of 43 studies were screened and 23 were excluded because they did not evaluate people with SMA. Twenty studies were evaluated, based on the inclusion criteria: quantitative assessment of cognitive skills; written in English or Spanish, and on the exclusion criteria: review studies (n=5; two about cognition in neuromuscular diseases and three about locomotion in SMA); letter to the editor (n=1); studies with no cognitive assessment (n=5). Therefore, we included nine studies from this search.

Data extraction and quality assessment

As the nine selected studies were non-randomized, they were analyzed by the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I)⁷. ROBINS-I is a tool for evaluating the risk of bias of non-randomised studies, whose results may be biased by sampling and interventions. ROBINS-I evaluated the risk of bias of the research question and the outcome and results. It also examined how the confounders and co-interventions were addressed

and the risk of bias judgements⁷.

We classified bias with ROBINS-I guidelines and described the design, bias, participants, evaluation protocol, main findings of the selected studies (Table 1). The eligibility and the bias of each study were independently evaluated by two investigators (GJP and MCV). All items scored distinctly by the examiners were discussed and rescored with a consensual classification.

Due to the heterogeneity of samples (involving types I, II and/or III of SMA) and testing protocols, we could not run a meta-analysis of results.

Results

The main findings of the nine studies are presented below and the risk of bias is classified by ROBINS-I in Table 1.

TABLE 1

The studies described the cognitive aspects of children and adolescents with SMA type I, II and III. In general, three studies described cognitive performance as normal^{8,9,10}. In addition, three studies reported that the cognitive performance was above average in some aspects^{5,11,12} (Table 1). Three studies described cognitive performance as below average^{4,13,14}. Only three studies used the same scale^{5,8,9} (Wechsler Intelligence Scale for Children), therefore, metanalysis was not possible.

Discussion

The present study evaluated the evidence in the literature about cognitive outcomes in children with SMA. We found that three studies

described the cognition of children with SMA as normal⁸⁻¹⁰, three as above average^{5,11,12}, and three as below average^{4,13,14}.

Most studies that concluded that cognition was normal⁸⁻¹⁰ or above average^{5,11,12} evaluated language^{8,9,12}, visuospatial perception^{4,5,8-11,12}, and memory^{5,8,10,11,13}. Children with SMA type I were included in only two of these six studies, and only if they could perform hand movements and verbal responses^{5,9}. Three of these six studies were from the same group and evaluated similar tasks, involving language skills acquisition^{10,11,12}.

The studies that observed that children with SMA showed below average cognitive performance investigated visual and auditory attention^{4,14} and executive function^{4,12}. Children with SMA type I were included in all these studies. Therefore, this systematic review suggests that children with SMA type I are more likely to have cognitive impairment (attention and executive function deficits)^{4,12,14}.

This difference between SMA types was reported by Sieratzki & Woll (2002)². They wrote a letter to the editor, reinforcing the findings of von Gontard et al. (2002)⁵. They stated that although cognition was normal, there was a difference between SMA types. Sieratzki and Woll² concluded that the attention of children with SMA type I, who suffer from more severe paralysis, was strongly focused on the approach to one target. Opposite, children with SMA type III had higher functional independence and could screen their surroundings for interesting targets².

The following pattern was observed in the review: from 1992 to 2002, studies concluded that cognition was normal^{8,9,10}; from 2002 to 2009 studies concluded that cognition was above average^{5,11,12}. More recent studies reported

that cognitive performance was below average^{4,13,14}. This pattern suggests that previous non-reported cognitive impairment in SMA (mainly in type I) is being detected. Such findings may be due to the development and application of new cognitive evaluation protocols, which include patients with very limited motor skills.

Sampling was very heterogeneous, and some studies did not include children with SMA type I^{8,10,11-13} (or excluded some children with SMA type I^{9,10}), because evaluation required hand coordination and/or verbal responses. Only Barja et al. (2013)¹⁴ and Polido et al. (2017)⁴ developed protocols that did not depend on hand coordination and speaking. In these two studies, the responses involved eye movements, detected by an eye tracking device and only children with SMA type I participated. Children with SMA type I may need mechanical ventilation, nursing care, gastrostomy, tracheostomy, and therapies (motor and respiratory physiotherapy, occupational therapy, phonaudiology for alternative communication and dysphagia). All these adaptations are fundamental for their cognitive-motor development, but do not assure normal/typical development, as the interaction with the environment remains restricted.

As treatment (drugs and rehabilitation) becomes more effective, children with SMA (mainly the ones with types I and II) survive longer^{15,16}. Facing these new outcomes, health professionals must think beyond survival. Specialized assessment and intervention can help children to interact and develop their cognition^{4,14}. If cognitive performance is preserved, or even optimized, children with SMA can compensate for the poor motor repertoire and oral communication, achieving greater independence, autonomy and quality of life.

The diversity of cognitive assessment protocols made comparison difficult, since each study approached specific aspects of cognition. Standardized tools are needed to assess the cognitive skills. Data about people with different types of SMA must be evaluated and analysed separately.

Cognitive performance is directly related to motor skills, for example, locomotion. In the study by Dunaway et al. (2012)¹⁷, family members were instructed to stimulate children with SMA to use the power wheelchair. Two scales of mobility and quality of life were applied. Five one-year-old-children with SMA (four diagnosed with type II and one with type I) participated. Children achieved independence on all items of the mobility scale and increased the scores of the quality of life scale at the age of eight months. The authors concluded that cognitive skills are required to use a power wheelchair. Children with SMA, usually type II, can use power wheelchairs before the age of two, which favors cognitive and motor development¹⁷. More specifically, there is a relationship between self-locomotion and spatial language terms¹⁸ and language was described as preserved in all studies that included tests for this aspect of cognition.

This systematic review showed that there is no evidence of cognitive impairment in children with SMA types II and III. Although there is little evidence in the literature about the cognitive performance of children with SMA, children with SMA type I are more likely to be affected. Attention and executive function seem to have higher risk of being impaired. More tests have to be developed for properly assessing the cognition of patients with SMA, specially for more severe forms.

References

- 1 Fenichel GM. Clinical Pediatric Neurology: A signs and symptoms approach. Saunders: Elsevier, 2009.
- 2 Sieratzki JS, Woll B. Cognitive function in children with spinal muscular atrophy. *Neuromuscular Disorders* 2002;**12**: 7-8.
- 3 D'Angelo MG, Bresolin N. Cognitive impairment in neuromuscular disorders. *Muscle & Nerve* 2006; **34**(1): 16-33.
- 4 Polido GJ, Barbosa AF, Morimoto CH, et al. Matching pairs difficulty in children with spinal muscular atrophy type I. *Neuromuscular Disorders* 2017; **27**: 419-427.
- 5 von Gontard A, Zerres K, Backes M, et al. Intelligence and cognitive function in children and adolescents with spinal muscular atrophy. *Neuromuscular Disorders* 2002; **12**: 130-6.
- 6 Moher D, Liberati A, Tetzlaff J, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 2009; **6**(6): e1000097.
- 7 Stern JAC, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016; **355**: i4919.
- 8 Billard C, Gillet P, Signoret JL, et al. Dystrophy: a reappraisal and comparison with spinal muscular atrophy. *Neuromuscular Disorders* 1992; **2**: 371-8.

- 9 Billard C, Gillet P, Barthez M-A, et al. Reading ability and processing in Duchenne muscular dystrophy and spinal muscular atrophy. *Developmental Medicine & Child Neurology* 1998; **40**: 12-20.
- 10 Rivière J, Lécuyer R. Spatial cognition in young children with spinal muscular atrophy. *Developmental Neuropsychology* 2002; **21**: 273-83.
- 11 Rivière J, Lécuyer R. The C-not-B error: a comparative study. *Cognitive Developmental* 2003; **18**: 285-297.
- 12 Rivière J, Lécuyer R, Hickmann M. Early locomotion and the development of spatial language: evidence from young children with motor impairments. *European Journal of Developmental Psychology* 2009; **6**(5): 548-566.
- 13 Chung BHY, Wong VCN, Ip P. Spinal muscular atrophy: survival pattern and functional status. *Pediatrics* 2004; **114**: 548-53.
- 14 Barja S, Muñoz C, Cancino N, et al. Estimulación audiovisual en niños con limitación grave de la motricidade: mejora su calidad de vida? *Revista de Neurologia* 2013; **57**: 103-11.
- 15 Parente V, Corti S. Advances in spinal muscular atrophy therapeutics. *Ther Adv Neurol Disord* 2018; **11**: 1756285618754501.
- 16 Zanoteli E, Reed UC. Therapeutic advances in 5q-linked spinal muscular atrophy. Avanços terapêuticos na atrofia muscular espinhal ligada ao cromossomo 5q. *Arquivos de Neuropsiquiatria*. *In press*.

17 Dunaway S, Montes J, O'Hagen J, et al. Independent mobility after early introduction of a power wheelchair in spinal muscular atrophy. *Journal of Child Neurology* 2012; **28**: 576-82.

18 Oudgenoeg-Paz O, Rivière J. Self-locomotion and spatial language and spatial cognition: insights from typical and atypical development. *Front Psychol* 2014; **2**(5): 521.

Table 1: Risk of Bias in Non-Randomized Studies – of Interventions (ROBINS-I)⁵

Authors/ Year/ Title/ Study design/ Overall bias	Participants	Evaluation protocol	Main findings	Risk of bias
Billard et al., 1992⁸ <i>Cognitive functions in Duchenne muscular dystrophy: a reappraisal and comparison with spinal muscular atrophy</i> Cross-sectional Moderate risk of bias	Duchenne muscular dystrophy (n=24): 12 to 16 years (mean 14 years); spinal muscular atrophy (n=17) types II and III); 12 to 16 years (mean 14 years). No control group.	Assessment was made by a single-blind evaluator. Three cognitive areas were assessed: Language (MacCarthy intelligence scale for children, North syntactic screening test, Alouette test for reading age and the verbal scale of the Wechsler intelligence scale: information, similarities, arithmetic and vocabulary); Visuospatial (the performance scale of the Wechsler intelligence scale: picture completion, picture arrangement, block design and object assembly); Attention-memory (selective auditory response and <i>Batterie d'Efficience Mnésique</i> : global verbal and visual memory).	Normal performance of children with spinal muscular atrophy. Children with spinal muscular atrophy showed higher scores on Wechsler intelligence scale (normal level) than children with Duchenne muscular dystrophy (below normal). Children with spinal muscular atrophy showed higher scores on the North syntactic screening test and on the global verbal and visual memory. Only 61% of the participants with Duchenne muscular dystrophy had normal reading age compared to 100% of participants with spinal muscular atrophy.	Muscle strength/ function and cranial nerves functions were not assessed and may have influenced results. Bias due to confounding. No control group: spinal muscular atrophy was compared to Duchenne muscular dystrophy. Children with spinal muscular atrophy type I were not included. Schooling and social class were not controlled. Bias in selection of participants. Sometimes the examiner helped the patient with hand manipulation. Tests with motor components and/or time limits were used. Bias in measurement of outcomes.
Billard et al., 1998⁹ <i>Reading ability and processing in Duchenne muscular dystrophy and spinal muscular atrophy</i> Cross-sectional Moderate risk of bias	Duchenne muscular dystrophy (n=21): 8 to 13 years (mean 11 years); spinal muscular atrophy I and II (n=11): 6 boys, 8 to 13 years (mean 11 years). Control group (n=42): 22 boys, 6 to 14 years (mean 9 years).	Wechsler intelligence scale: information, similarities, vocabulary and arithmetic (verbal tasks); picture completion, picture arrangement, object assembly and block design (non-verbal tasks); only children with spinal muscular atrophy and Duchenne muscular dystrophy were tested. Language: <i>Batterie d'évaluation du langage</i> ; (word repetition, picture naming); <i>Test de Vocabulaire Actif et Passif</i> (word comprehension); North syntactic screening test. Reading ability: <i>La pipe et le rat</i> ; reading aloud test.	Normal performance of children with spinal muscular atrophy. Children with spinal muscular atrophy and with Duchenne muscular dystrophy did not differ in Wechsler intelligence scale total scores. Children with Duchenne muscular dystrophy showed lower scores in similarities and arithmetic (verbal tasks). Children with spinal muscular atrophy showed significantly higher reading skills than children with Duchenne muscular dystrophy.	Muscle strength/ function and cranial nerves functions were not assessed and may have influenced results. Bias due to confounding. Children with spinal muscular atrophy who were able to read but had severe motor impairment were excluded from the protocol. Schooling and social class were not controlled. Bias in selection of participants. Wechsler intelligence scale was not applied in the control group. Bias due to missing data. Tests with motor components and/or time limits were used. Bias in measurement of outcomes.

Rivière & Lécuyer, 2002¹⁰ <i>Spatial cognition in young children with spinal muscular atrophy</i> Cross-sectional Low risk of bias	Spinal muscular atrophy type II (n=12, 7 boys, 2 years), 12 healthy children (1 year and 6 months), 12 healthy children (2 years), 12 healthy children (2 years and 6 months), 12 healthy children (3 years).	A spatial location memory test was used. A toy was hidden in one of three cups aligned horizontally on a table. The tabletop was rotated 180 degrees and the child participated in three trials. The task was to find the hidden toy.	Normal performance of children with spinal muscular atrophy. There was no difference between groups. All groups showed normal spatial location performance. Locomotor impairment does not appear to be a risk factor for slowing down in the development of spatial perception.	This study evaluated only children with one type of spinal muscular atrophy (type II). Diagnosis was not genetically confirmed. Bias in selection of participants. This study explored a very specific developmental phase. Each trial ended when the child searched for the hidden toy (correct versus incorrect location). Therefore, only chi-square tests were possible. Bias in measurement of outcomes.
von Gontard et al., 2002⁵ <i>Intelligence and cognitive function in children and adolescents with spinal muscular atrophy</i> Cross-sectional Low risk of bias	96 children and adolescents with Spinal muscular atrophy: 18 with type I, 58 with type II and 20 with type III (6 to 18 years); 45 non-affected siblings: mean age 11 years; 59 healthy children without affected siblings: mean age 11 years.	Raven colored and standard progressive matrices Kaufman assessment battery for children (6 to 11 years): Gestalt closure, number recall, word order, matrix analogies, spatial memory, photo series, faces and places, arithmetic, riddles, reading/understanding, sequential/simultaneous processing scale, achievement. Wechsler intelligence scale (12 to 18 years): information, comprehension, arithmetic, similarities, vocabulary, number recall.	Normal/ above normal performance of children with spinal muscular atrophy. Children and adolescents with spinal muscular atrophy have normal intelligence. Adolescents with spinal muscular atrophy showed higher intelligence than controls, probably due to environmentally mediated factors (strategies to compensate their physical handicap). There were no differences between the performances of types I, II and III.	From a sample of 261 patients, 128 deceased (mostly of type I) and six were excluded due to language difficulties. Some patients classified as type I were borderline between type I and II. Only 83 patients underwent genetic testing. Bias in selection of participants.
Rivière & Lécuyer, 2003¹¹ <i>The C-not-B error: a comparative study</i> Cross-sectional Moderate risk of bias	14 children with spinal muscular type II aged 1 to 3 years (mean 2 years, 6 boys) and 14 controls (7 boys).	A spatial location memory test involving invisible displacements of an object was used. A toy was hidden under one of three cloths. The child had to find the hidden toy. The misplacement of the hidden toy is known as the C-not-B error.	Normal/above normal performance of children with spinal muscular atrophy. The performance of children with spinal muscular atrophy was better than the performance of the control group. Inhibitory mechanisms present in children with spinal muscular atrophy are not as well developed in healthy children, who tend to show more impulsive responses.	Reaching and grasping are critical for this task. Therefore, muscle strength may have influenced in movement inhibition. Bias due to confounding. This study evaluated only children with one type of spinal muscular atrophy (type II). Diagnosis was not genetically confirmed. Bias in selection of participants. Each trial ended when the child searched for the hidden toy (correct versus incorrect location). Therefore, only chi-square tests were possible. Bias in measurement of outcomes.

<p>Chung, Wong & Ip, 2004¹³</p> <p><i>Spinal muscular atrophy: survival pattern and functional status</i></p> <p>Cohort study</p> <p>Moderate risk of bias</p>	<p>Children and adults with spinal muscular atrophy (n=83), aged 1 to 40 years (22: type I, 9 boys; 26: type II, 9 boys; 16 type IIIa, 9 boys; 19 type IIIb, 7 boys)</p>	<p>Parents/caregivers were interviewed for the scoring of the functional independence measure for children. The questionnaire consisted of three domains: selfcare, mobility and cognition. The cognition domain evaluated comprehension, expression, social interaction, problem solving, and memory and the maximum score is 35. This domain aimed to assess the real-life performance in daily activities, which required executive function.</p>	<p>The performance of children with spinal muscular atrophy was below normal.</p> <p>The percentage of individuals who had achieved functional cognitive independence were spinal muscular atrophy II: 60%; spinal muscular atrophy IIIa: 78%; spinal muscular atrophy IIIb: 90%. The cognition scores of participants with spinal muscular atrophy types III and II were higher than the scores of participants with type I.</p>	<p>Schooling and social class were not controlled. Bias due to confounding.</p> <p>There was no control group. Some participants were not genetically tested for spinal muscular atrophy. Bias in selection of participants.</p> <p>Intervention discontinuation was likely to be related to prognostic factors: higher mortality among more severe cases (probably type I). Bias due to missing data.</p> <p>Only one domain of the functional independence measure for children evaluated cognition and no other scales were used. Bias in measurement of outcomes.</p>
<p>Rivière et al., 2009¹²</p> <p><i>Early locomotion and the development of spatial language: evidence from young children with motor impairments</i></p> <p>Cross-sectional</p> <p>Moderate risk of bias</p>	<p>12 children with spinal muscular atrophy type II (2 to 3 years, mean age 3 years) and 12 controls.</p>	<p>The acquisition of language (the understanding and the production of specifically spatial terms) was evaluated in a series of 22 pictures. The understanding and the production of the words in, on, under, above, in front of, behind, near, far, in the upper region, in the lower region were tested (in French).</p>	<p>Normal/above normal performance of children with spinal muscular atrophy.</p> <p>There was no difference between the two groups in the comprehension task.</p> <p>In the production task, the spinal muscular atrophy group showed better performance than controls when producing the words for the relations in front of and behind.</p>	<p>Only one type of spinal muscular atrophy was evaluated. Participants were not genetically tested for spinal muscular atrophy. Bias in selection of participants.</p> <p>This study explored a very specific developmental phase and some tasks were too difficult for both groups. Bias in measurement of outcomes.</p> <p>Chi-square tests compared the percentage of correct answers but no data about variability was presented. Bias in selection of the reported result.</p>
<p>Barja et al., 2013¹⁴</p> <p><i>Estimulación audiovisual en niños con limitación grave de la motricidad: ¿mejora su calidad de vida?</i></p> <p>Case series</p> <p>Serious risk of bias</p>	<p>3 children with spinal muscular atrophy type I; 2 with neuropathy; 3 with myopathy. All children were classified as V in the Gross Motor Function Classification System</p>	<p>Audiovisual stimuli were used for evaluation/training (4 weeks, twice a day). Attention was assessed by Tobii P10 with the software Catch-me (gaze viewer, eye tracking device). Animation figures were based on the country's flag and other images and the sounds were based on farm animals. Blood pressure, heart/respiratory rates, peripheral oxygen saturation, facial expressions,</p>	<p>The performance of children with spinal muscular atrophy was below normal.</p> <p>There was attention improvement. Patients had difficulty following the objects and showing other communicative responses. Five patients improved their eye tracking performance. Stimuli were well tolerated, with no</p>	<p>The study did not perform standardized ophthalmologic evaluation. Bias due to confounding.</p> <p>The study did not include a healthy control group; the sample was heterogeneous and small. Bias in selection of participants.</p> <p>Only qualitative data was available. Bias in measurement of outcomes.</p> <p>Some patients were not evaluated or followed. Bias due to missing data.</p>

		ocular and extremity movements and presence of crying were also evaluated.	change in baseline variables.	
<p>Polido et al., 2017⁴</p> <p><i>Matching pairs difficulty in children with spinal muscular atrophy type I</i></p> <p>Cross-sectional</p> <p>Low risk of bias</p>	<p>12 children with spinal muscular atrophy type I (3 to 9 years)</p> <p>12 healthy children (3 to 9 years)</p>	<p>Matching pairs in four tasks with growing complexity (task 1: matching pairs of the same figures; task 2: matching a figure with its corresponding color; task 3: matching letters in uppercases and lowercases; task 4: matching arabic and written numerals). The task involved attention, spatial location processing and executive function.</p> <p>An eye tracking device (Tobii P10) and a notebook were used. Responses were detected by the tracker when children gazed the stimulus for two seconds.</p>	<p>The performance of children with spinal muscular atrophy was below normal. There were no differences between the groups in the number of correct answers in task 1 (which had few pairs). In the other three tasks, children with spinal muscular atrophy presented poorer performance than controls (less accuracy and longer times). Children with spinal muscular atrophy showed more difficulty when the number of stimuli and the complexity of the task were increased.</p>	<p>The study did not perform standardized ophthalmologic evaluation. Some children may have performed poorly because they were not familiar with the equipment. Bias due to confounding.</p> <p>The study evaluated only one type of spinal muscular atrophy. Bias in selection of participants.</p>

3 SEGUNDO ARTIGO

Matching pairs difficulty in children with Spinal Muscular Atrophy type I

Revista: Neuromuscular Disorders

Fator de impacto (2016): 3,107

Qualis (2015): A2 – Educação Física

Data da submissão: 12/08/2016

Publicação: maio/2017

Available online at www.sciencedirect.com

ScienceDirect

Neuromuscular Disorders 27 (2017) 419–427

www.elsevier.com/locate/nmd

Matching pairs difficulty in children with spinal muscular atrophy type I

Graziela Jorge Polido^a, Alessandra Ferreira Barbosa^a, Carlos Hitoshi Morimoto^b,
Fátima Aparecida Caromano^a, Francis Meire Favero^c, Edmar Zanoteli^d, Umbertina Conti Reed^d,
Mariana Callil Voos^{a,*}

^a Department of Physical Therapy, Speech Therapy and Occupational Therapy, Faculty of Medicine, University of São Paulo, São Paulo, SP, Brazil

^b Computer Science Department, Institute of Mathematics and Statistics, University of São Paulo, São Paulo, SP, Brazil

^c Department of Neurology, UNIFESP (Federal University of São Paulo), São Paulo, SP, Brazil

^d Department of Neurology, Medical School of the University of São Paulo, University of São Paulo, São Paulo, SP, Brazil

Received 12 August 2016; received in revised form 30 November 2016; accepted 18 January 2017

Abstract

This study aimed to investigate the performance on pair-matching tasks in children with Spinal Muscular Atrophy type I (SMA-I) and the relationship between this performance and motor function, functional independence and quality of life. SMA-I ($n = 12$; 6.0 ± 2.3 yrs; 9 boys, 3 girls) and control sex-, age-matched children ($n = 12$; 6.2 ± 2.6 yrs) performed four pair-matching figure, number and letter tasks. The eye tracker detected eye movements. SMA-I children were assessed with CHOP INTEND, Pediatric Evaluation of Disability Inventory, and Pediatric Quality of Life Inventory. Analysis of variance showed that SMA-I children had a lower percentage of correct answers and longer timed performance compared to controls ($p < 0.05$). Pediatric Evaluation of Disability Inventory score (social function domain) was correlated to the percentage of correct answers on the pair-matching tasks on task 1 ($r = 0.81$; $p = 0.001$) and task 2 ($r = 0.66$; $p = 0.020$). Pair-matching performance of SMA-I children was poorer than the performance of control children. There was a relationship between pair-matching performance and social function. The restricted interaction with the environment, due to severe paralysis and poor verbal communication, is associated with cognitive difficulties in SMA-I children. The eye tracker was helpful in cognitive assessment of SMA-I children, who responded to the cognitive tests with eye movements.

© 2017 Elsevier B.V. All rights reserved.

Keywords: Spinal muscular atrophy; Cognition; Visual perception

1. Introduction

Spinal Muscular Atrophy (SMA) is an autosomal recessive motor disease [1], which results in progressive muscle atrophy and weakness. The incidence is 1:6000 to 1:11,000 live births [2,3]. The clinical spectrum ranges from early death in the first months postpartum to a normal adult life with only mild weakness [4]. In all types of SMA, weakness is described as being more proximal than distal and sensitivity is preserved [4].

According to the functional capacity and prognosis, SMA is classified in four phenotypes. Children with SMA-I, whose first symptoms are observed before six months of age, do not develop sitting control. Children with SMA-II show the first symptoms between six and eighteen months of life and can

maintain sitting posture independently [4]. Children with SMA-III develop independent gait because the first symptoms are noticed between eighteen months of age and early adolescence. SMA-IV begins in adulthood [2,5]. Studies about the natural history of the disease showed that 68% of children with SMA-I die in the first two years of life and 82% do not survive longer than four years, mostly due to improper respiratory support [2,6].

Children with SMA-I have difficulty communicating, because most of them cannot speak and all of them have very poor global motor control [7,8]. Eye control and vision are usually functional, even when the child has strabismus [9]. Therefore, eye movements can be used for interaction and communication in children with SMA-I. Interacting and communicating are key factors for cognitive development, which depends on both genetic and environmental aspects and involves attention, perception, memory and executive functions [10]. Considering that the acquisition of fine motor control to handle objects

* Corresponding author. Universidade de São Paulo, R Cipotânea, 51, Cidade Universitária, 05360-000 São Paulo, Brazil. Fax: +55 11 3091 7451.

E-mail address: ftmarivoos@gmail.com (M.C. Voos).

<http://dx.doi.org/10.1016/j.nmd.2017.01.017>

0960-8966/© 2017 Elsevier B.V. All rights reserved.

and body muscle weakness and severely delayed motor development (absence of head control, moving hands to midline, reaching, rolling, sitting with support), fasciculation of the tongue and absence of tendon reflexes.

2.2. Clinical scales

Children with SMA-I were evaluated with CHOP INTEND (The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders) [20], PEDI (Pediatric Evaluation of Disability Inventory) [21] and PedsQL (Pediatric Quality of Life Inventory) [22–24].

CHOP INTEND is a scale for neuromuscular diseases, which evaluates spontaneous movements of the upper limbs, lower limbs, neck and trunk. It consists of 16 items with a maximum score of 64 points. Each item is scored from zero to four: zero when the child cannot perform the tasks and four for spontaneous movements against gravity. Both sides are evaluated and the best side is considered for scoring. Lower scores denote poorer motor function [20].

PEDI is a general scale for assessing children with disabilities. The child is scored as either capable of doing (score 1) or unable (score 0) to do each of the items, which are listed in order of mastery. Caregiver assistance is measured on a 6-point rating scale from complete independence (score five) to total assistance (score zero). The self care and social function domains of PEDI were used, consisting of 73 and 65 points, respectively. There are eight questions on self care domain and five on social function. We did not assess mobility because most children with SMA-I score zero on all items of this domain. Lower scores mean higher dependence [21].

PedsQL evaluates the quality of life. It is specific for neuromuscular diseases and considers the family and the child's answers. There are 25 questions for the family, scored as zero for never, one for almost never, two for a few times, three for often, four for almost always. Children aged five to seven years answer a reduced version of 17 questions, scored only as zero, two and four. Children aged between eight and eighteen years answer the full questionnaire, with 25 questions scored from zero to four. Lower scores indicate a lower quality of life [22].

2.3. Experimental protocol

Children with SMA-I and controls were evaluated from June to December 2015. Assessments were made in two sessions, with one week interval between them. On the first session, the clinical tests were performed (CHOP INTEND, Pediatric Evaluation of Disability Inventory, Pediatric Quality of Life Inventory) and on the second session, the four pair-matching tasks.

During the evaluation, children from the control group sat on a regular chair, facing a table, on which they should place their elbows and hold the chin with their hands. Children with SMA-I were positioned on their respective adapted wheelchairs and tables.

A notebook (15" display, 30.5 × 24.5 cm screen, 1024 × 768 pixel resolution) and an eye tracker device were used. The eye

tracker was approximately 40 cm away from the child's face and the center of the display was at the same height of the child's eyes. A five point calibration procedure was performed with each child before the experiment. Calibration was viable with all children, including three children from the SMA-I group, who had divergent ocular deviation (V, A. and P.). On these cases, the eye tracker selected the dominant eye independently to evaluate the performance properly. In all tasks, item selection was made after a two-second fixation. Figures were displayed in 2 × 2 cm squares.

To familiarize the children with the device, they were allowed to practice the selection of random visual targets for two minutes prior to each task. After the training session, children from three to five years old performed Task 1 and Task 2 only and children aged six to nine years old performed all 4 tasks. The scores and timed performances on all tasks were registered. The maximum time allowed to perform each task was 480 seconds (eight minutes). When the maximum time has exceeded, the child was allowed to finish the task (if wanted) and the maximum possible time was given (480 s). The maximum time was predetermined based on a pilot study with six children with SMA-I. This pilot study showed that after 480 s performing a figure-matching task, children did not benefit from additional time.

2.3.1. Task 1: matching objects, animals and fruits

This task had two parts. In part A, children were asked to match two identical red cars, black and white balls and blue butterflies. Each figure was displayed in a yellow square. After that, in part B, children had to match fruits (bananas, lemons, oranges, grapes, strawberries, melons, apples and kiwis). Each figure was displayed in a black square. The maximum possible total score was 11 points.

2.3.2. Task 2: matching figures and colors

In this task, children were asked to match a figure with its corresponding color. The figures were butterfly – blue, apple – green, car – black, basketball – orange, banana – yellow, and lion – beige. Each figure was displayed in a white square. The maximum possible score was 6 points.

2.3.3. Task 3: matching letters

In this task, children had to match upper and lower cases, written in black: Aa, Bb, Dd, Ee, Gg, Mm, Hh, Rr, Tt and Ll. Each figure was displayed in a black square. The maximum possible score was 10 points.

2.3.4. Task 4: matching numbers

In this task, children had to match numerals in words and Arabic from one – 1 to ten – 10. The maximum possible score was 10 points.

2.4. Statistical analysis

Analyses of variance (ANOVA) compared the scores of SMA-I group (n = 12) and control group (n = 12) on tasks 1 and 2. The Mann–Whitney U test compared the scores of SMA-I group (n = 6) and control group (n = 6) on tasks 3 and 4. The U test is recommended for small samples (around 5 individuals)

influences cognitive functions, the severe motor paralysis in children with SMA-I may be related to cognitive delay.

Eye movement detection systems can be an efficient communication tool for children with SMA-I [7]. However, no cognitive function testing has been performed so far with any standardized tool. Few studies discussed the cognitive performance of children with SMA-I. Some argue that cognition is preserved or even optimized [11–16]. Other studies hypothesized (but did not investigate) the presence of some cognitive impairment in this population [13,17].

All children have the right to be assessed and treated. However, health professionals currently face several difficulties evaluating, treating and following the cognitive performance of children with SMA-I. For this reason, a cognitive assessment task was developed and tested with an eye tracker device (Tobii-PCEye 2013) [18]. The pair-matching tasks aimed to measure the cognitive performance on a visual-cognitive-motor task, providing standardized scores and timed performances.

We hypothesized that children with SMA-I would have difficulty performing figure, number, and letter matching tasks and that the performance on such tasks would be correlated to the performance on clinical tests. The aim of this study was to evaluate the cognitive performance on pair-matching tasks and to investigate possible relationships of pair-matching performance and clinical scales in children with SMA-I.

2. Method

The study was approved by the Institution Ethics Committee (protocol 46899015.1.0000.0076). At least one parent of each child (mother or father) received information about the study

and signed a consent form prior to the participation of their children.

2.1. Participants

Twenty-four children between three and nine years old (Table 1) were assessed, 12 with diagnosis of SMA-I (homozygous deletion of *SMN1* gene) with a type I clinical phenotype (i.e. onset of manifestations before 6 months of age and not able to sit unassisted) [19] and 12 age- and sex-matched controls (nine boys and three girls in each group), with normal or corrected to normal vision. All children with SMA-I from a Brazilian Association of SMA (Non-Governmental Institution *AME Viver*) were invited thru letter and the parents of 12 children agreed to participate in this study. Children aged 3–9 years old from two schools of the same city were invited thru letter and 37 parents manifested availability to participate. Twelve children were selected to form a sex- and age-matched control group and parents gave informed consent prior to evaluation.

We considered as inclusion criteria for both groups (1) having clinical stable condition, (2) having ages between three and nine years old, (3) being born with Apgar score above seven, (4) not having previous history of epilepsy, hypoxemia, repeated bronchopneumonia (more than two episodes in one year) or any clinical/genetic disorder, and (5) attending school regularly.

Although we considered onset of manifestations before 6 months of age and not being able to sit unassisted as inclusion criteria for children with SMA-I [19], it is important to mention that all children with SMA-I showed global hypotonia, facial

Table 1
Performance on tasks 1–4 (number and percentage of correct answers and time).

Children			Task 1 (11 trials)			Task 2 (6 trials)			Task 3 (10 trials)			Task 4 (10 trials)		
No.	Group	Age	Correct (n)	Correct (%)	Time (s)	Correct (n)	Correct (%)	Time (s)	Correct (n)	Correct (%)	Time (s)	Correct (n)	Correct (%)	Time (s)
1	SMA-I	36	0	0	0	0	0	0	0	0	480	0	0	480
2	SMA-I	38	4	36	480	0	0	480	0	0	480	0	0	480
3	SMA-I	44	0	0	480	0	0	480	0	0	480	0	0	480
4	SMA-I	51	3	27	480	0	0	480	0	0	480	0	0	480
5	SMA-I	54	11	100	478	6	100	408	0	0	480	0	0	480
6	SMA-I	68	1	9	480	0	0	480	0	0	480	0	0	480
7	SMA-I	84	3	27	480	2	34	480	0	0	480	0	0	480
8	SMA-I	86	11	100	480	6	100	260	1	10	480	1	10	480
9	SMA-I	94	3	27	480	1	17	480	0	0	480	0	0	480
10	SMA-I	101	11	100	247	6	100	341	0	0	480	1	10	480
11	SMA-I	106	11	100	286	6	100	281	0	0	480	2	20	480
12	SMA-I	108	4	36	480	0	0	480	0	0	480	0	0	480
1	Control	34	11	100	366	6	100	225	0	0	480	0	0	480
2	Control	36	11	100	217	6	100	229	2	20	480	0	0	480
3	Control	45	11	100	268	6	100	110	0	0	480	0	0	480
4	Control	45	11	100	123	6	100	123	0	0	0	0	0	0
5	Control	60	11	100	118	6	100	132	1	10	480	0	0	480
6	Control	83	11	100	63	6	100	67	10	100	244	0	0	480
7	Control	85	11	100	86	6	100	73	5	50	480	0	0	480
8	Control	85	11	100	86	6	100	40	10	100	227	10	100	206
9	Control	86	11	100	206	6	100	151	2	20	480	2	20	480
10	Control	106	11	100	68	6	100	42	10	100	89	10	100	114
11	Control	119	11	100	81	6	100	38	10	100	70	10	100	68
12	Control	119	11	100	94	6	100	46	10	100	68	10	100	68

Fig. 1. Percentage of correct answers and timed performance of SMA-I and control groups on tasks 1 and 2. Scores and timed performance of SMA-I and control groups on tasks 1 and 2 ($n = 12$ in each group).

[25]. The number of correct answers on each task, of each group, for each stimulus was registered and compared by chi-square tests.

The relationships between the scores on clinical scales (CHOP INTEND, PEDI and PedsQL) and the scores on the pair-matching tasks 1 and 2 were investigated by Spearman correlation tests in children with SMA-I. As only six children with SMA-I performed tasks 3 and 4, this investigation was not possible with these scores. Correlations with coefficients $r > 0.69$ were considered strong; correlations with coefficients $0.70 > r > 0.39$ were considered moderate.

3. Results

The clinical and experimental assessment protocol of children with SMA-I and controls is displayed in Table 1. All children were able to calibrate and use the eye tracker.

Two children from the SMA-I group could not perform task 1 and scored 0 (two boys aged three and four years old). Six children with SMA-I scored between 1 and 4 and four children scored 11 (100%) on task 1. All children of the control group scored 11 on task 1. On task 2, six children with SMA-I scored 0, one child scored 1, one child scored 2 and four children scored 6 (100%). All children from the control group scored 6 (100%) on the second task.

SMA-I and control groups were compared by ANOVA on tasks 1 and 2, considering the percentage of correct answers and the timed performance as dependent variables. There was a significant difference between the percentage of correct answers and the time performances of the SMA-I and control groups in all pair-matching tasks. The SMA-I group had a lower percentage of correct answers, $F(1,22) = 21.09$; $p < 0.001$; effect size = 0.489. There were less correct answers on task 2 than on task 1, $F(1,22) = 4.66$; $p = 0.041$; effect size = 0.193. There was an interaction between groups and tasks, $F(1,22) = 4.56$; $p = 0.044$;

effect size = 0.172. As an interaction was found, *post hoc* Tukey tests were run (Fig. 1).

Tukey tests showed that SMA-I group had a lower percentage of correct answers, compared to the control group (task 1: $p = 0.002$; task 2: $p < 0.001$). The SMA-I group had a lower percentage of correct answers on task 2 than on task 1 ($p = 0.030$). The control did not show a significant difference between the percentage of correct answers on tasks 1 and 2 ($p = 0.999$) (Fig. 1).

SMA-I group showed longer times on tasks 1 and 2, $F(1,22) = 96.31$; $p < 0.001$; effect size = 0.814. Timed performance on task 2 was longer than on task 1, $F(1,22) = 4.83$; $p = 0.039$; effect size = 0.180. There was no interaction between groups and tasks, $F(1,22) = 0.88$; $p = 0.359$; effect size = 0.038, therefore, *post hoc* Tukey tests were not run.

The number of correct answers of each group for each stimulus of tasks 1A and 1B is displayed in Table 2. Chi-square tests showed no significant differences between the responses to the three stimuli of the trials of task 1A (butterfly, car and ball). However, the SMA-I and control groups responded differently to stimuli of task 1B (banana, lemon, orange, grape, strawberry, melon, apple, kiwi) and significant differences in the number of correct answers were found (Table 2).

The SMA-I and control groups responded differently to stimuli of task 2 (butterfly, apple, car, ball, banana, lion) and significant differences in the number of correct answers were found. The control group showed a significantly higher number of correct answers for these trials (Table 3).

Tasks 3 and 4 were performed only by children above six years of age, because these tasks involved reading skills. As there were only six children aged seven to nine years old in each group, the non-parametric Mann–Whitney U tests were used for the comparisons.

On task 3, only a seven year old boy from the SMA-I group scored 1 and the other children scored 0. In the control group,

Table 3
Number of correct answers on task 2.

Child	Group	Age (months)	Butterfly	Apple	Car	Ball	Banana	Lion	Total
1	SMA-I	36	0	0	0	0	0	0	0
2	SMA-I	38	0	0	0	0	0	0	0
3	SMA-I	44	0	0	0	0	0	0	0
4	SMA-I	51	0	0	0	0	0	0	0
5	SMA-I	54	1	1	1	1	1	1	6
6	SMA-I	68	0	0	0	0	0	0	0
7	SMA-I	84	0	1	1	0	0	0	2
8	SMA-I	86	1	1	1	1	1	1	6
9	SMA-I	94	1	0	0	0	0	0	1
10	SMA-I	101	1	1	1	1	1	1	6
11	SMA-I	106	1	1	1	1	1	1	6
12	SMA-I	108	0	0	0	0	0	0	0
Total			5	5	5	4	4	3	27
1	Control	34	1	1	1	1	1	1	6
2	Control	36	1	1	1	1	1	1	6
3	Control	45	1	1	1	1	1	1	6
4	Control	45	1	1	1	1	1	1	6
5	Control	60	1	1	1	1	1	1	6
6	Control	83	1	1	1	1	1	1	6
7	Control	85	1	1	1	1	1	1	6
8	Control	85	1	1	1	1	1	1	6
9	Control	86	1	1	1	1	1	1	6
10	Control	106	1	1	1	1	1	1	6
11	Control	119	1	1	1	1	1	1	6
12	Control	119	1	1	1	1	1	1	6
Total			12	12	12	12	12	12	72
Chi-square (SMA-I X control) p			0.0017*	0.0017*	0.0017*	0.0017*	0.0005*	0.0005*	0.0001*

* Significant difference ($p < 0.050$).

proper stimulation can cause or increase developmental impairments. Regardless of being primary or secondary to the disease, the present study showed difficulty on a pair-matching task on children with SMA-I.

Task complexity increased gradually from task 1 to 4, as the difference between the performances of the groups. This shows that even children with SMA-I who regularly go to school and receive formal education may have difficulty retaining,

Fig. 2. Percentage of correct answers and timed performance of SMA-I and control groups on tasks 3 and 4. Scores of SMA-I and control groups on tasks 3 and 4 ($n = 6$ in each group).

Table 2
Number of correct answers on tasks 1A and 1B.

Child	Group	Age (months)	1A Butterfly	1A Car	1A Ball	1B Banana	1B Lemon	1B Orange	1B Grape	1B Strawberry	1B Melon	1B Apple	1B Kiwi	Total
1	SMA-I	36	0	0	0	0	0	0	0	0	0	0	0	0
2	SMA-I	38	1	1	1	0	0	0	0	0	0	1	0	4
3	SMA-I	44	0	0	0	0	0	0	0	0	0	0	0	0
4	SMA-I	51	1	1	1	0	0	0	0	0	0	0	0	3
5	SMA-I	54	1	1	1	1	1	1	1	1	1	1	1	11
6	SMA-I	68	1	0	0	0	0	0	0	0	0	0	0	1
7	SMA-I	84	1	1	1	0	0	0	0	0	0	0	0	3
8	SMA-I	86	1	1	1	1	1	1	1	1	1	1	1	11
9	SMA-I	94	1	1	1	0	0	0	0	0	0	0	0	3
10	SMA-I	101	1	1	1	1	1	1	1	1	1	1	1	11
11	SMA-I	106	1	1	1	1	1	1	1	1	1	1	1	11
12	SMA-I	108	1	1	1	0	0	1	0	0	0	0	0	4
Total			10	9	9	4	4	5	4	4	4	5	4	62
1	Control	34	1	1	1	1	1	1	1	1	1	1	1	11
2	Control	36	1	1	1	1	1	1	1	1	1	1	1	11
3	Control	45	1	1	1	1	1	1	1	1	1	1	1	11
4	Control	45	1	1	1	1	1	1	1	1	1	1	1	11
5	Control	60	1	1	1	1	1	1	1	1	1	1	1	11
6	Control	83	1	1	1	1	1	1	1	1	1	1	1	11
7	Control	85	1	1	1	1	1	1	1	1	1	1	1	11
8	Control	85	1	1	1	1	1	1	1	1	1	1	1	11
9	Control	86	1	1	1	1	1	1	1	1	1	1	1	11
10	Control	106	1	1	1	1	1	1	1	1	1	1	1	11
11	Control	119	1	1	1	1	1	1	1	1	1	1	1	11
12	Control	119	1	1	1	1	1	1	1	1	1	1	1	11
Total			12	12	12	12	12	12	12	12	12	12	12	132
Chi-square (SMA-I X control) p			0.1397	0.0641	0.0641	0.0005*	0.0005*	0.0017*	0.0005*	0.0005*	0.0005*	0.0017*	0.0005*	0.0001*

* Significant difference ($p < 0.050$).

one child scored 2, one child scored 5 and four children scored 10 (100%). The SMA-I group showed a lower percentage of correct answers ($p = 0.003$; $Z = -2.96$) and longer times ($p = 0.028$; $Z = 2.19$) than the control group (Fig. 2).

On task 4, three children with SMA-I scored between 1 and 2 and the others scored 0. In the control group, one child scored 2, one scored 0 and four children scored 10 (100%). The SMA-I group showed a lower percentage of correct answers ($p = 0.037$; $Z = -2.08$) and longer times ($p = 0.028$; $Z = 2.20$) than the control group (Fig. 2).

The SMA-I group showed a floor effect in the percentage of correct answers (most children showed a low percentage of correct answers), while the control group showed higher variability. The SMA-I group showed a ceiling effect on timed performance (most children showed long times), while the control group showed higher variability (Fig. 2).

The number of correct answers of each group for each stimulus of tasks 3 and 4 is displayed in Tables 4 and 5. Chi-square tests showed significant differences between the responses to all letters of the trials of task 3, except letter T (Table 4). The SMA-I and control groups responded differently to most stimuli of task 4 (numbers 1, 3, 5, 6, 8, 9, 10) and the control group showed a significantly higher number of correct answers for these numbers (Table 5).

The relationships between the percentage of correct answers on tasks 1 and 2 and the scores on the clinical scales of children with SMA-I were tested by Spearman correlation tests

(Table 6). Children with higher scores on social function domain of PEDI also showed a higher percentage of correct answers on task 1 ($r = 0.81$; $p = 0.001$) and task 2 ($r = 0.66$; $p = 0.020$).

4. Discussion

This study investigated the pair-matching performance of children with SMA-I, assessed by an eye tracker device. As eye movements are preserved in children with SMA-I [7], they can be a way of communicating with these children [7,18] and evaluating them. The cognitive skills of most children with SMA-I are not formally evaluated due to their difficulties answering to cognitive tests.

We were able to use the eye tracker with children with strabismus. The tasks could be solved even by three year old children, however children aged four or older showed better understanding and cooperation. The pair-matching tasks showed significant differences between SMA-I and control groups. Children with SMA-I showed poorer performance and required longer times to complete the tasks, compared to the control group. There are studies that argue that SMA-I is strictly a motor disease and does not cause cognitive impairment [11,12]. It is unknown if the genetic errors that cause SMA-I may also cause cognitive impairment or if the lack of environmental interaction is responsible for the difficulties observed in the present study. Considering both possibilities, the lack of cognitive assessment and follow-up and the lack of

Table 4
Number of correct answers on task 3.

Child	Group	Age (months)	A	B	D	E	G	H	L	M	R	T	Total
7	SMA-I	84	0	0	0	0	0	0	0	0	0	0	0
8	SMA-I	86	0	0	0	0	0	0	0	0	0	1	1
9	SMA-I	94	0	0	0	0	0	0	0	0	0	0	0
10	SMA-I	101	0	0	0	0	0	0	0	0	0	0	0
11	SMA-I	106	0	0	0	0	0	0	0	0	0	0	0
12	SMA-I	108	0	0	0	0	0	0	0	0	0	0	0
Total			0	0	0	0	0	0	0	0	0	1	1
7	Control	85	1	1	0	0	1	1	0	1	0	0	5
8	Control	85	1	1	1	1	1	1	1	1	1	1	10
9	Control	86	0	0	0	1	0	0	1	0	0	0	2
10	Control	106	1	1	1	1	1	1	1	1	1	1	10
11	Control	119	1	1	1	1	1	1	1	1	1	1	10
12	Control	119	1	1	1	1	1	1	1	1	1	1	10
Total			5	5	4	5	5	5	5	5	4	4	47
Chi-square (SMA-I X control) p			0.0034*	0.0034*	0.0143*	0.0034*	0.0034*	0.0034*	0.0034*	0.0034*	0.0143*	0.0790	0.0001*

* Significant difference ($p < 0.050$).

processing or expressing cognitive information. Besides, children with SMA-I may start school later. They also have more comorbidities and miss more classes, which can impair learning.

The stimuli analysis showed that the number of pairs influenced the performance. Task 1A showed a higher number of correct answers than the other tasks. As 1A only required attending to six stimuli (3 pairs), this task was less challenging for divided and selective attention. Tasks 1B, 2, 3 and 4 had 6–10 pairs of stimuli; therefore, they required much more attention for pair-matching and the attentional capacity limits were exceeded. Stimuli may have competed for attentional resources, e.g. due to superposed cortical representations [26]. If the child was engaged to find a pair for a stimulus, a similar stimulus may have acted as a distractor (e.g. melon and lemon, which had similar shape and color). The central bottleneck may have limited the number of stimuli that could be simultaneously processed [27].

In general, older children showed a higher number of correct answers than younger children. In tasks 3 and 4, even in the

control group, younger children showed some incorrect answers, because some children are still learning how to read at the age of seven years. However, regardless of the nature of the stimuli, children with SMA-I showed significantly poorer performance than control children. As the development process and the way children generalize their knowledge is complex and unpredictable, it is difficult to anticipate which stimuli will be more familiar to children with or without SMA-I.

It was interesting to observe that the pair-matching performance was related to the social function. This reinforces the idea that children with a higher social function are more frequently exposed to a broader variety of visual stimuli, which may have facilitated the tasks. Pair-matching involves focused attention and executive function, optimized by enriched environments and interaction [28].

It is possible and necessary to develop a cognitive assessment protocol to evaluate and follow children with SMA-I. Even in children born with preserved cognition, it is possible that the lack of cognitive stimulation generates cognitive delay. The tasks used in the present study can assess,

Table 5
Number of correct answers on task 4.

Child	Group	Age (months)	1	2	3	4	5	6	7	8	9	10	Total
7	SMA-I	84	0	0	0	0	0	0	0	0	0	0	0
8	SMA-I	86	0	1	0	0	0	0	0	0	0	0	1
9	SMA-I	94	0	0	0	0	0	0	0	0	0	0	0
10	SMA-I	101	0	0	0	0	0	0	0	0	1	0	1
11	SMA-I	106	0	0	0	0	1	0	0	0	0	1	2
12	SMA-I	108	0	0	0	0	0	0	0	0	0	0	0
Total			0	1	0	0	1	0	0	0	1	1	4
7	Control	85	0	0	0	0	0	0	0	0	0	0	0
8	Control	85	1	1	1	1	1	1	1	1	1	1	10
9	Control	86	0	0	0	1	0	0	1	0	0	0	2
10	Control	106	1	1	1	1	1	1	1	1	1	1	10
11	Control	119	1	1	1	1	1	1	1	1	1	1	10
12	Control	119	1	1	1	1	1	1	1	1	1	1	10
Total			4	4	4	5	4	4	5	4	4	4	42
Chi-square (SMA-I X control) p			0.0143*	0.0790	0.0143*	0.0790	0.0143*	0.0034*	0.0790	0.0143*	0.0034*	0.0143*	0.0790

* Significant difference ($p < 0.050$).

Table 6

Correlation between the number of correct answers on tasks 1 and 2 and clinical scales.

	CHOP INTEND	PEDI self care	PEDI social function	PedsQL
Task 1	r = 0.026 p = 0.935	r = 0.341 p = 0.277	r = 0.808** p = 0.001**	r = 0.271 p = 0.394
Task 2	r = 0.082 p = 0.799	r = 0.327 p = 0.298	r = 0.659* p = 0.020*	r = 0.265 p = 0.405

* Moderate significant correlation.

** Strong significant correlation.

and possibly monitor children with SMA-I. The use of proper equipment (e.g. eye trackers) for assessment and interaction is fundamental to prevent cognitive delay and optimize cognitive performance as a therapeutic approach.

Although voluntary movements are poor, some other movements could be explored as responses to cognitive assessing children with SMA-I (e.g. head inclination; shoulder elevation/protraction; hip adduction/abduction; ankle, toe, wrist, finger extension/flexion). If voluntary movements become functional, with environmental modifications as consequences, they may be preserved for longer periods. Future studies can investigate if higher environmental interaction will result in higher functional independence and higher quality of life for children with SMA-I and their families.

Children discharged from hospitals to home care show lower risk of infections. In home care, children receive all professional assistance and life support equipment, such as mechanical ventilation, tracheostomy tube, gastrostomy tube, suction machine, suction catheters, and gloves. With this support, life expectancy has been increasing. Therefore, new approaches must be taken not only for survival but also for providing a higher functional independence and a better quality of life for children with SMA-I. Public health policies must ensure that children diagnosed with SMA-I receive not only mechanical ventilation but also eye tracking equipment and software for interaction. Software can not only help teachers learn these children, but also motivate learning, communication and recreational activities for these children.

A previous study showed that higher environmental interaction is associated to a higher quality of life in children [15]. A previous study with six children with SMA and one child with congenital muscular dystrophy investigated the impact of environmental interaction on quality of life when power mobility was precociously proposed. The quality of life was assessed with children and with their parents using PedsQL. The study showed that children with more difficulty exploring the environment also had lower cognitive performance, social function and quality of life. After the introduction of power mobility, parents had more positive feelings about their children, regarding behavioral and independence aspects. Therefore, there was a change on their perception about their children [15]. Children with SMA-I are currently living longer and health professionals must consider technology to increase their functional independence and quality of life [15,29].

As a limitation of the study, we must mention that the lack of familiarity with some stimuli, the arbitrary selection of stimuli,

the equipment and the therapist may have impaired performance of both groups. Studies with larger populations will provide further information about cognitive performance and the possible relationship with SMA-I genetic subtypes. Besides, longitudinal follow-up and other cognitive tasks may clarify the questions raised by the present study about the cognitive development of children with SMA-I. The present study shows a very specific aspect of cognitive performance, but opens a new discussion whether cognitive delay would be primary (genetic) or secondary (environmental) in SMA-I.

Children with SMA-I showed difficulty matching pairs of figures, numbers and letters. The pair-matching performance was related to the social function. The restricted interaction with the environment, due to severe paralysis and poor communication, may be associated with such difficulty.

Acknowledgements

CIVIAM BRASIL ceded Tobii-PCEye (Fabricator: Tobii Dynavox/City: Danderyd/Country: Sweden) for four months for the assessment of patients with SMA-I and controls.

PedsQL ceded free for this study.

Celso Masahiro Shimabukuro – technical consultancy.

Antonio Diaz Tula – statistical consultancy.

Rafael Alves dos Santos – technical consultancy.

Felipe Knöller Bastos – technical consultancy.

Juliana Rosa Messias – NGO AMEVIVER.

References

- [1] Arnold WD, Porensky PN, MCGovern VL, Iyer CC, Duque S, Li X, et al. Electrophysiological biomarkers in spinal muscular atrophy: preclinical proof of concept. *Ann Clin Transl Neurol* 2013;1(1):34–44.
- [2] Finkel RS, McDermott MP, Kaufmann P, Darras BT, Chung WK, Sproule DM, et al. Observational study of spinal muscular atrophy type I and implications for clinical trials. *Neurology* 2014;83(9):810–17.
- [3] Montes J, Glanzman AM, Mazzone ES, Martens WB, Dunaway S, Pasternak A, et al. Spinal muscular atrophy functional composite score: a functional measure in spinal muscular atrophy. *Muscle Nerve* 2015;52(6):942–7.
- [4] Wang CH, Finkel RS, Bertini ES, Schroth M, Simonds A, Wong B, et al. Consensus statement for standard of care in spinal muscular atrophy. *J Child Neurol* 2007;22(8):942–7.
- [5] Finkel RS, Bertini E, Muntoni F, Mercuri E, ENMC SMA Workshop Study Group. 209th ENMC International Workshop: outcome measures and clinical trial readiness in spinal muscular atrophy 7–9 November 2014, Heemskerk, The Netherlands. *Neuromuscul Disord* 2015;25(7):593–602.
- [6] Finkel RS, Weiner DJ, Mayer OH, McDonough JM, Panitch HB. Respiratory muscle function in infants with spinal muscular atrophy type I. *Pediatr Pulmonol* 2014;49(12):1234–42.
- [7] Kubota M, Sakakihara Y, Uchiyama Y, Nara A, Nagata T, Nitta H, et al. New ocular movement detector system as a communication tool in ventilator-assisted Werdnig-Hoffmann disease. *Dev Med Child Neurol* 2000;42(1):61–4.
- [8] Qian Y, McGraw S, Henne J, Jarecki J, Hobby K, Yeh W. Understanding the experiences and needs of individuals with spinal muscular atrophy and their parents: a qualitative study. *BMC Neurol* 2015;15:217.
- [9] Thuetell MJ, Erik PP, Leigh RJ. Abnormal eye movements in Kennedy disease. *Neurology* 2009;72(17):1528–30.
- [10] Townend GS, Marschik PB, Smeets E, van de Berg R, van den Berg M, Curfs LM. Eye gaze technology as a form of augmentative and alternative communication for individuals with Rett syndrome: experiences of families in the Netherlands. *J Dev Phys Disabil* 2016;28:101–12.

- [11] Billard C, Gillet P, Signoret JL, Uicaut E, Bertrand P, Fardeau M, et al. Cognitive functions in Duchenne muscular dystrophy: a reappraisal and comparison with spinal muscular atrophy. *Neuromuscul Disord* 1992;2(5–6):371–8.
- [12] Billard C, Gillet P, Barthez M-A, Hommet C, Bertrand P. Reading ability and processing in Duchenne muscular dystrophy and spinal muscular atrophy. *Dev Med Child Neurol* 1998;40(1):12–20.
- [13] von Gontard A, Zerres K, Backes M, Laufersweiler-Plass C, Wendland C, Melchers P, et al. Intelligence and cognitive function in children and adolescents with spinal muscular atrophy. *Neuromuscul Disord* 2002;12(2):130–6.
- [14] Rivière J, Lécuyer R. Spatial cognition in young children with spinal muscular atrophy. *Dev Neuropsychol* 2002;21(3):273–83.
- [15] Dunaway S, Montes J, O'Hagen J, Sproule DM, De Vivo DC, Kaufmann P. Independent mobility after early introduction of a power wheelchair in spinal muscular atrophy. *J Child Neurol* 2012;28(5):576–82.
- [16] Oudgenoeg-Paz O, Rivière J. Self-locomotion and spatial language and spatial cognition: insights from typical and atypical development. *Front Psychol* 2014;5:521.
- [17] D'Angelo MG, Bresolin N. Cognitive impairment in neuromuscular disorders. *Muscle Nerve* 2006;34(1):16–33.
- [18] CIVIAM. Tobii PC eye to go: control the computer with your eyes [Tobii PC eye to go: controle o computador com os olhos]. Available from: <http://www.civiam.com.br/civiam/index.php/tobii/peye-tobii-controlar-computador-olhos-mouse-teclado-virtual.html>. [Accessed 20 September 2013].
- [19] Munsat TL, Davies KE. International SMA consortium meeting 26–28 June 1992, Bonn, Germany. *Neuromuscul Disord* 1992;2(5–6):423–8.
- [20] Glanzman AM, Mazzone E, Main M, Pelliccioni M, Wood J, Swoboda KJ, et al. The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND): test development and reliability. *Neuromuscul Disord* 2010;20(3):155–61.
- [21] Feldman AB, Haley SM, Coryell J. Concurrent and construct validity of the Pediatric Evaluation of Disability Inventory. *Phys Ther* 1990;70(10):602–10.
- [22] Davis SE, Hynan LS, Limbers CA, Andersen CM, Greene MC, Varni JW, et al. The PedsQL in pediatric patients with Duchenne muscular dystrophy: feasibility, reliability, and validity of the Pediatric Quality of Life Inventory Neuromuscular Module and generic core scales. *J Clin Neuromuscul Dis* 1998;11(3):97–109.
- [23] Iannaccone ST, Hynan LS, Morton A, Buchanan R, Limbers CA, Varni JW. The PedsQL™ in pediatric patients with spinal muscular atrophy: feasibility, reliability, and validity of the Pediatric Quality of Life Inventory™ Generic Core Scales and Neuromuscular Module. *Neuromuscul Disord* 2009;19(12):805–12.
- [24] Kaufmann P, McDermott MP, Darras BT, Finkel RS, Sproule DM, Kang PB. Prospective cohort study of spinal muscular atrophy types 2 and 3. *Neurology* 2012;79(18):1889–97.
- [25] Winter JCF. Using the Student's t-test with extremely small sample sizes. *Pract Assess Res Eval* 2013;18(10):1–12.
- [26] Roland PE, Zilles K. Structural divisions and functional fields in the human cerebral cortex. *Brain Res Brain Res Rev* 1998;26(2–3):87–105.
- [27] Pashler H. Dual-task interference in simple tasks: data and theory. *Psychol Bull* 1994;116(2):220–44.
- [28] Dishion TJ. Social influences on executive functions development in children and adolescents: steps toward a social neuroscience of predictive adaptive responses. *J Abnorm Child Psychol* 2016;44(1):57–61.
- [29] Kocova H, Dvorackova O, Vondracek P, Haberlova P. Health-related quality of life in children and adolescents with spinal muscular atrophy in the Czech Republic. *Pediatr Neurol* 2014;50(6):591–4.

4 GENERAL DISCUSSION

The present study aimed to investigate the cognitive development of children with SMA (Study 1) and to describe the visual, cognitive and motor performance of children with SMA-I (Study 2).

In Study 1, we found a high heterogeneity of assessment protocols. Nine studies met inclusion/ exclusion criteria of our systematic review, but each one used different scales to evaluate the cognitive performance. Only three studies¹⁹⁻²¹ used the same task: the Wechsler Intelligence Scale for Children (WISC). WISC assesses verbal and perceptual-motor skills. The operational intelligence quotient (IQ) involves completing figures and assembling cubes. The verbal IQ evaluates arithmetic and vocabulary¹⁹⁻²¹.

Therefore, we evaluated the studies with the risk of bias in non-randomized studies – of interventions (ROBINS-I). ROBINS-I describes seven domains, the first two referring to the pre-intervention phase, one in the intervention phase and four domains in the post-intervention phase. The endpoint is classified into four options: low, moderate, serious or critical risk of bias²⁷. Three had low risk of bias, five presented moderate risk of bias and one presented a serious risk of bias.

Two studies evaluated cognitive performance with Tobii PCEye^{16,28}. Ocular movements can provide responses in tasks that involve attention and perception, e.g. following moving objects on the screen, matching figures.

These tasks also evaluate the ability of solving problems (executive function)¹⁶. The studies with eye tracking devices showed that cognitive deficit may be present in children with spinal muscular atrophy, especially type I, due to environmental interaction restrictions^{16,28}. Visual performance has been very poorly explored in people with SMA-I. Considering that visual control may compensate for the motor restrictions imposed by tetraplegia, future studies should address this issue. In clinical practice we observe a higher frequency of strabism in people with SMA-I. However, we did not find studies that provided detailed description about cranial nerves testing and outcomes in this population.

There may be differences between the cognitive performance and the type of SMA that the child presents. This hypothesis was previously suggested by Sieratzki and Woll (2002)²⁹, von Gontard et al. (2002)¹⁹, Chung, Wong & Ip (2004)²⁵ and Polido et al. (2017)¹⁶. However, the first two authors explored tasks that involved intelligence, cognitive function, verbal and spatial perception, which are preserved in children with SMA-I. The last two authors described tasks involving spatial attention and executive function, which were difficult for children with SMA-I.

Many studies used tasks that required writing and reading abilities. These protocols excluded children with poor motor performance and/or who could not speak. Others compared children with SMA with children with Duchenne, which may have overestimated the skills of children with SMA^{20,21,30}.

In Study 2, we used an eye tracker, and did not exclude children that needed mechanical ventilation/ tracheostomy and/or who could not speak. We

evaluated attention, perception and executive function. These cognitive tasks can be tested regularly to evaluate or follow children with SMA. They can also evaluate the effectiveness of interventions or stimulate cognitive abilities. Monitoring the natural course of the disease also allows the detection of changes, providing baseline for comparisons.

We observed that children with better social function, who effectively participate in the community, showed better cognitive performance. This finding reinforces the importance of including these children in schools and community. A higher social participation will contribute to improving the quality of life of children with SMA.

This study expands the theoretical background about the cognitive performance of children with SMA and contributes to clinical practice. Most approaches focus on respiratory and motor areas; however, interdisciplinarity is a key component in SMA treatment. The assessment protocol of the present study can be used by any health professional.

5 CONCLUSION

Considering the findings of Study 1, we can conclude that (1) the cognitive performance of children with SMA is heterogeneous; (2) children with more severe muscular weakness (diagnosed as SMA-I) tended to show more cognitive impairment than children with better motor outcomes; (3) few studies investigated cognitive outcomes in children and adolescents with SMA.

Study 2 showed that (1) children with SMA-I presented more errors than typically developing children; (2) children with SMA-I required longer times to perform cognitive tasks, even with the eye tracking device and (3) the eye tracking device can evaluate and stimulate their cognitive repertoire.

Therefore, the cognitive development of children with SMA should be followed, especially in children with SMA-I. More studies should evaluate and, if necessary, intervene to prevent cognitive impairment in people with SMA. The proper cognitive development will facilitate autonomy and interaction.

6 REFERÊNCIAS BIBLIOGRÁFICAS

- 1 Battista V, Schroth MK, Apkon S, Battista J, Clark J, Crawford T, et al. SMA Care Series – Understanding Spinal Muscular Atrophy (SMA). Disponível em: <<http://www.curesma.org/documents/support--care-documents/understanding-sma.pdf>> Acessado em: 10 de novembro de 2016.
- 2 Fagoaga J, Girabent-Farrés M, Bagur-Calafat C, Febrer A, Steffensen BF. Evaluación funcional para personas no ambulantes afectas de atrofia muscular espinal y distrofia muscular de Duchenne. Traducción y validación de la escala Egen Klassifikation 2 para la población española. *Rev Neurol*. 2015; 60: 439-446.
- 3 Krosschell KJ, Maczulskib JA, Crawfordc TO, Scottd C, Swobodae KJ. A modified Hammersmith functional motor scale for use in multicenter research on spinal muscular atrophy. *Neuromuscul Disord*. 2006; 16: 417–426.
- 4 Glanzman AM, Mazzone ES, Main M, Pelliccioni M, Wood J, Swoboda KJ, et al. The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND): test development and reliability. *Neuromuscul Disord*. 2010; 20(3): 155–61.
- 5 Mazzone ES, Montes J, Main M, Mayhew M, Ramsey D, Glanzman AM, et al. Old measures and new scores in SMA patients. *Muscle and Nerve*. 2015 Sep; 52(3): 435-7. Doi: 10.1002/mus.24748.
- 6 Krosschell KJ, Scott CB, Maczulskib JA, Lewelt AJ, Reyna SP, Swobodae KJ. Reliability of the Modified Hammersmith Functional Motor Scale in Young Children with Spinal Muscular Atrophy. *Muscle Nerve*. 2011; 44: 246–251.
- 7 De Sanctis R, Coratti G, Pasternak A, Montes J, Pane M, Mazzone ES, et al. Developmental milestones in type I spinal muscular atrophy. *Neuromuscular Disorders*. 2016; 26: 754–759.

8 Reed UC and Zanoteli E. Therapeutic advances in 5q-linked spinal muscular atrophy. Avanços terapêuticos na atrofia muscular espinhal ligada ao cromossomo 5q. *Arquivos de neuropsiquiatria*. In press.

9 Finkel RS, Chiriboga CA, Vajsar J, Day JW, Montes J, De Vivo DC, et al. Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study. *Lancet*. 2016 Dec; 388 (10063): 3017-26. [https://doi.org/10.1016/S0140-6736\(16\)31408-8](https://doi.org/10.1016/S0140-6736(16)31408-8).

10 Finkel RS, Mercuri E, Darras BT, Connolly AM, Kuntz NL, Kirschner J, et al. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. *N Engl J Med*. 2017 Nov; 377 (18): 1723-32. <https://doi.org/10.1056/NEJMoa1702752>.

11 Caligari M, Godi M, Guglielmetti S, Franchignoni F, Nardone A. Eye tracking communication devices in amyotrophic lateral sclerosis: impact on disability and quality of life. *Amyotroph Lateral Scler Frontotemporal Degener*. 2013 Dec; 14(7-8): 546-52. Doi: 10.3109/21678421.2013.803576.

12 Guimarães MR. Curso de Embriologia Ocular/ 2003. Disponível em: <http://ibb.unesp.br/Home/Departamentos/Morfologia/MaterialDidatico/Embriologia_Ocular.pdf> Acessado em: 2 de fevereiro de 2018.

13 Voos MC, Moura MCS, Caromano FA, Hasue RH. A influência do ambiente no desenvolvimento motor: revisão de literatura. *Temas sobre Desenvolvimento*. 2013; 19 (106).

14 Rago AL. Aprendendo a Aprender... Juntos: O Trabalho em Grupo no Atendimento a Crianças com Deficiência Visual e Deficiência Neuromotora. *Constr psicopedag*. 2009 Dez; v.17 n.15.

15 Belini AEG, Fernandes FDM. Olhar de bebês em desenvolvimento típico:

correlações longitudinais encontradas. *Rev soc bras fonoaudiol*. 2007; 12(3): 165-173.

16 Polido GJ, Barbosa AF, Morimoto CH, Caromano FA, Favero FM, Zanoteli E, Reed UC, Voos MC. Matching pairs difficulty in children with spinal muscular atrophy type I. *Neuromuscular Disorders*. 2017 May; 27: 419-427.

17 Kubota M, Sakakihara Y, Uchiyama Y, Nara A. New ocular movement detector system as a communication tool in ventilator-assisted Werdnig-Hoffmann disease. *Developmental Medicine & Child Neurology*. 2000; 42: 61-64.

18 Cincotti F, Mattia D, Aloise F, Bufalari S, Schalk G, Oriolo G. Non invasive Brain-Computer Interface system: towards its application as assistive technology. *Brain Res Bull*. 2008; 75: 796–803.

19 von Gontard A, Zerres K, Backes M, Laufersweiler-Plass C, Wendland C, Melchers P, et al. Intelligence and cognitive function in children and adolescents with spinal muscular atrophy. *Neuromuscular Disorders*. 2002; 12: 130-6. 9

20 Billard C, Gillet P, Barthez M-A, Hommet C, Bertrand P. Reading ability and processing in Duchenne Muscular dystrophy and spinal muscular atrophy. *Developmental Medicine & child neurology*. 1998; 40: 12-20.

21 Billard C, Gillet P, Signoret JL, Uicaut E, Bertrand P, Fardeau M, et al. Dystrophy: a reappraisal and comparasion with Spinal Muscular Atrophy. *Neuromuscular Disorders*. 1992; 2: 371-8.

22 Rivière J, Lécuyer R, Hickmann M. Early locomotion and the development of spatial language: evidence from young children with motor impairments. *European Journal Of Developmental Psychology* 2009; 6(5): 548-566.

23 Rivière J, Lécuyer R. Spatial cognition in young children with spinal muscular atrophy. *Developmental Neuropsychology*. 2002; 21: 273-83.

- 24 Rivière J, Lécuyer R. The C-not-B error: a comparative study. *Cognitive Developmental* 2003; 18: 285-297.
- 25 Chung BHY, Wong VCN, Ip P. Spinal Muscular Atrophy: Survival Pattern *and Functional Status. Pediatrics*. 2004; 114: 548-53.
- 26 Souza JGS, Pamponet MA, Souza TCS, Pereira AR, Souza AGS, Martins AMEBL. Instrumentos utilizados na avaliação da qualidade de vida de crianças brasileiras. Tools used for evaluation of Brazilian children's quality of life. *Rev Paul Pediatr*. 2014; 32(2): 272-8. Doi: 10.1590/0103-0582201432214313.
- 27 Sterne JAC, Hernán MA, Reeves BC, Savovic J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016: 355; i4919.
- 28 Barja S, Muñoz C, Cancino N, Núñez A, Ubilla M, Sylleros R, Riveros R, Rosas R. Estimulación audiovisual en niños con limitación grave de la motricidad: ¿mejora su calidad de vida? *Revista de Neurología*. 2013; 57: 103-11.
- 29 Sieratzki JS, Woll B. Cognitive function in children with spinal muscular atrophy. *Neuromuscular Disorders*. 2002; 12: 7-8.
- 30 D'Angelo MG, Bresolin N. Cognitive Impairment in Neuromuscular Disorders. *Muscle & Nerve*. 2006; 34: 16-33.

APÊNDICES

Apêndice A – Projeto de Pesquisa

Resumo

Contextualização: Crianças com atrofia muscular espinhal tipo I (AME I, Werdnig-Hoffmann) tinham como expectativa de vida os três anos de idade e, atualmente, estão atingindo idade escolar. A doença é rara e há pouquíssimas referências sobre o desempenho cognitivo de crianças com AME I, devido ao baixo desempenho motor e, na maioria das vezes, também à ausência de comunicação oral. **Objetivos:** Investigar o desempenho cognitivo de crianças com diagnóstico médico de AME I, com atividades realizadas no computador com rastreador de olhar (*eye-tracking*). **Método:** Serão avaliadas 12 crianças com AME I, com idades entre 3 e 10 anos, avaliadas, numa primeira sessão, por meio das escalas PedsQL (Pediatric Quality of Life Inventory), Chop Intend e PEDI (Pediatric Evaluation of Disability Inventory). Na segunda sessão realizarão 5 tarefas de associação de figuras. O desempenho será medido pelo número de acertos e pelo tempo de execução de cada atividade. O grupo controle será composto por 12 crianças de idade e gênero pareados. **Justificativa:** Não foram encontrados na literatura testes que avaliassem atenção, percepção, memória, função executiva e integração sensório-cognitivo-motora, especificamente de crianças com AME I. Essas informações podem fundamentar as decisões terapêuticas, sobre comunicação, desempenho nas atividades funcionais, desenvolvimento, déficits cognitivos e motores. **Expectativa do estudo:** Testar o rastreador de olhar e o programa Tobii PCEye, como uma ferramenta clínica para fornecer informações sobre a resposta cognitiva, como atenção, percepção, memória, função executiva e integração sensório-cognitivo-motora. As tarefas realizadas no computador tem como objetivo avaliar e melhorar a comunicação e interação destas crianças, testando formas de desempenho sensório-cognitivo-motor, favorecendo

futuros estudos para criação de dispositivos para brincadeiras, comunicação, desenvolvimento intelectual e motor.

Descritores: Atrofia Muscular Espinhal; AME I; cognição; avaliação sensório-cognitivo-motora; werdnig-hoffman; PEDI; Chop Intend; PedsQL.

Introdução

A Atrofia Muscular Espinhal (AME) é uma doença de herança autossômica recessiva. Algumas vezes é percebida nos primeiros três meses de vida, conhecida então como tipo I, forma infantil grave, denominada doença de Werdnig-Hoffman. A AME, em sua forma clássica, ligada às mutações do gene SMN no locus 5q11.2, é a doença mais frequente dentro do grupo de doenças que causam a síndrome da criança hipotônica. Nas formas de início precoce, a insuficiência respiratória restritiva é inevitável e a sobrevida é condicionada ao uso de suporte respiratório. Não são observadas alterações sensoriais.

Antigamente, a maioria das crianças com AME não sobreviviam além dos 3 anos de idade, atualmente com a internação domiciliar, a sobrevida vem aumentando. Até o presente momento, não existe cura, a prevenção é feita por meio de aconselhamento genético, o tratamento é medicamentoso e a fisioterapia é sempre benéfica em todas as formas.

Com relação aos aspectos cognitivos, Billard, C.; Gillet P.; Signoret J. L.; Uicaut E.; Bertrand P.; Fardeau M.; et al. (1992); Billard C, Gillet P, Barthez M, Hommet C, Bertrand P. (1998); Hardiman, O. (2000); Von Gontard, A.; Zerres, K.; Backes, M.; Laufersweiler-Plass, C.; Wendland, C.; Melchers, P.; et al. (2002); Rivière, J. (2007); Ocasio-Silva, M. A.; McBride, A.; Moberg-Wolff, E. (2008) e Barja, S.; Muñoz, C.; Cancino, N.; Núñez, A.; Ubilla, M.; Sylleros, R.; et al. (2013), acreditam que as habilidades cognitivas de crianças com AME é normal. Sieratzki, J. S.; Woll, B. (2001),

acreditam que, desde cedo, essas crianças passam a moldar estratégias para se adequar as condições motoras e assim, desenvolvem os aspectos cognitivos.

Já Rivière, J.; Lécuyer, R. (2001) e Dunaway, S.; Montes, J.; O'Hagen, J.; Sproule, D. M.; Vivo, D. C.; Kaufmann, P. (2012), acreditam que o desenvolvimento cognitivo de crianças com AME é parcialmente normal, que depende dos aspectos analisados. E no estudo de Chung, B. H.; Wong, V. C.; Ip, P. (2004), eles relatam que apesar de aspectos cognitivos preservados, as crianças com AME sempre precisariam de assistência nas soluções dos problemas.

O estudo de Raaphorst, J.; de Visser, M.; Van Tol, M. J.; Linssen, W. H.; Van der Kooi, A. J.; de Haan, R. J.; *et al.* (2011), mostra que crianças com AME tiveram disfunções executivas e de memórias, porém não apresentaram alterações visuo espaciais.

Os pesquisadores Oudgenoeg-Paz, O.; Rivière, J. (2014) encontraram em seus trabalhos, crianças com AME que apresentaram desempenho cognitivos esperados para idade ou acima da média.

Ainda sobre o estudo de Von Gontard, A.; Zerres, K.; Backes, M.; Laufersweiler-Plass, C.; Wendland, C.; Melchers, P.; *et al.* (2002), foi encontrado desempenho cognitivo acima da média em adolescentes com AME.

E por fim, dos 14 artigos analisados, os pesquisadores D'Angelo, M.G.; Bresolin, N. (2006), acreditam ser necessários maiores estudos para definir o desempenho cognitivo de crianças com AME.

Acreditamos que as habilidades cognitivas dependem de múltiplos fatores, incluindo a idade cronológica, idade do diagnóstico, características do relacionamento familiar, tipos e frequências das estimulações recebidas. Quanto mais precoce a

estimulação sensório-cognitivo-motora é oferecida, maiores as chances de crianças com AME apresentarem desenvolvimento cognitivo adequado para a idade.

Objetivos

- Avaliar o desempenho sensório-cognitivo-motor de crianças com AME I, comparado a crianças saudáveis, pareadas por idade e gênero, por meio do programa Tobii PCEye e rastreador de olhar (*eye-tracking*) e relacionar esse desempenho com a pontuação nas escalas Chop Intend, PesdQL (Pediatric Quality of Life Inventory), módulo neuromuscular e PEDI (Pediatric Evaluation of Disability Inventory), domínio autonomia e função social.
- Avaliar se o programa Tobii PCEye é uma ferramenta apropriada para crianças com AME I.
- Avaliar se o programa Tobii PCEye é uma ferramenta sensível para diferenciar o desempenho cognitivo de crianças com AME e de crianças saudáveis.

Material e Método

Delineamento do estudo

Experimental observacional.

Local

Será realizado no domicílio de cada criança ou na escola no período do intervalo. Será efetuado um banco de dados de filmes para futuras pesquisas, que será pertencente ao Laboratório de Ciências e Cognição da USP, de responsabilidade da Profa. Dra. Mariana Callil Voos.

Sujeitos

Participarão 12 crianças com diagnóstico médico de AME I, com idades entre 3 e 10 anos, cujos pais fazem parte da ONG AMEVIVER. Serão comparadas com grupo controle de 12 crianças saudáveis de idade e gênero pareados, selecionadas em uma escola regular.

Materiais

Notebook com o programa Tobii PCEye, escalas Chop Intend, PEDI, PedsQL módulo neuromuscular, câmera e tripé.

Procedimento

As crianças com AME I serão avaliadas clinicamente numa primeira sessão, utilizando-se as escalas Chop Intend, PEDI e PesQL. A Chop Intend é uma escala específica para doenças neuromusculares, a qual avalia movimentos espontâneos de membros superiores, membros inferiores, cervical e tronco, consiste em 16 itens, sendo a pontuação máxima de 64 pontos. Cada item é pontuado de zero a 4, sendo zero quando não realiza e aumenta progressivamente até 4 para medir movimentação espontânea a favor ou contra a gravidade. Ambos os lados são avaliados e é considerado o melhor lado para soma do resultado, sendo que, quanto menor a pontuação, menor a movimentação ativa. Da escala PEDI, foram utilizados os domínios auto-cuidado e função social. Trata-se de uma escala geral, para avaliar crianças com deficiência, consistindo em 73 e 65 pontos, respectivamente. O escore zero é atribuído quando a criança é incapaz de realizar a atividade e 1 para capaz. Para soma geral também são consideradas as necessidades de assistência do cuidador, sendo 8 questões na área de auto-cuidado e 5 na área de função social, pontuando com 5 para independente, 4 para supervisionado, 3 para assistência mínima, 2 para assistência moderada, 1 para máxima e 0 para assistência total, sendo que, quanto menor a pontuação, maior a disfunção. A escala PedsQL avalia a qualidade de vida, específica para doenças neuromusculares, com relato da família e

da própria criança, são 25 perguntas para a família, pontuadas com 0 para nunca, 1 para quase nunca, 2 para algumas vezes, 3 para frequentemente, 4 para quase sempre. Para crianças de 5 a 7 anos são 17 perguntas, pontuadas somente com 0, 2 e 4, e 8 a 12 anos, são 25 perguntas, pontuadas de 0 a 4, para adolescentes de 13 a 18 anos são 25 perguntas pontuadas de 0 a 4. Quanto menor a pontuação, pior a qualidade de vida.

As crianças com AME I (segunda sessão) e as crianças saudáveis, que compõem o grupo controle (sessão única), serão avaliadas em sessões individuais, por meio de 5 tarefas de associação. Todas as crianças saudáveis serão posicionadas sentadas em cadeira comum, com uma mesa à frente solicitado que apoiem os cotovelos na mesa e o queixo nas mãos. As crianças com AME I serão posicionadas em suas cadeiras de rodas adaptadas, com bandeja (mesa). À frente das crianças será colocado o *notebook* com o programa Tobii PCEye acoplado, que permite executar qualquer tarefa com os movimentos oculares e fixação ocular. As tarefas de associação apresentadas serão precedidas de 3 tentativas de treino e o desempenho será avaliado por tempo e acerto. Caso a tarefa seja completada, a criança irá para a próxima, caso ultrapasse o tempo limite, estipulado como 480 segundos (8 minutos), a criança poderá finalizar a tarefa, se desejado, porém os acertos não serão pontuados. A primeira tarefa é de associação de figuras, para juntar os pares de carro (na cor vermelha), bola (na cor branca e preta) e borboleta (na cor azul), sendo o fundo das células onde há cada imagem na cor amarela. A segunda tarefa será de associação de frutas, para juntar os pares de banana, limão, laranja, uva, morango, melão, maçã e kiwi, sendo o fundo das células onde há cada fruta na cor preta. A terceira tarefa será de associação de figura e cor, com pares, borboleta - azul, maçã - verde, carro - preto, bola de basquete - laranja, banana - amarela, leoa - bege. A quarta tarefa será de associação de letras maiúsculas e minúsculas, com pares de Aa, Bb, Dd, Ee, Gg, Mm, Hh, Rr, Tt e Ll. A quinta, e última tarefa, será de associar numerais por extenso e em

algarismo arábico, com pares de 1 - um até 10 - dez. Todas as tarefas serão realizadas com seleção por meio do olhar, considerando como tempo limite para a realização dos jogos 480 segundos (8 minutos).

Análise de dados

O tempo e o número de acertos dos grupos serão comparados por meio de análises de variância, com $p < 0.05$.

CRONOGRAMA

ATIVIDADE	1º SEMESTRE 2015	2º SEMESTRE 2015	1º SEMESTRE 2016
Coleta de dados	X	X	
Análise de dados		X	
Escrita da dissertação no formato de artigo		X	
Encaminhamento do artigo e defesa de mestrado			X

Duração do estudo: 18 meses

PREVISÃO DE GASTOS

O estudo prevê gastos com demandas gráficas, materiais de escritório, combustível, participação em eventos e revisão de idioma e de estatística para publicações, que serão assumidos pelos pesquisadores.

Referências Bibliográficas

Barja, S.; Muñoz, C.; Cancino, N.; Núñez, A.; Ubilla, M.; Sylleros, R.; *et al.* Audiovisual stimulation in children with severely limited motor function: does it improve their quality of life?. *Rev Neurol* 2013; 103-111.

Billard, C.; Gillet P.; Signoret J. L.; Uicaut E.; Bertrand P.; Fardeau M.; *et al.* Cognitive functions in Duchenne muscular dystrophy: a reappraisal and comparison with spinal muscular atrophy. *Neuromuscular Disorders* 1992; v.2, p.371-378.

Billard C, Gillet P, Barthez M, Hommet C, Bertrand P. Reading ability and processing in Duchenne muscular dystrophy and spinal muscular atrophy. *Developmental Medicine G Child Neurology* 1998; 12-20.

Chung, B. H.; Wong, V. C.; Ip, P. Spinal muscular atrophy: survival pattern and functional status. *Pediatrics* 2004; 114.

D'Angelo, M.G.; Bresolin, N. Cognitive impairment in neuromuscular disorders. *Muscle&Nerve* 2006.

Dunaway, S.; Montes, J.; O'Hagen, J.; Sproule, D. M.; Vivo, D. C.; Kaufmann, P. Independent mobility after early introduction of a power wheelchair in spinal muscular atrophy. *Journal of Child Neurology* 2012; 576-582.

Fenichel, G. M. Clinical pediatric neurology: a signs and symptoms approach. 6 ed ed. Philadelphia: Saunders/Elsevier; 2009.

Hardiman, O. Pitfalls in the diagnosis of motor neurone disease. *Hosp Med* 2000; 767-771.

Marcondes, E.; Vaz, F. A. C.; Ramos, J. L. A.; Okay, Y. *Pediatric básica: pediatria clínica geral*, Tomo II. 9 ed. São Paulo: Sarvier ; 2003.

Ocasio-Silva, M. A.; McBride, A.; Moberg-Wolff, E. Cerebral palsy masking spinal muscular atrophy. *J Pediatr Rehabil Med* 2008; 179-183.

Oudgenoeg-Paz, O.; Rivièrè, J. Self-locomotion and spatial language and spatial cognition: insights from typical and atypical development. *Article* 521 2014; vol 2.

Raaphorst, J.; de Visser, M.; Van Tol, M. J.; Linssen, W. H.; Van der Kooi, A. J.; de Haan, R. J.; *et al.* Cognitive dysfunction in lower motor neuron disease: executive and memory deficits in progressive muscularatrophy. *J Neurol Neurosurg Psychiatry* 2011; 170-175.

Rivièrè, J. Self-produced locomotion and spatial cognition: a new light from spinal muscular atrophy. *Arch Pediatr* 2007; 279-284.

Rivièrè, J.; Lécuyer, R. Spatial cognition in young children with spinal muscular atrophy. *Developmental Neuropsychology* 2001; 273-283.

Sieratzki, J. S.; Woll, B. Cognitive function in children with spinal muscular atrophy. *Neuromuscular Disorders* 2001; 693-696.

Tecklin J. S. *Fisioterapia Pediátrica*. São Paulo: Artmed; 2002.

Reed, U. C. Amiotrofia espinhal infantil. In: Kim, C. A.; Albano, L. M. J.; Bertola, D. R. *Genética na prática pediátrica*. São Paulo: Manole; 2010.

Von Gontard, A.; Zerres, K.; Backes, M.; Laufersweiler-Plass, C.; Wendland, C.; Melchers, P.; *et al.* Intelligence and cognitive function in children and adolescents with spinal muscular atrophy. *Neuromuscular Disorders* 2002; 130-136.

Apêndice B – Aprovação do Projeto de Pesquisa

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Nova Proposta de Avaliação Sensorio-Cognitivo-Motora de Crianças com Atrofia Muscular Espinhal tipo I - Doença de Werdnig-Hoffman

Pesquisador: Mariana Caill Voos

Área Temática:

Versão: 2

CAAE: 46899015.1.0000.0076

Instituição Proponente: Departamento de Fisioterapia, Fonoaudiologia e Terapia Ocupacional

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 1.194.133

Apresentação do Projeto:

o mesmo

Objetivo da Pesquisa:

os mesmos

Avaliação dos Riscos e Benefícios:

O autor coloca que o estudo envolve riscos mínimos, pois a criança sempre estará acompanhada de um adulto, e trata-se apenas de avaliação clínica e/ou realização dos jogos.

Os benefícios envolvem jogar com um equipamento de ponta e inovador, e ainda fornecer orientações às crianças com atrofia muscular espinhal e aos pais, a respeito de mobilização e posicionamento.

Comentários e Considerações sobre a Pesquisa:

o mesmo.

Considerações sobre os Termos de apresentação obrigatória:

Apresentou no Método Item referente aos aspectos éticos da pesquisa, porém não citou a Resolução CNS nº 466/12 - Conselho Nacional de Saúde;

Apresentou a carta convite aos pais das crianças do grupo experimental citado no texto;

TCLE esta adequado, em forma de carta convite, e especificando que a criança sera filmada e que o filme fara parte do banco de dados da pesquisadora para futuros estudos;

Endereço: Av. Profº Lineu Prestes, 2565
Bairro: Cidade Universitária CEP: 05.508-000
UF: SP Município: SAO PAULO
Telefone: (11)3091-0457 Fax: (11)3091-0452 E-mail: cep@hu.usp.br

HOSPITAL UNIVERSITÁRIO DA
UNIVERSIDADE DE SÃO
PAULO - HU/USP

Continuação do Parecer: 1.194.133

Cita no TCLE o Comitê de Ética do HU-USP para consulta a dúvidas.

Recomendações:

Redigir no Método que serão seguidas as diretrizes da Resolução CNS nº 466/12 do Conselho Nacional de Saúde.

Conclusões ou Pendências e Lista de Inadequações:

Apenas o acima citado nas recomendações.

Considerações Finais a critério do CEP:

O projeto foi apresentado e aprovado na reunião de hoje. Lembramos que cabe ao pesquisador elaborar e apresentar a este Comitê, relatórios parciais e final, de acordo com a Resolução nº 466/2012 do Conselho Nacional de Saúde, Inciso XI.2, letra "d".

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Outros	Certificado Congresso 2014.pdf	22/03/2015 20:01:01		Aceito
Outros	LICENCA PEDSQLUA_pedsq_graziela_orqe_polido_#1133.pdf	22/03/2015 20:11:57		Aceito
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_466154.pdf	15/05/2015 10:17:53		Aceito
Outros	Carta convite AME.pdf	24/07/2015 12:26:47		Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	Termo de Consentimento.pdf	15/06/2015 14:45:04		Aceito
Outros	Orçamento.pdf	30/06/2015 20:07:44		Aceito
Outros	Cronograma.pdf	30/06/2015 20:08:04		Aceito
Outros	Compromisso Pesquisador.pdf	30/06/2015 20:08:16		Aceito
Outros	Benefícios.pdf	30/06/2015 20:08:30		Aceito
Outros	Cadastro protocolos pesquisa.pdf	30/06/2015 20:30:05		Aceito
Projeto Detalhado / Brochura	Projeto Graziela Polido 2015.pdf	24/07/2015 12:25:37		Aceito

Endereço: Av. Prof. Lineu Prestes, 2565
Bairro: Cidade Universitária CEP: 05.508-000
UF: SP Município: SÃO PAULO
Telefone: (11)3091-0457 Fax: (11)3091-0452 E-mail: cep@hu.usp.br

HOSPITAL UNIVERSITÁRIO DA
UNIVERSIDADE DE SÃO
PAULO - HU/USP

Continuação do Parecer: 1.194.133

Investigador	Projeto Graziela Polido 2015.pdf	24/07/2015 12:25:37		Acelto
TCLE / Termos de Assentimento / Justificativa de Ausência	CartaTCLE2015.pdf	24/07/2015 12:26:09		Acelto
Outros	Carta convite Grupo Controle.pdf	24/07/2015 12:26:38		Acelto
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_P ROJETO_468154.pdf	24/07/2015 12:28:31		Acelto
Folha de Rosto	folharostoGraziela.jpg	06/07/2015 18:17:43		Acelto
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_P ROJETO_468154.pdf	06/07/2015 18:19:47		Acelto

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

SAO PAULO, 24 de Agosto de 2015

Assinado por:
Maurício Seckler
(Coordenador)

Endereço: Av. Profº Lineu Prestes, 2595
Bairro: Cidade Universitária
UF: SP Município: SAO PAULO CEP: 05.508-000
Telefone: (11)3091-9457 Fax: (11)3091-9452 E-mail: cep@hu.usp.br

Apêndice C – Resumo apresentado no Congresso da World Muscle Society (WMS) 2015

VISUAL-COGNITIVE-MOTOR SKILLS IN CHILDREN WITH SPINAL MUSCLE ATROPHY - TYPE I

Mariana Voos¹, Graziela Polido¹, Alessandra Barbosa¹, Francis Favero², Fátima Caromano¹

¹ USP (University of São Paulo. Faculty of Medicine. Department of Physical Therapy, Speech Therapy and Occupational Therapy). São Paulo/ SP/ Brazil.

² UNIFESP (Federal University of São Paulo, Neurology). São Paulo/ SP/ Brazil.

Abstract

Due to their severe motor paralysis and poor oral communication, it is difficult to evaluate and follow children with spinal muscle atrophy type I (SMA-I, Werdnig-Hoffman). Studies have shown contradictory findings about cognitive skills in SMA-I. Genetic alterations and the lack of environmental interaction due to the severe paralysis may interfere with cognitive development. We aimed to (1) propose the use of TOBII-PCEye, (2) investigate the visual-cognitive-motor performance of children with SMA-I, (3) compare children with SMA-I to healthy controls. Twelve children (3-10 yrs old) with SMA-I and 12 matched controls were assessed. Children with SMA-I were positioned on adapted wheelchair, facing the notebook with TOBII-PCEye. Figures and colors association tasks were proposed for all children. For the 7-10 yrs old children numbers and letters association tasks were also proposed. The figures were displayed in 4x4cm squares. The response required was selecting each correct pair of squares by 2000ms eye fixation. The number and percentage of correct answers was

registered. ANOVAs compared the scores of the groups. Children with SMA-I were also assessed with Chop Intend (CI), Pediatric Evaluation of Disability Inventory (PEDI) and Pediatric Quality of Life Inventory (PedsQL). TOBII-PCEye quantified the visual-cognitive-motor performance of the children with SMA-I. Correct answers varied from 0% to 100% with a median of 40% correct answers on the visual-cognitive-motor task for children with SMA-I and 70% for controls ($p < 0.05$). Children with SMA-I scored 3-40% on CI, 5-20% on PEDI and 29-59% on PedsQL. Despite having low motor performance, functional independence and quality of life, children aged 4 yrs or older could perform TOBII-PCEye tasks. The figures association difficulty, shown by many children with SMA-I, suggests that the genetic alterations and the restricted environmental interaction can contribute to cognitive impairment.

Key-words: muscle paresis, muscular atrophy, neuromuscular manifestations.

MATCHING PAIRS DIFFICULTIES IN CHILDREN WITH SPINAL MUSCULAR ATROPHY TYPE I SUGGEST COGNITIVE IMPAIRMENT

Graziela Jorge Polido¹, Alessandra Ferreira Barbosa¹, Fátima Aparecida Caromano¹, Carlos Hitoshi², Edmar Zanoteli³, Umbertina Conti Reed³, Mariana Callil Voos¹

¹ USP (University of São Paulo. Faculty of Medicine. Department of Physical Therapy, Speech Therapy and Occupational Therapy). São Paulo/ SP/ Brazil.

² USP (University of São Paulo. Faculty of Mathematics and Statistics). São Paulo/ SP/ Brazil.

³ USP (University of São Paulo. Faculty of Medicine. Clinics Hospital. Department of Neurology). São Paulo/ SP/ Brazil.

BACKGROUND: Although children with Spinal Muscular Atrophy Type I (SMA-I, Werdnig-Hoffman) present a life expectancy of about two years, many of them are currently reaching the school age. Due to poor motor performance and oral communication, it is difficult to access the cognitive performance of children with SMA-I. **OBJECTIVE:** This work investigates the cognitive performance of children with SMA-I using eye tracking. **METHOD:** Twenty-four children (3-9yrs): children with SMA-I (n=12) and age- and sex-matched controls (n=12), nine boys and three girls in each group. Children performed four matching tasks involving figures, numbers and letters, by making eye movements, detected by eye tracking. Children with SMA-I were

assessed with CHOP INTEND, PEDI (Pediatric Evaluation of Disability Inventory) and PedsQL (Pediatric Quality of Life Inventory). **RESULT:** Children with SMA-I showed poor motor performance, but could respond to the cognitive tests with eye movements. The number of correct answers was significantly lower and the timed performance was significantly higher in children with SMA-I in comparison to the control group. **CONCLUSION:** The difficulty associating figures, shown by most children with SMA-I, suggests that the restricted interaction with the environment, due to severe paralysis and poor verbal communication, is associated with poorer cognitive outcome.

Key words: spinal muscular atrophy, cognition, visual perception.