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Dysfunctional Voiding of Non-Neurogenic Neurogenic Bladder: A Urological Disorder Associated with Down Syndrome

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1. Introduction

Down syndrome (DS), the most common chromosomal abnormality with a prevalence of 1 case per 600 live births (Dennis & Marder,2001), has many manifestations that can affect multiple organ systems (American Academy of Pediatrics Comittee on Genetics, 2001; Kallen et al., 1996) including urological abnormalities which have been recognized throughout urinary tract (Ariel et al., 1991; Berg et al.,1960; Ahmed, 1990; Kravtzova et al., 1975; Handel et al., 2003; Kupferman et al., 1996; Bielek et al., 1996; Narashiman & Gupta, 2004; Koksal et al., 2003; Lang et al., 1987; Paulozzi et al., 1997). The extra copy of chromosome 21 has been suggested as an actor underlying the accompanied phenotypic abnormalities in the syndrome (Lejeune, 1959).

Berg et al. described the first cases of urological anomalies associated with DS in their study of 141 DS autopsy cases and found 1 patient (0.7%) with renal agenesis and 5 patients (3.6%) with horseshoe kidney (Berg et al., 1960). Glomerular microcysts, renal hypoplasia and obstructive uropathy have also been recognized as the most common upper urinary tract anomalies in DS and their incidences were reported by Ariel et al. who examined 124 autopsy cases of DS for abnormalities in urinary tract system to be as high as 23.7% (23 of 97 patients), 21.4% (18 of 84 patients), and 6.45% (8 of the 124 cases), respectively (Ariel et al., 1991). In addition, simple renal cysts were also found in 7 of 124 cases (5.6%).

Anomalies in ureteral structure has also been identified in DS (Ariel et al., 1991; Kravtzova et al., 1975; Handel et al., 2003). The incidence of obstructed megaureter or hydroureteronephrosis was reported in 2 of 124 cases (1.6%), while ureteral atresia was seen in 1 of 124 cases (0.8%) (Ariel et al., 1991). In addition, vesicoureteral reflux (Kravtzova et al., 1975), ureterovesical junction and ureteropelvic junction obstructions have also been described in patients with trisomy 21 (Handel et al., 2003).

Trisomy 21 is one of genetic disorders that can also be accompanied by some urological abnormalities in lower urinary tract. Non-neurogenic neurogenic bladder (NNB) has been reported as a functional lower urinary tract abnormality seen in DS. Handel et al. retrospectively reviewed 26 patients with trisomy 21 and found 4 patients (15.4%) with NNB (Handel et al., 2003). Posterior urethral valve has also been identified in patients with trisomy 21 (Bielek et al., 1996; Narashiman & Gupta, 2004; Koksal et al., 2003; Lang DJ et al., 1987). Bielek et al who reviewed 48 cases of posterior urethral valves found 4 patients with

DS (Bielek et al., 1996). Hypospadia has also a higher incidence in patients with the syndrome (Paulozzi et al., 1997).
There is a lack of awareness regarding DS related urological manifestations in daily clinical practice. The associated urological anomalies have received little attention from physicians especially for NNB which often cause the delay in referring the patients for further management. In this chapter we will focus on the NNB which represents voiding dysfunction due to functional bladder outlet obstruction recognized in DS. The discussion will include the evaluation and management of this particular disorder. Urodynamic assessment as the most important part in the diagnosis of NNB will also be described.

2. Dysfunctional voiding of non-neurogenic neurogenic bladder in Down Syndrome

2.1 Historical note

Non-neurogenic neurogenic bladder, the most severe form of dysfunctional voiding, is a pure functional bladder outlet obstruction without any neurological abnormalities which was described by Hinman (Hinman, 1986). However, it was first described by Beer who reported four patients with chronic urinary retention and upper urinary tract changes without any evidence of neurological pathology (Beer, 1915). He observed the disharmony between the detrusor and sphincter muscles in the patients.
Incoordination syndrome of voiding contraction reflex was also found by Laidley (Ladley, 1942). The syndrome was then called "achalasia of the urinary tract". Paquin et al. reported symptoms of dysfunctional voiding with large bladder in 27 children and the term "megacystis syndrome" was used to represent the syndrome (Paquin et al., 1960). Ambrose and Swanson reported the 13 children with hypertonic detrusor contraction without any neurologic lesion and labeled the syndrome as "hypertonic-type neurogenic bladder" (Ambrose & Swanson, 1960).
Hinman & Baumann reported voiding difficulties in children associated with upper urinary tract deterioration without any anatomical obstruction or neurologic lesion with the identified psychological disorder (Hinman & Baumann, 1972). The term "non-neurogenic neurogenic bladder" was introduced in order to emphasize the absence of neurologic lesions. The cases were followed for 15 years and then reported with new term "Hinman syndrome" according to the important of psychological factors which contribute to the syndrome and change the previous term which was not appropriate and cause confusion. However, the underlying psychological disturbances were not recognized in the syndrome as reported by Allan (Allan ,1977).
Non neurogenic-neurogenic syndrome in association with trisomy 21 was first identified by Handel et al. who reviewed 26 children with DS (all boys) and found higher incidence of NNB compare to other urological abnormalities in DS (Handel et al., 2003). Hicks et al reported the first women with NNB associated with DS and also found higher incidence of NNB cases in trisomy 21 (Hicks et al., 2007).

2.2 Epidemiology

The true prevalence of NNB has not been reported. The available prevalence is only based on data obtained from some centers. Groutz et al. reported that NNB was found in 2% of patients who underwent video-urodynamic studies but the real prevalence would be even

higher (Groutz et al., 2001). Jorgensen et al. reported lower prevalence of NNB (0.5%) among patients referred for urodynamic evaluation (Jorgensen et al., 1982).
Handel et al. reported a higher incidence of NNB in patients with trisomy 21. Among 26 patients with DS who were reviewed, 4 (15.4%) was reported to have NNB (Handel et al., 2003). Hicks et al also found higher incidence of NNB cases in DS (Hicks et al., 2007).[23] Non-neurogenic neurogenic bladder has been reported not only in infant and children but also in adult patients (Handel et al., 2003; Hicks et al., 2007; Jayanthi et al., 1997; Kai et al., 2007).

2.3 Etiology

The etiology of the disease is not clearly defined. Some evidences suggest overtraining of the pelvic floor to avoid urine loss due to not only various emotional conditions such as depression, phobias, stress, trauma associated with toilet training but also psychiatric diseases, the presence of detrusor overactivity and other associated voiding dysfunctions as an underlying factors which may contribute to cause NNB (Hoebeke et al., 1996; Koff et al., 1979; Goldston & Perlmutter, 1973; Schimtt, 1982; Ellsworth, 1995). The well known mental retardation and psychological problems in patients with DS may also explain the higher incidence of NNB in this trisomy 21.
In normal voiding function, bladder filling is accommodated at low bladder pressures with a bladder outlet that remains closed while bladder emptying requires a coordinated and sustained contraction of the bladder muscle with concomitant relaxation of the external urethral sphincter. The reflex of micturition is controlled by parasympathetic and somatic components of the sacral spinal cord and sympathetic innervation.
In NNB, functional bladder outlet obstruction is caused by active contractions of the voluntary external sphincters during voiding. The inability to inhibit the detrusor contraction reflex as well as overactivity of the external sphincter as compensation has become fundamental characteristics of patients with NNB (Hinman, 1986). The dyssynergistic voiding pattern created by the incoordination between the bladder and sphincter contraction reflex may result in impairment of renal function caused by functional obstruction (obstructive uropathy) due to unacceptable high voiding pressure with potential upper and lower urinary tract deterioration .

2.4 Diagnosis

General history-taking should include relevant questions for the screening of NNB. A thorough patient history will indicate incontinence associated with chronic urinary retention. History-taking in patients with DS is difficult especially in children due to the impairment of cognitive function and should be supplemented by information obtained from the parents. Because of the intelligence level, some of the existence as well as other underlying factors in patients with DS may be masked or neglected resulting in the delay of the diagnosis which often seen in clinical practice (Handel et al., 2003; Kai et al., 2007; Fernandez & Moore., 1986).
Although unerderlying factors could not be found in some cases, It is important to make sure that history taking have already included all the underlying factors of NNB which may guide to the diagnosis (Goldston & Perlmutter, 1973; Schmitt, 1982; Ellsworth et al., 1995). Neurological symptoms and abnormalities will not be present in NNB but should be confirmed by carefully clinical examination. Laboratory results may show elevated serum creatinine and reduce clearance or decreased renal function with or without signs of urinary tract infection in most of the cases.

Ultrasound is useful to evaluate bladder after voiding which can show residual urine volume as well as determine the bladder thickness. In addition, ultrasound is also important to detect the upper urinary tract dilatation with or without dilatation of the ureters as a complication of functional obstruction in NNB. In trisomy 21, this tool is also useful to identify other associated organ anomalies including abnormalities in the kidney.

To diagnose NNB in trisomy 21 patients, other associated anomalies such as Hirschsprung's disease, spinal cord defects, and posterior urethral valves must be excluded first before concluding that they have a functional rather than anatomical obstruction especially those who present with constipation, recurrent urinary tract infections, incontinence and voiding dysfunction (Handel et al., 2003). In order to rule out the neurological lesions, imaging studies of computed tomography (CT) scans and magnetic resonance imaging (MRI) should be performed (Johnson et al., 1992).

Non-neurogenic neurogenic bladder should be suspected if negative results have been confirmed by standard rectal biopsies and urological evaluation demonstrates the absence of anatomical obstruction and neurological evaluation including imaging studies confirms the absence of any neurologic lesions (Handel et al., 2003).

2.4.1 Voiding-cystourethrography

Voiding-cystourethrography is an important radiologic tool to show varying grade of vesico-ureter reflux in some cases of NNB. In addition, it also shows bladder appearance as a result of functional obstruction such as a trabeculated and enlarged bladder with a lot of residual urine still remains in the bladder after voiding without any evidence of mechanical obstruction (Fig. 1).

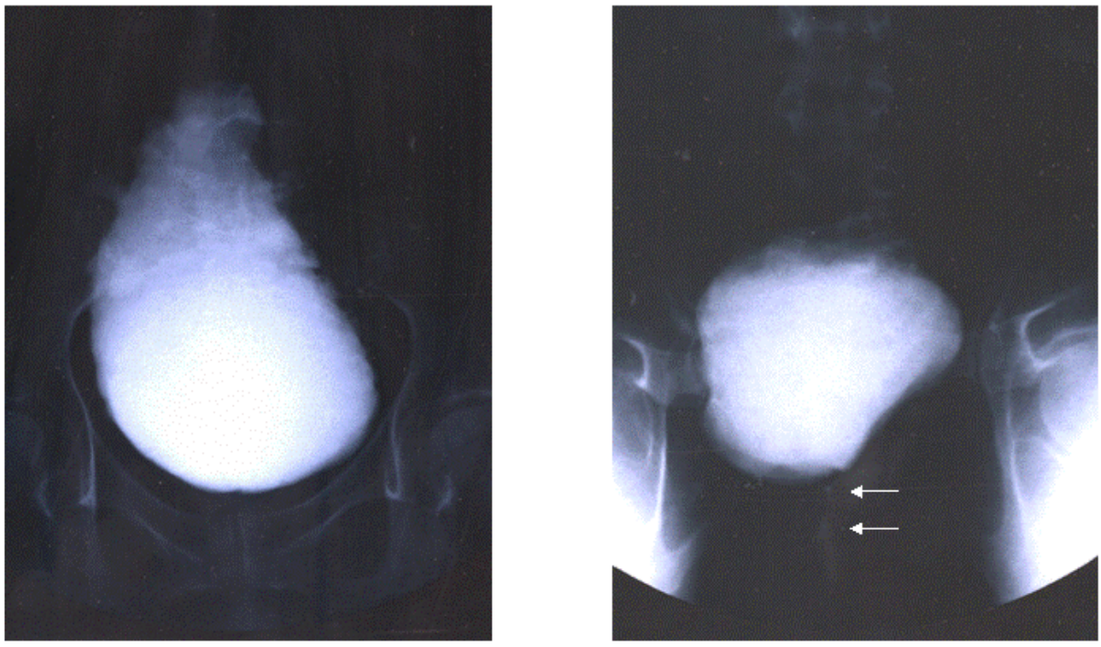

Fig. 1. Voiding cystourethrography shows a deformity of the bladder wall with trabeculation (left) and narrowing of the posterior urethra as pointed by white arrows with significant residual urine (right) without vesico-urethral reflux

In contrast, anatomical obstruction by posterior urethral valve can be identified by posterior urethral dilatation with poor visualization of the anterior urethra. However, it is important to note that the appearance of posterior urethra may entirely normal during early voiding but distended after contraction of the external sphincter as voiding progress which was found in 4 patients who previously diagnosed with NNB as reported by Johnson et al who reviewed the genitourinary images of six boys in whom NNB was diagnosed in the past 5 years (Johnson et al., 1992).

2.4.2 Uroflowmetry

Uroflowmetry is useful for the screening of NNB since it is able to measure the urinary stream during the voiding phase, providing information of bladder and outlet function (Allan & Bright, 1978; Stanton et al., 1983). In uroflowmetry measurement, it is important to pay attention on the the flow pattern beside other important parameters (Vijverberg et al., 1997). Normal urine flow is continuous bell-shaped curve. Continuous plateau shape curve (lower urinary flow rate with prolonged voiding time) is typical for anatomical obstruction.
In contrast, functional obstruction is typically reflected by a staccato pattern as interrupted flow of urine occurs due to uninhibited external sphincter contraction and usually demonstrates intermittency with reduced flow rates and prolonged voiding time (Fig. 2). The results also depend on the stage of the disease since the above pattern is hardly ever seen in advance cases with atonia of the bladder and poor detrusor contractility due to decompensated bladder. Uroflowmetry can also be used as a tool for follow-up of bladder training, and biofeedback training (Vijverberg et al., 1997; Hellstrom et al., 1987; Hjalmas, 1988; Griffiths & Scholtmeijer, 1984; Wear et al., 1979).

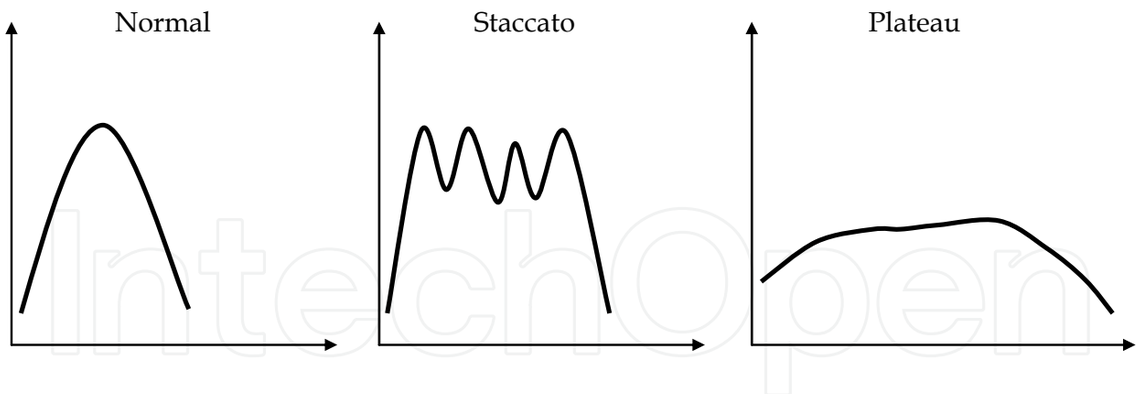

Fig. 2. The illustration of normal and abnormal uroflowmetry patterns.

2.4.3 Urodynamics

Urodynamics study is the gold standard for the diagnosis of patients with voiding dysfunction. (Nitti, 2005) Hypertonicity, instability with impaired external sphincter relaxation during micturation are typical characteristics in patients with NNB (Allan & Bright, 1978). Electromyography (EMG) shows a spastic activity with a high amplitude during voiding phase (Fig. 3).

True detrusor-external sphincter dyssynergia and NNB can be differentiated urodynamically (Rudy & Woodside, 1991). Detrusor-external sphincter dyssynergia is characterized urodynamically by increasing EMG activity during upslope and decreasing activity during down slope of the intravesical pressure tracing during a detrusor contraction. However, NNB is characterized urodynamically by quieting of the EMG during upslope and augmented activity during the down slope of the detrusor contraction.

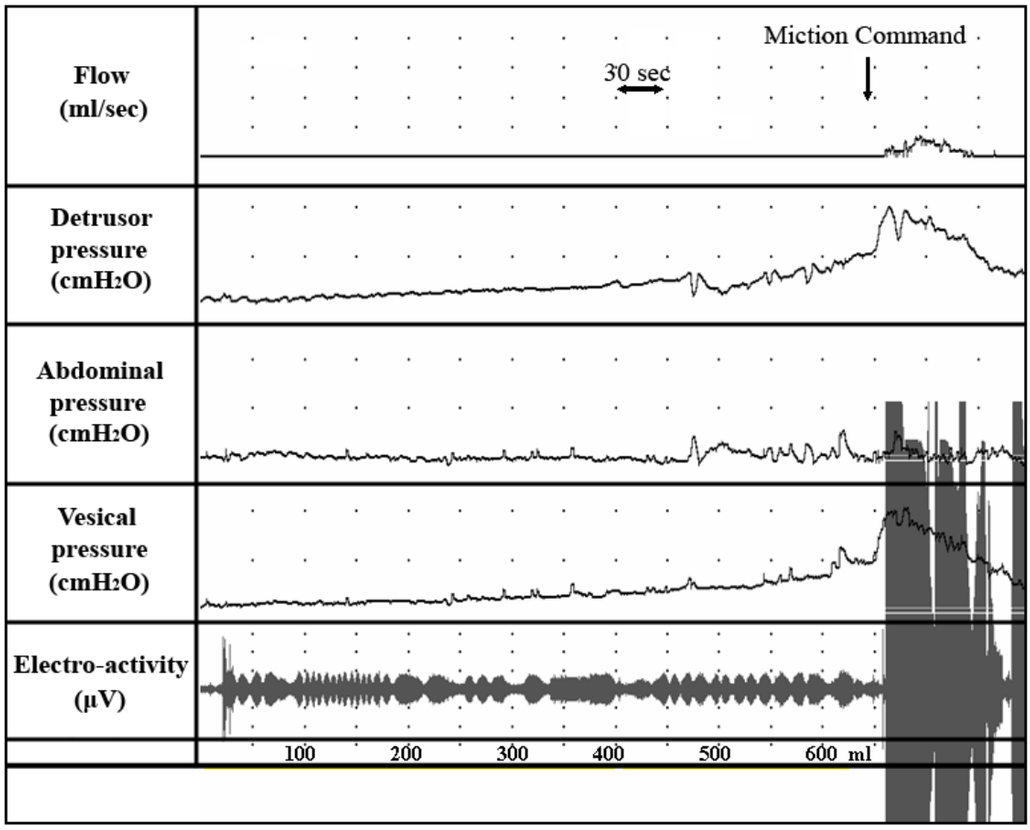

Fig. 3. Urodynamic results indcate a decrease in the bladder sensation without detrusor overactivity. A low urinary flow rate with a high detrusor pressure is shown in the voiding phase. Electromyography shows a spastic activity with a high amplitude during voiding. (Filling rate = 50 ml/min).

2.5 Management

Management of patients with NNB must be focused on the relaxation of external urethral sphincter muscle in order to obtain a more physiological micturation with relaxed sphincter muscle during voiding and to restore the balance of voiding and voluntary sphincter contraction reflex to prevent upper and lower urinary tract deterioration. The additional goals of treatment include prevention of urinary tract infections with proper antibiotics. The management should be addressed to all patients regardless of their intellectual capacity including those with trisomy 21. The intellectual Impairment of patients with DS may cause some difficulties in conducting the treatment.

Anti-cholinergics and alpha blocker therapy either alone or in combination may be useful in the treatment of NNB (Krane & Olsson, 1973; Paul et al., 1999; Bogaert et al., 2004) since significant improvement in emptying was shown in neurogenic cases treated with non selective alpha blocker (Krane & Olsson, 1973). If there is no response to conservative treatment, intermittent catheterization may be required. Trisomy 21 associated NNB patients with abnormal voiding mechanism against a closed sphincter may deal with the difficulty in conducting urethral clean intermittent catheterization due to their intellectual limitation (Handel et al, 2003).

Surgical treatment for renal preservation is also required for social continence. Self-catheterization protocols via the catheterizable stoma may allow trisomy 21 patients with a sufficient intellectual level master such techniques. Patients with NNB who are refractory to conservative treatment or present with an advanced pathological condition may require surgical intervention. Augmentation of the bladder in order to increase the bladder capacity may still be required in those in whom the upper tracts are threatened (Handel et al, 2003).

The use of Botulinum-A toxin injection into detrusor or the external sphincter may help cause striated muscle paralysis and may also restore voiding function especially in those who failed with drug therapy (Schurch et al., 1996). Patients with NNB in DS could also be performed such procedure. This particular treatment is dose dependent and also reversible. Injection may be necessary in every two months.

3. Summary

Children with trisomy 21 have many associated multi organ anomalies including urological abnormalities. Non-neurogenic neurogenic bladder is the most frequent DS associated lower urinary tract disorder. Early diagnosis and prompt management should be conducted in order to prevent upper urinary tract deterioration. According to the high incidence of NND in DS, early and regular sonographic and urodynamic evaluation of the bladder function is mandatory in patients with Down syndrome.

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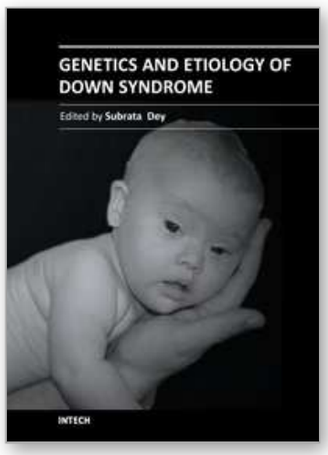

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This book provides a concise yet comprehensive source of current information on Down syndrome. Research workers, scientists, medical graduates and paediatricians will find it an excellent source for reference and review. This book has been divided into four sections, beginning with the Genetics and Etiology and ending with Prenatal Diagnosis and Screening. Inside, you will find state-of-the-art information on: 1. Genetics and Etiology 2. Down syndrome Model 3. Neurologic, Urologic, Dental & Allergic disorders 4. Prenatal Diagnosis and Screening Whilst aimed primarily at research workers on Down syndrome, we hope that the appeal of this book will extend beyond the narrow confines of academic interest and be of interest to a wider audience, especially parents and relatives of Down syndrome patients.

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