DOI: 10.1590/1809-2950/18001626022019

Analysis of the functional performance of infants with congenital zika syndrome: a longitudinal study

Análise do desempenho funcional de lactentes com síndrome congênita do zika: estudo longitudinal

Análisis del desempeño funcional de los lactantes con síndrome congénito del zika: estudio longitudinal

Danielly Laís Pereira Lima[1], Maria Lucia Galvão Carvalho Dias Correia[2], Milena Guimarães Monteiro[3], Karla Mônica Ferraz[4], Carine Carolina Wiesiolek[5]

ABSTRACT | This study aimed to longitudinally evaluate the functional performance of infants affected by Congenital Zika Syndrome (CZS). A study was carried out with infants from the *Laboratório de Estudos em Pediatria* of the *Universidade Federal de Pernambuco* and the *Aliança de Mães e Famílias Raras*, aged between 6 and 24 months, of both genders. The Pediatric Evaluation of Disability Inventory (PEDI) was applied to analyze functional performance in two evaluations, with a minimum of six months interval between them. Data analysis was performed using the *Wilcoxon* test. In the sample of 16 infants, we observed a change in the classification from normal to delay in the domains of self-care and social function, with a significant decrease in normative scores (p=0.001 and p<0.001, respectively); in the mobility, individuals initially classified with delay also presented reduction of normative scores (p=0.001), remaining in the same classification. Despite the significant increase in gross self-care scores (p=0.024) and mobility (p=0.001), infants remained classified as delayed. Caregiver care was analyzed in these evaluation, in which 100% of infants were delayed in all three domains of the PEDI, receiving maximum or full care. The main environmental modifications were those focused on the child. We concluded that infants with CZS presented significant delays in functional performance, with a slow evolution in the evaluated range.

Keywords | Child Development; Zika Virus; Infant.

RESUMO | O objetivo do estudo foi avaliar longitudinalmente o desempenho funcional de lactentes acometidos pela síndrome congênita do zika (SCZ). Realizou-se um estudo com lactentes provenientes do Laboratório de Estudos em Pediatria da Universidade Federal de Pernambuco e da Aliança de Mães e Famílias Raras, com idade entre 6 e 24 meses, de ambos os sexos. O Inventário de Avaliação Pediátrica de Incapacidade (PEDI) foi aplicado para análise do desempenho funcional em duas avaliações, com no mínimo seis meses de intervalo. A análise dos dados foi realizada pelo teste de *Wilcoxon*. Na amostra de 16 lactentes, observou-se que entre as avaliações houve mudança na classificação de normal para atraso nos domínios de autocuidado e função social, com diminuição significativa dos escores normativos (p=0,001 e p<0,001, respectivamente); na mobilidade, os lactentes inicialmente classificados com atraso também apresentaram redução dos escores normativos (p=0,001), mantendo-se na classificação. Apesar do aumento significativo nos escores brutos do autocuidado (p=0,024) e mobilidade (p=0,001), os lactentes continuaram classificados em atraso. Na assistência do cuidador, 100% dos lactentes se encontraram em atraso nos três domínios do PEDI, recebendo assistência máxima ou total. As principais modificações ambientais encontradas foram as centradas na criança. Em suma, os lactentes com SCZ deste estudo apresentaram atrasos significativos no desempenho funcional, com uma evolução lenta no intervalo de tempo avaliado.

Descritores | Desenvolvimento Infantil; Zika Vírus; Lactante.

Study conducted at the *Laboratório de Estudos em Pediatria* (Leped) of the Department of Physical Therapy of the *Universidade Federal de Pernambuco* (UFPE) and in the *Aliança de Mães e Famílias Raras* (Amar) – Recife (PE), Brazil.
[1]Universidade Federal de Pernambuco (UFPE) – Recife (PE), Brasil. E-mail: danilais.lima@gmail.com. Orcid: 0000-0001-6074-2602
[2]Universidade Federal de Pernambuco (UFPE) – Recife (PE), Brasil. E-mail: marialuciagalvao.fisio@outlook.com. Orcid: 0000-0003-1764-5959
[3]Universidade Federal de Pernambuco (UFPE), – Recife, (PE), Brasil. E-mail: milenaguimaraesm@gmail.com. Orcid: 0000-0002-0169-3609
[4]Universidade Federal de Pernambuco (UFPE) – Recife (PE), Brasil. E-mail: karla_monica@hotmail.com. Orcid: 0000-0002-2617-2164
[5]Universidade Federal de Pernambuco (UFPE) – Recife (PE), Brasil. E-mail: carinecwi@gmail.com. Orcid: 0000-0001-9705-6315

Corresponding address: Danielly Laís Pereira Lima – Rua Padre Carapuceiro, 537, block B, Boa Viagem – Recife (PE), Brazil – Zip Code: 51020-280 – E-mail: danilais.lima@gmail.com –
Finance source: Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) – Conflict of interests: nothing to declare – Presentation: Jan. 14th, 2018 – Accepted for publication: Oct. 8th, 2018 – Approved by the Research Ethics Committee of the Universidade Federal de Pernambuco under opinion No. 47494115.3.0000.5208.

RESUMEN | El objetivo del estudio fue evaluar longitudinalmente el desempeño funcional de lactantes con síndrome congénito del zika (SCZ). Se realizó un estudio con lactantes de entre 6 y 24 meses, de ambos los sexos, identificados por el Laboratorio de Estudios en Pediatría de la Universidad Federal de Pernambuco y por la *Aliança de Mães e Famílias Raras* (Alianza de Madres y Familias Raras). Se aplicó el Inventario de Evaluación Pediátrica de Discapacidad (PEDI) para análisis del desempeño funcional en dos evaluaciones, con al menos seis meses de intervalo. El análisis de los datos fue realizado por la prueba de *Wilcoxon*. En la muestra de 16 lactantes se observó cambio en los campos de autocuidado y función social, de "normal" para "retraso", con disminución significativa de los puntajes normativos (p=0,001 y p<0,001, respectivamente). En la movilidad, los lactantes inicialmente clasificados con retraso también presentaron reducción de los puntajes normativos (p=0,001), manteniéndose en la clasificación. A pesar del aumento significativo en los puntajes netos del autocuidado (p=0,024) y movilidad (p=0,001), los lactantes continuaron clasificados en retraso. En la asistencia del cuidador, un 100% de los lactantes se encontraban en retraso en los tres dominios del PEDI, recibiendo asistencia máxima o total. Las principales modificaciones ambientales encontradas fueron las centradas en el niño. En resumen, los lactantes con SCZ presentaron retrasos significativos en el desempeño funcional, con una evolución lenta en el intervalo de tiempo evaluado.

Palabras clave | Desarrollo Infantil; Virus del Zika; Infantil.

INTRODUCTION

The proliferation of the zika virus (ZIKV) became, from 2015, a public health problem in Brazil and in the world[1], with an increase in the incidence of neonates with cephalic perimeter of less than 33 centimeters, pointing to a possible relation with the infection ZIKV[2,3]. Subsequently, new neurological incidents in children were described, with or without the presence of microcephaly[2].

Microcephaly has been associated with a variety of sequelae, including developmental delays and intellectual deficits[3], visual[4] and auditory[5] impairment and epileptic seizures[6]. All these factors constitute congenital zika syndrome (SCZ)[7], in which, in addition to microcephaly, craniofacial disproportion, spasticity, seizures and irritability are reported[8]. Brain abnormalities have also been described in neuroimaging exams, such as cortical and subcortical calcifications, cortical malformations, lissencephaly and ventriculomegaly[9].

Considering the clinical picture presented by this population, Van der Linden et al.[10] suggest that children with SCZ have motor development deficits compatible with mixed cerebral palsy (CP). However, a recent study has shown that, unlike CP, there were changes over the course of a year in the pattern of central nervous system involvement in these children, which indicates the need for longitudinal studies to follow up this population[11].

Systematic evaluation in childhood, especially during the first years of life – moment of greater neuroplasticity – is fundamental for the understanding of clinical conditions and possible repercussions on child development. The assessment of the performance of children with SCZ is a recommendation of the World Health Organization[8] and of the Ministry of Health[12], which suggest the use of standardized instruments, such as the Pediatric Evaluation of Disability Inventory (PEDI)[13].

Thus, this study aimed to longitudinally evaluate the functional performance of infants affected by SCZ through continuous evaluation, in order to elucidate the impact of SCZ on child development.

METHODOLOGY

A longitudinal study was carried out between September 2016 and December 2017, in which infants with a diagnosis of SCZ, aged between 6 and 24 months old, of both gender, were included, constituting a non-probabilistic convenience sample. Infants with joint fixation, arthrogryposis, other congenital infections or associated genetic syndromes were excluded.

The diagnosis of SCZ was confirmed by serological test attesting to ZIKV infection, arboviral symptoms presented by the mother during pregnancy, as well as the presence of cortical or subcortical calcifications on a neuroimaging examination[9].

Instrumentation

The Pediatric Evaluation of Disability Inventory (PEDI), developed in 1992, was validated for Brazil by

Mancini[14] in 2005 and called Inventário de Avaliação Pediátrica de Incapacidade[13]. It aims to provide an assessment of children with disabilities regarding their functional abilities and performance[14]. It is applied through an interview with the caregiver, and functional performance is evaluated in three parts: part I – functional skills (subdivided into self-care, mobility and social function); Part II – caregiver care; and part III – environmental modifications. Functional performance is given by normative scores obtained from the sum of gross scores. Normative values between 30 and 70 classify the child with typical development; values below 30 are considered delay[13].

Data collection and ethical aspects

For the data collection, two evaluations (A1 and A2) were performed by a trained and experienced evaluator, with a minimum interval of six months between them, in which all infants remained in therapeutic follow-up. Mothers were invited to participate in the study via telephone or as they appeared at the collection sites. In the first evaluation (A1), information on maternal, childbirth and infant characteristics was obtained and applied to Part I of the PEDI. At this time, due to the age group of the infants, the mother and the evaluator did not found the child's conditions to attend the parts II and III items of the instrument. In the second evaluation (A2), parts II and III of the inventory were included, which are more complex items when compared to the items in part I, and that, due to the age group of the infants, at this moment of evaluation, would thus reflect typical aid and independence demands. Part II of the inventory addresses items about child independence, and Part III addresses the modifications used by the infant in performing functional tasks. The interviews were conducted in a reserved environment, with an average duration of 40 minutes. The re-evaluation by PEDI was carried out in the minimum interval of six months, a period similar to the stratification of the referred population for the normative sample of the Brazilian version, and because it is the time interval between age groups established in the manual of the inventory application for transformation of gross normative scores[13].

The study was approved by the Research Ethics Committee (CAAE: 47494115.3.0000.5208) and data collection was performed by signing a Free and Informed Consent Term.

Statistical analysis

Sociodemographic and clinical data were analyzed descriptively (frequency, mean and standard deviation). The Statistical Package for Social Science (SPSS, version 20.0) was used, considering a significance level of 5% for statistical tests. The normality of the data was verified by the *Shapiro-Wilk* test, and the *Wilcoxon* test was applied for the analysis of the part I domains of the PEDI between A1 and A2.

RESULTS

In the first trimester (62.5%), all (100%) presented arboviruses symptoms in gestation, with skin rash being the dominant symptom (50%), followed by arthralgia (18.8%) and fever (12.5%). The profile of infants evaluated is shown in Table 1.

Table 1. Profile of infants sample with congenital zika syndrome

Age in months (mean/SD)	
Initial Evaluation	10.8 (± 1.8)
Revaluation	20.9 (± 1.8)
Interval between evaluations in months (mean/SD)	9.94 (± 1.66)
Gender (n/%)	
Male	7 (43.7)
Female	9 (56.3)
Cephalic perimeter at birth in cm (mean/SD)	28.5 (± 3.0)
Osteomyoarticular changes (n/%)	
Spasticity	5 (27.7)
Congenital Hip Dislocation	3 (16.6)

SD: standard deviation; cm: centimeters.

The neuroimaging alterations found in infants were: calcifications (100%), ventriculomegaly (25%), lissencephaly (6.3%) and hydrocephalus (12.5%); 68.8% of the infants had ophthalmologic alterations and 18.8% had hearing alterations. Other alterations were seizures (75%) and gastroesophageal reflux (25%).

Regarding the therapeutic follow-up, all of them underwent physical therapy and occupational therapy, 68.8% were in follow-up of speech therapy, and 25% underwent botulinum toxin application. Surgical procedures were recorded in 43.8% of the sample (ventriculoperitoneal shunt, adenoidectomy and gastrostomy).

Table 2. Description of the functional abilities classification of infants with congenital zika syndrome

Functional Skills		A1 n (%)	A2 n (%)
Self-care*	Normal	10 (62.5)	1 (6.3)
	Delay	6 (37.5)	15 (93.7)
Mobility*	Normal	0 (0)	0 (0)
	Delay	16 (100)	16 (100)
Social Function*	Normal	13 (81.2)	0 (0)
	Delay	3 (18.8)	16 (100)

When analyzing the normative scores of the PEDI in A1, it was observed delay of the infants in the self-care domain, in the mobility and in the social function. In A2, there was a delay in the three domains, with significant changes between A1 and A2 (Tables 2, 3 and Figure 1). Despite the significant increase in gross self-care scores (p=0.024) and mobility (p=0.001) among the evaluations, infants remained classified as delayed.

Table 3. Analysis of the gross and normative scores of functional abilities of infants with SCZ between A1 and A2 evaluations

Functional Skills		A1**
Self-care	Gross	4.5/±3.32
	Normative	31.64/±15.39
Mobility	Gross	0.93/±0.25
	Normative	15.25/±3.63
Social Function	Gross	5.06/±1.81
	Normative	38.01/±11.34

* Significance level of 5%; ** Expressed in "mean/standard deviation".

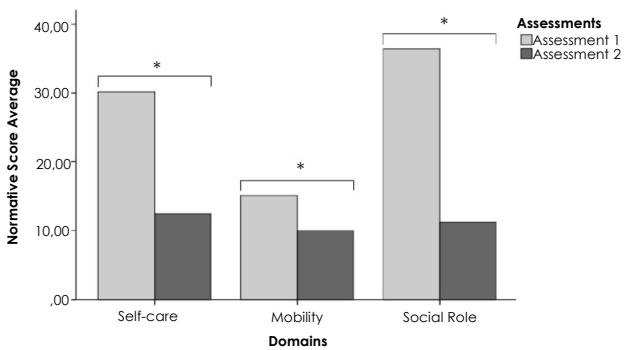

Figure 1. Comparison of the normative score averages between A1 and A2 for the PEDI domains of children with SCZ

* Significance level of 5%.

Regarding caregiver care, 100% were delayed in all three domains of the PEDI (Table 4), requiring full or maximum assistance in their activities. As to the frequency of modifications, all were child-centered and found only in the self-care domain.

Table 4. Analysis of gross and normative care scores of caregivers of infants with SCZ

Functional Skills		(mean/SD)
Self-care	Gross	1.43/±1.26
	Normative	20.3/±8.89
Mobility	Gross	0.31/±0.60
	Normative	<10/0
Social Function	Gross	0.87/±0.95
	Normative	16.92/±7.24

DISCUSSION

It is observed that infants affected by SCZ have delays in their functional performance, with a slight evolution over time. There were minimal gains in the analyzed time interval, especially in the area of mobility, with higher indices related to the total care of the caregivers and maximum dependence of the infants suggesting stagnation of the child development.

When analyzing the comparisons of the gross scores between A1 and A2, we observed a slight increase in the means. This gain reflects limited evolution in simple tasks, such as maintaining the sitting position with support.

However, in A1, most infants were adequate in the domains of self-care and social function. Nevertheless, when refinement of skills required for more complex activities should occur, infants scored fewer items than at the first assessment, demonstrating that they were unfit for adequate development as they grow older.

In the evaluation of mobility, infants showed delay in A1 and A2, since the instrument points out transfer activities, suggesting stagnation in the global motricity. This finding is attributed to the various alterations in the nervous system and associated deficits (sensorial, auditory, visual and perceptual) characteristic of this population[3-9], with consequent impairment in learning and acquisition of motor skills typical of this age group.

The literature points out that children with mobility difficulties suffer physical, social and mental impairment[15] and delays in sensory and perceptual development, with negative consequences on new movements and social interactions[16]. In addition, generalized immobility is related to the significant increase in the mortality of children with severe disabilities[17].

In 2016, a study conducted in Brazil[18] evaluated four infants with SCZ who presented atypical development, hypertonia, visual changes and poor voluntary motor function, similar findings to that of this study. However, to date, no studies have been found to assess the functional performance of children with SCZ.

The literature suggests that children with SCZ resemble children with CP[10]. Thus, impairments such as limited motor control and difficulties in activities of daily living (ADL), such as eating, dressing and walking[19], are evidenced for this population, making these children more predisposed to pain, functional limitations, worse quality of life indexes and dependence of the caregiver[20,21].

In children with CP, it is believed that the combination of adjuvant factors such as physical context and attitudes, social component and assistive technologies (AT) can influence the daily routine[22] and the routine of children with SCZ. The AT as an auxiliary tool is indicated to reduce the effort and energy expended by the caregivers, as well as to increase the independence of the child and improve their activity and participation[23], according to components of the International Classification of Functionality model[24].

Given the multiple disabilities in SCZ infants, it is fundamental to involve parents and caregivers in the treatment, since their orientation is related to better indices of functional performance and independence of children with special needs[23]. Our study alerts us to the high dependency ratios of the studied sample, strengthening the need for recommendations for the care of infants with SCZ, such as the involvement of the family in the therapeutic, home and AT treatment.

Another relevant point may have been the lack of availability of AT resources for this population, which in this context would appear as an auxiliary therapy that should be implemented in the rehabilitation of infants with SCZ because of the impact on functionality and caregiver care[25].

Our data confirm the need for therapeutic follow-up, already suggested in the literature[3], also indicating the need to target public policies with long-term follow-up and strategies.

The study showed some limitations, such as the presence of uncontrolled confounding factors (lack of control of the therapeutic follow-up and surgical procedures), the wide margin of PEDI score and a small sample size.

New longitudinal and prospective studies with a larger sample and follow-up time are necessary for a deeper understanding of the SCZ repercussions. However, this study collaborates with the understanding of longitudinal functional performance of these infants and the different interfaces in their life context and care.

ACKNOWLEDGEMENTS

To the Laboratory of Pediatric Studies of the *Universidade Federal de Pernambuco* and to the NGO *Aliança de Mães e Famílias Raras*.

REFERENCES

1. World Health Organization. Geneva: World Health Organization; 2016 [cited 2017 Aug 31]. WHO statement on the first meeting of the International Health Regulations (2005) (IHR 2005) Emergency Committee on Zika virus and observed increase in neurological disorders and neonatal malformations. Available from: http://www.who.int/mediacentre/news/statements/2016/1st-emergency-committee-zika/en/
2. Eickmann SH, Carvalho MDCG, Ramos RC, Rocha MA, Van Der Linden V, Silva PS. Síndrome da infecção congênita pelo vírus Zika. Cad Saúde Pública. 2016;32(7):1-3. doi: 10.1590/0102-311X00047716
3. Kapogiannis BG, Chakhtoura N, Hazra R, Spong CY. Bridging knowledge gaps to understand how Zika virus exposure and infection affect child development. JAMA Pediatr. 2017;171(5):478. doi: 10.1001/jamapediatrics.2017.0002
4. Ventura CV, Maia M, Ventura BV, van der Linden V, Araujo EB, Ramos RC, et al. Ophthalmological findings in infants with microcephaly and presumable intra-uterus Zika virus infection. Arq Bras Oftalmol. 2016;79(1):1-3. doi: 10.5935/0004-2749.20160002
5. Leal MC, Muniz LF, Ferreira TSA, Santos CM, Almeida LC, van der Linden V, et al. Hearing loss in infants with microcephaly and evidence of congenital zika virus infection – Brazil, November 2015 – May 2016. MMWR Morb Mortal Wkly Rep. 2016;65(34):917-9. doi: 10.15585/mmwr.mm6534e3
6. Alves LV, Cruz DDCS, van der Linden AMC, Falbo AR, Mello MJG, Paredes CE, et al. Crises epilépticas em crianças com síndrome congênita do Zika vírus. Rev Bras Saúde Matern Infant. 2016;16:33-7. doi: 10.1590/1806-93042016000s100003
7. Brasil. Ministério da Saúde. Orientações integradas de vigilância e atenção à saúde no âmbito da emergência de saúde pública de importância nacional: procedimentos para o monitoramento das alterações no crescimento e desenvolvimento a partir da gestação até a primeira infância, relacionadas à infecção pelo vírus zika e outras etiologias infeciosas dentro da capacidade operacional do SUS. Brasília, DF: Ministério da Saúde; 2017 [cited 2019 Apr 30]. Available from: http://portalarquivos.saude.gov.br/images/pdf/2016/12/orientacoes-integradas-vigilancia-atencao.pdf
8. World Health Organization. Screening, assessment and management of neonates and infants with complications associated with zika virus exposure in utero. Geneva: World Health Organization; 2016 [cited 2019 Apr 30]. Available from: http://www.who.int/csr/resources/publications/zika/assessment-infants/en/
9. Aragao MFV, van der Linden V, Brainer-Lima AM, Ramos RC, Rocha MA, Silva PS, et al. Clinical features and neuroimaging (CT and MRI) findings in presumed zika virus related congenital infection and microcephaly: retrospective case series study. BMJ. 2016;353(i1901):1-10. doi: 10.1136/bmj.i1901

10. van der Linden V, Pessoa A, Dobyns W, Barkovich AJ, Ribeiro EM, Leal MD, et al. Description of 13 infants born during october 2015-january 2016 with congenital zika virus infection without microcephaly at birth – Brazil. MMWR Morb Mortal Wkl. 2016;65(47):1343-8. doi: 10.15585/mmwr.mm6547e2

11. Petribu NC, Aragão MFV, van der Linden V, Parizel P, Jungmann P, Araújo L, et al. Follow-up brain imaging of 37 children with congenital zika syndrome: case series study. BMJ. 2017;359:j4188. doi.org/10.1136/bmj.j4188

12. Brasil. Ministério da Saúde. Secretaria de Atenção à Saúde. Diretrizes de estimulação precoce: crianças de zero a 3 anos com atraso no desenvolvimento neuropsicomotor decorrente de microcefalia. Brasília, DF: Ministério da Saúde; 2016. 123 p.

13. Haley SM, Coster WJ, Ludlow L, Haltiwanger J, Andrellos P. Pediatric evaluation of disability inventory: development, standardization and administration manual. Trustees of Boston University Boston, MA; 1992.

14. Mancini MC. Inventário de avaliação pediátrica de incapacidade (PEDI): manual da versão brasileira adaptada. Belo Horizonte: UFMG; 2005.

15. Zwicker JG, Missiuna C, Harris SR, Boyd LA. Developmental coordination disorder: a review and update. Eur J Paediatr Neurol. 2012;16(6):573-81. doi: 10.1016/j.ejpn.2012.05.005

16. Lee B-H. Relationship between gross motor function and the function, activity and participation components of the International Classification of Functioning in children with spastic cerebral palsy. J Phys Ther Sci. 2017;29:1732-6. doi: 10.1589/jpts.29.1732

17. Nissen S, Purssell E, Shaw K, Bailey C, Efstathiou N, Dunford C. Impaired mobility associated with an increased likelihood of death in children: a systematic review. J Child Heal Care. 2017;136749351773283. doi: 10.1177/1367493517732839

18. Botelho AC, Neri LV, Silva MQF, Lima TT, Santos KG, et al. Infecção congênita presumível por Zika vírus: achados do desenvolvimento neuropsicomotor: relato de casos. Rev Bras Saúde Matern. Infant. 2016(1):45-50. doi.org/10.1590/1806-9304201600S100004

19. Ryan J, Cassidy E, Nooduyn S, O'Connell N. Exercise interventions for cerebral palsy (Review). Cochrane Database Syst Rev. 2017;(6):1-199. doi: 10.1002/14651858.CD011660

20. Alriksson-Schmidt A, Hagglund G. Pain in children and adolescents with cerebral palsy: a population-based registry study. Acta Paediatr. 2016;105:665-70. doi: 10.1111/apa.13368

21. Mancini MC, Alves, Schaper C, Figueiredo EM, Sampaio, Coelho ZAC, et al. Gravidade da paralisia cerebral e desempenho funcional. Rev Bras Fisioter. 2004;8(3):253-60.

22. Brandao MB, Gonçalves SC, Carvalho LASRP, Crepaldi PV, Abrahão LC, Mambrini JVM, et al. Clusters of daily functioning and classification levels: agreement of information in children with cerebral palsy. J Pediatr Rehabil Med. 2012;5(3):151-8. doi: 10.3233/PRM-2012-0207

23. Pavão L, Silva S, Rocha C. Efeito da orientação domiciliar no desempenho funcional de crianças com necessidades especiais. Motricidade. 2011;7:21-9. doi: 10.6063/motricidade.7(1).117

24. Cury V, Mancini M, Melo A, Fonseca S, Sampaio R, Tirado M. Efeitos do uso de órtese na mobilidade funcional de crianças com paralisia cerebral. Rev Bras Fisioter. 2006;10(1):67-74. doi: 10.1590/S1413-35552006000100009

25. Henderson S, Skelton H, Rosenbaum P. Assistive devices for children with functional impairments: impact on child and caregiver function. Dev Med Child Neurol. 2008; 50(2):89-98. doi: 10.1111/j.1469-8749.2007.02021.x