W34: LUTS in Children and Adolescents, Role of Alcohol & Substance Abuse

Workshop Chair: Giovanni Mosiello, Italy

Start	End	Topic	Speakers
		Introduction :Lower urinary tract symptoms and dysfunctions in children and adolescents	Jian Guo Wen
		LUTS in children with Fetal alcohol spectrum disorders	Alex von Gontard
		LUTS and comorbidities in adolescents	Tufan Tarcan
		LUTS and Alcohol and substance abuse in adolescents	Giovanni Mosiello
		Questions	All
		LUTS Multidisciplinary approach in children and adolescents: what We can do for alcohol and substance abuse?	Giovanni Mosiello Jian Guo Wen Tufan Tarcan Alex von Gontard
		Take Home Messages	Giovanni Mosiello

Aims of Workshop

Lower Urinary tract symptoms (LUTS) in paediatrics and adolescents are mainly reported to functional disorders related to a delay of maturation control. Recently major attention has focused on the role of comorbidities in adolescents and young adults, where Increasing consumption of alcoholic, binge drinking and drunkeness is reported, as well as substance abuse (ketamine, methamphetamine). One indirect related consequence is Fetal alcohol spectrum disorders in individuals affected by prenatal alcohol exposure by mothers. Knowledges on alcohol and substance effects on LUTS on paediatrics and adolescents are very scant, aim of our workshop is to offer to health care providers instruments for better understanding their effects on LUTS.

Learning Objectives

increase knowledge on LUTS and the role of comorbities in children and adolescents

Target Audience

Urology, Urogynaecology and Female & Functional Urology, Bowel Dysfunction, Conservative Management

Advanced/Basic

Advanced

Suggested Learning before Workshop Attendance

1.Abrams P, et al Incontinence 6th ed 2017 chapter 9: Njiman R, et al ,959-1090
2 .Austin P et al /, Neurourol and Urodyn. 2016;35:471-481
3.De Gennaro M, et al ./J Urol 2010;184:1662-7.
4. Roozen S et al /JPed Urol(2020) 16, 386.e1e386.e11
5.Pike JR et al /Preventive Medicine 143 (2021) 106383
6.Yee CH et al / Hong Kong Med J 2019;25:438–43
7.Pal R et al /Drug and Alcohol Dependence 132 (2013) 189–194
8.Tam YH et al/Hong Kong Med J 2016;22:454–63
9.Palamar JJ et al / International Journal of Drug Policy 73 (2019) 81–87
10.Charrier L Ann Ist Super Sanità 2020 | Vol. 56, No. 4: 531-537

Lower urinary tract symptoms in children and adolescents

Jian Guo Wen

Lower urinary tract symptoms (LUTS) in children and adolescents are frequently confronted in clinical practice. Epidemiological studies have shown that LUTS can be seen in as high as 20% of school aged children. The most common LUTS are urgency; frequency and incontinence (include enuresis). LUTS have significant social consequences and sometimes clinical morbidities like urinary tract infections (UTI) and vesicoureteral reflux (VUR). A significant emotional and behavioral problems related to LUTS has been reported in children and adolescents.

LUTS are classified into either overactive bladder (OAB) or dysfunctional voiding. OAB is a term used for symptom of urinary urgency, usually accompanied by frequency and nocturia with or without urinary incontinence, in the absence of UTI. Dysfunctional voiding is a term used for increased activity of urethral sphincter or pelvic floor during voiding and presentation of a staccato pattern with or without an interrupted flow on repeat uroflow when EMG activity is concomitantly recorded in a neurologically intact child . Dysfunctional bowel emptying is often part of the whole clinical picture and bladder bowel dysfunction (BBD) is the term used to cover associated bladder and bowel disturbances

LUTS occur is mainly due to a filling-phase dysfunctions and/or voiding-phase dysfunctions of bladder . Filling-phase dysfunctions includes bladder oversensitivity, detrusor overactivity, low bladder compliance, abnormal maximum bladder volume, urethra/sphincter dysfunction。While voiding-phase dysfunctions might show an underactive bladder, acontractile detrusor, bladder outlet obstruction, bladder neck dysfunction, detrusor sphincter dyssynergia, dysfunction voiding, bladder and bowel dysfunction6,7,8。

Lower urinary tract dysfunction (LUTD) might be neurogenic and non-neurogenic. Alcoholism and substance abuse (ketamine, methamphetamine) induced LUTD has been reported in the literature , .

The diagnosis of LUTD is mainly based on medical history, physical exam, urinalysis and auxiliary examinations.The voiding diary, routine urine test, uroflowmetry+PVR measurement are frequently used to screen the dysfunction. Pressure/flow evaluation, especially video urodynamic study for neurogenic bladder or severe cases are basic test to category the LUTD, Synchro-cystourethrometry has been reported to be a useful urodynamic technology to precisely evaluate correlation between urethral instability (URI) and overactive bladder (OAB) in children .

The treatment of LUTD includes a multimodal approach according to etiology, symptoms and urodynamic classification. Current treatment protocol is mainly the urotherapy, alarm treatment, pharmacological therapy, botulinum toxin-A injections, neuromodulation,and surgical therapy。

Urotherapy is recommended by the ICCS as the first-line treatment for most types of LUTD. It uses non-pharmacological, non-surgical methods and focuses on behavioral interventions, largely based on cognitive-behavioral psychotherapy. The aim of urotherapy is to achieve the normalization of the micturition and bowel pattern and to prevent further functional disturbances by repeated training.

For cases who do not show satisfactory response to urotherapy and who have some conditions which may need specific treatment including ①Physiotherapy includes pelvic floor muscle awareness practices with repeated sessions of biofeedback visualization of uroflow curves and/or pelvic floor activity and relaxation.;②Clean intermittent self-catheterization for high volumes of post-void residual urine despite urotherapy and biofeedback;③Antimuscarinic drug therapy, if detrusor overactivity is present; ④If the bladder neck is associated with increased resistance to voiding, alpha-blocker drugs may be introduced. Specific medical treatment is added in the case of refractory OAB symptoms and recurrent UTIs. Recurrent UTIs and constipation should also be treated and prevented during the treatment period. Studies have shown that complications such as UTI and VUR may disappear as the LUTD improves9。

In summary, LUTD is common in children and adolescent. LUTS varied with difference in etiology, voiding types and related risk factors. UDS plays an important role in identifying the causes and guide the clinical treatment.

References:

Linde JM, Nijman RJM, Trzpis M, Broens PMA. Prevalence of urinary incontinence and other lower urinary tract symptoms in children in the Netherlands.J Pediatr Urol. 2019 ; 15(2): 164.e1-164.e7.

Dourado E R,de Abreu G E,Santana J C et al. Emotional and behavioral problems in children and adolescents with lower urinary tract dysfunction: a population-based study.[J] .J Pediatr Urol, 2019, 15: 376.e1-376.e7.

Austin PF, Bauer SB, Bower W, Chase J, Franco I, Hoebeke P, Rittig S, Walle JV, von Gontard A, Wright A, Yang SS, Nevéus T. The standardization of terminology of lower urinary tract
function in children and adolescents: update report from the standardization committee of the International Children's Continence Society. Neurourol Urodyn (2016). 35(4):471–481

Austin Paul F,Bauer Stuart B,Bower Wendy et al. The standardization of terminology of lower urinary tract function in children and adolescents: update report from the Standardization Committee of the International Children's Continence Society.[J] .J Urol, 2014, 191: 1863-1865.e13.

D'Ancona Carlos,Haylen Bernard,Oelke Matthias et al. The International Continence Society (ICS) report on the terminology for adult male lower urinary tract and pelvic floor symptoms and dysfunction.[J] .Neurourol Urodyn, 2019, 38: 433-477.

Incontinence in persons with fetal alcohol spectrum disorders: a polish cohort.Roozen S, Dylag KA, Przybyszewska K, Niemczyk J, von Gontard A, Peters GY, Kok G, Curfs L.J Pediatr Urol. 2020 Jun;16(3):386.e1-386.e11.

Cheung RY(1), Lee JH, Chan SS, Liu DW, Choy KW. A pilot study of urine cytokines in ketamine-associated lower urinary tract symptoms. Int Urogynecol J. 2014;25(12):1715-9.

Hua C, Wen Y, Zhang Y, Feng Q, He X, Li Y, Wu J, Feng J, Bauer SB, Wen J. The value of synchro-cystourethrometry for evaluating the relationship between urethral instability and overactive bladder. Int Urol Nephrol. 2018 Mar;50(3):441-449

Nieuwhof-Leppink AJ, Hussong J, Chase J, Larsson J, Renson C, Hoebeke P, Yang S, von Gontard A. Definitions, indications and practice of urotherapy in children and adolescents: - A standardization document of the International Children's Continence Society (ICCS). J Pediatr Urol. 2021;17(2):172-181

Alex von Gontard
LUTS in children with Fetal Alcohol Spectrum Disorder

Fetal Alcohol Spectrum Disorders (FASD) are the most common teratogenic disorders, caused by maternal alcohol consumption during pregnancy. In addition to the full manifestation, i.e. Fetal Alcohol with a world-wide prevalence of 2.9/1000 live births, FASD encompasses partial Fetal Alcohol Syndrome, Alcohol Related Birth Defects, Alcohol related Neurodevelopmental Disorder and Neurobehavioral Disorder associated with prenatal alcohol exposure.
FASD is diagnosed by a typical pattern of facial dysmorphia, growth problems (height/weight ≤10th percentile), CNS abnormalities and prenatal alcohol exposure.
Typical developmental problems include ADHD, cognitive abnormalities, conduct disorders, motor, speech and language disorders. Incontinence has been studied in two studies, only.
In the first study, a population-based cohort in a risk population in South Africa was recruited. The prevalence of FASD was 12.4%. Of the 8.5 year children (n=99), 71% had a developmental delay. 20.2% had any type of incontinence, 16.2% nocturnal enuresis (NE), 1% daytime urinary incontinence and 4% fecal incontinence. This is the first population-based study of incontinence in FASD world-wide. Standardized questionnaires and international guidelines (ICCS) were used. Incontinence present in 20% of children with FASD and monosymptomatic NE most common subtype, which could be due to maturational deficits of the central nervous system (CNS).
In the second study, a clinical sample of 71 children with FASD and a mean age of 10 years was examined in Krakow, Poland. The overall rate of incontinence was 23.9%, of NE 9.9%, of DUI 11.3% and of FI 12.7%. This is the first study of incontinence among children and adolescents with FASD in Europe. The overall rate of incontinence is comparable with South African cohort: However, NE was not the most common type, which might be due selection effects.
Because of high rates of incontinence, this should be routinely assessed in all children and adolescent with FASD. Individually adapted treatment is also recommended.

Roozen S, Olivier L, Niemczyk J, von Gontard A, Peters GY, Kok G, Viljoen D, Curfs L. (2017). Nocturnal incontinence in children with fetal alcohol spectrum disorders (FASD) in a South African cohort. J Pediatr Urol. 13:496.e1-496.e7.
Roozen S, Dylag KA, Przybyszewska K, Niemczyk J, von Gontard A, Peters GY, Kok G, Curfs L (2020). Incontinence in persons with fetal alcohol spectrum disorders: a polish cohort. J Pediatr Urol, 16(3):386.e1-386.e11

LUTS and comorbidities in adolescents
Tufan Tarcan

LUTS prevalence in adolescents vary from 9.3% to 46.4%. LUTS-associated comorbidities in adolescents include chronic renal failure, constipation, obesity, diabetes mellitus and pregnancy. The pathophysiological mechanism associated with the aforementioned co-morbidities may include hormonal or metabolic factors and pelvic floor dysfunctions.

In addition, there is another group of adolescents with psychosocial comorbidities that include attention deficit hyperactivity disorder (ADHD), anorexia nervosa, emotional and behavioral problems, stress, sexual abuse, drug abuse, low education, adverse childhood experiences and drug abuse. Drug abuse includes alcohol, ketamine, ecstasy (MDMA) and methamphetamine. The pathophysiological mechanisms associated with the psychosocial comorbidities are less investigated and poorly understood. The possible mechanisms and the available evidence will be discussed during the workshop.

Briefly, the causative mechanisms of LUT dysfunction (LUTD) in adolescents that are associated with the psychosocial co-morbidities can be multifactorial. The causative relation can be classified in 4 different groups:
1. LUTD can cause the onset of psychological symptoms.
2. Psychological symptoms can predict the onset of LUTD.
3. Psychological symptoms and LUTD both share common biological pathways.
4. LUTD and psychological symptoms/disorders can coexist without any causal association.

Risk factors for LUTD can interact with each other in an additive or even an exponential mode. Psychoneurobiological models include dysregulation of the hypothalamic- pituitary-adrenal (HPA) axis. This may result in increased CRF, ACTH, and cortisol release in depression and anxiety disorders. CRF is also shown to be involved in bladder function.

In conclusion, LUTS are prevalent in the general adolescent population. Due to the high rate and relevance in clinical practice, screening for psychological comorbidities is recommended for all age groups. It is important to obtain an accurate history regarding all possible comorbidities including psychotropic substance use. Further research is desperately needed to clarify the complex causal relation between LUTS and psychosocial comorbidities.

Suggested Readings:

1. von Gontard A, Vrijens D, Selai C, Mosiello G, Panicker J, van Koeveringe G, Apostolidis A, Anding R. Are psychological comorbidities important in the aetiology of lower urinary tract dysfunction-ICI-RS 2018? Neurourol Urodyn. 2019 Dec;38 Suppl 5:S8-S17.

2. Tarcan T, Selai C, Herve F, Vrijens D, Smith PP, Apostolidis A, Panicker JN, Kirschner-Hermanns R, Arlandis S, Mosiello G, Dmochowski R, Cardozo L, von Gontard A. Should we routinely assess psychological morbidities in idiopathic lower urinary tract dysfunction: ICI-RS 2019? Neurourol Urodyn. 2020; 39 Suppl 3:S70-S79.

LUTS and alcohol and substance abuse in adolescents
Giovanni Mosiello

Adolescence is a transitional phase of life, particularly susceptible to transgressions like smoking, cannabis use and harmful drinking [Ellickson PL 2003, Tomlison KL 2004). Of course occasionally consumption is different by abuse .Alcohol use disorder (AUD) or other substance use disorder (SUD) are an evolving concept, and literature on alcohol or other substance use in children and adolescents has focused mainly on prevention and social issues.Data by National Survey on Drug Use and Health showed nearly 1 million youths (ages 12 to 17) needed treatment for AUD or SUD in 2018 in USA USA Results from the 2018 National Survey on Drug Use and Health).
Higher prevalence rate for both cannabis and alcohol risk behaviour among adolescents with low Social economical status parental income, parental education and occupation) in comparison to adolescents with higher SES. Low socioeconomic status in childhood exacerbates the risk for heavy episodic drinking and smoking .Unemployment was a discrete predictor of binge drinking among adolescents, even when controlling for age, gender and education .Adolescents' use of cannabis does not systematically correlate with family affluence, socioeconomic or occupational status of the parents .The percentage of problematic consumers among cannabis consuming 4:1 in LL-students / HL -students. The prevalence rate of illegal drug use other than cannabis across the life span of LL- and ML-students was around 15%, double the rate observed for HL-students (Henkel and Zemlin, 2016).

ALCOHOL
The prevalence of alcohol or other substance-related disorders for adolescents has been related gto gender, race, and/or ethnic, anyway some common issues have been identified as an high incidence of alcohol and other substance use for adolescents with trauma histories (Finch AJ 2020).
Meanwhile a decrease in alcohol consumption is reported in Europe and North America (Looze MD, Eur J Public Health. 2015) ,Alcohol remains the most commonly substance used by adolescents: overall almost 60% have drunk alcohol in their lifetime, (Inchley J, 2020).
Two main models of alcohol consumption among adolescents have been described in the past : a) the "dry culture" model (Northern Europe), characterized by sporadic consumption, concentrated in the weekend, outside of mealtimes with the primary aim to get drunk (binge drinking – five or more drinks on one occasion) ; b) the "wet culture" (Mediterranean countries), characterized by more regular alcohol consumption, greater overall quantities, associated with meals and rituals. (Room R 2002). A recent italian study on 18,918 questionnaires in 15-year-old students (9,506 females and 9,412 males), demonstated that Dry / Wet culture is an old description.
Alcohol abuse in adolescence may have a variety of consequences: adverse social, physical, psychological, missing school, school failure, having unprotected sex (with unintended pregnancy and sexually transmitted diseases as consequences), destructive behaviour, increase in injury likelihood, violence and even deaths (car accidents, etc) (Marshall EJ, 2014, Currie D, 2005).
Alcohol is responsible of structural and functional alterations in the human adolescent brain.
Volumetric and connectivity differences for AU versus non-AU youth in prefrontal areas, including but not limited to, the right middle and superior frontal gyrus, left frontal cortex, frontal pole, and Inferior F.G.(Jacobus & Tapert, 2013; Lisdahl et al., 2013a; Welch, Carson, & Lawrie, 2013).
These areas are critically involved in the capacity and command of executive control.
Structural and functional differences for AU versus non-AU youth in: meso-corticolimbic reward system, a dopamine-based brain pathway that includes the dorsal striatum (caudate/putamen), thalamus, anterior cingulate, internal capsule and IFG. (Filbey et al., 2008, Robinson & Berridge, 2008; Spear, 2014; Volkow, Wang, Tomasi, & Baler, 2013). Adolescent AU females may be at heightened vulnerability for alterations in brain structure and function (Jacobus & Tapert, 2013; Lisdahl et al., 2013,Healey et al., 2014). The potential role of sex hormones in this equation provides an area for future investigation (Paus, 2010; Spear, 2014).
On a PubMed research :All available peer-reviewed magnetic resonance imaging (MRI) and functional magnetic resonance imaging (fMRI) studies of AU adolescents (aged 19 and under), considering the 21 studies (10 MRI and 11 fMRI) met the criteria for inclusion, Alcohol consumption during adolescence is associated with significant differences in structure and function in the developing human brain (Jacobus & Tapert, 2013; Lisdahl et al., 2013). Quantity of alcohol consumed is strictly related to and adolescent brain structure and function.Greater AU consumption was related to lower brain volume in several regions, less White Matter integrity and lower levels of (blood- oxygenation-level-dependent (BOLD) response (Fein et al., 2013; Lisdahl et al., 2013a; McQueeny et al., 2009; Tapert et al., 2003).
In LUTS treatment, before medication, patients are generally educated to modify their lifestyle factors including less alcohol intake (Gormley EA, 2015,), anyway Alcohol drinking showed inconsistent results regarding effects on LUTS. Modest alcohol intake is considered a favorable factor for LUTS, while excessive alcohol intake could lead to worse LUTS (Bradley CS , 2017). Heavy alcohol intake has negative effect on LUTS including incontinence, voiding, and storage LUTS (Joseph MA 2013, and at any level of drinking, on nocturia (Noh JW , 2020).

Possible mechanisms of alcohol intake/LUTS : increased sympathetic tone activity, diuretic effect (Van de Borne P, 1997). Studies on LUTS and alcohol presented No association in the EPINCONT study (Hannestad YS,2003), No association in Italian study of 5488 subjects (Bortolotti A , 2000)
While presented association in Boston area women study (Marezejian N 2012). So the association of alcohol and urinary incontinence are weak, and Low to moderate alcohol (ethanol) consumption has beneficial effects . What is low moderate? Moderate depends on age, sex, genetic characteristics, co-existing illnesses, and other factors. Moderate: is up to 1 drink/day for Woman and 2 drinks/ Day for Man, where 1 standard drink= 12-14 g of ethanol, which corresponds to 355 mL of beer, 148 mL of wine. Regarding the mechanism of action , Alcohol consumption has been related in many studies to be associated with LUTS; however, it is not well known how alcohol affects the bladder tissue per se.
Alcohol is converted to acetaldehyde primarily by alcohol dehydrogenase (ADH) and further to acetate by acetaldehyde dehydrogenase (ALDH) and xanthine oxidoreductase. Acetaldehyde plays a major role in alcohol-associated tissue toxicity .The epithelial lining of the urinary bladder (urothelium) is especially vulnerable as it is exposed to alcohol and its metabolites on both the serosal (interface with blood) and apical (interface with urine) aspect; in the latter case for long periods of time due to urine storage.(Molina PE 2014, Suh B 2014, Wallner M , 2008)
Alcohol use as a potential trigger for IC/BPS symptoms according to a survey conducted by the Interstitial Cystitis Network. 94% reported that their bladder symptoms worsened (Osborne J, 2010). 75% of patients reported in increase in pain after drinking alcohol. In conclusion
Neuroscience has shown that alcohol abuse during adolescence has a substantial impact on brain development, are bladder control centers involved? Bladder : the effects of alcohol on bladder wall are debated, scant data. Further studies could be useful in order to understand alcohol abuse effects on long-term on bladder function in youth people. Future questions :How to investigate ? Questionnaires? ICIQ screener? Diaries . When history taking ?in presence of relatives is reliable ?
In all adolescents or in Adolescents with secondary LUTS ?

SUBSTANCE

Every year in the United States, approximately 700,000 youth between the ages of 12 and 17 misuse opioids (Substance Abuse and Mental Health Services Administration, 2019). Initiation of one form of drug by a teenager almost inevitably exposes the individual to increased availability and social influence from a drug using network (Dishion and Tipsord 2011; Eitan et al. 2017; Otten et al. 2017) . Psychotropic substance use among adolescents is a growing concern worldwide and creates psychosocial, security, and health care issues. Substance abuse and adolescents has been related in the past mainly to some population at risk , but is common to observe worldwide, without relationship to region, sex, social inclusion, economical status, etc. Furthermore substance
Consumption isCommon to observe in Dance music parties, nightclubs and festivals, that gained popularity globally over the past decades (Watson, 2018). Individuals who attend these parties, where use of party drugs such as ecstasy (MDMA) is particularly prevalent (Hughes, Moxham-Hall, Ritter, Weatherburn, & MacCoun, 2017; Palamar, Acosta, Ompad, & Cleland, 2017; Palamar, Salomone et al., 2017; Palamar, Griffin-Tomas, & Ompad, 2015). In some countries Ketamine is one of the most commonly abused substance (45.6%), followed by cough mixture (31.5%), ecstasy (25.2%), methamphetamine (24.9%), and marijuana (23.0%). Of ketamine users, 60.7% had at least one LUTS. Female ketamine users were at a higher risk for LUTS than males. 77% prevalence rate of LUTS among a group of young methamphetamine (also known as 'ice') users (pathological dopaminergic mechanism plays a predominant role in methamphetamine-associated LUTS) Koo KC 2014 . Ketamine has gained reputation "club drug" among young people in the US, Europe, Australia and Asia. (Bruno et al., 2012; Morgan and Curran, 2012; Ramo et al., 2010). LUTS are associated with chronic ketamine use (2007, Shahani) . Dysuria, frequency, urgency, incontinence, nocturia and hematuria with ketamine abuse (Smith, 2010). Severe cases with significant bladder contraction resulting in secondary renal damage (hydronephrosis) reported (Chiew and Yang, 2009; Chu et al., 2008). Regarding methamphetamine: increased storage symptoms have been described.
In ketamine abuse, storage symptoms can be attributed to damaged mucosa and infiltration of inflammatory cells into the lamina propria of the bladder, eventually leading to chronic inflammation and fibrosis. In MA abuse storage symptoms can be the result of a dysfunctional dopamine pathway in detrusor control. Its structural similarity with monoamine neurotransmitters allow amphetamines to act as competitive substrates with dopamine's membrane transporters. It also promotes dopamine release from storage vesicles. Long-term exposure to amphetamines is resulting in dopamine neuron terminal damage or loss. MA-related urological pathology could be related to multiple actions rather than only dopaminergic axis and storage symptoms.
LUTS increased by release of norepinephrine from MA abuse, which may cause increased α-adrenergic stimulation of the bladder neck. Methamphetamines and MDMA exert an alpha-agonistic effect increasing the release of endogenous norepinephrine stores . Bladder neck is innervated primarily by alpha-adrenergic receptors: excessive and prolonged stimulation of these receptors by norepinephrine is resulting in urinary retention.MDMA and other amphetamine derivatives may cause bladder dysfunction, most likely from alpha-adrenergic stimulation of the bladder neck. The substance abuse should be considered in the differential diagnosis of young persons presenting with acute urinary retention in whom no structural abnormality of the genitourinary tract is evident.JH. Delgado, 2004. Neuroscience (Spear 2011) suggests that substance use during adolescence may alter the mesolimbic reward pathway as well as multiple frontal cortical regions of the brain . In conclusion Ketamine and MA are at high risk for LUTS

Substance abuse must be considered in Pediatric Urology practice , as in outpatient clinic , secondary LUTS, as in emergency , urinary retention. Long-term effects of substance abuse in adolescents's suprapontine micturition centers and bladder wall must be investigated.