

Underactive Bladder in Children

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Disclosure

- I will be discussing the off label use of medications
- I am not a paid speaker or on the speaker bureau of any company
- I am a consultant to and/or involved in clinical research with the following companies
 - Astellas
 - Laborie
 - Allergen
 - Franco Intelligent agent solutions



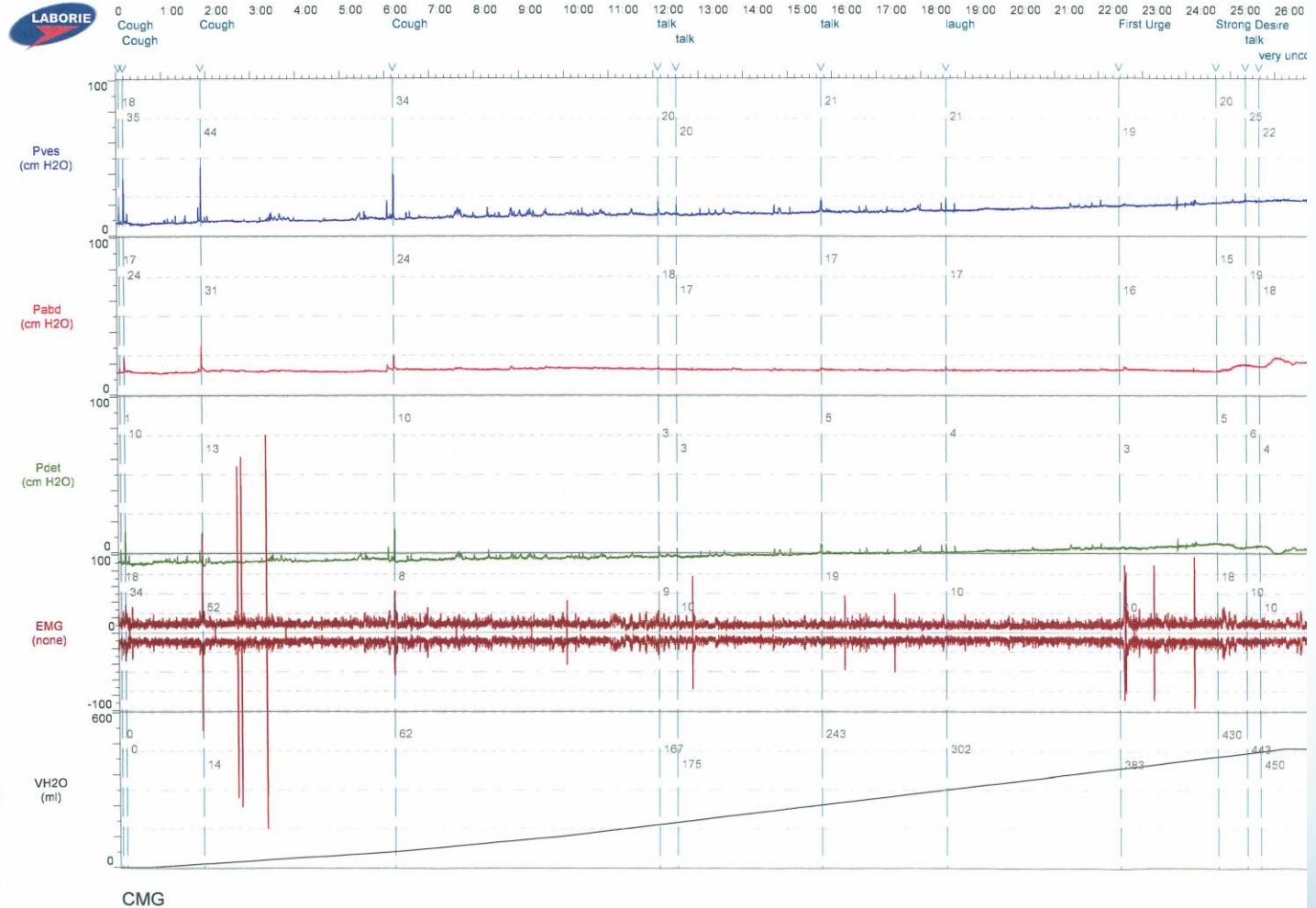
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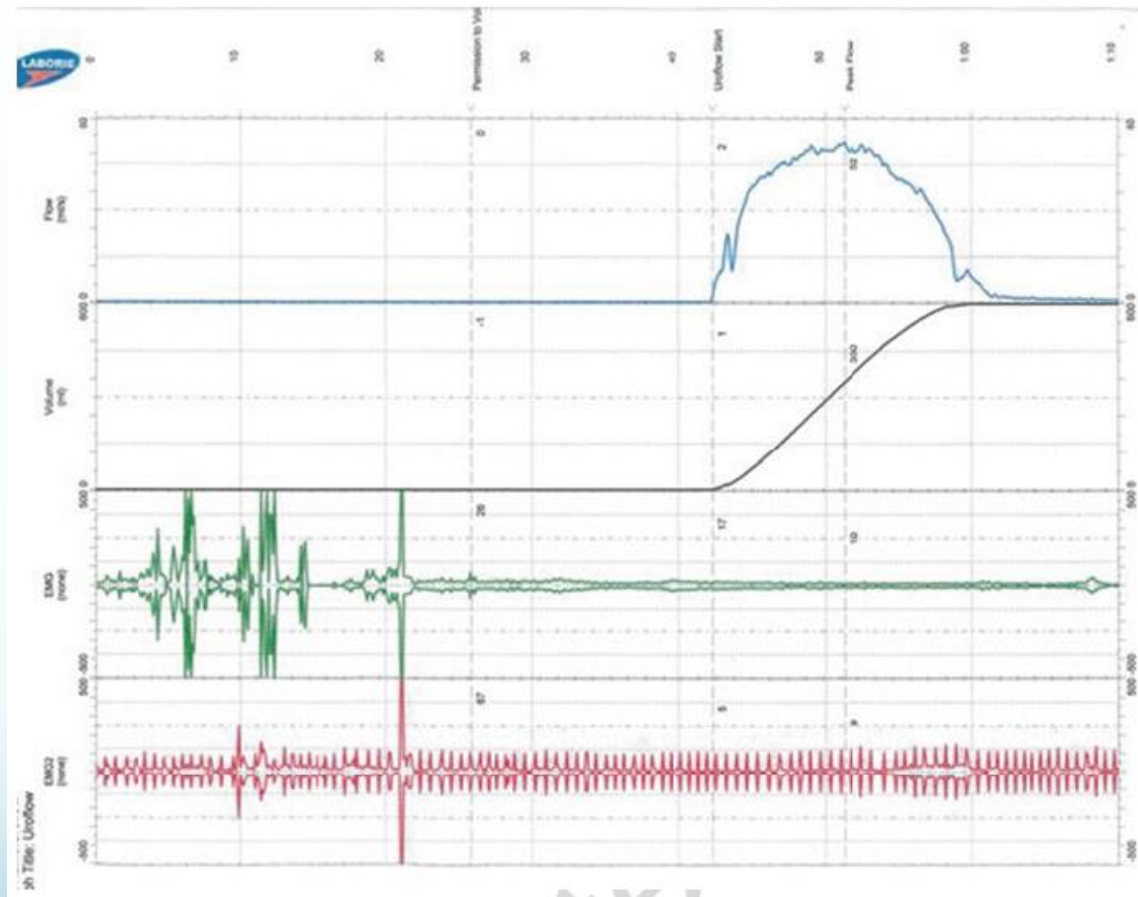
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Is this an UAB Patient?



Underactive Bladder (UAB)

- **International Children's Continence Society (Austin et al. J Urol 2014)**
- The children may have low voiding frequency in the setting of adequate hydration but may also have frequency due to incomplete emptying with prompt refilling of the bladder.
- “reserved for children who need to raise intraabdominal pressure to initiate, maintain or complete voiding i.e. straining.
- These children often produce an interrupted uroflow pattern and are usually found to have *detrusor under activity* (DUA) if examined with invasive urodynamics.
- Flow patterns may be plateau-shaped; pressure flow studies will distinguish it from bladder outlet obstruction” 2014).



Reports in the literature on UAB

- Firlit et al. described one of the earliest descriptions of DUA utilizing pressure flow studies (Firlit et al. 1977). They described what is the most common pattern seen in pediatric urology, the hyperactive external sphincter with detrusor hypotonia in 2/34 (6 %) of patients.
- Hoebeke in a 1000 patients saw an incidence of 4 % of children with expanded bladder capacities and hypocontractility (Hoebeke et al. 2001)
- Glassberg and his group have described detrusor underutilization at 5–9 % of cases seen for BBD (Glassberg et al. 2010; Van Batavia et al. 2011, 2014).



Most Recent Report

Paediatric idiopathic detrusor underactivity



Dr Joanna Clothier

ICCS/ESPU Prague October 2015

Methods

Retrospective review of paediatric video-urodynamic investigations performed at our hospital over a 5 year period (January 2010 to December 2014)

Excluded those with anatomical outflow obstruction (PUV) or neurological lesion

Patient notes and investigations reviewed

Values displayed as *average with range*

ICCS definitions used

Results

960 VUD investigations reviewed:

23 patients identified with idiopathic underactive detrusor (2.4%)

Demographics

15 female (65%)

Age at presentation to our service **10 years (range 5.2-14.8 years)**

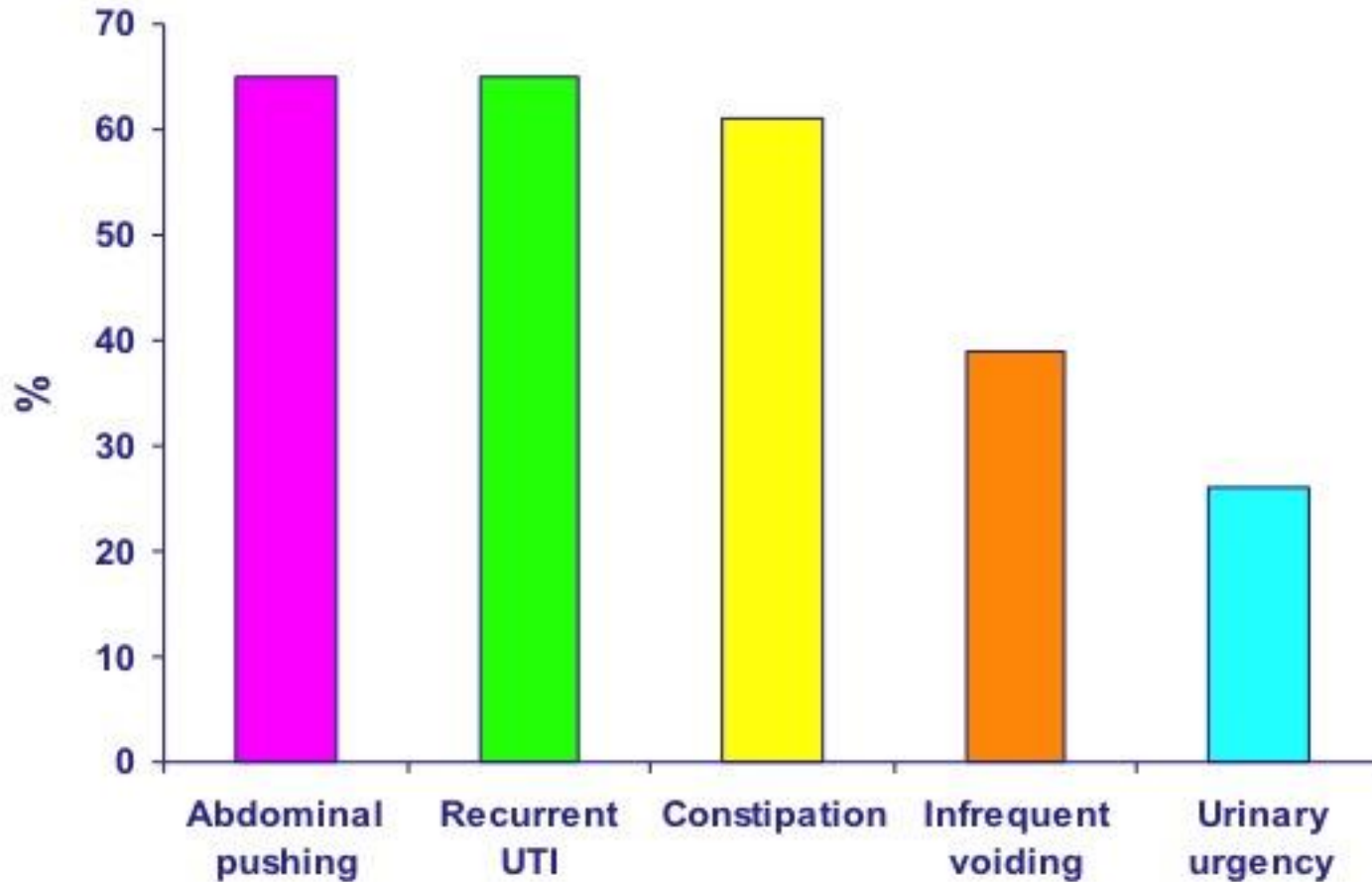
11 had co-morbidity

Presenting characteristics

3 presented acutely in urinary retention.

20 (87%) presented with urinary incontinence

Results – Symptoms at presentation

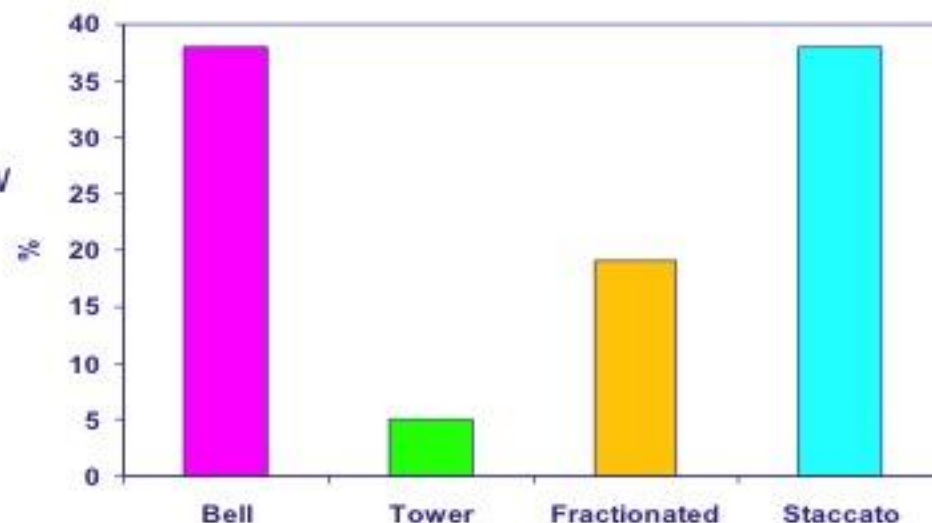


Results – Uroflow assessment

Uroflow assessment

19/23 successfully completed

19% had the described fractionated flow



Bladder capacity 143% of expected bladder capacity (range 35-247%)

1 small capacity

9 large capacity bladder (39%)

Post void residual 31% of total bladder capacity (0-97%).

6 (26%) had PVR > 40% of EBC

Results – Videourodynamic assessment

Storage:

17%	detrusor overactivity,
22%	VUR
65%	had bladder sensation

Voiding:

2/23	atonic bladders
20/23	unsustained bladder contractions with pDetQmax 41cmH ₂ O (15-68)
1/23	sustained but reduced strength (pDetQmax 29cmH ₂ O)

Results – Kidneys and subsequent management

Kidney:

30% had abnormal appearance on ultrasound scan:

- pelvicalyceal dilatation, n= 4
- thickened bladder wall, n=2
- scarred kidney, n=1.

30% patients had renal scarring on DMSA

4 (17%) had renal impairment (3 CKD II, 1 CKD IV)

Management:

14 patients CIC, (2 refused CIC)

9 timed double voiding and constipation management

4 Trial of neuromodulation (TENS, 80Hz, 200µsec)

Our Own Findings

- Few patients have all atonic detrusors
- Many void with bell curves and non fractionated curves
- Abdominal straining is used at the beginning or end of voiding by some but not all patients
- Urgency and urge incontinence is commonly seen in these patients
- High association with neuropsychiatric problems
- Constipation is prevalent in the group



Posterior Urethral Valves and UAB

- Hennis et al. (2012) In a systematic review of the literature of boys treated by endoscopic ablation of valves
 - hypocontractile bladder was seen in 35 % of patients 0–73 %, reported in eight studies.
 - PVR was found in 31 % (0–56 %).
- bladder hypocontractility increased during follow-up, ranging from 0–27 % to 21–71 %.
- The percentage of patients with PVR increased from 4 to 29 % during 4.5 years follow-up
- 0 to 43 % during 12.5 years after endoscopic valve ablation.



Posterior vs. Anterior Urethral Valves

- Is there a difference?
- Yes
- When?
 - Anterior valves will have gradual resolution of hypercontractility no one develops hypocontractility
 - (Kajbafzadeh et al. 2007)



Why?

- Collagen differences
 - Anterior Urethral valve patients are born with normal bladders and the obstruction grows as they mature
 - Spina bifida patients are not born with thickened bladders but with reversal of obstruction before puberty can have reversibility of bladder wall thickening if it does occur
- CNS or receptor changes imparted by obstruction in utero
 - High incidence of ADD/ADHD in boys with PUV and PBS
 - High incidence of coincident bladder neck obstruction (Glassberg)



Other causes of UAB

- Viral illness that can affect the motor tracts and lead to detrusor areflexia
 - Poliomyelitis: intact sensation
 - certain group A and B Coxsackie viruses (especially A7),
 - several echoviruses
 - enterovirus type 71 may produce similar findings, and typically these will be temporary.
 - West Nile virus infection can also cause an acute flaccid paralysis that is clinically indistinguishable from paralytic poliomyelitis due to polioviruses.



Other causes of UAB

- Lyme's disease
 - The first is direct invasion of the organism into the bladder,
- Neuroborreliosis leading to:
 - meningoencephalopathy,
 - transverse myelitis
 - Myeloradiculitis
 - demyelinating lesions of the spinal cord.



Other causes of UAB

- Vitamin B12, vitamin E deficiency and neurosyphilis
- cause posterior long tract disease by demyelination of the lateral and dorsal (posterior) spinal columns as well as peripheral nerves leading to loss of proprioception with signs of upper motor neuron disease such as Babinski's response.
- There is a loss of bladder sensation and increased residual urine due to detrusor areflexia.
- Sphincteric EMG is intact since the corticospinal tracts are not involved.
- Erectile function will also be affected



Other causes of UAB

- Wolfram syndrome:
- diabetes insipidus, diabetes mellitus, optic atrophy, neurosensory deafness, urinary tract dilatation,
- Bladder dysfunction:
 - 6 out of 14 patients (42 %) had atonic bladders
 - 45 % had elevated post-void residual
- death in the third to fourth decade of life.
- The causative gene (WFS1) which encodes the wolframin protein (in the endoplasmic reticulum) has been identified, and a number of loss-of-function mutations have been described



Other causes of UAB

- Weber et al. (2011) describe a homozygous loss-of-function mutation of muscarinic acetylcholine receptor M3 (CHRM3) (1q41-q44) in five brothers with a PBS-like syndrome.
- CHRM3 encodes the M3 subtype of muscarinic acetylcholine (ACh) receptors.
- This mutation leads to a megacystis and prune-like abdominal wall defects.
- Aside from the DUA in the bladder, all of the brothers exhibited dilated pupils that reacted poorly to light and dry mouth.



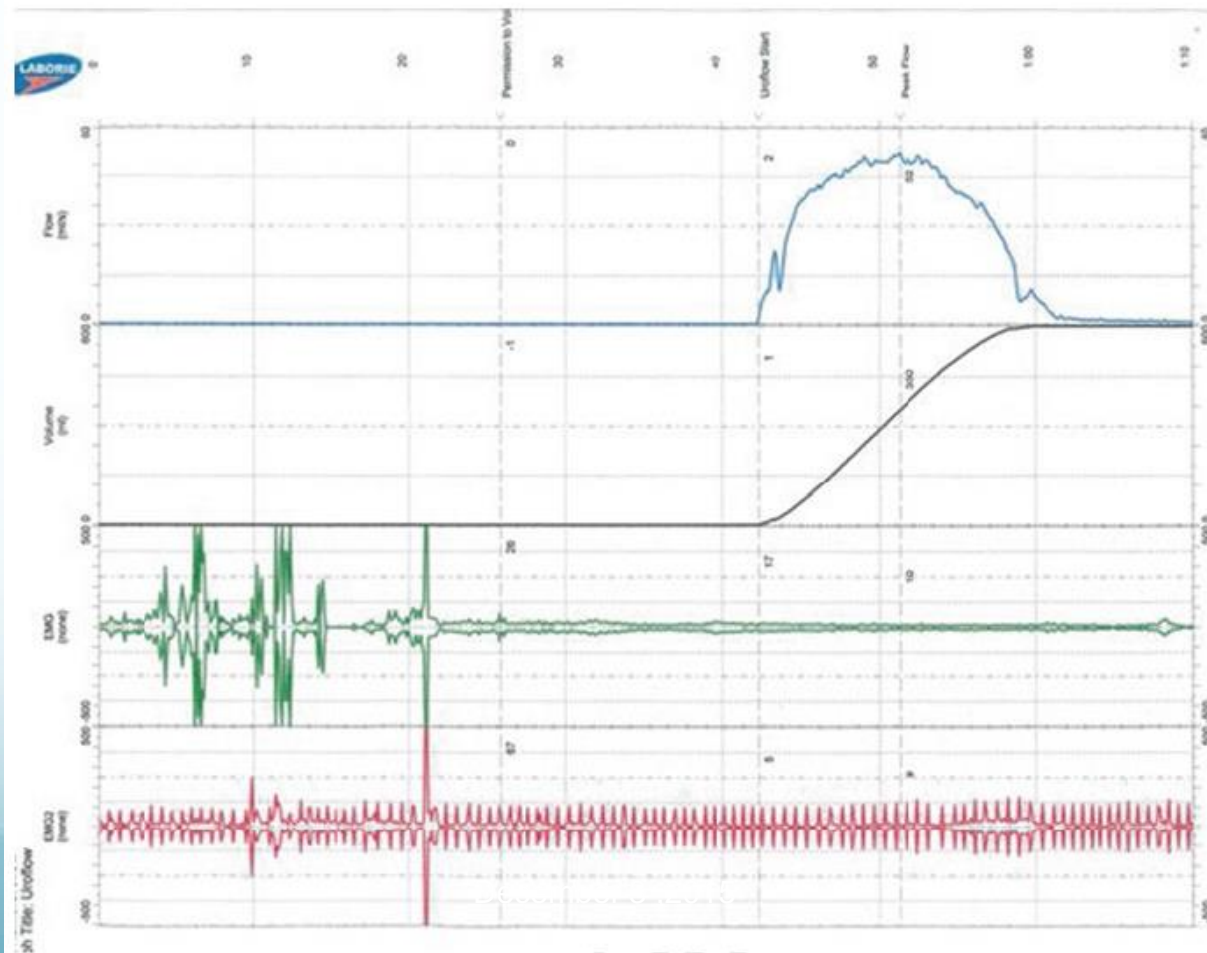
Other causes of UAB

- Mutation in ACTA2, R179H, that causes a syndrome characterized by dysfunction of smooth muscle cells throughout the body,(Milewicz et al. 2010).
 - aortic and cerebrovascular disease, fixed dilated pupils, hypotonic bladder, malrotation, hypoperistalsis of the gut, pulmonary hypertension
- The urinary and gastrointestinal problems found in these patients are similar to complications of megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS), an autosomal recessive condition typically lethal shortly after birth.
- The underlying genetic defect has not been identified, but the overlap of MMIHS with the ACTA2 R179H phenotype suggests a defect of smooth muscle cell contractile function, possibly from recessive or de novo ACTA2 mutations.
- congenital mydriasis has been reported in a patient with MMIHS.



A 14-year-old girl history of bilateral gd 5 vur and BND with a tower-type uroflow curve after Rx with alpha blockers and methylpehnidate

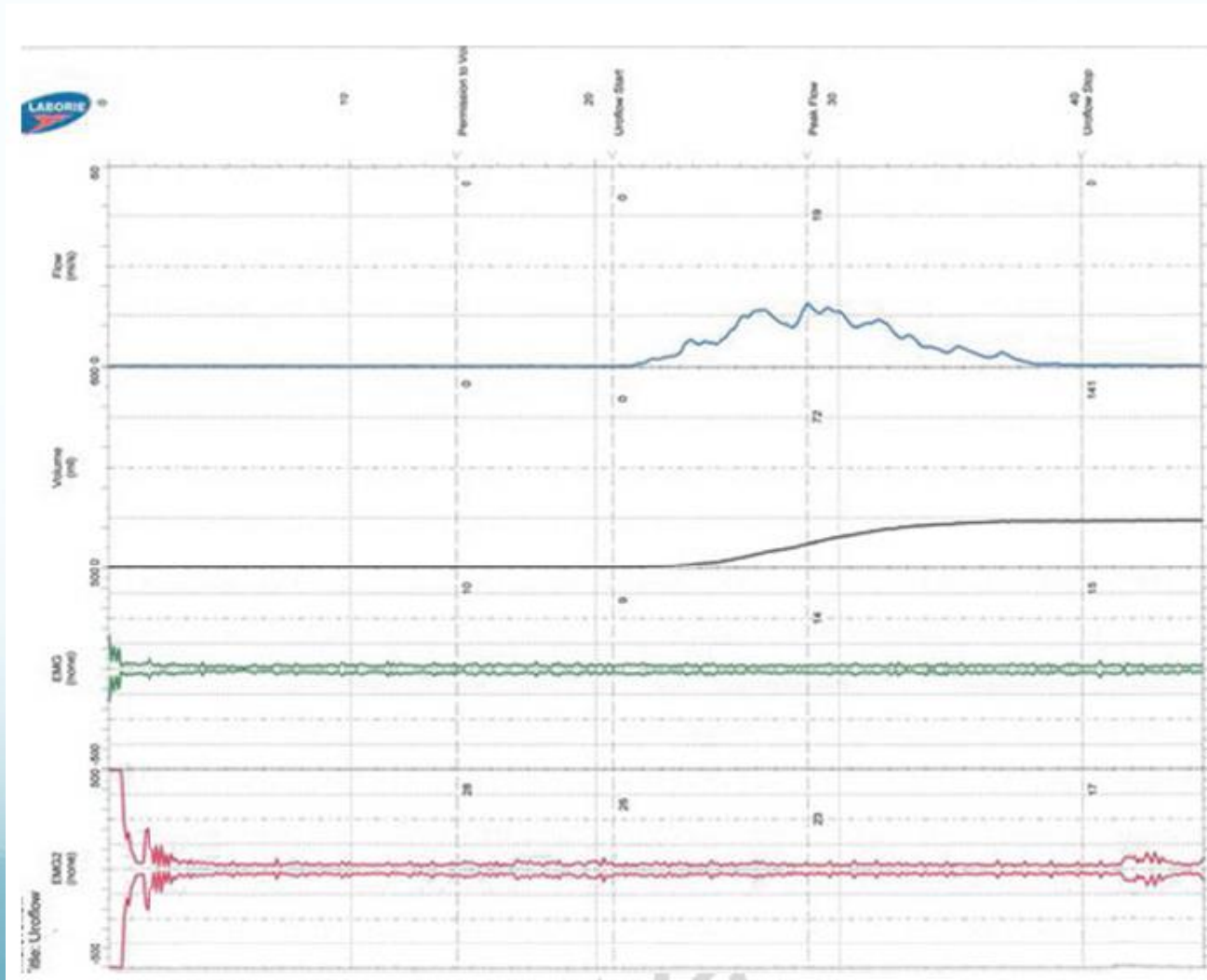
$Q_{\max} = 52 \text{ ml/s}$ expected 42 ml/sec
 $Q_{\text{avg}} = 17.1 \text{ ml/s}$ expected 17.9 ml/sec
voided volume of 600 ml PVR of 300 ml
 $Q_{\max}FI=1.23$ $Q_{\text{avg}}FI=0.96$



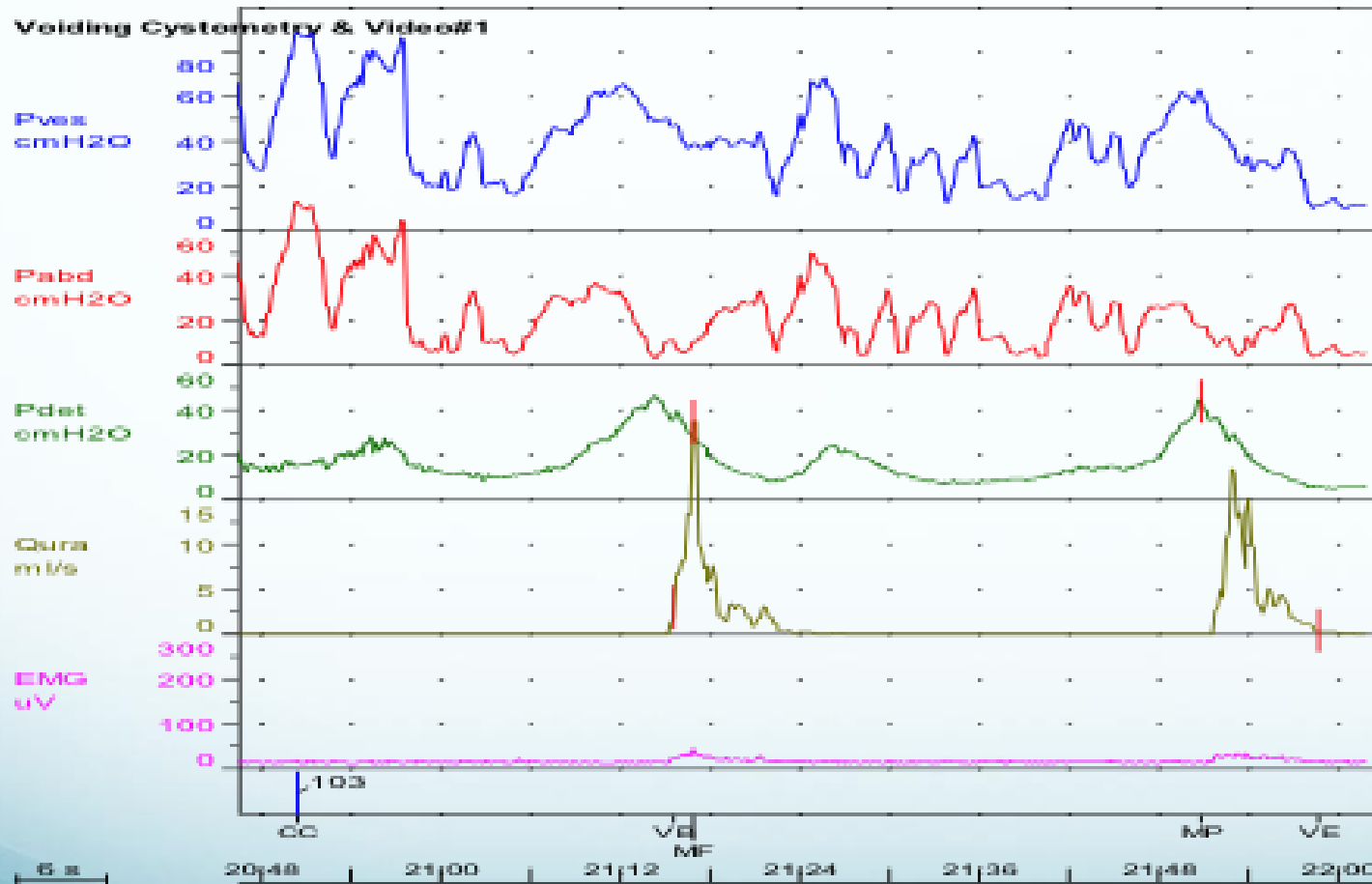
A 14-year-old girl with known autonomic dysfunction (orthostatic hypotension, positive tilt test) and bladder neck dysfunction on VCUG.

$Q_{max} = 18.5 \text{ ml/s}$ and $Q_{avg} = 7.6 \text{ ml/s}$. Voided volume = 140 ml and PVR = 214 ml $Q_{max}FI=0.59$ $Q_{avg}FI=0.48$

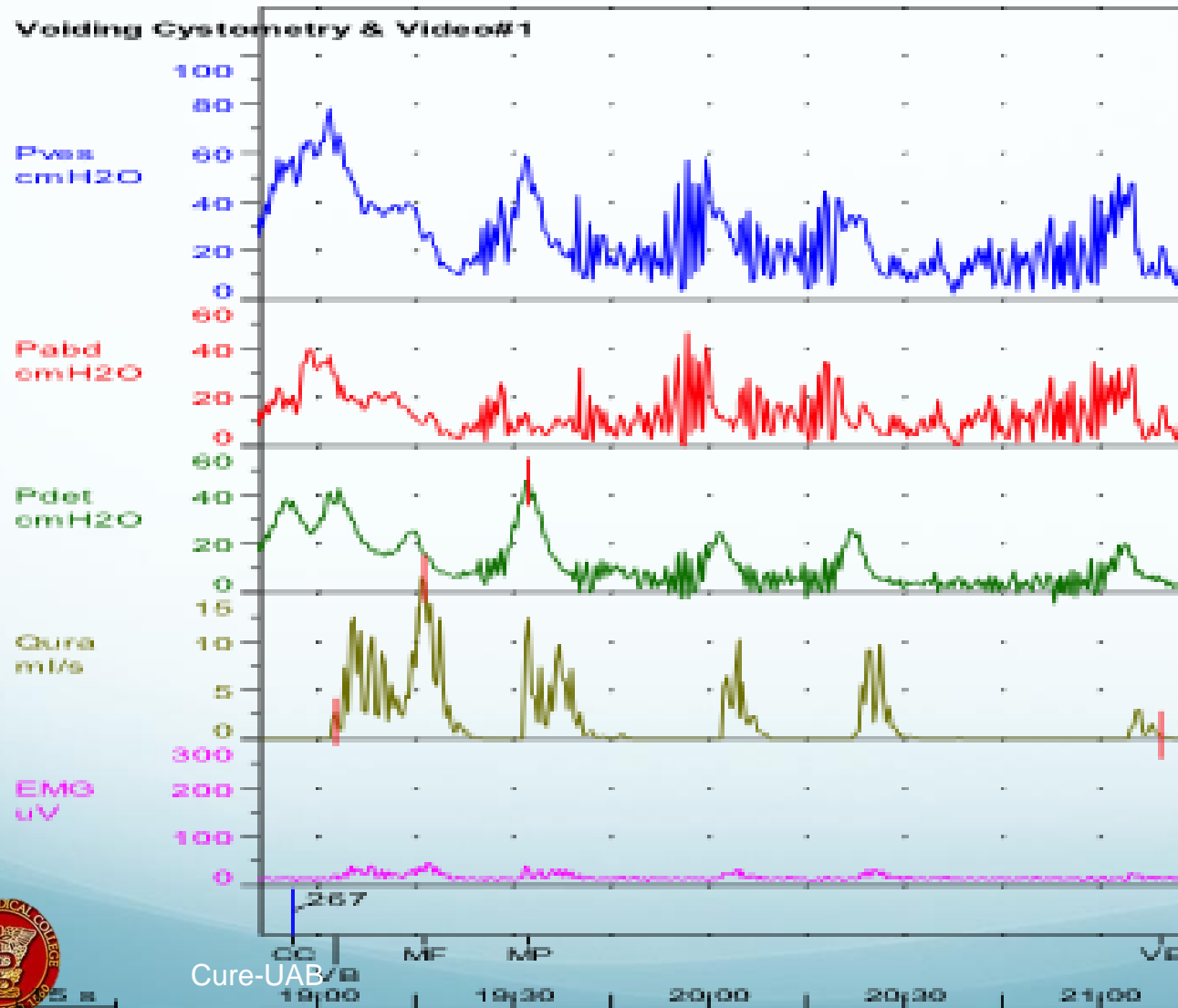
Bladder emptying was markedly improved on alpha-blockers but still remains high



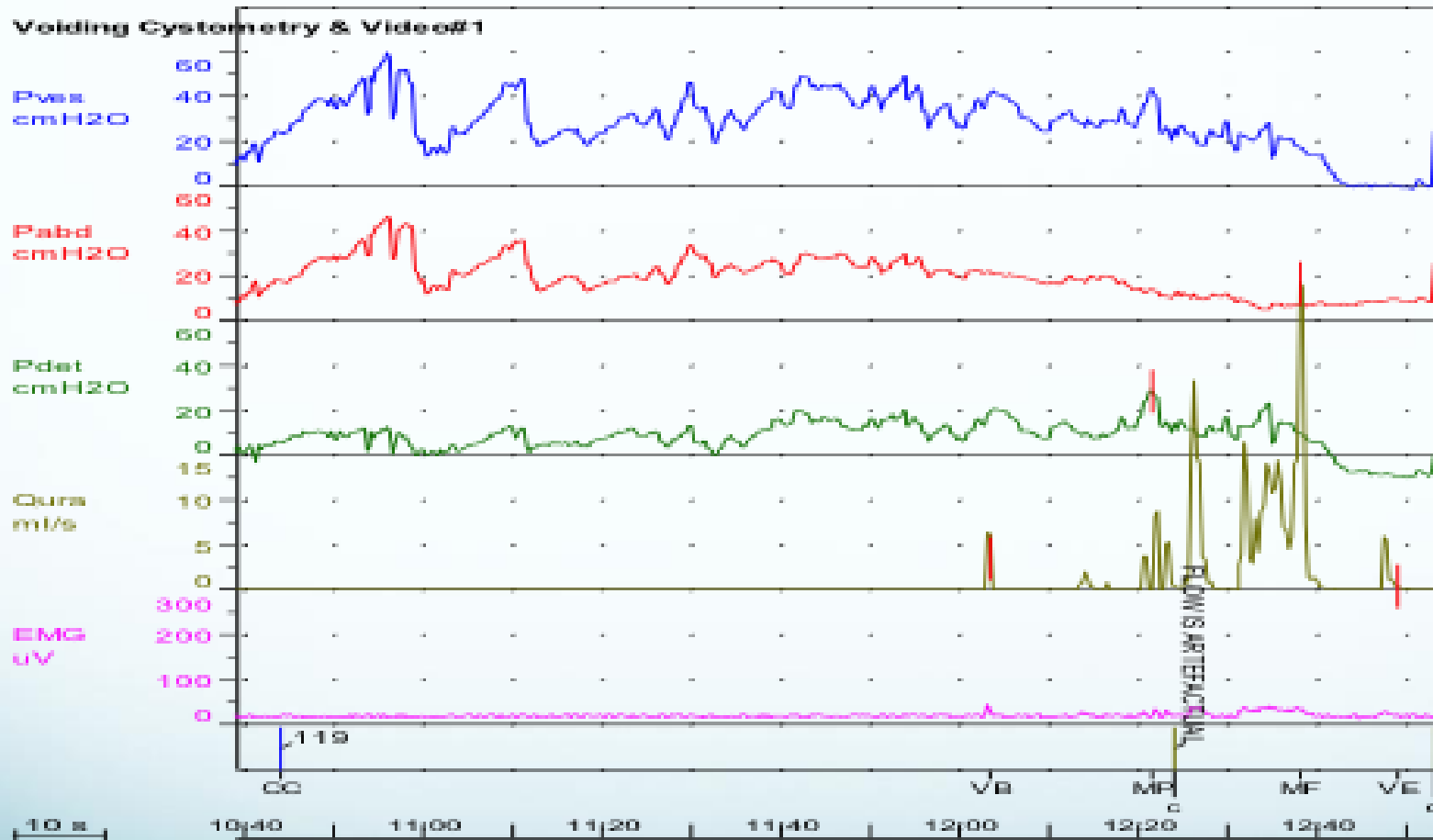
40 cm detrusor contractions and UAB



Unsustained Contractions

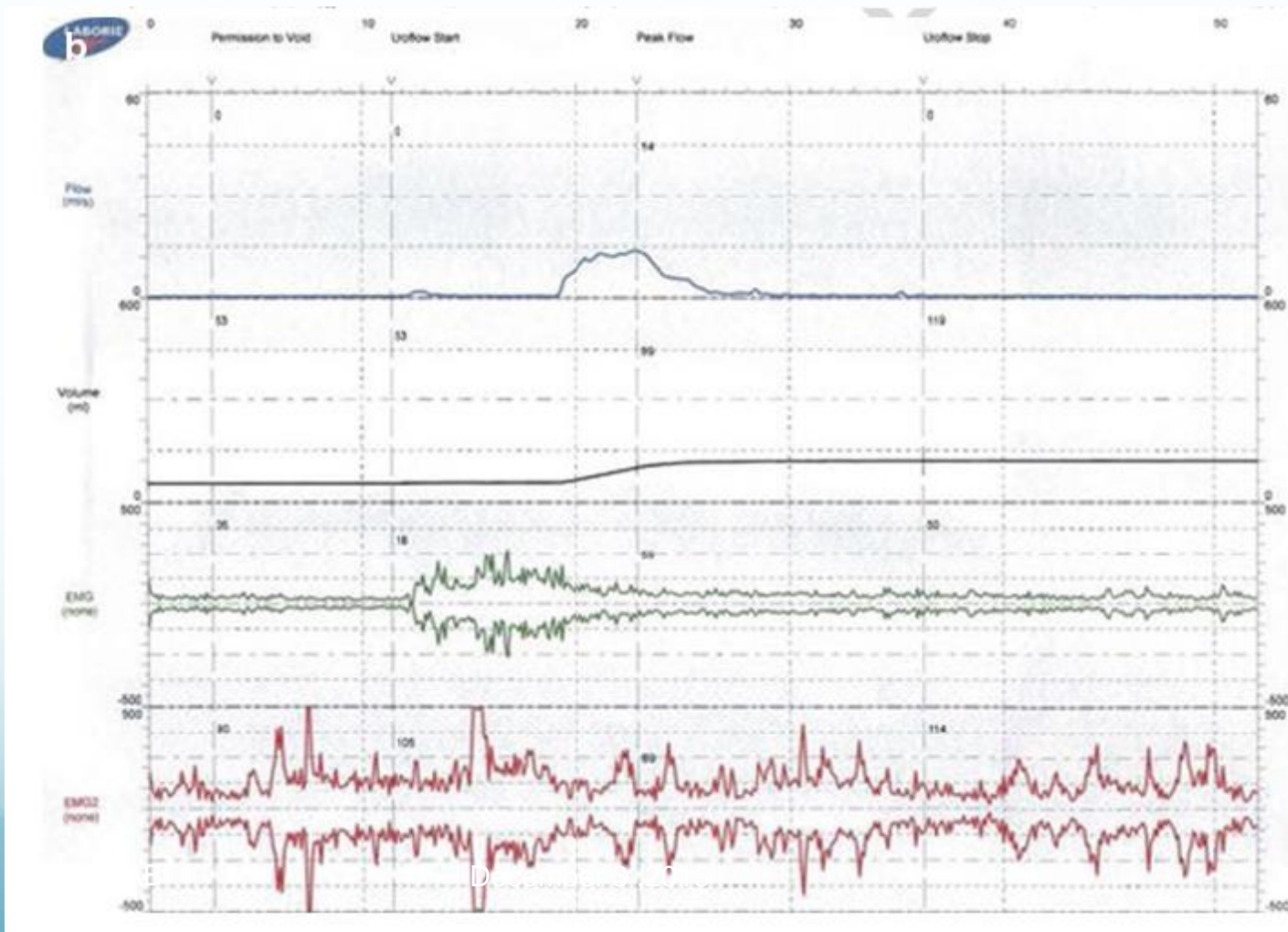


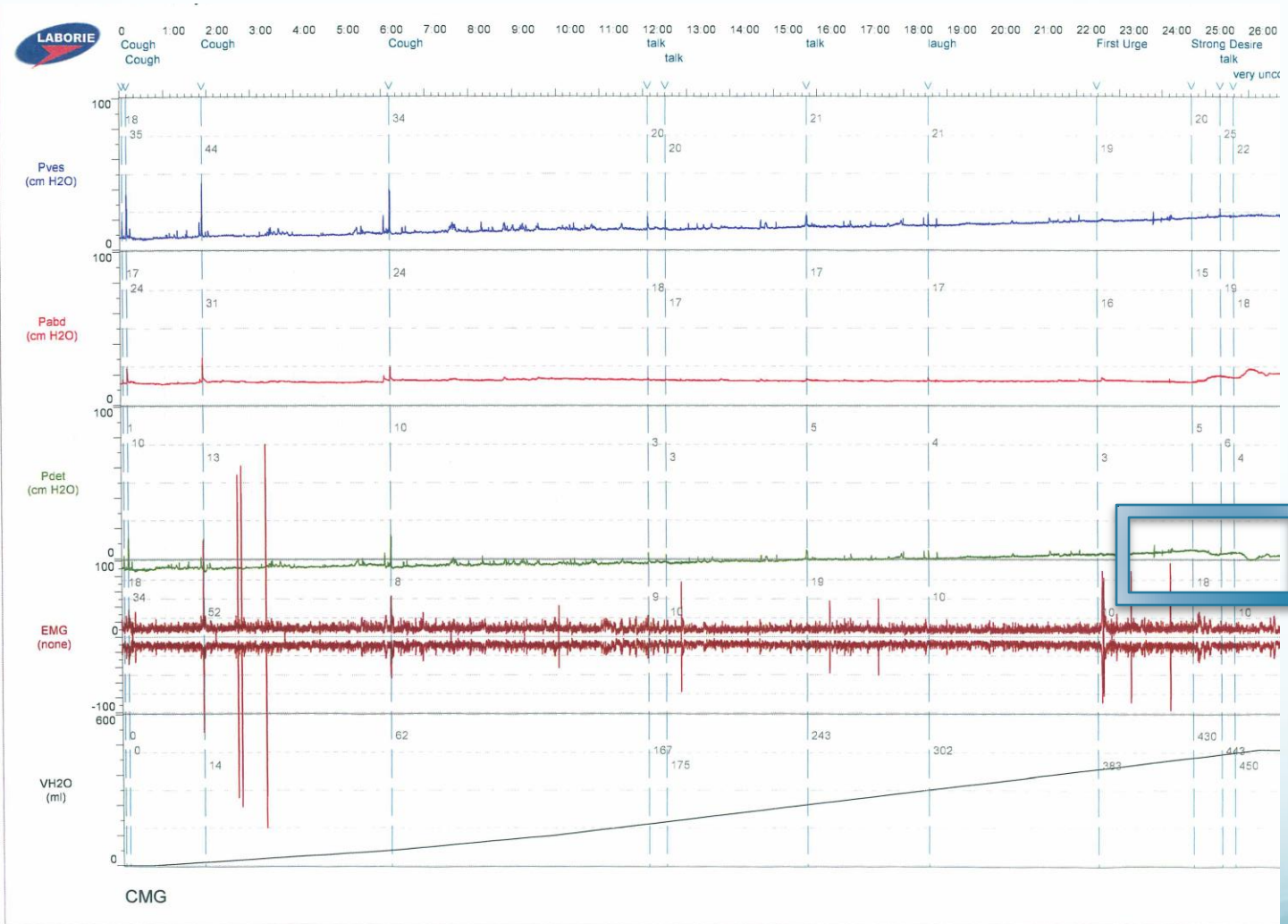
Weak Detrusor Contraction



A 12-year-old boy with Wolfram syndrome, OAB symptoms, and marked bladder under activity significant abdominal straining and EDSD at the start of urination that persists throughout the void.

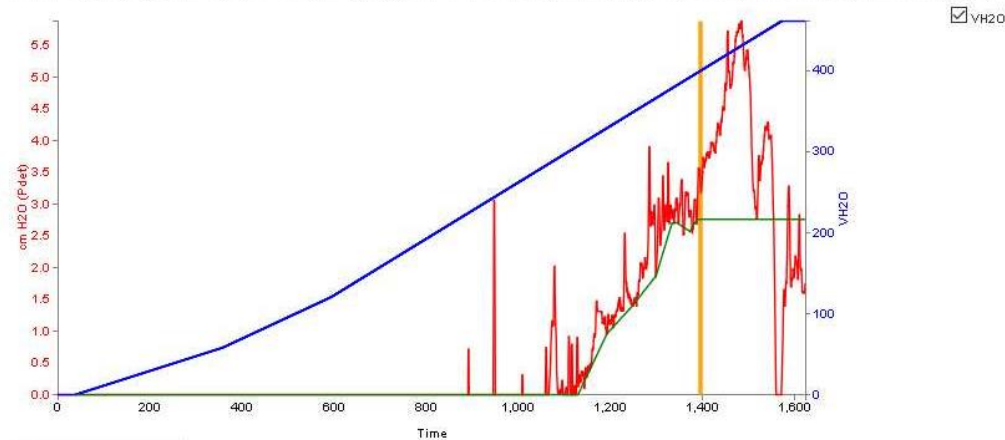
$Q_{max} = 13.8 \text{ ml/s}$, $Q_{avg} = 5.0 \text{ ml/s}$,
voided volume = 140 ml, and PVR = 140 ml





New Tool To Quantify Contractions

Move the orange vertical bar to identify Bladder Contractility work (left) and Detrusor Contraction work (right)



Calculate / Analyze

AUC-BC (Bladder Contractility work): 160.09 11.9%

AUC-DC (Detrusor Contraction work): 173.61 12.8%

AUC-VE (Smooth Muscle and Vesico Elastic work): 1017.63 75.3%

*Left of orange line is AUC-BC (Bladder Contractility work), the area bounded by red and green lines
Right of orange line is AUC-DC (Detrusor Contraction work), the area bounded by red and green lines
Below the green line is AUC-VE (Smooth Muscle and Vesico Elastic work)*

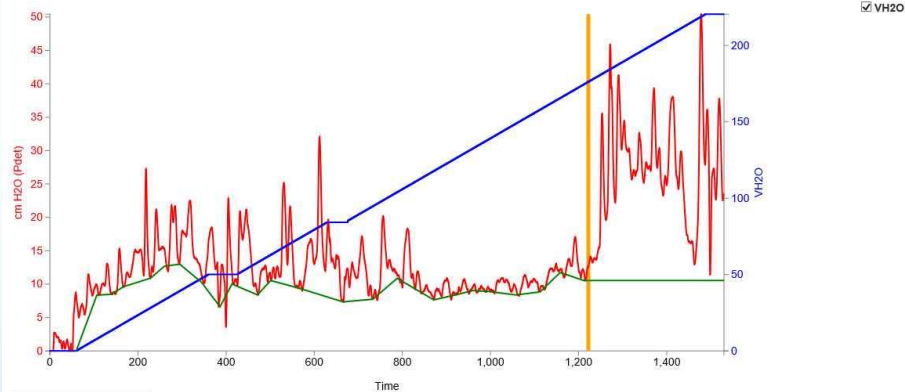
PoC system © 2015



New Tool to Quantitate Urodynamics

File under review: gangi

Move the orange vertical bar to identify Bladder Contractility work (left) and Detrusor Contraction work (right)



Calculate / Analyze

AUC-BC (Bladder Contractility work): 3341.75 14.8%

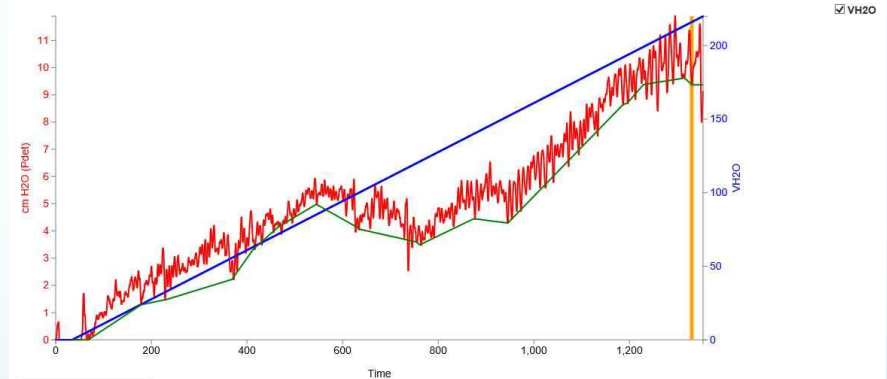
AUC-DC (Detrusor Contraction work): 5070.45 22.5%

AUC-VE (Smooth Muscle and Vesico Elastic work): 14087.27 62%

Activate Windows
Go to PC settings to activate Windows

File under review: cox urodyn

Move the orange vertical bar to identify Bladder Contractility work (left) and Detrusor Contraction work (right)



Calculate / Analyze

AUC-BC (Bladder Contractility work): 978.89 14.4%

AUC-DC (Detrusor Contraction work): 14.84 0.21%

AUC-VE (Smooth Muscle and Vesico Elastic work): 5845.72 85%

Activate Windows
Go to PC settings to activate Windows



First Step in the Treatment of UAB

- Timed Voiding
- Bowel Program
 - Miralax and senna
 - Propulsive aids (tegaserod and prucalpride)
- Eliminate obstruction
 - Biofeedback
 - Alpha blockers



IMPROVEMENT OF LOWER URINARY TRACT SYMPTOMS IN CHILDREN UTILIZING TEGASEROD

- 18 patients with severe constipation
- Elevated PVR's
- Recurrent UTI's
- Urinary incontinence
- All that had edsd had biofeedback or Botulinum Toxin A injections to the external sphincter for EDSD
- Those that had evidence of BN Dysfunction had been treated with alpha blockers

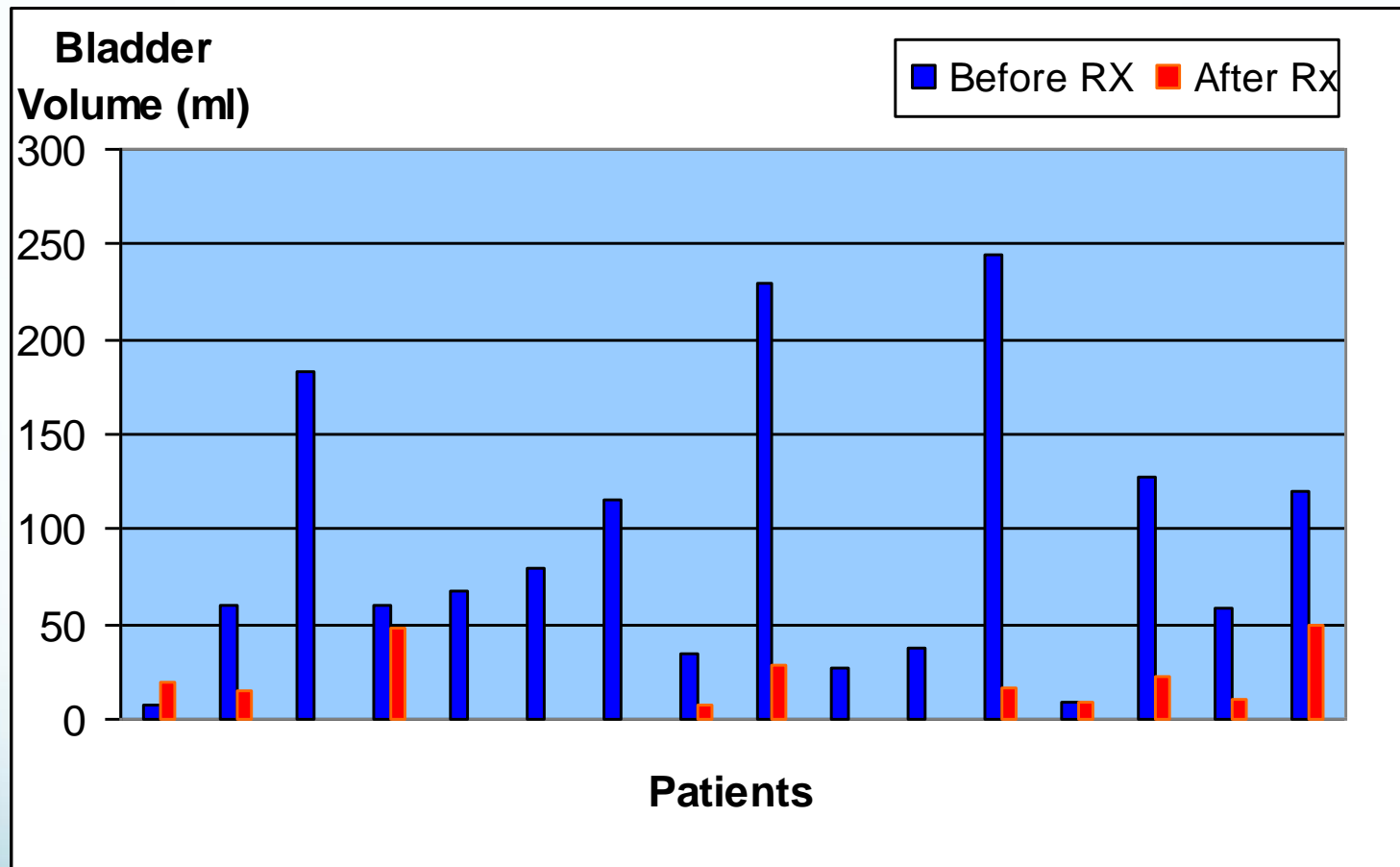


Results

- In All pts. with UTI's the infections ceased
- Incontinence episodes were improved in all patients
- 4/18 patients that had incontinence episodes did not have complete resolution (3/4 had Ψ issues that were not treated with meds)



PVR Before and After Tegaserod Treatment



Before=91.2 ml After= 14.2 ml

T Test P= .00003



Tegaserod Modulation of Visceral Sensitivity

- Coffin et al[i] and JM Sabaté[ii] et al have shown that tegaserod pretreatment can significantly reduce rectal sensitivity to distention in patients with IBS-C.
- These findings are suggestive of an inhibitory effect of tegaserod on neural pathways involved in visceral sensitivity in humans.

[i] Coffin B et al Aliment Pharmacol Ther 2003; 17:577-85

[ii] Sabaté JM, et al Neurogastroenterol Motil 2007 Nov 14 ;



5-HT Modulation of Visceral Sensitivity

- Serotonin (5-HT) inhibits spinal cord responses to afferent neuronal stimulation largely through the actions of 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptors which are plentiful in the dorsal horn
- Dorsal horn receives serotonergic neuronal input from the midbrain raphe nucleus
- There is an increase in the sensory threshold (volume distention) in initiating bladder contraction without effects on contraction amplitude or duration



Tegaserod and CNS

- 5-HT₄ receptors in the brain and detrusor*
- Tegaserod does cross the blood brain barrier
- Exhibits a low affinity inhibition of SERT via a noncompetitive binding mechanism.^{[i] [ii]} This can lead to synergism of action in which there is an elevated level of the 5-HT₄ agonist along with elevated levels of 5-HT due to reduced reuptake.

^[i] **Ismair MG, et al Digestion. 2007;75(2-3):90-5.**

^[ii] **Gershon MD, Tack J. Gastroenterology. 2007 Jan;132(1):397-414**

* **Tonini M et al Br J Pharmacol 1994 113:1**



Tegaserod and CNS

- Work by G Lucas et al [\[1\]](#) indicates that 5-HT₄ receptor agonist can act as putative antidepressant with a rapid onset of action.

➤ [\[1\]](#) Lucas G, et al Neuron 2007 Sep 6;55(5):712-25.



How did the 5-HT₄ Agonist Work?

- Duloxetine (SSRI/SNRI)
 - Can increase bladder capacity and sphincter tone without interfering with the normal voiding cycle
- We have found it useful in adolescents with OAB as well
- We can understand the improvement in OAB symptoms
- How Does it Improve bladder emptying?



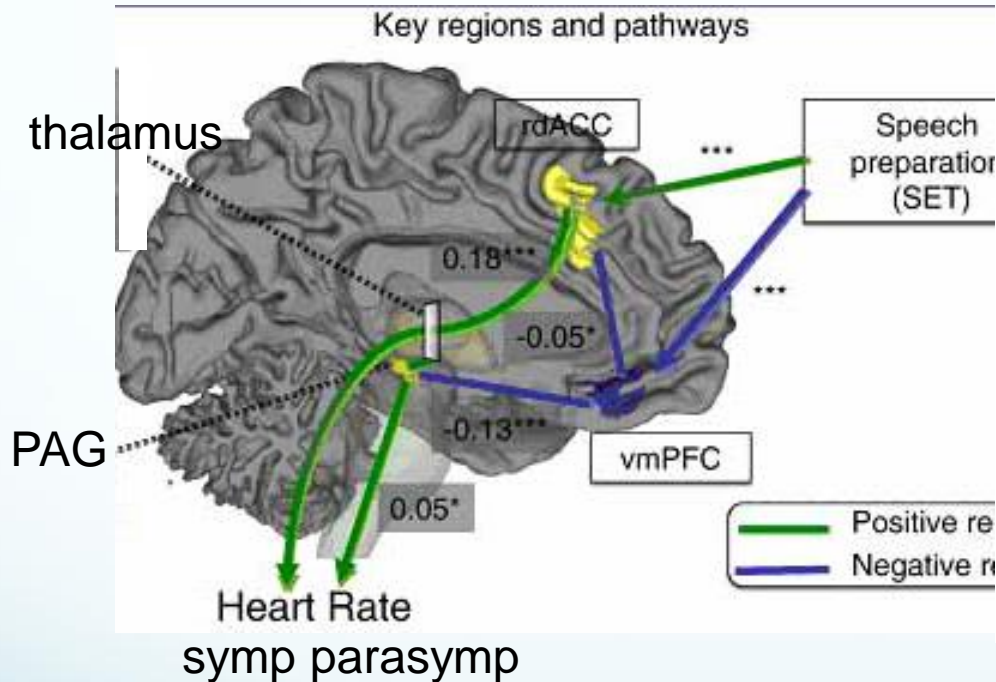
Non Serotonergic Agents

- Reglan (Metoclopramide HCl)
- is known to stimulate mobility of the upper G.I. tract.
- It's exact mode of action is not known, but it does appear that it sensitizes tissue to the actions of acetylcholine. Antagonizes central and peripheral dopamine receptors promoting antiemetic effect.
- The effects of Reglan can be abolished by anticholinergic drugs.
- This action may place its some of it's actions higher than the peripheral nerves or muscle.
- It may exert some action on the basal ganglia and alter dopaminergic and acetylcholinergic balance much like the phenothiazianes.
- Old publications have indicated that Reglan may have some effect on dog bladders under experimental conditions.



Ubiquitous Role of Sympathetic and Parasympathetic systems

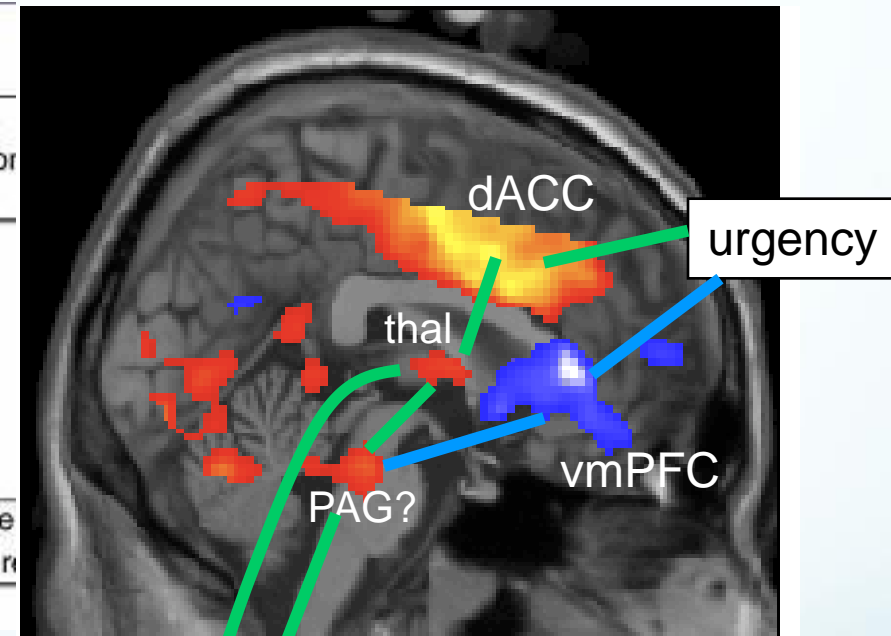
cardiac (Wager 2009)



Socially stressful task (speech preparation) deactivates vmPFC and activates dACC

- 2 mechanisms to increase heart rate

urge-incontinent adults



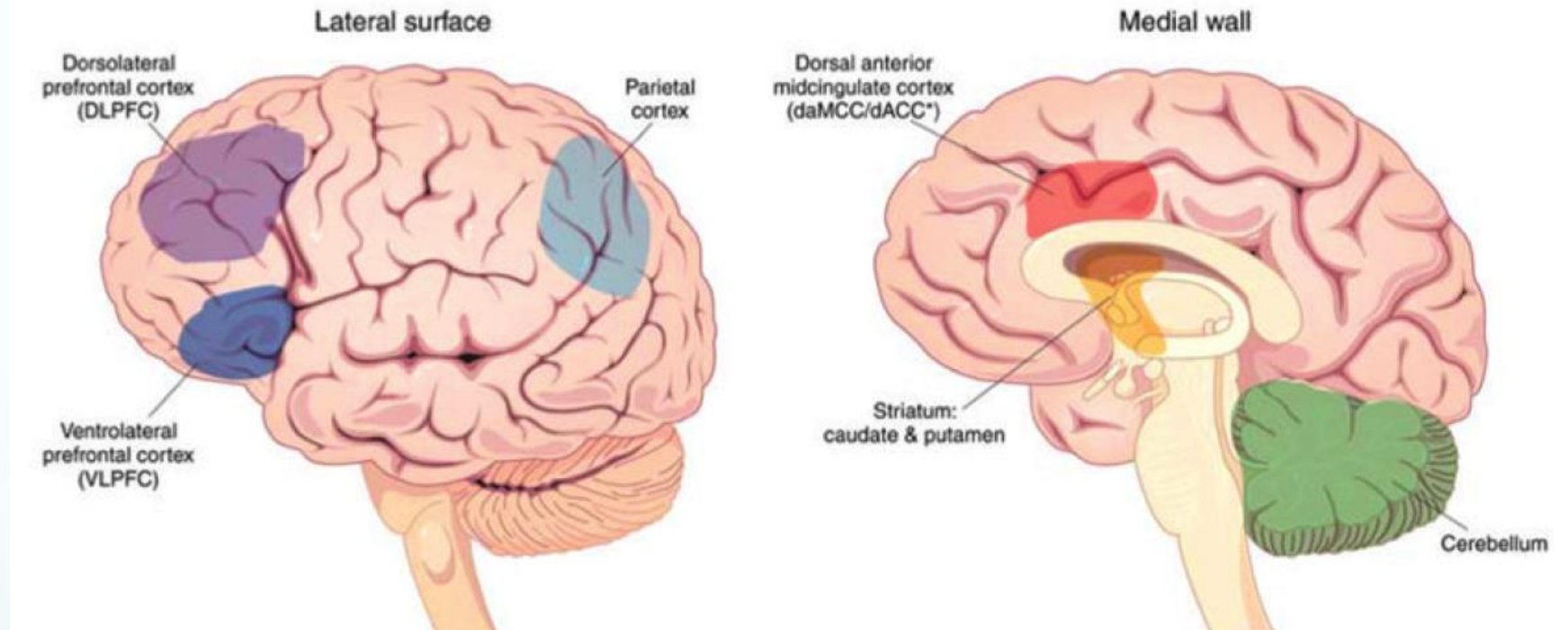
urgency

symp parasymp

Socially stressful situation (urgency) deactivates vmPFC and activates dACC

- 2 mechanisms to suppress voiding

Frontal Lobe Dysfunction And It's Relationship To Voiding Dysfunction



G Bush, M.D., Biol Psychiatry. 2011 June 15; 69(12): 1160–1167

The Cingulo-Frontal-Parietal Cognitive/Attention Network

The dorsal anterior midcingulate cortex [daMCC], dorsolateral prefrontal cortex [DLPFC], ventrolateral prefrontal cortex [VLPFC] and parietal cortex comprise the CFP network. These regions work in concert with each other and other regions such as striatum and cerebellum to support normal cognition, attention and motor control processes. All of these brain regions have been found to display functional and structural abnormalities in ADHD.

Frontal Lobe Dysfunction And It's Relationship To Voiding Dysfunction

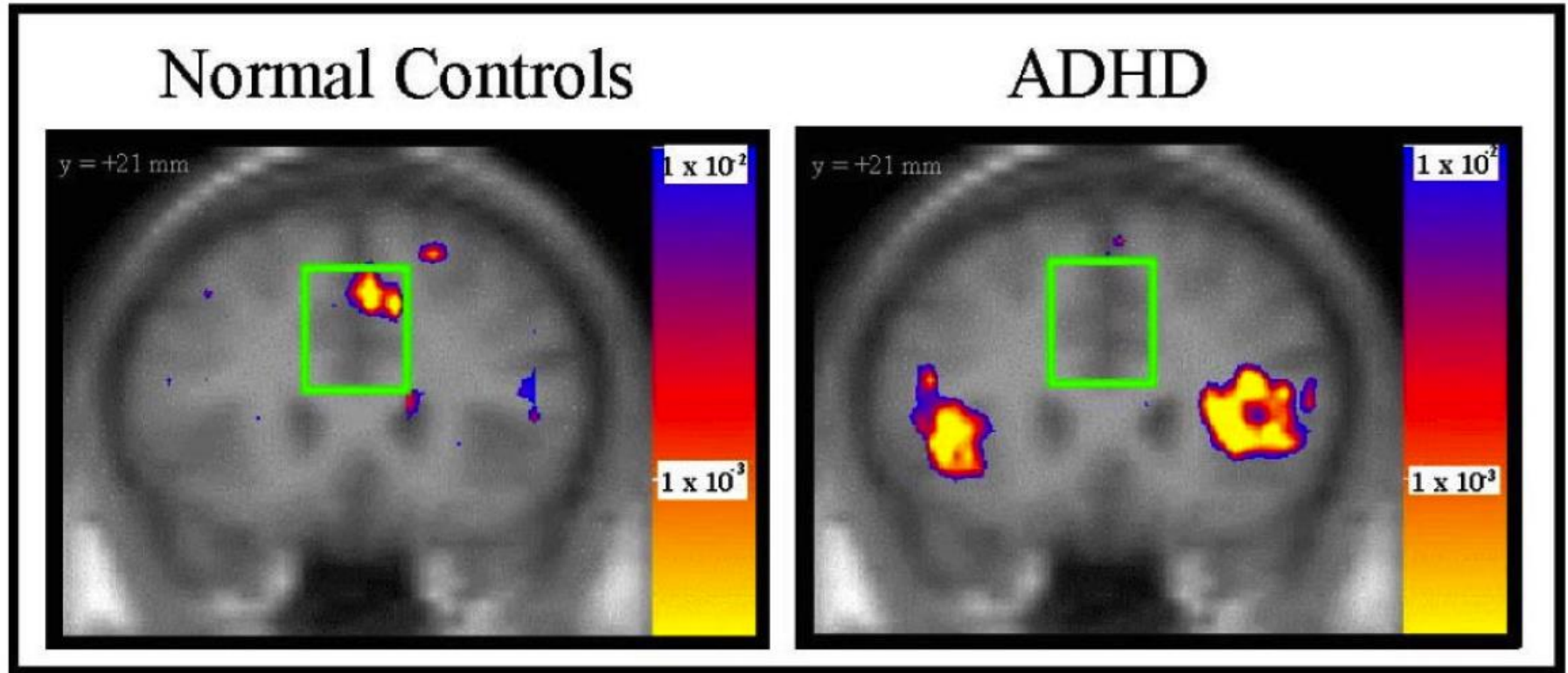
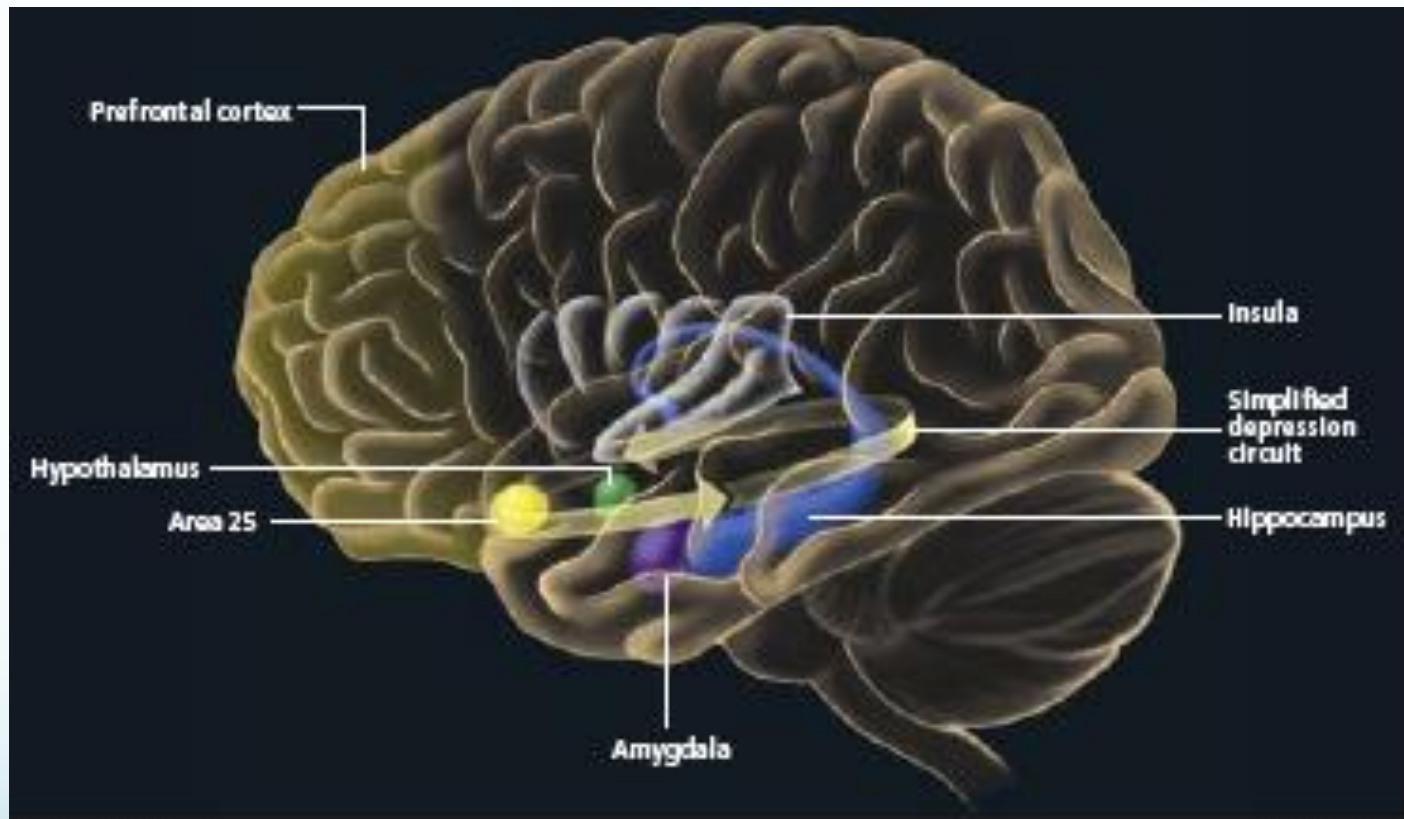


Figure 2. The daMCC Shows Hypofunction in ADHD during Counting Stroop
Dorsal anterior midcingulate cortex (daMCC) activated in healthy controls, but not in subjects with ADHD, during the Counting Stroop (30).

George Bush, M.D., Biol Psychiatry. 2011 June 15; 69(12): 1160–1167

How Can Depression Be Associated With Voiding Dysfunction?



How Can Depression Be Associated With Voiding Dysfunction?

- Cortical thinning in persons at increased familial risk for major depression
BS. Peterson et al PNAS April 14, 2009, vol. 106 no. 15 6273-6278
- Imaging studies of 131 people aged 6 to 54 with and without a family history of depression
- Brain scans showed a **28 % thinning in the right cortex** in people who had a family history of depression compared with people who did not.
- They did memory and attention tests on the study subjects and found the less brain material a person had in the right cortex, the worse they performed on attention and memory tests.
- Findings suggest rather strongly that if you have thinning in the right hemisphere of the brain, you may be predisposed to depression and may also have some cognitive and inattention issues,



How Can Depression Be Associated With Voiding Dysfunction?

Cortical thinning in persons at increased familial risk for major depression

BS. Peterson et al PNAS April 14, 2009, vol. 106 no. 15 6273-6278

- Whether familial risk is of a genetic or epigenetic origin, or some combination of these etiologies, cannot be determined from this publication
- Nevertheless, the presence of the findings:
 - across a wide age range,
 - the presence of the findings in children of the sample when analyzed separately
 - the absence of an interaction of age with risk group,
 - increased rates of anxiety disorders and MDD in childhood and adolescence that have been documented previously in this cohort suggest that the determinants of the cortical thinning probably are operative early.



Treatment options For Children with UAB

- **Reduce outlet resistance**
 - Alpha blockers for bladder neck dysfunction
 - Biofeedback for EDSD
 - Botulinum toxin injections into the external sphincter
- **Reduce uninhibited contractions**
 - Avoid anticholinergics
 - Consider non selective alpha blockers
 - Eliminate constipation
 - Control bowel overactivity
 - Consider a trial of imipramine for refractory OAB
 - Consider a trial of SSRI's for OAB resistant to imipramine



Treatment options For Children with UAB

- **Improve bladder emptying**
 - Sit to void (males)
 - Prucalpride or Tegaserod (off label use of medication, can be used to treat concomitant severe or refractory constipation)
 - Parasacral TENS
 - Sacral nerve stimulation with implantable stimulator
 - Intermittent catheterization
- **Detect neuropsychiatric problems and treat them**
- **Look for and treat Autonomic Dysfunction**



What Does This All Mean?

- Our assumptions and descriptions of the UAB are incorrect
 - High incidence of OAB
 - Many void without straining to void
 - No evidence of interrupted voiding in many children
 - Not everyone has a large bladder
- We need to better define the condition to improve reporting and research.



What Does This All Mean?

- In the pediatric patient with the exception of the posterior valve patients we may be looking at a very different mechanism for UAB than in adults
- These mechanisms are not local in the bladder
- High Prevalence Of Concomitant Constipation
 - Points to an association with either sympathetic dysfunction or serotonergic signaling abnormalities
- Possibly Central In Nature
 - Association with neuropsychiatric disorders is increased in this group of patients
 - Responds to serotonergic agents



Potential Avenues of Research

- Develop or reintroduce Serotonergic agonists for use in UAB patients
- Expand the use of SSRI's in this population of patients
- Are non selective alpha blockers better than anticholinergics in UAB patients for OAB symptoms
- Need for multicenter collaborative studies due to small number of patients
- We need to define what is the normal bladder emptying pressure
- Better system to define UAB
 - Type of detrusor contraction
 - Low pressure, sustained
 - Low pressure, interrupted
 - Interrupted, high pressure
 - Interrupted, low pressure
 - Presence or absence of OAB
 - Presence or absence of BND or EDSD



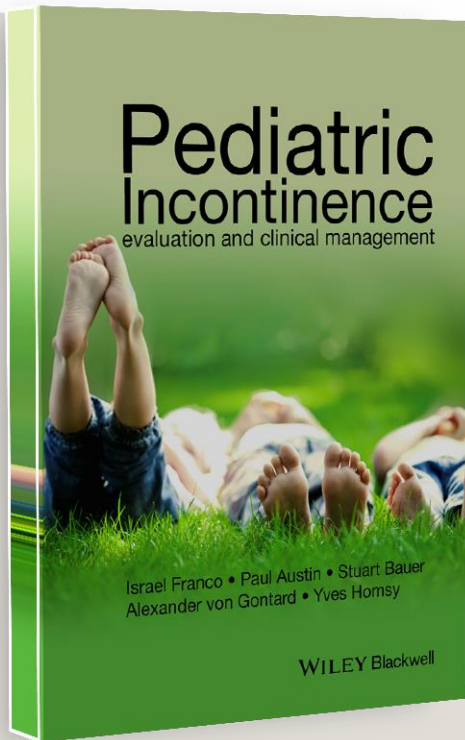
Thank You

- I would like to thank Drs. Clothier and Wright for the use of their data, which was presented at the World congress of Pediatric Urology/ICCS meeting in Prague, Czech Republic in October 2015.



Pediatric Incontinence: Evaluation and Clinical Management

Edited by Israel Franco, Paul Austin, Stuart Bauer, Alexander von Gontard, and Yves Homsy



Up to 15% of children aged six years old experience the common problem of incontinence. This book:

- Is edited by respected clinicians who write on their areas of expertise
- Provides practical, “how-to” guidance for patient care
- Reflects the latest guidelines from the ICCS, AUA, and EAU

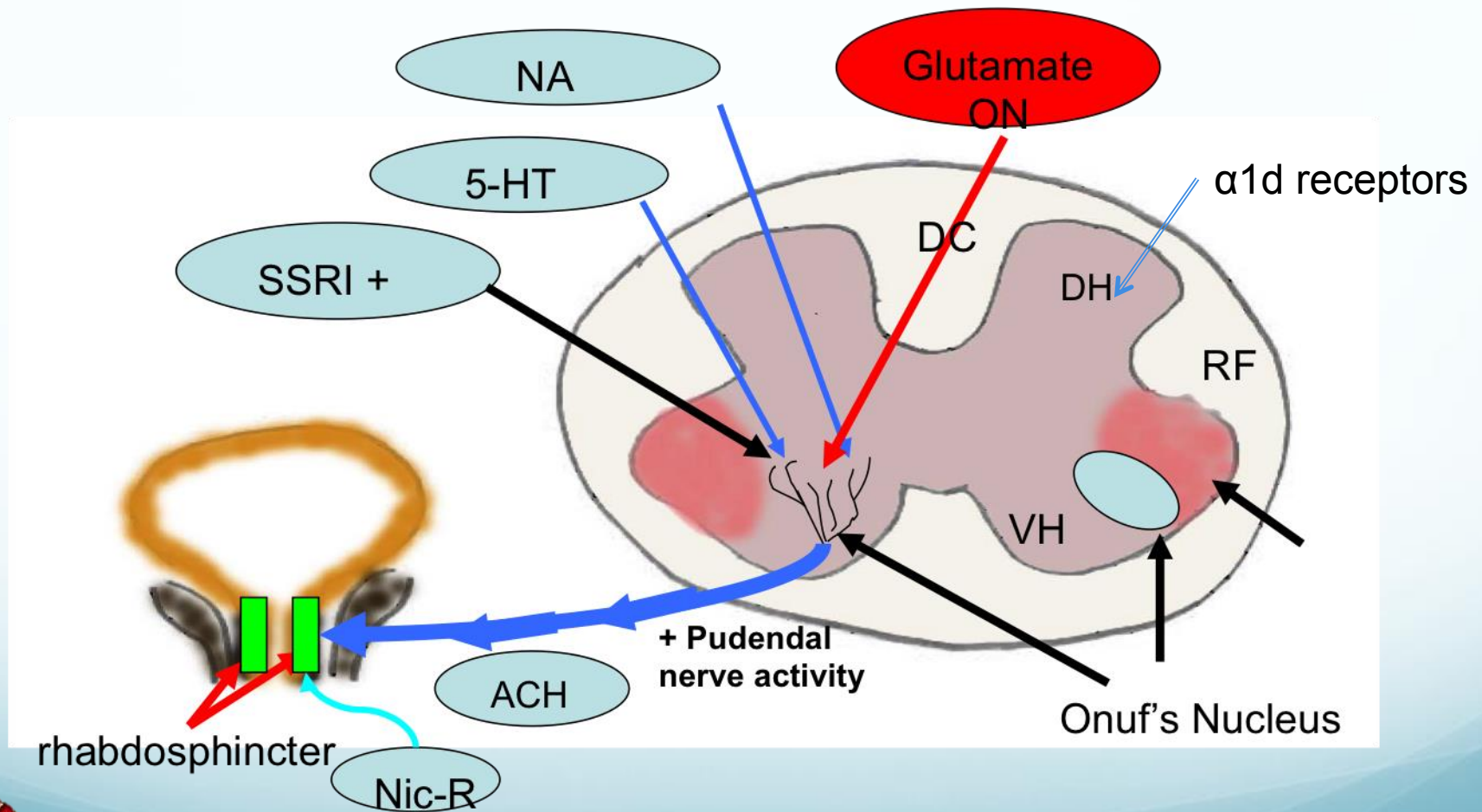
October 2015 | 9781118814796 | Approx. 360 pages | Hardcover
\$140.00 • £89.99 • €112.50
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Role of 5-HT in Storage



Role of 5-HT in Voiding

