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CONTENTS

Editorials

1 Superman and the Swiss Continence Foundation
Prokar Dasgupta

2 Professor Jean Jacques Wyndaele
Wagih S. El Masri and Stefan De Wachter

Comment

4 Plant sources of antimuscarinics
Clare J. Fowler

Original Article

8 A novel urodynamic model for lower urinary tract assessment in awake rats
Marc P. Schneider, Francis M. Hughes Jr., Anne K. Engmann, J. Todd Purves, Hansjörg Kasper, Marco Tedaldi, Laura S. Spruill, Miriam Gullo, Martin E. Schwab and Thomas M. Kessler

Comment

16 Anti-Nogo-A antibody: a treatment option for neurogenic lower urinary tract dysfunction?
Marc P. Schneider, Martin E. Schwab and Thomas M. Kessler

Original Article

18 Sensory evoked potentials of the bladder and urethra in middle-aged women: the effect of age
Flavia Gregorini, Stephanie C. Knüpfer, Martina D. Liechti, Martin Schubert, Armin Curt, Thomas M. Kessler and Ulrich Mehnert

Comment

26 The Swiss Continence Foundation Award: promoting the next generation in neuro-urology and functional urology
Ulrich Mehnert and Thomas M. Kessler

Original Articles

28 Forkhead box protein P3 (Foxp3) expression serves as an early chronic inflammation marker of squamous cell differentiation and aggressive pathology of urothelial carcinomas in neurological patients
Véronique Phé, Morgan Rouprêt, Olivier Cussenot, Emmanuel Chartier-Kastler, Xavier Gamé and Eva Compérat

33 Neurogenic lower urinary tract dysfunction (NLUTD) in patients with spinal cord injury: long-term urodynamic findings
Tim-Friedjof Schöps, Marc P. Schneider, Frank Steffen, Benjamin V. Ineichen, Ulrich Mehnert and Thomas M. Kessler

Reviews

39 Follow-up of the neuro-urological patient: a systematic review
Marcio Augusto Averbeck and Helmut Madersbacher

47 Management of sexual dysfunction due to central nervous system disorders: a systematic review
Giuseppe Lombardi, Stefania Musco, Thomas M. Kessler, Vincenzo Li Marzi, Michele Lanciotti and Giulio Del Popolo

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Editorial

Superman and the Swiss Continence Foundation

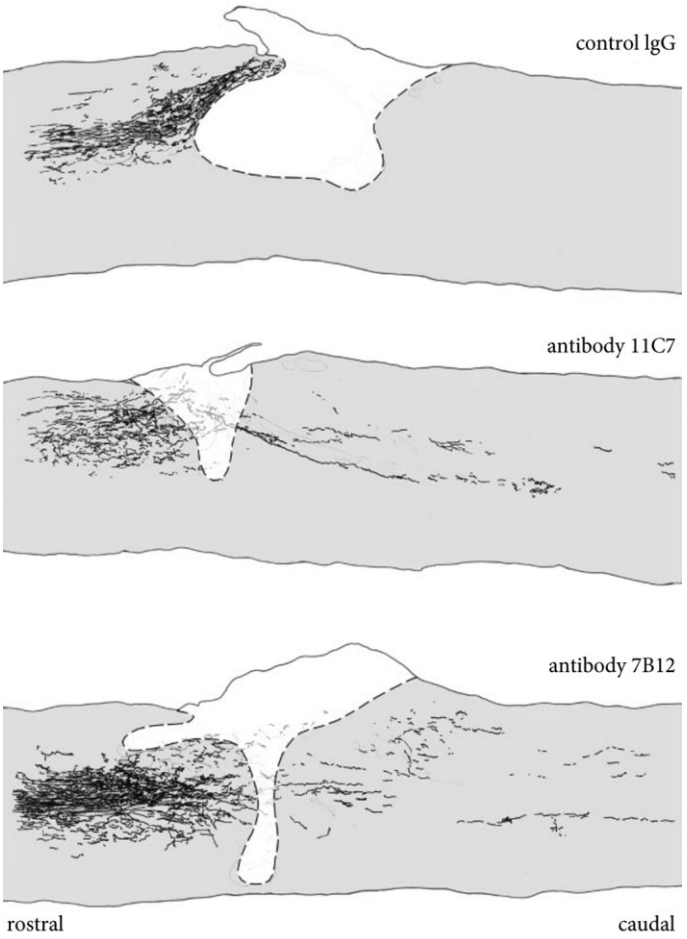
Like most kids growing up, Superman was one of my heroes. I was devastated when he sustained a spinal cord injury and spent the rest of his life as an ambassador for others thus affected. He dreamt of spinal cord regeneration one day but that did not materialise in his lifetime. The Christopher and Dana Reeve Foundation (http://www.christopherreeve.org/ and http://en.wikipedia.org/wiki/Christopher_and_Dana_Reeve_Foundation), is a unique source of information and includes the latest research on its NeuroRecovery Network (NRN).

Many years later, one afternoon in Zürich during the Swiss Continence Foundation 2014 annual meeting, I learnt about the exciting results of nerve regeneration with anti Nogo-A antibodies. I convinced the authors to submit the first results to the *BJUI* while further trials continue [1] (Fig. 1). This well-organised meeting, attracting the best brains in neuro-urology, was on this occasion honouring Prof. Jean Jacques Wyndaele, a stalwart in this field, on his retirement.

In this supplement, you will find the state of the art in neuro-urology in one single volume, including a paper by the winner of the Swiss Continence Foundation Award, Véronique Phé [2]. It is a must read for anyone interested in this field, as each of these papers is of the best quality and highly citable. We even managed to convince Prof. Clare J. Fowler, who taught me everything I know on the subject, to come out of retirement [3].

This year the *BJUI* is pleased to become the official journal of the Swiss Continence Foundation and through it the wider community of urologists, neurologists, andrologists, and neuro-rehabilitation experts working in this challenging and evolving field.

Fig. 1 This figure is taken from Schneider et al. [1].



Conflict of Interest

None declared.

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Editorial

Professor Jean Jacques Wyndaele

Already in the late 1970s, Jean Jacques Wyndaele expressed his interest in neuro-urology, a field where at that time the interested urologists were to be counted on the fingers of two hands. His meteoric rise in recognition as a leader in neuro-urology, his good reputation and his acknowledged achievements in the field were all predictable by most who met him.

Jean Jacques Wyndaele initially practiced in the University of Gent (Belgium). He was accredited as a urologist in 1980 and as a Rehabilitation Specialist in 1981. This dual training gave him an almost unique insight into the whole spectrum of problems individuals with neurogenic bladders and those who treat them face. The dual accreditation also gave him credibility to most of those involved in the various aspects of management of the patient with neurogenic bladder. In 1983, Jean Jacques obtained a Doctorate degree in Biomedical Sciences, which added significantly to his clinical armamentarium. During the following years he developed further as a neuro-urologist with special interest in developing tools to diagnose neurogenic impairment [1] and the continuous urological care in patients with neurogenic bladder [2].

In 1993, he moved to Antwerp and took the post of Professor and Chairman of the Department of Urology at the University of Antwerp and the University Hospital. Responsible for education, he trained many residents to become certified urologists. He also setup facilities for translational research, comprising both human and animal studies. One of his main scientific interests was the sensation in the lower urinary tract, which was before the era of the 'overactive bladder', an often neglected area of interest. Description of normal sensation [3] was a prerequisite to understand abnormal sensations, such as urgency and pain.

Jean Jacques Wyndaele is an active member of many National and International Professional Societies and held offices in many of these societies and organisations. He is a Fellow of the European Board of Urology, a Faculty Member of the European School of Urology including the European Association of Urology, a member of the AUA and of the International Continence Society. He held the position of Honorary Secretary International Spinal Cord Society (ISCoS) for 8 years and he is President of the ISCoS since September 2014. The ISCoS is privileged to have such an experienced, caring and well-respected President who will look after the interests of its members, as well as the patients they serve.

He is a member of Editorial Boards of several scientific journals and the Editor-in-chief of *Spinal Cord*. He has ensured that *Spinal Cord* attracts and publishes some of the best work related to the various aspects of spinal cord paralysis to enable readers from various disciplines to maintain a holistic approach to the problems of the patients and cross-fertilise ideas for further research.

Jean Jacques Wyndaele is author or co-author of 27 book chapters and >200 publications in peer-reviewed international and national journals. He introduced numerous candidates into research, and supervised 11 PhD and Medical Doctorate thesis.

His missionary zeal in education in developing countries has taken him around the world a few times. His generosity in time, effort and often personal finances, trying to help develop clinical urology laboratories in developing countries have helped many clinicians and an innumerable number of

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patients enormously. This has also earned him a reputation of brilliance, caring and humanity.

Although Jean Jacques may be retiring from clinical practice, he will continue to make significant contributions to education and research.

Conflicts of Interest

None disclosed.

Wagih S. El Masri and Stefan De Wachter*

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Comment

Plant sources of antimuscarinics

Clare J. Fowler

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Introduction

Previous publications have covered the use of capsaicin derived from chilli pepper (*Capsicum annuum*) as a bladder C-fibre neurotoxin [1], as well the possible use of the ultrapotent capsaicin analogue resiniferatoxin, which is extracted from *Euphorbia resinifera* [2]. Antimuscarinics were until very recently, the sole agents licensed to treat overactive bladder (OAB) and these too were originally obtained from plants. This brief overview describes the family of plants from which atropine and other antimuscarinics can be obtained.

Plants were originally classified according to morphological features, such as flower structure, but nowadays techniques using genome sequencing (https://genomevolution.org/wiki/index.php/Sequenced_plant_genomes) have led to reclassification of various groupings. Some rather unexpected relationships have been demonstrated, although the validity of the main family groupings has survived.

Antimuscarinics come from a group of plants within the family Solanaecea. This is a medium-sized family with 90 genera and 3000–4000 species and is sometimes referred to as the 'nightshade' or 'potato' family, reflecting two of its important genera. The family exhibits wide morphological and chemical diversity, and is of great economic importance (http://www.solanaceaesource.org/). It is distributed worldwide and is thought possibly to have originated in South America. (http://www.mobot.org/MOBOT/research/APweb/)

A group of plant-derived compounds of major pharmacological importance are the 'alkaloids'. Up until the early nineteenth century only acids had been obtained from plants, but in 1818 Meissner introduced the term 'alkaloid' to describe plant alkalis he had identified, morphine being the first [3]. Alkaloids are found in 15–30% of all flowering plants and are particularly common in the family Solanaceae. The tropane alkaloids are derived from the amino acids ornithine and phenylalanine and tropic acid, and include the substances that constitute the 'antimuscarinics.'

Antimuscarinics

The main naturally occurring antimuscarinics are hyoscyamine, atropine and hyoscine (known in the USA as scopolamine). In fact atropine is an artefact formed during the extraction of alkaloid from the plant, the naturally occurring material being hyoscyamine that is transformed into two optical isomers, one of which is atropine [3].

The antimuscarinics are substances that block the action of acetylcholine at the muscarinic receptors. Five types of muscarinic receptor have been identified and these are widely distributed throughout the body, in the CNS, the parasympathetic ganglia and various visceral smooth muscles [4]. Prominent antimuscarinic effects are due to their central actions in the brain resulting in alterations of consciousness, hallucinations and ultimately coma and death. Peripherally muscarinic receptors are associated with innervation by the parasympathetic nervous system, so that their blocking causes a dry mouth, blurred vision for near objects, tachycardia and constipation [4].

In the bladder the M3 muscarinic receptor is distributed throughout the detrusor muscle, urothelium and suburothelium, whereas the M2 receptor is functionally most relevant. Antimuscarinics were used initially to treat symptoms of OAB based on their mode of action on the parasympathetic innervation of the detrusor. However, as Andersson [5] pointed out their effect is predominantly during bladder filling when the parasympathetic efferent innervation is not active, and their effectiveness must be due in part to an action on the sensory innervation of the bladder.

Plant Sources of Tropane Alkaloids

Plants in the family Solanaceae, which produce the tropane alkaloids including the antimuscarinics, have well deserved sinister reputations for being poisonous, whilst other Solanaceae produce highly edible products. Table 1 gives the botanical Latin and common names of plants in the family Solanaecea, which are either poisonous or highly edible.

Atropa Belladonna (Deadly Nightshade) and Other Nightshades

Atropa belladonna is a potent source of atropine. The name Atropa comes from one of the three Fates of Greek

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Table 1 Some members of the family Solanaecea.

	Latin name	Common name
Poisonous	*Atropa belladonna*	Deadly nightshade
	Hyoscyamus niger	Henbane
	Mandragora officinarum	Common mandrake
	Datura stramonium	Jimson weed or thorn apple
Edible	*Solanum tuberosum*	Potato
	Solanum esculentum	Tomato
	Solanum melongena	Aubergine
	Capsicum annuum	Chilli

Fig. 1 Atropa belladonna (deadly nightshade) in flower.

mythology: Lachesis measured the thread of destiny at birth, Clotho spun it, controlling destiny and Atropos cut the thread of life, bringing death.

Deadly nightshade is an herbaceous perennial, growing well in damp, shady spots in some areas of the UK, but is generally uncommon. It grows to a height of 1.5 m and has branched stem with oval shaped, pointed leaves on alternate sides. In the early summer it produces brownish, tubular flowers (Fig. 1), which over ensuing months turn into hard green fruit that then ripen from to dark purple and shiny black [6] (Fig. 2). All parts of the plant are poisonous but the berries are particularly so.

Solanum dulcamara (woody nightshade) is a common perennial weed in the UK that has a long, trailing stem of up to 3 m. The leaves are dark green and pointed and the flowers have purple petals surrounding a yellow centre and produce shiny red berries in late summer (Fig. 3). The berries contain solanine (a glycoalkaloid), rather than atropine and so are not as poisonous as the berries of deadly nightshade.

Fig. 2 Fruits of deadly nightshade.

Fig. 3 Flowers of Solanum dulcamara (woody nightshade) amongst common weeds.

Solanum nigrum (black nightshade), likewise, grows as a weed on cultivated soil or wasteland in the UK, and fruits at any size between 15 and 60 cm high, forming clusters of white flowers that mature into first green then black, spherical berries (Fig. 4). This plant also contains solanine. Both black and woody nightshade are less toxic than deadly nightshade but can be confused because of the common name, 'nightshade' [6].

Hyoscyamus Niger *(Henbane)*

Henbane is an annual or biennial that grows to 75 cm and has a thick stem and toothed leaves. The plant is hairy and sticky and has an unpleasant smell. It produces flowers near the top of stems that are yellow with purple veins. The fruit hardens

Fig. 4 Solanum nigrum (black nightshade).

into spines and remain on the plant throughout winter. The whole plant is highly poisonous, containing a mixture of tropane alkaloids.

Mandragora Officinarum (Common Mandrake, Devil's Apples, Love Apple)

This plant is indigenous to Northern Italy, Western Balkans, Greece and Western Turkey, but can be cultivated in sheltered conditions in the UK. It is a perennial that produces a rosette of dark green leaves on emerging from ground in the spring, which are initially upright and then lie flat. It produces tubular bell shaped flowers in the spring that are followed by spherical yellow fruit (Fig. 5).

The special chemical properties of its root may have enhanced its reputation as highly desirable for its magical powers. Early herbals are illustrated by 'male or female' versions of the root showing the lower half of the body with gender attributes accordingly, and were very valuable, as they were believed to aid conception and expel demons from sick people [7]. So desirable were the roots that it was spread abroad that when the root was pulled from the ground a scream would be emitted that would kill any human who heard it. Thus it was that ingenious schemes were designed for a dog to be tied to the root and when called from a safe distance, pulled it up for its owner. It was to avoid being affected by hearing the screams from the root of the *Mandragora officinalis* that Harry Potter and his classmates wore ear defenders in their herbology class with Professor Sprout.

Datura Stramonium (Jimson Weed or Thorn Apple)

This plant is native to Central America but is found as a naturalised weed in Britain. It is a large annual growing up to

Fig. 5 Fruits of Mandragora officinarum, sometimes called 'devil's apples'.

1 m. The leaves are pointed at the edges and yellowish at the base. The flowers are white trumpets 10-cm long and the fruits are green, spiny ovals, hence the name 'thorn apple'. These split to reveal numerous black seeds. Tropane alkaloids are concentrated in the seeds although all parts of the plant are poisonous.

Throughout history the CNS toxicity of the plant has been put to use to quell invaders: its name Jimson weed commemorates the occasion when settlers arrived on Jamestown Island, Virginia in 1607 and found the island overrun by this weed. Many of them ate the plant and died after experiencing delusions, convulsions and respiratory failure. The nature of their deaths was remembered when troops subsequently arrived some 70 years later to commandeer the settlement, but were reduced to a state of helpless confusion by administration of the *Datura* leaves. Soldiers in North Africa were poisoned *en masse* by *Datura* in 1943, as were Roman soldiers around 38 BC [6].

'Witching Weeds'

The central antimuscarinics properties of the chemicals produced by these plants means that since the dawn of time, extracts have been used as remedies, poisons, magic potions and 'knockout' drops. In European countries henbane, mandrake and deadly nightshade were known as the 'witching weeds' and a salve made of these applied to skin apparently induced sensations of flying. Henbane mixed with opium poppy and mandrake was used as an anaesthetic, probably

with a narrow margin of safety. In South America, with its long history of shamanism, plants containing tropane alkaloids were used for mystical exploitation. The central effects of these antimuscarinics so dominate the clinical picture that the possible use of them in sub-lethal doses, for an action on the bladder is not mentioned in historic texts such as *Gerard's Herbal* or *Culpeper's English Physician*.

The first medical application of belladonna was to dilate the pupils, and in 1802, Himly encouraged ophthalmologists to use belladonna to examine the eye: plant extracts containing tropane alkaloids were inhaled and used as bronchodilators for the treatment of asthma [3]. Synthetic atropine analogues started to be produced in the mid nineteenth century and subsequently 'more drugs have been derived directly or indirectly from atropine than any other drug prototype'. Pharmaceutical companies have since synthesised a vast range of anticholinergic drugs by combining assorted amino-acids with amino-alcohols [3]. The currently available range of antimuscarinics to treat the OAB, are presumably part of that industry.

Why plants have evolved chemicals such as the tropane alkaloids is an unanswerable question, but it seems likely that they impart protection against invasion by pathogens or grazing animals. That these chemicals are also active in humans raises interesting questions about the phylogeny of the muscarinic receptors. Why some plant are poisonous to humans whilst others from the same Family produce highly delectable fruit or tubers, is inexplicable, but undoubtedly of the greatest benefit to mankind.

Conflicts of Interest

None disclosed.

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Abbreviation: OAB, overactive bladder.

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A novel urodynamic model for lower urinary tract assessment in awake rats

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M.P.S and F.M.H contributed equally and share the first authorship.
M.E.S and T.M.K contributed equally and share the senior authorship.

Objectives

To develop a urodynamic model incorporating external urethral sphincter (EUS) electromyography (EMG) in awake rats.

Materials and Methods

Bladder catheters and EUS EMG electrodes were implanted in female Sprague Dawley rats. Assessments were performed in awake, lightly restrained rats on postoperative day 12–14. Measurements were repeated in the same rat on day 16 under urethane anaesthesia. Urodynamics and EUS EMG were performed simultaneously. In addition, serum creatinine and bladder histology was assessed.

Results

No significant differences in urodynamic parameters were found between bladder catheter only vs bladder catheter and EUS EMG electrode groups. Urethane anaesthesia evoked prominent changes in both urodynamic parameters and EUS EMG. Serum creatinine was within the normal limits in all rats. Bladder weight and bladder wall thickness were significantly increased in both the bladder catheter only and the bladder catheter and EUS EMG group compared with controls.

Conclusions

Our novel urodynamic model allows repetitive measurements of both bladder and EUS function at different time points in the same rat under fully awake conditions and opens promising avenues to investigate lower urinary tract dysfunction in a translational approach.

Keywords

urodynamics, rat, external urethral sphincter (EUS), electromyography (EMG), urethane

Introduction

Lower urinary tract dysfunction (LUTD) is very common in neurological patients. It affects the lives of millions of people worldwide, has a major impact on quality of life and imposes a substantial economic burden for every healthcare system [1]. Particularly disastrous is detrusor–sphincter dyssynergia (DSD), where neuronal dyscoordination causes the detrusor to contract while preventing sphincter relaxation, resulting in dangerously high spikes in bladder pressure that may lead to kidney damage in the chronic state. Accurate diagnosis of DSD requires measurement of the function of both the detrusor and the external urethral sphincter (EUS). Critical to the development of new therapies to combat DSD and other LUTD are rodent models that accurately measure both parameters. Unfortunately, current models either lack EUS assessments or utilise anaesthesia that is likely to severely alter bladder function. Thus, we aimed to develop and establish an assessment protocol of lower urinary tract function in a rat model that incorporates the synchronous measurement of detrusor activity and EUS function in awake rats, in close analogy to the urodynamic assessment used clinically in humans.

Materials and Methods

Rats (details in Supplement 1): Age-matched female Sprague Dawley rats (260–300 g, aged 5 months, Harlan, Frederick, MD, USA) were used in all studies. All experiments were approved by the Institutional Animal Care and Use Committee (IACUC) at the Medical University of South Carolina (USA).

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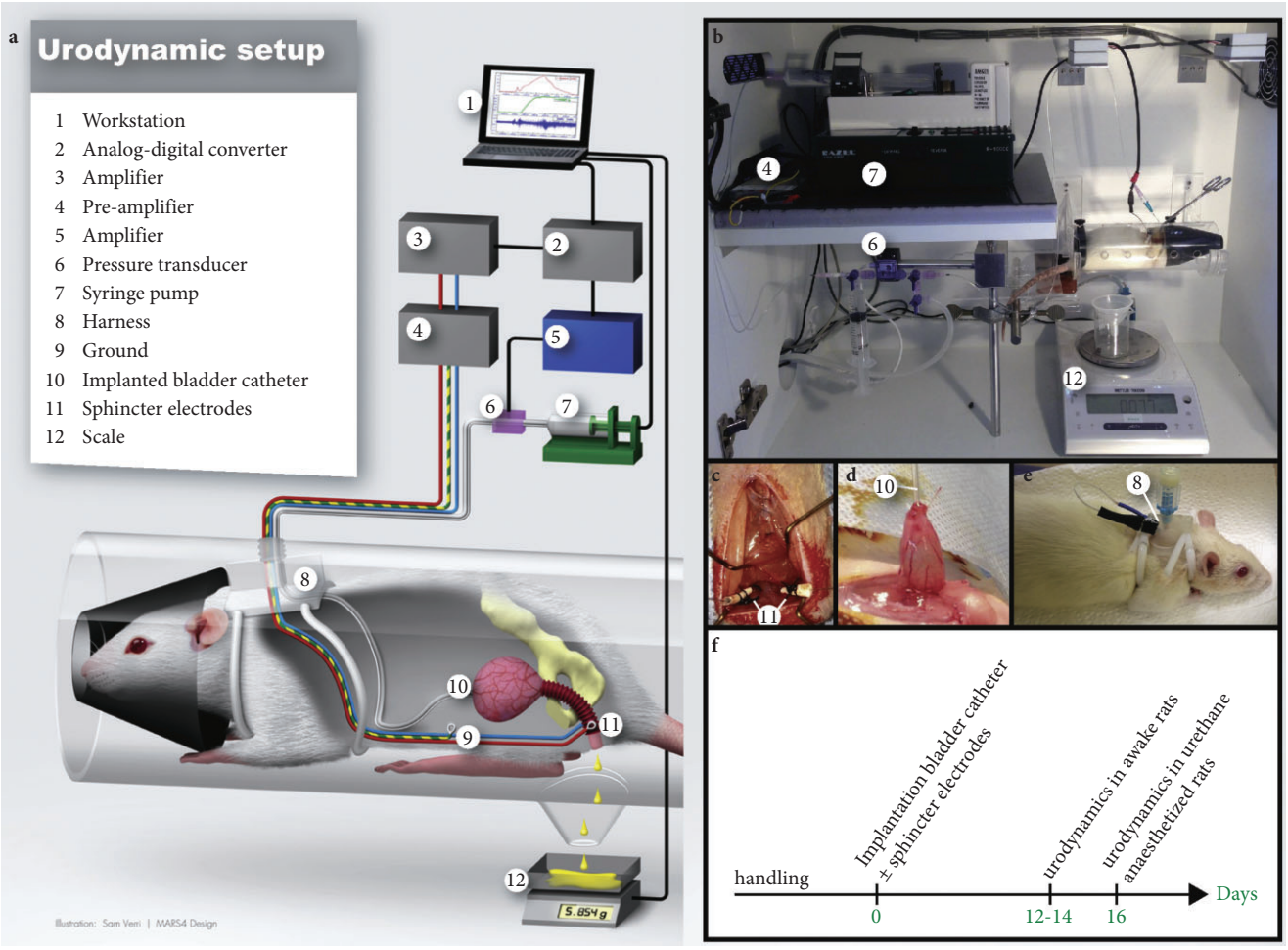
Fig. 1 (**a**) Scheme of the urodynamic setup. (**b**) Urodynamic laboratory station. (**c**) Intraoperative view of the urethra after bilateral implantation of the EUS EMG electrodes. (**d**) Intraoperative view of the bladder dome after implantation of the bladder catheter. (**e**) Rat with harness affixed. (**f**) Study timeline. Numbers in **b–e** relate to the legend in **a**.



Experimental design (details in Supplement 1): Rats were divided randomly into three groups: (i) bladder catheter only group (four rats), (ii) bladder catheter and EUS electromyography (EMG) group (six), and (iii) control (i.e. naïve) group (four). Controls were used for creatinine assessment and histology only. To minimise implant-associated bladder dysfunction, urodynamics were not performed immediately but on postoperative day 12–14 in all groups with simultaneous EUS EMG measurement (where appropriate) [2]. On day 16 the same rats were administered 600 mg/kg urethane and urodynamics/EUS EMG assessed 30 min later.

Surgery (details in Supplements 1 and 2): Rats were anaesthetised with ketamine/xylazine and bladder catheters inserted into the bladder dome and secured with a purse string suture. Where indicated, EMG electrodes were affixed to the fat tissue beside the EUS and a ground wire sutured to the abdominal muscle. The bladder catheter and wires were tunneled s.c. to the back of the neck and the rat fitted with an infusion harness (QC Single, SAI Infusion Technologies, USA) and allowed 12–14 days to recover.

Urodynamic and EUS EMG measurements (details in Supplement 1): As shown in Fig. 1a and pictured in Fig. 1b, awake rats were positioned in a modified restrainer (modified from item # HLD-RM, Kent Scientific, Connecticut, USA) with a funnel situated under the urethra, as previously described [3]. The restrainer was then placed in a modified Small Animal Cystometry Lab Station (Catamount Research and Development Inc.; St. Albans, Vermont, USA) with a scale below the funnel. The bladder catheter was attached to a syringe pump with an in-line pressure transducer and the electrodes (where relevant) connected to an amplifier/converter. Saline was instilled (120 μL/min) and all parameters (pressure, scale, voltage) recorded simultaneously for at least three voiding cycles.

Post-mortem assessments (details in Supplement 1): At the end of the experiment, blood was obtained by heart puncture and creatinine assessed by standard ELISA techniques. Bladders were removed, weighed and the central third fixed, embedded and sectioned (5 μm). Sections were then stained with haematoxylin and eosin (H&E) or Masson's trichrome stain using routine methods.

Statistical analysis (details in Supplement 1): Data are reported as mean ± standard deviation (SD). Comparing related and unrelated samples, the paired and unpaired *t*-test was used. To test for differences among the three groups, one-way ANOVA was used. The value of significance was considered at $P < 0.05$. Statistical analyses were performed using GraphPad Prism, version 6.01 (GraphPad Software, CA, USA).

Results

Urodynamic Investigation in Awake Rats

Rats tolerated the harness with the catheter port and the electrode plug very well; there were no losses (total 10 rats) over the 3 weeks of the experiment. The rats were acclimated to the urodynamic measurement cabinet for 5 days, after which they stayed in the restraint position during the 1-h measurement period without any signs of stress or discomfort. A typical analysis from a postoperative day 12–14 rat with bladder catheter and EUS EMG is depicted in Fig. 2a and includes a pressure tracing from the bladder, the determination of secreted urine (g on the scale) and the EUS EMG traces. An expanded graph of a single void is shown in Fig. 2b. Voiding consists typically of four phases [2,4], which are indicated on the figure. Phase α: initial increase of

Fig. 2 (**a**) 1625-s window of a representative urodynamic tracing from a rat with bladder catheter and EUS EMG showing three voiding cycles. The first voiding cycle includes moving artefacts and serves for adaptation of the rat. The second and third voiding cycles are representative for an awake rat regardless of group. The top panel shows the bladder pressure tracing, the middle panel the secreted urine weight tracing and the bottom panel the EUS EMG tracing. **biP**, baseline pressure: lowest pressure between two voids; **TP**, threshold pressure: pressure shortly before the void is started; **Pmax**, maximum voiding pressure: highest pressure during the voiding cycle. (**b**) 50-s window culled from **a**. Top panel is the pressure tracing, middle panel the scale tracing and the bottom panel the EUS EMG tracing. The voiding consists of four phases (adapted from [3, 4]): Phase **α**: initial increase of intravesical pressure with parallel increase of the EUS EMG activity due to the guarding reflex. Phase **β**: intravesical pressure increased with high-frequency oscillations during pulsatile flow of urine. The EUS EMG shows the specific slow wave bursting. Phase **γ**: rebound increase in intravesical pressure (end of pulsatile flow). The reappearance of the high-amplitude high-frequency bursting in the EUS EMG is indicative of a contraction and reappearance of the guarding reflex. Phase **δ**: rapid intravesical pressure decline to the level before the voiding contraction. (**c**) 4-s zoomed window from the EUS EMG from (**b**) before the voiding has started. Most prominent pattern is a low-amplitude high-frequency bursting. (**d**) 4-second zoomed window from the EUS EMG from (**b**) during the voiding. Most prominent pattern is a high-amplitude low-frequency bursting with medium-amplitude high-frequency bursting between the slow-wave bursting. (**e**) 4-s zoomed window from the EUS EMG from (**b**) after the voiding. Most prominent pattern is a high-amplitude high-frequency bursting.

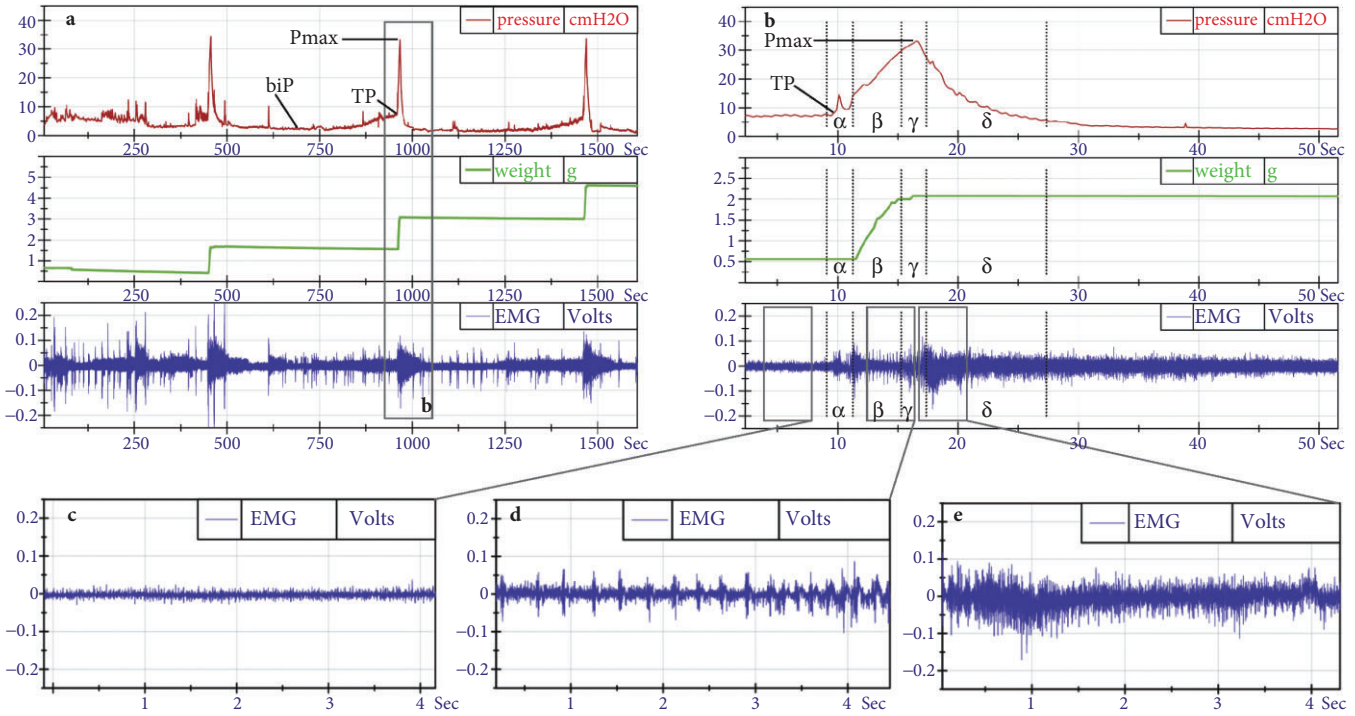


Table 1 Urodynamic variables in the bladder catheter only vs the bladder catheter and EUS EMG group.

Variable	Bladder catheter group	Bladder catheter and EUS EMG group	*P*
Mean (SD):			
Bladder compliance, mL/cmH_2O	0.27 (0.07)	0.21 (0.09)	0.3
Mean flow, μL/s	259.0 (59.2)	251.3 (74.63)	0.9
Voiding duration, s	5.97 (0.21)	6.71 (1.53)	0.4
Maximum voiding pressure, cmH_2O	38.90 (13.44)	42.19 (11.65)	0.7
Voided volume, mL	1.58 (0.42)	1.63 (0.31)	0.9

intravesical pressure with parallel increase of the EUS EMG activity due to the guarding reflex. Phase β: intravesical pressure increase with high-frequency oscillations (pulsatile flow of urine). The EUS EMG shows the specific slow wave bursting. Phase γ: rebound increase in intravesical pressure (end of pulsatile flow). The reappearance of the high-amplitude high-frequency bursting in the EUS EMG is indicative of a contraction and reappearance of the guarding reflex. Phase δ: rapid intravesical pressure decline to the level before the voiding contraction.

Quantitation of the urodynamic parameters (bladder compliance, mean flow, voiding duration, maximum voiding pressure and voided volume) in the rats with bladder catheter only and rats with bladder catheter and EUS EMG electrodes are presented in Table 1 and show that there were no significant differences between the two groups.

Urodynamic Investigation: Awake vs Urethane Anaesthetised Rats

To assess the effect of urethane anaesthesia and to compare our findings in Fig. 2/Table 1 to previous studies, all 10 rats were administered urethane on postoperative day 16 and urodynamics (± EUS EMG where relevant) assessed 30 min later. Rats from both groups were included in the analysis. Of the 10 rats, two had to be excluded: one bladder catheter and EUS EMG electrodes-implanted rat died immediately after urethane administration and another (bladder catheter only) was excluded due to dripping overflow incontinence after urethane injection. As shown in Fig. 3, urodynamic parameters were significantly altered between awake and urethane anaesthetised rats. Anaesthesia provoked a decrease in maximum voiding pressure (Fig. 3h; $P = 0.008$), as well as an increase in compliance (Fig. 3g; $P = 0.04$) and voided volume (Fig. 3i; $P = 0.03$). The mean flow rate ($P = 0.6$) and voiding duration ($P = 0.15$) were similar between both groups (data not shown).

EUS EMG parameters were also altered after urethane administration. (Fig. 3, five rats). A high-frequency pre-micturition burst, similar to the post-micturition burst, was prominent in awake rats (Fig. 3a,c) but highly reduced (in two of the five) or not detectable (in three of the five) in urethane anaesthetised rats (Fig. 3b,d). In addition, baseline amplitude of fast frequency bursting before and during the voiding was reduced in the anaesthetised rats. During voiding of urethane anaesthetised rats, high-frequency bursting activity was almost absent in the intervals between slow-wave bursting (Fig. 3d).

Post-mortem Analysis

As shown in Fig. 4a, serum creatinine levels in the experimental, implanted rats were within the normal range (<88 μmol/L) with no significant differences to the controls. However, bladder weight and bladder wall thickness were increased more than two-fold in both the bladder catheter only and the bladder catheter and EUS EMG group compared with controls (Fig. 4b,c). These same groups displayed marked muscular hypertrophy and urothelial hyperplasia (Fig. 4d–f). Masson's trichrome staining for collagen was similar in all three groups (Fig. 4g–i) and there were no signs of bacterial infection.

Discussion

Our present findings show that chronic, combined bladder catheter and EUS EMG electrodes in the same animal do not impair bladder function in the awake rat. On the other hand, urethane anaesthesia significantly alters both detrusor and EUS activities. To the best of our knowledge, this is the first presentation of a rodent urodynamic model for repetitive lower urinary tract assessment that includes EUS EMG analysis in an awake rat. Moreover, given the nondestructive nature of the measurements, this model allows for repetitive analysis at different time points in the same rat. Thus, our novel urodynamic rodent model opens promising avenues to investigate LUTD in a translational approach.

Anaesthetic drugs are well known to impair lower urinary tract function [5–7]. Thus, to represent the situation in everyday life as close as possible, human urodynamics (which includes EUS EMG) is performed in an awake state without anaesthetics [8]. However, in animals, all existing studies that included urodynamics and EUS EMG were carried out under anaesthesia [9–11]. Although urethane seems to be the best available anaesthetic to maintain the micturition response [2,12], it strongly impairs bladder function, leading to significant differences in urodynamic findings compared with the awake state [13]. In the present study, we observed lower baseline amplitude of high-frequency bursting before, during and after voiding in the urethane-treated rat, showing the lower basal EUS activity. Decreased EUS activity results in lower bladder outlet resistance, which might explain the lower maximum voiding pressure in the anaesthetised rats, as less pressure is needed to overcome a lower infravesical resistance.

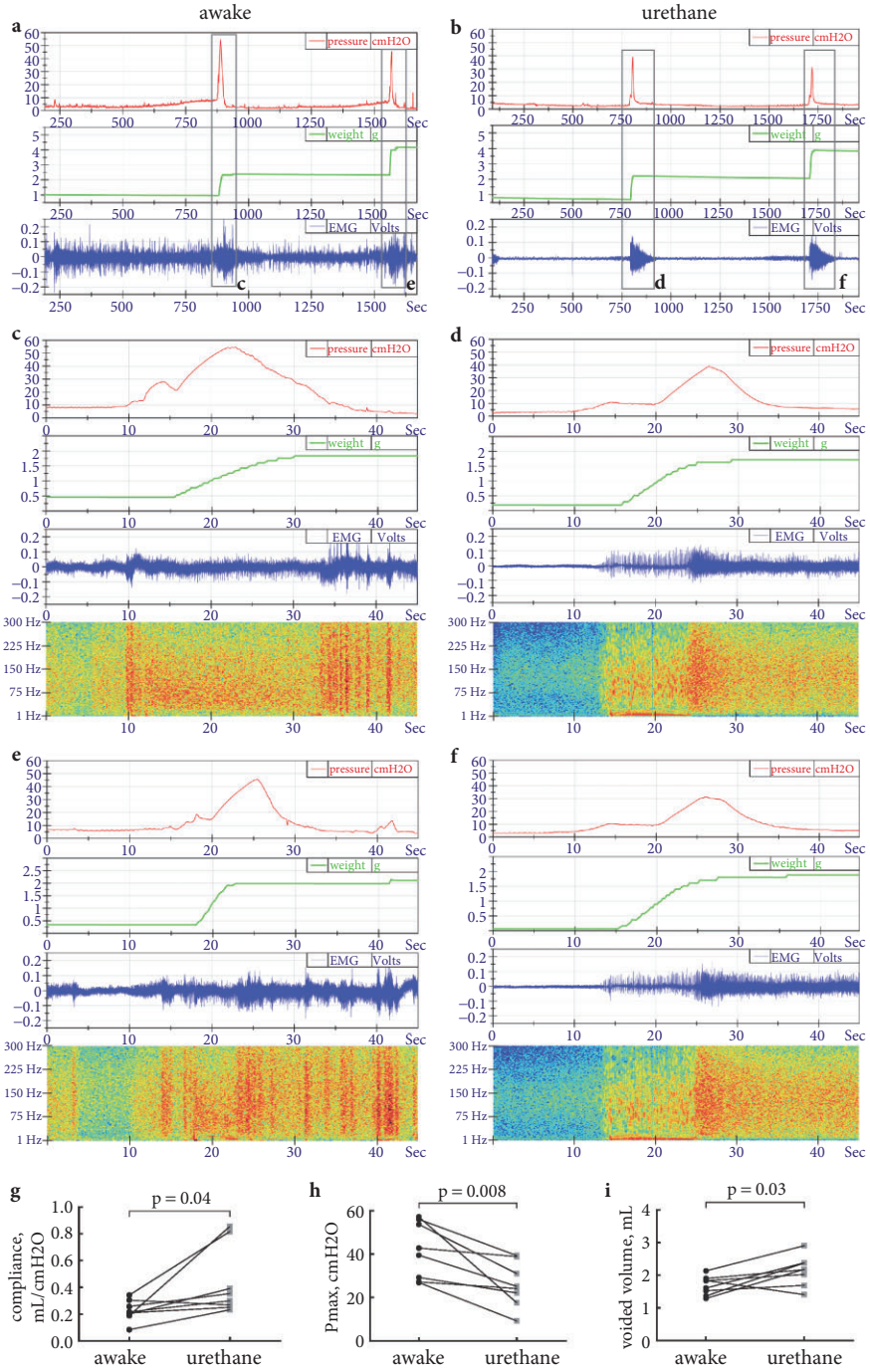
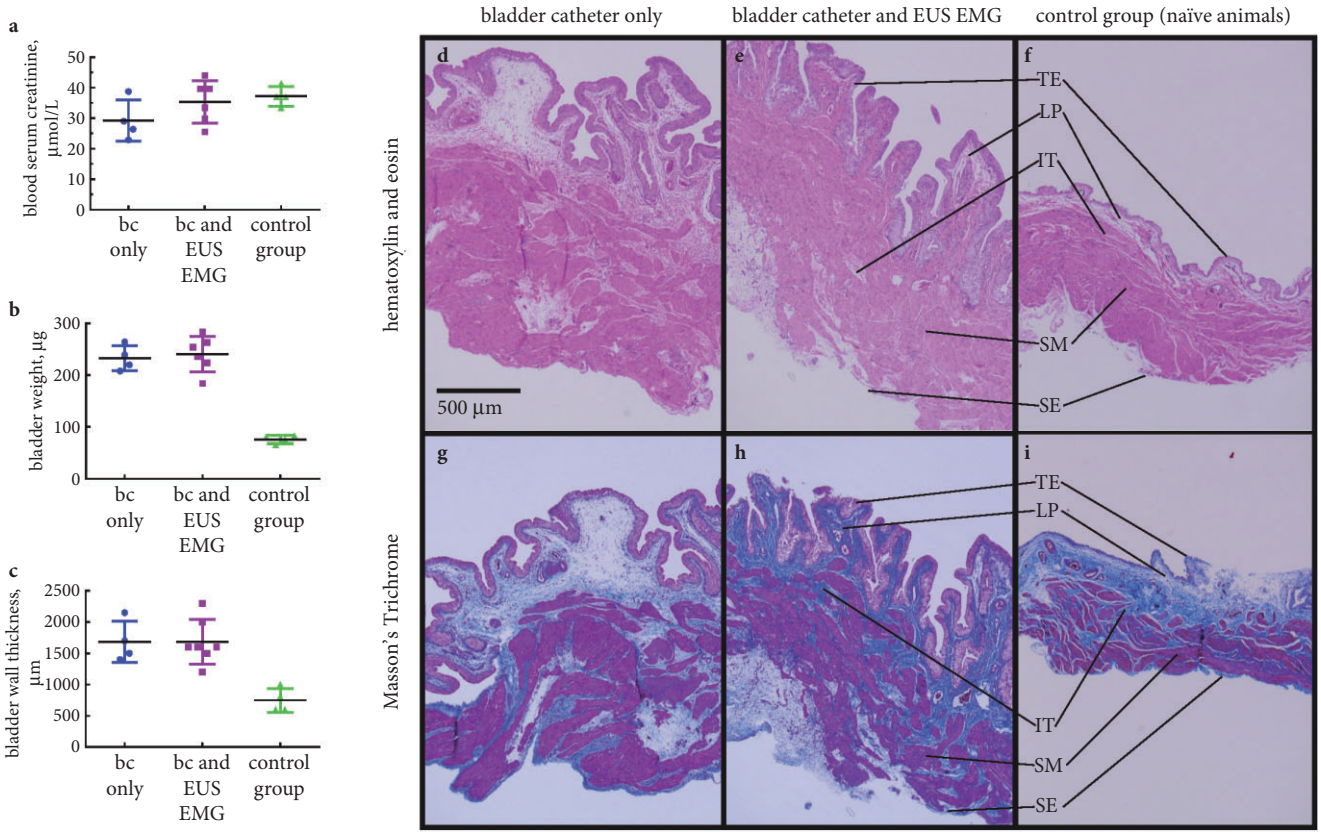


Fig. 3 (**a**) 1500-s window of **a** representative urodynamic tracing with two voiding cycles (**c** and **e**) in an awake rat. Top panel is the pressure tracing, middle panel the scale tracing showing the secreted urine and the bottom panel the EUS EMG tracing (**b**) 1875-s window of a representative urodynamic tracing with two voiding cycles (**d** and **f**) of the same but urethane anaesthetised rat. Top panel is the pressure tracing, middle panel the scale tracing and the bottom panel the EUS EMG tracing. (**c/e**) 45-s zoomed window from **a** showing urodynamic tracings with time matched frequency spectrograms (bottom panel) of the EUS EMG tracing. Red stands for high amplitude of the specific frequency at this time point, deep blue for low amplitude. Shortly before voiding a band of 4–12 Hz burst simultaneous with a second band of 30–300 Hz bursting is most prominent. During the voiding the 30–300 Hz bursting is less prominent (in five out of five rats). At the end of voiding the 4–12 Hz slow bursting disappears and the 30–300 Hz bursting gets very prominent for 5–10 s. (**d/f**) 45-s zoomed window from **b** showing urodynamic tracings with time matched frequency spectrograms (bottom panel) of the EUS EMG tracing. Red stands for high amplitude of the specific frequency at this time point, deep blue for low amplitude. Before voiding there is only very little bursting in any frequency. During the voiding the 4–12 Hz slow-wave bursting is very prominent (in five out of five rats). At the end of voiding the 4–12 Hz slow bursting disappears and the 30–300 Hz bursting gets very prominent for 5–10 s. (**g**) Bladder compliance of the individual rats in the awake vs the urethane anaesthetised state (eight rats, $P = 0.04$). (**h**) Maximum voiding pressure (Pmax) of the individual animals in the awake compared to the urethane anaesthetised state (eight rats, $P = 0.008$). (**i**) Voided volume of the individual rats in the awake vs the urethane anaesthetised state (eight rats, $P = 0.03$).

It is described in literature, based on urethane anaesthetised measurements, that the slow-wave bursting, the most prominent pattern during voiding, facilitates a sufficient urination [10]. Leung et al. [14] generally supported this opinion in a series of experiments using restrained, awake rats tested shortly after the implantation of the bladder catheter and EUS EMG electrodes. However, their model is hampered by the fact that measurements were performed immediately after surgery where postoperative pain and the anaesthetics used for the implantation surgery are likely to have affected bladder function. Additional, as mentioned by Andersson et al. [2], the implantation causes acutely smaller voiding volumes that corresponds with a frequency symptomatic that normalises after some days. In contrast, LaPallo et al. [15] assessed EUS EMG activity over time in unrestrained awake rats and did not detect EUS slow-wave bursting activity during voiding in ≈25% of the rats. Correlation of those studies with the present one is difficult since LaPallo et al. [15] did not

Fig. 4 (**a**) Blood serum creatinine levels in rats with bladder catheter only (**bc only**), combined bladder catheter and EUS EMG electrodes (**bc and EUS EMG**), **or** in control (naïve) rats (**control group**). (**b**) Bladder weights of the same groups depicted in a. (**c**) Bladder wall thickness of the same groups depicted in a. (**d/e/f**) Histological sections of bladders obtained from the same groups depicted in a and stained with H&E showing muscular hypertrophy, urothelial hyperplasia and increased oedema between the mucosal layer and the detrusor in the experimental groups as compared with the controls. (**g/h/i**) Histological sections of bladders dissected from the same groups depicted in a and stained with Masson's trichrome showing a proportional increase in collagen without increased fibrosis in the experimental groups as compared with the controls. TE, transitional epithelium; LP, lamina propria; IT, interstitial connective tissue; SM, smooth muscle bundles; SE, serosa.



assess bladder function with simultaneous intravesical pressure measurement. It is possible that the 25% of rats that did not display slow-wave bursting had LUTD. Moreover, there were significant differences in the electrode implantation techniques used in our present study vs that of LaPallo et al. [15]. In the LaPallo et al. [15] study, the EUS EMG electrodes were affixed intra-abdominally to the pelvic bone, whereas in the present study we have used an extra-abdominal pelvic approach and affixed the electrodes to the fat tissue beside the EUS (Fig. 1c and Supplement 2). These alternative approaches may contribute to the differences between the two studies.

Urethane is described by Hara and Harris [16] as having no single predominant target channel but rather affecting multiple channels simultaneously, suggesting that neurotransmitter systems in the CNS might also be affected. Thus, careful use of urethane as an anaesthetic for any neurophysiological measurements is highly warranted.

The pre-micturition high-frequency burst detected in our awake rats was almost identical to the post-micturition burst. Interestingly, Kakizaki et al. [11] also observed similar high-frequency bursting after induced reflex bladder contractions. One possible explanation for this phenomenon is that the pre-micturition burst might be due to an EUS contraction induced by the guarding reflex just before voiding begins. Under urethane anaesthesia this pre-micturition burst disappeared in our present study, similar to other published reports [10,17]. This result highlights the significant influence urethane exerts on lower urinary tract function.

One major issue in urodynamics in rats is the high inter-animal variability. As urodynamic assessment under urethane anaesthesia necessitates killing after investigation, many rats are needed per group to detect significant differences. Our novel urodynamic model allows for repetitive measurements at different time points in the same awake rat. Testing an animal before and after treatment allows that animal to serve as its own control and allows assessment relative to that animal's individual baseline. This eliminates the problems associated with inter-animal variability and

dramatically reduces the number of animals needed to detect significant changes, ultimately reducing experimental time, costs, and resources without compromising statistical quality.

The evidence is clear that anaesthetics affect bladder function, as shown by others [5–7] and the present study. Consequently, animal models that use anaesthetics are problematic and the translational value of the findings is questionable. Consistent with the International Continence Society Guidelines on Urodynamic Equipment Performance in humans [8], it is suggested that all urodynamic assessments in animal models be performed in an awake state to avoid major bias by narcotics.

A high-pressure system puts at risk the upper urinary tract. In humans, intravesical pressures that spike to >40 cmH_2O during the storage phase are generally agreed to jeopardise renal function, so that an appropriate treatment is needed [18]. Thus, the high spikes in pressure caused by detrusor overactivity and DSD can cause significant kidney damage and accurate diagnosis in humans requires measurement of both detrusor and urethral sphincter function [1]. Our present model allows for simultaneous detrusor and EUS assessment in awake rats for the first time and thus promises to be a very useful tool for future translational research on detrusor overactivity and DSD specifically, and LUTD in general. The absence of urethane narcosis is critical for these future studies as anaesthesia dampens pressure spikes. The risk that detrusor overactivity/DSD are not recognised under urethane anaesthesia is high and the effectiveness of a tested treatment may be underestimated.

The main limitation of the present study is the small number of rats investigated. However, our findings are well in line with the literature and our model combines for the first time bladder and EUS assessment in awake rats. Another limitation is that histology showed urothelial hyperplasia and detrusor hypertrophy in both the bladder catheter only, as well as the combined bladder catheter and EUS EMG electrode implanted rats. However, there was no increase in collagen content, suggesting that bladder catheter implantation did not cause bladder fibrosis. The implantation-induced tissue alterations need to be considered when bladder-specific processes are assessed. In humans, combined pelvic floor EMG and videocystourethrography (VCUG) during urodynamic investigation are the most acceptable and widely agreed methods for diagnosis of DSD [19], especially considering that both detrusor internal and external sphincter dyssynergia can be investigated. VCUG is not yet available in rats but we are working on some additional improvements and in the optimal case a video-urodynamic assessment could be established. Thus, detrusor internal sphincter dyssynergia (bladder neck dyssynergia) is currently not evaluated in our rat model. So far, EUS EMG signals were only analysed semi-quantitatively, this is according to urodynamic investigations in humans. However, software for quantitative assessments is under development.

In conclusion, our novel urodynamic model allows repetitive measurements of both bladder and EUS function at different time points in the same rat under fully awake conditions and opens promising avenues to investigate LUTD in a translational approach. In future studies, we will use this model to investigate major neurological diseases causing LUTD such as spinal cord injury [20], multiple sclerosis [21] and stroke [22], where we expect it to provide better understanding of the underlying mechanisms involved. In addition, our model can be used to assess new causal therapeutic options for these diseases.

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Conflicts of Interest

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All other authors have nothing to disclose.

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Abbreviations: DSD, detrusor–sphincter dyssynergia; EMG, electromyography; EUS, external urethral sphincter; H&E, haematoxylin and eosin; LUTD, lower urinary tract dysfunction; VCUG, videocystourethrography.

Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

Supplement 1 Methods.
Supplement 2 Video of catheter and electrodes implantation.

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Comment

Anti-Nogo-A antibody: a treatment option for neurogenic lower urinary tract dysfunction?

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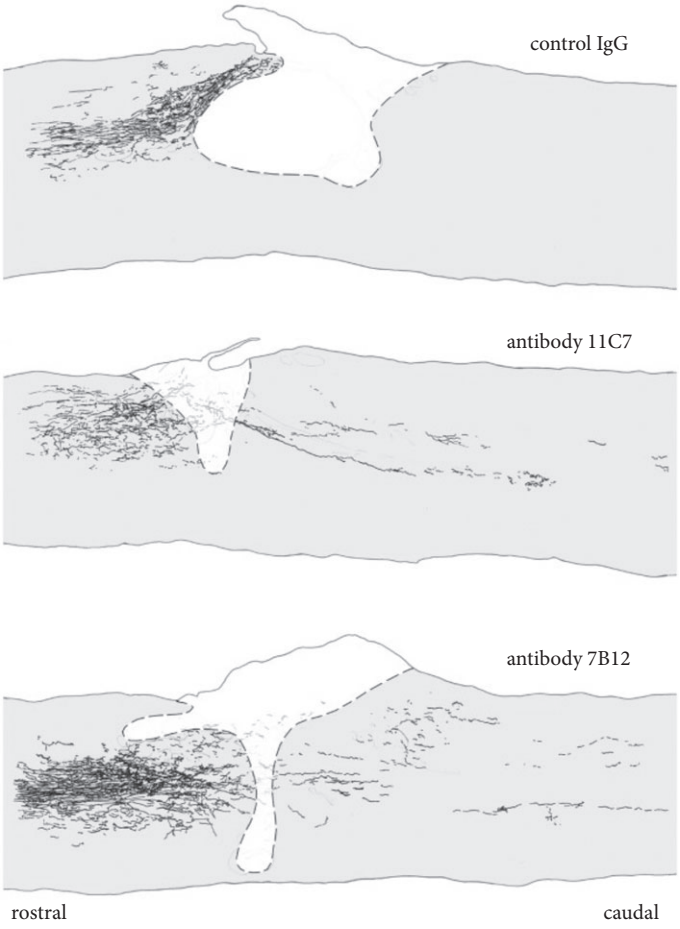
In the late 1980s, Caroni and Schwab [1] showed that the myelin membrane of oligodendrocytes inhibited nerve fibre growth in the CNS. A monoclonal IgM antibody against an unknown CNS myelin protein later known as Nogo-A induced substantial axonal sprouting and functional recovery *in vitro* and *in vivo*. Nowadays, the responsible neurite growth inhibitory surface protein, Nogo-A, and its receptors NgR1 and S1PR2 have been identified and well-studied [2,3]. Nogo-A destabilises the cytoskeleton via the rho/rho-associated protein kinase (ROCK) pathway causing growth cone collapse and inhibiting neuronal growth and plasticity by down-regulation of growth-associated genes. Nogo-A suppression or neutralisation leads to an increase in sprouting, axonal regeneration and neuronal plasticity and thereby to greater functional recovery after different types of CNS injuries.

In close collaboration with Novartis, a function blocking, high affinity human anti-human Nogo-A antibody (ATI355) was developed for intrathecal application. A clinical phase I study using this anti-Nogo-A antibody in patients with acute, severe spinal cord injury (SCI) was conducted by Novartis in several SCI centres in Europe and Canada. This phase I safety study has recently been completed successfully (http://clinicaltrials.gov/show/NCT00406016) and a placebo-controlled phase II 'proof-of-concept study' is in preparation. In addition, based on very promising findings in animal studies [2,4], trials assessing the effect of anti-Nogo-A in acute stroke and in amyotrophic lateral sclerosis (conducted by GlaxoSmithKline) are in preparation or on-going [5]. Importantly, anti-Nogo-A antibody treatment might also become an effective therapeutic option for neurogenic lower urinary tract dysfunction (NLUTD). Liebscher et al. [6] have found a significantly higher rate of corticospinal tract sprouting and regeneration after transection in adult rats when they were treated with function blocking antibodies against the neurite growth inhibitory protein Nogo-A as compared with control antibody treated rats (Fig. 1). The treated rats had significantly higher scores for various sensory-motor tests and showed improved recovery of locomotion and motor coordination. During the first 10 days

Fig. 1 Spinal cord injured rats were treated with two different IgG anti-Nogo-A antibodies (11C7 and 7B12). Reconstructions of the spinal hemicord with labelled corticospinal tract (CST), lesion site (light area), rostral (left side) sprouting zone, and CST fibres regenerating over tissue bridges (grey-shaded depiction) into the caudal spinal cord (right side). In both anti-Nogo-A antibody treated groups (11C7 and 7B12) were substantially more CST fibres regenerating (dark fibres on the right side of the lesion) compared with control IgG antibody treated rats. The anti-Nogo-A antibody treated rats had higher scores in sensory-motor tests and showed improved recovery of independent bladder voiding, locomotion and motor coordination. From Liebscher et al. [6] with permission.



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after SCI, the rats were not able to void and their bladders had to be emptied manually two to three times a day. In the control antibody treated group, voiding started to recover on average ≈24 days after SCI. Remarkably, voiding was restored >1 week earlier in the anti-Nogo-A antibody treated rats [6].

Suppression of Nogo-A or its receptor NgR1 enhances neurite growth in the adult CNS [2,7]. In the injured CNS, regenerative and compensatory sprouting as well as long distance regeneration of fibres in many parts of the spinal cord and brain are enhanced by functional blockade of Nogo-A signalling [2]. These processes probably lead to new connections and functional circuits, for example from the pontine micturition centre to the sacral micturition neurons, directly or via long proprio-spinal interneurones. In addition, anti-Nogo-A antibodies could induce plasticity in the circuits of the pontine and sacral micturition centres causing reorganisation.

To elucidate the mechanisms of action and the potential of anti-Nogo-A antibody therapy for treating NLUTD, animal studies with detailed urodynamic measurements in different neuronal disease models causing NLUTD are currently ongoing. In addition, urodynamic investigations are planned to assess lower urinary tract function in the coming clinical studies. Future animal and human studies will show if anti-Nogo-A antibody treatment has the potential to improve our management of NLUTD.

Conflicts of Interest

None disclosed.

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Abbreviation: NLUTD, neurogenic lower urinary tract dysfunction.

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Sensory evoked potentials of the bladder and urethra in middle-aged women: the effect of age

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F.G. and S.C.K. equal study contribution, i.e. shared first authorship

Objectives

To investigate feasibility, reproducibility and age dependency of sensory evoked cortical potentials (SEPs) after electrical stimulation of different locations in the lower urinary tract (LUT) in a cohort of middle-aged healthy women.

Subjects and Methods

In a group of 10 healthy middle-aged women [mean (SD) height 165 (5) cm and age 43 (6) years), electrical stimulation (0.5 and 3 Hz) was applied to the bladder dome, trigone, and proximal and distal urethra. SEPs were recorded at the Cz electrode with reference to Fz. All measurements were repeated three times with an interval of 3–5 weeks. Current perception thresholds (CPT), SEP latencies and amplitudes were analysed. Results were compared with a group of younger women published previously.

Results

LUT SEPs demonstrated two positive (P1, P2) and one negative peak (N1). The mean (SD) N1 latency was 108.9 (7.8), 116.2 (10.7), 113.2 (13.4) and 131.3 (35.6) ms for the bladder dome, trigone, proximal and distal urethra, respectively. N1 latencies, except for the distal urethra, were significantly shorter than those in younger women. Taking all data, i.e. young and middle-aged women, into account, there was a significant negative correlation between the variable age and CPT/dome ($r = -0.462$, $P = 0.04$) and N1 latency/dome ($r = -0.605$, $P = 0.005$) and a significant positive correlation between the variable age and N1P2 amplitude/dome ($r = 0.542$, $P = 0.014$).

Conclusion

LUT SEPs can be induced in middle-aged women with reliable N1 responses. Unexpectedly, N1 responses reveal a shortening with increasing age particularly when compared with younger women. Changes in sensory afferents may be explained by age-related qualitative reorganisations within the urothelium and suburothelium potentially altering afferent nerve excitability, which may have an impact on the development of non-neurological LUT symptoms (LUTS, e.g. overactive bladder) in women.

Keywords

sensory evoked potentials, lower urinary tract, bladder wall, current perception threshold, afferent nerve fibres, age

Introduction

LUTS, e.g. urinary urgency, frequency, and incontinence, have great impact on the health-related quality of life, including impairments in sexuality, emotional well-being and productivity at home and at work [1,2]. The estimated worldwide prevalence of LUTS is high, with 45% having at least one LUTS [3]. Consequently, there is an enormous economic burden for every healthcare system [4,5].

A large proportion of LUTS [i.e. overactive bladder (OAB) symptoms] affects the storage phase and is attributed to aberrant sensory function of the lower urinary tract (LUT) [1,3,6,7]. However, in many cases the exact causes of the aberrant LUT sensory function and the pathological mechanisms responsible for LUTS are unknown, which might be partly due to a lack of accurate and specific diagnostic tools. There is currently no objective and reliable clinical assessment tool of human bladder and urethral afferent nerve function and integrity available. Such an assessment tool would enable a greater understanding of the role of sensory nerves in LUTS (i.e. OAB).

Sensory evoked potentials (SEPs) after electrical, visual or auditory stimulation are a well-established and a daily used method to assess afferent nerve fibre function in humans. Stimulation of a certain nerve or dermatome with electric current is typically followed by an evoked potential, which can be measured along the spinal cord or on the cortex. Latency and amplitude of those potentials give information about the afferent nerve fibre function and is part of the

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neurophysiological armamentarium in the diagnosis of various neurological diseases [8]. Just recently, it has been shown that LUT SEPs can be reliably recorded after stimulation of the bladder dome, trigone, proximal and distal urethra in young healthy women [9].

However, LUT SEPs have not yet been precisely evaluated in healthy subjects of different age groups. This is of relevance when using such methods in diagnostics of LUTS, as the incidence of LUTS significantly increases with age [10,11]. With an increasing ageing population, LUTS will become even more prevalent [3]. Thus it will become particular important to have a better understanding of the underlying pathological mechanism that will allow to develop improved treatment strategies.

The aims of the present study were: i) to investigate the feasibility and reproducibility of SEP recording after electrical stimulation of different locations in the LUT in a cohort of middle-aged healthy women and ii) to explore any effect of age on LUT SEPs.

Subjects and Methods

Subjects

A group of healthy middle-aged female volunteers was recruited. Inclusion criteria were good mental and physical health, written informed consent, and age of ≥35 years. Exclusion criteria were any neurological or urological diseases, any gynaecological and urological operations (except caesarean section), current pregnancy or lactation, urinary tract infections, and any regular medication intake (except contraceptive medication). Inclusion and exclusion criteria were assessed by taking a full medical history, physical examination, urine analysis and a 3-day bladder diary using a day-time urinary frequency of >8, a night-time urinary frequency >1, episodes of urinary incontinence or urgency ≥1, as threshold values.

The experiment was approved by the local Ethics Committee (Kantonale Ethikkommission Zürich) and was conducted in accordance with the Declaration of Helsinki. This study was registered at cliniacltrials.gov (No. NCT01389921).

Electrical Stimulation

Cycles of bipolar square wave electrical stimulation 0.5 Hz/1.0 ms and 3 Hz/0.2 ms were applied to the bladder dome, trigone, proximal and distal urethra as previously described [9] using a special 8-F transurethral catheter (Unisensor AG, Attikon, Switzerland) (Fig. 1). To ensure a constant bladder volume during each stimulation, a 10-F catheter was introduced transurethrally and was left *in situ* to drain and refill the bladder before each single stimulation cycle. The bladder was gradually filled with 60 mL contrast medium (Ultravist 150™, Bayer AG, Switzerland) at room temperature (37 °C).

The catheter was placed under fluoroscopic control to ensure an exact and reproducible catheter position (Fig. 1). The sequence of LUT stimulation sites was randomised between either (1) bladder dome – trigone – proximal urethra – distal urethra or (2) distal urethra – proximal urethra – trigone – bladder dome. The electrical current for stimulation was generated using a Dantec Keypoint® 4 m (Neurolite AG, Belp, Switzerland). During electrical LUT stimulation subjects were supine and had their eyes closed.

Current perception thresholds (CPTs) were identified using the method of limits [12]. For the LUT SEPs, stimulation intensities were increased aiming at two- to three-fold of the CPT. All measurements were repeated three times at an interval of 3–5 weeks.

SEPs

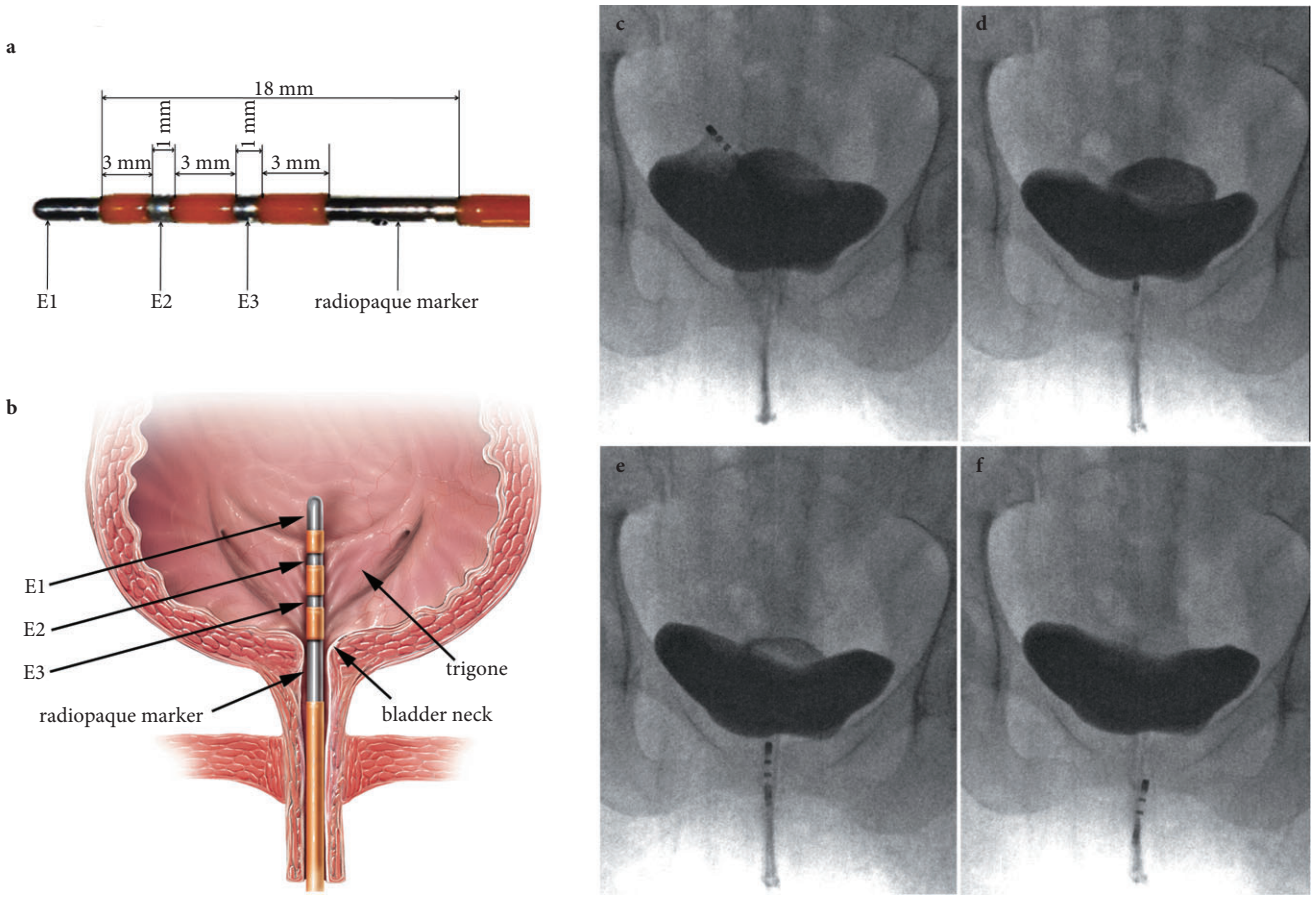
Three cortical electrodes were placed according to the international 10/20 electrode system [13] using an electroencephalogram cap (EasyCap, EasyCap GmbH, Germany) with the Cz electrode referenced to Fz. The ground electrode was placed at AFz position. SEPs were recorded with a sampling frequency of 500 Hz (0.5 Hz stimulation) and 5000 Hz (3 Hz stimulation), respectively, using BrainVision Recorder (BrainProducts, Munich, Germany).

The impedance level was kept below 20 kΩ at all electrodes. All data were, in addition to a 50 Hz Notch filter, filtered offline from 0.5 to 30 Hz for the 0.5 Hz/1.0 ms stimulation and from 0.5 to 70 Hz for the 3 Hz/0.2 ms stimulation using BrainVision Analyzer2 (BrainProducts, Munich, Germany). Subsequently, the filtered signal was segmented from −100 to +1000 ms for the 0.5 Hz stimulation and −50 to +200 ms for the 3 Hz stimulation. The segments of each measurement were averaged and the N1 latencies of the SEPs and the N1P2 peak-to-peak amplitude were determined semi-automatically using BrainVision Analyzer2.

Statistics

IBM® SPSS® Statistics 19 for Windows (IBM Chicago, Illinois, USA) was used to perform the following analysis: i) ANOVA to compare the latencies and amplitudes of the four stimulation sites of the LUT, ii) *t*-tests to compare the current results with the previous results in a younger subject group [9], iii) Correlations were calculated with Pearson's correlation coefficient between the variables age and LUT CPTs, age and LUT SEP latencies, and age and LUT SEP amplitudes using the data from all 20 subjects, i.e. both the young [9] and middle-aged group, and iv) Intraclass correlation coefficient (ICC) to test the reliability of SEP latencies, and SEP amplitudes. The alpha level used as a significance criterion for the statistical tests was 0.05. All values are given as mean (standard deviation, SD).

Fig. 1 Display of custom-made 8-F stimulation catheter. The catheter has three platinum stimulation electrodes E1–E3, each 1-mm wide, and a radiopaque marker 7-mm wide for precise positioning under fluoroscopic guidance. (**a**) Connecting pieces (orange areas) between electrodes are each 3-mm wide. Bipolar stimulation was applied at the bladder dome using E1 and E2, and at the trigone, and the proximal and distal urethra using E2 and E3. Schematic display of custom-made 8-F catheter in position for trigonal stimulation in the female LUT (**b**) Fluoroscopic images of catheter positioning at bladder dome (**c**), trigone (**d**), proximal urethra (**e**) and distal urethra (**f**). Adequate positioning and contact of electrodes to the bladder wall at the bladder dome was ensured by using the tip electrode (E1) and first ring electrode (E2) on the catheter for bipolar stimulation and by placing the catheter under fluoroscopic guidance to the dome, so that a slight uplift of the bladder dome area where the catheter was placed became visible. (**c**) For reliable placement of electrodes for trigonal stimulation, the upper margin of the radiopaque marker below the used ring electrodes E2 and E3 was always placed at the rim of contrast medium at the bladder neck (**b**, **d**). Stimulations were always performed at a bladder volume of 60 mL.



Results

Subjects

In all, 10 healthy women with a mean (SD) age of 43 (6) years, a mean (SD) body weight of 62 (11) kg, and a mean body height of 165 (5) cm were included. Three women had given birth to one or more children, one had an abortion and one was postmenopausal. All the women tolerated the investigations well. With exception of transient mild dysuria (burning sensation during micturition) after the investigation, no adverse events were reported or observed.

CPTs

The CPTs after 0.5 Hz/1 ms and 3 Hz/0.2 ms electrical stimulation are listed in Table 1. Stimulation with 0.5 Hz/1 ms resulted in generally lower CPTs than with 3 Hz/0.2 ms stimulation at all four LUT locations (Table 1).

CPTs at the bladder dome were significantly higher compared with the trigone ($P = 0.047$), proximal urethra ($P = 0.001$), and distal urethra ($P = 0.043$) using 0.5 Hz/1 ms stimulation and also compared with the proximal ($P < 0.001$) and distal urethra ($P = 0.041$) using 3 Hz/0.2 ms stimulation.

Compared with the group of younger women [9], the group of middle-aged women had significantly higher CPTs at the distal urethra using both, 0.5 Hz/1 ms and 3 Hz/0.2 ms stimulation but significantly lower CPTs at the bladder dome using 0.5 Hz/1 ms (Table 1).

SEPs

Using 0.5 Hz/1 ms, stable SEPs were cortically recorded after stimulation at the bladder dome, trigone, proximal urethra, and distal urethra (Fig. 2) in 26/30 (87%), 26/30 (87%), 27/30 (90%), and 25/30 (83%) measurements, respectively.

The mean (SD) N1 latency was 108.9 (7.8), 116.2 (10.7), 113.2 (13.4) and 131.3 (35.6) ms after stimulation of the bladder dome, trigone, proximal urethra, and distal urethra, respectively (Fig. 2, Table 2). Stimulation of the distal urethra resulted in a significantly longer ($P = 0.014$) N1 latency than stimulation of the bladder dome.

The mean (SD) N1P2 amplitude was 8.8 (4.2), 4.1 (1.2), 4.4 (1.7) and 4.1 (1.1) μV after stimulation of the bladder dome, trigone, proximal urethra, and distal urethra, respectively (Table 2). Stimulation of the bladder dome resulted in significantly higher N1P2 amplitudes ($P < 0.001$) compared with stimulation of the trigone, proximal urethra, or distal urethra.

Using 3 Hz/0.2 ms stimulation did not result in reliable SEPs.

Compared with the group of younger women [9], the N1 latencies of the middle-aged women were significantly shorter after stimulation of the bladder dome ($P < 0.001$), trigone ($P = 0.027$), and proximal urethra ($P = 0.015$) (Table 2). The N1P2 amplitude after bladder dome stimulation was significantly higher ($P = 0.041$) in the middle-aged women compared with the younger women (Table 2).

Table 1 CPT values acquired from different LUT sites at 0.5 and 3 Hz compared between a group of young (aged 20–35 years) and middle-aged (35–50 years) healthy women.

Stimulation site	Frequency, Hz	Group	Mean (SD) CPT, mA	*P*
Bladder dome	0.5	Young	7.64 (4.67)	0.009
		Middle-aged	5.12 (1.81)	
	3	Young	11.08 (7.90)	0.089
		Middle-aged	8.39 (3.15)	
Trigone	0.5	Young	1.76 (2.62)	0.094
		Middle-aged	2.72 (1.66)	
	3	Young	3.31 (3.39)	0.149
		Middle-aged	4.92 (4.99)	
Proximal urethra	0.5	Young	2.66 (3.46)	0.385
		Middle-aged	2.09 (0.67)	
	3	Young	3.70 (3.55)	0.884
		Middle-aged	3.60 (1.53)	
Distal urethra	0.5	Young	1.86 (1.32)	0.036
		Middle-aged	2.94 (2.36)	
	3	Young	3.49 (2.48)	0.041
		Middle-aged	4.99 (3.05)	

*t-test.

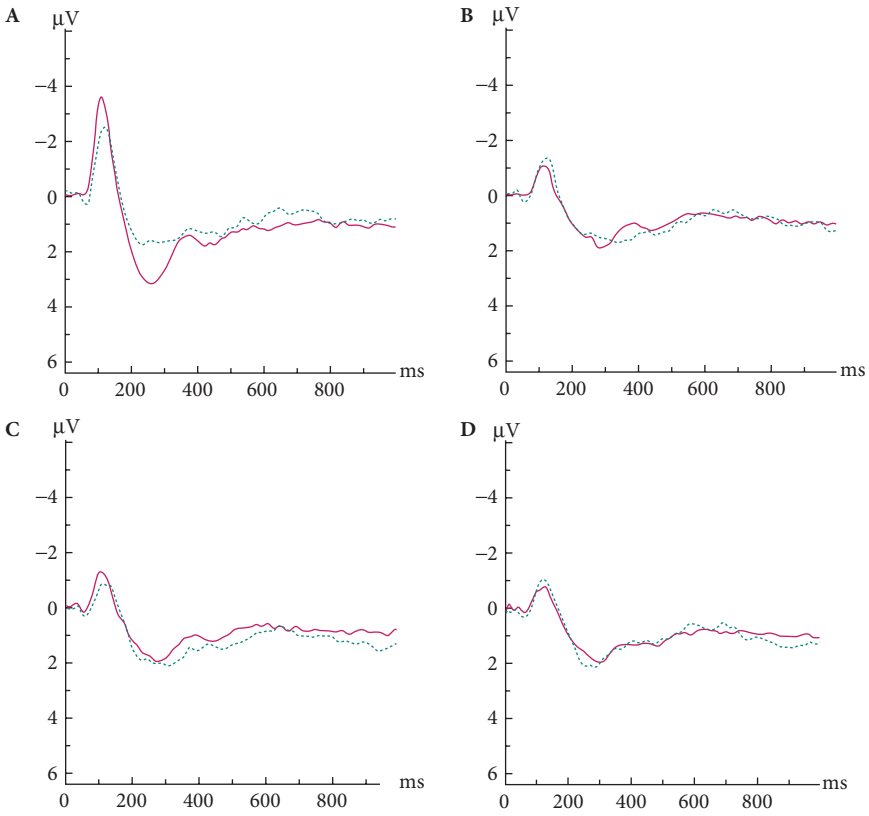


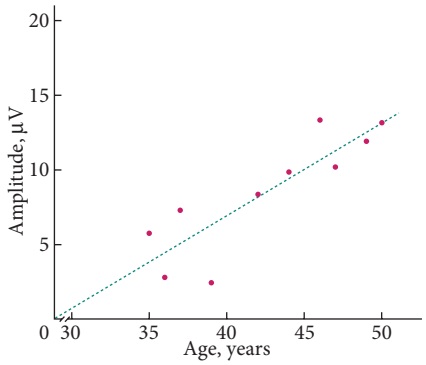
Fig. 2 Comparison of the evoked potentials after 0.5 Hz electrical stimulation of the bladder dome (**A**), trigone (**B**), proximal urethra (**C**) and distal urethra (**D**). Bold line, middle-aged women; dashed line, young women [9].

Table 2 Comparison of the N1 latency and the N1P2 amplitude between the group of young (20–35 years) and middle-aged (35–50 years) healthy women after electrical stimulation of the bladder dome, trigone, proximal and distal urethra.

	Mean (SD) N1 latency, ms			Mean (SD) N1P2 amplitude, μV		
Stimulation site	Young women	Middle-aged women	*P**	Young women	Middle-aged women	*P**
Bladder dome	122.0 (13.6)	108.9 (7.8)	<0.001	6.2 (4.7)	8.8 (4.2)	0.041
Trigone	124.5 (19.7)	116.2 (10.7)	0.027	4.8 (3.2)	4.1 (1.2)	0.216
Proximal urethra	123.3 (23.6)	113.2 (13.4)	0.015	5.6 (3.1)	4.4 (1.7)	0.166
Distal urethra	122.3 (20.5)	131.3 (35.6)	0.586	5.0 (2.9)	4.1 (1.1)	0.125

*t-*test.*

Fig. 3 Correlations between the variable age and N1P2 amplitude/dome ($r = 0.864$, $P = 0.001$) within the middle-aged cohort (10 women).



Correlations

There was a significant positive correlation between the variables age and N1P2 amplitude/dome ($r = 0.864$, $P = 0.001$) within the middle-age cohort (Fig. 3).

Considering both the young and middle-age cohort, there was in addition to the significant positive correlation between the variables age and N1P2 amplitude/dome ($r = 0.542$, $P = 0.014$) (Fig. 4c), there was also a significant negative correlation between the variables age and CPT/dome ($r = –0.462$, $P = 0.04$) (Fig. 4a) and between the variables age and N1 latency/dome ($r = –0.605$, $P = 0.005$) (Fig. 4b).

Reliability

The ICC of N1 latencies in the middle-aged cohort calculated from all three measurements was 0.27, 0.54, 0.66, and 0.27 after stimulation of the bladder dome, trigone, proximal and distal urethra, respectively.

Taking only the last two measurements (Visit 2 and 3) into account, the ICC of N1 latencies was 0.45, 0.71, 0.91, and 0.67 after stimulation of the bladder dome, trigone, proximal and distal urethra, respectively.

Discussion

The main findings of the present study are: 1) recording cortical SEPs after electrical 0.5 Hz/1 ms stimulation at the bladder dome and trigone, and proximal and distal urethra was reproducibly feasible in a cohort of middle-aged women, 2) the latencies from bladder dome, trigone, and proximal urethra were significantly shorter in the older women compared with the younger women, and 3) the bladder dome showed significantly higher amplitudes compared with the younger women.

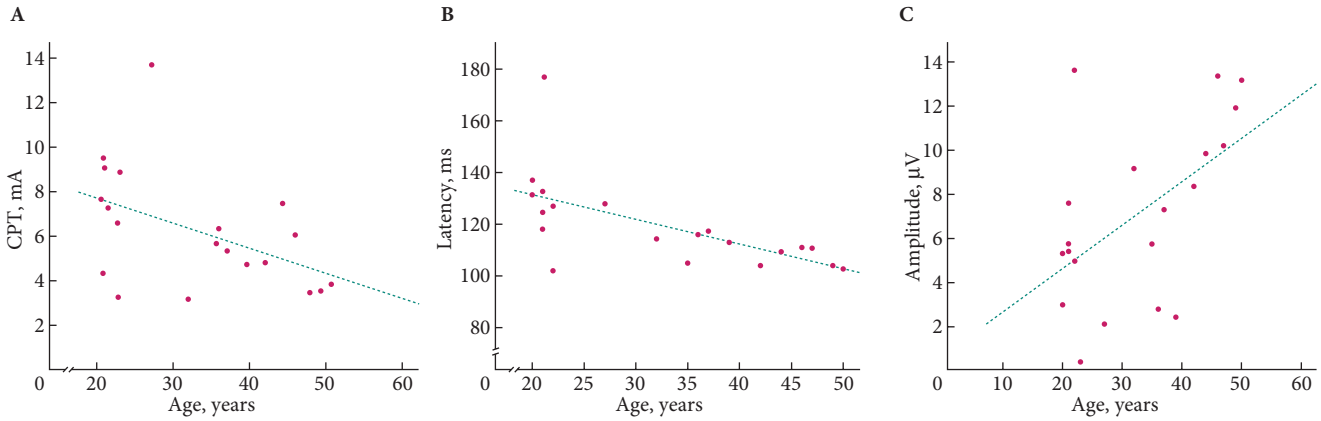
Similar to the previously investigated younger group of healthy women [9], in the present study we were also able to demonstrate the feasibility of cortical SEP recording after LUT electrical stimulation at four different sites in a group of middle-aged women. As demonstrated for the younger group, reliable LUT SEPs were only obtained with 0.5 Hz/1 ms but not when using 3 Hz/0.2 ms. Again, this lack of reliable SEPs using 3 Hz/0.2 ms stimulation could be explained by refractoriness or a lack of susceptibility of the available slow fibres, i.e. Aδ- and C-fibres, and/or the absence of faster conducting fibre populations, such as Aβ, as suggested in several animal studies [14].

Despite similarities between both groups there were also specific differences in CPTs, N1 latency, and N1P2 amplitude.

Consistent with Kenton et al. [15,16], CPTs of the distal urethra were significantly higher in the older women. Although the women in our present middle-aged group were not aged >50 years, such a CPT increase might indicate a first distinct urethral sensory loss correlating to previously reported age-related decline of pudendal innervation, i.e. reduced number and density of striated urethral sphincter nerve and muscle fibres [17,18] and reduced responsiveness to electrophysiological evaluation [19] with age.

Comparing the CPTs of the different LUT sites within both groups shows a similar pattern, with CPTs of the bladder dome being significantly higher than at all other sites. However, comparison between groups, revealed significantly lower CPTs of the bladder dome in middle-aged women, which seems to be in contrast to our results from the distal urethra and previous literature supporting the hypothesis that bladder and urethral hyposensitivity is associated with age and potentially causative for OAB [15,16].

Fig. 4 Correlations between the variable age and CPT/dome ($r = -0.462$, $P = 0.04$). (**A**), N1 latency/dome ($r = -0.605$, $P = 0.005$). (**B**), and N1P2 amplitude/dome ($r = 0.542$, $P = 0.014$). (**C**) using the data from all 20 women, i.e. both young [9] and middle-aged.



Unfortunately, recent published findings are based on studies that used very different designs, did not stimulate the bladder wall, or did not investigate a potential age effect, thus hampering a meaningful comparison with our present results. Not surprisingly there are conflicting results for bladder CPTs in patients with OAB, being reported to be lower [20] but also equal to controls without OAB [15,21]. However, the latter two studies [15,21] recorded CPTs at the trigonal or vesico-urethral junction but not at the bladder wall.

Age is the main risk factor for developing OAB, mainly characterised by urinary urgency and frequency, which both can be interpreted as hypersensitivity [20,22]. Assuming that our present findings are clearly an effect of age, we would rather expect decreasing bladder CPTs and SEP latencies with increasing age as seen in our group and consistent with the study by Lee et al. [20]. In this regard it is remarkable that not only the N1 latencies were significantly lower at the bladder dome, trigone and proximal urethra in the middle-aged group compared with the younger group but also that the N1P2 amplitude was significantly higher at the dome. Moreover, the N1P2 amplitude showed a significant positive correlation with age. Accumulating the data of all the women, i.e. young and middle-aged, correlation analysis showed that N1 latencies and CPTs recorded after stimulation at the bladder dome significantly decrease with age, whereas the N1P2 amplitudes after stimulation at the bladder dome significantly increase with age.

Beside possible involvement of changes in central pathways, the present finding further substantiates the hypothesis that age-related changes occur within the bladder wall and its associated afferent innervation, resulting in increased afferent excitability, which is in agreement with the findings of Daly et al. [23] in mice. Certainly, electrical stimulation of the bladder wall cannot readily be compared with distention of the bladder wall by continuous filling due to the different mechanism of each stimulus to elicit bladder afferent activity. While electrical current most probably directly approaches nerve terminals in the bladder wall causing afferent activity, gradual bladder distention seems to rather involve a cascade of receptor and neurotransmitter-related processes within the bladder wall [24]. Correspondingly, correlations between filling sensations and LUT CPTs have not yet been demonstrated [25,26].

Nevertheless, recent data from both animal and human studies provide evidence that the bladder urothelium closely interacts with the suburothelium and related afferent nerves [27–29]. Hence, age or disease-related changes at the urothelial and suburothelial level could alter afferent nerve excitability [11,28,29] and consequently also affect electrical sensory testing.

A potential example for such age-related urothelial and suburothelial changes could be an alteration of the coupling strength between cells, i.e. increase in density and distribution of connexins, that would influence the intensity and/or travel distance of the signal, i.e. electrical stimulation, within the newly formed syncytium, and consequently the number of afferent fibres stimulated [27]. Accordingly, afferent signal transduction is facilitated, resulting in increased SEP amplitudes and reduced latencies. However, this hypothesis requires further investigations combining electrophysiological with immunohistological assessments.

Whether the age-associated electrophysiological changes seen in our present study are truly involved in the development of OAB symptoms remains to be further elucidated, as most age-related changes of the LUT are individually regarded as not causing but potentially predisposing to OAB [30]. Moreover, not only local alterations in the LUT need to be considered but also age-related changes in supraspinal processing [31], which could have affected our present results. Consequently, different

causes of LUTS are possible, depending on the development of the most dominant predisposing factor(s) in relation to further pathological co-factors.

Interestingly, we observed lower reliability, i.e. ICC, values of the LUT SEP latencies in the middle-aged group compared with the younger group of women [9], especially for the dome and distal urethra. If such an effect on the reliability of latencies can be also attributed to an age-related cause remains questionable and the omission of the first of three measurements remarkably improved reliability values to at least fair but mainly good to excellent results. Thus, we would rather attribute this finding to the lower SEP response rate during visit 1, which is most probably related to a learning effect of the investigator team.

Although we present a feasible and objective approach to assess human bladder and urethral afferent nerve function, the small sample size limits our conclusions. However, we aimed to investigate middle-aged women as there is a lack of age-related data in women regarding LUT SEPs.

In conclusion, objective *in vivo* assessment of bladder afferent function in humans is still a challenge but is urgently needed to improve our understanding of the underlying, probably multifactorial, mechanisms and to tailor our treatment to the most dominant factors. Although LUT SEPs require further standardisation they offer the unique opportunity to investigate human LUT afferent function and thus help to improve our basic understanding.

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Trial Registration: http://www.clinicaltrial.gov; Identifier: NCT01389921

Conflict of Interest

The authors declare no conflicts of interest in preparing this article.

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Abbreviations: CPT, current perception thresholds; ICC, intraclass correlation coefficient; OAB, overactive bladder; SEP, sensory evoked potential.

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Comment

The Swiss Continence Foundation Award: promoting the next generation in neuro-urology and functional urology

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Introduction

Neuro-urology and functional urology are usually under-represented in the oncology dominated urological world. However, the prevalence of lower urinary tract symptoms (LUTS) is high and will increase further due to the increasing ageing population [1]. Also more and more neurological patients will require professional neuro-urological consultation and management due to the high prevalence and incidence of several neurological diseases with frequent and severe impairment of lower urinary tract (LUT) function.

LUT dysfunction not only impairs the quality of life of affected patients but also decreases productivity at home and work, resulting subsequently not only in the directly related costs of diagnosis and treatment but also in a significant economic burden for each society and healthcare system [2–4]. Hence, neuro-urology and functional urology are highly relevant medical specialties in great demand. Moreover, neuro-urology and functional urology are young, innovative, and highly dynamic disciplines bridging neurological, gynecological, gastroenterological, and urological aspects of diagnosis and management allowing a significant look beyond each medical specialty and thus offering many career options in the clinic and research or both.

Only in recent decades has it been progressively appreciated that the bladder is more than just a simple sack storing and releasing urine. The bladder wall is literally 'alive' comprising highly interactive layers communicating through a variety of receptors and neurotransmitters [5]. Also, we have learnt about the supraspinal network influencing LUT control and its alterations in disease or in response to interventions [6,7].

Despite such advances, many physiological and pathophysiological questions still remain unanswered. In addition, there is a limited choice of treatments and the existing treatments have resulted in only slight improvements. Hence, there is urgent need for more: More development and improvement of diagnostics and treatments, more basic understanding on the pathophysiology of LUT dysfunction, and, most importantly, more young clinicians and researchers taking care of patients and future research.

We need young appropriately trained and highly motivated clinicians and researchers to build the future of this speciality. Thus, it is our duty to support and encourage young talents in neuro-urology and functional urology, to retain them in the field, and to attract more to join.

The Swiss Continence Foundation Award (http://www.swisscontinencefoundation.ch) represents such support for young talents. It comes with prize money of CHF 10 000 and is awarded to the best of the candidates who have been invited from all incoming award applications to present their current work in neuro-urology and functional urology to an international expert jury and the auditorium of the International Neuro-Urology Meeting. This year, The Swiss Continence Foundation Award has been awarded for the second time during the International Neuro-Urology Meeting in Zürich, Switzerland (Figs 1,2)
and the prize-winning work of Véronique Phé entitled 'Foxp3 expression serves as a marker of squamous cell differentiation and aggressive pathology of urothelial carcinomas in neurological patients', is published in this *BJUI* supplement [8].

It was a great pleasure for all to have these young talents in the field among the more established experts, thereby providing them a platform for knowledge exchange, making new contacts, and career building.

We are delighted to announce next year's Award and encourage all young (age ≤35 years) clinicians and researchers but also all research group leaders and clinical programme directors working in the field of neuro-urology and functional urology to motivate their suitable candidates to

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Fig. 1 Assembly of the award jury and award candidates at The Swiss Continence Foundation Award ceremony 2014. The invited candidates presented their current work in neuro-urology and functional urology during the 3rd International Neuro-Urology Meeting, 28–30 August 2014 in Zürich, Switzerland. From left to right, back row: Thomas M. Kessler, Ulrich Mehnert, Gommert A. van Koeveringe, Emmanuel Chartier-Kastler, Helmut Madersbacher, Francisco Cruz, Véronique Phé, Claudius Füllhase, Bahareh Abtahi. Front row: Jetske van Breda, Katarina Tudor, Tom Macrelissen, Saladin H. M. Alloussi, Mohammad Rahnama'i.

Fig. 2 The Chairmen of The Swiss Continence Foundation together with the current Swiss Continence Foundation Award 2014 winner Véronique Phé and the very first award winner form last year, Claudius Füllhase. All Swiss Continence Award winners become members of the Swiss Continence Foundation Award Alumni Circle and will be invited to all future International Neuro-Urology Meetings as guests of honour. From left to right: Thomas M. Kessler, Véronique Phé, Claudius Füllhase, Ulrich Mehnert.

apply for The Swiss Continence Foundation Award 2015. Detailed application criteria are available at http://www.swisscontinencefoundation.ch.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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Forkhead box protein P3 (Foxp3) expression serves as an early chronic inflammation marker of squamous cell differentiation and aggressive pathology of urothelial carcinomas in neurological patients

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Objective

To establish whether the expression of forkhead box protein P3 (Foxp3) provides specific diagnostic information about neurological patients with urothelial carcinoma of the bladder (UCB).

Patients and Methods

UCB tissue samples from neurological patients were retrieved and compared with control samples. The expression of Foxp3 was analysed via immunohistochemistry of microarray tissue sections. The correlation between Foxp3 expression, histological parameters and tumour stage was assessed.

Results

Overall, 20 UCB tissue samples and 20 others without UCB from neurological patients, and 46 UCB tissue samples from non-neurological patients were analysed. The distribution of pT of UCB in the neurological patients was as follows: one low-grade pTa (5%), three high-grade pTa (15%), three pT1(15%), one pT2(5%), seven pT3(35%) and five pT4(25%). Squamous cell differentiation was seen in nine UCB samples (45%). Foxp3 expression was detected in tumour tissues, including one pTa high grade, one pT1, one pT2, five pT3 and five pT4 tumours. Foxp3 was expressed in 11/13 muscle-invasive tumours. All tumours displaying squamous cell differentiation expressed Foxp3. Foxp3 was not expressed in the pT3 tumours that displayed sarcomatoid and micropapillary properties. Among the bladder samples without UCB from neurological patients, no expression of Foxp3 was observed. Among the UCB samples from the non-neurological patients, only seven displayed squamous cell differentiation. All tumours that displayed squamous cell differentiation expressed Foxp3, including one pTa high grade, four pT3 and two pT4 tumours. Other tumours displaying urothelial differentiation did not express Foxp3. The expression of Foxp3 correlated to squamous cell differentiation in neurological ($P = 0.004$) and non-neurological UCB tissue ($P < 0.001$). In neurological, but not non-neurological UCB tissue, the expression of Foxp3 correlated with the muscle-invasive stage ($P = 0.022$).

Conclusions

Elevated expression of Foxp3 appears to be a characteristic of neurological patients presenting with aggressive UCB and squamous cell differentiation. Targeting Foxp3 may represent a novel strategy to improve anti-tumour immunotherapy for UCB.

Keywords

neurogenic, urothelial carcinoma, bladder cancer, squamous, inflammation

Introduction

Urothelial carcinoma of the bladder (UCB) represents the most common malignancy of the urinary tract. The estimated male : female ratio of UCB is 3:1 [1] and >90% of these malignancies are urothelial carcinomas. For patients with UCB, risk stratification is advocated to elaborate the appropriate management. In cases of non-muscle-invasive bladder cancer (NMIBC), a conservative approach combining transurethral resection of the bladder and intravesical instillation is considered. However, NMIBC recurs in 10–20% of cases and can even progress to a more advanced stage. In

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cases of muscle-invasive bladder cancer (MIBC), the natural history of the disease is much more aggressive, and the standard treatment is a radical cystectomy [2].

Patients with a neurogenic bladder also develop UCB. The frequency of UCB among these patients has been reported to be equivalent to that among the general population [3]. However, UCB in neurological patients displays specific histological properties due to bladder chronic inflammation. Indeed, unusual squamous or sarcomatoid cell differentiation of the tissue has been described in 19–52% of neurogenic UCB cases [4,5]. The natural history of squamous cell carcinomas (SCCs) is different from urothelial carcinomas. All current international guidelines on outcomes, treatment and follow-up are based only on urothelial carcinomas and not squamous cell carcinomas. Neurological patients represent a very specific subgroup for whom no specific recommendations exist. The life-expectancy of neurological patients is higher now and physicians have to face to the problems of an ageing population. So it is relevant to study selected markers of inflammation in this specific population who develop a specific type of UCB.

The molecular characteristics of SCC of the bladder have been studied, and the prognostic roles of different groups of biomarkers belonging to various cancer pathways, including inflammatory markers, cell cycle-related markers, and apoptotic markers, have been investigated [6]. Forkhead box protein P3 (Foxp3), has been identified as a specific marker of regulatory T-cells (Tregs) [7,8], which play an important role in the maintenance of immunological self-tolerance by suppressing immune responses against cancer. The hyper-accumulation of Tregs has been detected in oral SCCs where chronic inflammation essentially induced by smoking has been reported [9,10]. Furthermore their presence was correlated with reduced survival. The histological properties of SCCs in the bladder do not differ from those in the oral cavity. UCB carcinogenesis among neurological patients has never been investigated. As neurological patients often present UCB with a squamous differentiation and given that bladder chronic inflammation may induce this particular type of UCB, we hypothesised that a specific inflammatory pathway affecting UCB carcinogenesis and involving Tregs through Foxp3 might be involved. So the aim of the present study was to investigate the expression of Foxp3 in neurological patients with UCB.

Patients and Methods

Tissue Samples and Tissue Microarray (TMA) Construction

Non-muscle invasive and muscle-invasive UCB tissue samples from neurological patients were retrieved and compared with control samples after their written informed consent was provided. We started to prospectively collect bladder samples 10 years ago, as it is known that UBC develops after a long duration of neurological disease. For every UCB tissue sample from a neurological patient, two UCB tissue samples from a non-neurological patient of the same grade, stage and age were selected. Furthermore, bladder tissue samples without UCB from neurological patients undergoing cystectomy for refractory neurogenic detrusor overactivity were also retrieved. The collection and use of bladder tissue samples was performed following approval of the Local Ethics Committee and in accordance with all relevant laws, regulations, and codes of practice in France.

The original slides were reviewed by a senior uropathologist (E.C.) and were classified according to the WHO 2004 classification. The tumour stage (pT) was established according to the TNM 2009 Classification of Malignant Tumours [11]. A TMA was constructed using archived formalin-fixed paraffin-embedded bladder samples. Slides containing tumour and non-tumour tissue were selected and labelled with coloured ink. For each case, three cores of the tumour (0.6 cm in diameter) were transferred from the selected area to the recipient block. Serial 3-μm sections of the TMA block were generated and stained with haematoxylin-eosin to verify that the cores adequately represented the diagnostic areas.

Immunohistochemistry of the TMA Sections

Immunohistochemistry for Foxp3 was performed on the 3-μm TMA sections as described previously [12,13]. Antigen retrieval was performed by incubating the deparaffinised and rehydrated 3-μm tissue sections in buffer containing 10 mM Tris and 1 mM EDTA (pH 9.0) in a water bath at 97 °C for 30 min. Then, endogenous enzyme activity was blocked for 8 min using the enzyme blocker from the kit. Then, the sections were incubated with in a goat polyclonal anti-Foxp3 antibody (1/300, ref ab2481, Abcam, Cambridge, UK) for 60 min at room temperature, followed by the polymer/horseradish peroxidase reagent for 20 min. Brown staining was developed for 2 min using diaminobenzidine as the chromogen. Finally, the sections were lightly counterstained with Mayer's haematoxylin (Labonord, Templemars, France) and were mounted using aqueous medium (Glycergel, Dako). Samples from the thymus that were known to express each marker were used as positive controls; the negative control tissue was incubated in an irrelevant antibody.

Three high-power fields (×400) were selected from the tumour areas displaying lymphocytic inflammation. The expression of Foxp3 was analysed in the tumour and non-tumour tissue. According to the literature, Foxp3 staining was considered to be positive if its expression was nuclear [14].

Statistical Analysis

The correlation between the expression of Foxp3 and the differentiation status (squamous or non-squamous), and pT

Table 1 Histological characteristics and expression of Foxp3 in UCB tissue from neurogenic patients.

pT stage	Grade	Histological differentiation status	Expression of Foxp3
pTa	Low		Negative
pTa	High	Verrucous	Positive
pTa	High		Negative
pTa	High		Negative
pT1	High		Negative
pT1	High		Negative
pT1	High	Squamous	Positive
pT2	High	Squamous	Positive
pT3	High	Sarcomatoid	Negative
pT3b	High		Positive
pT3a	High	Squamous	Positive
pT3b	High		Positive
pT3	High	Squamous	Positive
pT3b	High	Squamous	Positive
pT3b	High	Micropapillary	Negative
pT4	High		Positive
pT4	High	Squamous	Positive
pT4	High	Squamous	Positive
pT4	High	Squamous	Positive
pT4	High	Squamous	Positive

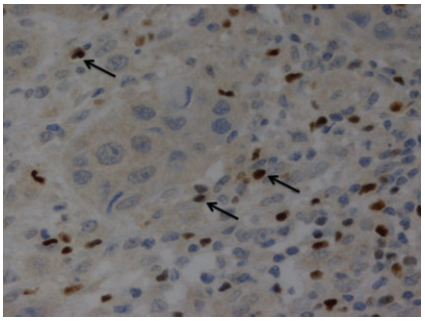
was determined via univariate analysis using Prism 6, GraphPad software. A $P < 0.05$ was considered to indicate statistical significance.

Results

Overall, 20 UCB tissue samples from neurological patients, 20 bladder tissue samples without UCB from neurological patients, and 46 UCB tissue samples from non-neurological patients were analysed. The neurological diseases were the following: 10 (50%) spinal cord injury, five spina bifida (25%), two multiple sclerosis (10%), two hereditary spastic paraplegia (10%) and one brain stroke (5%). Concerning the UCB from neurological patients, the distribution was as follows (Table 1): one low-grade pTa (5%), three high-grade pTa (15%), three pT1 (15%), one pT2 (5%), seven pT3 (35%) and five pT4 (25%). Squamous cell differentiation was seen in nine UCB samples (45%). Foxp3 expression was detected in one high-grade pTa, one pT1, one pT2, five pT3 and five pT4 tumours (Fig. 1). Foxp3 was only expressed in peritumoral lymphocytes. All tumours displaying squamous cell differentiation expressed Foxp3 (Fig. 1). The low-grade pTa tumour did not express Foxp3. In contrast, Foxp3 was expressed in 11/13 of the MIBC samples. The pT3 tumour samples lacking Foxp3 expression displayed micropapillary and sarcomatoid differentiation.

Foxp3 was never expressed in bladder from neurological patients without UCB. Overall, 46 UCB tumour tissues from non-neurological patients were analysed. Their distribution was as follows: three low-grade pTa (6.6%), eight high-grade pTa (17.4%), eight pT1 (17.4%), two pT2 (4.3%), 14 pT3 (30.4%) and 11 pT4 tumours (23.9%). All tumours displaying squamous cell differentiation expressed Foxp3, including one high-grade pTa, four pT3 and two pT4 tumours. The other tumours that displayed urothelial differentiation did not express Foxp3.

Fig. 1 UCB with a squamous differentiation from a neurological patient, numerous lymphocytes stained with Foxp3 (arrow) in the underlying lamina propria in contact with the urothelial carcinoma (haematoxylin and eosin × 400).



The expression of Foxp3 correlated with squamous cell differentiation in both neurogenic ($P = 0.004$) and non-neurogenic UCB ($P < 0.001$). In neurogenic, but not non-neurogenic, UCB, the expression of Foxp3 correlated with MIBC ($P = 0.022$).

Discussion

The development of UCB in neurological patients predominantly occurs after a long period of progression of their neuro-urological disease (frequently 15–20 years). The age of UCB at detection ranges from 48 to 71 years [5]. Therefore, UCB is more frequently diagnosed in young patients with neurogenic bladder than in the general population. However, this diagnosis is often established when UCB is locally advanced, and therefore, overall survival is low. Various risk factors, such as smoking, indwelling or supra-pubic catheterisation, chronic urinary tract infections and bladder stones, have been identified [5,15]. Consequently, a specific type of chronic inflammation appears to be involved in the development of UCB in this patient group. As inflammation is closely associated with the development of carcinoma, profiling the inflammatory expression patterns has come into focus.

UCB of patients with a neurogenic bladder often present with squamous cell differentiation [4]. In our present study, 45% of the UCB tumours displayed squamous cell differentiation; among these tumours, 71% were MIBC. These results are in accordance with previous studies that demonstrated that SCCs typically present with more advanced local stages [16]. Inflammation caused by chronic irritation appears to play a role in the development of this type of differentiation [15].

The present study investigated the expression of Foxp3 in UCB tissue from neurological patients for the first time. We found that all of the tumours from neurological patients and non- neurological patients displaying squamous cell differentiation expressed Foxp3 in peritumoral lymphocytes. Moreover, in neurological patients, the expression of Foxp3 significantly correlated with tumour aggressiveness (higher stage and higher grade). Consequently, specific inflammatory processes might affect carcinogenesis. So we proposed Foxp3 as an early chronic inflammation marker of squamous cell differentiation and aggressive pathology of UCBs in neurological patients.

Foxp3 has been identified as a specific marker of Tregs [7,8]. Tregs play an important role in the maintenance of immunological self-tolerance by suppressing immune responses against autoimmune diseases and cancer. Indeed, Tregs suppress the proliferation and function of effector T cells, and cancer cells may thereby escape the cytotoxic effects of effector T cells. Tregs are thought to act as key regulators of immunological self-tolerance [17]. The hyper-accumulation of Tregs has been detected in SCCs of other organs, e.g. the head and neck region [9,10], and has been correlated to pT stage and decreased survival [18]. The histological properties of SCCs in the bladder do not differ from those in the head and neck region. Another model of SCC is represented by carcinomas in the oral cavity; in this setting, the primary risk factor is chronic inflammation induced by smoking. An increased number of Foxp3-expressing Tregs in oral SCCs has been reported by Schwarz et al. [19], but given the few specimens, a significant correlation to pT stage could not be verified, contrary to our present report. In contrast, Schipmann et al. [20] reported that in oral SCC and in cutaneous SCC, the mRNA expression of Foxp3 was significantly higher than in normal skin. They suggested that SCCs recruited Tregs to their microenvironment, presumably to suppress immunosurveillance, thereby avoiding destruction by the immune system. Concerning cervical SCC, Loddenkemper et al. [21] showed that human papilloma virus-derived lesions contained a significantly higher number of infiltrating lymphocytes and Tregs expressing Foxp3 compared with three other common tumours. They suggested that the large number of Tregs in human papilloma virus-derived lesions enabled Tregs to counteract the host immune response.

A possible explanation for increased Foxp3 expression in SCCs is that the tumour cells secrete chemokines that attract Tregs expressing Foxp3 to migrate to the tumour [22,23]. An additional explanation for the increased number of Tregs in tumour tissue may be that locally produced proinflammatory cytokines can induce and expand Treg pools. Accumulating evidence indicates that Tregs expressing Foxp3 are recruited to human carcinomas and that their abundance may predict reduced survival [9,10,24]. The presence of Tregs has been suggested to explain the poor clinical efficacy of immunotherapeutic protocols for human tumours [25], and depleting these cells may improve anti-tumour immunity [26,27]. Tregs may represent a novel target for immunotherapy.

In the present study, the two cases of pT3 tumour tissue that did not express Foxp3 displayed sarcomatoid or micropapillary differentiation. Sarcomatoid properties in urothelial carcinomas comprise <1% of all UCB cases and affect patients with a mean age of 66 years [28]. Micropapillary carcinoma is known to be an aggressive type of UCB, which displays a high risk of metastatic disease, such as vascular invasion [29].

In conclusion, based on the present study, it appears that elevated expression of Foxp3 is a characteristic of neurological patients presenting with aggressive UCB and squamous cell differentiation. A Foxp3-mediated immunosuppressive profile appears to be displayed in tumour tissue from neurological patients presenting with aggressive UCB. Further studies will focus specifically on the clinical impact of the expression of Foxp3 in neurological patients with UBC. Because neurogenic bladder becomes a clinical problem at that age, it appears to be relevant to further investigate the long-term changes in the bladder.

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Conflicts of Interest

None disclosed.

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Abbreviations: Foxp3, forkhead box protein P3; (N)MIBC, (non-)muscle-invasive bladder cancer; SCC, squamous cell carcinoma; TMA, tissue microarray; Tregs, regulatory T-cells; UCB, urothelial carcinoma of the bladder.

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Neurogenic lower urinary tract dysfunction (NLUTD) in patients with spinal cord injury: long-term urodynamic findings

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Study registration number: NCT01293110

Objectives

To investigate long-term urodynamic findings in patients with spinal cord injury (SCI) with neurogenic lower urinary tract dysfunction (NLUTD).

Patients and Methods

A consecutive series of 246 patients with SCI (≥5 years since injury) and NLUTD were prospectively evaluated at a single university SCI centre. Data of the latest and earliest available urodynamic investigation were compared.

Results

Most of the patients had a thoracic SCI and American Spinal Injury Association (ASIA) impairment scale of A. The mean (SD) duration of SCI to the latest available urodynamic investigation was 17 (10) years and the mean patient age was 51 (14) years. At the earliest and latest available urodynamic investigation, more than half of the patients relied on intermittent self-catheterisation. During the course of disease, there was a relevant increase of patients undergoing onabotulinumtoxinA injections into the detrusor from 12% to 33%. Urodynamic findings at the earliest and latest available urodynamic investigation were within the safe limits and there were significant differences between both groups for maximum cystometric capacity ($P < 0.001$), compliance ($P < 0.001$) and maximum detrusor pressure during storage phase ($P = 0.008$). Vesico-uretero-renal reflux was detected in ≈5% and it was generally low grade.

Conclusions

Most of our regularly followed patients with NLUTD due to SCI for a mean of 17 years had urodynamic findings within the safe limits. Vesico-uretero-renal reflux was quite rare and generally low grade. Thus, regular follow-up with urodynamic investigation allowing for a patient-tailored management seems beneficial warranting randomised controlled longitudinal studies.

Keywords

neurogenic lower urinary tracts dysfunction, spinal cord injury, urodynamics, long-term findings

Introduction

Spinal cord injury (SCI) often causes neurogenic lower urinary tract dysfunction (NLUTD) [1]. Neuro-urological care aims to preserve or improve upper urinary tract function, control UTIs, and maintain a low-pressure bladder that is both continent and capable of emptying completely [2]. These goals are ideally achieved without an indwelling catheter or a stoma, and in a manner that is socially and vocationally acceptable to the patient avoiding complications, e.g. recurrent UTIs, urethral strictures, calculus disease, hydronephrosis, and renal failure [2]. In the past, renal disease was responsible for almost 50% of deaths in patients with SCIs [3]. Fortunately, this has changed dramatically. Today, urinary disease accounts for only ≈13% of deaths in patients with SCIs whereas pneumonia, influenza, non-urinary tract septicaemia, cancer, and ischaemic heart disease are more common causes of death [4,5]. The introduction of intermittent self-catheterisation (ISC) combined with antimuscarinic treatment and the use of regular urodynamic investigations has revolutionised the care of patients with SCI [6–8]. Thus, adequate function of the LUT is essential to prevent morbidity and mortality in patients with SCI, but publications investigating these patients in the long-term are scarce. We therefore assessed the long-term data of a strictly urodynamic-based treatment regime in patients with NLUTD due to SCI.

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Patients and Methods

From January 2010 to June 2014, a consecutive series of 246 patients with SCI (≥5 years since injury) with NLUTD were prospectively evaluated at the Spinal Cord Injury Center, Balgrist University Hospital, Zürich. Pregnant and breast feeding women and patients aged <18 years at latest evaluation were excluded. Data of the latest and earliest available urodynamic investigation were compared. The study was approved by the Local Ethics Committee, registered with ClinicalTrials.gov (study registration number: NCT01293110) and participants gave written informed consent. All methods, definitions, and units are according to the standards recommended by the ICS [9].

Neuro-urological evaluation consisted of medical history, clinical examination with determination of American Spinal Injury Association (ASIA) impairment scale [10], urine analysis, urine culture, urinary tract ultrasound, and video-urodynamic investigation including pelvic floor electromyography [1]. Video-urodynamics were performed according to good urodynamic practices using a multichannel urodynamic system as recommended by the ICS [11,12]. Patients were urodynamically investigated in a sitting position whenever possible. The bladder was filled with a 36 °C mixture of 0.9% NaCl solution and contrast medium at 20 mL/min.

The primary outcome measures were urodynamic parameters including maximum cystometric capacity, compliance, maximum detrusor pressure during storage phase, detrusor overactivity with and without incontinence, detrusor leak point pressure, detrusor sphincter dyssynergia and vesico-uretero-renal reflux. The secondary outcome measure was urinary tract ultrasound. Normal renal parenchyma thickness was defined as >12 mm, determined by the coronal measure of the distance between the renal sinus/parenchyma interface and the renal surface [13].

Data were approximately normally distributed and presented as mean (standard deviation, SD). Comparing related and unrelated quantitative data, the paired and unpaired *t*-test was used. Paired categorical data were compared using the McNemar test and Wilcoxon matched-pairs signed-ranks test. Statistical analyses were performed using GraphPad Prism version 6.01 (GraphPad Software, CA, USA) and IBM SPSS version 20 (IBM, NY, USA), with $P < 0.05$ considered to indicate statistical significance.

Results

The patients' characteristics are shown in Table 1. Of the 246 patients enrolled almost four out of five were men. Most of the patients had a thoracic SCI and ASIA impairment scale of A. The mean (SD) duration since SCI to the latest available urodynamic investigation was 17 (10) years and mean patient age at that time was 51 (14) years. The mean (SD) follow-up between the earliest and latest available urodynamic investigation was 6 (3) years.

Table 1 The patients' characteristics.

Variable	Value
Total number of patients	246
N (%):	
Gender	
Female	55 (22)
Male	191 (78)
Level of SCI:	
Cervical	54 (22)
Thoracic	138 (56)
Lumbar	47 (19)
Sacral	7 (3)
ASIA impairment scale:	
A	116 (47)
B	34 (14)
C	29 (12)
D	64 (26)
Unknown	3 (1)

Table 2 Type of bladder emptying according to lesion level.

Type of bladder emptying	At earliest available urodynamic investigation (n = 246)	At latest available urodynamic investigation (n = 246)
N (%):		
ISC	128 (52)	145 (59)
Cervical	18 (14)	19 (13)
Thoracic	75 (59)	93 (64)
Lumbar	29 (23)	29 (20)
Sacral	6 (5)	4 (3)
Spontaneous voiding	75 (30)	52 (21)
Cervical*	20 (27)	18 (35)
Thoracic†	40 (53)	19 (37)
Lumbar‡	14 (19)	12 (23)
Sacral	1 (1)	3 (6)
Indwelling catheter	43 (18)	49 (20)
Cervical	16 (37)	16 (33)
Thoracic	23 (54)	27 (55)
Lumbar	4 (9)	6 (12)
Sacral	–	–

**Including eight and five patients relying on a condom catheter at earliest and latest available urodynamic investigation, respectively; †Including 14 and two patients relying on a condom catheter at earliest and latest available urodynamic investigation, respectively; ‡Including two and one patients relying on a condom catheter at earliest and latest available urodynamic investigation, respectively.*

At the earliest and latest available urodynamic investigation (Table 2), more than half of the patients relied on ISC and there was a shift from spontaneous voiding towards ISC over time in patients with thoracic lesions. Thus, 67% (93/138) of the patients with a thoracic lesion performed ISC at the latest available urodynamic investigation compared with 35% (19/54), 62% (29/47) and 57% (4/7) of those with cervical, lumbar and sacral lesions, respectively. In addition, there were relevant differences according to lesion level in patients with an indwelling catheter: 30% (16/54), 20% (27/138),

Table 3 Neuro-urological medication according to lesion level.

Neuro-urological medication	At earliest available urodynamic investigation (n = 246)	At latest available urodynamic investigation (n = 246)
N (%):		
None	158 (64)	131 (54)
Cervical	33 (21)	28 (21)
Thoracic	86 (55)	69 (53)
Lumbar	32 (20)	28 (21)
Sacral	7 (4)	6 (5)
α-blockers	5 (2)	5 (2)
Cervical	1 (20)	1 (20)
Thoracic	3 (60)	2 (40)
Lumbar	1 (20)	2 (40)
Sacral	–	–
Antimuscarinics	53 (22)	28 (11)
Cervical*	9 (17)	4 (14)
Thoracic†	34 (64)	18 (64)
Lumbar‡	10 (19)	5 (18)
sacral	–	1 (4)
OnabotulinumtoxinA injections into detrusor	30 (12)	82 (33)
Cervical§	11 (37)	21 (25)
Thoracic¶	15 (50)	49 (60)
Lumbar**	4 (13)	12 (15)
Sacral	–	–

*Including two and no patients taking in addition an α-blocker at earliest and latest available urodynamic investigation, respectively; †Including one and two patients taking in addition an α-blocker at earliest and latest available urodynamic investigation, respectively; ‡Including one and two patients taking in addition an α-blocker at earliest and latest available urodynamic investigation, respectively; §Including six and seven patients taking in addition an antimuscarinic drug at earliest and latest available urodynamic investigation, respectively; ¶Including four and nine patients taking in addition an antimuscarinic drug at earliest and latest available urodynamic investigation, respectively; **Including two and no patients taking in addition an antimuscarinic drug at earliest and latest available urodynamic investigation, respectively.*

13% (6/47) and none (0/7) of the patients with cervical, thoracic, lumbar and sacral lesions relied on an indwelling catheter.

The percentage of patients under any neuro-urological medication increased from the earliest to the latest available urodynamic investigation (Table 3). Importantly there was a relevant increase of patients (with cervical, thoracic and lumbar but not sacral lesions) undergoing onabotulinumtoxinA injections into the detrusor from 12% to 33% and in parallel a decrease of antimuscarinic medication.

Video-urodynamic findings at the earliest and latest available urodynamic investigation were within the safe limits (Table 4). There were significant differences between both groups for maximum cystometric capacity ($P < 0.001$), compliance ($P < 0.001$) and maximum detrusor pressure during storage phase ($P = 0.008$).

Urinary tract ultrasound was normal in all but four (2%) patients, two with unilateral renal parenchymal scarring after recurrent pyelonephritis before establishing regular neuro-urological follow-up and two with grade I unilateral dilatation of the renal pelvis but with normal renal parenchyma and no signs of vesico-uretero-renal reflux.

Vesico-uretero-renal reflux was detected in ≈5% and it was generally low grade (Table 4).

Discussion

Main Findings

Most of our regularly followed patients with NLUTD due to SCI [mean (SD) duration of SCI 17 (10) years] had urodynamic findings within the safe limits.
Vesico-uretero-renal reflux was quite rare and usually low grade. During the course of disease, there was a relevant increase of patients undergoing onabotulinumtoxinA injections into the detrusor. Considering the findings of the present study, regular follow-up including urodynamic investigations seems warranted, as this allows for a patient-tailored management preserving/improving LUT and upper urinary tract function.

Findings in the Context of Existing Evidence

Morbidity and mortality of patients with SCI are closely related to LUT function. Elevated bladder pressure during the storage phase, either due to low-compliance bladder or detrusor overactivity, is the major cause of renal deterioration [14]. In addition, older patients and those with a longer duration of SCI have a substantially higher risk of urological complications [15]. At late-stage after SCI, a high probability of change in the LUT management methods was reported indicating the importance of long-term planning from the time of SCI to minimise late complications [15]. Indeed, since neuro-urological management has evolved from reflex voiding and indwelling catheters to the widespread use of regular urodynamics, ISC, and antimuscarinics, optimised bladder management has significantly contributed to the improved outcomes in patients with SCI [16–18], with an enormous decrease in morbidity and mortality due to urological complications [2,4,5,15]. This is consistent with the present study showing urodynamic findings within the safe limits at a mean (SD) of 17 (10) years after SCI.

Most of our present patients were on antimuscarinics and/or underwent regular onabotulinumtoxinA injections into the detrusor [19]. Antimuscarinics are the pharmacological first-line treatment for overactive bladder and all currently used antimuscarinics have well-established efficacy shown in systematic reviews [8,20,21]. Although onabotulinumtoxinA injections into the detrusor have become a popular, well-accepted second-line treatment with a recent USA Food and Drug Administration (FDA) approval in August 2011 for refractory neurogenic detrusor overactivity incontinence [22,23], several important issues such as optimal dosage and

Table 4 Video-urodynamic findings.

Video-urodynamics	At earliest available urodynamic investigation (n = 246)	At latest available urodynamic investigation (n = 246)	*P*
Mean (SD):			
Maximum cystometric capacity, mL	440 (180)	650 (355)	<0.001
Compliance, mL/cmH_2O	55 (40)	95 (88)	<0.001
Maximum detrusor pressure during storage phase, cmH_2O	25 (17)	34 (27)	0.008
N (%):			
Detrusor overactivity	59 (24)	130 (53)	<0.001
with incontinence	32 (13)	56 (23)	
Detrusor leak point pressure, cmH_2O	49 (23)	32 (25)	
Detrusor sphincter dyssynergia	72 (30)	61 (25)	0.001
Vesico-uretero-renal reflux:	11 (4)[I]	12 (5)[†]	0.99
Grade 1–3	11 (4)	11 (4)	
Grade 4–5	0	1 (0)	

[I]*Including two patients (1%) with bilateral reflux;* [†]*Including seven patients (3%) with bilateral reflux.*

injection technique, timing for repeat injection, short- and long-term safety, and exact mechanisms of action remain to be elucidated [24].

Implications for Practice

Our treatment strategy is based on urodynamic findings and this is supported by a retrospective study of 80 patients with SCI reporting that only urodynamic measurements are reliable to prevent upper urinary tract deterioration, as bladder function is unpredictable using other parameters [7]. In accordance with the literature [1,17,25,26], most of our present patients relied on ISC. Over time, there was a shift from spontaneous voiding towards ISC in patients with thoracic lesions and we found a relevant increase of patients with cervical, thoracic and lumbar lesions undergoing onabotulinumtoxinA injections into the detrusor. High-level SCI (also depending on the lesion completeness) might impede performing ISC and explains the relatively high proportion of 30% of our present patients with cervical lesions relying on an indwelling catheter. Recently, several authors [16,27] found the suprapubic catheter a valuable treatment option in patients with SCI. Although there is a lack of high-evidence level studies, we also support this view and prefer a suprapubic instead of a transurethral catheter.

Implications for Research

Despite the management of NLUTD improving dramatically, resulting in a substantial decrease in morbidity and mortality in patients with SCI, many important issues remain to be elucidated. Thus, the pathological mechanisms involved in NLUTD are still incompletely understood. Indeed, SCI is not a stable chronic disease and modification of bladder management was necessary in more than one fourth of 196 patients with SCI followed prospectively for 6 years [15]. Electrophysiological and structural/biochemical changes during the long-term course of SCI in patients may provide new insights into NLUTD warranting appropriately designed longitudinal studies applying a holistic approach, i.e. clinical, urodynamic, electrophysiological, structural/biochemical, and neuro-radiological assessments. Developing biomarkers for patients with SCI guiding assessment, treatment and surveillance of NLUTD would be of great interest and could completely revolutionise modern neuro-urology. Nerve growth factor may become a clinically important biomarker and preliminary findings are promising [28]. In addition, currently available treatment options need to be improved and new therapeutic targets have to be identified. Sacral neuromodulation [29] is a promising therapy but efficacy and safety have to be confirmed in randomised trials before more widespread use in patients with SCI can be recommended [30,31].

Limitations of the Study

Several limitations of the present study should be addressed. First, our study was not randomised but representative of everyday clinical practice. Thus, conclusions for patients without regular urodynamic follow-up are not possible warranting further investigations. Second, quality of life was not systematically assessed and could therefore not be evaluated. However, based on the present study's findings, we have introduced the Qualiveen questionnaire [32] in our routine neuro-urological evaluation. Third, our present patients underwent regular urinary tract ultrasound and video-urodynamics but not routine creatinine clearance and/or nuclear renal scan. However, it should be considered that creatinine clearance has little value as a screening measure for renal disease in patients with SCI because of its variability in serial testing [33]. In addition, in the case of sonographically normal renal parenchyma and no vesico-uretero-renal reflux in the video-urodynamic investigation, the value of a nuclear renal scan is unclear. In

fact, there is no generally agreed diagnostic tool/procedure to assess renal function of patients with SCI in regular follow-up [1].

Conclusions

Most of our regularly followed patients with NLUTD due to SCI (mean duration of SCI 17 years) had urodynamic findings within the safe limits. Vesico-uretero-renal reflux was quite rare and generally low grade. Thus, regular follow-up with urodynamic investigation allowing for a patient-tailored management seems beneficial warranting randomised controlled longitudinal studies.

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Conflict of Interest

None of the authors has a conflict of interest with this study.

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Abbreviations: ASIA, American Spinal Injury Association; ISC, intermittent self-catheterisation; (N)LUT(D), (neurogenic) lower urinary tract (dysfunction); SCI, spinal cord injury.

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Follow-up of the neuro-urological patient: a systematic review

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Objectives

To systematically review the long-term urological follow-up strategies for patients with neurogenic lower urinary tract dysfunction (NLUTD), focusing on three main groups of neurological diseases: (i) spinal cord injuries, (ii) spinal dysraphism, and (iii) multiple sclerosis.

Patients and Methods

Data acquisition comprised electronic search on the Medical Literature Analysis and Retrieval System Online (MEDLINE) database and the EMBASE database in August 2014 to retrieve English language studies. MEDLINE and EMBASE search included the following medical subject heading (MeSH) terms: (i) neurogenic bladder and (ii) neurogenic bladder dysfunction. Each of these terms was crossed with (i) long-term care and (ii) long-term surveillance. Only studies related to NLUTD and urological follow-up were included. Studies were also identified by hand search of reference lists and review articles.

Results

Initial records identified through database searching included 265 articles. In all, 23 articles were included in the quantitative synthesis. The proposed time schedule of investigations as well as the amount and type of investigation were different according to specific neurological lesions. They depend on the dysfunctional pattern of the lower urinary tract (LUT) and its risk profile. However, there is a lack of high-evidence level studies to support an optimal long-term follow-up protocol.

Conclusions

The goal of neuro-urological management is the best possible preservation of upper urinary tract (UUT) and LUT function in relation to the individual neurological disorder. Regular and risk adapted controls ('urochecks') allow detection of risk-factors in time before irreversible changes of the LUT and UUT have occurred. With risk- and patient-oriented lifelong regular urological care an optimised quality of life and life-expectancy can be achieved, although there is a complete lack of high-evidence level studies on this topic.

Keywords

neurogenic bladder, long-term care, urological diagnostic techniques

Introduction

Neurogenic lower urinary tract dysfunction (NLUTD) is not a static condition but follows its own natural history that can manifest in changes of the lower urinary tract (LUT) and upper urinary tract (UUT), firstly functional, later morphological, and may also affect, mostly deteriorate, sexual and bowel function.

The aetiology and the underlying pathophysiology of NLUTD are mainly responsible for the different risk profiles for LUT and UUT deterioration, which may be further influenced by age, gender and last but not least by the patient's self-discipline. Therefore it is understandable that there are no guidelines on long-term care that can be applied to all of these patients. They mostly focus on special patients groups, e.g. on spinal cord injuries (SCIs) [1–5] or patients with multiple sclerosis (MS) [6,7]. Therefore, also the intervals in which controls should be performed are different and depend very much on the current (actual) findings.

One prerequisite for effective long-term care is the information of the patient about 'her/his neurogenic bladder' and the impact of this condition on health, way of life and sexuality. Moreover, the patient should be informed about the pros and cons of various treatment options, including costs, as well as about the necessity that experts should be consulted when urological problems arise.

The aim of the present study was to systematically review the long-term urological follow-up strategies for patients with NLUTD, focusing on what should be included as general and/or specific investigations, and on what should the optimal time schedule for controls, according to three main groups of neurological diseases: (i) SCI, (ii) spinal dysraphism, and (iii) MS.

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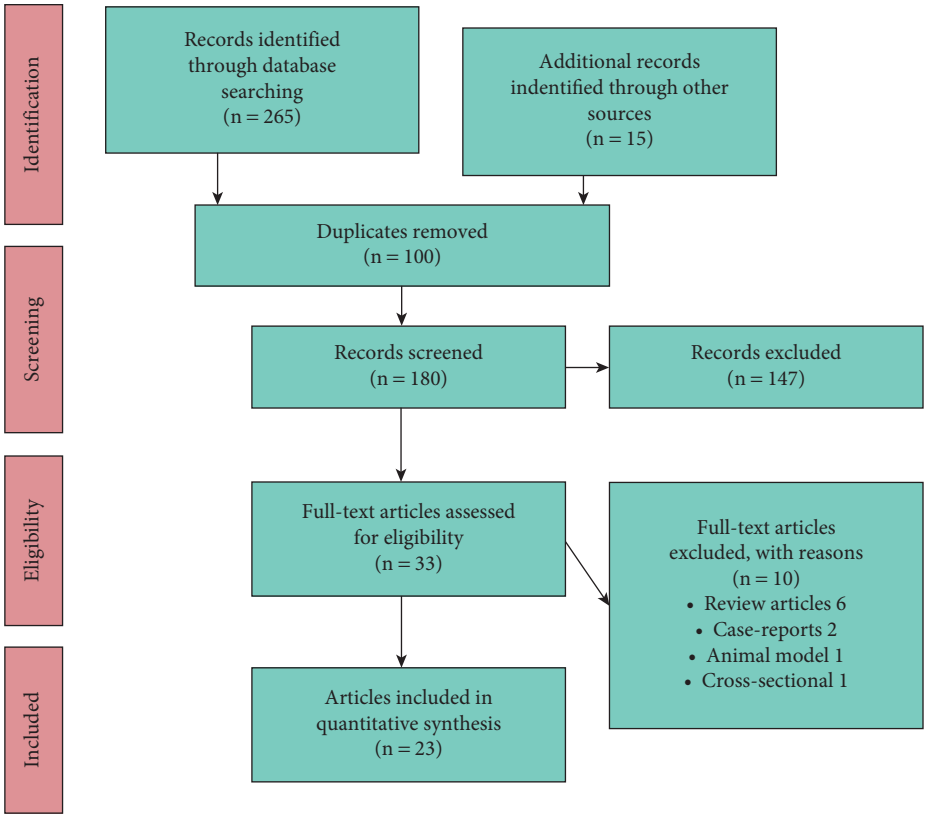

Fig. 1 Flow diagram of follow-up studies of the neuro-urological patient.

Patients and Methods

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement [8]. Data acquisition comprised electronic search on MEDLINE and EMBASE databases in August 2014 to retrieve English language studies. Medical subject heading (MeSH) terms included: (i) neurogenic bladder and (ii) neurogenic bladder dysfunction. Each of these terms was crossed with (i) long-term care and (ii) long-term surveillance. Only studies related to NLUTD and urological follow-up were included into this review article. Studies were also identified by hand search of reference lists and review articles.

Results

Initial records identified through database searching included 265 articles; 15 additional records were identified through other sources. The study selection procedure is described in Fig. 1.

After duplicates removal ($n = 100$), 147 of 180 screened articles were excluded because they were not related to the neuro-urological follow-up. In all, 23 of 33 full-text articles were included in the quantitative synthesis [1–7,9–24]. Thus, 10 articles were excluded because they did not bring additional information on the neuro-urological follow-up (six review articles, two case-reports, one animal model, one cross-sectional study) [25–34].

Most studies were focused on SCI (13 articles), spinal dysraphism (threee articles), and MS (twoarticles). Main results are presented on Table 1 [9–21].

Follow-up in Patients with SCI

In a comparative study to determine compliance with annual urological evaluations and renal function preservation in patients with SCI, Waites et al. [9] found that although serial examination of the urinary tract after SCI is important, nonetheless it might be acceptable to lengthen the periods between examinations after the first few years.

Yet, for LUT changes over time in suprasacral SCI, Cardenas et al. [10] compared video-urodynamic (VUD) findings with methods of bladder management. Maximum detrusor pressure decreased significantly over time for patients on external collectors ($P < 0.01$). Tests also indicated more severe bladder trabeculation in this group. It was concluded the results may reflect the effects of age, as well as reduced survival in those using external collectors with chronically elevated detrusor pressure.

McKinley et al. [11] analysed the incidence, risk factors, and trends of long-term secondary medical complications in patients with SCI, who had annual evaluations. The incidence

Table 1 Main results of studies on neuro-urological follow-up.

Reference	Publication year	Study type	LE	*n*	Most relevant results
Waites et al. [9]	1995	Prospective cohort	4	59	Serial examination of the urinary tract after SCI is important but that it might be acceptable to lengthen the periods between examinations after the first few years.
Cardenas et al. [10]	1995	Cross-sectional	3b	179	Patients who had external collector as bladder management were more likely to have severe bladder trabeculation due to chronically elevated detrusor pressure, when compared with patients on catheterisation.
McKinley et al. [11]	1999	Retrospective cohort	4	NR	Incidence of urinary stones was higher in patients with complete tetraplegia. Compliance with IC became less common at later follow-up.
Chen et al. [12]	2000	Cohort study (database estimative)	2b	8314	Within 10 years after injury, 7% of patients with SCI would develop their first kidney stone. The risk was greatest during the first 3 months after injury (31 cases per 1000 person-years).
Bartel et al. [13]	2014	Retrospective cohort	3b	93	Bladder stones were identified with suprapubic catheter in 11% (50/453), transurethral catheter in 6.6% (5/75), with IC in 2% (27/1315) and with reflex micturition in 1.1% (11/982), respectively. The mean time to stone development was 95 months.
Zhang and Liao [14]	2014	Prospective cohort	4	112	Lumbosacral SCI and chronic indwelling urethral and suprapubic catheterisation were predictors of UUT deterioration.
Capitanucci et al. [15]	1996	Prospective cohort	4	65	At long-term follow-up (2–14 years), UUT deterioration occurred in 15% and renal failure in 7.5% of children with occult spinal dysraphism.
Vainrib et al. [16]	2013	Retrospective cohort	4	118	Myelomeningocele patients should be followed in the long-run, even after bladder augmentation, as elevated detrusor pressures can still be seen.
Ciancio et al. [17]	2001	Retrospective cohort	4	22	A significant proportion of patients with MS with and without new urinary symptoms will develop changes in their underlying urodynamic patterns and detrusor compliance during a mean follow-up of 42 months.
Wiedemann et al. [18]	2013	Cross-sectional	3b	100	UDS showed urinary tract dysfunction in 78% of patients with MS with LUTS. Risk factors for pathological urodynamic findings were wheelchair dependency, use of more than one incontinence pad per day and a MS type other than relapsing-remitting.
Atan et al. [19]	1999	Prospective cohort	4	15	Continued routine urological surveillance for infection and stones is mandatory in patients who undergo ileovesicostomy.
Lawrenson et al. [20]	2001	Case-control (database estimative)	4	NR	Patients with paraplegia or neural tube defects were found to have a substantially increased risk of renal failure compared with the general population.
Cameron et al. [21]	2012	Systematic review	NA	NA	12 articles dealing with UTIs in neuro-urological patients. Symptoms used to predict UTI yielded mixed results and urine dipstick testing had the same accuracy as microscopy.

LE, level of evidence according to the Oxford Centre for Evidence-Based Medicine (2011); NR, not clearly reported; NA, not applicable.

of calculi (kidney and/or ureter) was 1.5% at 1-year follow-up and 1.9% at 5 years, and was more frequent in patients with complete tetraplegia. IC was the most common method of bladder management among patients with paraplegia but became less common at later visits after injury.

Chen et al. [12] have evaluated risk factors for kidney stones in patients with SCI. It was estimated that ≤10 years after injury, 7% of patients with SCI would develop their first kidney stone. The risk was greatest during the first 3 months after SCI (31 cases per 1000 person-years).

Bartel et al. [13] retrospectively assessed the occurrence of bladder stones in patients with SCI. Bladder stones were identified more often in patients with suprapubic catheters (11%). The recurrence rate was 23%, and was most frequent in the transurethral catheter group (40%).

Zhang and Liao [14] investigated risk factors predicting UUT deterioration in patients with SCI. UUT abnormalities were present in 23 patients (65.7%) in a spontaneous voiding group, 10 patients (20%) in the IC group, 15 patients (78.9%) with indwelling urethral catheterisation, and seven patients (87.5%) with suprapubic Foley catheterisation ($P < 0.001$). When dividing bladder management method into two groups, catheter-free (spontaneous and intermittent voiding) and indwelling catheter (urethral and suprapubic catheterisation), there was UUT dysfunction in 33 patients (38.3%) and 22 patients (81.5%), respectively ($P < 0.001$).

Follow-up in Patients with Spinal Dysraphism

Capitanucci et al. [15] evaluated the long-term urological follow-up in children with occult spinal dysraphism. Urinary incontinence was treated mainly by IC and antimuscarinics. At long-term follow-up (2–14 years), socially acceptable continence was achieved in 78% (57 children). UUT deterioration occurred in 15% and renal failure in 7.5%.

Vainrib et al. [16] assessed urodynamic findings in adult patients with neurogenic bladder and myelomeningocele before and after augmentation enterocystoplasty. Most patients maintain low bladder pressures for >10 years. Close

long-term follow-up should be maintained as elevated detrusor pressures can still be seen after reconstruction.

Follow-up in Patients with MS

Ciancio et al. [17] studied the urodynamic pattern changes in MS. Overall, 12 (55%) of 22 patients had a change in their urodynamic patterns and/or compliance during a mean follow-up interval of 42 ± 45 months between the urodynamic studies. It was concluded that urodynamic evaluations should be repeated at regular intervals in symptomatic patients to optimise clinical management, and reduce complications.

Wiedemann et al. [18] also studied LUTS in MS patients during rehabilitation. LUTS were evaluated with voiding diary, post-void ultrasound, and an urodynamic examination. The mean (SD) duration of MS was 10.26 (10.09) years and mean duration of LUTS was 6.9 (7.75) years. Urodynamics (UDS) showed urinary tract dysfunction in 78 of 100 patients with MS with LUTS, including detrusor overactivity in seven, increased bladder sensation without detrusor overactivity in 21, detrusor–sphincter dyssynergia (DSD) in 26, detrusor hypocontractility in 12, detrusor acontractility in four and unclear diagnosis in eight patients.

Other Follow-up Studies in Neuro-urological Patients

Atan et al. [19] followed neuro-urological patients with complications of previous bladder management, who underwent ileovesicostomy. All were either poor candidates for or refused continent urinary diversion or bladder augmentation cystoplasty. Long-term complications were stomal stenosis in two patients, bladder and kidney stone formation in five, and symptomatic UTIs in three.

Lawrenson et al. [20] studied renal failure risk in neuro-urological patients. All patients registered in the General Practice Research Database (GPRD) between 1994 and 1997, and aged 10–69 years were included in the study. The prevalence of renal failure in the general population was ascertained, and compared with the prevalence in patients with MS, paraplegia and neural tube defects. The age-standardised prevalence of renal failure in the GPRD population aged 10–69 years was 14 per 10 000. The rate ratio of renal failure compared with the general population in each of the years 1994–1997 for neural tube defects ranged between 6.8 and 9.0 in males and 9.2–11.5 in females, for paraplegia 4.1–9.0 in males and 4.0–7.0 in females, and for MS 0.4–1.3 in males and 0.5–2.2 in females. Their conclusion was that those neuro-urological patients should be regularly screened to detect renal impairment before the development of chronic renal failure.

For UTI screening, Cameron et al. [21] published a systematic review, which identified 12 articles dealing with neuro-urological follow-up. Routine urine culture was unnecessary in healthy, asymptomatic individuals with normal urine analysis.

Discussion

Regarding follow-up of the neuro-urological patient, there is a lack of high-level evidence studies and guidelines are mainly based on expert opinions. In the guidelines on *Bladder Management of Adults with Spinal Cord Injury* [1], nine panel members and a further 34 contributors, 13 of them expert reviewers of relevant scientific organisations, have elaborated the guidelines, which are based on 107 publications. The recommendations for long-term care in the manual *Neuro-Urology and Spinal Cord Lesion*, produced by the working-group 'Urological Rehabilitation of Spinal Cord Injury Patients' are based on the consensus of eight neuro-urologists with expertise. In the recommendations in *A Proposed Guideline or the Urological Management of Patients with Spinal Cord Injury*, eight experts from the UK were involved.

The value of adequate urological long-term care is also reflected in an article by Osterthum et al. [22] from the Netherlands, in which the causes of death after SCI during patient rehabilitation and the first 5 years after discharged are reported. In the Netherlands, from 12% of persons with SCI, who had survived the acute hospital phase and died during the follow-up (mean follow-up 5.2 years), the main causes of death were cardiovascular and pulmonary disease, none of the patients died from renal failure. This is very much in contrast to reports from only 20 years ago, when renal failure was the most frequent cause of death in patients with SCI [20].

On the other hand, according to Cameron et al. [21], no definitive recommendations on follow-up strategies can be made in NLUTD after SCI, except for routine renal ultrasound. UDS are regarded as an important part of screening but the frequency is unclear.

Burki et al. [23] addressed the effects of the European Association of Urology (EAU) *Guidelines on Neuro-Urology* and the proposed *British Guidelines for the Urological Management of Patients with SCI* in the UK. These authors concluded that there was a continued lack of high-quality evidence to support an optimal long-term follow-up protocol. Additionally, there was a lack of evidence on clinical outcomes when these guidelines had been strictly followed.

Follow-up strategies are essential to the neuro-urological patients, as NLUTD is often unstable and the symptoms may vary considerably, even within a relatively short period of time. Despite of the fact that prospective studies on the follow-up of these patients are scarce, there are three main points to be discussed: (i) what should be included as general and/or specific investigations, (ii) what is the optimal time

schedule for controls, and (iii) who should be responsible for counselling the patients?

The follow-up of the neuro-urological patients comprises (A) General and (B) specific investigations. The following recommendations are mostly based on expert opinions, some of them published in relevant guidelines.

A. General Investigations

An interim history should address changes with respect to previous investigations, related to bladder emptying, continence, non-febrile or febrile UTIs, antibiotic treatment received, mode of defecation, sexual function, spasticity if present, and use of medication.

a) Clinical investigations should evaluate the physical status, including rectal investigation of the prostate and rectum (to exclude faecal impaction). The neuro-urological status should comprise the evaluation of spasticity, sensation in the sacral dermatomes S3–S5, anal inspection, sphincter tone, anal reflex, bulbocavernosus reflex, voluntary contraction of sphincter ani, and pelvic floor muscle. They should also comprise 'non-invasive' UDS, such as a bladder (catheterisation) diary, observation of voiding or uroflowmetry and post-void residual urine volume (PVR) observation (also as a prerequisite for further urodynamic investigation) (expert opinions).
b) Laboratory investigation must comprise urine status, leucocyte count, bacteria count, antibiogram when needed, blood investigation with erythrocyte sedimentation rate, blood count, C-reactive protein (CRP), creatinine, urea, uric acid, electrolytes, and PSA, if applicable. Normal serum creatinine does not exclude renal dysfunction in patients with SCI, due to their reduced muscle mass, instead isotope clearance examination should be performed or cystatin C evaluated. In long-term antimuscarinic treatment, liver function should be assessed (expert opinions).
c) Ultrasound investigation of the UUT and LUT should be evaluated, including PVR.

B. Specific Investigations

Special investigations should be performed for special indications, depending on type of the neurogenic bladder, risk factors, and therapy performed. They comprise invasive UDS (cystometry, pressure-flow-studies, VUDS), voiding and/or cystourethrography, especially in patients using IC, and endoscopy (restricted indications see below). For kidney morphology and function (see above), Intravenous urography (IVU) is rarely indicated nowadays for evaluation of renal pelvis and ureters.

Specific investigations should be performed by urologists with neuro-urological experience, aimed at specific patient groups.

The value of cystoscopy for traumatic SCI patients, managed with indwelling catheter, was recently investigated by El Masri et al. [7], and their conclusion was that cystourethroscopic surveillance in high-risk patients with indwelling catheter is essential to diagnose and manage complications at an early stage. However, it is important to recognise that findings detected with endoscopy did not show a significant difference in the symptomatic and in the asymptomatic group.

UDS are the only method to evaluate the pressure situation in the LUT during storage and emptying. The indication of which type of UDS should be performed, a simple cystometry, pressure-flow studies, or VUDS, are again dependent on previous findings and risk factors.

More comprehensive information is provided by VUDS, informing additionally about the radiological appearance of the bladder, bladder neck, and posterior urethra during filling and emptying. A urethrogram is indicated in male patients using IC, and should be performed from time to time routinely or when the patient complains about difficulties with catheterisation. To evaluate the renal pelvis and the ureters also nowadays an IVU may be indicated.

With cerebral diseases the risk for UUT damage is low. Therefore, e.g. in a stroke patient with overactive bladder symptoms, UDS is not necessary when voiding is without PVR. In suprasacral SCIs, invasive UDS, or preferably VUDS, should be performed regularly, at least during the first 3–5 years after the injury, as the change in compliance and pressure due to increasing DSD may be present before symptoms occur, and can then be diagnosed in time before possibly irreversible changes in the urinary tract have occurred. UDS are not essential for every patient with MS. However, despite there being no strong evidence to suggest that repeated examinations may change outcomes, UDS are particularly useful to evaluate the pattern of LUT dysfunction in patients with refractory symptoms, especially in those with failure of conservative urological management or risk of UUT deterioration (expert opinions).

Also sacral and subsacral lesions deserve regular controls, especially when the bladder is expressed by Valsalva or Crede, as these manoeuvres may create unphysiologically high intravesical pressure, causing vesico-uretero-renal reflux. But also a low-compliance bladder may develop over time despite an incompetent sphincter, a condition only detected by UDS.

Regular ultrasound assessment is advisable. It cannot substitute invasive UDS/VUDS, because at the time when ultrasound shows changes in the LUT and UUT these changes may already have caused damage to the LUT and UUT. This statement is based on clinical experience, as no comparative studies are available to document the level of evidence and the grade of recommendation. Also with sacral/subsacral lesions and documented neurogenic detrusor acontractility, a low

compliance bladder can occur over time, which again can only be diagnosed with invasive UDS.

For the time schedule for controls in the guidelines on *Bladder Management for Adults with Spinal Cord Injuries: A Clinical Practice Guideline for Health-Care Providers*, published in 2006 [1], the authors state that 'no studies have been done on the optimal frequency of follow-up evaluations', and this is also true for the following recommendations. Experts agree that the time schedule for controls and the amount of investigations to be done depend primarily on risk factors. Patients without a history of recurrent UTI based on the interim history, without risk factors in previous investigations, and without significant PVR, should perform self-control of urine (strip-test) routinely once a month or if UTI is suspected. This is the case when the GP or the urologist should be contacted. Annual ultrasound of kidney and bladder, including PVR, should be performed. In general, in patients with SCI, invasive UDS should be performed after initial rehabilitation yearly during the first 3 years, and thereafter every 2 and 3 years.

What Are the Risk Factors and How to Detect Them?

Amongst general risk factors, based on history and/or clinical/radiological findings, the German working group [35] mentions febrile UTI, recurrent UTI (more than two episodes per year), hypotensive crisis (related to autonomous dysreflexia), increased PVR on multiple measurements, increase or new occurrence of urinary incontinence and/or voiding problems, hydronephrosis (ultrasound), change of bladder morphology (trabeculations, pseudo-diverticulae), persistent abnormal laboratory findings (CRP, leucocytes, kidney function, as well as any indication for deterioration of kidney functions). If these risk factors are present, consultation with an experienced neuro-urologist or neuro-urological centre is regarded as essential.

Zhang and Liao [14], retrospectively analysing medical records and UUT images of 112 patients, found as predictors for UUT deterioration, lumbar–sacral SCI, chronic indwelling urethra and suprapubic catheterisation. However, there are patients with risk factors that may remain clinically silent over a longer period of time, which can only be detected by UDS/VUDS. The guidelines for urological care of patients with SCI edited by the German working group on urological rehabilitation of patients with SCI (2007) has mentioned as urodynamic risk factors for UUT deterioration, related to (VUDS), high pressures during the filling place, a low compliance of <20 mL/cmH_2O, a high leak-point pressure (LPP), prolonged detrusor contraction, and low reflex volume with high PVR. For high pressure during the voiding phase, a maximum detrusor pressure in men of >80 cmH_2O and in women of >60 cmH_2O were regarded as risk factors, as well as significant DSD, and high PVR (>100 mL or more than 30% of functional bladder capacity). For the pressures, most authors refer to the paper of Wang et al. [24]. This study was done in children with myelodysplasia, and in this group the crucial detrusor LPP was 40 cmH_2O: >40 cmH_2O deterioration of the UUT could be expected in 89%, if below in only 10%. However, this is a single-centre observation, it was never reproduced and it was only done in children. Surprisingly and strangely enough, there are no studies have been done to date in adults to correlate the detrusor storage and/or voiding pressures with UUT changes.

Table 2 Recommendations for follow-up, according to the EAU guidelines on Neuro-Urology [4]].

Recommendations	LE	Grade
In high-risk patients, the UUT should be assessed at least every six months	4	A
In high-risk patients, physical examination, and urine laboratory should take place every year	4	A
Any significant clinical changes should instigate further, specialized, investigation	4	A
Urodynamic investigation is a mandatory baseline diagnostic and in high-risk patients, should be done at regular intervals	3	A

LE, level of evidence according to the Oxford Centre for Evidence-Based Medicine (2011).

Other risk factors were prolonged detrusor contractions, autonomic dysreflexia, vesico-ureteric-renal reflux and influx into the male adnexa. However, these statements are obviously based on expert opinion and not on controlled studies. Autonomic dysreflexia is a medical emergency and is often related to urological, gastrointestinal or gynaecological problems, and manipulations. If there is a history of autonomic dysreflexia, urodynamic investigations should be done under continuous blood pressure and pulse monitoring and physicians must be aware of treatment cascade.

The Guidelines of the EAU on Neuro-Urology [4] recommend regular 'urochecks', whose intervals depend on the type of neurogenic lesion, as well as on the dysfunctional pattern. According to these guidelines, control intervals of >2 years are not recommended. Ultrasound of the urinary tract and PVR assessment should be performed if possible every 6 months, including a clinical investigation with blood and urine parameters once a year (Table 2) [4].

In the *A proposed guideline for the urological management of patients with spinal cord injury* [3], ongoing surveillance and the need for ultrasound controls of the UUT and PVR evaluation once a year are postulated.

Experts of a round-table on long-term care of patients with SCI during the first International Neuro-Urology Meeting in Zürich (2012) came to the conclusion that non-invasive UDS must be part of a routine 'urocheck', as only the results of these investigations allow the detection of risk-factors in time, before irreversible damage has occurred. In patients with MS

the same rules as for patients with SCI should be applied, once a high PVR and/or recurrent UTIs occur [5].

Basically the general investigations (see above) could be done by the general urologist or by a GP with a relevant interest in neuro-urological problems. However, if risk factors are present, the 'urocheck' should be performed by the neuro-urologist responsible at a neuro-urological centre.

When to Introduce IC?

Most studies report the beneficial results with IC; however, distinct indications can be drawn from the literature only indirectly. The indications for IC are: (i) inadequate detrusor contraction (too weak for balanced voiding or too strong creating a high pressure situation in the bladder during storage and/or voiding), (ii) unbalanced voiding due to functional outflow obstruction, and (iii) a PVR urine of ≈100 mL or >30% of functional bladder capacity, which are regarded as a risk factors. Although IC is mentioned in almost all guidelines and recommendations as the method of choice to empty the neurogenic bladder, the indications are not reported specifically and can only be extracted indirectly.

Conclusions

NLUTD is not a static condition, but follows its own natural history that can manifest in changes of the LUT and UUT, firstly functionally, later on morphologically. Such a development is promoted by risk-factors mostly based on high-pressure situations in the bladder during storage and/or voiding, some of them are recognisable from clinical symptoms, and others remain clinically silent over a long time, and can only be detected by (video-) urodynamic investigations. The time schedule of investigations, as well as the amount and type of investigation, is different in different neurological lesions. They depend on the dysfunctional pattern of the LUT and its risk profile. Regular and risk adapted controls ('urochecks') allow the detection of risk-factors in time before irreversible changes of the LUT and UUT have occurred.

The goal of a neuro-urological follow-up is the best possible preservation of UUT and LUT function in relation to the individual neurological disorder. With a risk- and patient-oriented lifelong regular urological care, an optimised quality of life and life-expectancy can be achieved, although there is a complete lack of high-evidence level studies on this topic.

Conflicts of Interest

H.M. reports other from Apogepha Germany, other from Astellas, Austria, other from Wellspect, Sweden, other from Montavit, Austria, outside the submitted work.

M.A. has nothing to disclose.

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Abbreviations: CRP, C-reactive protein; DSD, detrusor–sphincter dyssynergia; EAU, European Association of Urology; GPRD, General Practice Research Database; IC, intermittent catheterisation; LPP, leak-point pressure; (N)LUT(D), (neurogenic) lower urinary tract (dysfunction); MS, multiple sclerosis; PVR, post-void residual urine volume; SCI, spinal cord injury; UUT, upper urinary tract; (V)UDS, (video-) urodynamics.

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Management of sexual dysfunction due to central nervous system disorders: a systematic review

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Objective

To systematically review the management of sexual dysfunction due to central nervous system (CNS) disorders.

Patients and Methods

The review was done according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Studies were identified independently by two reviewers using electronic searches of MEDLINE and OVID (from January 2004 to August 2014) and hand searches of reference lists and review articles.

Results

In patients with CNS disorders, neuro-urological assessment is recommended for both genders before starting any treatment for sexual dysfunction. For men, blood sexual hormones evaluation is the main investigation performed before phosphodiesterase type 5 inhibitors (PDE5Is) treatment, whereas there is no consensus on routine laboratory tests for women. PDE5Is are the first-line medical treatment for men, with the most robust data derived from patients with spinal cord injury assessed by validated questionnaires, mainly the International Index of Erectile Function-15. There is no effective medical treatment for sexual dysfunction in women. Sacral neuromodulation for lower urinary tract dysfunction may improve sexual dysfunction in both genders.

Conclusions

Although sexual dysfunction is a major burden for patients with CNS disorders, high-evidence level studies are rare and only available for PDE5Is treating erectile dysfunction. Well-designed prospective studies are urgently needed for both genders.

Keywords

neurogenic sexual dysfunction, neurogenic erectile dysfunction, phosphodiesterase type 5 inhibitors

Introduction

Sexual dysfunction in patients affected by neurological disorders has many causes. A conceptual model for sexual problems was initially proposed to characterise three levels of influence in patients with multiple sclerosis (MS): primary, secondary and tertiary sexual dysfunction. Actually this model is valid for all neurological patients and should always be included in the diagnostic algorithm to address the appropriate examinations and therapies for sexual dysfunction as well. Primary sexual dysfunction results from neurological lesions directly affecting the neural pathways subserving sexual function. Neurological diseases affecting the cerebrum, brain stem, spinal cord, spinal roots or peripheral nerves including the autonomic nervous system, can alter sexual function [1,2].

Sexual dysfunction includes decreased or loss in libido, painful or uncomfortable genital sensations (burning, tingling, numbness), and/or altered orgasmic response in both women and men. Women may experience decreased vaginal lubrication and dryness, anorgasmia, and low sex drive [3,4]. Men may have difficulty achieving and/or maintaining an erection, and diminished frequency of ejaculation [5–7]. Secondary sexual dysfunction arises as a consequence of disability caused by poor bladder and bowel control, fatigue, muscle weakness, spasticity, immobility, tremor, cognitive impairment, and sensory problems. Secondary sexual dysfunction can also be a result of non-neurological co-morbidities, e.g. hypertension, diabetes, depression, hypercholesterolaemia, obesity, and chronic smoking. In addition, medications that are used for the neurological conditions (spasticity, urinary frequency, sensory pain, etc.) and non-neurological co-morbidities (hypertension, diabetes, depression, etc.) can further contribute to secondary sexual dysfunction. Tertiary sexual dysfunction is related to psychological, social and cultural issues that affect sexual response. These variables can include anxiety, low self-esteem, altered marital and family roles, changes in body image, and fear of rejection by the partner [8–11]. For each individual

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with a neurological disease, these three levels are interconnected and may fluctuate, interfering with each other continuously throughout life, generating or leading to a worsening of sexual impairments. Before addressing sexual dysfunction in a patient with a neurological disease, attitude towards sex, sexual orientation and cultural influences should be determined. Involvement of the patient's partner is recommended, if appropriate, when the quality of the relationship and the patient/partner needs and expectations of therapy have been assessed. Neurogenic sexual dysfunction often severely disrupts quality of life, so that healthcare professionals must be involved in treating an individual's sexual health [12,13]. In the present study, we aimed to systematically assess the management of sexual dysfunction due to CNS disorders.

Patients and Methods

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement [14]. Two authors (M.L and S.M.) independently searched MEDLINE and OVID using the following terms: 'neurogenic sexual dysfunction' (OR) 'neurogenic erectile dysfunction' (OR) 'spinal cord', 'multiple sclerosis', 'Parkinson's disease', 'stroke', 'epilepsy', 'spina bifida' (AND) 'sexual dysfunction' (OR) 'erectile dysfunction' (OR) 'sexual function' (AND) 'treatment'. Search criteria were limited to humans, adults, and full-text English articles. All relevant papers published in English from 2004 to 2014 were retrieved. References of selected articles and international guidelines were hand searched to identify additional reports. All identified studies were screened for eligibility, in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* [15]. As this systematic review focused on the management of sexual dysfunction due to CNS disorders, studies on patients with peripheral neuropathy or surgical disruption of the genital autonomic nerve supply were excluded as were studies on fertility issues. Data extraction was independently performed by three authors (M.L., S.M., G.L.) followed by crosschecking and clarification of any differences by the senior author (G.D.P.).

Results

The flow diagram of literature searches and results is shown in Fig. 1. We identified 302 records. In all, 256 reports were assessed for eligibility, with 31 articles finally included in this systematic review.

Men

The assessment of neurogenic erectile dysfunction (ED) is based on various mandatory steps. Overall the assessment criteria stemmed from data on patients with neurogenic ED

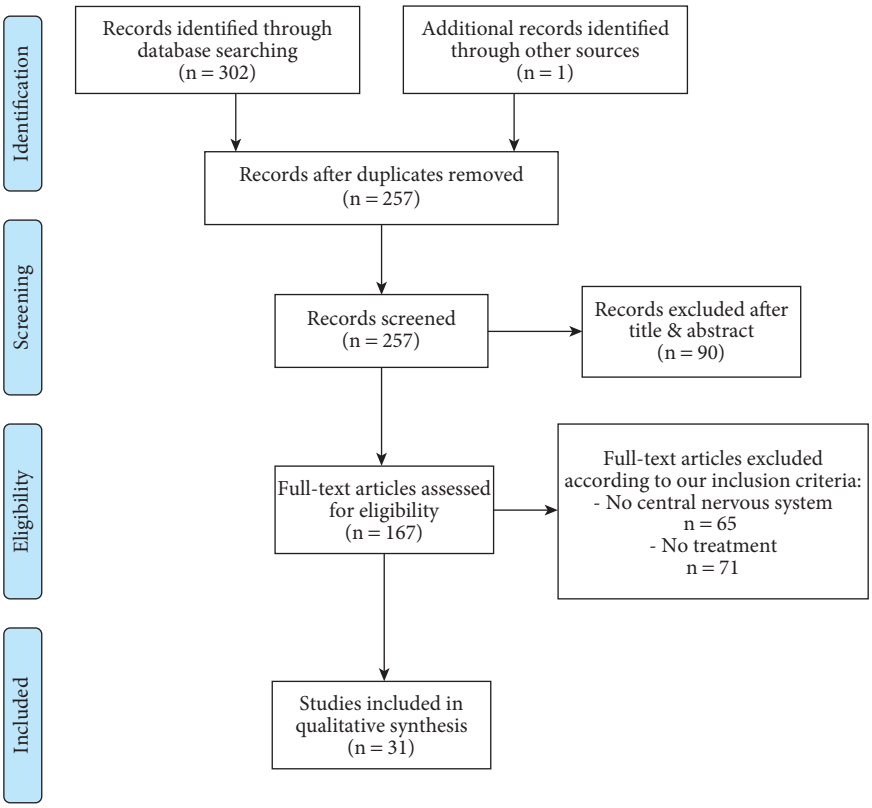

Fig. 1 PRISMA flow diagram.

treated with phosphodiesterase type 5 inhibitors (PDE5Is) [16–21].

History

Literature reported absolute exclusion criteria to better evaluate PDE5Is efficacy and avoid possible bias in clinical trials: patient's age (<18 years), concomitant neurological illness, neurological instability (no modification of previous neurological status in the past 6 months). Neurological patients were excluded if not in a stable partnership (relationship of <6 months) or were unable to attempt sexual intercourse at least once a week.

Moreover, current treatment with nitrates or nitric oxide donors, uncontrolled major psychiatric disorder or significant cardiovascular disease (stroke or myocardial infarction 6 months prior absolutely excluded the possibility of starting PDE5Is therapy) [16–21].

Conversely, the presence of co-morbidities such as diabetes or behavioural factors (e.g. chronic smoking or alcohol abuse) negatively influencing erectile function were not always considered absolute contraindications but they often required blood tests such as chemistry profile and glycated haemoglobin to determine whether using ED therapies would be possible [16,18,22,23].

General Assessment

Resting hypotension (systolic blood pressure <90 mmHg) or hypertension (systolic blood pressure >170 mmHg) were reported as exclusion criteria [16,22–24].

Uro-genital malformations and/or abnormalities, e.g. penile curvature or severe hypospadias, were reported as exclusion criteria for neurogenic ED treatment [22,23,25,26].

Neuro-physical Assessment

Safarinejad [20] reported neurophysiological studies, such as pudendal nerve cortical somatosensory evoked potentials (SEPs) and tibial nerve cortical SEPs before starting PDE5Is.

Men with spinal cord injury (SCI)

The American Spinal Injury Association (ASIA) Impairment Scale (AIS) was used to determine the level of lesion and their impairment grade: complete (AIS A) vs incomplete (AIS B–D) [16–20].

Through AIS, Khorrami et al. [19] defined two groups of lesions: the upper motoneurone (UMN) lesion referring to injuries above the thoracic (T) levels at or above T11 and lower MN (LMN) lesion with a level lower than T11.

Evaluation of erectile function

Some authors reported the presence of residual erectile function only in men with SCI, evaluating reflexive erection and/or psychological erection through the Erectile Assessment Score (EAS), which varies from 1 (no response) to 5 (full rigidity) [16,18,22,23].

Additionally, some authors performed intracavernosal injection (ICI) with prostaglandin E_1 (10–20 μg). Patients unable to obtain a valid erection were excluded from PDE5Is therapy because vascular disease was the main cause of their ED [17,21,24].

Men with MS

All men with MS treated with PDE5Is underwent standard neurological examinations using the Kurtzke Expanded Disability Status Scale (EDSS). A score >6 always indicated exclusion from PDE5Is treatment [21,24,27].

Outcome Measures for Neurogenic ED

Various outcome measures for evaluating the efficacy of neurogenic ED treatments were used. The most frequently used tool to specifically assess erectile function is the International Index of Erectile Function composed of 15 questions (IIEF-15) [16,21,24,27–30].

Laboratory Investigations

Before starting therapy, most authors performed blood sexual hormonal tests. Only patients with normal sexual hormonal profile levels were included [16,21–26].

PDE5Is Treatment

Men with SCI (Table 1)

The clinical efficacy of sildenafil (Viagra®), vardenafil (Levitra®), and tadalafil (Cialis®) is documented. More than 80% of patients reported trauma as the cause of their SCI [17–19,22,23,28]. UMN lesions, the preservation of residual erection with a score >2 on the EAS, and incomplete lesions (AIS A vs incomplete AIS B–D) represented positive prognostic factors for the success of PDE5Is therapy [22,25,29].

Furthermore, the medium- and long-term efficacy of sildenafil and tadalafil has also been documented in follow-ups of up to 10 years [16,22].

Significant statistical improvement ($P < 0.01$) on antegrade ejaculation using question 9 of the IIEF-15 was detected at the end of the clinical trials using tadalafil, vardenafil and sildenafil [25,29,31].

In studies comparing several ED treatments, Del Popolo et al. [17] showed that for patients with SCI tadalafil 10 mg was more effective at 12–24 h after dosing than sildenafil 50 mg.

Moemen et al. [26] evaluated the efficacy, safety and patient preference for different ED treatments. One 20-patient group

Table 1 PDE5i results for neurogenic ED in SCI patients.

	Reference (year)	Type of Trials			Study duration, weeks	Number of patients on PDE5Is (dose, mg)/total	IIEF-15 domains	SEP (1–5)	GEQ (1–2)	Other tools	*P*
		Multicentre	RCT	Control group							
Sildenafil											
	Ergin et al. [18] (2008)	Yes	Yes	Placebo	16	50 (50–100)/100	EF OS				*<0.05** *<0.01*
	Khorrami et al. [19] (2010)	No	Yes	Placebo	24	59 (25–100)/105				IIEF-5	*<0.05***
	Lombardi et al. [16] (2009)	No	No	N/A	480	37 (50–100)/37	EF, SS, OS				*<0.05*
	Moemen et al. [26] (2008)	No	No	N/A	4–8	60 (25–100)/60				IIEF-5	*<0.01*
	Soler et al. [31] (2007)	No	Yes	Tadalafil (10–20 mg) Vardenafil (10–20 mg)	≈40	57 (50–100)/90	EF, SS, OS, EJ, OF				*<0.05*
Tadalafil											
	Morgentaler et al. [30] (2006)	Yes	No	N/A	12	49 (10–20)/49	EF, OS, SS	SEP 1–5			*<0.01*
	Giuliano et al. [25] (2007)	Yes	Yes	Placebo	12	142 (10–20)/186	EF, EJ	SEP 2	GEQ 1,2		<0.01
	Lombardi et al. [22] (2009)	No	No	N/A	144	74 (10–20)/74	EF, OS,SS	SEP 2,3			*<0.01*
	Del Popolo et al. [17] (2004)	No	Yes	Sildenafil 50 mg	12	28 (10)/28		SEP 2,3			*<0.01*
Vardenafil											
	Giuliano et al. [28] (2006)	Yes	Yes	placebo	12	207 (5–20)/418	EF	SEP 2,3			*<0.01*
	Giuliano et al. [29] (2008)	Yes	Yes	placebo	12	207 (5–20)/418	EJ,OF				*<0.01*
	Kimoto et al. [23] (2006)	Yes	No	N/A	12	32 (10–20)/32	31% on 10 mg reached a mean EF > 26.9 at 4 weeks			N/A	N/A

*RCT, randomised controlled trial; N/A, not available; EF (1–5, 15), erectile function domain using questions 1 to 5 and 15; EJ (9), ejaculation frequency using question 9; SS (6–8), sexual satisfaction domain using questions 6 to 8; OF(10), orgasmic function using question 10; OS (13–14), overall satisfaction domain using questions 13 and 14; GEQ 1, global efficacy questions 1 and 2; SEP(1–5), sexual encounter profile questions 1 to 5; *Only for the 20 patients with incomplete lesion. **Only for patients with UMN lesion (37/45 using sildenafil vs 7/27 treated with placebo).*

was given ICI (10 μg prostaglandin E_1 or 0.5 mL Trimix) for 1 month and was then shifted to sildenafil. In all, 18 patients reached normal scores in the erectile domain of the IIEF questionnaire composed of five questions (IIEF-5) both with sildenafil and ICI vasoactive medication. However, 14 of 20 patients reported that they preferred sildenafil due to its easier administration. Another group of 20 patients used a vacuum device for 1 month, and subsequently sildenafil for 1 month. In all, 14 patients reached a normal erectile domain score with the vacuum device compared with 18 with sildenafil. None from this group was satisfied by the vacuum device therapy.

Finally, Soler et al. [31] in a randomised controlled trial comparing three different PDE5Is, showed that only the sildenafil group had a statistically significant improvement on the ejaculation and orgasmic domains of the IIEF-15. All three groups showed a significant amelioration on erectile function, satisfaction and overall satisfaction.

MS

Three sildenafil studies reported contradictory efficacy results for patients with MS with ED. Fowler et al. [27] showed an 89% improvement rate in erectile function of the patients selected. Lombardi et al. [21,22] using tadalafil (10 or 20 mg) confirmed a high percentage of erectile function enhancement, similar to the Fowler et al. study. In all, 70 of 92 patients (76.1%) who completed the 12-week treatment reached a normal score for the IIEF-15 erectile function domain. On the contrary, Safarinejad [20] did not find sildenafil improved erectile function at all compared with placebo.

Parkinson's disease

One study of Safarinejad et al. [24] was selected according to our criteria. In all, 116 patients in the sildenafil 100 mg group showed a significant increase in the IIEF erectile function score and in the percentage of 'Yes' responses to the Global Efficacy Questions 2 and 3 ($P < 0.001$) compared with 115 patients in the placebo group. A normal erectile function domain score (≥26) was achieved by 56.9% and 8.7% of the patients in the sildenafil and placebo groups, respectively ($P = 0.001$).

Side-Effects of PDE5Is

The most common side-effects reported in men with neurogenic ED using PDE5Is were headache and flushing. A low percentage of patients (<5%) discontinued treatment for severe adverse events (AEs) correlated to the drug assumption [16–21,24].

Other Treatments for Neurogenic ED

Drug therapy

Fampridine (also known by its chemical name of 4 aminopyridine, or 4-AP) is a specific drug used for neurogenic spasticity in patients with chronic and incomplete SCI or MS. One study evaluated the impact of this drug on erectile function as well. Two domains of the IIEF-15, erectile function ($P = 0.016$) and orgasmic function ($P = 0.032$), were significantly improved at the end of the 12-week treatment compared with placebo in only one (SCI-F301) of the two identical double-blind placebo-controlled studies including 185 male patients. In all, 19 patients (16.7%) discontinued because of severe AEs. The authors did not report data on previous treatments for neurogenic ED [32].

Strebel et al. [33] showed disappointing results with fixed dosages of sublingual apomorphine (3 mg). Only two of 22 patients were able to achieve valid sexual intercourse. In all, 11 patients of 22 presented side-effects, and two of them discontinued the treatment for intolerable AEs.

Pohanka et al. [34] reported that 14 patients with advanced Parkinson's disease and treated with a fixed dose of 3 mg of pergolide mesylate (Permax®) showed statistical improvement in all IIEF-15 domains compared with baseline up to the final 12-month follow-up. Concerning the IIEF-15 erectile function domain their mean score increased from 9.3 to 23.9 at the final follow-up ($P < 0.01$).

In a prospective randomised, double-blind trial comparing the effects of 3-months anastrazole plus testosterone (18 patients) vs testosterone plus placebo (18 patients) in hypogonadic epileptic men, Herzog et al. [35] found both groups significantly increased their scores ($P < 0.001$) on the IIEF-5.

Perineal electrostimulation

In a study by Shafik et al. [36], 18 patients with MS with neurogenic ED showed a substantial rise in intracavernosal pressure during repetitive percutaneous perineal electrostimulation lasting from 15 to 20 min ($P < 0.05$).

Neuromodulation

In two studies in which men with incomplete SCI were submitted to a monolateral sacral S3 electrode implant for their neurogenic LUTS (NLUTS) the evaluation of erectile function was assessed at baseline and in the follow-ups after permanent sacral neuromodulation (SNM) (Medtronic®, Minneapolis, MN, USA) at 3 months and subsequently every 6 months after permanent SNM using the IIEF-5. Scores ≥25%, compared with baseline, of the total IIEF-5 score indicated remarkable enhancement on erectile function, and those patients were considered 'responders'. An IIEF-5 score of ≥22 represents normal erectile function. Overall, 10 of 22 men with incomplete SCI reached and maintained a normal IIEF-5 score for >3 years at the final follow-up. However, four patients were contralaterally re-implanted on the S3 root during follow-up because they had lost clinical voiding and erectile function benefits [37,38].

On the contrary, 10 patients with complete lesions according to the AIS had bilaterally implanted sacral S3 lead during their shock phase to prevent neurogenic detrusor overactivity. Two patients reported subjective amelioration on erectile function at 6 and 24 months follow-ups, respectively [39].

Penile prosthesis

As for penile prosthesis, Zermann et al. [40] showed that sexual intercourse was possible for 77 of 92 patients with SCIs (83.7%) with a mean follow-up of ≈7 years for patients who had exclusively undergone penile prosthesis for ED. Several types of penile prosthesis were used. Only nine patients were included pre-sildenafil release and they were 'non-responders'. During follow-ups, 12 patients (16.3%) did not use the prosthesis for sexual intercourse. They complained about instability of the erect penis or symptoms related to the concord phenomenon.

Women

History

Women with a previous history of sexual dysfunction before their diagnosis of neurological illness were excluded for treatments [32,41–44].

Furthermore, a woman's neurological status had to be stable for ≥6 months before therapy. Only sexually active women were included [32,41–44].

Information regarding the correlation between the use of specific medication for their neurological disease and sexual response was requested: 'not related', 'partially related' and 'totally related' [44].

Specific Neurological Assessment

The AIS assessment provided inclusion/exclusion criteria or predictable factors for success on the basis of the level and degree of lesion. Women with the ability to perceive T11–L2 pinprick sensations may have psychogenic genital vasocongestion. Reflex lubrication and orgasm are more prevalent in women with SCI who had preserved the sacral reflex (S2–S5). For those with complete SCI of the sacral segment, arousal and orgasm may be evoked through stimulation of other erogenous zones above the level of lesions such as the breasts, lips, and ears [2,45].

Neurophysiological assessment using pudendal and tibial SEPs was reported by one author [42].

Specific Questionnaires for Assessing Primary Sexual Dysfunction

The tools most used for neurological females were the Female Sexual Function Index (FSFI) and the Sexual Function Questionnaire (SFQ) (Table 2).

Table 2 Results on neurogenic female sexual dysfunction.

Reference (year)	Neurological disease	Type of trial	Study duration, weeks	Treatment dose, mg	Number of patients treated/total included	Outcome measures	Domains	P
Dasgupta et al. [42] (2004)	MS	Cross over RCT placebo controlled / open label extension phase	28 / 36	Sildenafil 25–100	19 completed RCT phase 12/19 completed the extension phase	SFQ	Lubrication Orgasm	<0.05 <0.05
Cardenas et al. [32] (2014)	Incomplete SCI	Two Multicenter RCTs placebo controlled	12	Fampridine 25 twice daily	14/27 17/31	FSFI		>0.05 >0.05
Lombardi et al. [43] (2009)	Incomplete SCI	Open label Prospective study	≈96	Permanent SNM	4/9	FSFI	4 maintained up to the final follow-up total score of the FSFI ≥26.55 and a 50% of FSDS score	
Alexander et al. [41] (2011)	SCI	RCT placebo controlled	16	Sildenafil 25–100	67/129	SFQ		>0.05
Gil-Nagel et al. [44] (2005)	Epilepsy	Multicenter open label prospective trial	32	Lamotrigine 100–200/day	33/60 naïve group 27/60 shifted group	CSFQ	All domains Desire/frequency and desire/interest	<0.05 <0.05

RCT, randomised controlled trial; FSFI, female sexual function index questionnaire composed of 19 items in six domains (desire, arousal, lubrication, orgasm, satisfaction, and pain as well as a total score); SFQ, sexual function questionnaire composed of 34 items in eight domains (arousal-sensation; arousal-lubrication; arousal-cognitive; desire, enjoyment, orgasm, pain and partner); CSFQ, changes in sexual functioning questionnaire including 14 items in five dimensions (desire/frequency, desire/interest, pleasure, arousal excitement and orgasm).

Specific Questionnaires for Secondary/Tertiary Sexual Dysfunction Conditions

A number of questionnaires or other objective evaluations (e.g. urodynamics, bladder diary) combined with specific questionnaires for primary sexual dysfunction (e.g. FSFI) were used to evaluate the degree of secondary factors influencing sexual function such as: bladder, bowel function, spasticity, and depression [32,37].

Laboratory Investigations

There is no recommended consensus about routine laboratory tests for neurological women with sexual dysfunction. Pregnancy was reported by some authors as an exclusion criterion for treatment [32,42,43].

Treatment Options for Neurogenic Primary Sexual Dysfunction in Females

There are no evidence-based therapeutic options to treat neurological women with sexual dysfunction.

Drug therapy

Dasgupta et al. [42] in a double-blind, randomised, placebo-controlled, crossover study investigated the positive effects on FSFI on women with MS of sildenafil starting with 50 mg and dose adjustment (25–100 mg) for tolerability or greater efficacy. In a double-blind placebo-controlled, flexible-dose study with a larger cohort of females with SCIs, Alexander et al. [41] showed a lack of clinically meaningful benefits with sildenafil.

Two phase III, multicentre, randomised, placebo-controlled clinical trials evaluating the use of fampridine sustained-release tablets to treat spasticity in females with incomplete chronic SCI did not show an amelioration in female sexual function [32].

Gil-Nagel et al. [44] in an open, prospective, multicentre study showed that females naïve to other anti-epileptic drugs who initiated lamotrigine for various seizure types gained more benefits in sexual function than women who switched to lamotrigine from previous anti-epileptic drugs inducing the hepatic P450 enzyme such as valproate, carbamazepine and phentyoin.

Neuromodulation

Female patients who underwent SNM for NLUTS were also evaluated for sexual dysfunction.

Lombardi et al. [43], in a 2-year follow-up after permanent SNM, reported that 36.5% of females with SCI and sexual dysfunction obtained positive effects on sexual response and showed a remarkable concomitant improvement through the Female Sexual Distress Scale (FSDS) questionnaire, which measures sexually related distress.

Discussion

Many individuals with neurological disorders have impaired sexual function that require various steps to manage challenges, starting with an accurate assessment of the disorder such as to tailor diagnostic investigations and treatments to each individual. Ideally, due to the complexity of sexual issues for neurological patients, management should be based on multidisciplinary teamwork starting at the onset of the neurological diagnosis and lasting for life. Scheduled follow-ups at rehabilitation centres or in neurological departments must comprehend sexuality issues. Therefore, cooperation among medical specialists and other health professionals is needed [10,46]. Although the PLISSIT (Permission, Limited Information, Specific Suggestions, and Intensive Therapy) model, which has health professionals actively addressing primary, secondary, and tertiary factors, has been successfully applied only to patients with SCI, it could be useful for all neurological patients [2].

No data have been found about treatment of sexual dysfunction in spina bifida adults over recent decades. One possible reason may be the difficulty in evaluating their sexual dysfunction and its impact on their quality of life, due also in part to psychogenic issues. Adolescents with spina bifida cannot have proper knowledge of sexuality because they have never experienced it. Ideally an appropriate sex education starting in childhood and taking into account all aspects related to sexuality should be provided for their sexual health [47–49].

Neuro-physiological investigations are not mandatory for neurological patients before starting sexual dysfunction treatment, neither to determine the severity of ED in men, nor the type and degree of female sexual dysfunction. Moreover, their role as predictive factors for the success of ED and female sexual dysfunction therapies is controversial. A hypothesis, especially relevant for women, is that several neurophysiological tests do not examine certain aspects that may influence female sexual response such as marital satisfaction and marital communication, according to the Basson et al. [50] model.

For the evaluation of blood sexual hormones, most studies on males with neurogenic ED performed hormonal assessment before oral treatments at baseline in order to avoid ED related to sexual hormonal abnormalities [16,20–23,25,26].

It is well documented that neurological patients have higher risks of hormonal modifications (mainly low levels of testosterone) compared with the non-neurological population [51]. Checking the hormonal status may discriminate between possible therapies and help to decide appropriate treatment. In

women of reproductive age, a correlation between female sexual dysfunction and blood sexual hormonal status is not demonstrated. However, the interaction between the CNS and female sexual function hormones and their aetiological roles in sexual dysfunction is complex. A strategy that includes blood sexual hormonal assessment and subsequent hormonal replacement is still undefined [52,53]. Both testosterone and oestriol have been found to induce anti-inflammatory, as well as neuroprotective effects in MS [53]. Furthermore, oestrogen replacement probably benefits women with SCI more than it does non-neurological patients. In fact, oestrogens prevent osteoporosis, which is accelerated in the paralyzed and not charged areas [52,54].

Despite those potential benefits, there are some negative aspects to using hormonal therapies on neurological patients. For example, females with an absence or reduction of lower limb motility may have a high risk of thromboembolism. Again, the use of sexual hormones on females with catamenial epilepsy may increase the rate of seizures [1,4].

For specific neurogenic ED treatments, the existing body of evidence suggests that the PDE5Is sildenafil, vardenafil and tadalafil are first-line therapies for patients with SCI. However, no information has been reported to date on the efficacy/safety of the newer PDE5Is, avanafil and mirodenafil. Data on PDE5Is used on other patients with neurogenic ED are partial or missing. For male patients with Parkinson's disease and MS, the existing results are encouraging. For other central neurological diseases, such as MSA and epilepsy, data seems to suggest avoiding the use of PDE5Is as a first-line treatment for neurogenic ED due to possible severe AEs. Hussain et al. [55] showed that three of six patients with MSA had a severe blood pressure plunge 1 h after sildenafil was administered (systolic blood pressure <65 mmHg and diastolic blood pressure <55 mmHg). Instead, information is currently insufficient to speculate whether PDE5Is may prompt epileptic seizures in previous non-epileptic subjects, and whether they may increase ictal episodes in pharmacologically well-controlled seizure disorders [55–57]. However, the choice of anti-epileptic drug seems to be one cause of sexual dysfunction that is modifiable. Sexual dysfunction is related to anti-epileptic drugs that induce the hepatic P450 enzyme with a progressive increase of sex-hormone-binding-protein levels and consequently a decrease in free, bioavailable testosterone [58]. This may explain the improvement in epileptic hypogonadic men on sexual function treated with testosterone [35].

Similarly, women who had previously used anti-epileptic drugs inducing cytochrome P450 improved sexual function less than women who started lamotrigrine as first monotherapy [59,60].

International guidelines recommend ICI vasoactive drugs as a second-line treatment [2]. However, data on the efficacy of ICI vasoactive medications for neurogenic ED are lacking following the release of PDE5Is. Thus, no studies have been done that exclusively include PDE5I non-responders or offer different possible solutions as second-line treatment, alone or combined (vacuum device, testosterone, ICI plus PDE5Is, or PDE5Is plus testosterone).

In addition, there are no data on the daily use of PDE5Is as penile rehabilitation for patients with a CNS disorder, compared with those with a peripheral neurological disease, to favour the enhancement of angiogenesis and neurogenesis of corpora cavernosa function [61].

For specific treatments for primary female sexual dysfunction, data are poor and controversial. Particularly, sildenafil has been tested only on female patients with MS and SCI for possible benefits in arousal response, although these findings need to be confirmed with larger cohorts [41,42].

A common treatment for NLUTS for both genders is permanent SNM. The presence and impact of this therapy on sexual function has been evaluated by validated questionnaires at baseline and during follow-up after permanent SNM implantation in the medium- and long-term [43,52,56].

The objective assessment of sexual function in a treatment approved for NLUTS is a new strategy of evaluation. Although definitive SNM is not yet indicated for sexual dysfunction, an objective evaluation approach regarding sexual function should be recommended for all neurological patients [37,38,43,62,63]. The mechanism of SNM on sexual function is unknown, but potential direct mechanisms are possible. Positive findings in neurological females compared with non-neurological patients supported this thesis [43,63]. Only continual monitoring of patients who have undergone permanent SNM may clarify possible predictable and positive factors on sexual dysfunction, such as stimulation setting parameters [37,38,43,63].

A similar methodological approach was recently reported on, which evaluated the impact of fampridine (a drug mainly used for lower limb motility) on sexuality, using validated questionnaires for both genders [32]. At the same time, during primary treatment (such as PDE5Is) for sexual dysfunction, objective assessment should also be done to evaluate impact on secondary conditions that may interfere with therapeutic success [64]. This holistic methodology may help to select an appropriate and patient-tailored treatment. Based on the multiple factors that influence neurogenic sexual dysfunction, creating specific questionnaires for these patients is necessary.

Conclusions

Although sexual dysfunction is a major burden for patients with CNS disorders, high-level evidence is only available on PDE5Is that treat ED; well-designed prospective studies are urgently needed for both genders.

Conflicts of Interest

G.D.P. consultant for: Hollister, Ipsen, Allergan, Wellspect, Apogepha; Honorary Speaker: Astellas, Allergan, Sigma Tau; Trials: Pfizer, Allergan, Ipsen, Recordati, Astellas.

All other author have nothing to disclose.

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Abbreviations: AE, adverse event; ASIA, American Spinal Injury Association; AIS, ASIA Impairment Scale; EAS, Erectile Assessment Score; ED, erectile dysfunction; FSDS, Female Sexual Distress Scale (questionnaire); FSFI, Female Sexual Function Index; ICI, intracavernosal injection; IIEF(-5)(-15), International Index of Erectile Function questionnaire (composed of five questions) (composed of 15 questions); (L)(U)MN, (lower) (upper) motoneurone; MS, multiple sclerosis; MSA, multiple system atrophy; NLUTS, neurogenic LUTS; PDE5I, phosphodiesterase type 5 inhibitor; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SCI, spinal cord injury; SEP, somatosensory evoked potential; SFQ, Sexual Function Questionnaire; SNM, sacral neuromodulation.