Neurological outcomes of congenital Zika syndrome in toddlers and preschoolers: a case series

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Summary

Background Congenital Zika syndrome causes a spectrum of neurological symptoms with varying effects on function that require different therapeutic strategies. To date, this spectrum of effects and its clinical implications have not been completely described. We describe the neurological examination findings in toddlers and preschoolers, including predominant symptom complexes and comorbidities.

Methods This study is a case-series neurological evaluation of 75 children with congenital Zika syndrome in Campina Grande, Brazil. The study is part of a cohort of children with congenital Zika syndrome that started in 2015 and is still ongoing. Children with Zika virus infection detected during pregnancy (mothers exhibited rash and were followed and diagnosed by fetal ultrasound abnormalities or RT-PCR) or through microcephaly screening after birth, using Intergrowth 21 guidelines, were selected by laboratory and radiological criteria. Children were examined during a 10-day period in September, 2018, and underwent neurological interview, examination, and assessment of functional outcomes and comorbidities. Children were divided in groups of predominant corticospinal or neuromuscular clinical signs and the associations between these groups and clinical comorbidities were assessed.

Findings All of the children recruited to the study from Nov 29, 2015 to Nov 30, 2017 had imaging correlates of congenital Zika syndrome. Children were assigned to groups depending on the signs exhibited, either corticospinal or neuromuscular, with or without dyskinetic signs. 75 children completed the evaluation, 38 (51%) girls and 37 (49%) boys. Median age was 33 months (range 26–40 months; IQR 29–34). Microcephaly was present at birth in 56 (75%) children, and 19 (25%) children were born with normal head circumference, 15 of whom later developed microcephaly. Neurological examination grouped four children as having isolated dyskinetic signs, 48 children were assigned to the corticospinal group and 23 into the neuromuscular group. Dyskinetic findings were present in 30 (40%) children, either alone (four [5%]) or combined with corticospinal (19 [40%] of 48) or neuromuscular (seven [30%] of 23) findings. Comorbidities were highly prevalent, and the neuromuscular group had worse functional outcomes, evaluated by gross motor function ($p=0·026$), manual abilities ($p=0·0013$), and communication function ($p<0·0005$) classification scales, than the corticospinal group, whereas pneumonia ($p<0·0005$) and urinary tract infections ($p<0·0005$) were more frequent in the corticospinal group. Cortical hyperexcitability was supported by several clinical correlates, such as early onset epilepsy, persistence of primitive reflexes, and dystonia.

Interpretation We describe distinct neurological profiles in the congenital Zika syndrome spectrum, with functional outcomes tending to correlate with these groups. The clinical division of children based on the disease signs proposed here is supported by the literature on central and peripheral nervous system pathology in congenital Zika syndrome. The high prevalence of dyskinetic symptoms merits special attention.

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Introduction

During the 2015–16 epidemic of Zika virus disease in Brazil, the term congenital Zika syndrome was proposed to describe affected newborns who had a variable combination of microcephaly and other developmental problems.[1] Radiological[2] and neuropathological[3] investigations revealed the unique aspects of congenital Zika syndrome in the neonatal period, including severe disruption of brain anatomy through imaging correlates and neuropathology. Zika virus is highly neurotropic, affecting progenitor cells and disrupting radial neuronal migration to external cortical layers.[3] Zika virus infection results in a series of malformations and calcifications at unique brain sites, including the cortico-subcortical junction and the basal ganglia.[2] The spinal cord and peripheral nervous system are also affected, as reported in imaging, histopathology, and neurophysiological studies.[3,4]

Although the classic description of congenital Zika syndrome is of very compromised children, Zika virus

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Research in context

Evidence before this study

Congenital Zika syndrome is a new disease and its full spectrum is still under investigation. The clinical effect of the disease during neonatal and infant ages have been described and, although variable outcomes are possible, a very severe presentation is the expected outcome for those born with small head circumferences. Abnormal neuropathology of peripheral nervous system and muscular fibres had been reported as well as a high frequency of epilepsy and dystonia. Before starting the case series we considered two requirements, the first of which was to describe the neurological outcomes of children with congenital Zika syndrome up to the age of 3 years, especially because the existing literature focused on younger children, and the second was to comprehensively describe the neurological picture and correlate this to clinical and functional outcomes in children with congenital Zika syndrome. We searched PubMed, SciELO, and Literatura Latino-Americana e do Caribe em Ciências da Saúde databases from inception to Jan 10, 2020, using the terms "Zika", "Congenital Zika Syndrome", "STORCH", "image", "neuropathology", "nervous system", "brain", "microcephaly", "neurological syndrome", "epilepsy", "clinical outcomes", and "cerebral palsy". Because congenital Zika syndrome is a novel disorder, all articles were considered relevant. Some articles were excluded from the final list by because they only confirmed findings from other studies. Articles with similar results or messages were evaluated and sorted by their relevance.

Added value of this study

This case series organises the clinical neurological findings reported in children of preschool age with congenital Zika syndrome and point to potentially different functional outcomes according to the classification of neurological findings. We describe the expected frequency of different neurological syndromes, considering children with comparable criteria to those of our cohort. We highlight the need for special clinical attention according to the neurological syndrome presented: children presenting with the neuromuscular syndrome had a worse prognosis. We bridge some correlations between our clinical findings and published literature on congenital Zika syndrome and propose theoretical considerations regarding possible correlations with neuropathological and image findings reported in the literature and the frequency of certain signs and symptoms we describe.

Implications of all the available evidence

This case series provides more detail on the spectrum of congenital Zika syndrome clinical and neurological manifestations. It includes 75 children from a cohort started at the first months of the congenital Zika syndrome epidemy. The children included in the cohort are the oldest children with congenital Zika syndrome described to date. Because the children included have a very severe neurological impairment, the detailed examination—which includes specific descriptions of neurological signs—contributes to more detailed disease classification and can stratify the risk of poor functional outcomes and occurrence of clinical comorbidities that otherwise might be neglected. It adds to the policy of clinical management according to the presented neurological syndrome, preventing potential complications in those pertaining to specific groups. A subgroup of children with extrapyramidal symptoms that must be specifically searched and further investigated has been highlighted. The case series proposes future lines of investigation regarding the pathological process of Zika virus infection and neurodevelopment in general, and it draws together common questions to be addressed in cohorts from different origins.

does not affect all babies equally. Abnormal neurodevelopment was described during the first 18 months in children exposed to Zika virus in utero and those born without congenital Zika syndrome, highlighting the need for developmental surveillance of all newborns exposed to Zika virus.[5] In another large cohort of babies exposed to the virus without congenital Zika syndrome,[6] below average neurodevelopment and abnormal eye or hearing assessments were reported in 31·5% of children aged between 7 months and 32 months. Language function was most commonly affected, with 51 (35%) of 146 children scoring below average.

In a population cohort from Rio de Janeiro and Belo Horizonte, Brazil, the mothers of 82·9% of babies with microcephaly were infected with Zika virus during the first trimester of pregnancy versus 28·9% of babies born with microcephaly to mothers infected with Zika virus during the second trimester.[7] Differences in the prevalence of congenital Zika syndrome-associated microcephaly in different populations increased suspicion of other factors influencing the virulence of the infection.[8]

3 years after the end of the epidemic, several reports on motor development,[9] epilepsy,[9] vision,[10] and hearing[11] of children with congenital Zika syndrome were published. Although specific aspects of the congenital Zika syndrome have been addressed, a fundamental gap in the knowledge remains regarding the detailed description of clinical profiles and possible correlations with neuroradiological and neuropathological findings.

Within this context, this Article describes the neurological outcomes of toddlers and preschoolers, up to the age of 3 years and 4 months, with congenital Zika syndrome, with a particular focus on the description of the neurological syndrome and its association with functional outcomes and comorbidities.

Methods

Study design and setting

This study was done in Campina Grande, northeast Brazil, recruiting children born between May 29, 2015, and July 5, 2017, to mothers infected with Zika virus during pregnancy and followed up at the Instituto de Pesquisa Professor Joaquim Amorim Neto, Campina Grande, Brazil. This cohort has already originated a consistent body of information on Zika virus and congenital Zika syndrome.[2,3]

The original cohort consisted of 112 children with Zika virus detected during pregnancy (mothers exhibited rash and were followed up and diagnosed by fetal ultrasound abnormalities or RT-PCR) or through microcephaly screening after birth, using Intergrowth 21 guidelines.[12] Children without typical CT findings of congenital Zika syndrome[2] were excluded as were babies with congenital syphilis, toxoplasmosis, rubeola, cytomegalovirus, and herpes infections (detect through serologies). Follow-up of head circumference is described in accordance with US CDC guidelines.[13] Ethics approval (CAAE 91054418.1000.5182) and written informed consent were obtained.

Epidemiological and general health variables

Epidemiological data were obtained during admission by a structured interview. The maternal variables of interest were educational attainment and presence and timing of rash during pregnancy. Children's data on all relevant comorbidities–number of episodes of pneumonia and urinary tract infection; presence of dysphagia, hip dislocation (supplemented by imaging findings), sleep problems (abnormalities to start or maintain sleep, diurnal somnolence or abnormal movements during sleep), and epilepsy were collected from parent's accounts and medical records.

Gross motor function,[14] manual abilities,[15] eating and drinking capacity,[16] and communication function[17] classification scales were used to assess the children. Scores of these functional scales ranged from independent performance (level 1) to severely affected and totally dependent (level 5). A questionnaire based on the 23 items of the performance subscale of the Test of Infant Motor Performance, following the original authors' recommendations.[18] Although this test is designed for children up to age 4 months, we aimed to discriminate motor performance nuances considering a group of severely impaired children.

Neurological variables

Neurological examinations were done by three certified paediatric neurologists (HVFSP, SPS, and APRLA) and the observations recorded in a form containing closed and open-ended questions. Each child was evaluated by two of the three paediatric neurologists. Examinations were done as recommended by the literature.[19] General Movements Assessment were done by one (HVFSP) fulled trained paediatric neurologists,[20] the assessment complemented the interpretation of the findings. Descriptions of posture, muscle tone, strength, reflexes (deep-tendon, plantar, and primitive), number of involuntary movements, and events considered unusual by the parents (such as frequent startle or the fluttering of the eyelids) were recorded. The examination was separated into three domains according to motor findings: corticospinal, neuromuscular, or dyskinetic. Children were assigned to the corticospinal or neuromuscular groups on the basis of their predominant signs, with or without dyskinetic findings.

Statistical analysis

Groups with corticospinal and neuromuscular findings were compared through statistical tests according to the type of variable. Children who presented with dyskinetic findings alone were excluded from the main analysis. Clinical comorbidities (epilepsy, dysphagia, hip dislocation, and sleep disorders) were analysed by Pearson's χ^2 test. When the number of children or number of events to be compared between groups were small, Fisher's exact test was an alternative to a χ^2 test. The gross motor function, manual abilities, eating and drinking capacity, and communication function classification scale scores were analysed by the Cochran–Armitage test for trend, a modification of Pearson's χ^2 test. Pneumonia and urinary tract infections were tested considering the number of episodes and were treated as numerical variables, as was the Test of Infant Motor Performance-based questionnaire scores. For questionnaire scores, normality of distribution was tested with a Shapiro test and the equality of medians for two independent samples was done with a Mann–Whitney U test. Results were controlled for the presence of dyskinetic signs using the Cochran–Mantel–Haenszel test, an extension of the χ^2 test of association. For interval variables, the Van Elteren test was used. Results were deemed significant if $p<0\cdot05$.

Role of the funding source

The funder of the study had no role in the design of this study, execution, analyses, interpretation of the data, or decision to submit results. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication

Results

Of the full initial cohort of 112 children, six died during the first 24 h after birth and one died at age 6 months because of pneumonia after an episode of bronchoaspiration. Data on three of the children who died 24 h after birth were published.[3] 30 children (17 [57%] girls and 13 [43%] boys) could not attend follow-up because of the distance from their home to the study centre and unavailability of sponsored or subsidised transportation. 75 children were included in this case series. At birth, microcephaly was present in 23 (77%) of 30 children who

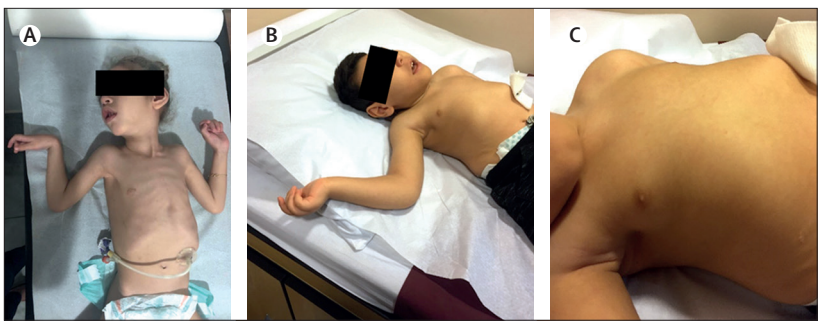

Figure 1: **Typical posture of children from the neuromuscular subgroup**
(A) Hypotonic face (34-month-old boy). (B) Flexion of the arms with open hands and dropped fists (40-month-old boy). (C) Bell-shaped thorax (40-month-old boy). The boy included in B and C is the same child.

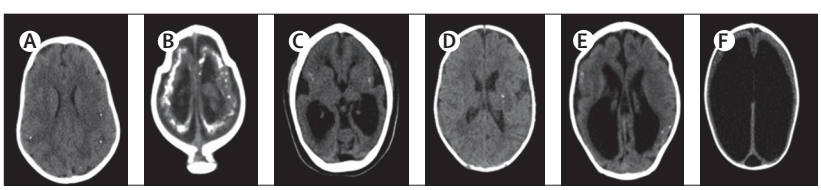

Figure 2: **CT images of representative patients with congenital Zika syndrome**
The children all had subcortical calcifications and cortical dysplasia and variations in disease involvement. (A) Scant calcification foci. (B) Multiple coalescent foci. (C) Cortical dysplasia that diffusely affected both cerebral hemispheres. (D) Child had focal dysplasia in the temporal and insular lobes. (E) Diffuse pachygyria and cortical thickening. (F) Agyria with diffuse cerebral parenchymal thinning, associated with obstructive hydrocephalus.

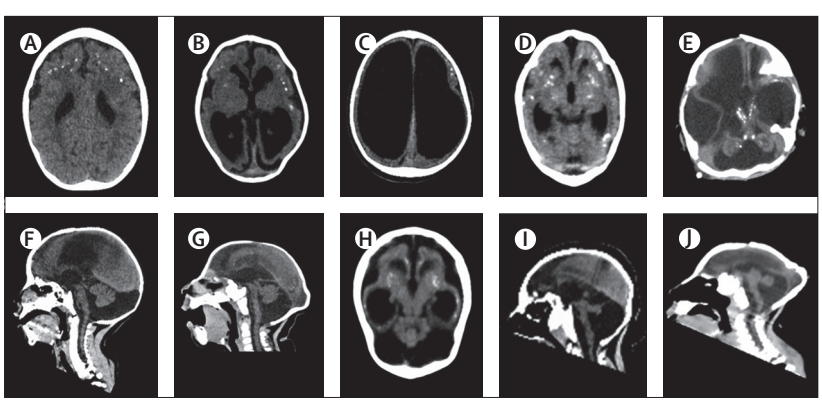

Figure 3: **CT images of representative patients with congenital Zika syndrome who exhibited distinct neuroimaging findings**
(A) Slight cerebral volume reduction. (B) Moderate cerebral volume reduction and ex-vacuo ventriculomegaly. (C) Severe cerebral volume reduction and obstructive hydrocephalus. (D) Calcifications in the basal ganglia and thalamus. (E) Calcifications in the brainstem and cerebellum and cerebellar hypoplasia affecting the vermis and hemispheres. (F) Brainstem hypoplasia with normal segmentation and corpus callosum hypoplasia. (G) A dysmorphic (unsegmented and extremely thin) brainstem with cerebellar vermis hypoplasia and dysmorphism, corpus callosum hypoplasia, and a parieto-occipital step. (H) Cerebellar hypoplasia affecting the vermis and hemispheres and corpus callosum hypoplasia. (I) Corpus callosum hypoplasia. (J) Cerebral volume reduction and a parieto-occipital step.

See Online for appendix

could not attend the clinic, and was present in 75% of the entire study population (56 of 75 children; (p=0·82). The median z score was –2·4 (IQR –3·26 to –1·10) in children who could not attend the clinic versus –2·8 (IQR –3·76 to –1·78) for all children included in the study (p=0·397). All the children included in the study had image correlates of congenital Zika syndrome. 75 children completed the research protocol. Clinical recommendations for epilepsy treatment and other comorbidities were made during subsequent follow-up visits.

Our sample consisted of 38 girls (51%) and 37 boys (49%). The median age was 33 months (range 26–40 months; IQR 29–34 months). 43 (58%) mothers completed 11 years of education, two (3%) were illiterate, five (7%) had a higher education, and 25 (33%) had between 1 and 10 years of education. Congenital Zika syndrome was confirmed by PCR in 15 (20%) children and presumed in 60 (80%) children on the basis of characteristic neuroimaging findings. Children who had congenital Zika syndrome confirmed by PCR also had imaging correlates; thus, all children had imaging findings characteristic of congenital Zika syndrome (appendix pp 1–4). Rash during pregnancy was reported by 66 (88%) of the 75 mothers, appearing at a median gestational age of 12 weeks (range 6–34 weeks; IQR 8–16). The median head circumference at birth was 29·7 cm (range 23–35 cm; IQR 29–32).

Initial examinations showed that motor signs co-occurred in many children. Pyramidal signs, with brisk deep tendon reflexes, were most frequent, reported in 70 (93%) of 75 children. However, in some children predominant signs were mostly neuromuscular or dyskinetic. On the basis of predominant motor signs 48 (64%) children were assigned to the corticospinal group. Children in this group had a predominance of pyramidal signs, with a variable combination of hypertonicity, crossed, spastic legs, brisk reflexes, clonus; cortical thumbs, and the Babinski and Hoffman signs. 23 (31%) children were assigned to the neuromuscular group. Children in this group were mainly hypotonic. Some exhibited flexed arms and elevated shoulders, suggesting an adaptive postural fixation (figure 1A and B) for better head and neck control. Doughy muscles and an easily overcome spastic resistance were reported. In these children, the distal deep tendon reflexes (ankle jerk and brachioradialis) were frequently weaker than at proximal sites. A bell-shaped chest was also common, occurring in 13 (57%) children in this group (figure 1C). Hypotonicity was reported in the hands and feet of 18 (78%) children in the neuromuscular group, leading to wrist drop, open hands, and flaccid feet in most children. Many had puffy feet, with no plantar arching (appendix p 5). Four (5%) children were assigned to the isolated dyskinetic signs group. In addition, dyskinesia was present in 19 children in the corticospinal group and seven in the neuromuscular group. Overall, 30 (40%) children had dyskinetic signs. The main type of dyskinetic sign was global and segmental dystonia (27 (90%) of 30 children; appendix p 9), followed by chorea (three (10%) of 30 children). An additional finding not included in classification was dyskinetic movement of the mouth and tongue, with frequent tongue protrusion in reported in 23 of 75 children.

The most characteristic finding of congenital Zika syndrome identified from head CT were calcifications at the junction of grey and white matter, present in all

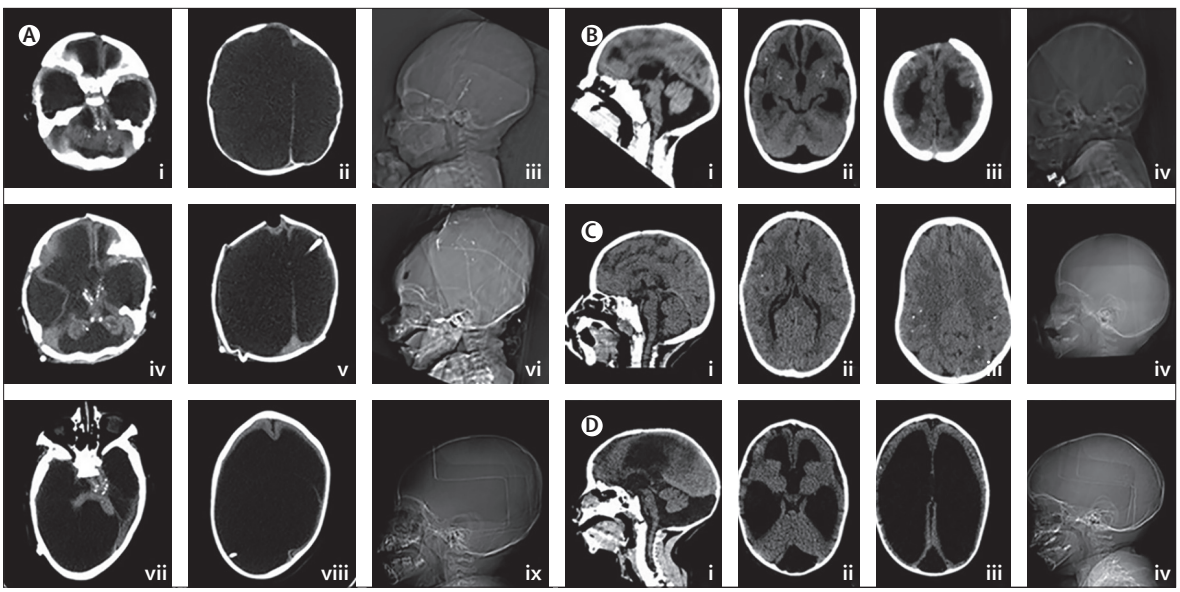

Figure 4: **Neuroimaging of children with congenital Zika syndrome born without microcephaly and whose head circumference has remained normal**
(A) CT scans and x-rays of a child aged 25 months at day 1 (CT scan i and ii; x-ray iii), at month 1 (CT scan iv and v; x-ray vi), and at month 25 (CT scan vii and viii; x-ray ix). Congenital Zika syndrome was confirmed by PCR. There is severe hydrocephalus and thinning of the cerebral parenchyma at birth and follow-up. Of note are the subcortical (i and iv), diencephalic (i, iv, and vii), brainstem (i, iv, and vii), and cerebellar calcifications (i, iv, and vii) and cerebellar and brainstem dysplasia (i, iv, and vii). (B) CT scan (i–iii) and x-ray (iv) of a child at age 2 months. Maternal infection with Zika virus was confirm by presence of a rash at 8 weeks gestational age. Congenital Zika syndrome confirmed by imaging. Corpus callosum hypoplasia (i and ii) and subcortical and basal ganglia calcification with severe, diffuse cortical dysplasia (ii and iii). (C) CT scan (i–iii) and x-ray (iv) of a child aged 18 months (normal head circumference maintained at age 35 months). Maternal infection with Zika virus was confirm by presence of a rash at 8 weeks gestational age. Congenital Zika syndrome confirmed by imaging. CT scan shows subcortical calcification with corpus callosum hypoplasia (i) and mild focal cortical dysplasia in (ii and iii). D) CT scan (i–iii) and x-ray (iv) of a child aged 29 months. Congenital Zika syndrome confirmed by imaging). Corpus callosum, cerebellar, and brainstem hypoplasia (i and ii), severe and diffuse cortical dysplasia (ii and iii), and hydrocephalus and subcortical calcification (iii) are shown.

75 children. The number of calcifications was variable, from scant and sparse to multiple and coalescent (figure 2A and B). Cortical dysplasia was also reported, in variable presentations, in 66 (85%) children—from small and focal to large and diffuse lesions in both hemispheres (figure 2C and D). Cortical dysplasia appeared as agyria or pachygyria (Figure 2C, D, and E), or as a very thin cortex with agyria, associated with loss of white-matter volume or hydrocephalus. 59 (79%) children exhibited cerebral volume reduction (figure 2F), ranging from slight to severe (figure 3A, B, and C).

Calcifications were reported in the basal ganglia of 47 (63%) children, and less frequently in cerebellum (three [4%] children), brainstem (five [7%] children), and midbrain (five [7%] children; figure 3D), in which calcifications in the midbrain were associated with obstructive hydrocephalus (figure 3B).

Posterior fossa findings included brainstem hypoplasia in seven (9%) children (figure 3F) and brainstem dysplasia in nine (12%) children (figure 3G). Cerebellar volume was also reduced in 13 children (17%), in whom the vermis more affected than the hemispheres (figure 3E, G, and H).

Corpus callosum dysgenesis was reported in 60 (80%) children and was proportional to cerebral volume reduction. A parieto-occipital step could also be seen in some children (figure 3G and J).

19 (25%) children were born with a head circumference within normal range (appendix pp 6–8). Of these children, 15 subsequently developed slow cephalic growth, and met the US CDC definition of microcephalic by Sept 10, 2018, to Sept 20, 2018 (appendix pp 6–8).[13,14] Image correlates of these children revealed that, although their head circumference was within normal range at birth, their brain anatomy was universally disrupted; a seemingly normal head circumference reflected ex-vacuo ventriculomegaly in many children. Detailed descriptions of imaging findings in these 19 children with normal head circumference at birth are given in the appendix (pp 6–8); imaging correlates of the four children with normal head circumference on follow-up are shown in figure 4A–D. One child had a small number of subcortical calcifications, one had hypertensive hydrocephalus, and two had ex-vacuo ventriculomegaly. The frequency of specific imaging abnormalities on CT did not differ between groups.

Functional scales showed a predominance of severe impairment (figure 5). On the gross motor function and manual abilities classification scales, grade 5 impairment was documented in all children in the neuromuscular group, all of whom were fully dependent. Comparison between groups showed that gross motor function ($p=0·026$), manual abilities ($p=0·0013$), and communication function ($p<0·0005$) classification scale scores were worse in the neuromuscular group

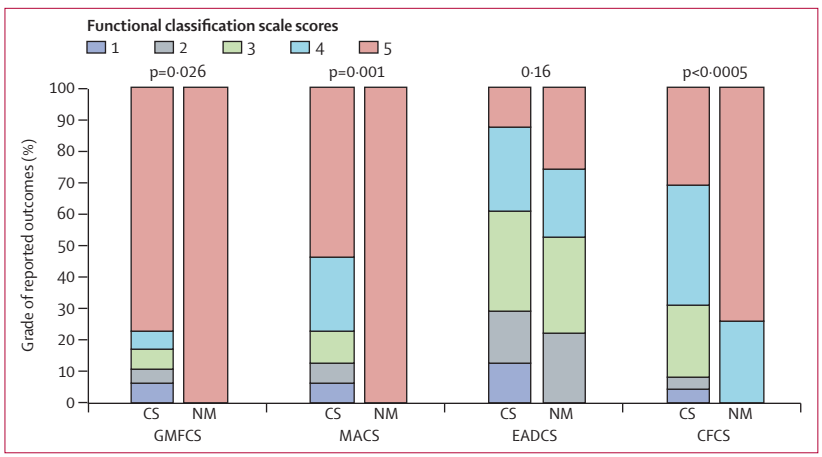

Figure 5: **Percent age distribution of functional outcomes from grade 1 to 5 within the CS and NM groups**
CS=corticospinal. NM=neuromuscular. GMFCS=gross motor function classification scale. MACS=manual ability classification scale. EADCS=eating and drinking ability classification scale. CFCS=communication function classification scale.

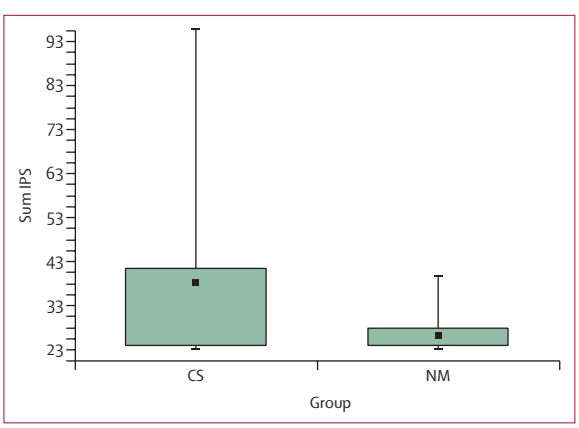

Figure 6: **Comparison of Test of Infant Motor Performance subscale scores between the CS and NM groups**
Although the difference between the groups was not statistically significant (p=0·06), variability was greater in the CS group. CS=corticospinal. NM=neuromuscular. SUM IPS=Sum of Items of the Performance Subscale of the Test of Infant Motor Performance test.

than in the corticospinal group; the eating and drinking capacity classification scale scores did not significantly differ between groups. The questionnaire based on the performance subscale of the Test of Infant Motor Performance test yielded scores ranging from 23 to 96; 50 children had test scores lower than 40. There was no difference in the Test of Infant Motor Performance-based evaluation between the corticospinal group and neuromuscular group (p=0·06; figure 6). The presence of dyskinetic signs did not influence results.

Comorbidities were highly prevalent. Epilepsy occurred in 52 (69%) of children, 45 (60%) children had dysphagia, 28 (37%) had sleep disorders, and 32 (43%) had hip dislocation.

Pneumonia occurred in 35 (47%) children, and 33 (44%) children had urinary tract infections. Both pneumonia and urinary tract infections were more common in the corticospinal group than in the neuromuscular group when comparing the total number of episodes occurring within the group over the same period (p=0·001; table). The hearing of eight (11%) of 75 children and vision of 29 (39%) children was affected by congenital Zika syndrome, as evaluated by general interview and clinical examination. During examination, children had a very low sensory threshold to sound and touch, which elicited global muscle contraction, startles, and irritability. In three children, sound stimuli elicited reflex tonic seizures.

Testing for primitive reflexes[24] revealed persistent and often intense reactions. Moro (or startle) and palmoplantar responses could be elicited in 30 (40%) children, the asymmetric tonic neck reflex in 32 (43%) children, and the orofacial reflex in 34 (45%) children. An automatic gait movement pattern was present in three (4%) children to such an intensity that it was mistaken for a behavioural issue. The Babkin reflex was very brisk in four (5%) children. Five (7%) children exhibited a loop of palpebral responses elicited by ocular proximity, sound stimulus, or touching the nose or elsewhere on the face. Family members and health-care personnel named this the butterfly sign because of the response of the fluttering eyelids.

Three (4%) children showed clinical signs that are considered very similar to those described for infants younger than 16 weeks old during the General Movements Assessment[25] described by Prechtl and colleagues.[25] One child exhibited continuous rotation of the arm. Flexion of legs over the trunk, followed by slow relaxation was reported in the other two children.

The main qualitative findings in this case series were pyramidal findings of variable intensity, reported in 70 (93%) of 75 children, with a high prevalence of clinical comorbidities. The neuromuscular group were characterised by flexed arms, open hands, and dropped fists; a bell-shaped thorax and restrictive respiratory mechanics; puffy feet; reduced distal deep tendon reflexes; and worsening posture control after administration of botulinum toxin. The corticospinal group presented signs related to cortical excitability, including a low startle threshold; irritability to sound and tactile stimulus; a high prevalence of treatment-refractory epilepsy early in the course of the disease; intense, persistent primitive reflexes; persistence of general movements in motor repertoire; and reflex epilepsy. Lastly, children with dyskinetic signs were characterised by irritability—possibly secondary to pain and discomfort; fluctuant tonus, worsening of spasticity, with intense dystonia in some patients; and frequent tongue protrusion or oral dyskinesia.

Discussion

Most of the children had multiple comorbidities and complex medical needs. No child had a completely normal neurological examination or CT scan. Children with

	Number of children with the comorbidity per group (cumulative number of episodes)			Total number of comorbidity incidence (%)	Reported prevalence of comorbidities in similar cohorts (%)	Comparison between corticospinal and neuromuscular groups p value
	Corticospinal group	Neuromuscular group	Dyskinetic group			
Epilepsy	35	16	1	52 (69%)	70%[19]	0·99
Pneumonia*	24 (43)	10 (19)	1	35 (47%)	Not described	<0·0005
Urinary tract infection*	24 (53)	6 (14)	3	33 (44%)	22·7%[20]	<0·0005
Dysphagia	27	18	0	45 (60%)	86%[21]	0·69
Hip dislocation	20	12	0	32 (43%)	55%[22]	0·82
Sleep disorder	20	8	0	28 (37%)	34·1%[23]	0·52

Comparison between the corticospinal group (n=48) and the neuromuscular group (n=23) for clinical comorbidities and comparison with data for congenital Zika syndrome in other series. The four children with dyskinetic findings alone were excluded from statistical analysis. *Cumulative number of episodes per group.

Table: **Prevalence of clinical comorbidities in the IPESQ cohort compared with other congenital Zika syndrome series.**

congenital Zika syndrome who are born with microcephaly are documented as having severe impairment,[9] which is consistent with our findings. Four children had exclusively dyskinetic findings (dystonic movements of the hands and feet under specific postures), which should alert clinicians to a wide variety of possible clinical presentations.

In northeast Brazil, the incidence of microcephaly in mothers with Zika virus is ten times higher than in the south of the country.[8] Local factors influencing the severity of congenital Zika syndrome have been proposed as a hypothesis for the differences in microcephaly prevalence. Because the cohort was recruited from the northeast of Brazil the profile of our sample might be influenced by these unknown factors.

Of the 19 children born with a normal head circumference, 15 had postnatal slowing of head growth. The slowing of head growth has been described before in congenital Zika syndrome,[26] and it seems to be mostly the result of total or partial resolution of ventriculomegaly. Although unlikely, a progressive condition caused by a chronic, indolent viral disorder cannot be completely ruled out because we did not test for the presence of Zika virus or asses the immunology profile of the cerebrospinal fluid. All the children had neuroimaging findings typical of congenital Zika syndrome, including the 19 born with a normal head circumference. Of these 19 children, four had maintained a normal head circumference at the time of evaluation (Sept 10–20, 2018). Three of them were very affected, with ventriculomegaly or hydrocephalus. Thus, we conclude that normal head circumference should never be used to exclude suspected cases from follow-up, and neuroimaging should be done in all suspected cases.

Although important as a diagnostic tool for congenital Zika syndrome because no difference between the corticospinal and the neuromuscular groups with CT imaging could be documented, clinical presentations might be better understood in future through MRI and neurophysiological findings.

Our study revealed a common combination of motor signs and worse functional outcomes for children in the neuromuscular group. There is mechanistic evidence to support the neuromuscular findings observed in some children with congenital Zika syndrome. Previous studies have described neurogenic muscular dystrophy and histological evidence of peripheral nerve atrophy identified post mortem;[3] dysmaturation of nerve cells, hypomyelination, and loss of descending axons and spinal cord neurons;[27] and abnormal electroneuromyography in children born with arthrogryposis.[4] Several factors might contribute to a broad clinical spectrum in a single patient, and the hypotonic, sometimes dystrophic appearance, combined with CNS injury with corticospinal and dyskinetic signs presented by children with congenital Zika syndrome, results in a semiotic puzzle to the diagnostician. Previous studies have also described variable muscle tone, a high prevalence of dyskinetic findings, and a trend toward longer persistence of primitive reflexes.[26]

Although children in the neuromuscular group had worse gross motor function, manual ability, and communication classification scale scores than did those in the corticospinal group, scores for the ability to eat and drink classification scale were not significantly different between the two groups. However, the use of substances to thicken water and food consistency, which might have influenced these results, was not recorded.

Epilepsy was reported in 69% of the children in this series versus in 70% of children as reported by van der Linden and colleagues,[19] suggesting that epilepsy is the most frequent comorbid condition in children with congenital Zika syndrome. Urinary tract infections occurred in 44% of the children, a higher prevalence than previously reported.[20] Dysphagia was reported in 45% of the children, lower than in previous studies of congenital Zika syndrome.[21] Pneumonia and urinary tract infections were more common in the corticospinal group; as a result, careful respiratory follow-up and urodynamic evaluation are warranted to investigate these findings.

Hip dislocation was present in 43% of the children, which is consistent with estimates of around 55% in

another report.[22] Overall, 37% of children had sleep problems, which is also consistent with previous studies.[23]

Dyskinetic signs were present in 40% of the children (with four children only exhibiting dyskinetic signs), and most of these children had dystonia; a similar prevalence was reported in other case series.[9] These numbers far exceed the reported prevalence of dyskinetic signs in children with cerebral palsy (1–2% in most series).[28] Children with congenital Zika syndrome have a nearly 30 times higher prevalence of involuntary movements, sometimes misinterpreted as irritability or spasticity. In many of the children in this series, dystonic posture of the fingers and toes had been disregarded as a source of discomfort and an inability to complete voluntary movements. Adequate treatment after a more accurate detection of these signs might help to improve quality of movement and diminish discomfort.

Basal ganglia calcifications are common imaging correlates of congenital Zika syndrome,[2] and prevalence of involuntary movements in children with the syndrome is expected to be higher because of these anatomic lesions. However, the main dyskinetic manifestation in congenital Zika syndrome is dystonia, which has multiple causes—including grey-matter hyperexcitability. Thus, a cortical excitable state might influence the frequency of dystonic movements.[29] Hyperexcitability is also suggested by the high prevalence of early-onset epilepsy;[8] the high intensity and persistence of primitive reflexes;[23] and certain reactions rarely seen in this age group, such as the Babkin sign and brisk palpebral reflexes. Together, these suggest a poor cortical inhibitory drive and dysregulation of sensorimotor mechanisms.

Even more intriguing is the presence of movements resembling those pertaining to the General Movements Assessment repertoire observed in three children; these movements are usually seen only up until the third month of postnatal life and are excellent markers of cerebral palsy. Dyskinesia of the mouth and tongue, reported in 22 children, resembled the movements observed during the Movement Optimality Score evaluation of the General movements protocol.

General movements are the spontaneous elegant movement pattern initiated in 10-week-old fetuses and which continue until around the third month of postnatal life. These movements are believed to originate from neurons in the subplate zone. The subplate zone involutes as a result of programmed cell death at the same time when general movement patterns also fade,[30] justifying their concomitant disappearance.[7] These signs could be correlates of the typical calcification pattern observed in congenital Zika syndrome at the cortical and subcortical junction, where subplate neurons are normally expected to disappear.

Of note, Einspieler and colleagues[7] described "wiggling-oscillating" of the arms and legs and "repetitive and long lasting tongue protrusion" in children with congenital Zika syndrome evaluated by the General Movements Assessment.[7] Pathological aspects of the subcortical zone in the brains of children with congenital Zika syndrome might reveal a disruption of the programmed cell death sequence and the possibility of a surviving group of subplate neurons responsible for persistence of abnormal general movements in some children.

Poorer functional outcomes can be expected for children with neuromuscular signs, as suggested by the results from evaluation of manual abilities and communication function classification scale. Respiratory findings should be investigated because the pulmonary mechanics of severely hypotonic patients with a bell-shaped thorax would be expected to increase the occurrence of pneumonia.

Early classification of children with congenital Zika syndrome into the neuromuscular and corticospinal subgroups, oriented by clinical signs (hypotonia, distal deep tendon reflex reduction, and bell-shaped thorax), might predict higher risk of poor functional outcome and determine differences in the course of clinical comorbidities. Finally, the excitability imbalance observed in this cohort must be further documented because it might represent the basis for the high prevalence of epilepsy, dystonia, and other potentially disturbing signs and symptoms.

This is the largest case series of neurological evaluation of toddlers and preschoolers with congenital Zika syndrome to date. All the children had CT images typical of congenital Zika syndrome and most were severely functionally compromised, but they might not represent the full spectrum of congenital Zika syndrome, which also includes less severely affected children. The distribution of neurological findings disclosed a subgroup with predominantly neuromuscular signs, which is supported by recent neuropathological reports of peripheral nervous system abnormalities. Data on clinical comorbidities were obtained both by interviewing parents and by a review of medical records, but the information obtained regarding the comorbidities was not specific, and additional studies are warranted. Furthermore, some findings reported were unexpected, including the observation of primitive reflexes and persistence of general movements, which should be investigated further. Although the full spectrum of congenital Zika syndrome is still yet to be fully described, more specific clinical classification might help to understand pathologic aspects of the disease and anticipate the profile of functional outcomes.

Contributors

HVFSP, examined the children and contributed to the analysis, discussion, and main interpretation of results and writing of the Article. SPS examined the children, organised the data and analysis, and contributed to the discussion of results and the production of graphs. APRLA examined the children and organised the data. PSO-S obtained, produced, and interpreted the images, and contributed to the discussion of the results. EOF examined the children's motor functions. JST, RVBF, and MMRA, organised the epidemiological information, and reviewed the literature. FT-M contributed to image interpretation and discussion,

and figure production. AM interpreted the results, and contributed to the discussion and writing of the Article.

Declaration of interests

We report no competing interests.

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