Journal of Paediatrics and Child Health

doi:10.1111/jpc.16139

ORIGINAL ARTICLE

# Effect of neurodevelopmental treatment in children with congenital Zika syndrome: A pilot study

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**Aim:** To evaluate the effects of neurodevelopmental treatment (NDT) in children with congenital Zika syndrome (CZS).

**Methods:** This prospective, interventional cohort study involved children with CZS undergoing follow-up at a specialist centre in northeastern Brazil. The duration of the proposed NDT protocol was 1 year, with 45-min sessions delivered one to five times weekly. Motor function, weight, height, head circumference and the incidence of comorbidities were evaluated in children before protocol initiation and then at 3, 6 and 12 months of treatment.

**Results:** Thirty children were evaluated (age mean 30.1 ± 3 months). Motor function improved from baseline to 6 months ($P = 0.001$). No difference in weight and head circumference *z*-score ($P = 0.51$ and $P = 0.29$, respectively), but an increase in height *z*-score ($P < 0.001$) was observed over the evaluation period. There was a reduction in the incidence of upper respiratory tract infections, pneumonia and urinary tract infections over the follow-up period.

**Conclusions:** NDT proved to be a viable treatment approach that can improve motor function and reduce the incidence of comorbidities in children with CZS, while having no harmful effects on their growth.

**Key words:** comorbidities; motor function; physiotherapy; rehabilitation.

**What is already known on this topic**

1 Children with CZS experience comorbidities that need to be managed throughout their lives.
2 Children with CZS can improve motor functions after intervention programs. conducted by specialized professionals.
3 NDT can promote neuromuscular relaxation and improve the motor control of children with motor impairment.

**What this paper adds**

1 Children with CZS can improve motor function after a no intensive physiotherapy protocol.
2 A specialized intervention can reduce incidence of comorbidities with no weight loss in children with CZS.
3 Neurodevelopmental treatment is a plausible approach to treating children with SCZ.

Congenital Zika syndrome (CZS) results from the effect of Zika virus infection on fetal development and involves a range of severe brain damage.[1,2] Clinical manifestations of different levels of severity have been described in CZS, including microcephaly, muscle tone abnormalities, dysphagia and seizures, as well as respiratory impairment, and neuropsychomotor development and growth delays.[3–6]

In addition to the direct consequences of nervous system impairments, children with neurological disease, such as CZS, experience several comorbidities that need to be managed throughout their lives.[7,8] In children with CZS, our multidisciplinary team has observed a high incidence of pneumonia, hospitalisations, urinary tract infections (UTIs) and upper respiratory tract infections (URTIs) that compromise infant motor development and therapeutic success. In this way, Aragao *et al.* reported that diseases such as pneumonia had been the main cause of death in children with CZS.[9] These findings support the need for strategies that control the occurrence of these comorbidities not only to prevent the occurrence of death and improve quality of life, but also to favour rehabilitation success of children with CZS.

Despite the severe motor impairment presented by the majority of children with CZS,[4,10] few studies have focused on investigating the effects of rehabilitation programs focused on this specific population.[11–13] Of those, one pilot study conducted with

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Funding: This study received support from the Coordination for the Improvement of Higher Education Personnel (CAPES)/Ministry of Education (MEC) (Grant no. 443372/2016-0), Technological Development (CNPq) (Grant no. 440619/2016-5). This study was also supported by the Department of Science and Technology, Secretariat of Science, Technology and Strategic Supplies, Ministry of Health.

Conflict of interest: None declared.

Accepted for publication 14 July 2022.

32 children with CZS and their mothers investigated the effects of a family-focused intervention program on children's motor and cognitive function.[11] Although the mothers perceived an improvement with respect to the functional goals achieved by their children, no improvement was found in motor or cognitive function following the intervention. Recently, another pilot study reported an improvement in motor function in seven children with CZS following the application of a protocol of intensive physiotherapy involving 2-h sessions five times a week over 1 year.[13] The proposed intervention had no adverse effect on the children's body weight.

Those preliminary findings suggest that further investigation is required into the effects of intervention programs in children with CZS. The objective of the present study was to evaluate the effects of neurodevelopmental treatment (NDT) on motor function, growth and the incidence of comorbidities in children with CZS.

## Methods

This prospective, interventional cohort study was developed at the *Professor Joaquim Amorim Neto Research institute* (IPESQ) in the city of Campina Grande, state of Paraiba, northeastern Brazil, where ongoing care is provided to children with CZS. Some of these children have been monitored since pregnancy. The internal review board of the *Alcides Carneiro University Teaching Hospital* approved the study protocol. Before any evaluation was conducted, the mothers or guardians of all the children involved signed an informed consent form.

### Sample

The sample was obtained by non-probability convenience sampling from children seen at a centre care linked to *IPESQ* that provides multidisciplinary care for children with CZS. The inclusion criteria were: (i) a diagnosis of CZS in accordance with the Centers for Disease Control and Prevention criteria[14]; (ii) being enrolled in the physiotherapy program; and (iii) undergoing follow-up every 3 months at *IPESQ*. Children with microcephaly and/or brain damage of other aetiologies, including those triggered by other infectious agents, were excluded from the study. Children who had not attended at least one session of NDT-based physiotherapy per week over the study period were excluded from the analysis.

### Evaluation procedure

Following the consent process, the children's motor function was evaluated using the Gross Motor Function Measure (GMFM-88) and all were classified according to the Gross Motor Function Classification System (GMFCS). Weight, height, head circumference and the incidence of comorbidities were also investigated.

The GMFM-88 is a scale that is widely used to evaluate children's gross motor skills as they perform 88 tasks separated into five dimensions: (A) Lying and Rolling; (B) Sitting; (C) Crawling and Kneeling; (D) Standing; and (E) Walking, Running and Jumping.[15] Each one of the tasks evaluated is scored from 0 (does not initiate the task) to 3 (completes the task), based on the child's ability to perform the task. The total GMFM score is calculated from the sum of scores for each dimension (GMFM-A, GMFM-B, GMFM-C, GMFM-D and GMFM-E).

The GMFCS scale is used to classify the mobility and functionality of children with cerebral palsy, taking age into consideration. According to this ordinal scale, children are classified from level I, corresponding to minimal limitations, to level V, which corresponds to severe limitations.[16] Anthropometric variables (weight, height and head circumference) were measured by pediatric scales (Welmy, Santa Bárbara d'Oeste, São Paulo, Brazil), a portable stadiometer and a non-elastic tape measure, respectively. Using the absolute values of the anthropometric variables, the *z*-scores for head circumference, height and weight were calculated using the World Health Organization Anthro® software program, version 3.2.2.[17] These values were used to compare anthropometric variables between assessments. Specifically, regarding weight. Children were classified as very low weight-for-age ($z$-score $< -3$), low weight-for-age ($z$-score $> -3$ and $< -2$), appropriate weight-for-age ($> -2$ and $< +2$) and above the expected weight-for-age ($z$-score $> 2$).[18] Finally, the occurrence of comorbidities such as pneumonia, hospitalisations, UTI and URTI in the last month was measured by interviews with child's parents in each evaluation period.

The children who participated in the present study were evaluated at four different moments over the intervention protocol: prior to implementation of the protocol (baseline) and then at 3 months (first evaluation), 6 months (second evaluation) and 12 months (third evaluation) after implementation. All variables were measured by health professional as physical therapists, nurses and biomedical professionals, who have experience in caring for children with CZS and in the assessment instruments used in this study.

### Intervention protocol

The proposed intervention protocol consisted of individualised physiotherapy conducted under the supervision of instructors and therapists with specialist training in NDT and experience in treating children with CZS. Also known as the Bobath concept, NDT is a problem-solving approach focused on the treatment of functional impairments, postural alignment and movement.[19] Therefore, NDT is an individualised approach aimed at improving functionality and, consequently, the quality of life of individuals with neurological deficits.[19]

Over a 1-year period, all the children attended 45-min physiotherapy sessions from one to five times weekly, depending on the child's overall condition, with the criteria taken into consideration being the child's weight and level of motor impairment as well as the availability of the mother/caregiver to take the child to the place where the therapy was provided.

The treatment programs were structured in accordance with the individual needs of each child, taking into consideration motor potentiality, physical and cognitive status and performance in the motor evaluation established using the GMFM-88. Therefore, in accordance with the principles of NDT,[20] each child's possibilities were first observed in terms of their functional capacity. Using specific manoeuvre techniques, the objectives of this highly individualised treatment were to influence movement, improve the child's postural alignment and stimulate the practice of relevant functional skills.[20]

During the follow-up routine carried out by the Support Center for Children with Microcephaly, where the present study was performed, mothers/caregivers of children with CZS receive

information regarding the daily care of their children and postures to be adopted during daily routine. However, no additional or specific instructions were provided to mothers/caregivers who took part in this study. Besides that, mothers did not participate in therapy sessions, or were instructed to perform any exercise programs at home.

### Statistical analysis

A database was created using RedCap software. Measures of central tendency and dispersion were used to conduct a descriptive data analysis and statistical inference was then calculated. Continuous variables such as weight, height and head circumference *z*-score were analysed using one-way analysis of variance (ANOVA) with Bonferroni correction. Categorical variables such as the GMFM-88 scores (total score and the score for each dimension) were analysed using the Friedman test. These analyses were performed independently for each of two groups: the children classified as GMFCS level V and those classified as any GMFCS level other than V.

For the categorical variables such as comorbidities, including pneumonia, hospitalisations, UTIs and URTIs, baseline results were compared with the results at each one of the subsequent evaluations using the $X^2$ test. All the analyses were performed using MedCalc software, version 19.0.7 (MedCalc Software bvba, Ostend, Belgium), with statistical significance set at 5%.

## Results

Thirty children were included in the study, 43.3% ($n = 13$) of them boys. Age at baseline ranged from 21 to 35 months (mean $30.1 \pm 3$ months). According to the GMFCS, 93.3% ($n = 28$) of children had severe motor impairments and were classified as level V, with only one child being classified as level III and one as level II. No children presented change in this classification throughout the assessments (Table 1).

Over a year of follow-up, the number of NDT sessions per child ranged from 53 to 167, with a mean of $38.5 \pm 15.6$ sessions between baseline and 3 months of treatment, $32.1 \pm 16.4$ between 3 and 6 months, and $26.5 \pm 11.8$ between 6 and 12 months. The proportion of children who attended a mean of over three sessions a week decreased from 43.3% ($n = 13$) in the interval between baseline and 3 months to 33.3% ($n = 10$) between 3 and 6 months and to 23.3% ($n = 7$) between 6 and 12 months of intervention.

For most of the children, that is, those classified as GMFCS level V, no statistically significant difference was found in the total GMFM-88 score over the follow-up period ($P = 0.19$). Considering each GMFM-88 dimensions independently, differences between the evaluations were found only for dimension A (Lying and Rolling) ($P = 0.021$), with a statistically significant difference when the evaluation at 6 months was compared with the other evaluation moments ($P < 0.05$). No other statistically significant differences were found for any other GMFM-88 dimensions when results were compared with baseline (Fig. 1).

**Table 1** General characteristics of the sample

| | *n* (%) | Mean (SD) | Range |
|---|---|---|---|
| Sex | | | |
| Female | 17 (56.7) | | |
| Male | 13 (43.3) | | |
| Age at baseline evaluation (months) | | 30.1 (3) | 21–35 |
| Gestational age at birth (weeks) | | 38.2 (2.2) | 32–41 |
| Weight (g) | | | |
| At birth | | 2670.0 (568.3) | 1060–3730 |
| At baseline | | 9871.3 (2359.2) | 1038–13 200 |
| Length/height (cm) | | | |
| At birth | | 45.3 (3.0) | 36–51 |
| At baseline | | 86.5 (4.7) | 79–96 |
| Head circumference (cm) | | | |
| At birth | | 29.5 (2.0) | 23–32 |
| At baseline | | 40.8 (2.4) | 37–46 |
| Microcephaly at birth† | | | |
| No | 5 (17.2) | | |
| Mild | 9 (31.0) | | |
| Severe | 15 (31.0) | | |
| GMFCS at baseline evaluation | | | |
| Level II | 1 (3.1) | | |
| Level III | 1 (3.1) | | |
| Level V | 28 (93.3) | | |

GMFCS, Gross Motor Function Classification System. † At the initial evaluation, anthropometric data at birth were missing for one child.

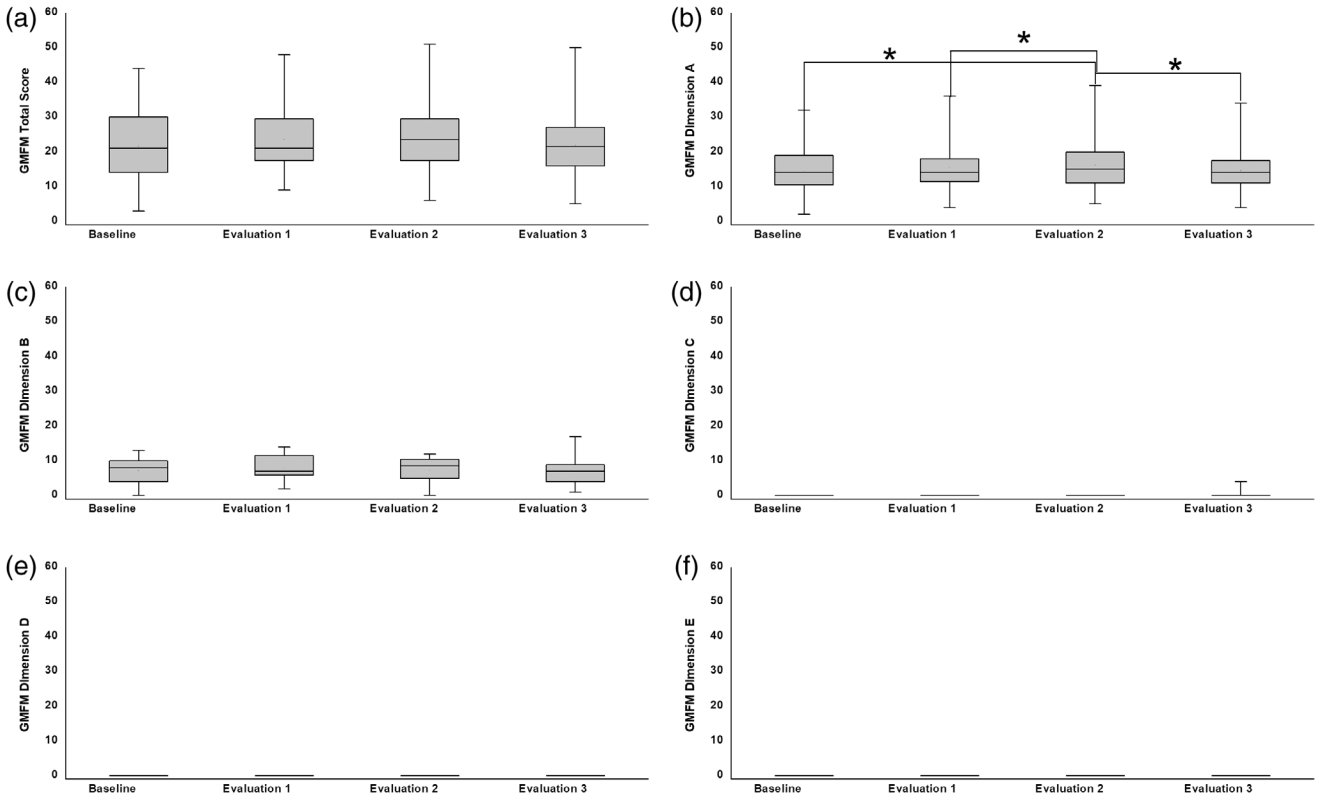


**Fig. 1** Graphs representing the median GMFM scores for the children classified as GMFCS level V over the follow-up period. (a) Total score; (b) Dimension A – Lying and rolling; (c) Dimension B – Sitting; (d) Dimension C – Crawling and kneeling; (e) Dimension D – Standing; (f) Dimension E – Walking, running and jumping. Statistically significant difference ($P < 0.05$). GMFM, Gross Motor Function Measure.

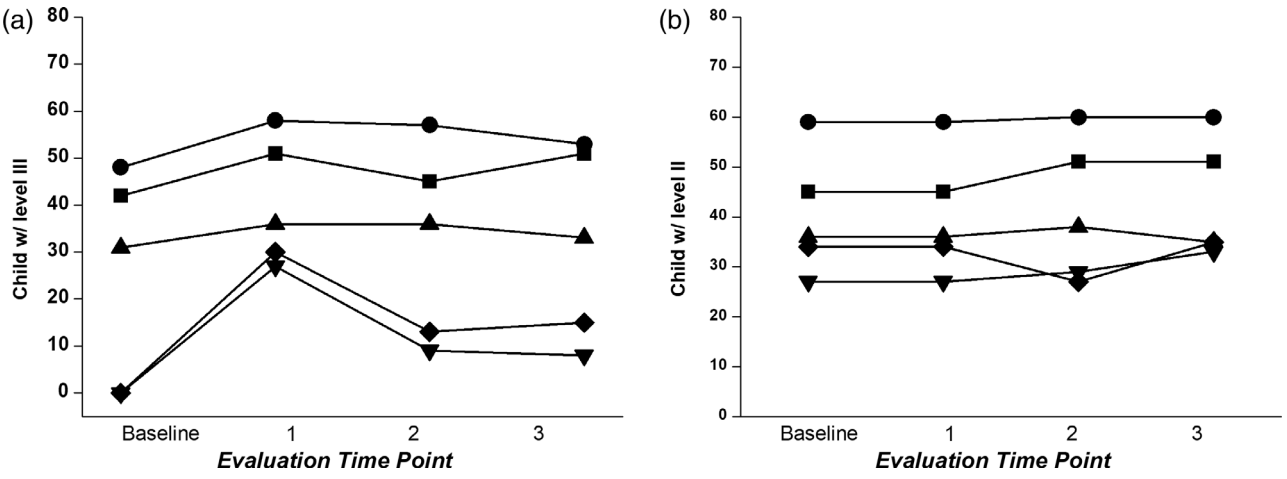


**Fig. 2** GMFM scores (dimensions A–E) of the two children classified as GMFCS levels other than V. (a) A child with GMFCS level III; (b) A child with GMFCS level II. GMFCS, Gross Motor Function Classification System; GMFM, Gross Motor Function Measure. (a): (–■–) Dimensão A, (–●–) Dimensão B, (–▲–) Dimensão C, (–▼–) Dimensão D and (–◆–) Dimensão E. (b): (–■–) Dimension A, (–●–) Dimension B, (–▲–) Dimension C, (–▼–) Dimension D and (–◆–) Dimension E.

For the two children classified as other GMFCS levels than V, improvements or stability were observed in GMFM-88 Total scores throughout evaluation period, except children level III that presented a decrease in this score between 3 and 6 months. Scores of each GMFM-88 dimension are individually represented in Figure 2.

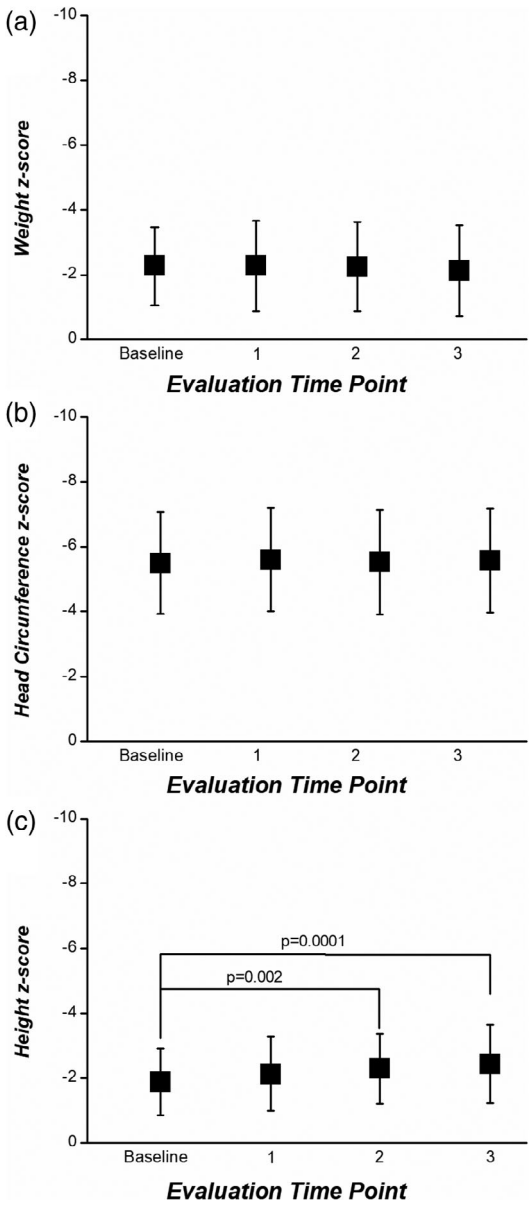


**Fig. 3** Progressive difference in the anthropometric parameters over the follow-up period: (a) Weight, (b) head circumference and (c) height.

Regarding anthropometric parameters, for weight *z*-score, no difference was observed in weight of children throughout the evaluation period ($P = 0.51$). The number of children with adequate weight-for-age remained the same ($n = 14$) and there was a reduction in the number of children with very low weight-for-age ($n = 10$), when baseline was compared to the 3- ($n = 5$; $P = 0.0004$) and 6-month ($n = 9$; $P = 0.003$) evaluations. In this case, an increase of children with low weight-for-age was observed at 3- and 6-month evaluations. When baseline was compared to the 12-month evaluation, however, a reduction was found in the number of children with adequate weight-for-age ($n = 13$) and in those with very low weight-for-age ($n = 8$; $P = 0.003$), associated with an increase of children with low weight-for-age ($n = 9$). There was an increase in height *z*-score over the evaluations, with statistically significant differences were observed when baseline was compared to 6- ($P = 0.002$) and 12-month ($P = 0.0001$) evaluations. Finally, no difference was observed in head circumference *z*-score, when the baseline was compared to other assessments ($P = 0.29$). Changes in anthropometric *z*-score parameters are shown in Figure 3.

Comorbidities in the month referring to baseline accounted for five children being hospitalised and for two being diagnosed with pneumonia, three with a UTI and 14 with a URTI. After 3 months of treatment, in the month of the first evaluation, no child was hospitalised ($P = 0.003$) and none were diagnosed with a UTI ($P < 0.001$) or with pneumonia ($P < 0.001$); however, nine children were diagnosed with a URTI ($P = 0.53$). After 6 months of treatment, in the month of the second evaluation, no child was hospitalised ($P = 0.0003$) or diagnosed with pneumonia ($P < 0.001$); however, one child was diagnosed with a UTI ($P = 0.74$) and three with a URTI ($P = 0.47$). Finally, in the month of the third evaluation, at 12 months of treatment, three children were hospitalised ($P = 0.42$), one was diagnosed with a UTI ($P = 0.53$), there were no cases of pneumonia ($P < 0.001$) and five were diagnosed with a URTI ($P = 0.75$). No deaths occurred during the study period.

## Discussion

Over the year of follow-up, NDT proved to be a viable motor intervention in children with CZS. There was a reduction in the incidence of those comorbidities that tend to be common in this population, and stability in weight *z*-score throughout the study period. Furthermore, improvements were recorded in motor function, particularly with respect to dimension A (laying and rolling) of the GMFM-88 in children with severe motor impairment (GMFCS level V). On the other hand, children with less severe motor impairment, classified as GMFCS levels II or III, experienced an improvement in motor function, as reflected in an increase in their total GMFM-88 score. Nevertheless, the very small number of children classified as GMFCS II or III avoids any conclusions from being reached.

These results do not corroborate the findings of a pilot study that evaluated the effects of a family focused intervention program in which the mothers were responsible for stimulating their children, with the therapist being responsible for monitoring the child, holding weekly support groups and making two home visits over a follow-up period of 16 weeks. That study found that, despite an improvement in the mothers' perception with respect to the effects of the intervention, there was no difference in the children's motor or cognitive function measured using the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III scale).[11] This is the only previous study that does not report improvements in motor function after intervention programs in children with CZS.

Improvements in head and trunk alignment and in social interaction were described in a child with CZS after 6 weeks of home physiotherapy conducted by physiotherapists in addition to activities carried out by the parents.[12] Furthermore, an intense intervention program delivered by physiotherapists resulted in positive effects on the motor function of seven children with CZS evaluated using the GMFM-88.[13] Those findings suggest the capacity of

children with CZS to improve motor functions after intervention programs conducted by specialised professionals; however, the generalisation of their results is limited by the sample size. Results of the present studies reinforce the importance of rehabilitation programs conducted by trained professionals in achieving a positive effect on the motor function of children with CZS. It is important to emphasise, however, that even in therapeutic protocols where parents are not active elements as proposed here, parents have fundamental for stimuli children at home and for bringing children to therapeutic session.

The present results show no improvement in the total GMFM-88 score in the majority of the children evaluated, despite an improvement in the scores for dimension A (laying and rolling). These results can be explained considering that almost entirely of evaluated children have severe motor impairment, been classified as GMFCS level V (93.3%). Children classified in this level usually do not have independent mobility and are dependent for most aspects of daily life.[16,21] Frequently, these children catch a plateau in motor skill development earlier than children in other GMFCS levels.[22] Considering these findings, we do not expect improvements in GMFM-88 dimensions after dimension A (laying and rolling) or dimension B (sitting). However, the importance of small progress in motor control on the quality of life of these children cannot be disregarded.

Diseases related to the lungs such as pneumonia have been described as the main cause of death in children with CZS and such illnesses are directly related to the common occurrence of dysphagia and micro-aspiration.[9] In the present study, no deaths occurred during the follow-up period, with a reduction being found in the incidence of comorbidities such as pneumonia and UTI. This fact may be related to the increase in mobility and axial muscle control that could have led to changes not only in nutritional efficacy, but also in the functioning of diaphragm and accessory muscles of respiration, which are essential for the mechanics of pulmonary ventilation in addition to helping reduce constipation and, consequently, UTI.

Children with CZS commonly present with hyper-excitability and increased muscle tone in the first months of life. Together with hyperreflexia, this could erroneously suggest that the child had achieved neck control.[23] As they become older, these children begin to present with axial hypotonia and appendicular hypertonia, making the impaired motor control in the neck and trunk clearly identifiable.[23,24] Added to this, the disappearance of the primitive reflexes of sucking and swallowing, as well as oropharyngeal impairments, can result in nutritional inefficacy, micro-aspiration, nutritional deficiencies and the occurrence of recurrent pneumonia.[23,25] The gains in performing tasks in supine position that require control of the neck and trunk muscles such as lifting the head in the prone and supine positions and rolling, as evaluated in dimension A (laying and rolling) of the GMFM-88, suggest improvement in the activation of the axial muscles that could benefit feeding and minimise secondary complications in children with severe motor impairment,[26] such as the great majority of the children who participated in this study.

Gastrointestinal and urinary complications are common in children with motor impairment, little mobility and with insufficient fluid intake, since constipation, associated with faecal impaction, can compress the bladder and lead to incomplete emptying and a greater risk of UTI.[27] On the other hand, diminished mobility and deficits in neuromuscular control also appear to be related to severe impairment of pulmonary function in children classified as GMFCS levels III, IV or V.[28–30] In this way, through the use of specific positions and postures, NDT is able to promote neuromuscular relaxation and improve the motor control of children with severe motor impairment,[31] with a consequent improvement in the mechanics of breathing, peristalsis and voluntary movement. Furthermore, the manoeuvres proposed in NDT are based on identifying specific biomechanical stiffness and misalignments in each individual child,[20] which could have contributed towards the reduction in the incidence of comorbidities in these children with CZS.

Little research has been done on the progress made by children with CZS participating in rehabilitation protocols or on the optimal evaluation instrument with which to measure these children's progress. For this study, we opted to use the GMFM-88, since this instrument has been widely used to evaluate motor function in children with neurological impairments; however, this is an exclusively quantitative measurement that does not take quality of life or small improvements in motor function into consideration. The choice of evaluation instruments has previously been described as a reason for the lack of scientific evidence in paediatric rehabilitation programs, with a need having been suggested[32,33] for qualitative evaluation instruments with which to measure elements such as biomechanical alignment, the ease of initiation, speed, smoothness and the efficiency of movement.[33] Besides that, opinion of health professionals and parents about improvements of children may represent an important element to be evaluated after invention programs. This is because these individuals can evaluate children over a longer period of time, identifying individual improvements that can have particular importance for each child.

Another relevant point with respect to the proposed treatment protocols concerns gain or stability in weight, length/height and head circumference. The evaluation of these measurements in children with CZS has been the focus of previous studies aimed at increasing understanding on the natural progression of the disease[34,35] and the growth of children diagnosed with this pathology.[36] In rehabilitation programs for children with CZS, one of the concerns is that the energy expended during the intervention could have a negative effect on the child's weight, particularly in cases of nutritional inefficacy.[23,25,35] Therefore, the absence of any deficits in weight or growth in the children of this cohort suggests that NDT is safe insofar as the maintenance of weight is concerned. Notwithstanding, despite the gains or stability in weight, height and head circumference, the children in the present study are still below the expected values for age,[37] which could be explained by their severe neurological impairment.

Another point that draws attention in this study is the reduction in attendance at physical therapy sessions after 3 months of intervention. This is concerning for long-term therapy which these children need. The causal factors underlying this reduction may include social issues of CZS,[38] particularly difficulties with transportation, the long distances that have to be covered to obtain specialist health care and the fatigue of carers, all of which could limit the participation of children in rehabilitation programs. This finding highlights the importance of training professionals to carried out rehabilitation programs closer to the

children's home. In addition, therapeutic programs for these children should also include therapies with their mothers, in order to reduce their physical and mental burden.

The inadequacy of the instrument used to evaluate motor function represents a limitation of the present study. As previously described, GMFM-88 could have masked possible progress in motor function achieved by the children evaluated here, which, although evident to the professionals and parents, was insufficient to be reflected in the GMFM-88 score. The absence of monitoring the activities and positions adopted by children at home is also a limitation that needs to be taken into consideration in future studies. Nevertheless, the most important limitation of this study was the fact that most of the children in this sample were classified as GMFCS level V. A new study is being developed that will use the International Classification of Functioning, Disability and Health (ICF) to evaluate the effects of motor intervention programs on the body functions, activity and participation of children with CZS.

As we are dealing here with children with severe neurological impairment, victims of a new disease, an improvement in motor function is not the only objective of rehabilitation programs. Improving quality of life, as reflected in a reduction in mortality and in the number of hospital admissions, should be considered a positive result and should be included in scales aimed at evaluating children with severe motor impairment. Evaluating an improvement in quality of life of children with severe neurological damage and proposing interventions for this purpose is of the utmost importance in countries such as Brazil where pregnancy interruption is not allowed and where these children will have to be followed up for undefined periods of time.

## Conclusions

NDT is a safe and feasible therapeutic approach that can reduce the incidence of respiratory and urinary comorbidities in children with CZS and improve their motor function, with no harmful effects on their growth. These results emphasise the need for rehabilitation programs for children with CZS and severe motor impairment using instruments capable of detecting small gains in motor function, improvements in quality of life and reductions in comorbidities.

## Acknowledgements

The authors would like to thank the entire research department at IPESQ, as well as the children and their mothers or guardians for having participated in this study.

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The Secret Sky - Under the Sea by Fatima Mian (age 15) from Operation Art