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### RESEARCH ARTICLE

#### NON-NEUROGENIC BLADDER DYSFUNCTION IN CHILDREN: DIAGNOSIS AND PROCEDURE.

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#### Abstract

Bladder dysfunction is a urinary problem commonly found in children, may be neurogenic, anatomical, and non-neurogenic dysfunction. The problem is often accompanied by urinary tract infections, *vesicoureter reflux*, and *renal scarring*, potentially leading to chronic kidney disease, as well as having severe physical and psychosocial effects on the child. Clinical manifestations of bladder dysfunction appear to be in accordance with urinary pathophysiology, ie, storage or micturition disorders (*voiding*), with terminology referring to the consensus of the *International Children's Continent Society (ICCS) 2015*. Diagnosis is made clinically by anamnesis and physical examination with the main principle of getting rid of neurological and anatomical abnormalities, and routine urine recording. The modalities of investigation can be noninvasive (*urinalysis, ultrasound, uroflowmetry*) or invasive (*sistogram*). Comprehensive management of non-neurogenic bladder dysfunction consists of *urotherapy* (including *biofeedback therapy*), *pharmacological therapy*, *surgical therapy*, and *neuromodulation* or *neurostimulation*.

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#### Introduction:-

Bladder dysfunction is one of the most common urinary problems in children. Such dysfunction may be caused by nerve abnormalities (called neurogenic or neuropathic dysfunction) or without nerve abnormalities; called non-neurogenic or non-neuropathic dysfunction. Bladder dysfunction is also known as *lower urinary tract dysfunction (LUTD)* in the form of a set of symptoms called *lower urinary tract symptoms (LUTS)*; as well as bladder (bowel) dysfunction or dysfunctional elimination syndrome if accompanied by defective disorders.<sup>1-4</sup>

Clinical manifestations of bladder dysfunction vary widely, depending on the pathophysiology of filling or emptying of the bladder.<sup>3,5-7</sup> Filling or storage dysfunction such as overactive or underactive bladder, urge syndrome, urinary incontinence and incontinence triggered laughter (*giggle incontinence*). Dysfunctions during emptying include urinary dysfunction, staccato voiding, infrequent voiding, Hinman syndrome, Ochoa syndrome, and postvoid dribbling. Other manifestations include enuresis, polakiuria, holding maneuvers, vaginal reflux, and detrusor dysfunction.

The incidence of bladder dysfunction each year is estimated at 40%, with the most common complications or comorbidities being urinary tract infections, vesicoureter reflux, and scarring leading to kidney failure.<sup>1-3,8</sup> As many as 22% of school-aged children in America have at least one complaints of bladder dysfunction, the most common are holding maneuvers (19.1%), and urgency syndrome (13.7%).<sup>3</sup> Overactive Bladder is the most common

dysfunction in children aged 5-7 years, with prevalence in Japan and Korea respectively 17.8% and 16.6%.<sup>3</sup> Studies at the RSCM Children's Health Department mentioned urinary incontinence occurred in 35 children, with details of 22 children with neurogenic dysfunction, 4 children with non-neurogenic dysfunction, and 9 children with anatomical abnormalities.<sup>9</sup> Girls are more likely to experience bladder dysfunction than boys,<sup>10,11</sup> are also often accompanied by *vesicoureter reflux* and recurrent secondary urinary tract infections.<sup>3,8,12</sup>

Non-neurogenic bladder dysfunction affects the quality of the child's life both physically and psychosocially.<sup>1-3,6</sup> Physical effects include anatomical damage and renal function and urinary tract, either due to secondary infection in the form of renal scarring, *vesicoureter reflux*, or obstruction leads to chronic kidney disease. Psychosocial effects include impaired concentration or learning disorders, decreased self-confidence, and mental / emotional disturbance due to urinary problems. Therefore, non-neurogenic bladder dysfunction in children needs to be alerted by health practitioners, especially in diagnosing and planning patient management in medical, surgical and psychological conditions.

### **Anatomy of the Bladder:-**

The bladder is a pouch that holds urine, associated with the kidney through two ureters and in the distal portion of the urethra. The bladder consists of smooth muscles that are anatomically divided into corpus and *trigonum*. Histologically, the bladder wall consists of the mucosal layer, *submucosal layer*, *muscular layer*, and *serous layer*. The smooth muscle in the corpus is called the *detrusor muscle*. In the *trigonum* region, there are two ureteric estuaries and the base of the urethra. Around the base of the urethra there is a smooth muscle called the sphincter of the *urethra internum* that serves to maintain urethral tone so that urine does not come out of the bladder through the urethra. Outside the bladder, the urethra passes through the urogenital diaphragm consisting of the muscles of the transverse fibers, and this arrangement of muscles and latitudes is called the external urethral sphincter. The external urethral sphincter contracts continuously so that the urine does not come out of the bladder. This external urethra sphincter can relax both because of reflexes and because of control of the brain.

The bladder gets the innervation of the sacral II-IV spinal cord that exits as the parasympathetic nerve of the pelvic plexus and the sacral plexus to the bladder as the *pudendal nerve*. Parasympathetic nerve stimulation of the *pudendal nerve* causes contraction of the detrusor muscle and relaxation of the internal urethral sphincter.

The sympathetic nerves for the bladder originate from the thoracic spinal cord XI - lumbar II. This nerve passes through the hypogastric plexus to the bladder. The sympathetic nerves have alpha and beta receptors. The alpha receptor is located in the smooth muscle of the bladder neck around the base of the urethra. The stimulation of the alpha receptor causes contraction of the lower part of the bladder and inhibits bladder emptying. In contrast, inhibition of alpha receptors causes bladder neck relaxation and micturition. The beta receptor is located in the bladder corpus. Beta receptor stimulation causes relaxation of the detrusor muscle thus increasing bladder capacity, and vice versa, beta receptor inhibition causes detrusor muscle contraction resulting in urinary expenditure due to increased intra-vascular pressure.

### **Terminology:-**

The terminology of the syndrome or symptoms used in bladder dysfunction in children comes from the terminology published by the International Children's Continent Society (ICCS) in 2015.<sup>1,3,7</sup> The terminology uses child age limits above 5 years according to DSM-5 and ICD criteria -10 for urinary incontinence disorder. Clinical symptoms are summarized in Table 1. The following are the most common syndromes of non-neurogenic bladder dysfunction in children.

**Overactive Bladder (OAB)**, a complaint of urgency and increased frequency of urination with or without incontinence. Diagnosis is made clinically based on the definition. **Urinary dysfunction (dysfunctional voiding)**, occurs in children who perform urinary sphincter contractions during urination, often with constipation and/or *enkopresis*. The most common pattern of urination is the stakato form, followed by an interrupted or mixed pattern. Such contractions need to be demonstrated by the *pelvic floor muscle electromyography (EMG)* simultaneously in *urodynamic* or *uroflowmetry* studies. An EMG examination is considered if the patient fails conservative therapy (constipation management and urination exercise) for 3 months.

**Voiding postponement**, occurs in children especially in the toilet-training phase. Similar to constipation, the habit of delaying urination is often caused by distractions from toys, electronic devices, or television. The behavior continues

on holding maneuvers, frequent urination, urgency, and incontinence during the day. A total of 45% of patients had improved frequency wetting (wetting) with scheduled urination exercises.

**Extraordinary daytime urinary frequency**, characterized by a slight void volume (less than 50% bladder capacity) with frequencies greater than 8x / day. Bladder capacity (mL / kg) can be calculated by the formula (age in + 2 years) x 30, and the outcome is multiplied by 7 in children <1 year. Other comorbid symptoms include dysuria, urinary flow changes, daytime incontinence, enuresis, drinking, without an increase in urine volume. In contrast to other manifestations, this form occurs more frequently in boys and is self-limited.

**Less active bladder (underactive bladder)**, characterized by less frequent urination (2-4 times / day), and wheezing behavior during urination. Children usually encourage the abdomen to increase intraabdominal pressure, either start urination or complete urination. This form of dysfunction often occurs on the first day of school, also accompanied by symptomatic or asymptomatic bacteriuria, dribbling, enuresis, and / or constipation / enkopresis. Uroflowmetric examination can show interrupted pattern with many residues. The main therapy in this form is urotherapy with intensive programs, may be accompanied by the administration of alpha or other invasive modalities such as *clean intermittent catheterization (CIC)*.

Hinman's syndrome, the heaviest form of non-neurogenic micturition dysfunction. This syndrome is due to psychosocial disorders and acquired behaviors characterized by micturition dysfunction resembling neurological disease. Although functional, Hinman's syndrome often presents symptoms suggestive of obstruction such as dilatation, thickening of the bladder wall and trabeculation, and decreased renal function that resembles the posterior urethral valve or urethral stricture. In contrast to neurological dysfunction, Hinman syndrome patients exhibit normal neurologic and back examinations on magnetic resonance imaging (MRI) examination. Common symptoms include incontinence, urgency, frequency, enuresis, rarely urination, incomplete urination, straining, urinary tract infections, and abdominal pain. Hinman syndrome patients consciously perform external sphincter contractions and pelvic floor muscles that persist in intermittent urine flow, increased residual volume, and increased *intravesical pressure*.

**Table 1:-**Definition of Clinical Symptoms of Bladder Dysfunction in Children.

| Terms  | Definition  |
|--|---|
| Symptoms during bladder filling (storage symptoms)           |   |
| Increased or decreased urinary frequency                     | Normal urinary frequency depends on age, diuresis, and amount of child drinking. As many as 95% of school-age children urinate as much as 3-8 times / day. The frequency of urination is called increasing if more than 8 times / day, while decreasing if less than 3 times / day.   |
| Incontinence   | Involuntary urinary excretion, may be continuous or intermittent. Continuous incontinence, if urinary excretion occurs continuously throughout the day and night, is generally associated with congenital malformations (ectopic eczema or ureter), loss of functional external urethral sphincter, or iatrogenic sphincter.<br>Intermittent incontinence, if urinary expenditure occurs in discrete amounts, either daytime incontinence, or nighttime (enuresis). |
| Urgency  | A sudden urge to urinate in a child who has already had urinary control often shows bladder over activity.  |
| Nocturia   | The child awakens at night only to urinate, not always due to bladder dysfunction, excluding enuresis, and not causing incontinence.  |
| Symptoms of emptying vesicles (voiding or emptying symptoms) |   |
| <i>Hesitancy</i>   | The child is difficult to start urination.  |
| <i>Mengedan (straining)</i>                                  | Child effort to increase intra-abdominal pressure to start and maintain the urination process.  |
| <i>Weak stream</i>   | Urine emission (clinically or <i>uroflowmetry</i> ) is weak.  |
| <i>Intermittency</i>   | The process of urination is intermittent with several episodes stopping.  |
| Disuria  | Discomfort or burning during urination. Dysuria early in urination associated with the source of pain in the urethra, while dysuria at the end of urination associated with the source of the bladder.<br>Other symptoms  |

| Other symptoms                                |   |
|---|---|
| <i>Holding maneuvers</i>                      | A set of child behaviors to delay urination or suppress urgency associated with bladder overactivity. These behaviors include standing on the tip of your toes, crossing your legs, groping or suppressing the genitalia or stomach and holding the perineum. |
| <i>Incomplete emptying</i>                    | Children feel no lampias when urinating and the bladder is still full so the child wants to urinate again.  |
| Retensurin                                    | The inability of the child to urinate with persistent effort and full jar.  |
| <i>Post micturition dribble</i>               | Urine drips involuntarily as soon as it is finished, may occur in the vaginal reflux of a girl or syringe in a boy.   |
| <i>Spraying (splitting)</i>                   | Urine splitting or spray, associated with mechanical obstruction in the meatus or prepusium.  |
| Pain in the lower urinary tract and genitalia |   |
| Bladder pain                                  | Complaints of suprapubic pain or uncomfortable or distressing sensations in the bladder.  |
| Urethral pain                                 | Complaints of pain in the urethra   |
| Genital pain                                  | Vaginal pain or itching is usually associated with local irritation due to incontinence in women, whereas in men there is pain in the penis and episodic priapism that can be caused by full bladder, constipation, or urine trapping in phimosis.            |

### Lower Urinary Tract and Pathophysiology:-

The lower urinary tract consists of the bladder and urethra. The bladder wall is covered by smooth muscle arranged in a circular outer layer, extending and circularly back in the inner layer.<sup>13</sup> The connection between the bladder and the urethra is coated with thicker muscle fibers, called the external urethral sphincter and the internal urethral sphincter. The external sphincter is innervated by the central somatic nervous system, whereas the internal sphincter is innervated by the autonomic nervous system. The process of urinary control is governed by the central nervous system from the fetus to adulthood and almost always occurs when the child is awake.<sup>3,6</sup> In the bladder transition phase from the infantile form to the adult form, the dis-coordination between the detrusor muscle and the urethral sphincter may occur transiently and normally as long as the children undergo toilet training. The change in urinary control starts from the gradual change of functional bladder capacity, the maturation of detrusor-sphincter coordination, and the gradual development of conscious control of the sphincter-sphincter-perineal complex.

Bladder has a dual function, namely the function of storing and emptying.<sup>3,13</sup> During the filling or storage phase, the urethral sphincter closes and the urinary bladder is filled through the ureter to a certain capacity that causes excitement to urinate. In the emptying phase, the sphincter relaxes and the bladder muscle contracts to remove urine into the urethra. Bladder dysfunction may be a dysfunction in the storing or discharge mechanism.<sup>3,7</sup> Dysfunction in the filling phase can be mediated by the inability of the sphincter to close, the weak bladder wall, as well as the small bladder capacity or excessive urinary excitement with minimal volume. Disfuncti when emptying occurs due to sphincter's inability to relax (open the urethra), as well as weakness of detrusor muscle to remove urine from the bladder.

### Diagnosis of Non-neurogenic Bladder Dysfunction:-

Bladder dysfunction is established through anamnesis, physical examination, and investigation.<sup>3,4,7</sup> The main principle in establishing the diagnosis of non-neurogenic dysfunction is to exclude neurogenic and structural causes in patients.<sup>2</sup> In addition, routine urine recording is strongly recommended to recognize the amount volume), pattern, and urinary frequency of children.<sup>1,7</sup> Recording of urine volume may help estimate the maximum urine volume compared with estimated bladder capacity. Urinary disorders are often accompanied by digestive problems such as constipation or alvi incontinence so that it needs to be evaluated.<sup>11,14</sup>

The history focuses on childhood voiding complaints while observing the behavior and stages of child development.<sup>4</sup> Urinary processes are examined in detail, especially in frequency, recording number and patterns of childhood voiding, as well as other complaints such as pain or other neurological disorders. In addition to physical complaints, children need to be asked about problems or psychosocial effects associated with urinary disorders. Past medical history or treatment should also be evaluated.

Physical examination is focused on urinary tract and genital organ.<sup>4</sup> Congenital urinary tract abnormalities are commonly accompanied by ear deformities so that the ears need to be examined, whether there are congenital

abnormalities of the outer ear or inner ear. The abdomen is palpated to look for mass, full bladder, or gastrointestinal problems that often accompany urinary problems. Backs are examined to look for spinal deformities, a history of trauma or surgery, and neurological function. External genitalia are examined to look for anatomical abnormalities of urogenital tract or sexual abuse.

Semi-quantitative urinary processes may be evaluated using a scoring system, including dysfunctional voiding system score (DVSS), dysfunctional voiding and incontinence score system (DVISS), and incontinence index-pediatric symptom (ISIP, for children aged > 11 years).<sup>1, 7, 15</sup> The DVSS questionnaire is useful for quantifying LUTS degrees, and there is another pediatric urinary incontinence quality of life score (PIN-Q) to measure the emotional impact of urinary incontinence in children. Other studies have shown that DVISS can screen for more voiding symptoms than patient or family complaints, and better in determining the degree of disease than ultrasonography (USG).<sup>15, 16</sup>

The modalities of investigation on urinary disorders can be divided into noninvasive and invasive examinations.<sup>4, 7</sup> The recommended investigation in the first child is complete urinalysis. The examination is very important to rule out urinary tract infections, which marked an increase in the number of leukocytes in the urine, pyuria, bacteriuria, and increased nitrate. Urine culture is recommended in patients with clinical features of urinary tract infection. Specific gravity is useful for assessing urine concentration. Hematuria, proteinuria, and glycosuria may indicate kidney abnormalities in children.

Advanced investigations include ultrasound, urodynamic studies, voiding cystourethrogram (VCUG), and MRI. Renal and urinary tract ultrasound examinations are not recommended for routine use at an early stage. Ultrasound may be considered as one of the noninvasive modalities to see the coordination between bladder contraction and external sphincter relaxation. In addition, the volume of post-abnormal residue can be measured and determine the patient's prognosis. The residual volume is called increasing by > 30 ml or > 21% estimated bladder capacity in children aged 4-6 years or the residual count > 20 mL or > 15% estimated bladder capacity in children aged 7-12 years.<sup>7</sup> Increase in residual volume post-exposure at risk is 2.7 times for post-therapy failure.<sup>16</sup>

Noninvasive urodynamic examinations include uroflowmetry and urodynamics with electromyography (EMG) pelvic floor muscles. The results of uroflowmetry examination are classified in curve form according to ICCS classification, ie bell, tower, staccato, interrupted, and plateau forms.<sup>4, 7</sup> EMG examination may add information about neuromuscular role in urination process, but interpretation of uroflowmetry results with EMG is very difficult and dependent on the ability of the examiner.<sup>17</sup>

*Cystometry* and *videourodynamics* are invasive tests that can provide in-depth information about the capacity, compliance, and contractility of the bladder. Voiding cystourethrogram (VCUG) is recommended in cases of recurrent ISK fever to exclude vesicoureter reflux, especially if ultrasound results indicate upper urinary tract abnormalities and / or bladder wall thickness or trabeculation found, associated with obstructive symptoms, particularly the posterior urethral valve in male patients -laki.<sup>1</sup>

Spinal MRI examination is recommended to exclude neurogenic causes, such as tethered cord syndrome or neurologic abnormalities or skin or bone abnormalities in the spine.

#### **Management of Non-neurogenic Bladder Dysfunction:-**

Management consists of behavioral modifications such as standard urotherapy, biofeedback, pelvic floor rehabilitation, neuromodulation, gastrointestinal regulation (if accompanied by gastrointestinal dysfunction), medical therapy, and / or surgical therapy. Studies in Brazil suggest that treatment can begin as soon as possible after clinical diagnosis is made with simple investigations (including ultrasound and uroflowmetry).<sup>10</sup>

The success of the therapy is assessed based on the development of symptoms from the beginning to the end of therapy, assessment of response during therapy, and the development of children after therapy up to a certain period.<sup>7</sup> Patient response is classified into complete response (100% symptom reduction), partial response (50-99% reduction) and non-response (<50% reduction). Relapse is indicated if the patient has repeated complaints more than 1 time / month. Continued success is indicated if there is no relapse within 6 months after discontinuation of therapy, whereas complete success is stated if there is no relapse up to 2 years.

**Behavioral Therapy:-**

*Uroterapi* is a non-pharmacologic and non-abrasive procedure in children with lower urinary tract symptoms consisting of child and carer education, adequate hydration, scheduled voiding, and pelvic floor muscle exercises.<sup>1,7</sup> This therapy aims to optimize relaxation and contraction of muscles at the right time with the success rate reaches 50%. Education is provided to improve patient and family knowledge about symptoms and treatment options, in an easy-to-understand language. Adequate hydration is given to optimize the mechanism of filling and discharging of the bladder during urination. Children are encouraged to drink according to daily fluid requirement, or alternatively is to drink a glass of water each urinate. Children are advised to urinate every 2-3 hours with the help of a timer, when the child wakes up to make regular urination patterns. In addition, the child is advised to fill the urinary diary and answer the urine score regularly as one of the monitoring of treatment response.

Good posture and posture need to be taught to children and caregivers. One type of exercise is Kegel exercises in large children to increase contraction and relaxation of pelvic muscles in overactive bladders or micturition dysfunction. Biofeedback therapy is a series of pelvic floor muscle therapy using urodynamic and pelvic floor EMG instruments while teaching patients to control pelvic floor muscles consciously during urination, using direct animation or urodynamic analysis results.<sup>18</sup> The therapy aims to achieve conscious urethral sphincter control in children.

**Pharmacological Therapy:-**

Pharmacologic therapy is considered if the patient does not improve after 6 months of urotherapy with or without biofeedback therapy.<sup>1,2,18</sup> The primary choice for overactive bladder is the anticholinergic class, one of which is oxybutin. Oksibutinin is a cholinergic receptor of M1, M2, and M3 with an initial dose of 0.1-0.2 mg / kg / times maximum 5 mg / times, given with a frequency of 2-3x / day. Selective alpha-blocking drugs, such as tamsulosin (0.2-0.4 mg / day) can help relax the external sphincter, help bladder emptying in overactive bladder children, incontinence, and recurrent urinary tract infections.<sup>1</sup> On the other hand, the use of alpha blockers in children is off-label.<sup>18</sup> Prophylactic antibiotics are indicated in children with vesicoureter reflux and bladder dysfunction.

**Surgical Therapy:-**

Surgical therapy is indicated in bladder dysfunction accompanied by structural abnormalities or not resolved with behavioral and pharmacological therapy. Surgical therapies that are often used include injections of botulinum A toxin in overactive bladder and neurostimulation therapy or neuromodulasi.<sup>1,3,18</sup> Botulinum toxin A has long-term therapeutic effect (up to 9 months), is reversible, and inhibits disease in chemical denervation, can be administered several times without losing the desired therapeutic effect. Toxins work by inhibiting the release of presynaptic acetylcholine in neuromuscular links. Complications of such therapy is damage to the bladder muscle wall due to injection.<sup>1,18</sup>

**Neuromodulation:-**

*Neurostimulation or neuromodulation* is currently the latest therapy in the management of bladder dysfunction, especially in overactive bladder. Neural activity can be altered (modulated) through electrical or chemical stimulators on the central or peripheral nervous system.<sup>7,18,19</sup> Stimulators can be mounted in a sacral nerve stimulator, or transcutaneously through sacral transcutaneous stimulation (TENS) or paratibial stimulation PTENS). Neurostimulation can reduce anticholinergic needs and improve the quality of life of children.

**Conclusion:-**

Non-neurogenic bladder dysfunction is one of the most common complaints that can potentially reduce the quality of life of children, both physically and psychosocially. Clinical manifestations of bladder dysfunction vary widely, depending on the pathophysiology of the bladder during storage or voiding. Diagnosis may be clinically enforced according to the ICCS definition, and childhood urine recording is critical for evaluating voiding complaints. Until now there are various investigations, both noninvasive and invasive, which can help evaluate urinary disorders in children. Bladder dysfunction therapy consists of *urotherapy, pharmacological therapy, surgical therapy, and neurostimulation or neuromodulation.*

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