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Incidence of Urinary Tract Infection in Children and Young People with Neurological Disorders

Aline Marzola De Rezende[1], Francisco de Agostinho Júnior[2], Paula Cristina Cola[1], Daniel De Bortoli Teixeira[1], Isabela Bazzo Da Costa[2]*, Lara Cristina Casadei Ubeda[2], Elizandra Aparecida De Oliveira Lopes[2], Paulo Cezar Novais[2]

[1]Postgraduate Program in Structural and Functional Interactions in Rehabilitation, University of Marilia, Marilia, Brazil

[2]Department of Medicine/Biomedicine, University of Marilia, Marilia, Brazil

Research Article

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***For Correspondence**
Isabela Bazzo Da Costa, Department of Medicine/Biomedicine, University of Marilia, Marilia, Brazil

Email: isabelabazzo@hotmail.com

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Abstract

Lower Urinary Tract Dysfunction (LUTD) describes disorders of micturition, in the absence of neurological disease or obstructive urinary tract pathology. Urinary Tract Infection (UTI) is characterized by bacterial invasion and multiplication, affecting the kidneys and urinary tract. The aim of this study was to investigate the incidence of subclinical urinary tract infection in 25 children and young people from University of Marilia, with neurological disorders by urine collection and examination. The results showed that 8.33% of patients with cerebral palsy were positive for the urine culture test, with *Klebsiella* sp being the identified agent; while among patients with other syndromes, 16.67% were positive in the urine culture test for the agents *Klebsiella pneumoniae* and *Escherichia coli*. It was concluded that care, as well as attention to the initial symptoms of urinary tract infections in children and young people with neurological disorders, are extremely important, as they are determinant for a quality of life for these patients who, in most cases, have cognitive limitations, motor and communication aspects regarding the need to urinate.

INTRODUCTION

Lower urinary tract dysfunction (LUTD) is characterized by disturbances in any of the stages of urination - filling or emptying, in the absence of neurological disease or obstructive pathology of the urinary tract, its symptomatological prevalence in children ranging from 2% to 25% [1]. Filling signs are marked with increasing or decreasing voiding frequency, incontinence, urgency, or nocturia. The signs of voiding are characterized by hesitation, straining, weak stream, intermittent stream, holding maneuvers, and feeling of incomplete emptying, post-void dribbling and dysuria. The comorbidities commonly associated with LUTD are urinary tract infection, asymptomatic bacteraemia, constipation and/or faecal incontinence, vesicourethral reflux, emotional disturbances and intellectual deficits [2]. Lower urinary tract dysfunctions manifest symptomatically as urinary incontinence, urgency, frequency, hesitancy and urinary tract infection. Possible reasons for the propensity for urinary tract infections include vesico urethral reflux and incomplete bladder emptying resulting from detrusor hyperreflexia and sphincter dyssynergia. In addition, impaired cognition and the inability to diffuse bladder fullness and the need to urinate, alongside impaired mobility, may also account for the tendency to urinary retention and the concomitant risk of urinary tract infections [3,4]. Urinary Tract Infection (UTI) is a common pathology, which occurs at all ages, but intensifies during the first year of life, due to the greater number of congenital malformations, especially the posterior urethral valve; which predominantly affects males. From this period onwards, throughout childhood, and especially in the preschool phase, girls are affected by UTI 10 to 20 times more than boys. In adult life, the incidence of UTI in females is more incident than in males, having a greater expression at the beginning of sexual activity, being also observed sometimes during pregnancy or menopause, thus 48% of women have at least one episode of UTI in your lifetime [5]. Neurological disorders are characterized by disorders of brain function, related to a wide variety of physical, behavioural and mental characteristics, which include disorders such as autism, attention deficit hyperactivity disorder, Cerebral Palsy (CP), among others [6]. CP is a common cause of childhood morbidity, which includes seizure disorders, mental retardation, vision abnormalities, problems with the respiratory muscles, and lower urinary tract dysfunction [7]. The voiding dysfunctions resulting from neurological injuries are based on changes in detrusor function, external sphincter and/or associations. In a topographic categorization, neurological lesions can be analysed in suprapontine, medullary and subsacral (cauda equina and peripheral nerves) [8]. Brain fields such as

the insula, anterior cingulate cortex, and prefrontal cortex are responsible for dominating and monitoring the bladder [2].

Urinary tract infections in children with CP in developed countries range from 8.5% to 56.7%; while in Nigeria, the prevalence found was 38.5%; and the most common pathogens found are: *Escherichia coli*, *Proteus* spp, *Enterococcus faecalis, Klebsiella* spp and *Staphylococcus* spp [9]. Analysing children with ADHD and children with ADHD and enuresis, highlighted that those with enuresis provided a shorter reaction time in neuropsychological tests that assess attention performance, demonstrating a worse inhibitory domain. Understanding this pathophysiological correlation and the importance of treating comorbidities in patients with neurological disorders creates a very favourable treatment suggestion in patients with LUTD [10,11]. The treatment mainly aims to eradicate the bacteria from the urinary tract, with consequent improvement of symptoms. General guidelines, such as recurrent UTI, adequate water supply and correction of urination and bowel habits are important, increasing the effectiveness of drug treatment and the interval between possible infections. The treatment of associated perineal pathologies *(leucorrhea and balanoposthitis)* is also important for the clinical improvement of the patient [12]. Drug therapy must be carefully chosen, taking into account the repercussion that may have on the normal intestinal flora, since this is the main reservoir of uropathogenic bacteria. In this circumstance, the use of lamino-culture is recommended, the result of which can be obtained quickly, approximately 18-24 hours, confirming or ruling out the diagnosis of UTI. The choice of antimicrobial is usually based on observation of the therapeutic response and on the possibility of recurrence or reinfection in the short term [13]. Considering that children and young people with neurological disorders, due to the lack of control of the urinary sphincter, may be susceptible to subclinical infections, a microbiological and chemical investigation can contribute to the diagnostic definition. Thus, the objective of this study was to investigate the incidence of subclinical urinary tract infection in these patients.

MATERIALS AND METHODS

Participants who met the inclusion criteria were invited to participate in the study, upon accepting the invitation, they and their guardians were informed in detail about the research procedures. At this moment, the signing of the Free and Informed Consent Term was requested in two copies (Appendix). This study was carried out on the premises of the "Ambulatório Amor de Criança", maintained by the "Associação Beneficente Hospital Universitário", and the Clinical Analysis Laboratory of the University of Marilia, located at street.

Dr. Próspero Cecílio de Coimbra, 80 – Jd. São Gabriel, in the city of Marilia/SP. We evaluated 25 children and young people with neurological disorders, aged from zero to 21 years old, who are monitored monthly or bimonthly at the outpatient clinic, and as they attended the service, the person responsible was approached by applying some questions to verify if the profile fitted the inclusion and exclusion criteria, and if admitted, they were sent to the accredited laboratory for subsequent urine collection and examination using a safe method.

The inclusion criteria were:

- Children and young people with neurological impairments
- Use of diapers. The exclusion criteria were
- Use of antibiotic therapy in the last 30 days
- Impossibilities of collection
- Absence of material

Urine samples were obtained by collecting a vesicle probing technique using a previous antisepsis protocol and later the samples were submitted to laboratory analysis through urinalysis I and urine culture by the accredited.

Laboratory

The antisepsis protocol and technique applied to obtain the samples was the Standard Operating Procedure of "Hospital Beneficent Unimar."

- Hand hygiene (wash or apply alcohol gel).
- Guide the patient and/or companion regarding the procedure.
- Put on gloves.
- Perform intimate hygiene on the patient with soap and water before catheterization.
- Place the patient in the supine position, with the knees bent and the feet supported on the stretcher/bed, keeping the legs apart. In the case of boys, place the patient in the supine position, with the legs extended in abduction.
- Open the probing kit and then dispose of all sterile material in the sterile field.
- Pour deeming agent into the kit dome. 8 - Open the aesthetic gel tube and puncture it with a sterile needle, then pour a little gel on the open gauze.
- Put on sterile gloves with aseptic technique.

- With tweezers and gauze soaked in deeming agent, perform antisepsis of the perineal region, passing the gauze only once in a single direction, from the pubis towards the anus.
- In the case of girls, move the labia major apart from the vagina with the non-dominant hand without the forceps, using the thumb and the first or second finger and in the case of boys, with the non-dominant hand, hold the body of the penis, keeping the it at a 90 degree angle in the pubic region, exposing the glans completely.
- Hygiene genitals and urethral meatus, using one gauze at a time and using one way.
- Wait for it to dry.
- Keeping the non-dominant hand moving the genitals away, lubricate the tip of the probe with sterile gel.
- Introduce the probe until the urine reflux, connect the 10 mL syringe to its extension, aspirate the flow and store it in a sterile container.
- Proceed with the correct identification and forward it for analysis.

In the analysis of the urine, the following general characteristics were observed:

Physical aspects

Analyse the hygiene and normality of the genitalia, collect the sample preferably after cleaning the genitalia with soap and water. In patients with voiding control, the medium stream is the ideal way of collection, with a minimum interval of two hours after the last void. In patients without voiding control, urine should be collected in three ways: collection bag, bladder catheterization and supra pubic puncture. When the collection bag is used changes should be performed at most every 30 minutes, until the urine sample is obtained. The criteria recommended by some authors, such as the habit of collecting urine, is an aggressive method and can damage the urethral mucosa. It presents less security and is not very objective, considering the high number of exams that are performed. It is important that the urine is processed promptly so that there is no loss of formed elements or bacterial propagation. Therefore, urine collection should be performed close to the examination site. The colour is variable and depends on the greater or lesser concentration of urinary pigments, drug substances or pathological elements eliminated. Ur chrome a product of endogenous metabolism, produced at a constant rate, is primarily responsible for the yellow colour. Altered Colours: Dark yellow: infections such as cystitis, pyelonephritis, always accompanied by turbidity. Reddish: presence of haemoglobin, always remembering that haematuria of glomerular origin never has clots, whereas in other types of haematuria, such as trauma or tumours, they are often present. Orange: due to medications such as pyridines. Amber or yellow-brown: problems with the liver or biliary tract, with the presence of bile pigments, mainly bilirubin. Bluish: use of medication methenamide Green from Pseudomonas infections. Purpura: *Klebsiella* infection. Light yellow or colourless: due to the dilution that this urine presents, where the first case can occur in poorly diluted urine and the second in much diluted urine.

As for volume, polyuria can characterize diabetes mellitus, certain disorders of the nervous system, contracted kidney, emotions, cold, psychogenic polydipsia and excessive fluid intake. Oliguria: in the following cases: acute nephritis, heart and lung diseases, fever, diarrhoea, vomiting, shock, dehydration, toxic tubular nephropathy and haemorrhagic infarction of the kidney.

Anuria: volume of less than fifty 50 mL in 24 hours, due to urinary excretory tract obstructions, severe kidney injury or acute renal failure.

Analysis for deposits: Normal: negative. Altered: Positive: presence of dissolved or suspended elements, which appear by precipitation, or are constituted by formed elements, such as epithelial cells, pyocytes, bacteria or red blood cells.

Urine appearance: Normal: clear. Altered: slightly cloudy or cloudy (due to the presence of crystals, red blood cells, leukocytes, mucus, casts, bacteria, epithelial cells, as well as the presence of external contaminants such as talc and medications.

Chemical aspects

Presence of blood nephropathies (pyelonephritis glomerulonephritis and nephritis) kidney stones, tumours and tubular necrosis.

Presence of leukocytes: pyuria may occur in cystitis, nephropathies (pyelonephritis, nephritis and glomerulonephritis), tumour, acute tubular necrosis, renal failure, prostatitis and urethritis. Glycosuria occurs in patients with diabetes mellitus, where blood glucose exceeds 160 mg/dL and with glomerular alterations. Ketone bodies: by glucose deficiency, use of fatty acids as a source of energy, and these, when degraded, form ketone bodies and in cases of febrile illnesses. Bilirubin and Urobilinogen Obstructive jaundice (cholangitic, obstructive, or neoplastic), hepatocellular jaundice (infectious, toxic, or cirrhotic), and hemolysis (hemolytic anemia). As for density, values up to 1,001: chronic renal failure, diabetes and hypertension and body hydration Density up to 1040: dehydration, diarrhoea, vomiting, fever, diabetes mellitus, glomerulonephritis, proteinuria, and renal failure. The presence of protein, due to an organic cause, is when it is associated with systemic disease or with some demonstrable renal pathology, such as perennia proteinuria (not caused by primary renal disease, such as fever, venous congestion, renal hypoxia, hypertension), renal proteinuria (primary kidney disease, such as glomerulonephritis, nephritic syndrome) and post-renal proteinuria (protein that passes into the urine at some point in the urinary tract distant from the renal parenchyma, such as infection of the pelvis or catheter, cystitis, urethritis, prostatitis). The pH analysis can be shown to be altered in alkalosis or

metabolic acidosis, with crystals in the sediment and can be altered by food and medication. The presence of positive nitrite represents nitrifying bacteria in the urine (gram negative). However, it can be observed in sedimentoscopy the presence of bacteria, but not nitrifying, thus not being detected in the chemical analysis of urine. The procedure for analysing the urinary sediment was performed as follows: Homogenization of the urine sample (without shaking), Transfer of approximately 10 mL in a conical bottom tube. Reagent strip passage and annotation of the results. Centrifuge the sample for 10 minutes at 3,300 revolutions per minute. Forming the sediment decanting the supernatant liquid (about 9 mL) stirring the residue at the bottom of the tube (about 1 mL). Transfer a small portion, approximately 40 µL to the Neuberger chamber. Cover the chamber with a coverslip and observe the sample under a microscope with the objective lens at 40X magnification. Counting in the chamber was done by counting one of the four side quadrants, multiplying the result by 1,000. For the count of pure urine, five central quadrants were counted and the number of cells obtained was added, divided by 5 (averaging) × 25 × 10,000. Appropriate samples for urine culture examination were collected aseptically. The ideal sample volume was 5 mL and sample handling was performed inside the biological safety cabinet. The cabin was irradiated with ultraviolet light for a minimum of 15 minutes before being used. The vial/tube cap was opened carefully avoiding the creation of sprays or aerosols. The streak seeding technique, which aims to obtain the growth of the microorganism in the culture medium, was performed aseptically, sowing the microorganism with the aid of a 10µ disposable loop, making streaks on the surface (apex) of the medium (agar Cled/MacConkey). The sting seeding technique, which aims to verify the biochemical reactions of microorganisms in EPM/MILI/CITRATE medium, was performed with the sterilization of the nickel-chromium needle loop to sow the microorganism with the aid of the loop, making a sting. In the center of the culture medium, penetrating to half its height. After the incubation period, the results were interpreted, as follows:

Mobile bacteria: growth throughout the culture medium or immobile bacteria: growth only at the bite site. The technique of seeding in depletion, which aims to obtain isolated colonies, allowing distinguishing the different microorganisms in a material or poly microbial culture through its colonial's morphology, was carried out with the seeding of the material or the microbial culture with the aid of a loop. 10 µ, making streak sequences on the surface of the Petri dish culture medium. Then, the material was transferred to the medium ("Exhaustion" Initial) and streak sequences were made in order to obtain the depletion of the loop inoculum (striations from the edge to the centre of the plate) and consequently allow the microorganisms to spread. Develop to form isolated colonies. Buckling the loop between each streak sequence increases the probability of obtaining isolated colonies. In data analysis the variables were described according to the study diagnoses, Cerebral Palsy and Syndromes. Preliminarily, for the quantitative variables (age, number of diaper changes, density and pH), the presence of data normality was verified using the Kolmogorov-Smirnov test at 5% probability. Thus, for the description of these variables, the mean and standard deviation values (variables with normal distribution - parametric) and median and interquartile range (non-parametric variables) were estimated. For parametric variables, the comparison between diagnoses was performed using Student's t test. On the other hand, for those with non-norma (non-parametric) distribution, the Mann-Whitney test was used, both at 5% probability. For the qualitative variables (urine colour, appearance and urine culture) the absolute and relative frequencies of occurrences were estimated as a function of the diagnoses. The association of these variables with the diagnoses was assessed using Fisher's exact test at 5% probability. All analyses were performed using the R software - R Development Team, 2019. About the ethical considerations - the research project was sent for consideration and approval by the Research Ethics Committee involving human beings at the University of Marília-Unimar (CEP-UNIMAR), following all the ethical precepts provided for in Resolution 466/12 of the National Health Council. Data collection was initiated only after the issuance of the substantiated opinion issued by CEP-UNIMAR.

RESULTS AND DISCUSSION

Mann-Whitney test represent the median and interquartile range of the data; for Fisher's exact test, the results of the absolute and relative frequencies of the occurrence of events are presented; for Student's t test, the mean and standard deviation values are presented (Table 1).

Table 1 Characterization of the variables analysed according to the patient's diagnosis, Cerebral Palsy (CP) and Syndrome.

Variables		CP	Syndrome	p-value
Age (years)	-	6 (11,8)	3 (3,75)	0,1648*
Diaper changes	-	6 (1,25)	6 (1,0)	0,539*
Urine color	Yellow	6 (50%)	1 (8,33%)	0,06482**
	Citrine yellow	4 (33,33%)	6 (50%)	-
	Light yellow	1 (8,33%)	2 (16,67%)	-
	Dark yellow	1 (8,33%)	0 (0%)	-
	Straw yellow	0 (0%)	3 (25%)	-
Aspect	Slightly cloudy	1 (8,33%)	0 (0%)	0,422**
	Clear	9 (75%)	8 (66,67%)	-
	Cloudy	2 (16,67%)	4 (33,33%)	-
Density	-	1018 (5,9)	1018 (6,1)	0,9197***
pH	-	6,71 (0,50)	6,25 (0,84)	0,118***
Urine culture	Negative	11 (91,67%)	10 (83,33%)	1**
	Positive	1 (8,33%)	2 (16,67%)	-

The results of this study did not show a statistically significant difference between individuals with cerebral palsy, when compared to patients with other syndromes, both groups with neurological impairments; the results of this study showed that 8.33% of the patients with cerebral palsy were positive for the urine culture exam, with *Klebsiella* sp being the identified etiological agent; while among patients with other syndromes, 16.67% were positive in the urine culture test for the etiological agents *Klebsiella pneumoniae* and *Escherichia coli*. UTI is one of the most common and important clinical challenges in children; a single UTI event is sufficient to lead to major renal scarring, and that it may eventually progress to renal hypertension as a long-term consequence [9]. Factors that contribute to the increased likelihood of acquiring a UTI include loss of bladder control, difficulty in postural neuro motor control, poor cognition, limited ability to communicate with the need to urinate, constipation; these factors are inherent to children with cerebral palsy. Worldwide, this infection ranges from 8.5% to 56.7%, while in Africa and Nigeria, for example, the prevalence found was 38.5%. Was growth of Escherichia coli in a urine culture exam performed in an 11-year-old Asian girl with Down syndrome, whereas in our study, a patient with Xq28 duplication syndrome also presented a positive urine culture for the same etiologic agente [14].

The most common pathogens found in UTI include *Echerichia coli, Proteus, Enterococcus faecalis, Klebsiella spp, and Staphylococcus spp* [9]. Uropathogenic *Escherichia coli* strains are responsible for 30% of nosocomial urinary tract infections, infections that affect children usually arise from accumulation of urine due to urinary tract blockage, and these strains can reside in the colon and then be introduced into the urinary tract. Urethra Initially, urinary tract infection develops by colonization of the per urethral region by enteric pathogens. Several virulence factors promote the migration of bacteria to the bladder and kidneys; *E. coli* has a bacterial membrane structure that facilitates its effective adhesion to the uro epithelium, in addition, *E. coli* strains have a specific type of fimbriae, another bacterial membrane structure, which increases the virulence, actively participating in the initial phase of urethral colonization [15]. Cerebral palsy encompasses a series of non-progressive motor development disorders caused by damage to the central nervous system, which may occur during pregnancy or early childhood; these disorders compromise movement, neurological disorders, posture, cognition and perception in individuals, which leads to a limitation of their activities. In patients with cerebral palsy, there is an estimated prevalence of 30% of dysfunctional voiding symptoms, such as polyuria, urinary incontinence or urinary tract infection [16-18]. Urinary incontinence is usually more common in children with cerebral palsy when compared to normal children, among the factors that predispose to incontinence we can mention the deficiency of cognitive ability, communication and reduced mobility of these children [3]. In a study carried out with 29 patients with cerebral palsy, where they evaluated urodynamic findings, correlating them with impaired motor function due to neurological disorders, observed that in 13 of the 29 symptomatic patients (56.5%), had recurrent urinary tract infection (3 to 12 infections per year), and 21 of 23 symptomatic patients (91%) had urinary incontinence. Eleven patients (47.8%) had a combination of recurrent urinary tract infections and urinary incontinence. Two patients (8.7%) had only recurrent urinary tract infections. In our study, only 1 patient (8.33%) of the 12 with cerebral palsy had a positive urine culture with the etiological agent *Klebsiella* ssp [16]. Although the symptoms of lower urinary tract infection are associated with poor quality of life in individuals with cerebral palsy, parents and physicians do not provide the necessary attention as in physical rehabilitation, which ends up being the main focus; in addition to the significant cost of treating urinary tract dysfunction; Genitourinary-related problems become very common at hospital admission in adults with cerebral palsy. Attention to the incidence of lower urinary tract infection in individuals with cerebral palsy raises the awareness of parents and physicians, thus indicating the need for evaluation and treatment [18]. The literature reports in several studies related to lower UTI in patients with neurological disorders, that the accumulation of urine is one of the main causal factors of these infections, since strains of microorganisms can reside in the colon, which can easily colonize the colon. Urethra of these patients since this infection develops by colonies in the peri urethral region [15]. In our study, as demonstrated by the results, there is an average of 6 diaper changes daily, both for patients with cerebral palsy and for other syndromes, this practice may be determinant for the low incidence rate of urinary tract infection in children with neurological impairments investigated in our work. A study among 33 children with cerebral palsy in the paediatric neurology unit of the University Hospital of Mersin, Turkey, where they investigated urodynamic findings in order to determine a correlation between urinary tract dysfunction and urinary tract deterioration in these children, and found more than 2 episodes of complicated urinary tract infection per year in 4 of these children, 12.1% [19]. Reported in a paediatric clinical case that a 2-year-old child had hyper ammonemic encephalopathy secondary to a urinary tract infection caused by *Corynebacterium riegellia* urease-producing bacterium, which leads to an increase in of urinary ammonia, contributing to a significant increase of this in the blood circulation, thus invariably resulting in several harmful effects, such as cerebral edema and endocranial hypertension, with a wide spectrum of symptoms, such as mood and personality alteration, cognitive dysfunction, ataxia, convulsions and alterations in the level of consciousness, which may even lead to drowsiness, even to the death of the patient. Hyper ammonia encephalopathy is a characteristic lesion of astrocytic predominant cytotoxic cerebral edema [20]. The damage caused by UTI is quite complex, with deleterious effects on the body, which result in a serious health problem for the patient, from encephalopathy due to cytotoxicity caused by urease-producing bacteria, for example; even to severe lesions that affect the upper urinary tract, which may, in some situations, progress to chronic kidney disease. In children with neurological disorders, caretakers must pay extra attention to diaper changes and perianal hygiene, since the etiological agents that cause this infection colonize the mucosa in this region.

CONCLUSION

Care and attention to the initial symptoms of urinary tract infections in children and young people with neurological impairments are extremely important, as these are crucial for a quality of life for these patients who, in most cases, have cognitive, motor and cognitive limitations. Communication about the need to urinate

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