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ORIGINAL RESEARCH

Effect of Intensive Physiotherapy Training for Children With Congenital Zika Syndrome: A Retrospective Cohort Study

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Abstract

Objective: To investigate the effect of intensive physiotherapy training on the motor function of children with congenital Zika syndrome (CZS).

Design: A retrospective cohort study.

Setting: A support center for children with microcephaly.

Participants: Children (N=7) aged 14 to 18 months old who were diagnosed with CZS and previously monitored more than 1 year.

Interventions: A 2-stage protocol repeated uninterruptedly for 1 year. In the first stage, the children were submitted to 1 hour of conventional physiotherapy and 1 hour of suit therapy 5 times a week for 4 weeks. The second stage consisted of 1 hour of suit therapy 3 times a week for 2 weeks.

Main Outcome Measures: Gross motor function measure (GMFM) and body weight.

Results: Six evaluations were conducted approximately 3 months apart. An increase in the overall GMFM score was observed between the first and second ($P=.046$), first and third ($P=.018$), first and fourth ($P=.018$), first and fifth ($P=.043$), and first and sixth evaluations ($P=.018$). Differences in the scores of the individual GMFM dimensions were found only for dimension A (lying and rolling) between the first and fourth evaluations ($P=.027$) and for dimension B (sitting) between the first and third ($P=.018$), first and fourth ($P=.046$), and first and sixth evaluations ($P=.027$). No difference was found in body weight between the first and sixth evaluations ($P=.009$). During follow-up, only 1 child required hospitalization, and another had increased irritability.

Conclusions: Children with CZS were able to perform 2 hours of motor physiotherapy daily with no serious complications, resulting in an increase or stabilization in GMFM scores.

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In 2016, an association was confirmed between intrauterine Zika virus infection and fetal brain abnormalities such as microcephaly.[1] Various forms of brain damage have been reported, including diverse forms of calcification (particularly subcortical and in the basal nuclei), compensatory ventriculomegaly, malformations of cortical development, brainstem or cerebellar hypoplasia, and dysgenesis of the corpus callosum.[2-5] Until now, calcifications at the gray-white matter junction have only been described in children infected with Zika virus during intrauterine life, making this a characteristic of congenital Zika syndrome (CZS).[1,3,6,7]

Despite severe brain damage, not all children infected by Zika virus during pregnancy die. Just in the state of

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Pernambuco, 456 cases of CZS were registered as of June 2018, with 164 deaths recorded.[8] Survivors often have certain clinical characteristics, including abnormal muscle tone, hyperreflexia, irritability, deglutition disorders, and uncontrolled seizures.[2]

Intervention protocols aimed at improving motor function in children with CZS are urgently required to develop their potential and minimize disabilities and morbidities. Physiotherapy based on the principles of cerebral plasticity and motor learning appears to represent an option for therapy.[9,10] Structured motor practice could lead to structural and functional changes in the central nervous system.[11,12] This study aimed to investigate the effect of a protocol of intensive training on motor function and clinical complications (irritability, hospitalization, and weight loss) in children with CZS.

Methods

A retrospective cohort study was conducted using data from the medical records of children with CZS who received care at a support center for children with microcephaly at Campina Grande, Paraiba, Brazil, and who participated in a physiotherapy program implemented in July 2017. The physiotherapy program was implemented at the beginning of care and is duly recorded in each child's individual medical records. Data from these medical records were used for this study, which was approved by the research ethics committee of Alcides Carneiro University Hospital.

Sample

The inclusion criteria were a confirmed or probable diagnosis of CZS according to the case definitions established by the Centers for Disease Control and Prevention,[13] participation in the intensive physiotherapy program for 1 year, and the availability of adequate records of the child's progress during physiotherapy. The exclusion criteria were microcephaly of other causes, incomplete clinical records, having not yet initiated intensive training or not yet completed the full program, uncontrolled seizures, hip subluxation, and weight less than 9.8 kg as recommended in the PediaSuit[a] protocol.[14,15]

Intervention protocol

A program of intensive physiotherapy training involving 6-week cycles, each consisting of 2 stages, was repeated uninterruptedly for 1 year. In the first stage, children participated in 2-hour physiotherapy sessions 5 times a week for 4 weeks. These sessions included 1 hour of conventional physiotherapy, followed by 1 hour of motor physiotherapy using a therapy suit (PediaSuit). The second stage consisted of 1-hour sessions of suit therapy 3 times a week for 2 weeks (fig 1).

This protocol was repeated 6 times over a 1-year period, with no time gap between the 2 stages of the program. As it consisted of intensive physiotherapy training for children with severe brain damage of unknown course, the second stage of the protocol served as a maintenance phase to avoid excess calorie expenditure or weight loss. This design was conceived because studies have suggested that weight gain is lower in children with CZS compared with children with typical development.[16,17]

Specialist physiotherapists conducted the sessions, which were individualized for each child, taking their next functional activity level into consideration.[18-20] The exercises performed in the first stage consisted of conventional physiotherapy exercises such as joint mobilization, stretching, exercises to promote neck control and core stability, neurorehabilitation and automatic postural responses and positions, functional activities, and so on.[18,19] In the second stage, the children used therapy suits and performed exercises aimed at strengthening muscles and correcting posture, as well as functional exercises. The complete PediaSuit protocol was not performed owing to the high calorie expenditure required. Therapy suits were used to stimulate proprioception, muscle contraction, and postural stability. Traction bands were placed on the trunk to stimulate muscle control by stabilizing this area and the antigravity muscles.[15] The ability exercise unit was also used to stimulate postural stability and muscle resistance, according to the functional ability of each child.[15]

If previously controlled seizures became uncontrolled during the program or if the child succeeded in sitting unaided, the protocol was interrupted or altered. The children were given regular clinical support throughout the study. Missed sessions, convulsive seizures, increased irritability, and hospitalizations were recorded.

Data collection and procedures

Data were collected from each individual child's clinical records between June 2017 and August 2018. Data on gross motor function, measured using the Gross Motor Function Measure (GMFM), weight, convulsive seizures, and hospitalizations were recorded every 3 months on an evaluation form created at our institute. Records of missed sessions were dichotomized into fewer than 40% or 40% or more of sessions missed. Abnormalities in cortical development were classified as severe (agyria, pachygyria, or malformations of cortical development) or mild (simplified gyral pattern) according to magnetic resonance imaging findings.

The gross motor function classification system was used to evaluate motor function. Five levels define a child's independence and functionality according to age, with level I referring to independent children and level V to children with severe handicaps.[21] The GMFM, which is widely used to evaluate children with cerebral palsy,[22-25] was used to evaluate motor function. This ordinal scale consists of 88 tasks divided into 5 dimensions: A, lying and rolling; B, sitting; C, crawling and kneeling; D, standing; and E, walking, running, and jumping. Each task is rated from 0 (unable to initiate the task) to 3 (completes the task). The overall score is the sum of the scores for all activities performed, whereas the scores for the dimensions consist of the sum of the scores for the activities performed in each individual dimension. Physiotherapists performed all evaluations. The physiotherapist responsible for a child's treatment did not participate in the evaluation of that child. The kappa coefficient (kappa 0.8) was calculated for the initial evaluation to determine agreement between evaluators.

List of abbreviations:

CZS congenital Zika syndrome
GMFM gross motor function measure

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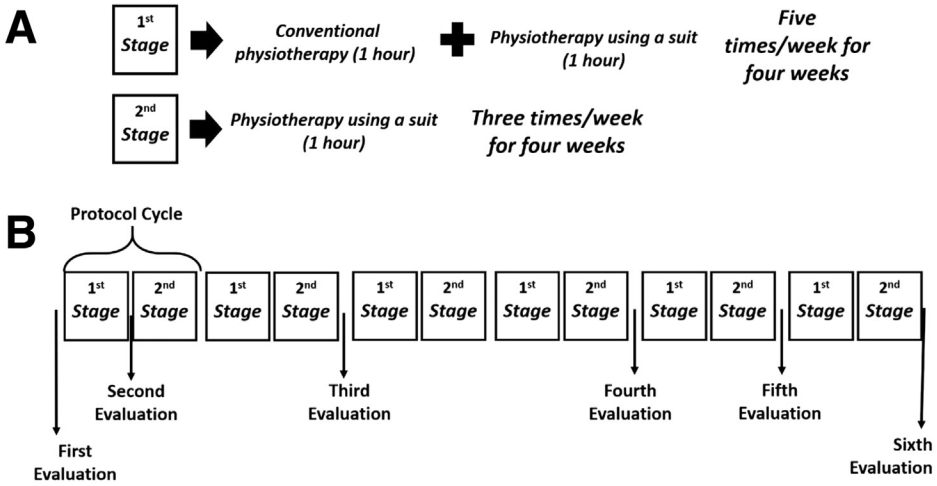


Fig 1 Description of the intervention over 1 year. Description of each stage in the intervention (A) and description of the evaluation moments throughout the follow-up period (B).

Statistical analysis

Statistical analysis was performed using MedCalc, version 17.9.7,[b] based on one evaluation conducted more than 3 months before initiating the protocol (first evaluation) and then at 1 (second evaluation), 3 (third evaluation), 6 (fourth evaluation), 9 (fifth evaluation), and 11 (sixth evaluation) months after initiation.

A descriptive analysis was performed for the variables: weight, gross motor function classification system, the overall GMFM score and the score for each individual GMFM dimension, maternal age, gestational age at birth, symptoms of maternal Zika infection, head circumference and weight at birth, first and fifth minute Apgar scores, presence of abnormalities of cortical development, use of anticonvulsants, microcephaly at birth, microcephaly at the sixth evaluation, and missed physiotherapy sessions. Weight changes were evaluated using the paired *t* test to compare weight at the first evaluation with weight at the sixth evaluation. The overall GMFM score and the score for each GMFM dimension at the first evaluation were compared with the scores obtained at subsequent evaluations using the Wilcoxon test for paired samples. Pearson's linear correlation coefficient was calculated to evaluate the association between the overall GMFM score at the first and sixth evaluations and factors such as having missed sessions, head circumference, birthweight, prematurity, and the number of anticonvulsants used. Spearman's correlation coefficient was used to evaluate the association between the overall GMFM score at the sixth evaluation and prematurity. The significance level was established at 5%.

Results

All 7 children had the characteristic calcifications at the gray-white matter junction and only 1 child (child 4) had no severe abnormalities of cortical development. Table 1 lists the general characteristics of the mothers and children, and table 2 lists the individual characteristics of each child.

The overall GMFM score increased between the first (median, 20) and second evaluations (median, 33; increase of 33.8%; $P=.046$), between the first and third evaluations (median, 36; increase of 56.8%; $P=.018$), between the first and fourth evaluations (median, 30; increase of 72.9%; $P=.018$), between the first and fifth evaluations (median, 30; increase of 73.4%; $P=.043$), and between the first and sixth evaluations (median, 32; increase of 79.5%; $P=.018$).

There were significant changes in GMFM dimensions A and B. In dimension A, an improvement of 25% occurred between the first and fourth evaluations (median scores, 13 and 20; $P=.027$). For dimension B, differences were found between the first and third (median, 8 and 15; $P=.018$), first and fourth (median, 12; $P=.046$), and first and sixth evaluations (median, 12; $P=.027$). Figure 2 shows the GMFM scores for the entire group throughout the study, and figure 3 shows the overall GMFM score for each child (fig 3A) and the imaging tests revealing the neurologic damage (fig 3B).

None of the children lost weight between the first and sixth evaluations (10.2±1.4 vs12.2±2.0; $P=.0090$) (fig 4). Only 1 child (child 1) was hospitalized and another (child 7) experienced increased irritability. Overall, 188 physiotherapy sessions were scheduled, and the mean number of missed sessions was 27±13.2, with children 2 and 7 missing more sessions (38 [20.2%] and 51 [27.1%], respectively).

One child (child 6) made rapid progress in motor function, sitting without support, and crawling after 3 months of therapy. The protocol for that child was modified, being initially reduced to 1 hour of conventional physiotherapy and 1 hour with a therapy suit 3 times a week and then to 45 minutes of conventional physiotherapy twice weekly.

The number of missed sessions was associated with the overall GMFM score at the sixth evaluation ($r=-0.80$; $P=.031$), but not at the first evaluation ($r=-0.53$, $P=.19$) for the children who had missed the greatest number of sessions having the poorest motor performance at the final evaluation.

Discussion

The initial hypothesis that an intervention protocol consisting of intensive physiotherapy training could improve motor function in children with CZS was partially confirmed. This indicates the

Table 1 General characteristics of the study sample

Characteristics	n (%) or Mean ± SD
Characteristics related to the mother	
Age, y	
Range	21-35
Mean ± SD	29.3±4.3
Married	
Yes	7 (100)
No	0
Parity	
Primipara	3 (42.9)
Multipara	4 (57.1)
Type of childbirth	
Vaginal delivery	2 (28.6)
Cesarean section	5 (71.4)
Symptoms of infection	
In the first trimester of pregnancy	5 (71.4)
In the second trimester of pregnancy	2 (28.6)
Characteristics related to the child	
Sex	
Female	2 (28.6)
Male	5 (71.4)
Gestational age at birth	
Range	34-40
Mean ± SD	36±2.0
Prematurity	
Yes	3 (42.9)
No	4 (57.1)
Diagnosis of CZS	
Confirmed	3 (42.9)
Probable	4 (57.1)
Baseline GMFCS	
II	1 (14.3)
IV	1 (14.3)
V	5 (71.4)
Anticonvulsant use	
Yes	3 (42.9)
No	4 (57.1)
Microcephaly at birth	
No	2 (28.6)
Mild	1 (14.3)
Severe	4 (57.1)
Microcephaly at sixth evaluation	
Mild	1 (14.3)
Severe	6 (85.7)
Missed sessions	
<40%	5 (71.4)
≥40%	2 (28.6)

Abbreviation: GMFCS, gross motor function classification system.

capacity of cerebral plasticity in these children and highlights the need for intensive, specialized physiotherapy to minimize motor sequelae and even to maintain already acquired motor skills. Despite the intensive protocol, none of the children lost weight, and only 1 required hospitalization and 1 experienced increased irritability.

The fact that no child lost weight suggests that the possible increased calorie expenditure during physiotherapy had no negative effect on weight gain. Although the sample evaluated in this study was small, this finding was reassuring for the team providing care to these children, because there was initial concern that an intensive physiotherapy program could exert harmful effects, particularly in children with such severe neurologic damage.

In relation to the progress made in motor function, improvements were only observed when each evaluation time point was compared with the first evaluation. Furthermore, although the difference was statistically significant, there was a broad range in the overall GMFM scores, suggesting that not all children responded similarly, with the difference in GMFM scores being minimal in some children. This slow progress in motor function could be associated with the severe brain damage found in the children evaluated or may even be related to the number of physiotherapy sessions missed. Another point that should be discussed in future studies is whether the improvement found could be owing to the acquisition of motor skills typical for age.

Except for children 4 and 6, the overall scores stabilized or even decreased in the other children after the fourth week of the intervention. This finding merits further investigation, taking into consideration the possibility of fatigue or even of a plateau in the acquisition of motor skills caused by the severity of the neurologic damage. As is clear from the brain images of each individual child, brain damage is most severe in children 2, 3, 5, and 7. Nevertheless, in child 1, there was also a decrease in motor progress, even though the brain damage was not as severe as in the other children. Because this is a new disease, the extent of the brain lesions and their effects on children's clinical development are not yet fully understood. Further studies with larger sample sizes and involving detailed neuroradiological parameters need to be carried out.

In relation to the other children, there was a decrease rather than stabilization in the overall GMFM score in child 2 at certain evaluation points. This could be related to the number of missed physiotherapy sessions, suggesting the importance of repetition to improve or even maintain motor skills.[26]

The best progress found was in children 4 and 6. A rapid improvement in motor function was seen in child 6, whose intervention protocol was amended from the third evaluation onwards. Although neuroimaging confirmed more severe brain damage compared with child 4, this was the child who adapted most rapidly to the intervention. Because the child's mother was a physiotherapist, home physiotherapy was initiated on the fourth day of life, suggesting that motor stimulation from the very first days of life may have been the differentiating factor in this case. Nevertheless, this is merely a hypothesis that cannot be confirmed from currently available data.

In child 3, the brain parenchymal volume was severely reduced, with agyria associated with severe abnormalities in the structures of the posterior cranial fossa (cerebellar dysmorphia and hypoplasia, as well as cerebellar vermis hypoplasia). Even with such severe brain damage, the child achieved and maintained some motor skills, suggesting that cerebral plasticity can occur even when the brain parenchyma is almost totally absent.

Motor training is a critical factor for cerebral plasticity.[11,12,27] Although changes in cerebral plasticity cannot be confirmed from these data, this would appear to explain the improvement or stabilization in motor function. Our results corroborate a previous report of an improvement in motor function in children with

Table 2 Individual characteristics of each participant

Child no.	Sex	GA, wk	Birthweight, kg	HC at Mirth, cm	Classification of Microcephaly at Birth	Neuroimaging Findings	GMFCS	Age at Ev1, mo	GMFM at Ev1	GMFM at Ev6	GMFM Ev6-Ev1	HC at Ev6, cm	Microcephaly at Ev6
1	M	35	2.190	31	Normal HC	Subcortical calcifications, gyral pattern simplification, mild ventriculomegaly, mild brain volume reduction	V	18	18	29	11	45	Severe microcephaly
2	F	34	1.060	23	Severe microcephaly	Subcortical calcifications, severe brain volume reduction, compensatory ventriculomegaly, lissencephaly, corpus callosum hypoplasia, cerebellar vermis hypoplasia	V	17	17	21	4	37.5	Severe microcephaly
3	M	38	2.950	28	Severe microcephaly	Subcortical calcifications, lissencephaly, severe brain volume reduction, severe compensatory ventriculomegaly, cerebellar dysmorphism and hypoplasia and cerebellar vermis hypoplasia, no corpus callosum, excess scalp	V	14	19	32	13	38	Severe microcephaly
4	M	35	2.025	31	Normal HC	Subcortical calcifications, simplification of gyral pattern	IV	18	45	127	82	45.5	Mild microcephaly
5	M	38	2.480	28.5	Severe microcephaly	Subcortical calcifications, compensatory ventriculomegaly, pachygyria, brain volume reduction, posterior fossa enlargement and cerebellar vermis hypoplasia	V	16	24	32	8	40	Severe microcephaly
6	F	40	2.860	30.5	Severe microcephaly	Subcortical calcifications, frontal lissencephaly, brain volume reduction, compensatory ventriculomegaly, cerebellar vermis hypoplasia and dysgenesis of corpus callosum	II	16	116	201	85	42.5	Severe microcephaly
7	M	38	1.750	27	Severe microcephaly	Subcortical calcifications, pachygyria, brain volume reduction, compensatory ventriculomegaly	V	14	20	23	3	42	Severe microcephaly
Mean			2.787	28.42				16.14	37	66.42	29.42	41.5	
SD			0.61	2.65				1.55	33.48	64.91	34.36	2.92	

Abbreviations: Ev1, evaluation time point 1; Ev6, evaluation time point 6; GA, gestational age; GMFCS, gross motor function classification system; HC, head circumference.

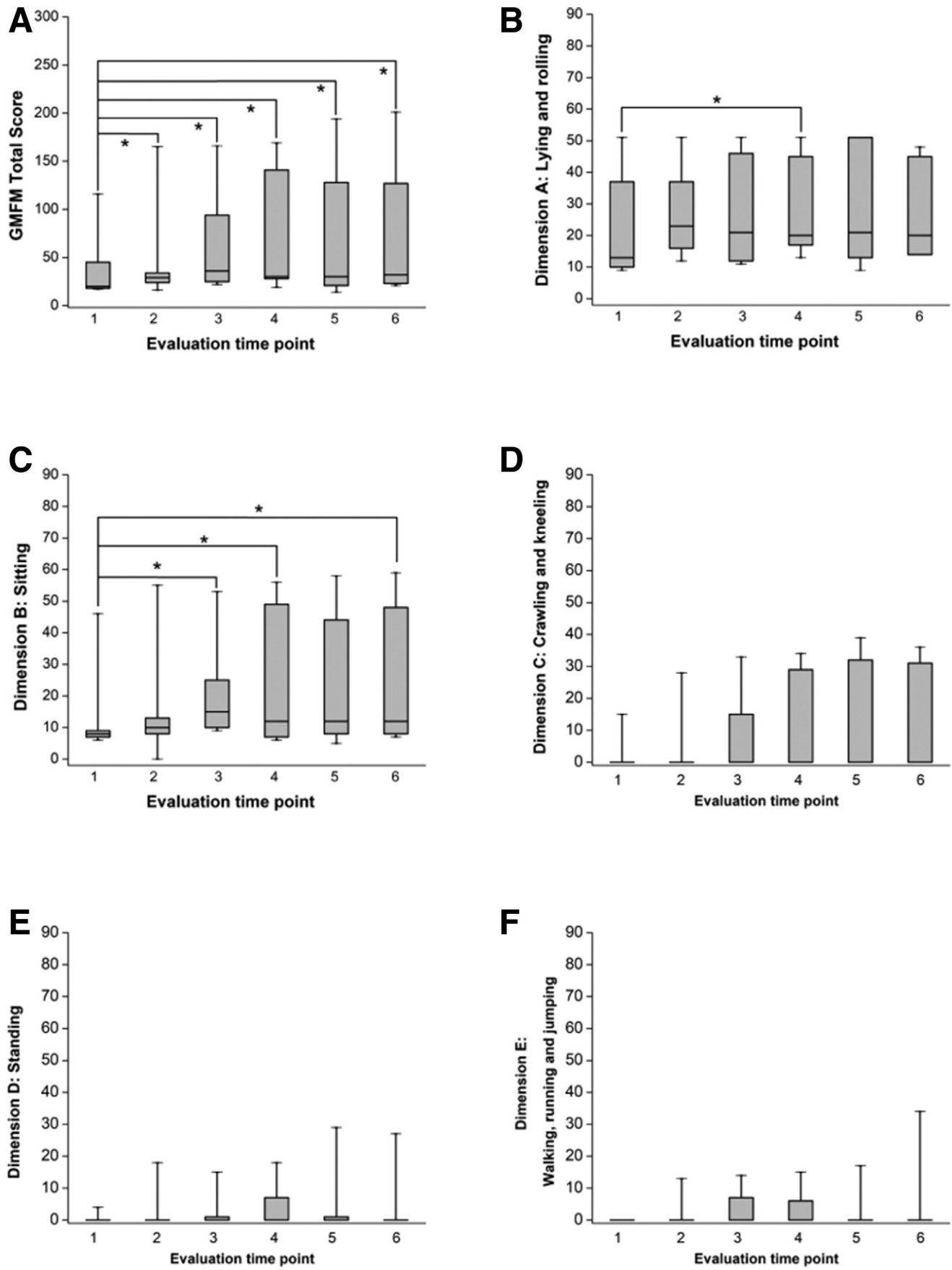
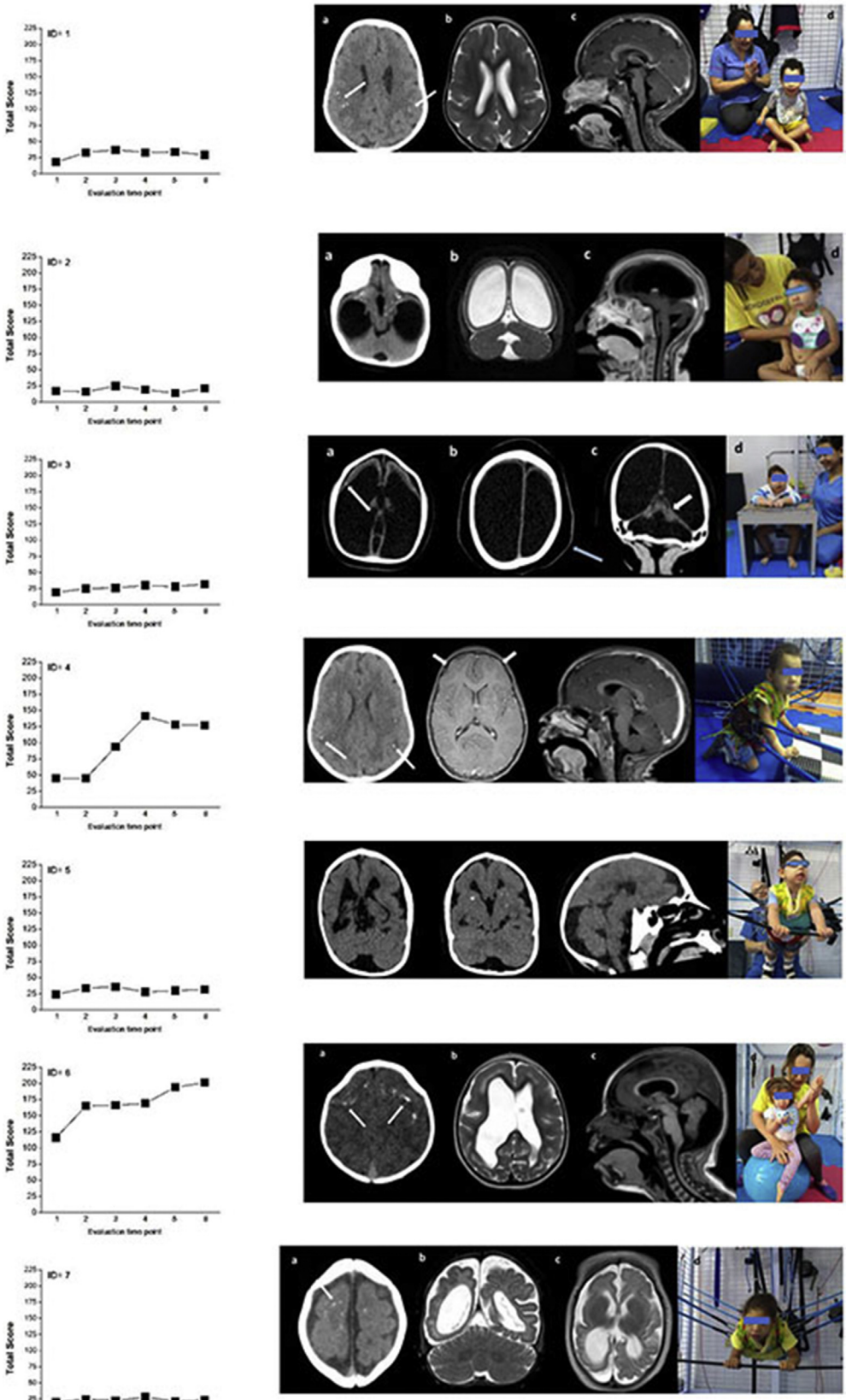


Fig 2 Graphs representing the median GMFM scores over the analysis period. Overall (A); dimension A: lying and rolling (B); dimension B: sitting (C); dimension C: crawling and kneeling (D); dimension D: standing (E); and dimension E: walking, running, and jumping (F). ∗Significant difference ($P<.05$).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microcephaly and pontocerebellar hypoplasia resulting from genetic mutations.[23,28]

In children 2 and 7, there was less variability in overall GMFM scores throughout the intervention, perhaps owing to 2 factors. First, the number of missed physiotherapy sessions may restrict progress. Because motor learning is a process associated with practice and environmental interaction,[26] practice and repetition are essential elements for motor learning and for the success of therapy.[29] Pearson's coefficient corroborated this hypothesis, with a strong negative correlation between missed sessions and the overall GMFM score at the sixth evaluation. Secondly, children 2 and 7 were uncooperative during physiotherapy. Missing sessions could have hampered the child's familiarization with the treatment environment. Although common in children with CZS,[30,31] irritability increased in only child 7, and that same child had missed a considerable number of physiotherapy sessions. Nevertheless, whether the symptom resulted from neurologic damage or from having missed sessions, making adaptation difficult, was impossible to define.

Comparison between the first and sixth evaluations showed that none of the children had lost weight and motor function had improved in the majority of cases, even if only slightly, or had stabilized, suggesting that this intensive physiotherapy program exerted no harmful effects. Similar findings have been reported in children with cerebral palsy from other causes.[19]

Although no harmful effects were recorded during the study, analysis of the cases showed an obvious improvement in motor function in only 2 of the 7 children evaluated, suggesting the need for further studies to evaluate other endpoints such as a reduction in morbidity and admissions to hospital.

Nevertheless, before proposing therapy for these children, some issues that can affect daily compliance with intensive physiotherapy programs must be considered. In general, the per capita income of families of children with CZS is low, their education is poor,[32,33] and transportation to the treatment center may represent a barrier. Furthermore, the additional burden on the family and fatigue in the child are factors that must be considered when making a clinical decision regarding the most appropriate intervention protocol for each child. Individualized protocols that take the severity of brain damage, clinical conditions, and family demands into consideration, and stimulate the potential of each child both in terms of improving motor function and quality of life, would be the best option.

Study limitations

The number of participants included in this study was small. Notwithstanding, this is a new disease involving severe neurologic impairment and the children's response to the proposed physiotherapy program was unpredictable. Therefore, an initial study had to be conducted with children who adapted well to the method. The absence of a control group precluded the possibility of determining whether progress in motor function occurred owing to the intervention or whether it was part of the children's natural development. The retrospective nature of the study was also a limitation. However, the importance of motor rehabilitation was highlighted and development over the intervention period was poorer in the children who missed the greatest number of sessions.

In 2017, knowledge on the disease was insufficient to provide any guidance for this study. Therefore, this retrospective cohort study was initiated and served as a pilot study. Furthermore, the absence of any evidence on intensive physiotherapy programs involving use of a PediaSuit in this population could also be considered a limitation, because the selection of this protocol was based solely on experience in clinical practice.

Identifying the best instrument to measure progress in motor function in children with CZS may also be challenging. The GMFM scale requires important motor progress to be made before a significant increase is obtained. Therefore, it cannot capture the small improvements described by physiotherapists and families. New evaluation scales may need to be developed to enable even slight progress to be registered. In addition, the reductions in the number of hospitalizations, morbidity, and mortality are positive factors that must be evaluated.

Conclusions

These results show that children with CZS can participate in intensive physiotherapy programs with no adverse effect on weight or admissions to the hospital. Nevertheless, the exact effects of therapy dosage and whether these effects are similar with less intensive programs need to be investigated in future studies. Although only an initial step in evaluating physiotherapy programs in children with CZS, the importance of this study lies in the fact that it is the first, that most of the children coped well with daily sessions, and that those who missed fewer sessions responded better to therapy. Future studies should be conducted to evaluate other protocols and to determine the ideal dosage of physiotherapy for these children, also bearing in mind families' difficulties in accessing treatment centers and the severity of brain damage.

Fig 3 Progression in the overall GMFM score. Child 1: computed tomography (a, subcortical calcifications [arrows]); magnetic resonance imaging (b, simplified gyral pattern, mild ventriculomegaly, slight reduction in brain size; c, simplified gyral pattern); d, child performing physiotherapy. Child 2: computed tomography (a, compensatory ventriculomegaly, subcortical calcifications [arrows]); magnetic resonance imaging (b, lissencephaly, severe reduction in brain size, compensatory ventriculomegaly; c, cerebellar vermis hypoplasia); d, child performing physiotherapy. Child 3: computed tomography (a, severe compensatory ventriculomegaly, subcortical calcifications [arrow]; b, lissencephaly, severe reduction in brain size, severe compensatory ventriculomegaly, excess scalp skin [blue arrow]; c, cerebellar dysmorphia and hypoplasia, and dysmorphia and hypoplasia of the cerebellar vermis); d, child performing physiotherapy. Child 4: computed tomography (a, calcifications [arrows]); magnetic resonance imaging (b and c, simplified gyral pattern); d, child performing physiotherapy. Child 5: computed tomography (a, ventriculomegaly, pachygyria, reduced brain size; b, subcortical calcifications [arrows]; c, increased posterior fossa and hypoplasia of the cerebellar vermis); d, child performing physiotherapy. Child 6: computed tomography (a, subcortical calcifications [arrow]); magnetic resonance imaging (b, frontal lissencephaly, reduction in brain size, compensatory ventriculomegaly; c, hypoplasia of the cerebellar vermis and dysgenesis of the corpus callosum); d, child performing physiotherapy. Child 7: computed tomography (a, subcortical calcifications [arrow]); magnetic resonance imaging (b and c, pachygyria, reduction in brain size, compensatory ventriculomegaly); d, child performing physiotherapy.

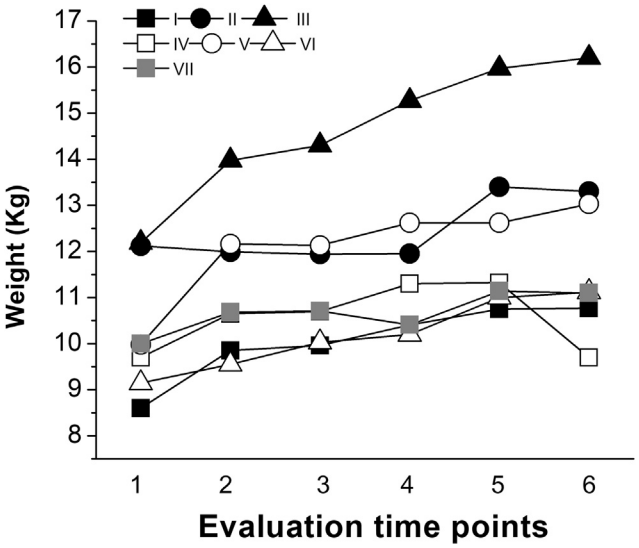

Fig 4 Individual representation of the progression of body weight over the analysis period.

Suppliers

a. PediaSuit; PediaSuit.
b. MedCalc, version 17.9.7; MedCalc Software Ltd.

Keywords

Motor activity and motor skills disorders; Rehabilitation; Zika virus infection

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