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A retrospective review of the long term clinical outcomes of patients with neurogenic lower urinary tract dysfunction following transverse myelitis

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Abstract

Aims: Transverse myelitis (TM) is an inflammation of the spinal cord which causes neurological deficit in motor, sensory, and autonomic pathways. Persistent neurogenic lower urinary tract dysfunction (NLUTD) is common even where motor and sensory impairment is recovered. Long term follow-up is required to ensure optimal bladder management and protection of the upper tracts. We describe the clinical outcomes for a cohort of patients with TM who have received neurourological follow-up in a specialist center.

Methods: A retrospective review of TM patient records was performed. Current pharmaceutical and surgical management, upper tract status, and patient reported symptoms are reported. Changes in urodynamic parameters and bladder emptying technique between current and baseline were analyzed.

Results: Sixty patients with NLUTD following TM were identified. The mean age at onset of NLUTD was 29 years (0–77 years). The mean follow-up was 13 years. 55% of patients were taking antimuscarinic medication, 53% of patients had intradetrusor botulinum toxin injections and 5% had bladder augmentation surgery. Forty-one patients had a baseline and recent urodynamic study which could be compared. Fifty-three of fifty-eight patients with a recent renal ultrasound had normal renal appearance. Four had mild hydronephrosis and one more extensive hydronephrosis.

Conclusion: TM can have a persistent effect on lower urinary tract function. There is potential for upper tract damage if bladder management is not optimized. We have demonstrated that in a specialist neurourology unit within a tertiary center, one can provide acceptable long term outcomes following international guidelines.

Abbreviations: AM, anti-muscarinic; BTX-A, botulinum toxin A; CISC, clean intermittent self-catheterization; CYP, children and young people; IDUC, indwelling urethral catheter; MCC, maximum cystometric capacity; MDP, maximum detrusor pressure; NDO, neurogenic detrusor overactivity; NLUTD, neurogenic lower urinary tract dysfunction; SCI, spinal cord injury; SPC, suprapubic catheter; TM, transverse myelitis.

1 | INTRODUCTION

Transverse myelitis (TM) is an immune mediated inflammatory process which affects the spinal cord bilaterally at one or more levels. It is characterized by neurological deficit in motor, sensory, and autonomic pathways.[1] In 60% of cases the origin is unknown but presumed to be post a viral infection whereas in a further 40% of cases it is associated with an autoimmune disorder. The reported prevalence is 1.34–4.6 cases per million of the population and it is equally prevalent across age, gender, and ethnicity.[1] There is no cure, but it is usually treated in the acute phase with steroids or plasma exchange[2]; the majority of those affected will make a full recovery; although, many are left with a degree of long term motor and sensory deficit. However, TM can also affect the ascending and descending tracts responsible for bladder and bowel functions which can lead to development of neurogenic lower urinary tract dysfunction (NLUTD) and neurogenic bowel dysfunction (NBD) including neurogenic detrusor overactivity (NDO) and damage to the upper tracts if left untreated. The degree of bladder dysfunction does not appear to correlate with recovery of motor and sensory deficit, and over 90% of patients exhibit some form of NLUTD. However, there is a paucity of data regarding the long term urological outcomes of patients who acquire spinal cord injury (SCI) following TM infection.[3–5] In the United Kingdom, guidelines for the management of patients with NLUTD are produced by National Institute of Health and Social Care (NICE) CG148 Urinary incontinence in neurological disease[6] and the annual EAU guidelines on neurourology.[7] The main difference between the two guidelines relates to the frequency of urodynamics in follow-up.[8] However, both guidelines are based on expert panels rather than high level evidence as there little data on the benefit of assessment of the urinary tract in neurological disease.

The aim of the study was to evaluate the long term clinical management of a group of adults and children and young people (CYP) with NLUTD following TM who have been treated within the setting of a specialist tertiary care center in accordance with guidelines. Current pharmaceutical and surgical interventions, upper tract status and lower urinary tract symptoms are reported. Initial and current bladder emptying technique is described and changes in urodynamic parameters based on use of routine surveillance investigations are analyzed.

2 | METHODS AND MATERIALS

Patients with a diagnosis of TM were identified from the electronic records and a retrospective review of the notes was performed. The study was registered and approved as a Service Evaluation. Patient demographics with respect to sex, age, age at onset of TM, level and severity of motor and sensory dysfunction and initial bladder emptying technique were recorded from discharge summary. Current bladder emptying technique, pharmaceutical and surgical intervention and patient reported incontinence and infections were identified from most recent clinic letter. The baseline and most recent urodynamic reports and renal ultrasonography were analyzed. Urodynamics were performed according to the current best practice.[9]

3 | RESULTS

Seventy-six patients were identified, of whom 60 (38 male and 22 female) have received regular neurourological follow-up at our center. Patient demographics are shown in Table 1. The mean length of follow-up was 13 (range: 1–51) years.

3.1 | Bladder emptying

Initial and current bladder emptying technique are shown in Table 1. Clean intermittent self-catheterization (CISC) was the most popular method of bladder emptying at both initial discharge (43%) and currently (52%). A total of 40 patients had remained on the same bladder emptying technique and 20 had changed. Figure 1 shows the conversion from initial bladder emptying technique to that currently used.

3.2 | Patient reported lower urinary tract symptoms

Urinary incontinence and recurrent infections stratified by bladder emptying technique are shown in Table 1. A total of 14 of 60 patients reported incontinence, with voluntary voiders showing the highest percentage (44%); 8 of 60 patients reported recurrent UTIs with the highest proportion amongst patients who used a combination of CISC and voiding.

3.3 | Pharmacological management

Anti-muscarinic (AM) medications were used in 55% of patients and beta-3 agonist (β3-A) medication was used in 5% of patients. Twenty-three (38%) were not taking any medication at last follow-up visit; however, 12 of these had undergone injections of botulinum toxin into the bladder. The breakdown of pharmaceutical management by bladder emptying technique is shown in Table 2.

TABLE 1 Demographic details of patients identified from electronic medical records as having a diagnosis of transverse myelitis. Level of injury and degree of deficit. Initial and current bladder management technique and current status with respect to incontinence and recurrent infections

Total		60		
Male		38		**63%**
Female		22		**36%**
Age	**Mean**	**Range**	**Adult**	**CYP**
Current age (years)	42	5–80	51	9
Age at onset of TM (years)	29	0–77	34	26
Elapsed time since TM (years)	13	1–51		
		Degree of deficit		
Spinal level	**Total**	**Complete**	**Incomplete**	**Unknown**
Cervical	24	8	16	0
Thoracic	32	9	22	1
Lumbar	3	0	2	1
Unknown	1	0	1	0
Bladder emptying	**Initial**	**Current**	**Leakage**	**Recurrent UTI**
Reflex voiding	3 (5%)	2 (3%)	3 (100%)	0 (0%)
IDUC	9 (15%)	3 (5%)	0 (0%)	0 (0%)
CISC	26 (43%)	31 (52%)	5 (16%)	3 (10%)
CISC and voiding	4 (7%)	3 (5%)	0 (0%)	1 (33%)
SPC	7 (12%)	11 (18%)	2 (18%)	3 (27%)
Voluntary voiding	10 (17%)	10 (17%)	4 (44%)	1 (11%)
Strain void/crede	1 (2%)	0 (0%)	–	–

Note: Degree of deficit was determined by the American Spinal Injuries Association Impairment Score (AIS) A–E. Complete injury is associated with a AIS of A, where as an incomplete injury is associated with an AIS of B, C, D, or E. Bladder emptying technique at discharge and at latest clinic visit and patient reported incontinence and infections.

Abbreviations: CISC, clean intermittent self-catheterization; CYP, children and young people; IDUC, indwelling urethral catheter; SPC, suprapubic catheter; TM, transverse myelitis.

3.4 | Surgical interventions and intradetrusor botulinum toxin A injections

Intradetrusor botulinum toxin A (iBTX-A) injections (abobotulinum and onabotulinum toxin) were offered where pharmaceutical management either did not adequately suppress NDO, or it caused intolerable side effects including dry mouth and blurred vision. Thirty-two of sixty patients (53%; both adults and CYP) have received one or more iBTX-A injections (see Table 2).

Bladder augmentation surgery was offered when bladder capacity or storage pressures were not adequately managed with pharmaceutical techniques or iBTX-A. Three patients (5%) have had bladder augmentation surgery, all of whom had childhood onset TM.

3.5 | Urodynamics results

Fifty-three patients had a recent urodynamics study; the urodynamic parameters stratified by bladder emptying technique are shown in Table 3. Thirty-one of fifty (62%) patients demonstrated NDO, six (12%) had low-compliance, and sixteen (32%) had normal detrusor function. The highest maximum detrusor pressure (MDP) was seen in those using reflex voiding (86 cmH_2O) and the lowest MDP was seen in the CISC users. The CISC users had the greatest median maximum cystometric capacity (MCC; 475 ml) whereas the reflex voiders and indwelling urethral catheter (IDUC) users had the smallest. With respect to the eight patients who currently used voluntary voiding, the median % void was 80% (range: 69–100%), median Q_{max} 16.5 ml/s

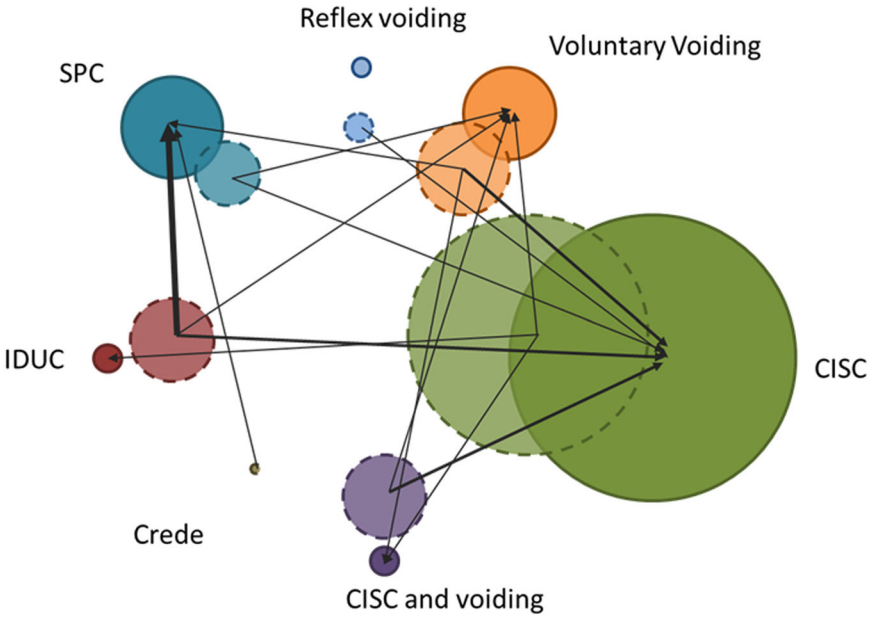

FIGURE 1 Change in bladder emptying technique from initial management to current management. Initial bladder management is shown in the circles with a dashed line, and current management is shown by the circles with solid line. The size of the circle represents the number of patients using each technique. The arrowed lines denote the change in technique for individual patients. The thickness of the line denotes the number patients making the change. CISC, clean intermittent self-catheterization; IDUC, indwelling urethral catheter; SPC, suprapubic catheter

(range: 4–21 ml/s), and median MDP void 80 cmH_2O (range: 10–130 cmH_2O).

3.6 | Comparison between baseline and current urodynamics

A comparison between baseline and most recent urodynamics was possible in 41 patients. The median time between investigations was 5.6 (range: 0.2–29) years. Urodynamic parameters are shown in Table 3 and Figure 2. A Wilcoxon signed-rank test showed a significant increase in the MCC between baseline and current urodynamics but no difference in the MDP. The proportion of patients with NDO decreased from 73% to 61% following appropriate treatment, with a corresponding increase in the proportion with normal detrusor activity from 15% to 24%.

3.7 | Renal ultrasonography

Fifty-eight of sixty patients had renal ultrasonography every 12–24 months. The median time since most recent scan was 12 months (range: 1–112 months). Fifty-three patients had normal renal appearance. Four patients had mild hydronephrosis, however, there was no evidence of ureteric reflux on most recent video-urodynamic studies, the mean time since onset of TM in the four patients was 32 years. For these four patients the median MDP at baseline urodynamics was 27 cmH_2O (range: 10–84 cmH_2O) and at the most recent 14.5 cmH_2O (range: 3–20 cmH_2O). The median MCC was 450 ml (110–510 ml) and it is not clear from the notes whether a repeat scan with empty bladder was performed to see whether hydronephrosis was still present. One patient had dilatation of the renal pelvis; a concurrent videourodynamic study showed grade 4 ureteric reflux.

4 | DISCUSSION

TM is an inflammatory process which causes damage to the spinal cord resulting in motor, sensory and autonomic dysfunction. Although some recovery can occur within the first 2 years, up to 95% of patients have some residual NLUTD. The long term urological outcomes of patients with a traumatic SCI are well documented; however, there are fewer reports of the outcomes following TM. TM affects both the adult and CYP population. There are several small cohort and case studies of outcomes in pediatrics. Tanaka et al.[3] reported on the long term follow-up of 22 pediatric patients with TM between 1984 and 2004. Nineteen had persistent bladder dysfunction and functional motor recovery was not correlated with bladder recovery. They recommend that all

TABLE 2 Table showing pharmaceutical and surgical interventions stratified by current bladder emptying technique

		Pharmaceutical and surgical bladder intervention					
		Pharmaceutical				Surgical	
Bladder emptying	Number (%)	AM	β3-A	None	Unknown	BTX-A	Bladder augmentation
Reflex voiding	2 (3%)	1		1		0	
IDUC	3 (5%)	1		2		1	
CISC	31 (52%)	18	2	10	1	18	2
CISC and Voiding	3 (5%)	1		2		3	
SPC	11 (18%)	8		3		7	1
Voluntary Voiding	10 (17%)	4	1	5		3	
Total	60	33 (55%)	3 (5%)	23 (38%)	1 (2%)	32 (53%)	3 (5%)

Abbreviations: AM, anti-muscarinic; BTX-A, botulinum toxin A; CISC, clean intermittent self-catheterization; IDUC, indwelling urethral catheter; SPC, suprapubic catheter; β3-A, beta-3 agonist.

patients receive initial baseline evaluation and on-going follow-up. DaJusta et al.[4] performed a retrospective chart review of 14 children (8 boys and 6 girls) who were treated to TM in their center between 1995 and 2004. They reported a correlation between complete motor recovery and complete bladder recovery (defined as normal voiding with no medication to suppress over-activity). However, where there was no or only partial motor recovery, bladder function remained impaired and required long term follow-up to protect upper tracts. Gliga et al.[5] reported on the urodynamic outcomes of 28 patients with TM who were referred to their tertiary

TABLE 3 Urodynamic parameters taken from the most recent urodynamics study where available showing median and interquartile range for maximum cystometric capacity (MCC) in ml and maximum detrusor pressure in cmH_2O and bladder activity shown by bladder emptying technique

		MCC (ml)		MDP (cmH_2O)		Bladder activity		
Bladder emptying	*n*	Median	IQ range	Median	IQ range	NDO	Low compliance	Normal
Reflex voiding	2	163		86		100%	0%	0%
IDUC	3	110		28		100%	0%	0%
SPC	9	210	125–280	15	7–34	25%	38%	38%
CISC	28	475	325–585	16.5	8–40	58%	12%	31%
CISC and voiding	3	260		60		67%	0%	33%
Voluntary voiding	8	200	85–572	51.5	18–115	75%	0%	25%
Total	53					31 (62%)	6 (12%)	16 (32%)

	Baseline urodynamics Median (IQ range)	Current urodynamics Median (IQ range)	*p* Value
MCC (ml)	250 (150–435)	350 (200–500)	.02
MDP (cmH_2O)	34 (20.5–64)	22 (12–61.5)	.21 (NS)
Bladder activity			
NDO	30 (73)%	25 (61%)	
Normal	6 (15%)	10 (24%)	
Low compliance	6 (15%)	6 (15%)	
Total	41	41	

Abbreviations: CISC, clean intermittent self-catheterization; IDUC, indwelling urethral catheter; MDP, maximum detrusor pressure; SPC, suprapubic catheter.

Note: NDO—neurogenic detrusor overactivity denoted by a bladder contraction in excess of 10 cmH_2O. Comparison between MCC and MDP taken from baseline and current urodynamics where both were available for an individual patient. *p* Value denotes significance of difference using a Wilcoxon sign rank test.

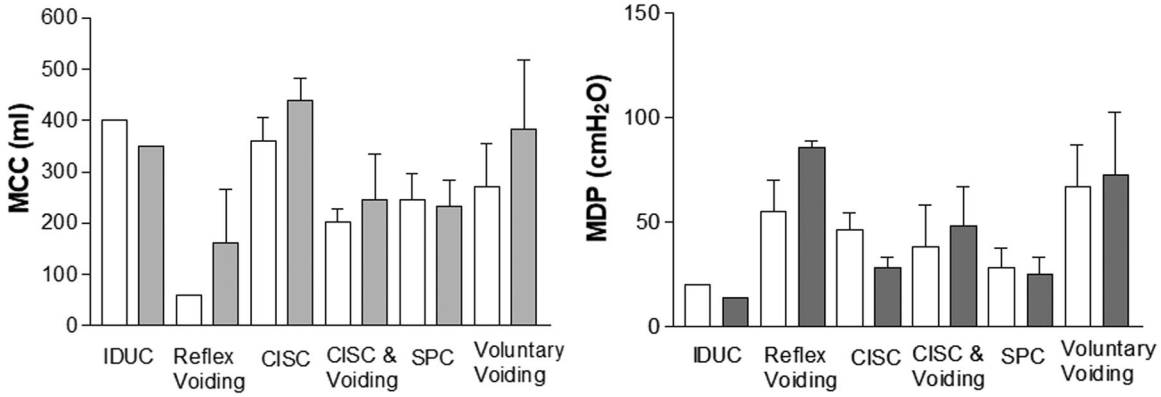

FIGURE 2 Graphs showing a comparison of urodynamic parameters maximum cystometric capacity (MCC) and maximum detrusor pressure (MDP) taken from urodynamic tests performed at baseline (white bars) and current (gray bars) stratified by current bladder emptying technique where both results were available. *n* Values for each group $n = 1$ for indwelling urethral catheter (IDUC), $n = 2$ for reflex voiding, $n = 23$ for clean intermittent self-catheterization (CISC), $n = 3$ for CISC and voiding, $n = 8$ for suprapubic catheter (SPC), $n = 4$ for voluntary voiding

center for urological follow-up. They also reported that urological outcomes were not correlated with motor outcomes. They highlight the need for all patients with TM to receive urological evaluation with on-going surveillance and individualized management; however, they note that as a tertiary referral center they only received patients who had persistent troublesome lower urinary tract symptoms. Our experience is similar with a significant proportion of patients who had TM developing persistent NLUTD which requires long term urological follow-up.

This retrospective review of patients with TM within our tertiary center identified 76 patients of which 60 (75%) have receieved neurourological follow-up as per NICE and EAU guidelines including regular urodynamics and renal ultrasound. With respect to the remaining 25% it is unclear whether they did not have significant LUTS or whether they were receiving urology management elsewhere. Of the 60 patients currently receiving follow-up, 51 are adults and 9 are children. However, in total 26 patients contracted TM whilst under 18 years and but have since become adults. The average time since acquiring TM is 13 years with a range of 1–51 years. Therefore this retrospective review represents a longer follow-up of a larger mixed age group than previously reported, with outcome information including changes in management and urodynamic results over time.

4.1 | Bladder emptying

Ideal bladder management includes a safe and efficient means of bladder emptying.[6,7] If voluntary voiding results in abnormal voiding pressures or incomplete emptying, patients are recommended to use catheterization to drain the bladder. The gold standard is CISC by patient or carer. Where this is not possible, an indwelling catheter may be used, with suprapubic catheter (SPC) preferable to IDUC. In our patient cohort, 52% of patients at last clinic review were performing CISC, 17% voiding on urge, and 5% were combining CISC and voiding. In the Gliga study,[5] a much larger proportion of patients (42.9%) were voiding on urge, with only 35.7% performing CSIC and 1% combining CISC and voiding. Amongst the children in the Tanaka review,[3] 72.7% were performing CISC and 27.2% were voiding, none appeared to have an indwelling catheter. Although CISC is always recommended where safe natural voiding has not been demonstrated on urodynamics, not all patients are compliant and continue to void on urge. Indwelling catheters were used by 23% of patients who could not perform CISC due to limited hand function, or patient choice, with 18% having an SPC and 5% an IDUC demonstrating our preference for SPC over IDUC which can cause urethral cleavage. Gliga et al.[5] report a similar proportion of patients having an indwelling catheter (17.9%) but does not differentiate between SPC or IDUC. None of the children in the Tanaka study[3] appeared to have an indwelling catheter. A very small percentage of our patients were reflex voiding (3%) as this would not normally be recommended. The previous studies do not differentiate reflex voiding from voluntary voiding (which may include voiding on NDO contractions) so it is not possible to make accurate comparisons. In the current longitudinal study we were able to investigate the changes in bladder emptying technique from discharge to current management. The greatest change was conversion from IDUC on discharge to SPC currently, which again indicates our preference for SPC over IDUC due to the potential long term damage to the

urethra. There was also an increase in patients performing CISC compared to on-discharge. The one patient who had been using the Crede maneuver since childhood was converted to an SPC as this technique is no longer advised. The individual changes in bladder emptying technique are probably due to a combination of patient choice and convenience and neurourological advice.

4.2 | Pharmaceutical management

Anti-muscarinic/cholinergic medication is the first line treatment for controlling NDO associated with NLUTD. However, these can have intolerable side effects in high doses including dry mouth and blurred vision; they can also cause constipation which can exacerbate the existing NBD. More recently, older style AMs have been implicated in the development of dementia in older adults[10] which have caused some patients to stop medication. In addition, AMs are contra-indicated in those patients who have closed angle glaucoma or inflammatory bowel disease. In our cohort, 55% of patients take one or more AM to control NDO, with a further 5% taking a β3-A. This compared with 64% of the children in the Tanaka review[3] who were reported to be taking AMs, and 50% of patients in the Gliga study[5] who were started on AMs. Of the patients in our cohort not taking AM, about 50% have had iBTX-A injections, and the remainder either do not require medication, or have chosen not to take it. Although AM is the first line treatment for NLUTD, newer pharmaceutical treatments are needed, as side effects can be intolerable, and some patients NDO remains intractable despite taking maximum dosage of multiple drugs.

4.3 | Surgical management

iBTX-A injections have been used effectively in the management of NLUTD since 2000.[11] Fifty-three percent of the patients in our cohort had received iBTX-A injections to maintain safe storage pressures. This represents a higher proportion of patients than reported in previous studies; Tanaka et al.[3] described only 1 pediatric patient of 22 and Gliga et al.[5] only 5 of 28 adult patients receiving iBTX-A injections. The greater prevalence of this treatment option in our center is probably due the more recent data collection and early adoption of this intervention, including in pediatric cases. The duration of effect of iBTX-A injections have been reported to be between 3 and 18 months, therefore, regular, on-going repeated injections will be necessary to control NDO. There is some anecdotal evidence that the efficacy of the injections may diminish with time and repeated injections,[12] therefore, this technique may not provide a long term solution. Three of our patients have had bladder augmentation surgery to improve bladder capacity and reduce bladder pressure; all had childhood onset TM and felt that this intervention provided the best long term bladder management option. This compares with 4 of the 22 children in the Tanaka study[3] who had bladder augmentation surgery.

4.4 | Urodynamic results

Urodynamic investigations can determine whether the current treatment regime is effective or whether there have been changes in bladder function. Our practice is to undertake urodynamics at baseline and then at least every 2 years, or when there is a change in symptoms including increased incontinence or infections. Videourodynamics can also be useful for determining whether vesicoureteric reflux is present. Of total patients, 73% had NDO at baseline which compares with 76% of the adult patients in the Gliga study.[5] However, the most recent urodynamics demonstrated that even with neurourological input and management in-line with current guidelines, 61% still had some degree of NDO although the MDP was reduced demonstrating that NLUTD following TM is persistent and that this should be monitored with regular surveillance to ensure protection of the upper tracts. This was comparable with the results from the Tanaka study[3] which showed that 59% of the children had NDO on urodynamics at an average of 2.2 years postdisease onset. When urodynamic results were stratified according to bladder emptying technique it was clear that those using CISC had the greatest bladder capacity. Those using voluntary voiding had a bimodal distribution of capacity, which may represent the fact that some patients were not following recommendations for optimized management. Patients with indwelling catheters or reflex voiding had the smallest bladder capacity. The highest bladder pressures were seen in the reflex voiders and a proportion of the patients using voluntary voiding who were probably effectively reflex voiding as they were voiding on NDO contractions.

4.5 | Renal ultrasound

The protection of the upper tracts is of paramount importance in reducing morbidity and mortality in patients with NLUTD including that caused by TM.

Regular renal ultrasonography provides a safe, effective means of surveillance of upper tract health. It can provide early identification of hydronephrosis, formation of calculi and cortical thinning. These can then be followed up with invasive screening such as MAG-3 and CT urogram. Four patients were identified as having mild hydronephrosis, although urodynamic parameters were not dissimilar to other patients and no reflux was present. Importantly, in our cohortonly one patient (17-year-old male patient who was using voluntary voiding), had extensive hydronephrosis and dilatation of renal pelvis, with grade 4 ureteric reflux on videourodynamic study. He had only been recently referred to the neurourology service and an indwelling catheter was immediately placed to protect the upper tracts until further management options were discussed. Tanaka et al.[3] reported that 5 of 19 pediatric cases had upper tract changes with one displaying chronic renal insufficiency. They reported that delayed onset of CISC was correlated with low bladder compliance and upper tract changes. Renal ultrasonography is undoubtedly important in the on-going surveillance of patients with NLUTD after TM and the identification of patients who are at high risk of developing upper tract damage.

5 | LIMITATIONS OF STUDY

The major limitation of this retrospective review is the lack of quality of life data based on bladder diaries or validated questionnaires to compare with the clinical management and objective urodynamic data collected.

6 | CONCLUSION

TM can have a persistent long term effect on the lower urinary tract even where there is some motor and sensory recovery. There is a potential for upper tract damage and significant morbidity can arise if bladder management is not optimized. This is all the more important as the average age of diagnosis is quite young (<30 years). There are differences in the UK and European guidelines on the management of patients with neurogenic bladder dysfunction. The EAU guidelines strongly recommend regular routine surveillance urodynamics and renal ultrasound for all patients with NLUTD, whereas the NICE guidelines only recommend this in "high risk" patients with little detail on how these patients are identified initially, or on when they may become "high risk." We believe that specialist neuro-urological management should include regular urodynamic investigations and upper tract imaging as an aid in the decision making process to ensure a safe bladder storage pressure and satisfactory emptying technique in an individualized manner. In patients with NLUTD, preservation of upper tract function is of paramount importance. Therefore, ensuring safe storage and voiding pressure is the fundamental principle of neurourological management and one needs to have a proactive approach with regular follow-up and investigations to identify and treat any significant neurogenic bladder dysfunction. We have demonstrated that in a specialist neurourological within a tertiary center, one can provide acceptable long term outcomes with respect to urodynamics parameters and upper tract function following international guidelines. However, patient quality of life and experience of bladder management following TM has not been fully explored and invites further study.

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