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Classification of Congenital Zika Syndrome: Muscle Tone, Motor Type, Body Segments Affected, and Gross Motor Function

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ABSTRACT

Aim: To identify abnormalities in muscle tone and motor function associated with congenital Zika syndrome (CZS).

Method: A cross-sectional observational study involving 96 children (55 males) with CZS at a mean (SD) age 35.2 ± 2.9 months. Children's muscle tone was investigated using the *pull to sit, scarf sign, shoulder suspension* and *ventral suspension* tests and the modified Ashworth scale (MAS). Motor impairment was determined using the Gross Motor Function Classification System (GMFCS) and body segments most affected with motor impairment.

Results: 58 (60,5%) children tested positive for ≥1 maneuver used to evaluate muscle tone, while 38 (39.5%) tested negative in all the tests. MAS score was >0 for at least one of the appendicular muscles in 91 children (94.8%). In 88 children (91.7%), all four limbs were affected.

Conclusion: Findings suggestive of axial hypotonia and appendicular hypertonia associated with severe motor impairment were prevalent in children with CZS.

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muscle hypertonia; muscle hypotonia; muscle tone; Zika virus

Introduction

Between the years 2015 and 2016, Zika virus caused an outbreak of disease that led to a series of brain malformations in children born to infected mothers. Today, the wide spectrum of clinical and radiological findings associated with brain malformations caused by Zika virus infection during pregnancy is referred to as congenital Zika syndrome (CZS).[1] During fetal development, the target of Zika virus appears to be the neural progenitor cells, with consequent deregulation of cell cycle progression and a reduction in neuronal growth,[2] as well as cell migration to the more external layers of the cerebral cortex.[3]

Neuroimaging findings in children with CZS most commonly include microcephaly resulting from a reduction in the volume of the brain parenchyma, ex-vacuo ventriculomegaly, hypoplasia of the brainstem and/or cerebellum, delayed cortical development predominantly in the frontal lobe, dysgenesis of the corpus callosum, white matter abnormalities, delayed myelination, and calcifications, particularly at the gray and white matter junction and in the basal nuclei.[4] The latter, up to now, have only been described in children with CZS.[4,5] The spinal cord is also affected in children with CZS, with a reduction in its thickness and in the nerve roots of the ventral horn, probably resulting from the reduction in the corticospinal tract.[3,6]

In addition to those imaging findings, a range of impairments has been described in children with CZS, including epileptic seizures that are difficult to control,[7] severe impairment to cognitive and motor function,[8–10] sensory abnormalities,[9] dysphagia,[11,12] visual defects,[9] abnormalities in muscle tone, irritability,[9,13] and others.[13,14]

As a consequence of the severe damage to the brain and spinal cord, abnormal muscle tone has been described in these children. Although hypertonia was reported in 74.7% of 83 children with CZS evaluated by Del Campo et al.,[13] in all four patients described by Botelho[15] and in all 14 cases described by Van der Linden et al.,[11] muscle tone in children with CZS has yet to be fully characterized.

Muscle tone is one of the elements that affect selective motor control.[16] Children with abnormal muscle tone would not be able to complete the appropriate motor repertory and consequently, stabilize their body. Additionally, abnormal muscle tone is one of the elements that influence impaired selective motor control in children with neurological impairment,[17–19] which could prevent the children from reaching initial developmental milestones such as neck control. In children with CZS, the situation is even more complex due to the variety of forms of brain damage, with a broad range of neurological conditions and muscle tone characteristics having been described.

Pereira et al.[14] recently drew attention to this variability in a report on 75 children with CZS. Four of the children had symptoms of dyskinesia alone, while 48 (64%) had corticospinal signs, with various combinations of hypertonicity, involuntary crossing of the legs and spasticity, exaggerated deep tendon reflexes and clonus other than a positive Hoffman's sign and Babinski sign, and 23 (31%) showed signs of neuromuscular impairment, with the presence of hypotonia and weak deep tendon reflexes in the distal tendons. Findings of dyskinesia were present in 30 children (40%), either alone or in combination with corticospinal or neuromuscular clinical signs.[14]

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Within this context and considering the range of neurological findings described in children with CZS, the objective of this paper was to report on the abnormalities in muscle tone and motor function impairments in preschoolers who had been conceived during the Zika virus epidemic in 2015–2016 that occurred in northeastern Brazil and in whom the infection was confirmed.

Materials and Methods

A cross-sectional observational study nested within a cohort study conducted at the *Instituto de Pesquisa Professor Joaquim Amorim Neto* (IPESQ) in Campina Grande, Paraiba, Brazil. Motor development was evaluated between August and September 2018. The internal review board of the Alcides Carneiro University Teaching Hospital approved the study protocol. The mothers of all the children included signed an informed consent form.

Participants

Children with a diagnosis of CZS, who had been born during the epidemic of Zika virus infection in Brazil in 2015 and 2016 and who were receiving healthcare at a center for children with microcephaly linked to IPESQ were included in the study. IPESQ has been monitoring children with CZS since 2015, in some cases even prenatally. CZS was diagnosed according to the Centers for Disease Control and Prevention criteria.[20] Children with microcephaly and/or brain damage of other causes including infection by other agents were excluded.

Data Collection Procedures

The children's general data (age, weight, length and head circumference [HC] at birth and at the evaluation, 1st and 5th minute Apgar scores and gestational age at birth) were obtained from the child's health records and the records kept during their care at IPESQ (Table 1).

Table 1. General characteristics of the sample.

Characteristics	n	%
Gestational age (weeks)		
Mean (SD)	38.3 (2.1)	
Range	32–41	
Premature		
Yes	18	18.8
No	74	77.1
Sex		
Female	41	42.7
Male	55	57.3
Head circumference (cm)		
At birth		
Mean (SD)	29.9 (2.0)	
Range	23–35	
At evaluation		
Mean (SD)	41.6 (2.6)	
Range	37–48	
Age at evaluation (months)		
Mean (SD)	35.2 (2.9)	
Range	25–40	
Apgar		
1st Minute Median (IQR)	9 (8–9)	-
5th Minute Median (IQR)	9 (9–9)	-

SD: Standard deviation; IQR: Interquartile range.

Evaluation of Motor Function

Motor impairment was classified using the Gross Motor Function Classification System (GMFCS), which categorizes the child into one of five levels based on his/her ability to perform activities of daily living, with level I being the best and level V the worst classification of motor function.[21–23]

Evaluation of Muscle Tone

The *pull to sit, ventral suspension, scarf sign* and *shoulder suspension* tests were used to evaluate tone in the axial and proximal appendicular muscles.[24] *Pull to sit* consists of placing the child in the dorsal decubitus position, holding his/her hands and pulling slowly to a seated position to evaluate axial tone in the neck and back and appendicular tone in the shoulders and arms. Typically developing children should respond to traction in the arms and shoulders, accompanying the movement of the trunk with head movement. In the *ventral suspension* test, the child is suspended in a prone position by a hand under the chest and abdomen. *Ventral suspension* is performed to evaluate tone in the extensor muscles of the head and trunk. In children with no muscle tone problems, arms and legs should remain flexed and the child should be able to support his/her head above the horizontal plane. Hypotonic infants remain draped over the examiner's hands.[24]

The *scarf sign* is performed with the child in the dorsal decubitus position. While taking the infant's hands, the arm is drawn across the chest toward the opposite shoulder to evaluate appendicular tone in the shoulder. In infants with no muscle tone problems, it should be possible to take the elbow across to the midline; however, in the hypotonic infant, the elbow crosses this line without resistance. In *shoulder suspension*, the examiner picks the infant up, holding him/her under the arms to evaluate appendicular tone and neck control. In this test, hypotonic infants tend to slip through the examiner's hands.

All the maneuvers are classified as positive or negative according to the expected motor and postural responses. Children classified as positive in at least one maneuver were considered to have motor and/or muscle tone abnormalities.

To confirm the classification of appendicular tone, muscle resistance to passive movement was evaluated using the modified Ashworth scale (MAS).[25] The muscle groups of the upper limbs were the shoulder flexors and adductors, elbow extensors and flexors, wrist extensors and flexors, and finger flexors. The muscle groups of the lower limbs were the hip flexors, hip adductors, knee flexors and extensors, and the plantar flexors and dorsiflexors.

The MAS classifies muscle resistance to passive movement into six levels: **0** – No increase in muscle tone, **1** – Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion (ROM), **1+** – Slight increase in muscle tone, manifested by

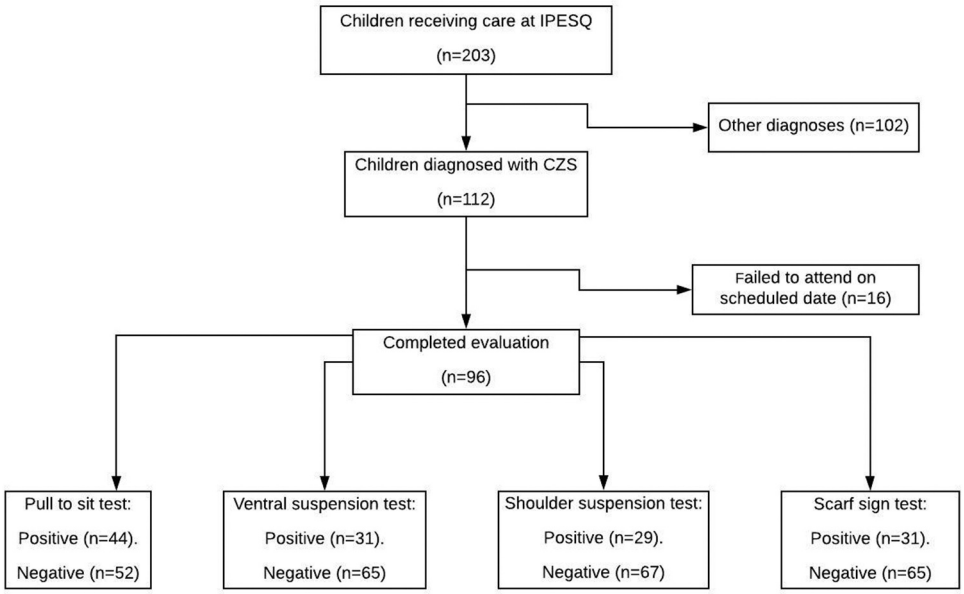

Figure 1. Flowchart showing the selection of participants and the results of the evaluation of muscle tone. IPESQ: *Instituto de Pesquisa Professor Joaquim Amorim Neto*; CZS: congenital Zika syndrome.

a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM, **2** – More marked increase in muscle tone throughout most of the ROM, but affected part(s) easily moved, **3** – Considerable increase in muscle tone, passive movement is difficult, and **4** – Affected part(s) rigid in flexion or extension.[26] Children with scores >0 were classified as having hypertonia. A score of 1 or 1+ in at least one muscle group was categorized as mild hypertonia, a score of 2 in at least one muscle group as moderate, and a score of 3 or 4 in at least one muscle group as severe.

Body Segments Most Affected with Motor Impairment

According to the body segments most affected, children were classified as having: hemiparesis (when motor impairment was predominantly on one side of the body), quadriparesis (when motor impairment was bilateral, affecting both upper and lower limbs, with no difference between them), or diparesis (when motor impairment was predominantly in the lower limbs).[27]

Trained physiotherapists, all experienced in the care of these children and in the evaluation, instruments used, conducted the assessments. These professionals had an average of 8 years' experience working as physiotherapists and since 2017 had been directly involved in the care of children with CZS.

Statistical Analysis

A database was created using RedCap. Descriptive analysis included means and standard deviations for *age, head circumference at birth, current head circumference* and *gestational age*. The muscle tone tests were classified individually as positive or negative, with the frequency of response for each test being determined later. To evaluate appendicular tone according to MAS, the frequency of each one of the classifications was determined per muscle group analyzed. Finally, the frequency of children at each GMFCS level was determined, as well as the frequency of children in relation to the body segments most affected with motor impairment. All the analyses were performed using MedCalc, version 19.0.7 (MedCalc Software bvba, Ostend, Belgium).

Results

Ninety-six children with CZS were evaluated, with 65 (67.7%) having microcephaly at birth and 93 (96.8%) having microcephaly at the time of evaluation. The general characteristics of these children are shown in Table 1.

Forty-four children (45.8%) were classified as positive in the *pull to sit* maneuver, 31 (32.2%) in *ventral suspension*, 29 (30.2%) in *shoulder suspension*, and 31 (32.2%) in *scarf sign*. Eleven children (11.5%) tested positive in all the tests, 13 (13.5%) in three, 19 (19.8%) in two and 15 (15.6%) in at least one test, while 38 (39.5%) tested negative in all the tests, suggesting the absence of hypotonia (Figure 1). Figure 2 shows children participating in the *pull to sit* (A and B), *ventral suspension* (C and D), *shoulder suspension* (E and F) and *scarf sign* (G and H) tests.

MAS evaluation of appendicular tone showed resistance to passive movement in 76 children (79%) in the elbow flexors, in 59 (61.4%) in the finger flexors, 56 (58.3%) in the elbow extensors, 53 (55.2%) in the shoulder adductors, 46 (47.9%) in the shoulder flexors, and 43 (44.8%) in the wrist flexors (Table 2). For the lower limbs, there was resistance to passive movement in 76 children (79%) in the plantar flexors, in 63 (65.6%) in the plantar dorsiflexors, 59 (61.4%) in the hip flexors, 55 (57.2%) in the hip adductors, 52 (54.2%) in the knee flexors and 50 (52.0%) in the knee extensors (Table 2).

Based on MAS scores, 91 children (94.8%) had increased appendicular tone in at least one muscle group, characterizing appendicular hypertonia. Of these children, hypertonia was mild in 52 (57.1%), moderate in 27 (29.7%) and severe in 12 (13.2%).

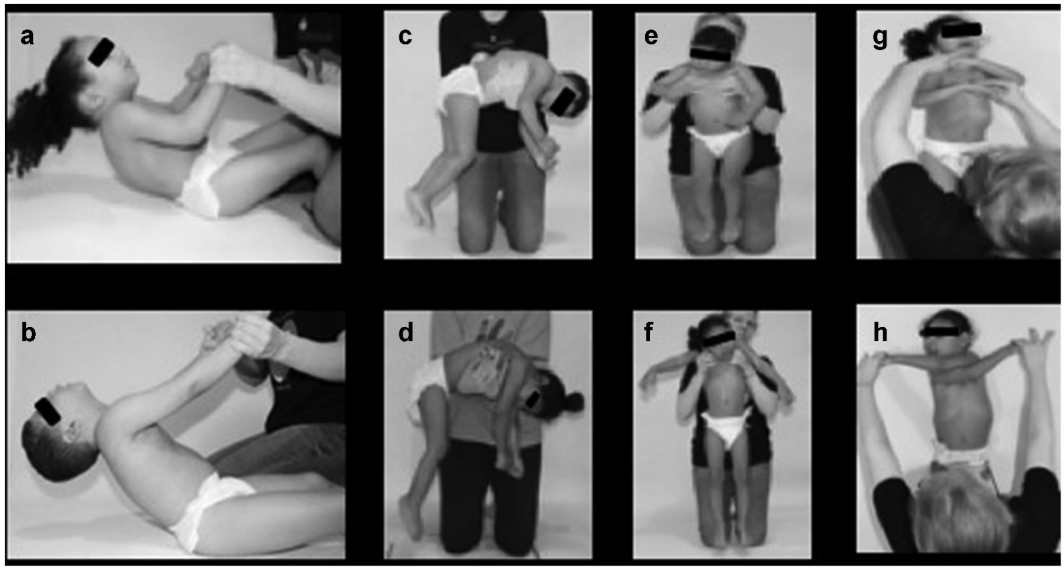

Figure 2. Photographs illustrating the maneuvers performed, resulting either in negative or positive tests. *Pull-to-sit test (A: Negative; B: Positive); Ventral suspension test (C: Negative; D: Positive); Shoulder suspension test (E: Negative; F: Positive); Scarf sign test (G: Negative; H: Positive).*

Eighty-eight children (91.7%) were classified as having quadriparesis, 3 (3.1%) as having diparesis, 1 (1%) hemiparesis and 4 (4.2%) as having no motor impairment. In relation to the GMFCS level of impairment, 86 children (89.6%) were classified as level V, 2 (2.1%) as level IV, 1 (1.0%) as level III, 2 (2.1%) as level II and 5 (5.2%) as level I.

Discussion

The evaluation of muscle tone in children with CZS shows a high frequency of positivity for hypotonia in the tests of axial tone, and a high frequency of scores >0 in the MAS, with the involvement of certain muscle groups, compatible with non-generalized hypertonia. The prevalence of quadriparesis was also high, as was the prevalence of severe motor impairment.

Although a wide spectrum of motor impairment has already been described in children with CZS, the typical phenotype of this syndrome remains to be established. Studies have described severe motor impairment,[8] associated with hypertonia.[15,28,29] However, the fact that the methods used to evaluate muscle tone in those studies were insufficiently described renders comparison impossible. Furthermore, the children evaluated were younger than those in the present sample, also hampering comparison,[13] since, during motor development, other disorders such as the occurrence of convulsive seizures, sensory impairment and delayed motor development may affect muscle tone.[30] Moreover, this is a disease that has only recently been described and the resulting brain abnormalities are severe, with little information available on how peripheral innervation is affected; therefore, characterizing muscle tone remains challenging.

Although studies have highlighted hypertonia as the principal characteristic of muscle tone in children with CZS,[10,15,28] we noticed major difficulties in neck and trunk control during therapeutic care, which motivated us to analyze the characteristics of muscle tone. The high prevalence of abnormalities in the tests evaluated here led us to consider axial hypotonia as the principal characteristic of muscle tone, with compensatory appendicular hypertonia as a means of maintaining a minimum of postural control.

Bodensteiner et al.[24] stated that hypotonia is difficult to classify and is mostly identified at the end of the first year of life. Hypotonia can be associated with lesions to the suprasegmental or segmental structures of the CNS. In the case of suprasegmental lesions, hypotonia is generally associated with widespread injury to the CNS including the basal nuclei and the red nucleus, the cerebellum and precentral gyrus, commonly resulting in clinical signs such as delayed cognitive development, convulsions and hyperreflexia.[31] This is commonly associated with severe motor impairment, hampering possible differentiation between hypotonia and muscle weakness. Remarkably, lesions to the cerebellum and basal nuclei are characteristic of CZS, supporting the hypothesis of hypotonia.

Different degrees of brain damage can result from intrauterine Zika virus infection.[4,29] This variation in brain structural changes could justify differences in muscle tone ranging from normal axial tone to hypotonia with no neck control.

An interesting finding is that although many children showed positive signs suggestive of axial hypotonia, they had scores >0 for appendicular tone in MAS, suggesting the presence of a mixed pattern. This suggests that hypertonia of the extremities may act as a compensatory mechanism to improve trunk and neck support.

In a series of studies published in 2014, Gogola et al.[17,32,33] described postural tone compensatory patterns of the stabilizing muscles in children with hypotonia.[17,32,33] The clinical findings in the children in the present study were similar to those of spastic hypotonia described by those authors in which appendicular tone increases to compensate for the hypotonia. Therefore, according to those authors, hypotonia is the principal problem and hypertonia would represent a compensatory response, hence a secondary problem.[17]

Table 2. Degree of resistance to passive movement of the upper limb and the lower limb muscles according to the modified Ashworth scale.

		Modified Ashworth Scale						
		0	1	1+	2	3	4	Median (IQR)
		n (%)						
Upper Limbs								
Shoulder flexors	R	51 (53.1)	31 (32.3)	11 (11.5)	3 (3.1)	0 (0)	0 (0)	0 (0–1)
	L	50 (52.1)	31 (32.3)	13 (13.5)	2 (2.1)	0 (0)	0 (0)	0 (0–1)
Shoulder adductors	R	44 (45.8)	36 (37.5)	11 (11.5)	4 (4.2)	0 (0)	1 (1)	0 (0–1)
	L	43 (44.8)	37 (38.5)	11 (11.5)	4 (4.2)	0 (0)	1 (1)	0 (0–1)
Elbow flexors	R	19 (20)	54 (56.8)	15 (15.8)	4 (4.2)	2 (2.1)	1 (1.1)	0 (1–1)
	L	24 (25)	52 (54.2)	13 (13.5)	3 (3.1)	3 (3.1)	1 (1)	0 (0.25–1)
Elbow extensors	R	39 (41.1)	35 (36.8)	14 (14.7)	6 (6.3)	0 (0)	1 (1.1)	1 (0–1)
	L	42 (43.8)	41 (42.7)	9 (9.4)	2 (2.1)	1 (1)	1 (1)	1 (0–1)
Wrist flexors	R	61 (63.5)	25 (26)	8 (8.3)	1 (1)	1 (1)	8 (8.3)	0 (0–1)
	L	63 (65.6)	27 (28.1)	2 (2.1)	2 (2.1)	1 (1)	1 (1)	0 (0–1)
Wrist extensors	R	77 (80.2)	19 (19.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0–0)
	L	76 (79.2)	19 (19.8)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0–0)
Finger flexors	R	39 (40.6)	39 (40.6)	12 (12.5)	5 (5.2)	0 (0)	1 (1)	1 (0–1)
	L	37 (38.5)	39 (40.6)	15 (15.6)	4 (4.2)	0 (0)	1 (1)	1 (0–1)
Lower Limbs								
Hip flexors	R	37 (38.5)	47 (49)	8 (8.3)	3 (3.1)	0 (0)	1 (1)	1 (0–1)
	L	40 (41.7)	44 (45.8)	8 (8.3)	3 (3.1)	0 (0)	1 (1)	1 (0–1)
Hip adductors	R	42 (45.2)	27 (29)	13 (14)	6 (6.5)	4 (4.3)	1 (1.1)	1(0–2)
	L	38 (40.1)	33 (35.5)	11 (11.8)	5 (5.4)	5 (5.4)	1 (1.1)	1 (0–1.25)
Knee flexors	R	43 (45.3)	35 (36.8)	14 (14.7)	13 (3.2)	0 (0)	0 (0)	1 (0–1)
	L	43 (45.3)	37 (38.9)	13 (13.7)	2 (2.1)	0 (0)	0 (0)	1(0–1)
Knee extensors	R	47 (49.5)	33 (34.7)	12 (12.6)	2 (2.8)	1 (1.1)	0 (0)	0.5(0–1)
	L	45 (47.4)	34 (35.8)	14 (14.7)	2 (2.1)	0 (0)	0 (0)	1(0–1)
Plantar dorsiflexors	R	36 (37.9)	37 (38.9)	12 (12.6)	3 (3.2)	2 (2.1)	5 (5.3)	1(0–1)
	L	32 (33.7)	40 (42.1)	11 (11.6)	6 (6.3)	2 (2.1)	4 (4.2)	1(0–1)
Plantar flexors	R	23 (24.2)	38 (40)	15 (15.8)	7 (7.4)	7 (7.4)	5 (5.3)	1(0.25–3)
	L	19 (20)	40 (42.1)	16 (16.8)	7 (7.4)	8 (8.4)	5 (5.3)	1(1–3)

IQR: Interquartile range; R: Right; L: Left.

Wheeler et al. evaluated motor development in 47 children with CZS aged 16 months and also concluded that it was the hypertonia present in those children that was responsible for maintaining them in the position in which they had been placed, hence not constituting a voluntary action.[29] Pereira et al.[14] clinically evaluated children with CZS and found that many of the children classified with hypotonia presented with flexed arms and raised shoulders, suggesting postural adaptations. These statements may reinforce our hypothesis that appendicular hypertonia occurs as a compensatory mechanism, since, when the children are placed in certain positions such as the prone position, they generally manage to remain in it, probably due to compensatory hypertonia to overcome the effects of gravity, with reflexes in the cervical region being exacerbated. Nevertheless, this is merely hypothetical and requires further investigation in future studies.

Most children evaluated here had severe motor impairment and were classified as GMFCS level V. This could be explained by the severe brain damage and could be aggravated by abnormalities in muscle tone. In neurologically healthy children in the first years of life, performing different motor activities at an increasing level of complexity enables subsystems of the nervous system to develop as a result of the constant process of feedback, a fact that affects the characteristics of muscle tone throughout motor development. According to Gogola et al.,[32] the motor activity of children with normal muscle tone is essential to the maturation of the brain structures responsible for erect posture, characterizing the intense process of neuroplasticity experienced in this phase of development.[18]

Two points are noteworthy. First, the compensatory increase in muscle tone could lead to soft tissue abnormalities and fatigue, resulting in complications such as pain, shortening and contractures, later resulting in deformities including hip luxation that are intensified by disuse.[34] Secondly, the lack of neck control, whether due to hypotonia, weakness or muscle fatigue, may severely impair the children's quality of life, increasing the risk of choking and consequent aspiration pneumonia, an issue that merits investigation in future studies.

Therefore, the motor impairment experienced by children with CZS can be explained not only by neural factors and the reduced feedback from the CNS that facilitates cortical changes and the acquisition of motor skills but also by muscle factors such as morphological and chemical changes in muscle fibers resulting from inertia.[29] These factors appear to result in a greater exacerbation of the compensatory increase in muscle tone, further aggravating the motor condition over time. Furthermore, a histological study showed atrophy of the peripheral nerve in a child who died and in whom an autopsy was performed.[6,35] Greater understanding is required of the effect of the damage caused by the virus to the peripheral nervous system on muscle tone in these children.

Understanding the behavior of muscle tone in children with CZS is of the utmost importance, since the choice of therapeutic interventions, including the application of botulinum toxin and the static and dynamic postures adopted during physiotherapy, aimed at the motor development of these children, depend on whether hypertonia is true or compensatory.

Limitations

Most of the children investigated in studies published up to the present time had severe motor impairment.[8,29,36–38] Nevertheless, mild motor impairment and even typical motor development have been found in some children. In the present study, there was no great variability in motor function, which constitutes a limitation. Future studies need to be conducted with subgroups of children with CZS classified according to the severity of neurological damage and with children exposed to Zika during pregnancy but without brain damage.

Other significant limitations include the fact that the tests and evaluations used in the present study were those described by Bodensteiner[3] to evaluate muscle tone in premature infants. Furthermore, although positivity suggests hypotonia, when the test is classified as negative it is impossible to determine whether there is hypertonia or normal muscle tone, with further evaluations being required. The choice of the evaluation instruments used in the present study was based on the absence of a single-specific instrument capable of evaluating the presence of hypotonia and hypertonia in young infants.

Despite these limitations, the present study introduces new findings that may add to current knowledge on the natural course of CZS and provides useful information for care protocols, since most of the papers highlight hypertonia as the principal abnormality in muscle tone. Cohort studies should be conducted to monitor possible changes in muscle tone in these children over time and to evaluate the effect of muscle relaxants, as well as the association with neuroimaging findings. More detailed studies on muscle activity should be performed, including evaluations using electroneuromyography.

Conclusion

These results show the characteristics of muscle tone in children with CZS, suggesting axial hypotonia associated with hypertonia of the appendicular muscle groups. These abnormalities appear to affect the motor function of these children that are already impaired as a result of the brain lesions.

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Declaration Of Interest Statement

The authors report no conflict of interest.

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