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RESEARCH ARTICLE

Urological outcomes in children with congenital Zika syndrome: The experience of a cohort in Campina Grande, Brazil

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Abstract

Objective: To describe the urological outcomes in children with congenital Zika syndrome (CZS) and investigate the relationship between clinical and urological findings in this population.

Methods: This cross-sectional study involved children with CZS followed up by a referral centre for children with microcephaly in the state of Paraiba in northeast Brazil. The urological evaluation included clinical history, urine culture results, ultrasonography of the urinary tract, and urodynamic evaluation, following the protocol proposed by Costa Monteiro et al. (2017). Descriptive statistical analysis was performed in addition to association and correlation tests, considering clinical and urodynamic variables.

Results: Among the 88 children with CZS (35.5 ± 5.5 months), 97.7% had microcephaly, and 51% presented urinary tract infection (UTI) confirmed with clinical history and lab tests. The number of confirmed UTI episodes varied from one to 14 per child. The urodynamic evaluation confirmed the presence of an overactive bladder in 78 children and incomplete voiding in 50. Urodynamic findings were associated with the number of confirmed UTI episodes, child's sex, and actual weight, in addition to the use of anticonvulsant and myorelaxant drugs.

Conclusions: UTIs were confirmed in most children. Other urological outcomes observed were overactive bladder and low bladder capacity, which were associated with the number of confirmed UTI episodes, use of anticonvulsants and myorelaxants, and the child's sex and weight. These are treatable conditions, and it is paramount that paediatricians, neonatologists, and infectious disease specialists are aware of them to make clinical decisions and help reduce the risk of renal damage and other morbidities.

KEYWORDS
congenital abnormalities, congenital Zika syndrome, microcephaly, neurogenic bladder, neurological lower urinary tract dysfunction

INTRODUCTION

Zika virus (ZIKV) is an arbovirus transmitted to humans mainly through the *Aedes aegypti* mosquito bite; however, sexual and blood transmission has also been reported.[1] Human infection was associated with mild symptoms until 2015, when it was proven that Zika can be vertically transmitted to the foetus when pregnant women are infected, causing brain damage due to the ability of ZIKV to efficiently infect human cortical neural progenitor cells, resulting in reduced growth and dysregulation.[2]

The relationship between intrauterine ZIKV infection and brain abnormalities was first reported in northeast Brazil. The principal investigator of our group was the first to report the presence of ZIKV in the amniotic fluid of two foetuses with brain abnormalities detected by her with obstetric ultrasonography. Reverse transcription-polymerase chain reaction confirmed the presence of ZIKV in the fluid.[3]

The infants' mothers had reported exanthema during pregnancy that was later linked to ZIKV disease. Since then, our cohort followed up with mothers affected with ZIKV during pregnancy and their children and has been considered a pioneer Zika cohort in Brazil. Finding the link between the mother's infection with ZIKV and the presence of the virus in the amniotic fluid of the foetus with brain abnormality constitutes the first step toward understanding the role of ZIKV as a teratogenic agent. Although microcephaly is the most widely recognised sign, it is only one of the clinical characteristics of congenital Zika syndrome (CZS).[4]

During the Brazil outbreak from 2015 to 2016, ZIKV was confirmed in 18 Brazilian states, with most cases in the northeast region; there were 3474 confirmed cases between 2015 and 2018, and countless other cases are still not clarified.[5] Currently, 7 years after its first publication, much has been discussed about brain patterns,[2] neurological conditions,[6] growth,[7] and motor, cognitive, and sensory impairment.[8] Two recently published systematic reviews confirmed the importance of continuous monitoring of these children and their growth to better understand and control postnatal complications.[9, 10]

Recognising that ZIKV affects many structures of the central nervous system, including those that control physiological functioning of the bladder and urinary sphincter, supports the hypothesis that intrauterine ZIKV infection can affect urinary function.[11–14] A study conducted in Rio de Janeiro, including children with confirmed CZS, was the first to describe a urodynamic pattern suggestive of neurological lower urinary tract dysfunction (NLUTD), with reduced bladder capacity and higher vesical pressure during bladder filling in this population.[13] Other studies were also published supporting the presence of urological outcomes in children with CZS.[12–15] Nevertheless, the vast majority of children affected with CZS have not been investigated for urological sequels.

NLUTD causes urinary tract infection (UTI) and incontinence and may increase the risk of chronic kidney disease, which is preventable through early diagnosis.[16–18] In our CZS cohort, we frequently observed the occurrence of febrile UTIs in children. Considering the published evidence of a possible relationship between CZS, NLUTD, and UTI, we applied a protocol used in previous studies[12, 13] to investigate urological outcomes in children with CZS. This evaluation was performed to confirm the outcome and better understand the effects of ZIKV infection during intrauterine life on the urinary system and its related factors. Therefore, this study aimed to describe the urological outcomes of children with CZS and investigate the relationship between clinical and urological findings in this population.

MATERIALS AND METHODS

This descriptive and cross-sectional study involved children with CZS followed up by a support centre for children with microcephaly, affiliated Professor Joaquim Amorim Neto Research Institute (IPESQ) in Campina Grande, Paraiba, Brazil. This centre provides multidisciplinary care for children with CZS from several states in Brazil and other countries in Latin America and Africa. For this reason, many mothers reside in a support home while their children undergo rehabilitation programmes; our research group could closely follow the impact of CZS on their routine.

Some children in this cohort have been followed up since 2015, many of them since pregnancy. This follow-up was initiated after the first published study reporting the association between ZIKV infections and foetal brain malformations by a local physician specialising in foetal medicine.[2] Therefore, this is considered a pioneer Brazilian cohort of children with CZS. This cohort was formed in the direct monitoring of mothers and children, including the first cases of this pathology described in the literature during the ZIKV outbreak in Brazil.

CZS was defined by the spectrum of symptoms observed in infants exposed to ZIKV in utero whose mothers had a non-negative test for ZIKV infection associated with clinical factors, such as severe microcephaly with the skull partially collapsed, decreased brain tissue related to brain damage, damage to the back of the eyes, and joints with limited range of motion.[19–21] Children with CZS included in this study were followed up by IPESQ. Children with microcephaly and/or brain damage from other causes were excluded from the study and children who underwent urological evaluation between December 2018 and May 2019 were included.

Gestational age was corrected according to the first-trimester ultrasonography.[22] Microcephaly at birth was defined according to the Intergrowth-21st standards for head circumference (HC)[5] and subsequently evaluated with a z-score for HC, weight, and length calculated using WHO Anthro Software.[23] Based on the z-score values obtained, the weight and length of the evaluated children were classified as follows: very malnourished or below the expected length (z-score < -2), adequate weight or height (z-score between 2 and -2), and overweight and above the expected length (z-score > 2).[5] According to HC measurements, children were classified as having no microcephaly (z-score < -2), mild microcephaly (z-score of -2 to -3), or severe microcephaly (z-score < -3).[24] In addition, when the z-score was >2, the child was classified as having macrocephaly.

First, general data were collected from the clinical records and maternal reports concerning mothers' demographics (age, schooling, per capita income, living conditions, and lived areas), pregnancy (whether symptoms of Zika virus infection had occurred, and if yes, at which gestational age), delivery (gestational age, if the baby was premature, the mode of delivery, the first and fifth minute Apgar scores, birth weight, birth length, and HC), and information about the child (sex, age, weight, length, and HC at first urological evaluation; history of UTI; the number of confirmed UTI episodes; constipation; and whether the child required a diaper, and if yes, number of diapers per day).

The urological evaluation was based on the 2017 protocol to investigate NLUTD in CZS.[18] Urine culture, renal and bladder ultrasonography, and urodynamic assessment were used to evaluate the child's urinary system. UTI episodes were

confirmed based on the clinical history and laboratory test results. Constipation was assessed following the criteria to evaluate neurogenic bowel dysfunction in children with CZS,[15] including frequency of bowel emptying, the colour and aspect of faeces according to the Bristol Stool Scale,[25] and use of bowel emptying manoeuvres, laxative, suppositories, and/or enemas.

Finally, motor function was classified using the Gross Motor Function Classification Scale (GMFCS), a five-level scale that defines a child's independence and functionality according to age, where Level I refers to independent children and Level V to children with a severe handicap.[26] This assessment was performed by physical therapists who had experience in the application of this scale and the care of children with CZS. These professionals have been working in research and clinical assistance for this population since 2017 when motor function evaluation first began after training. This experience enabled these professionals to treat children with CZS and identify specificities of the population, such as clinical signs of UTI.

Ultrasonography was used to measure kidney dimensions, bladder wall thickness, and post-void urinary residual (PVR). A Samsung Elite WS80 machine with a convex (2–9 MHz) and linear (3–12 MHz) probe were used.

Urine culture samples were collected using catheterization 10 days before urodynamic evaluation to rule out or, if confirmed, treat UTI on time to perform the test. Moreover, a clinical evaluation, including recent clinical history and macroscopic evaluation of urine, was performed to exclude UTIs on the day of the urodynamic evaluation. In cases of suspected UTI, a urological evaluation was suspended. The prognostic importance of urodynamic testing was explained to the parents, who were encouraged to remain in the room with the children for reassurance during the procedure.

Urodynamic evaluation was performed using Dynapack MPX 816 equipment (Dynamed) and consisted of cystometry and electromyography. Cystometry (CMG) was performed to study bladder behaviour during the filling and voiding phases. Before catheterization, we evaluated the diaper wetness on arrival and asked the parents about the time the child had last voided or performed clean intermittent catheterization (CIC). The PVR was measured at the beginning and end of CMG, whenever the child was able to void.

The bladder-filling rate was established by calculating 5% of the expected bladder capacity for age.[27] Since children with CZS expressed no desire to void in our series, maximum bladder capacity was measured just before the child voided or had a significant leak, when basal bladder pressure remained >40 cmH_2O during the filling phase, when the volume infused reached 1.5 times the expected bladder capacity, or when the child showed signs of pain and/or discomfort.[27] Bladder behaviour during the urodynamic evaluation was classified as normal, underactive, overactive, or low compliance.[18] A normal bladder is expected to be relaxed during the filling phase until the maximum bladder capacity is reached. At this point, sustained bladder contraction is expected to initiate, and the urethral sphincter is expected to relax to allow complete emptying without leaving any urinary PVR. An overactive bladder, the most frequent in children with CZS, is diagnosed when bladder contractions are identified during the filling phase, raising the intravesical pressure and causing early emptying before reaching maximum bladder capacity.

Electromyography was performed to evaluate urethral sphincter function using surface electrodes placed on the perianal region and left leg. Detrusor-sphincter synergy was diagnosed if the sphincter remained contracted when the bladder was relaxed during the filling phase and relaxed when the bladder pressure increased, particularly during the emptying phase, allowing the bladder to empty. Conversely, in detrusor-sphincter dyssynergia, the sphincter fails to relax in response to an increase in bladder pressure and remains contracted during the emptying phase, hampering voiding and increasing pressure.[27]

Patients with low compliance and an overactive bladder were treated with anticholinergics (chloridrate of oxybutynin). CIC was recommended considering the patient history of UTI and when PVR was >20% of the maximum bladder capacity.[18] To increase treatment adherence, parents were trained to perform CIC. Antibiotics were prescribed for the treatment of confirmed UTIs according to the susceptibility test, as well as a prophylactic measure according to the clinical and laboratory history of recurrent UTIs.

The urodynamic variables evaluated were bladder pressure during the filling and emptying phases, bladder capacity, bladder compliance, detrusor-sphincter activity during the filling and emptying phases, and PVR, which was measured after voiding was completed.

After recording the data, a descriptive analysis was performed. The mean, standard deviation, and range were calculated for continuous variables, such as age and maximum bladder pressure. For categorical variables such as GMFCS level and detrusor-sphincter activity, absolute and relative frequencies were calculated. In addition, Spearman's association and Pearson's correlation tests were performed to evaluate the possible relationship between clinical and maternal variables and urological and urodynamic variables. All analyses were performed in MedCalc version 17.9.7 (MedCalc Software) and a 5% level of significance was adopted. When sample calculation was not performed, a post hoc power analysis for correlation tests was conducted using G*Power 3.1 software, considering $\alpha = 0.05$ and a total sample size of 88 participants.

This study was approved by the research ethics committee. Parental written informed consent was required for the inclusion of the patient in the study. Parents of the patients discussed in this manuscript provided written informed consent to publish the details of this study.

RESULTS

General characteristics of the study population

Of the initial cohort of 118 children, parental consent was refused in six cases, 21 children failed to complete the study,

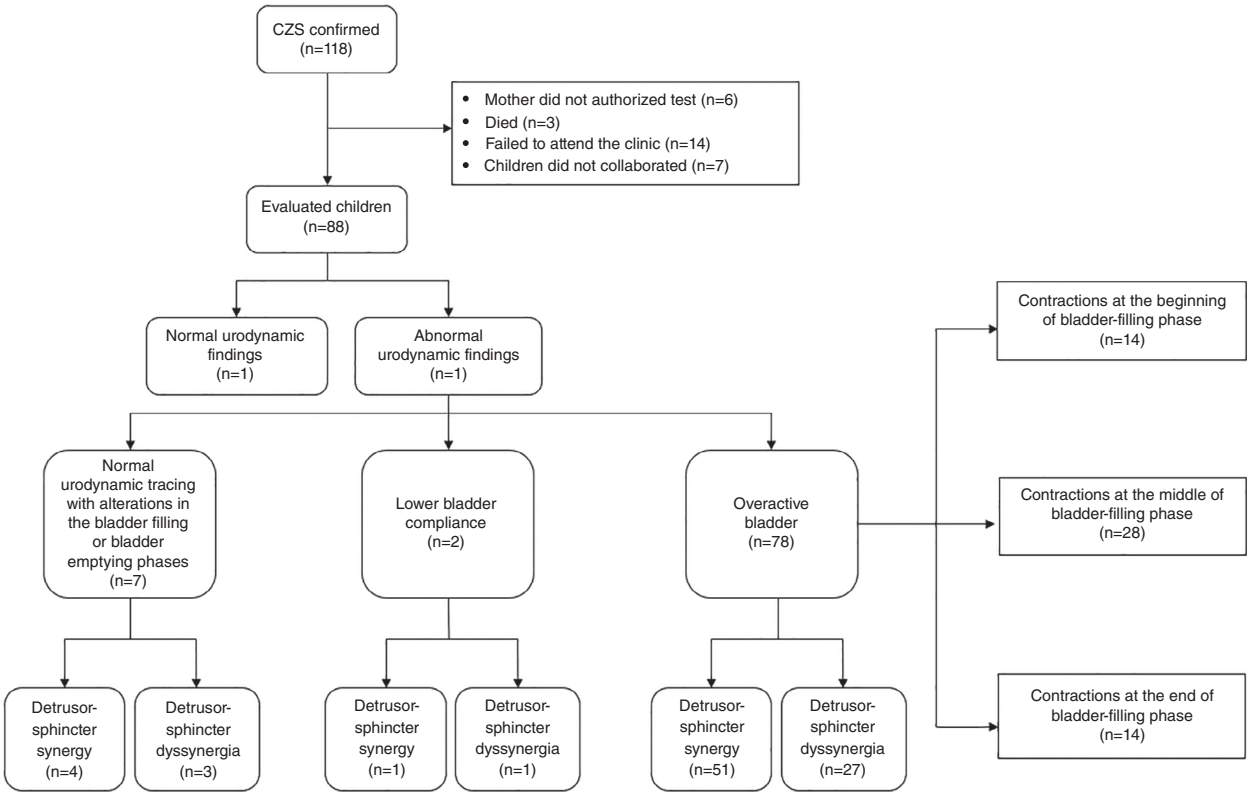

FIGURE 1 Flowchart describing the inclusion of children with congenital Zika syndrome (CZS) in the study and findings at first urological evaluation, 2018–2019

and 3 children died from respiratory failure before completing the urological protocol. Therefore, 88 children completed the assessment and were included in this study (Figure 1).

Among the 88 mothers, ages ranged from 17 to 40 years (mean 25.6 ± 5.8 years), school years ranged from 3 to 18 years (mean 10.5 ± 2.7 years), and per capita monthly income varied from $7.9 USD to $324.9 USD (mean $89.4 ± 63.8). Most participants (86.4%) lived in urban areas. Seventy-three mothers (82.9%) reported exanthema during pregnancy at a mean gestational age of 12.4 ± 6.4 weeks (range 6–32 weeks), mostly in the first trimester.

Of the 88 children, 47 were male (Table 1), 12 (13.6%) were premature, and 64 (72.7%) had microcephaly at birth. The mean age at the time of urological evaluation was 35 ± 5.5 months. At this time, 86 (97.7%) patients had microcephaly, 41 (46.6%) were malnourished, 29 (33%) were below the expected length for age, and 85 (96.6%) were classified as GMFCS Level V (Table 1).

Forty-five children (51.1%) had a history of UTI with the number of UTI episodes varying from 1 to 14 per child (1.37 ± 2.21 episodes), 55 children (62.5%) were constipated, and all children were in diapers, using a mean of 5.3 ± 1.5 diapers per day (range 2–10) (Table 2). Regarding urine culture performed 10 days before the urodynamic evaluation, six children were confirmed to have UTI by *Escherichia coli* and were treated on time to perform the test.

Renal and bladder ultrasonography

At ultrasonography, the mean longitudinal diameter of the right kidney was 6.7 ± 0.6 cm, (range 8–5.5 cm) and the left kidney was 6.8 ± 0.8 cm (range 8.1–3.5 cm) (reference values for 2–3 years, female: 7.07 cm and male: 6.94 cm).[28] PVR mean, measured in 39 children, was 19.1 ± 18.6 ml (range 75.3–0.8 ml). Eighty children (90.9%) had thickening of the bladder wall (mean thickness 2.4 ± 0.5 mm) (reference value 2.13 mm).[29] Two children had duplication of the pyelocaliceal system and one had a small kidney cyst measuring 1.1 cm. The thickness of the bladder wall was associated with the presence of changes in bladder capacity (rho = 0.26, p = 0.02, power = 0.71); children who presented changes in bladder capacity presented a greater thickness of bladder wall (children with altered bladder capacity 2.6 ± 0.6 mm vs. children with normal bladder capacity 2.2 ± 0.9 mm, p = 0.004).

Urodynamic evaluation

Neurological LUTD was confirmed in 87 children (98.9%), while urodynamic testing was normal in one child (1.2%). On cystometry, 78 children (88.6%) had an overactive bladder and two had low bladder compliance. Seven patients (7.9%) presented normal urodynamic trace during

TABLE 1 Epidemiological characteristics of children with congenital Zika syndrome

Characteristics	*n* (%)	Mean ± SD	Range
Sex			
Female	41 (46.6)		
Male	47 (53.4)		
At birth			
Gestational age		38.2 ± 1.9	32–41
Head circumference[a]		29.7 ± 1.9	23–35
Microcephaly			
No	20 (22.7)		
Yes	64 (72.7)		
Classification of microcephaly			
Mild	22 (34.4)		
Severe	42 (65.6)		
Weight[a]		2.7 ± 0.5	1.1–4.2
Height[a]		45.6 ± 3.1	36–53
At urodynamic evaluation			
Age (months)		35 ± 5.5	12–43
Head circumference		41.3 ± 2.7	36–48.5
Microcephaly			
No	2 (2.3)		
Yes	86 (97.7)		
Classification of microcephaly			
Mild	4 (4.7)		
Severe	82 (95.3)		
Weight		11.2 ± 3.8	7–19.9
Height		88.4 ± 5.8	72–97
GMFCS level			
I, II, III e IV	3 (3.4)		
V	85 (96.6)		

Abbreviations: GMFCS, Gross Motor Function Classification Scale; SD, standard deviation.
[a]Missing data in four cases.

TABLE 2 Clinical characteristics of the children with congenital Zika virus

Characteristics	*n* (%)
Number of diapers used per day	
2–4	25 (28.4)
5–7	56 (63.6)
8–10	7 (8.0)
Clinical/urological signs and symptoms	
Urinary tract infection	45 (51.1)
Constipation	55 (62.5)
Abnormal ultrasound scan	19 (21.6)
Abnormal urodynamic evaluation	87 (98.9)
Urine culture prior to urodynamics	
Negative	82 (93.2)
Positive (*Escherichia coli*)	6 (6.8)
History of urinary tract infections reported prior to examination	
None	43 (48.9)
1–5	41 (46.6)
≥6	4 (4.5)

Note: "Abnormal" = Children who showed any type of alteration/unexpected finding in the proposed assessments.

cystometry, but urodynamic measurements showed problems with bladder capacity and/or bladder emptying: three had problems in the filling phase (two with increased and one with reduced bladder capacity, compared to the capacity expected for age), two in the emptying phase resulting in PVR, and two in both phases (reduced bladder capacity and incomplete bladder emptying with PVR).

Among the 88 children, bladder capacity was above the expected value for age in 6 (6.81%), normal in 1 child (1.13%), and below in 82 children (93.18%). The pressure at maximum bladder capacity was >40 cmH_2O in 31 children (35.2%), while in 60 (68.2%), the maximum bladder capacity was half of what was expected for age. Mean bladder capacity was 52.5 ± 39.4 ml (range 6–210 ml), mean compliance was 1.9 ± 0.8 ml/cmH_2O (range 0.06–16.7 ml/cmH_2O), and mean bladder pressure at maximum bladder capacity was 39.42 ± 22.4 cmH_2O (range 6–99 cmH_2O) (Table 3).

Of the 78 children with an overactive bladder, bladder contractions started at the beginning of the filling phase in 14 (17.9%), halfway in 28 (35.9%), and at the end of the filling phase in 36 (46.2%).

Electromyography showed normal sphincter activity in 64.8% of children. The sphincter activity increased during the voiding phase, and the sphincter remained contracted, hampering voiding in 31 patients (35.2%), which was considered suggestive of detrusor-sphincter dyssynergia. Although 87 (89.8%) children urinated by the end of the test, voiding was incomplete in 50 children (56.8%), with a mean PVR of 12.5 ± 11.7 ml (range 1–53 ml) (Table 3).

Relation between urological and clinical findings

An association was found between PVR and use of anticonvulsant drugs (rho = −0.31, $p = 0.03$, power = 0.85), and children taking anticonvulsants had a lower PVR (use of anticonvulsants 6.4 ± 11.1 ml vs. non-use of anticonvulsants 11 ± 8.7 ml). We also observed a correlation between PVR and number of UTIs ($r = 0.22$, $p = 0.03$, power = 0.55), a higher PVR was observed in children who had a higher number of UTI episodes; an association between bladder pressure at voiding and the child's sex (rho = 0.23, $p = 0.03$, power = 0.59), males had higher pressure (male 71.3 ± 29.7 ml/cmH_2O vs. female 60.92 ± 35.7 ml/cmH_2O); and a correlation between bladder pressure at voiding and the child's current weight ($r = -0.26$, $p = 0.01$, power = 0.71), higher voiding pressure was observed in children with lower weight.

TABLE 3 Findings at first urodynamic evaluation of children with congenital Zika syndrome

Urodynamic findings	*n* (%)	Mean ± SD	Range
Diagnostic urodynamic testing			
Normal urodynamic findings	1 (1.1)		
Abnormal urodynamic findings	87 (98.9)		
Bladder abnormalities detected at testing			
Overactive bladder	78 (88.6)		
With contractions right from the beginning of the bladder filling phase	14 (17.9)		
With contractions from halfway through the bladder-filling phase	28 (35.9)		
With contractions only at the end of the bladder-filling phase	36 (46.2)		
Low compliance bladder	2 (2.3)		
Normal urodynamic tracings with abnormalities in bladder capacity and/or in bladder emptying	7 (8)		
Maximum bladder capacity			
0%–50% of expected capacity for age	60 (68.2)		
>50%–100% of expected capacity for age	22 (25)		
>100% of expected capacity for age	6 (6.8)		
Pressure at maximum bladder capacity			
0–40 cmH_2O	56 (64.4)		
>40 cmH_2O	31 (35.6)		
Pressure during involuntary loss of urine or voiding			
0–40 cmH_2O	21 (24.1)		
>40 cmH_2O	66 (75.9)		
Behaviour of the urethral sphincter			
Detrusor-sphincter synergy	57 (64.8)		
Detrusor-sphincter dyssynergia	31 (35.2)		
Urine loss observed during examination			
Yes	19 (21.8)		
No	68 (78.2)		
Voided at the end of the examination			
Yes	86 (98.9)		
No	1 (1.1)		
Post-void residual urine (ml)		12.5 ± 11.7	1–53
Post-void residual urine (% of bladder capacity)		25.6 ± 18.6	1–76.9

Note: "Abnormal" = Children who showed any type of alteration/unexpected finding in the proposed assessments.

On the other hand, leak point pressure was associated with the use of muscle relaxant drugs (rho = −0.46, $p = 0.04$, power = 0.99), and children taking muscle relaxants had lower pressure (use of muscle relaxants 41.2 ± 32 cmH_2O vs. non-use of muscle relaxants 72.1 ± 37.4 cmH_2O), and a correlation with the child's age ($r = -0.51$, $p = 0.02$, power = 0.99), younger children had lower leak point pressure. Finally, the pressure at the maximum bladder capacity was correlated with the number of UTI episodes ($r = -0.25$, $p = 0.02$, power = 0.67), lower pressure was observed in children with a higher number of UTI episodes, and child's current weight ($r = -0.28$, $p = 0.007$, power = 0.77), children with higher weight had lower maximum capacity.

DISCUSSION

The urological evaluation described in this study confirmed NLUTD in 98.9% of children with CZS. In addition, we observed a relationship between clinical and urological findings, specifically the number of UTI episodes, use of anticonvulsant and myorelaxant drugs, as well as the child's sex and actual weight.

The fact that previous studies were published in urological settings only may have delayed non-urologists' access to the information. To our knowledge, this is the first study of its kind to be published in a non-urological setting. This is very important because most urological outcomes described in children with CZS are treatable; therefore, paediatricians,

neonatologists, and infectious disease specialists should be aware of the need to investigate them to make clinical decisions and referrals to help reduce the risk of renal damage and other morbidities. All the children in our group had access to treatment, anticholinergic drugs were affordable, and parents were trained to perform CIC, although adherence to CIC varied among families. This is a frequent problem in other cohorts.

One of the risk factors for NLUTD is the bladder wall thickness, evaluated using ultrasonography of the urinary tract, for which sensitivity is around 95% when bladder thickness is ≥3.3 mm.[30] The mean bladder wall thickness exceeded the risk threshold in eight children (9.1%) included in the present study; of these, five (62.5%) also had a history of UTI. Ultrasonography results also confirmed, on average, a reduced bladder capacity and PVR above the threshold of 20% of bladder capacity, reinforcing the urodynamic evaluation results. These findings were also reinforced by the correlation between changes in bladder capacity and bladder wall thickness in the investigated children.

The presence of an overactive bladder was also confirmed in this cohort, as previously reported. However, the percentage of children affected varied among studies.[12–15] One hypothesis that may explain this discrepancy is the level of neurological impairment. Most of the children evaluated in our study presented with severe motor impairment and seizures that were difficult to control, requiring the use of myorelaxants and anticonvulsant drugs.

A higher frequency of neurogenic bladder is also reported in children with severe motor impairment and seizures caused by cerebral palsy (CP).[31] In this study, the majority of children presented an overactive bladder at a percentage that was in agreement with two previous studies (95.45% and 91.3%),[12, 13] and higher than a third one (59.2%).[14]

The age of children also varied among studies, and whether age influences the evaluation of bladder behaviour has been wondered. It is currently accepted that infants have small bladders and present physiological and transient dyscoordination of the detrusor-sphincteric unit during micturition, which subsides as the child grows.[32] In this way, bladder control of a neurologically healthy child is expected to improve from the age of 2 years. The children evaluated in this study had a mean age of approximately 35 months and remained incontinent, with a high prevalence of urological alterations, suggesting that these results are independent of the children's age.

One limitation of our study was the ability to better evaluate the influence of severe motor impairment and seizures on urological outcomes. Subgroup analysis, comparing children with severe and non-severe motor impairment and seizures, was not possible because 96.6% of patients in the present study presented GMFCS Level V. Comparison among studies was compromised by the lack of published information related to the level of neurological impairment in other CZS cohorts. Future studies involving children with CZS and different levels of neurological impairment are required to confirm this hypothesis.

The number of UTI episodes was related to urodynamic variables such as PVR and pressure at maximum bladder capacity. Higher PVR and lower pressure were observed in children with more UTI episodes. These results are in line with previous reports and may be related to insufficient bladder activity and incomplete voiding.[33]

Moreover, the data presented here suggest a relationship between myorelaxant use and lower leak point pressure. Impairments in urinary continence were previously described as a side effect of the chronic use of myorelaxants in children with CP.[34] This is the first study to investigate this relationship in children with CZS. More studies are necessary to better understand the relationship between urodynamic changes and muscle tone changes presented in children with CZS,[35] and its connection to neurological damage and the chronic use of anticonvulsants and myorelaxants.

Interestingly, all published studies of NLUTD in patients with CZS reported cases, where the urodynamic traces were normal but urodynamic measurements, were not, supporting the need to carefully examine all aspects of urodynamic evaluation and compare with clinical outcomes before concluding with the need for treatment. In the present study, the urodynamic evaluation was normal in one child, a result that was also reported in two children in the Bahia study.[14]

Bladder capacity was below the mean expected value in the general paediatric population, adjusted for age in 80 patients in this cohort. The mean bladder capacity was 44.8% of the expected volume. In 21.6% of cases, urine leakage started during the filling phase, before voiding, thereby reducing bladder capacity.[12] A good-sized, relaxed bladder during the filling phase is important for the health of the upper urinary tract and continence.

NLUTD is common in children with neurological impairments, mainly myelomeningoceles. It was found in 99% of cases, detrusor overactivity in 48%, low bladder compliance in 49%, and increased bladder capacity in 2% in a study with 104 patients who were not undergoing any urological treatment.[36] In a group of 42 patients followed up for a mean of 7 years, LUTD was found in 92.9% of cases, reflex detrusor activity in 17%, detrusor-sphincter dyssynergia in 7.1%, and detrusor areflexia in 83%.[37]

In cases of CP of other origins, a prevalence rate of 80% has been found, with most cases consisting of overactive bladder[38]; patients with CP are less likely to have urinary incontinence, with rates of 44.3% being reported from a study of 97 patients with a mean age of 8 years (5–18 years),[39] and of 77.4% in another study in which 31 individuals of 4–16 years of age were evaluated.[40] We observed a high prevalence of neurological LUTD (98.9%) in our patients, including 88.6% of overactive bladder and 35.2% of detrusor-sphincter dyssynergia. When compared to studies including other causes of LUTD, these findings seem to reinforce the ability of the ZIKV to affect brain neurons, as

well as the entire central and peripheral nervous systems.[41, 42]

The present study reinforces the need to investigate NLUTD in patients with CZS. Some discrepancies require further investigation. As children with CZS are turning older, new studies are being conducted in relation to follow-up and to compare findings between cohorts.

Another limitation of this study is that the evaluation of the urinary system began as late as approximately 3 years of age. It is unknown whether the bladder was affected at an early stage or whether this was part of the disease process. In addition, it was not possible to determine the relationship between the use of anticonvulsants and muscle relaxants and urological outcomes. Many children had started using anticonvulsants and muscle relaxants before they were referred to our centre. Therefore, it was not possible to determine the duration of use before the urological evaluation started. Patients will need to be re-evaluated to enhance understanding of this progression.

CONCLUSION

The frequency of NLUTD in this cohort was 98.9%, with most children having an overactive bladder and a confirmed UTI. Urological findings included thickened bladder wall, low bladder capacity, increased detrusor pressure during the bladder-filling and emptying phases, and elevated post-void residual urine. All of these are treatable risk factors for upper urinary tract deterioration. Adequate treatment based on urodynamic diagnosis, including anticholinergic drugs and intermittent urethral catheterization, can help mitigate complications and prevent kidney damage.

Considering that these are treatable conditions that are related to long-term consequences, clinical factors related to urodynamic findings represent important information for these professionals. It is also important to understand and reduce the risk of CZS by preventing vertical transmission of the virus. Despite the reduction in new cases of CZS, warning pregnant women about the risk of ZIKV infections during pregnancy should continue to be a part of prenatal routine care.

These findings are important for implementation in the urinary tract. In addition, these findings can help with bladder relaxation, increase bladder capacity and compliance, and reduce the risk of urinary incontinence. Intermittent bladder catheterization, indicated in cases of high post-voiding residue, ensures adequate bladder emptying and helps reduce urinary infection. Health professionals should be aware of the occurrence of CZS.

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