W15: Neurodegenerative disease's impact on bladder function: A multidisciplinary approach in diagnosis, treatment and improving quality of life
Workshop Chair: Christian Cobreros, Argentina
03 September 2019 14:00 - 15:30

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Aims of Workshop
In the past decades, the aim of the urologist was to treat the neurogenic bladder dysfunction through antimuscarinics and surgical procedures (e.g. bladder augmentation). More recently, new drugs have been approved and new surgical procedures have been developed, but more importantly a new role for the multidisciplinary approach has been established. We will encourage this new concept of treatment to the audience, taking into account differences in incomes of different societies. This a new workshop based on the state of the art knowledge and latest techniques that are available and with an international pannel of experts we will extent our experience in working under different economic circumstances.

Learning Objectives
Identify the different patterns of neurological bladder impacts of neurologic diseases.

Target Audience
Urology, Conservative Management

Advanced/Basic
Intermediate
Understanding differences in neurodegenerative diseases

Christian Cobreros

Understanding clinical presentations in lower urinary tract dysfunction due to neurological disorders is very challenging. Nevertheless, we know that a wide variety of neurological conditions, acute or chronic, may affect the functionality of the bladder, or sphincter, or the pelvic floor musculature innervation resulting in different conditions as well as similar ones. Their clinical presentations is determined by the site and the nature of the lesion.

In a simple classification, but a very useful one, is to base the clinical urodynamic findings in terms of the lesion level, we also expected classical symptoms for each level:

- **Suprapontine lesion**: detrusor overactivity due the lack of cortical inhibition, so storage symptoms are to be expected.
- **Pontine micturition**: if its preserved the control of the coordination of detrusor–sphincter mechanism will be preserved, as this center is the responsible for the coordination of the relaxation of the sphincter and pelvic floor musculature during bladder contraction
- **Infrapontine-suprasacral lesions**: this patient may present with a variety of clinical presentations due to a complete or partial lesion, in case of cortex and coordinated signal from the pontine center are injured the patient could present with neurogenic and detrusor over activity and sphincter dyssynergia
- **Sacral micturition center**: when this center is compromise we should expect involuntary contractions of the bladder as if it is a reflex center for bladder contractions
- **Infrasacral lesions**: In these lesions, even the reflex bladder contractions are lost due to and interruption of the signals between the bladder and all micturition centers, which will result in a clinical manifestation of a neurogenic detrusor underactivity or areflexic detrusor or even a sphincter deficiency.

Although this systematic and practice review of lesion level of neurogenic urological disease the clinical presentations in neurogenerative diseases may vary form presented above, and this classification although its more useful in traumatic lesions but in the clinical practice in neurogenerative diseases we should expected some evolution of the clinical presentations and in some cases a completed different pattern within the clinical evaluation due to a progressive neurological disease.

**Suprapontine Lesion (Brain)**

**Cerebrovascular Accident (Stroke)**

- acute phase of CVAs patients
- post-acute (chronic) phase of stroke
LUT dysfunction following stroke

Degeneration disease and syndromes

- Parkinsonian Syndrome
- Multiple System Atrophy
- Alzheimer disease
- Intracranial tumors

Spinal cord: Infrapontine-Suprasacral lesions

- Demyelination (multiple sclerosis, transverse myelitis)

Spinal Cord and Peripheral Nervous System: Sacral-Infrasacral lesion

- Intervertebral Disk Prolapse
- Peripheral Neuropathies (Diabetes Diabetes mellitus, radiation therapy)

Urodynamic assessment in this population. When? Why? Are there any other diagnostic methods that you should use?

Gustavo Garrido

Neurodegenerative disorders (ND) such as Parkinson’s Disease (PD), Alzheimer Disease (AD), Multiple Sclerosis (MS), Multisystemic Atrophy (MSA) and other forms, are systemic diseases which leads to loss of control of various motor and non-motor systems including the lower urinary tract. They are chronic and progressive challenging clinical entities which severely affects quality of life. Frequently associated with lower urinary tract dysfunction like urinary incontinence, nocturia or urinary retention, they often lead to complications like dermatitis, urinary tract infections, social retraction and could be the reason for early institutionalization.

ND and Benign Prostate Hyperplasia (BPH) is highly prevalent in late middle-aged men, as Urinary Incontinence (UI) is in middle-aged women, making the chance of concomitance of both pathology highly probable. This situation is a complex picture for decision making.

Urodynamic studies are a useful diagnostic approach for understanding bladder and urethral dysfunction associated with neurodegenerative disorders.

Overactive detrusor is the most common finding in urodynamic tests, however weak or absent voluntary detrusor function is also a common finding. Findings like Detrusor-sphincter dyssynergia (DSD) is not uncommon. And half of the patients with PD have mild urethral obstruction, due to impaired relaxation or delayed striated sphincter relaxation (also known as Sphincter bradykiniesia). In addition, the DSD is present in almost half of patients with MSA and Detrusor Hyperactivity during bladder filling phase with Impaired Contraction during voiding (DHIC) is not uncommon.

Differentiating among different urodynamic conditions is particularly important for the evolution and prognosis of lower urinary tract symptoms (LUTS), especially during the early course of the disease.

Urodynamic investigations in patients with ND is crucial for a correct diagnosis that leads to a better comprehension about the physiopathology of such complex diseases.

Is it always easy to differentiate urgency from another clinical presentation of these patients (e.g. pain, hypersensitivity, bladder irritation, infection)? How can we avoid over medication?

David Castro-Diaz

Many different conditions affecting the lower urinary tract function origin in the nervous system and it is important to recognise that lower urinary tract symptoms (LUTS) may be one of the first signs of neurodegenerative disorders such Alzheimer’s disease (AD), Parkinson’s disease (PD), dementia and PD-related disorders, Huntington’s disease (HD), Spinocerebellar ataxia (SCA or Spinal muscular atrophy (SMA).

The symptom “Urgency”, defined as “the complaint of a sudden compelling desire to pass urine, which is difficult to defer”, is sometimes one of the first symptoms indicating a neurodegenerative disorder which may later lead the patient to a fatal outcome. PD patients and others with neurodegenerative disorders suffer loss of dopaminergic neurons inducing deficit or abnormality of
the neurologic control of micturition. More than 60% of patients with PD have LUTS and 30% refer urinary incontinence. Patients suffering neurodegenerative disorders often express LUTS and its onset may even serve as a diagnostic marker. Patients with bladder pain syndrome/Interstitial cystitis (BPS/IC) and those with hypersensitive bladder, usually refer the symptom of urgency as linked to fair to pain while patients with neurodegenerative disease or overactive bladder may express urgency as linked to fair to incontinence. However, differentiating urgency from another clinical presentation is not easy particularly in patients with cognitive disorders.

The onset of disease and timescale of symptoms may give clues to the cause of urinary problems. In some cases, LUTS occur early, in the course of disease, whereas in others they may develop later, and could be confused with dysfunctions of a non-neurogenic origin, such as benign prostate enlargement or bladder outlet obstruction. The extent to which symptoms ‘bother’ the patient is important and should be determined both subjectively and objectively, through a proper clinical history and the use of a voiding diary, questionnaires and quality of life evaluation. This approach enables us to match therapy with patient’s motivation and to monitor the success of treatment. The physical status of the patient will have an important influence on the capabilities for maintaining a therapeutic strategy.

Attention should be paid to any medications taken by the patient, as several drugs can have detrimental effects on the urinary tract. For example, diuretics prescribed for hypertension are associated with bladder overstretching. Furthermore, the use of any antihypertensive agent in younger patients should alert the urologist to the likelihood kidney dysfunction due to obstructive uropathy. Drugs that can alter the functioning of the urinary tract include opiate-containing painkillers, which reduce bowel motility and antiparkinsonian agents which act as parasympatholytics and so impair detrusor contractility. Muscle relaxants used to treat spasticity may also cause bladder hypocontractility and urinary retention; alternatively, they can induce pelvic floor laxity leading to stress incontinence.

Sufferers of neurodegenerative disorders and elderly people require taking multiple medications which may have side effects and unwanted drug reactions. Muscarinic receptors antagonists have been shown to cause cognitive disorders in elderly patients and should be used with caution in patients with neurodegenerative disorders preferably choosing those drugs which do not cross the blood-brain barrier. As some commonly used drugs have antimuscarinic properties it is important to avoid overmedication that may increase the exposure to side effects. Potential signs of overmedication include drowsiness, physical complications like dry mouth and ulcers, confusion, withdrawal from family or friends, hallucinations, dizziness or falls, fractures and seizures.

**Oral medication. What do we have today? Is combination better? How to decide when to move to another step?**

Christian Cobreros

We will review the most current literature on oral medication for neurogenic bladder to treat not only detrusor overactivity, but also to improve bladder capacity, compliance and to treat urinary incontinence.

Medical therapies will be discussed in this section as we do have another section in which advances therapies as onatoxinabotulinum will be discussed.

At the same time we will go into the improvement of quality of life of single drug vs combination and when it’s the optimal time to move to the next step.

**Drugs that have action in the storage phase**
- Antimuscarinic drugs
- Choice of Antimuscarinic agents
- Side-effects
- Why do they have such a great drop out?
- Agonist β3
- Its combination better?

**Drugs that have action in the pressure flow phase**
- Alpha blockers
- Phosphodiesterase inhibitors (PDE5Is)

**Drugs with different mechanisms of action**
- Detrusor underactivity
- Decreasing bladder outlet resistance
- Increasing bladder outlet resistance

Is combination better?
When to move to the next step?
Surgical approach: neurostimulation, botulinum toxin, neuromodulation, bladder augmentation

Carlos D'Ancona

The surgical approach in neurogenic detrusor overactivity is indicated when failures occur in pelvic floor muscles training and drugs administration. The classification of failure is not well defined but we can consider it to be, when the patient is unsatisfied.

Between neurostimulation, neurotoxin, neuromodulation and bladder augmentation, the question is how to choose one of this? Transcutaneous or percutaneous nerve stimulation is a minimal invasive treatment with good response in patients with multiple sclerosis and Parkinson’s disease. The botulinum toxin has the advantage that is reversible after 8 to 12 months. Can be use as test before a definite treatment. The results of BT are excellent improving in symptoms, in urodynamics and Quality of Life. There is still the question for how long it is possible to use this treatment. Many papers show that it is effective for more than 10 years.

For neuromodulation treatment, there should be some neuronal connections between the bladder and brain. So, patients with complete spinal cord injury are not a candidate for implantation of neuromodulation. However, patients with multiple sclerosis and Parkinson disease present good results with a long follow up.

Performing bladder augmentation decreased much due to the other techniques used. This technique presents some adverse effects such as bladder stone, urinary tract infection, perforation of the reservoir and others. The advantages of this technique are the long-term good results. Myelomeningocele and spinal cord injury patients have a great life expectancy and this technique should be considered.

Bladder outlet obstruction in neurodegenerative patients

Gustavo Garrido

Neurodegenerative Disorders (ND) and Lower Urinary Tract Symptoms (LUTS) due to Bladder Outlet Obstruction (BOO) caused by Benign Prostate Hyperplasia (BPH) are very frequent findings in middle-aged men. Different ND can present contrasting urodynamic conditions which makes treatment decision a challenging circumstance.

ND are systemic diseases which involves neuronal degeneration, leading to a loss of control of various motor and non-motor systems, including the lower urinary tract. Motor symptoms such as gait difficulties, postural instability, rigidity and resting tremor are frequent and have a direct impact in LUTS management. LUTS could precede non-motor symptoms like orthostatic hypotension and other motor disorders in early stages of the disease leading to increased urological pharmacological related treatment adverse effects.

Dementia, cognitive impairment and hallucinations are not uncommon in patients with PD and must be taken in account at the time of BOO treatment.

Published data indicate a high incidence of postprostatectomy urinary incontinence in patients with ND and particularly PD, compared to those without ND who undergo surgery. However poor outcomes of patients following prostate surgery might be a result of the inadvertent inclusion of patients with MSA, which are misdiagnose as PD. And more than half of all MSA patients have urinary symptoms before development of motor symptoms, resulting in a risk of inappropriate indication of BPH surgery.

Surgical treatment of patients with ND and comorbid BPH can be performed in selected patients. The correct neurologic diagnosis together with the exact urodynamic condition are crucial in the decision for best treatment strategy.

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Neurodegenerative disease’s impact on bladder function: A multidisciplinary approach in diagnosis, treatment and improving quality of life

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Neurodegenerative disease’s impact on bladder function: A multidisciplinary approach in diagnosis, treatment and improving quality of life

UNDERSTANDING CLINICAL DIFFERENCES IN NEURODEGENERATIVE DISEASE

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Neurodegenerative disease’s impact on bladder function: A multidisciplinary approach in diagnosis, treatment and improving quality of life


NLUTSD are one of the most challenging problems in urology

WORLDMAP DEMOGRAPHIC AGING IS PROVING THAT HEALTHCARE IS IMPROVING

NEUROGENIC LOWER URINARY TRACT DYSFUNCTION (NLUTD) OF THE URINARY BLADDER AND URETHRA

CENTRAL OR PERIPHERAL NERVOUS SYSTEM DISEASES

THE TYPE OF DYSFUNCTION DEPENDS ON DAMAGE LEVEL, INTENSITY, AND EXTENT

TIME-LENGTH OF SPECIFIC DISORDER
(Multiple Sclerosis, Parkinson disease, Dementia, etc)

NEUROLOGICAL CLINICAL PRESENTATIONS ARE NOT AN STATIC CONDITIONS

NEUROGENIC LOWER URINARY TRACT DYSFUNCTION (NLUTD) OF THE URINARY BLADDER AND URETHRA

SYNDROME (BOO...)

TREATMENT

ALtered BEHAVIOR

IMPAIRED ATTENTION

This clinical scenarios may all be combined together, so it’s important to differentiate the symptoms in early stages

ALZHEIMER’S DISEASE / WML / DEMENTIA WITH LEWY BODIES

Alzheimer’s disease (AD)

- Alzheimer’s disease is the most common cause of dementia
- In Western countries is the most common cause of moving into a nursing home

Urinary Incontinence

Significant relationship with

Advance age

Deficits in attention

Reduced verbal fluency

Late disorder

Urinary Incontinence in AD is more than a consequence of an specific disorder of the urinary tract related with neuronal injury

OAB

Impaired attention and orientation

Reduced Environmental Self awareness

Increase the impact of OAB


The management of NLUTD in Alzheimer’s disease (AD) is difficult for several reasons:

1. Impaired attention and orientation interfere with the self-management of an OAB due to preventing voiding, double voiding, or an adequate response to urgency.

2. Antimuscarinic drugs may worsen cognition and interact with acetylcholinesterase inhibitors given to improve cognition and activity of daily living.

Time of onset of Urinary Incontinence is important

MARKER OF INSTITUTIONALIZATION

PREDICTOR OF POOR OUTCOME

There is an alteration of the bladder circuit of micturition determined by PET studies which show the lowest presentation of NDO in urodynamic tests.
PARKINSON'S DISEASE

PARKINSON'S DISEASE:

The most common degenerative neurological disease

Motor Symptoms:
- Reduced/degeneration of nigrostriatal dopaminergic neurons
- Non-Motor
  - Dysphagia (30–42%)
  - Constipation (50%)
  - Orthostatic hypotension (20–58%)
  - Depression (5–10%)
  - Cognitive decline (4 times higher than healthy individuals)
  - Sexual dysfunction (63–83%)

LUTS

Urgency, Nocturia, Frequency

[The net effect of the basal ganglia on the micturition reflex is inhibited.]

NON-MOTOR SYMPTOMS:

- Incomplete bladder emptying
- Urodynamically incomplete bladder emptying
- Higher frequency of nocturnal voiding
- Higher nocturnal urine production
- Increased detrusor storage pressure
- Urge incontinence
- Less bladder capacity

As in other Basal Ganglia disease Urinary Symptoms preceeds motors manifestations in MSA

This indicates that many of these patients seek urological advice early in the course of their disease.
Multiple sclerosis

All the pathways can be affected simultaneously or not. So there are a lot of variable symptoms and combinations of them that can be present in clinical presentation.

MRI findings could be present without clinical significance first of all, at the first stages of the disease (during the first years) but they can turn into clinically significant.

TAKE HOME MESSAGES

IN NEURODEGENERATIVE DISEASES:

- CLINICAL UROLOGICAL MANIFESTATIONS SHOULD NOT BE TAKEN AS A UNIQUE MANIFESTATION; AGE, COGNITIVE IMPAIRMENT, MOTOR DISABILITY, COMORBID CONDITIONS SHOULD BE CONSIDERED FOR A PROPER DIAGNOSIS

- CLINICAL AND URODYNAMICS UROLOGICAL FINDINGS CAN CHANGE OVER TIME DUE TO CHANGES IN THE NEUROLOGICAL DISORDER

- UROLOGICAL MANIFESTATIONS CAN PRECEDE OTHER MANIFESTATIONS FOR YEARS

- URODYNAMICS ASSESSMENT IS NECESSARY FOR DETECTING NDO WITH BLADDER OUTLET OBSTRUCTION AS IT IS A THREATENING CONDITION

THANK YOU

GRACIAS

OBRIGADO
Urodynamic Assessment in This Population. When? Why? Are There Any Other Diagnostic Methods That You Should Use?

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Universidad de Buenos Aires
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Affiliations to disclose:
Nothing to Declare

Funding for speaker to attend:
Self-funded
Institution (non-industry) funded
Sponsored by:

Symptoms
38% to 71% patients with PD reported symptoms
• Storage Symptoms: urgency, frequency, nocturia, incontinence
• Voiding Symptoms: hesitancy, poor stream, interrupted stream, double voiding

Men >60 years may have BOO due to BPH.

Women may have SUI.


Symptoms
Severity of LUTS increases with Progression of PD

Other Autonomic Dysfunctions are present

Impacts QoL


Falls
Falls are one of the most serious complications of gait disturbances in Parkinson’s disease (PD).

More than 50% of PD patients fall at least twice in a given year and 1/5 of these patients experience trauma including bone fractures and intracranial hematomas as a result of a fall.

Urinary Incontinence was the factor that most significantly predicted falls status.

In a study of PD and multiple system atrophy (MSA) patients, found urinary symptoms in 72% of PD patients that were mainly attributed to DO (81%) and external sphincter relaxation problems (33%)

Multiple Sclerosis

Over 80% of patients with multiple sclerosis report the incidence of LUT symptoms.

LUT symptoms generally appear after a mean of 6 years of evolution of the neurological disease
- Urgency: 38–99%
- Frequency: 26–82%
- Urg incontinence: 27–66%
- SUI: 56%
- Voiding Symptoms: 6–49%
- Both storage and voiding symptoms coexist in 50% of patients


Evolution MS

The prevalence of DSD increases with the duration of multiple sclerosis.

DSD:
- 13% after 48 months of evolution
- 13% between 48 months and 109 months,
- 48% 109 months after diagnosis


Urodynamic in MS

Detrusor overactivity: 34–91%
Detrusor underactivity: 37%
Low bladder compliance: 2–10%
DSD–sphincter dyssynergia (DSD): 5–60%
DSD + detrusor overactivity: 43–80%
DSD + detrusor underactivity: 5–9%

Urodynamics in MS?

The International Francophone Neuro-Urological Expert Study Group (GENULF) recommends using urodynamics in the initial diagnosis of patients.

Urodynamic investigations:
- patients with risk factors predisposing to upper urinary tract damage
- concomitant SUI
- failure to first-line treatment
- if surgical treatment is being considered


Nocturia

Considerable impact on QOL
Associated with sleep disturbances, falls, hip fractures and greater mortality.

Possible Causes:
- sleep disorders
- reduced bladder capacity and DO
- Nocturnal polyuria


Non-Motor Symptoms:
- nocturia (77.3%)
- Urinary urgency (61.9%)
- Constipation (58.8%)
- Dementia (52.6%)
- Nocturnal polyuria (52.6%).


Dementia and Related Diseases

LUTS in dementia patients can be caused
- by the dementia itself
- by the neurological and urological pharmacotherapy
- by the ageing bladder or comorbidities.

Urgency and UI: Lewis Body Dementia > ALD
Detrusor Overactivity: LBD > ALD


Cerebral Spinal Fluid Tap Test in NPH

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Urodynamic testing after lumbar puncture may predict the outcome of a shunt operation in these cases.


The recovery rate of bladder function after shunt surgery ranges 30–70% of patients.

The recovery rate of OAB and urinary incontinence in INPH ranges around 20-80%.


Conclusions

Multiple and Diverse Variety of Symptoms
Multiple and Diverse Urodynamic Conditions
Check NMS [Autonomic Dysfunction] / Nocturia / Falls / QoL
Bladder Diary
PVR (MSA)
CFS Tap Test (NPH)
Identify Risk Factors (WMD)
Urodynamic / Videourodynamic...Always

For vascular incontinence, early identification of risk factors and initiation of secondary prevention are necessary.

Control of vascular risk factors: hypertension, dyslipidemia and diabetes.

Prevention might arrest the disease progress.

Correct Diagnosis

As many as 50% of MSA patients are commonly misdiagnosed as having PD. It is important to distinguish these 2 similar clinical entities because their urologic management is different.

David Castro-Díaz

Affiliations to disclose:
- Boston Scientific
- Contura
- Neomedic
- Medtronic

Funding for speaker to attend:
- Self-funded
- Institution (non-industry) funded

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- Astellas
- Boston Scientific
- Contura
- Neomedic
- Medtronic

It is always easy to differentiate urgency from another clinical presentation of these patients (e.g., pain, hypersensitivity, bladder irritation, infection)? How can we avoid over medication?

David Castro-Díaz
Spain

It is always easy to differentiate urgency from another clinical presentation of these patients (e.g., pain, hypersensitivity, bladder irritation, infection)? How can we avoid over medication?

David Castro-Díaz
Spain

### Neurodegenerative disorders

- Alzheimer's disease (AD) and other dementias.
- Parkinson's disease (PD) and PD-related disorders.
- Prion disease.
- Motor neurone diseases (MND).
- Huntington's disease (HD).
- Spinocerebellar ataxia (SCA).
- Spinal muscular atrophy (SMA).

### Parkinsonian syndromes

Include PD and atypical parkinsonism.

- Multiple system atrophy (MSA).
- Progressive supranuclear palsy (PSP).
- Corticobasal degeneration (CBD).
- Dementia with Lewy bodies (DLB).

### Neurodegenerative disorders

- Increase number of people with Neurodegenerative disorders due to worldwide aging.
- 24.2 million people living with dementia in 2001 & 4.6 million new cases annually.
- Predicted to double every year to 80 million cases by 2040.
- Total cost of brain disorders in 2010=798 billions€ in Europe (105b for dementia & 14b for PD).
- Need for medical care and hospital visits & reduce QoL among elderly.
- High rate of dementia & dependence (PD and ND 70% in within 8 years).

### Symptoms of advanced disease & comorbidity expected to rise accordingly


### Bladder dysfunction

- Integrated part of the syndrome.
- Due to other conditions.
- A consequence of the treatment given.

### Comorbidity: - Complications

Cognitive dysfunction & dementia - LUTS impact.

LUT dysfunction rarely link to the neurologic disorder:

- Multiple phenotypes sharing burden of disease progression without hope for cure.
- It is important to identify symptoms & complications leading to further loss of mobility and poor QoL.
- Mixed pathology is common.
- Psychological factors & cognitive deficit interfere with coping.
- LUTS have major impact on patients to stay independent.

Degeneration of dopaminergic neurons of substantia nigra & depletion of striatal dopamine.

Depression of cortical activity induces executive dysfunction.

Degeneration of olivary nuclei leads to hyperactivity of glutamatergic & excitatory input to thalamus & cortex-decrease activity of RAS, dopaminergic pathway - Neurogenic detrusor overactivity.
LUT Symptoms in Parkinson Disease

Nocturia is the most common complaint = 60%
Urgency = 33% to 54%
Frequency= 16% to 36%
Urinary incontinence= 26% ♂ and 28% ♀

Storage Symptoms
- Nocturia
- Urgency
- Frequency
- Urinary incontinence

Voiding Symptoms
- Hesitancy & poor stream
- Straining to void


LUTD In PD follow the onset of motor disturbances by 4 to 6 years

First symptoms in multiple system atrophy

What Causes Urgency?

OAB vs BPS
Urodynamics findings between LUTS in PD and BPH/BOO

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<th>Urodynamic Parameter</th>
<th>Parkinson Disease</th>
<th>BPH/BOO</th>
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<tbody>
<tr>
<td>Detrusor Overactivity</td>
<td>Phasic at low volume</td>
<td>Mostly terminal</td>
</tr>
<tr>
<td>DOA incontinence</td>
<td>More common</td>
<td>Less common</td>
</tr>
<tr>
<td>Pressure flow</td>
<td>Non-obstructed voiding</td>
<td>Obstructed voiding</td>
</tr>
<tr>
<td>Sphincteric activity</td>
<td>Bradypause</td>
<td>Normal guarding reflex</td>
</tr>
<tr>
<td>Postvoid residual</td>
<td>Insensate</td>
<td>Can be elevated</td>
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Adapted from Defreitas GA 2003

Urodynamic abnormalities may differentiate between MSA and PD

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<tr>
<th>Urodynamic Parameter</th>
<th>PD</th>
<th>MSA</th>
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<tbody>
<tr>
<td>Detrusor overactivity</td>
<td>All small fill more profound</td>
<td>All larger fill less profound</td>
</tr>
<tr>
<td>Sensation</td>
<td>More sensate</td>
<td>Delayed</td>
</tr>
<tr>
<td>DEED</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Straining/weak stream</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Voiding efficiency</td>
<td>Preserved</td>
<td>Improved</td>
</tr>
<tr>
<td>PVR</td>
<td>Insignificant</td>
<td>High</td>
</tr>
<tr>
<td>Bladder neck on VUD</td>
<td>Closed</td>
<td>Open</td>
</tr>
</tbody>
</table>

Adapted from Brucker B 2017

Pharmacotherapy for LUTD

- Alpha adrenergic agonists: (Retention & related symptoms)
- Alpha adrenergic antagonist: (SUI)
- Antimuscarinic agents (UR & constipation)
- Angiotensin converting enzyme (ACE) inhibitors (cough)
- Calcium channel blockers (UR & constipation)
- Cholinesterase inhibitors (increase bladder contractility)
- Diuretics
- Psychotropic drugs
- Opioid antagonists
- Other drugs (pyridines, gabapentin, glitazones, non-steroidal anti-inflammatory agents)

Older people and patients with neurodegenerative diseases take multiple drugs
Many of them are over-the-counter (OTC) medications, vitamins or supplements
Adverse drug reactions result in >700,000 visits to emergency/year

Antimuscarinic treatment in PD’s patients

Antimuscarin treatment in PD’s patients

<table>
<thead>
<tr>
<th>Comparison of senior plaque in Parkinson’s disease cases grouped according to antimuscarinic drug treatment: none, short-term (&lt;2 a), long-term (&gt;2 a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None (CN)</td>
</tr>
<tr>
<td>Amyloid plaque densities are more than 2.5-fold higher in cases treated with antimuscarinic medication in the long-term compared with untreated or short-term treated cases.</td>
</tr>
</tbody>
</table>

Anticholinergic load in older people

<table>
<thead>
<tr>
<th>Drugs commonly prescribed to older patients, 14 produced detectable anticholinergic effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranitidine</td>
</tr>
<tr>
<td>Codeine</td>
</tr>
<tr>
<td>Warfarin</td>
</tr>
<tr>
<td>Trazodone</td>
</tr>
<tr>
<td>Nifedipine</td>
</tr>
</tbody>
</table>

The drugs in the study that showed no detectable anticholinergic effects were: Propranolol, Salicylic acid, Nortriptyline, Insulin, bosentan, Dilazep, Atenolol, Metoprolol, Timolol
How to avoid over medication

Recommendations of the American Geriatrics Society

- Ask before taking an OTC
- Make a list and keep it updated
- Review your medications
- Ask questions (why, how, when, etc.?)
- Organize your medications
- Follow directions
- Report problems
- Medication don’ts
Neurodegenerative disease's impact on bladder function: A multidisciplinary approach in diagnosis, treatment and improving quality of life

AIMS OF ORAL TREATMENT IN PATIENTS WITH NDO

This presentation leads primary to specific issues in pharmacotherapy in neurogenic patients.

Oral medication
What do we have today?
Its combination better?
How to decide when to move to another step?

Dr. Christian Cobreros
Urology Division - Hospital Carlos G. Durand
IUBA - Instituto Urologico de Buenos Aires
Buenos Aires - Argentina

Oral bladder relaxants: Antimuscarinics

Antimuscarinics

Dr. Christian Cobreros
HOSPITAL CARLOS G. DURAND – BUENOS AIRES
IUBA – INSTITUTO DE UROLOGIA DE BUENOS AIRES
Buenos Aires - Argentina
**Antimuscarinics**

**Antimuscarinic Agents**

- **Blood-Brain Barrier**
  - Cognitive Impairment
  - How Much?
  - Bias in Research Trials
  - Clinical Trials are done in patients with intact hematocerebral barrier
  - It’s blood-barrier intact in stroke, dementia, or other neurological diseases?
  - In dementia concomitant treatment with doparil should be avoided

**Antimuscarinics Drug Interactions**

- SLOW GASTROINTESTINAL MOTILITY
- CHOLINESTERASE INHIBITORS
- PRESCRIBING CASCADE

**Beta 3 Adrenoreceptor agonist**

- **M** of A: activation of adenyl cyclase with the subsequent formation of cAMP
down-regulation of Ach release, resulting in an inhibitory control of parasympathetic activity

**What is said in the guidelines?**

- **Prescribers**
  - Tolterodine
  - Ditropan
  - Bethanechol
  - Bethanechol
  - Ditropan
  - Ditropan

- **What about patients with cognitive impairment in this population?**
  - Antimuscarinic drugs improve bladder storage function
  - High incidence of side effects although controlled-released have less side effects that immediate release preparations

- **In patients with cognitive impairment, antimuscarinics should be prescribed with a warning, cause there are proves that oxybutynin caused significant memory deterioration**

**Beta 3 Adrenoreceptor agonist**

- Bladder evacuation per 24 h
- Incontinence episodes per 24 h
- Improvements in bladder capacity
- Compliance
- Storage phase pressure

- Sakakibara et al., 2015
  - Retrospective study
  - Mirtazapine for a period of at least 6 weeks
  - N: 15 NDO SCI
  - Mean age: 70
  - Mean ± SD
  - Comparably with patients with spinal cord injury
  - Maximal pressure of contractions decreased
  - 30% drop out for adverse events
  - 53:1021

- **Beta 3 Adrenoreceptor agonist**
  - **M** of A: activation of adenyl cyclase with the subsequent formation of cAMP
down-regulation of Ach release, resulting in an inhibitory control of parasympathetic activity

- **What about refractory patients for an oral antimuscarinic?**
  - Can I use double therapy with antimuscarincs?
  - CAN I USE DOUBLE THERAPY WITH ANTIMUSCARINCS?
  - Effective treatment of neurogenic overactivity
  - Potential can alter the absorption of other drugs
  - Associated with the treatment of neurogenic detrusor overactivity in SCI patients with spinal cord injury
  - Antimuscarinics

- **Beta 3 Adrenoreceptor agonist**
  - Mirtazapine
  - Wöllner et al., 2014
  - Promotion of transitional hypermotility by T3 agonist in patients with spinal cord injury
  - Minimal pressure of contractions decreased
  - 30% drop out for adverse events
  - Results of a prospective open label study
  - Mean ± SP

- **What about antimuscarinics drug interactions?**
  - Slow gastrointestinal motility
  - Cholinesterase inhibitors
  - Prescribing cascade

- **Antimuscarinics**
  - NDO and OAB in spinal cord injury patients with SCI
  - 20% of drop out for adverse events
  - Double treatment alternatives to Ditropan. If a patient experiences headache, cervical cold sensation, 5-HT2 agonist in patients who have killed 1 or at least two ADR

- **Beta 3 Adrenoreceptor agonist**
  - Mirtazapine: an alternative in NDO if antimuscarinic is unsatisfactory

- **What about antimuscarinics in children: long term results of a prospective open label study**
  - Significant:** (cognitive impairment should not occur

- **Antimuscarinics**
  - NDO and OAB in spinal cord injury patients with SCI
  - 20% of drop out for adverse events
  - Double treatment alternatives to Ditropan. If a patient experiences headache, cervical cold sensation, 5-HT2 agonist in patients who have killed 1 or at least two ADR
What is “refractory to pharmacotherapy” or “drug”?

FURTHERMORE, THE MANAGEMENT IN THIS SITUATION IS INCORRECTLY NAMED second line treatment? third line management? step up treatment?

ICI guidelines
AUA guidelines
FDA

after attempting to treat OAB for 3 months with an AM, taking the step toward “second line” therapy is worthwhile and justified

ICSI guidelines
AUA guidelines
FDA
injections for adults with OAB who "cannot use or do not adequately respond to a class of medications known as anticholinergics."

So independently of the definitions

HOW DO WE TREAT THIS PATIENTS WHEN ORAL TREATMENT FAILED OR ADVERSE EVENTS CANT BE TOLERATED?
Neurodegenerative Disease: Surgical Approach
Carlos D'Ancona
Professor Urology
Unicamp

Affiliations to disclose:
No conflict of interest

Funding for speaker to attend:
- Self-funded
- Institution (non-industry) funded
- Sponsored by:

Definition of failure

Quality of Life
Combination of clinical and urodynamics
  • Urinary incontinence
  • Pdet.max > 40 cmH₂O


Definition of success

1. Protection of upper urinary tract
2. Improvement of urinary incontinence
3. Restoration (or partial restoration) of LUT function
4. Improvement of patient’s QoL


Surgical Approach

- Parkinson’s disease
- Botulinum toxin
- Sacral neuro modulation
- Bladder augmentation
Effective doses were 200–300 U for Ona/A and 500–750 U for Abo/A injected under cystoscopic guidance in 20–30 sites preserving or not the trigone.

Controlled studies with placebo

Significant results with 200–300 U BoNT-A

88% need CIC

Significant improvement of urgency, frequency, nocturia and urinary incontinence

Improvement of urodynamics results

Espontaneous voiding
Saral 84% obtain > 50% improvement
SNM is usually offered if the neurological disorder can be considered stable or slowly progressive
It has been reported that the loss of efficacy over time is a result of a new relapse.
One study found that patients with relapsing disease required the adjustment of the stimulation parameters.

The Management of Lower Urinary Tract Dysfunction in Multiple Sclerosis
Jure Tomšič 2, Jakob N. Pankner 2

Saral neuro modulation
• 84% obtain > 50% improvement
• Eight patients with implanted SNM undergoing MRI at 1.5 Tesla without safety concerns

Augmentation Cystoplasty in Patients with Multiple Sclerosis
Zacharias M. 1, Phelan 1, Bhat 1, Pena-Navarro 1, Vázques 1, López 1, Zuberi 1, Urbanic M. 2

9 patients
Increase maximal cystometric capacity
Decrease detrusor pressure

17 patients
15 were followed up for 15 months
14/15 (93%) had successful outcomes based on Patient Global Impression of Improvement
93% continent
Conclusion - MS

- Botulinum toxin → good results
- SNM → select cases
- Surgery → failure of others methods

Parkinson Disease

- Corpo striatum
- Produção de dopamina e acetilcolina
- Controle do movimento/ postura

Blackett et al. 2009

- 200U BoNT A
- 20 sites include trigone
- No urinary retention

BMC Urology

Preserved micturition after intradetrusor onabotulinumtoxinA injection for treatment of neurogenic bladder dysfunction in Parkinson’s disease

- 200U BoNT A
- 20 sites include trigone
- No urinary retention
4 of 6 patients SNM are implanted

Parkinson disease is progressive and may have variable responses over time

Conclusion - PD

Botulinum toxin → good results
SNM → select cases
Surgery → exceptional

Spinal cord injury

Prospective and randomized study of SCI

Group I
- 33 patients
- Oxbutinin 5mg. three times a day

Group II
- 28 patients
- Intradetrusor Onabotulinumtoxin A
**Demographic data**

| Group | Oxibutinin | Onabotulinumtoxina | P  
|-------|------------|--------------------|----
| Sex (M/F) | 26/7 | 23/5 | 0.743*  
| Age (years) | 31.94 ± 8.73 (median) | 30.54 ± 11.06 (median) | 0.839**  
| Time of lesion (months) | 25.24 ± 10.29 (median) | 23.75 ± 8.73 (median) | 0.533**  
| Lesion level | | |  
| T1-T6 | 23 | 21 | 0.956***  
| T7-T12 | 9 | 7 |  
| L1 | 1 | 0 |  
| ASIA score | | |  
| A | 20 | 16 | 1.000***  
| B | 11 | 10 |  
| C | 2 | 2 |  
| D | 0 | 0 |  

**Etiology**

- Car accidents
- Gun fire
- Falls

**Maximal cystometric capacity**

- TBA
- Oxibutinin

**Pdet.max**

- TBA
- Oxibutinin

**UI episodes decreased**

- TBA
- Oxibutinin

**QoL – ICIQ-SF**

- TBA
- Oxibutinin
Comparing the objective response (urodynamic study) and subjective (quality-of-life questionnaires) of the two drugs, BoNT A proved to be more effective than oxybutynin in all evaluated parameters, as well as having a better tolerability profile.

Ferreira RS, D'Ancona CAL, Oelke M, Carneiro MR. Einstein (Sao Paulo). 2018, 6;16(3)

40% discontinued of these:
52% no response
42% patient’s request

8 articles met all inclusion criteria
During the test phase, the merged success rate was 45%
99 patients underwent SNM implantation
Success rate of permanent SNM was 75%
Elevated filling pressure
Diminished bladder capacity
Not responsive to other treatments


It is very effective
88% satisfaction score in spinal cord injury
Failure of conservative treatment
More permanent solution

Change in bladder capacity + 130%
Change in bladder compliance + 87%
Change in presence of detrusor overactivity -54

>90% achieved nocturnal continence
91-100% achieved diurnal continence
QoL improved rates 90%
92% satisfaction in long term follow up
**Conclusion**

- Preserve upper urinary tract
- Promote continence
- Listen to the patient
- The treatment should be adjusted to each patient’s needs

**Conclusion - SCI**

- Botulinum toxin → good results
- SNM → partial lesion
- Surgery → excellent

**Great benefit in female wheelchair patients**
Bladder Outlet Obstruction in Neurodegenerative Patients
Prof. Dr. Gustavo L. Garrido
Hospital de Clínicas “José de San Martín”
Universidad de Buenos Aires
Argentina

PD and BPH are frequent concomitant diseases.

The severity of neurological impairment was assessed with the Unified Parkinson’s Disease Rating Scale (UPDRS).

Alpha Blockers and PD
The use of alpha blockers in mild/moderate obstructions offers limited but positive voiding improvement.

The severity of neurological impairment was a good predictor of the clinical response
UPDRS < 70 have 3:1 higher chance of clinical improvement than scores > 70
In contrast, urodynamic parameters did not predict treatment outcomes. 

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>12 weeks</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First desire to void (sec)</td>
<td>186±31.7</td>
<td>182±18.8</td>
<td>0.996</td>
</tr>
<tr>
<td>Maximum cystometric capacity (mL)</td>
<td>346±189.3</td>
<td>337±129</td>
<td>0.590</td>
</tr>
<tr>
<td>Bladder compliance (mL/cmH2O)</td>
<td>12.9±19.2</td>
<td>11.6±10.8</td>
<td>0.471</td>
</tr>
<tr>
<td>Residual volume (mL)</td>
<td>38.0±13.5</td>
<td>34.0±11.3</td>
<td>0.262</td>
</tr>
<tr>
<td>Peak flow rate (mL/sec)</td>
<td>7.4±1.8</td>
<td>6.4±1.7</td>
<td>0.176</td>
</tr>
<tr>
<td>Detrusor pressure at Qmax (cmH2O)</td>
<td>20.8±10.2</td>
<td>16.7±6.9</td>
<td>0.020</td>
</tr>
<tr>
<td>Outlet obstruction index 2.2±1.5</td>
<td>3.1±0.9</td>
<td>0.051</td>
<td></td>
</tr>
</tbody>
</table>

Note: Non-compliance during pressure flow study.


Patients may be treated with a combination of alphablocker and anticholinergic/anti-muscarinic therapy. Beware with orthostatic hypotension, which is already common in the PD population.

PD and BPH Surgery

Retrospective study
N: 23 PD (MSA excluded). Completed TURP
Median Age: 73 yrs
Hoehn and Yahr Scale: 2
14 preoperative indwelling urinary catheter
TURP restored voiding in 9 patients (64%), and only 5 patients (36%) required catheterisation postoperatively.


Patients who are able to contract the sphincter are unlikely to develop urgency urinary incontinence after a prostatectomy, whereas the risk of post-prostatectomy incontinence is high in those who are unable to voluntarily contract the sphincter ani.


PD and BPH Surgery

The indication for prostatic surgery must be carefully considered and preceded by precise clinical, urodynamic and sometimes electromyography evaluation.

MSA and BOO

There is a consensus between experts that the incontinence of MSA rarely improves after prostate surgery.

If there is a clinical suspicion that a patient has MSA, only non-surgical management of bladder symptoms should be considered.

MSA and BOO

A useful discriminator for the differential diagnosis of MSA from PD
Post-void residuals >100 ml.

MSA and BOO

Another predictor of MSA was an open bladder neck at the start of bladder filling without accompanying DO, which was found in 53% of patients with MSA but no PD patients.

The most important predictor of MSA was the neurogenic change of sphincter EMG, which is rarely seen in patients with PD. This simple test can differentiate MSA from PD.


Dementia and BPH Surgery

Limited evidence on outcomes of surgical
N:13
Age: 74 to 98.
4/13 urinary retention.
Postoperative complications:
• 1 acute myocardial infarction
• 1 multiple gastric ulcers
• 1 decubitus ulcers
3 died beyond 3 months
Mean followup 26 months.
6 patients reported good urination
3 reported improvement although requiring IC
1 developed mild incontinence.


Green-LightPV
N:4 with severe dementia (Performance status of >3).
Mean age: 81 years old (range 67–94)
Mean prostate volume: 63.8 ml (range 19–120).
Mean peak flow rate increased to 18 ml/s
Mean post-void residual urine decreased to 46.9 ml at 3 months.
No postoperative complications were observed.


Conclusions

Alpha Blockers
Unified Parkinson’s Disease Rating Scale (UPDRS).
Combined Therapy (Beware Orthostatic Hypotension)

Surgery and PD: OK
Check External Sphincter: VSC / EMG
Caution in MSA (PVR / VideoUrodynamics)

Surgery and Dementia: OK