

International Children's Continenence Society (ICCS)

Educational Course 2015 on Enuresis and Incontinence

in collaboration with the Japanese Society on Enuresis and Japanese Society of Pediatric Urology

Dates: June 28 (Sun.) - 29 (Mon.), 2015

Venue: Juroku Plaza, Gifu, Japan



Chairman of Local Organizing Committee:

Akihiro Kawauchi

Professor and Chairman, Department of Urology, Shiga University of Medical Science
Director, Japanese Society on Enuresis
Director, Japanese Society of Pediatric Urology

International Faculty:

Paul Austin (USA)

Kristian Vinter Juul (Denmark)

Tryggve Nevéus (Sweden)

Jens Peter Nørgaard (Denmark)

Søren Rittig (Denmark)

Johan Vande Walle (Belgium)

Stephen Shei-Dei Yang (Taiwan)

Local Organizing Committee:

Shuichiro Fujinaga

Saitama Children's Medical Center

Hidehiro Kakizaki

Asahikawa Medical University

Kazunari Kaneko

Kansai Medical University

Hideo Nakai

Jichi Medical University, Children's
Medical Center Tochigi

Yoshiyuki Ohtomo

Juntendo University Nerima Hospital

Tomonori Yamanishi

Dokkyo Medical University

Shigeru Yoshida

Kishokai Medical Corporation

Website ⇨ <http://i-c-c-s.org/>



Greeting

It is a great pleasure to welcome you to the International Children's Continenence Society (ICCS) Educational Course 2015 held at Juroku Plaza in Gifu, Japan from June 28 to 29, 2015.

It is the first ICCS Educational Course held in Japan. International and Japanese experts will showcase the latest concepts and researches on enuresis and incontinence, and help expanding our knowledge in the fields.

Gifu is about 20 minutes by train from Nagoya, and the Juroku Plaza is adjacent to the Gifu station.

I hope you will enjoy the meeting with fruitful discussions.

Akihiro Kawauchi
Chairman, ICCS Educational Course 2015
Department of Urology,
Shiga University of Medical Science

General Information

Language

English is official language. Japanese interpretation is available in all sessions.

会の公式言語は英語です。全てのセッションで日英同時通訳が入ります。

Registration

June 28, 2015 8:30-17:00 June 29, 2015 8:30-14:30

Registration fee: 10,000JPY

*On-site Registration only. We accept cash (Japanese yen) only.

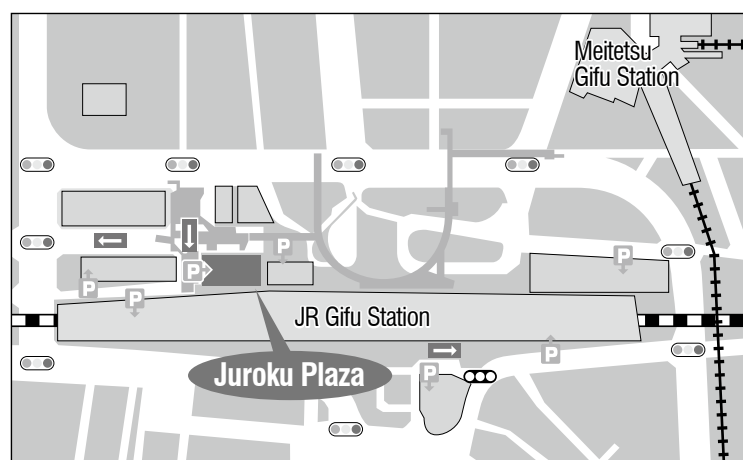
Exhibition

June 28, 2015 9:00-18:00 June 29, 2015 9:00-16:30

Welcome Party

June 28, 2015 18:00 at La Rose Provence, 1F, Juroku Plaza

Venue



Juroku Plaza

1-10-11 Hashimoto-cho, Gifu, Gifu, 500-8856, Japan
Tel: +81- 58-262-0150

Access

JR Gifu Station 2mins. on foot
Meitetsu Gifu Station 7mins. on foot
Central Japan International Airport
about 25mins. by Meitetsu train to Kanayama station,
then about 30 mins. by JR train to JR Gifu station

Contact

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Program

Day-1 Sunday, June 28

9:00 **Opening remarks**

Chair: Yoshiyuki Ohtomo (Juntendo University Nerima Hospital, Japan)

9:05 **Enuresis – Pathophysiology overview:** Tryggve Nevéus (Uppsala University Children's Hospital, Sweden)

9:20 **Recent findings on pathophysiology of nocturnal enuresis 1**

Sleep: Johan Vande Walle (University Hospital Ghent, Belgium)

The relationship of obstructive sleep apnea and enuresis: Johan Vande Walle (University Hospital Ghent, Belgium)

Genetics and enuresis: Søren Rittig (Skejby Sygehus, Aarhus University Hospital, Denmark)

10:20 **Coffee break**

Chair: Shuichiro Fujinaga (Saitama Children's Medical Center, Japan)

10:40 **Recent findings on pathophysiology of nocturnal enuresis 2**

Nocturnal polyuria: Søren Rittig (Skejby Sygehus, Aarhus University Hospital, Denmark)

Bladder: Akihiro Kawauchi (Shiga University of Medical Science, Japan)

11:20 **The psychological problems in nocturnal enuresis, a result or a cause?:**

Yasuyuki Naitoh (Kyoto Prefectural University of Medicine, Japan)

11:45 **Luncheon Seminar: Desmopressin in night-time voiding dysfunctions in child and adult**

Chair: Kazunari Kaneko (Kansai Medical University, Japan)

Desmopressin: the story and development of Melt tablets for children with bedwetting:

Jens Peter Nørgaard (University of Aarhus, Denmark)

Consequences of nocturia in the elderly and enuresis in the childhood:

Kristian Vinter Juul (Ferring International Pharma Science Centre, Denmark)

Co-sponsored by: *FERRING Pharmaceuticals Co., Ltd., Kyowa Hakko Kirin Co., Ltd.*

Chair: Kazunari Kaneko (Kansai Medical University, Japan)

13:15 **ICCS terminology:** Paul Austin (St. Luis Children's Hospital, Washington University School of Medicine, USA)

13:30 **Diagnostic approach to nocturnal enuresis:** Tomonori Yamanishi (Dokkyo Medical University, Japan)

14:00 **Web based clinical support tool:** Shigeru Yoshida (Kishokai Medical Corporation, Japan)

14:15 **Regional differences in history of and approach to nocturnal enuresis**

Japan: Masuji Hattori (Hyogo College of Medicine, Japan)

Taiwan: Stephen Shei-Dei Yang (Taipei Tzu Chi Hospital and Buddhist Tzu Chi University, Taiwan)

United States: Paul Austin (St. Luis Children's Hospital, Washington University School of Medicine, USA)

European countries: Søren Rittig (Skejby Sygehus, Aarhus University Hospital, Denmark)

15:15 **Coffee break**

Chair: Shigeru Yoshida (Kishokai Medical Corporation, Japan)

15:35 **Treatment strategy of nocturnal enuresis:** Søren Rittig (Skejby Sygehus, Aarhus University Hospital, Denmark)

15:55 **How to use treatment modalities?**

Alarm: Atsuko Hata (Kitano Hospital, The Tazuke Kofukai Medical Research Institute, Japan)

Desmopressin: Yoshiyuki Ohtomo (Juntendo University Nerima Hospital, Japan)

Treatment aspects of nocturnal enuresis- How to use other treatment modalities focus on the difficult patient:

Johan Vande Walle (University Hospital Ghent, Belgium)

17:25 **Combination therapy:** Shuichiro Fujinaga (Saitama Children's Medical Center, Japan)

17:50 **Closing remarks of the day**

18:00 **Welcome party**

Day-2 Monday, June 29

Chair: Hidehiro Kakizaki (Asahikawa Medical University, Japan)

9:00 **Nonmonosymptomatic Nocturnal Enuresis (NMNE):**

Stephen Shei-Dei Yang (Taipei Tzu Chi Hospital and Buddhist Tzu Chi University, Taiwan)

9:20 **Refractory and adult nocturnal enuresis (NMNE):**

Stephen Shei-Dei Yang (Taipei Tzu Chi Hospital and Buddhist Tzu Chi University, Taiwan)

9:40 **Diagnostic approach to incontinence:** Paul Austin (St. Luis Children's Hospital, Washington University School of Medicine, USA)

10:00 **Neurogenic bladder and overactive bladder:** Paul Austin (St. Luis Children's Hospital, Washington University School of Medicine, USA)

10:20 **Coffee break**

Chair: Tomonori Yamanishi (Dokkyo Medical University, Japan)

10:40 **Bladder bowel dysfunction:** Shina Kawai (Jichi Medical University, Children's Medical Center Tochigi, Japan)

11:00 **Posterior urethral valve and incontinence:** Hideo Nakai (Jichi Medical University, Children's Medical Center Tochigi, Japan)

11:20 **Dysfunctional voiding:** Hidehiro Kakizaki (Asahikawa Medical University, Japan)

11:45 **Lunch**

Chair: Hideo Nakai (Jichi Medical University, Children's Medical Center Tochigi, Japan)

13:15 **Urotherapy:** Tryggve Nevéus (Uppsala University Children's Hospital, Sweden)

13:35 **Nursing care and medical support for incontinence children:** Naoko Kamata (Hyogo Prefectural Kobe Children's Hospital, Japan)

13:55 **Emotional and behavioral disorders associated with enuresis:** Yuko Ishizaki (Kansai Medical University, Japan)

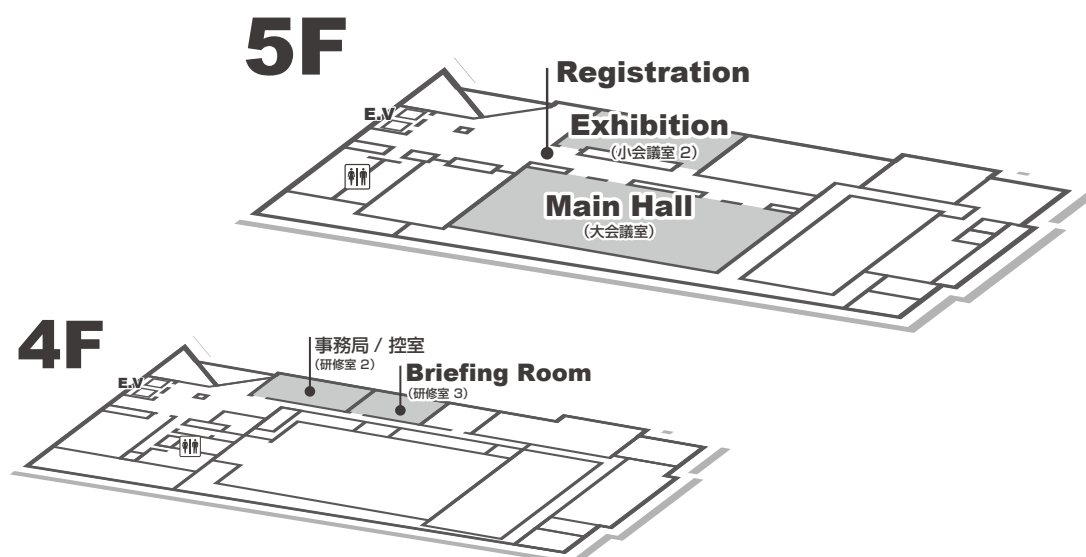
14:15 **Relationship between symptoms in children and adults:** Shunji Akashi (Shintoshin Child Clinic, Japan)

Chair: Akihiro Kawauchi (Shiga University of Medical Science, Japan)

14:35 **Case discussion**

16:30 **Closing remarks**

Venue Map



Abstracts

Day-1 Sunday, June 28

Enuresis – Pathophysiology overview

Tryggve Nevéus, M.D., Ph.D.

Uppsala University Children's Hospital, Sweden

Education, clinical

Medical studies at Uppsala University, Uppsala, Sweden. Graduated 1990.

Residency, paediatrics, completed 1999 at Uppsala University Children's Hospital, Sweden.

Postspecialist education in paediatric nephrology at Uppsala University Children's Hospital, Uppsala, and Sahlgrenska University Hospital, Gothenburg, Sweden, completed 2001.

Senior Consultant in Paediatric Nephrology and head of section for Paediatric Nephrology at Uppsala University Children's Hospital, Uppsala, since 2001.

Visiting Consultant in Paediatric Nephrology at Karolinska University Hospital, Stockholm 2008-2010

Society

Secretary General of the International Children's Continence Society (ICCS), from 2006 to 2012. President of the ICCS since 2014.

Enuresis has long been known to be strongly influenced by hereditary factors. Several different "enuresis genes" have been found, but there is no clear correspondence between genotype and phenotype (subtype of enuresis).

As shown first by the Aarhus group in the 1980s, many enuretic children have nocturnal polyuria, often secondary to a nocturnal lack of the anti-diuretic hormone vasopressin. This explains the enuresis in a large sub-group of children, but certainly not all. Unsurprisingly, nocturnal polyuria is most common among children who respond to desmopressin therapy.

Given the prominent role of detrusor overactivity in the pathogenesis of day-time incontinence, and the great overlap between the two conditions, it is not surprising that the detrusor plays a major pathogenetic role in nocturnal enuresis as well. It has been shown that nocturnal detrusor overactivity is especially common among desmopressin non-responders. Further support for the detrusor overactivity hypothesis is provided by the finding that children with enuresis go to the toilet more often than dry children, that they void smaller volumes and that urgency symptoms are more common in this group. The association between constipation and detrusor overactivity is also relevant: constipation is common among bedwetting children.

Almost all enuretic children are difficult to wake up from sleep. This subjectively low arousability has also been demonstrated objectively. However, that the sleep is "deep" does not necessarily mean that it is good. The sleep quality of enuretic children may in fact often be poor.

Thus, the majority of enuretic children wet their beds either because 1) the kidneys produce more urine at night than the bladder can hold or 2) the bladder has a tendency towards uninhibited detrusor contractions; but in both cases 3) the children fail to wake up from the arousal stimuli from the expanded or overactive bladder.

Although the old opinion that enuresis mainly is a psychiatric disorder has been abandoned it is still clear that psychiatric problems are quite common among enuretic children. This is probably explained by 1) effects of the enuresis on the child's self-esteem, and 2) the fact that, for unclear reasons, enuresis is more common in children with neuropsychiatric disturbances such as ADHD.

There is a small subgroup of enuretic children with heavy snoring and sleep apnoeas due to enlarged tonsils or nasal polyps, who become dry when the upper airway obstruction has been removed. The enuresis of these children could be explained by low arousability due to repeated arousal stimuli.

In rare cases, enuresis can be the presenting symptom of polyuric conditions such as diabetes mellitus or renal tubular disorders, or be caused by neurogenic or anatomic malformations. These cases can usually easily be detected by reacting to warning signs in the child's case history.

Recent findings on pathophysiology of nocturnal enuresis 1 “Sleep”

Johan Vande Walle, M.D.

Chair, Paediatric Nephrology and Rheumatology

Director, Safepedrug Consortium,

Academic chair of Department of Paediatrics and Genetics,

University Hospital Ghent, Belgium

Born in 1957, studies medicine and health sciences university Ghent 1975-1982. Training in pediatrics 1982-1987 University hospital Ghent. 1987-1991 training as pediatric nephrologist in Nijmegen and Utrecht Netherlands. In 1991 initiation of a pediatric nephrology department in Ghent not only with major interest in dialysis, transplantation, renal physiology, acute renal failure and nephrotic syndrome, but also in pediatric drug development program on bladder dysfunction and enuresis in children.

He started in 1992 together with P. Hoebeke, (pediatric urologist) a multidisciplinary enuresis team PUNC (pediatric urology nephrology center). This team covers a multidisciplinary approach in clinical practice as in research, targeting the complexity of pathogenetic mechanisms involved in nocturnal enuresis and bladder dysfunction: the team includes pediatric nephrologists, urologists, urotherapists, physiotherapists, psychologists, sleep specialist, gastroenterologist and pharmacologist.

The tertiary care program targets the 4 major factors, involved in the pathogenesis of refractory enuresis : abnormalities in circadian rhythm of water- and sodiumhandling in the kidney, bladderdysfunction both in filling and emptying phase, abnormalities in sleep and arousal, as well as comorbidities (constipation, psychology, mental and motoric disabled).

This has resulted in individualised treatment regimens and the organization of voiding camps and the voiding school for refractory cases.

In the past decades research has been concentrating on the interface between nocturia/enuresis, circadian rhythm of renal functions, sleepdisturbances and concentration disorders. The center has a leading role in pediatric continence societies and guideline committees. More than 100 abstracts, 40 publications and 8 PhD's on the topic document the scientific work.

Recently he developed a safepedrug consortium on innovative drug research in paediatrics: The consortium is concentrating on antibiotics, antihypertensives, and drugs targeting antidiuresis and bladderdysfunction. The consortium includes researchlines in pharmacologic modelling, pediatric animal models, drugstudies on intensive care and neonatology as well as innovative ethical approach.

Nocturnal enuresis is classically attributed to a mismatch of nocturnal diuresis of nocturnal functional arousal in presence of deficient arousal. In presence of high arousability, it is widely accepted that children should wake up to void, and develop nocturia instead of enuresis, just like adults. But we cannot deny that the majority of children obtain continence without developing nocturia. The evidence of a decreased arousability in children is indirect and rather weak, and there is increasing evidence for more complex disrupted sleep.

The relationship between nocturnal enuresis and sleep and neuropsychological dysfunctions was first suggested by C.K. Yeung in a letter in the NEJM: he concluded to an interaction between bladder overactivity and brain arousability, a 'bladder-brain dialogue' in children with severe nocturnal enuresis based on an association between cortical arousals and unstable bladder contractions in children with a reduced functional bladder volume. The children had more light sleep associated with frequent cortical arousals but an inability to awaken completely, and all symptoms ameliorated when enuresis was successfully treated. His study population included clearly mainly OAB patients and the used treatment regimens were not reported.

The association between nocturnal enuresis and sleep was also investigated by our research group, but in a more homogeneous group of patients, without daytime symptoms and presence of nocturnal polyuria. Children with nocturnal enuresis have a more fragmented sleep as shown in the increased amount of cortical arousals and awakening. Moreover, they experienced more PLMS (Limb movements). These cortical arousals and PLMS are much higher in therapy resistant children with nocturnal enuresis. Enuresis and associated sleep disorder do correlate with neuropsychological functioning characteristics and especially attention deficit symptoms.

In a second phase we documented a possible causality by treating nocturnal enuresis and evaluating the effect of antidiuretic treatment (desmopressin melt) on neuropsychological functioning and sleep. The selection of only patients with MNE associated with nocturnal polyuria offered the advantage of a high predictable response-rate to desmopressin, making an interventional study feasible. Based on previous studies with appropriate patient selection, a response rate of at least 60% was expected¹⁴⁹⁻¹⁵². Selecting in a general nocturnal enuresis population would have led to unpredictable response rates due to different treatment options for different nocturnal enuresis subtypes based on the underlying pathophysiology.

Anti-enuretic response rate in the study was 82%. Moreover, the study demonstrated a significant decrease in PLMS and additionally improvement of neuropsychological functioning on several domains: QoL, executive functioning, internalizing problems and externalizing problems.

These studies demonstrate as such a possible causal effect between nocturnal polyuria, enuresis, disrupted sleep and attention deficit disorders, since treatment of nocturnal polyuria ameliorates the different comorbidities

1. Sleep fragmentation and periodic limb movements in children with monosymptomatic nocturnal enuresis and polyuria. Dhondt K, Van Herzele C, Roels SP, Raes A, Groen LA, Hoebeke P, Walle JV. *Pediatr Nephrol.* 2015 Jul;30(7):1157-62.
2. Periodic limb movements during sleep are associated with a lower quality of life in children with monosymptomatic nocturnal enuresis. Van Herzele C, Dhondt K, Roels SP, Raes A, Groen LA, Hoebeke P, Vande Walle J. *Eur J Pediatr.* 2015 Jul;174(7):897-902
3. Sleep fragmentation and increased periodic limb movements are more common in children with nocturnal enuresis. Dhondt K, Baert E, Van Herzele C, Raes A, Groen LA, Hoebeke P, Vande Walle J. *Acta Paediatr.* 2014 Jun;103(6):e268-72.
4. Abnormal sleep architecture and refractory nocturnal enuresis. Dhondt K, Raes A, Hoebeke P, Van Laecke E, Van Herzele C, Vande Walle J. *J Urol.* 2009 Oct;182(4 Suppl):1961-5.

Abstracts

Day-1 Sunday, June 28

Recent findings on pathophysiology of nocturnal enuresis 1 “The relationship of obstructive sleep apnea and enuresis”

Johan Vande Walle, M.D.

Chair, Paediatric Nephrology and Rheumatology
Director, Safepedrug Consortium,
Academic chair of Department of Paediatrics and Genetics,
University Hospital Ghent, Belgium

Born in 1957, studies medicine and health sciences university Ghent 1975-1982. Training in pediatrics 1982-1987 University hospital Ghent. 1987-1991 training as pediatric nephrologist in Nijmegen and Utrecht Netherlands. In 1991 initiation of a pediatric nephrology department in Ghent not only with major interest in dialysis, transplantation, renal physiology, acute renal failure and nephrotic syndrome, but also in pediatric drug development program on bladder dysfunction and enuresis in children.

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The correlation between nocturnal enuresis and obstruction of the upper airways (OSAS) is receiving increasing attention during recent years. The correlation between OSAS and nocturnal nocturia is a well established identity in adults with nocturia and coincides with nocturnal polyuria. It correlates with many comorbidities, including metabolic syndrome and increased cardiovascular mortality. Several factors are involved in the pathogenesis of the nocturnal polyuria, including abnormal circadian rhythms of several homeostatic mechanisms (bloodpressure, sleep, renal function) and vaso-active hormones. Major attention is giving to increased ANP levels overnight, resulting in high sodium excretion overnight.

OSAS in children is a well identified identity in children, but epidemiologic data on the enuresis/nocturia are less clear, and pathophysiologic characteristics of nocturnal polyuria are less described: 8-47% of children with OSAS caused by adenotonsillar hypertrophy have enuresis, but the prevalence of OSAS in children with NE is unknown. Release of upper airway obstruction by tonsillectomy and/or adenoidectomy (T&A) has been associated with complete resolution of NE in 31-76% of children within months of surgical, very suggestive for a causal relation. Most studies are however failing to characterise the enuresis-patients into NMNE and MNE according to the new ICCS standards, and have not documented the characteristics of the nocturnal polyuria, with emphasis on desmopressin response and solute handling.

Obstructive sleep apnea syndrome (OSAS) in children does not only present with symptoms of sleep disturbances but association has been reported with several comorbidities such as growth failure, enuresis, academic learning difficulties, and behavioral problems, including attention deficit/hyperactivity disorder- (ADHD-) like symptoms. Kovacevic demonstrated a trend to better QOL when therapeutic intervention results in achievement of continence.

Screening for OSAS in children with refractory enuresis seems to have a rationale, as well as questioning for enuresis in children with OSAS. There is enough evidence for treating the OSAS in

- 1) Lower health related quality of life and psychosocial difficulties in children with monosymptomatic nocturnal enuresis--is snoring a marker of severity? Wolfe-Christensen C, Kovacevic LG, Mirkovic J, Lakshmanan Y. J Urol. 2013 Oct;190(4 Suppl):
- 2) Enuretic children with obstructive sleep apnea syndrome: should they see otolaryngology first? Kovacevic L, Jurewicz M, Dabaja A, Thomas R, Diaz M, Madgy DN, Lakshmanan Y. J Pediatr Urol. 2013 Apr;9(2):145-50. doi: 10.1016/j.jpuro.2011.12.013. Epub 2012 Jan 27
- 3) Commentary to 'Adenotonsillectomy improves quality of life in children with nocturnal enuresis and sleep-disordered breathing'. Nevéus T. J Pediatr Urol. 2015 Apr 22

Recent findings on pathophysiology of nocturnal enuresis 1

“Genetics and enuresis”

Søren Rittig, M.D., DMSc

Skejby Sygehus, Aarhus University Hospital, Denmark

Søren Rittig graduated from Aarhus University Medical School in 1987 and passed the ECFMG (Educational Committee for Foreign Medical Graduates, U.S.A.) exam in 1990. He has completed a Research Fellowship at Aarhus University, Clinical Institute and Northwestern University Medical School, Dept. of Medicine, Chicago, USA. He became a specialist in Pediatrics in 2002 and has been consultant in Pediatric Nephrology at Aarhus University Hospital, Aarhus Denmark since 2004. In 2010 he defended his thesis on circadian regulation of urine output in normal children and children with nocturnal enuresis. He became full Professor in Pediatrics, Aarhus University in 2012. He has since Medical School been heavily involved in research in childhood incontinence, especially nocturnal enuresis. His research has been focusing especially on circadian rhythms and enuresis pathophysiology and treatment; e.g. the description of a deficient circadian rhythm of vasopressin secretion in nocturnal enuresis that was correctable with administration of the vasopressin analogue desmopressin. Since 1992, he has also been involved in molecular genetic research of inherited forms of diabetes insipidus and other renal tubular disorders and his laboratory has contributed with description of many mutations in familial diabetes insipidus. Søren Rittig has published app. 150 peer reviewed papers, 6 book chapters, and co-edited several supplements in International journals. Furthermore, he has supervised 20 PhD programmes. Since 1999, he has been director of Center for Child Incontinence in Aarhus and he is the current Scientific Chairman of the International Children's Continence Society (ICCS). He also currently holds the post as Board member of the European Society for Paediatric Nephrology (ESPN).

For more than a century, there has been strong evidence suggesting a genetic background behind nocturnal enuresis (NE). Formal genetic studies have been performed since the 1890ies and molecular genetics since 1995, highlighting that hereditary factors are highly relevant in the aetiology of NE. The reliability of formal and molecular genetic studies is though dependent on an exact definition of the phenotype. In the literature over the last decades a high proportion of NE with a positive family history was reported, showing that up to 77% of NE patients have a 1st degree relative who also had suffered from NE. Formal genetic approaches include family studies (1st degree relatives), twin and segregation studies (but no adoption studies), while molecular genetics have mainly been based on classic linkage studies and a few candidate gene association studies. Different modes of inheritance are seen in NE families; i.e. autosomal dominant and autosomal recessive modes of inheritance, as well as polygenic mode of inheritance together with the coexistence of different modes of inheritance. Linkage studies have been performed in large families with autosomal dominant modes of inheritance, replicating loci on several chromosomes (i.e. 13q, 12q, 8q, 22q11.21, 22q14 and 4p16). Furthermore, several candidate gene polymorphisms have been proposed (e.g. endothelial (eNOS) and neuronal (nNOS) NO synthase, dopamine D4, and Serotonin receptor 2A). Despite possible associations between these different gene polymorphisms and NE, the relevance of the individual polymorphism is not known, and so far, no clear genotype-phenotype correlations have been identified. Ongoing studies on large multiplex families are using a combination of linkage analyses with whole genome sequencing with the purpose of characterizing the genetic background in the families. Furthermore, an international biobank with a large number of family trios with well characterized phenotypes is being established. Such a strategy can be used for elucidating possible candidate genes as well as for GWAS studies with the aim of finding new enuresis genes.

In conclusion, new research using modern molecular techniques may provide further progress in the understanding of the genetic background behind enuresis. Besides adding to our understanding of NE pathogenesis such research may generate new treatments directed towards the underlying mechanism.

Abstracts

Day-1 Sunday, June 28

Recent findings on pathophysiology of nocturnal enuresis 2 “Nocturnal polyuria”

Søren Rittig, M.D., DMSc

Skejby Sygehus, Aarhus University Hospital, Denmark

Søren Rittig graduated from Aarhus University Medical School in 1987 and passed the ECFMG (Educational Committee for Foreign Medical Graduates, U.S.A.) exam in 1990. He has completed a Research Fellowship at Aarhus University, Clinical Institute and Northwestern University Medical School, Dept. of Medicine, Chicago, USA. He became a specialist in Pediatrics in 2002 and has been consultant in Pediatric Nephrology at Aarhus University Hospital, Aarhus Denmark since 2004. In 2010 he defended his thesis on circadian regulation of urine output in normal children and children with nocturnal enuresis. He became full Professor in Pediatrics, Aarhus University in 2012. He has since Medical School been heavily involved in research in childhood incontinence, especially nocturnal enuresis. His research has been focusing especially on circadian rhythms and enuresis pathophysiology and treatment; e.g. the description of a deficient circadian rhythm of vasopressin secretion in nocturnal enuresis that was correctable with administration of the vasopressin analogue desmopressin. Since 1992, he has also been involved in molecular genetic research of inherited forms of diabetes insipidus and other renal tubular disorders and his laboratory has contributed with description of many mutations in familial diabetes insipidus. Søren Rittig has published app. 150 peer reviewed papers, 6 book chapters, and co-edited several supplements in International journals. Furthermore, he has supervised 20 PhD programmes. Since 1999, he has been director of Center for Child Incontinence in Aarhus and he is the current Scientific Chairman of the International Children's Continence Society (ICCS). He also currently holds the post as Board member of the European Society for Paediatric Nephrology (ESPN).

Increased night-time urine production was proposed as a causative factor and named 'relative nocturnal polyuria' already in the early 1950-ies. However, such a hypothesis was not tested further until the early 1980-ies where standardized in-patient circadian studies demonstrated that enuresis patients showed an abnormally large nocturnal urine production that exceeded the cystometric bladder capacity. Since then, nocturnal polyuria at least in a sub-population of enuresis patients was confirmed using home recording methods, either by diaper weighing or timed urine collections. Furthermore, it was shown that nocturnal urine production is significantly larger during wet nights than dry nights and larger in patients who respond positively to desmopressin treatment. In 2006, an international consensus was obtained regarding the definition of nocturnal polyuria in children (nocturnal urine volume on a wet night > 130 % x expected bladder capacity for age that is currently used worldwide).

Renal factors: Detailed circadian studies have revealed several mechanisms behind nocturnal polyuria in enuresis. Firstly, a proportion of enuretic children with nocturnal polyuria have an abnormally low urinary osmolality during night indicating a problem with antidiuretic function. Secondly, some children have increased osmotic excretion due to decreased tubular reabsorption of particularly sodium, potassium and urea during night. Such patients are characterized by nocturnal polyuria with relative high urine osmolality and treatment resistance to desmopressin. Thirdly, some but not all studies have implicated an increased nocturnal GFR. Also, increased nocturnal urinary excretion of prostaglandins has pointed towards a possible role of the prostaglandin system.

Hormones: A number of hormone systems participate in the normal regulation of water and salt balance and several of these have been investigated in enuresis. Of these, only vasopressin (AVP) have been attributed a pathogenic role. Several independent studies of the circadian rhythm of plasma AVP have demonstrated a lack of the normal nocturnal rise seen in normal children. Furthermore, nocturnal plasma AVP levels are lower during wet nights than dry and lower in patients who respond positively to desmopressin. Thus, a circadian defect in AVP seems to play a role in patients with polyuria due to increased free water excretion. Hemodynamic factors: Blood pressure is an important factor behind the renal excretion of sodium and other solutes and recent studies have caused increased focus on the importance of nocturnal blood pressure levels behind nocturnal polyuria and natriuresis.

Intrinsic circadian rhythms: Urine output has a well-known circadian rhythm with a marked reduction during night and this rhythm is to large degree independent of external factors such as fluid intake. The exact role of the intrinsic circadian regulatory machinery behind enuresis pathogenesis is unclear but in theory circadian dysregulation could be the primary pathogenic mechanism in enuresis. The close proximity between the SCN and centers controlling AVP release (SON), sleep/arousal (locus coeruleus), micturition (PMC), and baroregulation (vasomotor center) could provide the basis for circadian dysfunction in one or more of these centers. This might also provide the pathogenic basis for the different subtypes of enuresis that exist.

Recent findings on pathophysiology of nocturnal enuresis 2 “Bladder”

Akihiro Kawauchi, M.D., Ph.D.

Professor and Chairman, Department of Urology, Shiga University of Medical Science, Japan

Education: 1978-1984 Kyoto Prefectural University of Medicine,
 1985-1990 Graduate School of Medicine for the Doctor's Program, Kyoto Prefectural University of Medicine

Related society membership:

Japanese Society of Pediatric Urology: Executive Director

Japanese Society on Enuresis: Executive Director

Japanese Society of Sleep Research: Councilor

International Children's Continence Society: member

Asia pacific association of pediatric urology: member

Field of specialty:

Pediatric urology, nocturnal enuresis, endourology, urologic oncology

Small bladder capacity is thought to be one of main causes of nocturnal enuresis. In normal children, nocturnal bladder capacity is larger than daytime bladder capacity. In enuretic children, however, bladder capacity at the time of enuresis was significantly smaller than daytime capacity. Thus, the difference in nocturnal bladder capacity between enuretics and nonenuretics may be one of the most important causes of monosymptomatic nocturnal enuresis.

Mechanism of alarm therapy is thought to increase bladder capacity, especially in the night. This may normalize the nocturnal bladder capacity in enuretics and lead to cure.

Abstracts

Day-1 Sunday, June 28

The psychological problems in nocturnal enuresis, a result or a cause?

Yasuyuki Naitoh, M.D., Ph.D.

Associate Professor, Department of Urology, Kyoto Prefectural University of Medicine, Japan

PROFESSIONAL BACKGROUND (EMPLOYMENT HISTORY)

- 1993- Resident in Department of Urology of Kyoto Prefectural University of Medicine Hospital
- 2000- Resident in Department of Urology of Osaka Medical Center and Research Institute for Maternal and Child Health
- 2005- Assistant Professor, Department of Urology of Kyoto Prefectural University of Medicine
- 2013- Associate Professor, Department of Urology of Kyoto Prefectural University of Medicine

For many years, it has been stated that a set of mental and psychological problems is one of the causes of nocturnal enuresis. In the first place, it is difficult to objectively determine that mental and psychological problems contribute to the onset of nocturnal enuresis. Recently, a set of these problems is suspected of being a result, not a cause of nocturnal enuresis.

At our institution, we evaluated Health Related Quality of Life (HRQOL) of children with nocturnal enuresis and demonstrated that their HRQOL was compromised by nocturnal enuresis. Conversely, the HRQOL was improved through appropriate treatment. In addition, we evaluated not only HRQOL of children with nocturnal enuresis but also HRQOL of their mothers and showed that the children's nocturnal enuresis had a negative impact on their mothers. As the nocturnal enuresis was cured, the HRQOL of mothers also demonstrated improvement.

In this session, we will report decreased self-esteem and HRQOL of children with nocturnal enuresis, their various mental and psychological problems due to the disease, as well as the impact of the disease on parents.

Luncheon Seminar: Desmopressin in night-time voiding dysfunctions in child and adult “Desmopressin: the story and development of Melt tablets for children with bedwetting”

Jens Peter Nørgaard, MD DMSc Professor

University of Aarhus, Denmark

Executive Director, Urology R&D, Ferring International Pharma Science Center, Copenhagen, Denmark

Medical doctor in 1981, specialising in urology and paediatric surgery. Completed his thesis on primary nocturnal enuresis in 1990, which has been widely published and referenced in the field. Founder of the International Enuresis Research Center (IERC) and the International Children's Continence Society (ICCS) and continues as an active member of these organisations. He has published more than 150 papers in peer-reviewed journals, mainly on disorders related to polyuria and use of desmopressin, as well as co – authored several text books. He has worked together with Ferring since 1984 on clinical research and developed treatment strategies for both primary nocturnal enuresis and nocturia which have formed the basis for Ferring's current work in this area.

After a long career as a specialist in Urology and Paediatric Urology Jens Peter Nørgaard joined Ferring as responsible for clinical science in urology in 1997. Since then he achieved professorships in Urology at the University of Lund in Sweden, University of Aarhus in Denmark and more recently University of Ghent in Belgium.

Through his extensive worldwide network of leading urologists he has worked on linking the pharmaceutical industry with academia and, among other things, developed new treatment concepts within the fields of bedwetting, nocturia and incontinence.

During more than 40 years desmopressin has been in clinical use for the treatment of polyuric conditions - starting with Central Diabetes Insipidus and expanding its use into bedwetting in children with nighttime polyuria and more recently into treatment of Nocturia in adults. Desmopressin (dDAVP) has as the only peptide undergone development from nasal drops to oral tablet solutions and also more recently into a Oral Disolution Tablet - called the MELT.

This new formulation was recently launched in Japan as the first oral desmopressin formulation in that country after two successful development programs for the treatment of Diabetes Insipidus and Primary Nocturnal Enuresis (bedwetting).

The presentation will cover the aspect of this new formulation in comparison with the old oral formulations and discuss the advantages of ODT as an oral formulation that can be taken without drinking water. Minimal food interaction, high compliance and not at least more predictable plasma levels due to increased bioavailability. Studies comparing these formulations will be discussed based on overseas data.

Abstracts

Day-1 Sunday, June 28

Luncheon Seminar: Desmopressin in night-time voiding dysfunctions in child and adult “Consequences of nocturia in the elderly and enuresis in the childhood”

Kristian Vinter Juul, M.D., Ph.D.

Global Scientific Affairs Urology, Ferring International Pharma Science Centre, Denmark

Education and academic degrees

- PhD, Doctor of Health Sciences, Universiteit Ghent 2013

Professional experience

2010-	Medical Science Director, Ferring Pharmaceuticals
2010	Head of Department, Clinical Business Operations, Lundbeck A/S
2008-10	Head of Department, Clinical Operations, Lundbeck A/S
2007-2008	Director, Clinical Operations, Santaris Pharma A/S
2007	Director, Global R&D, Coloplast A/S
2006-2007	Head, Clinical Development, R&D, Stoma Care Division, Coloplast A/S
2004-2005	Senior Clinical Trial Manager, Stoma Care Division, Coloplast A/S
2003-2004	Clinical Team Leader, Clin. Research Urology, Ferring Pharmaceuticals A/S
2001-2003	Clinical Research Manager, Clin. Op. (in 2002 Clin. Research Urology) Ferring Pharmaceuticals A/S
1997-2001	Clinical coordinator, A/S GEA Pharmaceuticals

Specialities: Expert in Vasopressin and V2-receptor-related renal and extra-renal conditions:

- Diabetes Insipidus
- Monosymptomatic Nocturnal Enuresis
- Nocturia
- Haemophilia A
- von Willebrand Disease (VWD)
- Thrombocyte Dysfunction

In this presentation consequences of nocturia in the elderly will be reviewed with special focus on importance of sleep and the impact and costs of nocturia. Nocturia is a symptom which can result from many different conditions with various underlying pathophysiologies including most commonly, nocturnal polyuria. Nocturia symptoms occur in men and women of all ages, becoming more frequent with age. Clinically meaningful nocturia has been defined based on expert opinion as “waking-up 2 or more times per night to void...where each voiding episode is preceded and followed by sleep.”

This broadly accepted threshold of 2 or more voids per night is the level at which significant bother and disease burden occur. Consequences and burden of nocturia are not trivial, since the associated sleep disruptions may lead to low sleep quality, as well as impacting daily life with fatigue, decreased productivity and poorer quality of life.

Similarly, consequences of enuresis in the childhood will be discussed with emphasis on the clinical questions: Why treat, and what is the impact of bedwetting on the patient and family. Enuresis is a common condition that can be upsetting and disruptive to family life. Recent trials shows that the child’s sleep architecture and cognition may be affected by repeated bladder signalling. The consequences of enuresis can be summarised as follows:

- Enuretic children suffer from low self-esteem
- Enuresis—as well as daytime incontinence—is more common among children with neuropsychiatric disturbances, such as attention deficit hyperactivity disorder (ADHD)
- Enuretic children and adults have, in general, more depressive problems and problems at school and work

Finally, to summarise the real-life experience with enuresis, pharmacoepidemiological analysis based on Danish Medicines Agency will be presented, involving data from 40,596 enuresic children 2004-11. Through the National Prescription Registry was identified 40,596 patients (< 18 years) with 214,220 prescriptions. Sixty-six % were male, mean age 9.2 yrs. (± 3). Additionally, information on concurrent medication was obtained. Prescription data were linked to data from the National Patient Registry. Of 40,596 patients, 66% were melt-users, 18% used tablets, and 17% nasal-spray. Among melt-users, 26% used 60 μg , 66% 120 μg and 8% 240 μg . twenty-two % of girls were prescribed 60 μg compared to 16 % of boys. Treatment time after titration varied with dose and gender from 422.52 days for girls using 240 μg to 520.2 days for boys using 120 μg . Tablets and nasal-spray had shorter treatment duration. Of the 240 μg melt-users 8.4% had just 1 prescription. Corresponding numbers were between 22.9% to 52.1% for low-dose melt, tablet and nasal-spray. Most common co-medications were antihistamines (girls: 39.5%, boys: 54.1%) and antidepressants (girls: 19.7%, boys: 14.4 %). Ten % used OAB drugs. None of the desmopressin users were hospitalized with hyponatremia.

ICCS terminology

Paul Austin, M.D.

St. Luis Children's Hospital, Washington University School of Medicine, USA

Dr. Paul Austin is the Director of Pediatric Urology Research, Director of the Multidisciplinary Spina Bifida Program and Professor of Urologic Surgery at Washington University in St. Louis School of Medicine. Dr. Austin leads a robust basic science research program that is funded by the NIH and investigates the molecular pathways involved with renal injury resulting from obstructive uropathy. In addition to his basic science work, Dr. Austin is also recognized as a leading clinical trial investigator of lower urinary tract function and serves on global advisory panels for national and international urology clinical trials. Dr. Austin is the current General Secretary for the International Children's Continence Society and has served on the Executive Committees for the Society of Pediatric Urology and the Section on Urology of the American Academy of Pediatrics.

The impact of the previous International Children's Continence Society (ICCS) terminology documents on lower urinary tract (LUT) function in 1998 and 2006 resulted in the global establishment of uniformity and clarity in the characterization of LUT function and dysfunction in children across multiple healthcare disciplines.

The ICCS standardization and terminology workgroup assembled a new terminology document after a review of the literature LUT function over the last 7 years. The new ICCS terminology document provides a current and consensus update to the evolving terminology and understanding of LUT function in children. (*Journal of Urology*, 191 (6): 1863-1865, June 2014). The present document serves as a stand-alone terminology update reflecting refinement and current advancement of knowledge on pediatric LUT function.

This lecture will highlight important changes in the new terminology document and emphasize key standardization protocols in the evaluation and management of children with LUT dysfunction.

Abstracts

Day-1 Sunday, June 28

Diagnostic approach to nocturnal enuresis

Tomonori Yamanishi, MD

Department of Urology, Continence Center, Dokkyo Medical University, Japan

Education and Training:

1982	Graduated from Chiba University School of Medicine
1982-1983	Dept. of Urology, Chiba University School of Medicine, Residency
1983-1984	Kosei General Hospital
1984-1988	Asahi General Hospital, Naruto Hospital, Narita Red Cross Hospital
1988-1997	Assistant Professor, Department of Urology, Chiba University
1997-2001	Lecturer, Department of Urology, Chiba University School of Medicine
1999-2001	Honorary lecturer, Sheffield University, United Kingdom
2001-2009	Associate Professor, Urology, Dokkyo Medical University
2009-Present	Professor of Urology, Dokkyo Medical University
2011-Present	Chief of Continence Center, Dokkyo Medical University

Field of specialty:

Nocturnal enuresis, Neurourology, Incontinence, Benign Prostatic Hyperplasia

The major causes of nocturnal enuresis include decreased bladder capacity, nocturnal polyuria, and arousal disturbance. Therefore, the diagnosis of enuresis should be approached to investigate these causes.

Types of enuresis : enuresis should be divided into primary enuresis or secondary enuresis, and monosymptomatic enuresis (MNE) or non-MNE.

History: A questionnaire on family history, neurological and congenital abnormalities, urinary infection, bowel dysfunction (constipation), etc., should be taken.

Lower urinary tract symptoms (LUTS): LUTS should be carefully asked especially for non-MNE patients. They may have urgency urinary incontinence including overactive bladder, and overactive bladder symptom score (OABSS) is useful for screening overactive bladder in adults. However, children may be difficult in detecting LUTS. Holding maneuver may suggest overactive bladder symptoms, and dysfunctional voiding symptom score (DVSS) may be useful for detecting children's' LUTS.

Urinalysis: Urine gravity less than 1.022 or urine osmolality less than 800 mOsm/kgH₂O may suggest nocturnal polyuria. In urine sediment, white blood cell >5/HPF suggests urinary tract infection and red blood cell > 5/HPF may suggest microscopic hematuria.

Bladder diary and pad test: Bladder diary is useful especially in patients with non-MNE. Number of voids/day, number of voids /night, number of leak (day/night), and amount of leak (day/night) are calculated. In patients with nocturnal polyuria, nocturnal polyuria index (nPI=nocturnal urine volume/24hour urine volume=amount of enuresis+voided volume at wakeup) should be calculated. Functional bladder capacity (voided volume + postvoid residual urine volume) can be estimated as mean voided volume and maximum voided volume.

Uroflowmetry and measurement of postvoid residual urine volume (PVR): Some patients with urinary incontinence (non-MNE) may have dysfunctional voiding or congenital urethral stenosis such as posterior urethral valve. Uroflowmetry is useful not only for measuring average and maximum flow rates but also for analyzing flow curve. Normal flow curve is bell shaped, and abnormal flow curves include staccato pattern, intermittent pattern, tower shaped pattern, etc.

Optional studies: In enuretic patients refractory to conventional therapies the optional studies may be useful

Video-urodynamics (urodynamic study with/without voiding cysturethrography): The abnormal findings in enuresis may include detrusor overactivity, low compliance bladder, bladder outlet obstruction, or detrusor underactivity. Uroflowmetry combined with external-sphincter electromyography can detect dysfunctional voiding. Voiding cysturethrography is useful in detecting vesicoureteral reflux, bladder deformity, and congenital urethral stenosis such as posterior urethral valve.

Sleep studies: Electroencephalography may be useful in limited patients.

Web based clinical support tool

Shigeru Yoshida, MD

Vice Director & CMIO, Kishokai Medical Corporation, Japan

Education and Training:

1981-1987 Kobe University School of Medicine
1987-1988 Kobe University Hospital, Department of Pediatrics, Residency
1988 Hyogo Prefectural Kobe Children's Hospital, Residency
1988-1989 Kure Kyosai Hospital, Department of Pediatrics
1989-1996 Shinko Hospital, Department of Pediatrics
1996-2004 Kakogawa City East Hospital, Department of Pediatrics
2004-2013 Nagoya University Hospital, Medical IT Center, Director
2013- Kishokai Medical Corporation, Vice Director
2015 President of the 26th Annual Meeting of the Japanese Society on Enuresis

Field of specialty:

Nocturnal enuresis, Medical Informatics

We described the outline of a web-based database system recently developed in Japan, which is named "Sunshine Calendar on the Web".

"Sunshine Calendar on the Web" enables a patient to check wet or dry and to keep a daily behavioral record through the Web on PC or smartphone app at home. These data are transmitted to a data center via the Internet and stored securely.

Patient enrollment is very simple and quick according to the following procedure.

First, a doctor who wants to use this system sends mail to the administrator. The return mail contains the URL for the staff registration site and he can easily complete the registration.

Then he can mail to a patient for enrollment. The solicitation mail contains the URL for the patient enrollment site and the patient can easily complete the enrollment.

Finally, the patient is linked to the doctor and he can browse the patient's record at his office.

This system is not only useful for a daily practice but also has a potential for application to a large-scale study with huge amounts of data.

We hope new excellent evidence about nocturnal enuresis comes from this system in the near future.

Abstracts

Day-1 Sunday, June 28

Regional differences in history of and approach to nocturnal enuresis “Japan”

Masuji Hattori, MD, PhD

Professor, Department of Pediatrics, Hyogo College of Medicine, Japan

1972-1978 Hyogo College of Medicine
1978-1982 Department of Pediatrics, Hyogo College of Medicine
1982-1983 Shigei Medical Research Center & Hospital, Staff
1983- Department of Pediatrics, Hyogo College of Medicine
(1990-1991 University of Minnesota, USA, Research fellow)

Field of specialty:

Pediatric, Nephrology, Nocturnal enuresis, Vaccination, Injury prevention

In Europeans, image for nocturnal enuresis is anger. On the other hand, most Japanese feel that nocturnal enuresis is embarrassing. Patients and parents tend to want to hide the disease. Most Japanese also think that nocturnal enuresis disappears naturally. Dr. Sigmund S. Freud (1856-1939), a psychiatrist, considered enuresis to be a benign disease and deemed treatment for it to be unnecessary. The view of nocturnal enuresis in Japan is the same as it was for Dr. Freud. The Japanese doctor also nocturnal enuresis tend led the observation because disappear naturally without treatment. In the survey of pediatric clinic about nocturnal enuresis, clinic own management was 52 percent. The desmopressin therapy tended to selected than the enuresis alarm. As a therapy, the desmopressin therapy is 68 percent, the enuresis alarm is 32 percent, and the tricyclic antidepressants is 36 percent.

Therefore, it is important to view nocturnal enuresis as a treatable disease and that's why we have been working to change the perception of nocturnal enuresis. An example of this would be the message in press advertising, train advertising, and the movie CM, which is “Nocturnal enuresis that can be treated”. There was a large amount of consultation during the Nocturnal enuresis Telephone Center.

In comparison to the rest of the world, Japan delayed use of a new drug. The launch of MINIRIN Melt in Japan was in 2012. Delay of the release of MINIRIN Melt might have led to the delay of Nocturnal enuresis care.

The percentage of children with nocturnal enuresis is more than 10% at the elementary school grade of 1. The amount of children with Nocturnal enuresis are at least 80 million. When the trip and camp approaches, they will consult with a family doctor. We are creating a nocturnal enuresis clinic flow chart for the family doctor. With the use of the clinic flow chart, the number of children being treated will increase. We hope to help the children and families live without feeling embarrassment over nocturnal enuresis.

Regional differences in history of and approach to nocturnal enuresis “Taiwan”

Stephen Shei-Dei Yang, MD, PhD

Taipei Tzu Chi Hospital, New Taipei, Taiwan and Buddhist Tzu Chi University, Hualien, Taiwan

He is a board member and Chairman of Committee of in many domestic and overseas academic organizations (table 1), He is also an editor and reviewer of 11 domestic and international journals. His recent researches focus on establishing nomogram of pediatric lower urinary tract function and the effects of bladder bowel dysfunction (BBD) in children. International Children's Continence Society (ICCS) adopted his publication to establish normal reference values of pediatric LUT function in 2014. BBD has a strong impact on pediatric UTI and VUR. Recognition and Management of BBD to prevent UTI and to enhance resolution of VUR in children is one of the recent missions of ICCS' Standardization Committee in which he is the chairman.

Table 1. Academic services:

Vice president of Asian Association of UTI/STI (AAUS)
Board member of International Children's Continence Society (ICCS)
Board member of Asia Pacific Association of Pediatric Urology (APAPU)
Board member of Taiwan Urological Association (TUA)
Board member of Taiwan Continence Society (TCS)
Board member of Taiwan Andrological Association (TAA)
Chairman of Genital urinary tract infection/ Inflammation, TUA
Chairman of Standardization Committee, ICCS

Field of specialty:

Pediatric urology, Lower Urinary Tract (LUT) dysfunction, and minimally invasive surgery

Historical legends, folk stories or pictures concerning voiding, wetting and enuresis in Taiwanese children will be summarized and presented. In short, Most Taiwanese are ethnic Chinese, and the cultural and social responses are similar to that of China. Traditional Chinese medicine which is covered by the National Health Insurance has been used widely before and present.

Since Alarm therapy is not covered by the National Health Insurance in Taiwan, few doctors have such experience.

Taiwan has published treatment guideline on nocturnal enuresis in 2001.

At that time, imipramine is recommended as one of first line treatments (alarm and desmopressine). Most physicians in Taiwan used imipramine 25 mg per day, while few used up to 50mg per day. Up to now, there was no severe adverse effect report in children treated for enuresis. However, ventricular tachycardia had been reported in one girl who swallowed large amount of imipramine prescribed for her grandmother.

Abstracts

Day-1 Sunday, June 28

Regional differences in history of and approach to nocturnal enuresis “United States”

Paul Austin, M.D.

St. Luis Children's Hospital, Washington University School of Medicine, USA

Dr. Paul Austin is the Director of Pediatric Urology Research, Director of the Multidisciplinary Spina Bifida Program and Professor of Urologic Surgery at Washington University in St. Louis School of Medicine. Dr. Austin leads a robust basic science research program that is funded by the NIH and investigates the molecular pathways involved with renal injury resulting from obstructive uropathy. In addition to his basic science work, Dr. Austin is also recognized as a leading clinical trial investigator of lower urinary tract function and serves on global advisory panels for national and international urology clinical trials. Dr. Austin is the current General Secretary for the International Children's Continence Society and has served on the Executive Committees for the Society of Pediatric Urology and the Section on Urology of the American Academy of Pediatrics.

In this round table discussion session, I will highlight the common practice regarding the evaluation and care of children with enuresis in the United States. I will highlight the stakeholders that care for enuresis in the USA and evaluate the strengths and limitations within the healthcare system in the United States. Finally, I will discuss the common treatments used for enuresis in the United States.

Regional differences in history of and approach to nocturnal enuresis “European countries”

Søren Rittig, M.D., DMSc

Skejby Sygehus, Aarhus University Hospital, Denmark

Søren Rittig graduated from Aarhus University Medical School in 1987 and passed the ECFMG (Educational Committee for Foreign Medical Graduates, U.S.A.) exam in 1990. He has completed a Research Fellowship at Aarhus University, Clinical Institute and Northwestern University Medical School, Dept. of Medicine, Chicago, USA. He became a specialist in Pediatrics in 2002 and has been consultant in Pediatric Nephrology at Aarhus University Hospital, Aarhus Denmark since 2004. In 2010 he defended his thesis on circadian regulation of urine output in normal children and children with nocturnal enuresis. He became full Professor in Pediatrics, Aarhus University in 2012. He has since Medical School been heavily involved in research in childhood incontinence, especially nocturnal enuresis. His research has been focusing especially on circadian rhythms and enuresis pathophysiology and treatment; e.g. the description of a deficient circadian rhythm of vasopressin secretion in nocturnal enuresis that was correctable with administration of the vasopressin analogue desmopressin. Since 1992, he has also been involved in molecular genetic research of inherited forms of diabetes insipidus and other renal tubular disorders and his laboratory has contributed with description of many mutations in familial diabetes insipidus. Søren Rittig has published app. 150 peer reviewed papers, 6 book chapters, and co-edited several supplements in International journals. Furthermore, he has supervised 20 PhD programmes. Since 1999, he has been director of Center for Child Incontinence in Aarhus and he is the current Scientific Chairman of the International Children's Continence Society (ICCS). He also currently holds the post as Board member of the European Society for Paediatric Nephrology (ESPN).

In Europe, the perception of enuresis has changed dramatically during several centuries from being a condition due to bladder weakness, irritable bladder and weak sphincter, and deep sleep. Also, nocturnal enuresis was considered an emotional disturbance, - e.g. Freud thought urination was erotic and that wetting the bed was a frustrated sexual act. The parents considered heavy sleeping and emotional problems as the main causes of enuresis in children; physical causes rarely were believed to be important. "Waking up the child" from sleep to urinate and "talking about the problem" were the main methods that parents used to treat enuresis. Parents with a grade school level of education punished bed-wetting children at twice the rate of high school- and college-educated parents. In modern age, deep sleep and emotional problems were still regarded as predominant causes together with hereditary factors and the condition was often neglected by doctors. In some children, the condition was handled by school nurses and usually treated with a bedwetting alarm. During the early 1980-ties enuresis research was intensified clarifying several enuresis subtypes with different underlying mechanisms, e.g. nocturnal polyuria and low nocturnal bladder reservoir capacity, and diagnostic tools to identify these were developed. Also, psychological research concluded that the emotional symptoms observed in these children were secondary to the condition and attenuated after successful treatment. Instead, focus was directed towards psychological comorbidities such as ADHD and again diagnostic screening tools were developed. Alongside, the medical treatments became differentiated towards bladder reservoir problems (alarm) and nocturnal polyuria (desmopressin). The public awareness has now increased significantly and management of childhood incontinence has become part of the medical education at most universities. Currently, focus is on the role of sleep fragmentation and potential day-time neurocognitive consequences, and treatment protocols for the difficult patients.

Abstracts

Day-1 Sunday, June 28

Treatment strategy of nocturnal enuresis

Søren Rittig, M.D., DMSc

Skejby Sygehus, Aarhus University Hospital, Denmark

Søren Rittig graduated from Aarhus University Medical School in 1987 and passed the ECFMG (Educational Committee for Foreign Medical Graduates, U.S.A.) exam in 1990. He has completed a Research Fellowship at Aarhus University, Clinical Institute and Northwestern University Medical School, Dept. of Medicine, Chicago, USA. He became a specialist in Pediatrics in 2002 and has been consultant in Pediatric Nephrology at Aarhus University Hospital, Aarhus Denmark since 2004. In 2010 he defended his thesis on circadian regulation of urine output in normal children and children with nocturnal enuresis. He became full Professor in Pediatrics, Aarhus University in 2012. He has since Medical School been heavily involved in research in childhood incontinence, especially nocturnal enuresis. His research has been focusing especially on circadian rhythms and enuresis pathophysiology and treatment; e.g. the description of a deficient circadian rhythm of vasopressin secretion in nocturnal enuresis that was correctable with administration of the vasopressin analogue desmopressin. Since 1992, he has also been involved in molecular genetic research of inherited forms of diabetes insipidus and other renal tubular disorders and his laboratory has contributed with description of many mutations in familial diabetes insipidus. Søren Rittig has published app. 150 peer reviewed papers, 6 book chapters, and co-edited several supplements in International journals. Furthermore, he has supervised 20 PhD programmes. Since 1999, he has been director of Center for Child Incontinence in Aarhus and he is the current Scientific Chairman of the International Children's Continence Society (ICCS). He also currently holds the post as Board member of the European Society for Paediatric Nephrology (ESPN).

When considering the optimal treatment for nocturnal enuresis a thorough history and clinical assessment is mandatory. Importantly, it is essential to identify signs of bowel dysfunction (e.g. constipation) and daytime lower urinary tract symptoms as these symptoms have to be treated before nocturnal enuresis. Also, co-morbidity (e.g. ADHD) is important to identify as this may affect treatment outcome.

Monosymptomatic NE can usually be effectively treated in primary care by a general practitioner. Patient and family attitudes to treatment should be assessed since motivation and compliance are key factors in the success of any strategy. Two first-line treatment options for MNE exist (desmopressin and enuresis alarm), and initial selection between these should be guided by the family's level of motivation and their preference, or results of the bladder diary with consideration of family motivation. Information from the diaries will identify the subtype of MNE and allow further fine-tuning of treatment to the patient's characteristics:

- 1) Children with a normal urine output and normal bladder capacity can be allowed to choose between alarm and desmopressin
- 2) Children with smaller than expected bladder capacity for age will likely be desmopressin-resistant and more sensitive to the alarm
- 3) Children with NP and normal bladder volume will be more sensitive to desmopressin
- 4) If the diary indicates both excessive urine output and reduced bladder capacity, combination therapy using alarm and desmopressin to address the mixed etiology of the condition may be successful. This strategy may also be useful in lessening the burden of alarm treatment if the alarm is triggered several times per night

If the initial treatment attempt is unsuccessful it is recommended to use home recording of nocturnal urine production and daytime FV-charts to further characterize the underlying mechanism. Also, the registration could be done on treatment (e.g. desmopressin) in order to elucidate whether the treatment induced the wanted effect. This may uncover desmopressin resistant nocturnal polyuria due to high osmotic excretion or an underlying bladder dysfunction resulting in small MVV. In the former combination therapy with desmopressin and imipramine or indomethacine may be tried. In the latter, supplementary treatment with anticholinergics may be indicated.

In conclusion, most patients with MNE can be treated in primary care with either desmopressin or the enuresis alarm. In treatment resistant cases combination therapy with several treatments directed either against nocturnal polyuria or bladder dysfunction or both can be necessary.

How to use treatment modalities?

“Alarm”

Atsuko Hata, M.D., Ph.D.

Director, Department of Pediatrics, Division of Infectious Diseases, Department of Infectious Diseases, Department of Infection Control, Kitano Hospital, The Tazuke Kofukai Medical Research Institute, Japan

Education and Training:

- 1983-1989 Fukui Medical School
Residency,
- 1989-1990 Fukui Medical School
- 1990-1993 Kitano hospital, The Tazuke Kofukai Medical Research Institute,
Research,
- 1993-1997 Graduate School of Medicine, Osaka University, Department of Microbiology and Immunology
- 1997-1999 Stanford University, Department of Pediatrics, Division of infectious diseases, fellowship
Healthcare profession
- 1999-2015 Kitano hospital, The Tazuke Kofukai Medical Research Institute

Field of specialty:

Infectious diseases, Virology, Immunology, Kidney diseases, Nocturnal enuresis

Enuresis alarms, regarded as first-line therapy for primary mono-symptomatic nocturnal enuresis, are currently the most effective and safest treatment available. Alarms are electronic devices worn or placed in or beside the bed, providing a strong sensory signal, commonly a loud acoustic noise or vibration immediately after an episode of incontinence. Alarms of several types are available, but no one type has been demonstrated as superior. At first, an adult should sleep in the same room as a child. When a child gets wet, a loud alarm will sound. The adult then wakes the child, turns off the alarm, and accompanies the child to the toilet to finish emptying the bladder. Then the child will return into bed. Mechanisms of action of alarm treatment are still not fully understood. A main effect of the alarm treatment is recognized that alarms do not elicit an arousal reaction, but rather increase the bladder storage capacity by enhancing bladder control and urination.

First-line treatments for bed-wetting include alarm treatment and desmopressin. A Cochrane review of 13 trials with 576 patients comparing bed alarm therapy with no treatment or placebo revealed that the probability of treatment failure was much lower with bed alarm therapy than with the control therapy (relative risk [RR] = 0.38; 95% confidence interval [CI], 0.33–0.45). A systematic review showed that 66% of children treated with the alarm maintained 14 consecutive dry nights compared with 4% of untreated children after 10–20 weeks (RR for failure 0.38, 95% CI: 0.33–0.45). Meta analyses have shown that enuresis alarms are not inferior to desmopressin. Moreover, the alarm is the only treatment shown to treat bedwetting with a long-lasting effect. Treatment with the alarm had more persistent effectiveness than that with desmopressin or tricyclic antidepressants. Recently, an intention-to-treat analysis in a randomized prospective study found the long-term success rate to be significantly higher with desmopressin (68.8% vs. 46.2%).

The choice of therapy is based on the child's age, nighttime voiding patterns, and the motivations of the child and family. To avoid withdrawal from the alarm, the child and family must be well-motivated and well-informed about the alarm. After alarm initiation, physicians should follow up for at least four weeks to assess the response and compliance, troubleshoot any technical difficulty, and answer any question. If some sign of a response is apparent within 1–3 months of use, then therapy should be continued until 14 consecutive dry nights are achieved. If the alarm breaks, overlearning (giving extra fluids at bedtime after successfully becoming dry using an alarm) is a beneficial form of supplemental alarm training (RR = 1.92 for avoiding relapse; 95%CI, 1.27–2.92).

Abstracts

Day-1 Sunday, June 28

How to use treatment modalities? “Desmopressin”

Yoshiyuki Ohtomo, MD & PhD

Associate Professor, Department of Pediatrics, Juntendo University Nerima Hospital, Japan
Chief Pediatric Nephrologist, Juntendo University Graduated School of Medicine, Japan

Education & Training:

1981-1987 Juntendo University School of Medicine
1987-1988 Juntendo University Hospital
Residency of Pediatrics
1988-1992 Juntendo University Graduated School of Medicine
PhD student in renal pathology
1992-1996 Department of Woman & Child Health, Karolinska Institute
(Stockholm, Sweden)
PhD student in developmental renal physiology
1996-2002 Juntendo University Hospital
Senior Physician of Pediatric Nephrology
2002-2005 Division of Nephrology, Saitama Children's Medical Center
Head of the division
2005-2015 Juntendo University Nerima Hospital
Associate Professor of Pediatrics

Field of Specialty:

Pediatric Nephrology, Nocturnal Enuresis

Management of nocturnal enuresis may involve one or a combination of interventions, including, 1) education and advice (given the high rate of spontaneous resolution), 2) motivational therapy (eg, sticker or star chart), and 3) active therapy (desmopressin and enuresis alarms).

Desmopressin (a synthetic vasopressin analog) is a first-line treatment for enuresis in children older than five years whose bedwetting has not responded to advice about fluid intake, toileting, or an appropriate reward system.

It is an alternative to enuresis alarms for children and families who seek rapid or short-term improvement of enuresis; have failed, refused, or are unlikely to adhere to enuresis alarm treatment; and for whom an enuresis alarm is unsuitable.

Desmopressin works best for children with nocturnal polyuria and normal functional bladder capacity.

As an estimate, recent literature summarizes that 30% of children with enuresis are full responders and 40% have a partial response, whereas the relapse rate after discontinuation is high (60 to 70 percent).

Regularly, oral melt tablets are given 30 to 60 minutes before bedtime.

The initial dose is 120 mcg; if needed after 10 to 14 days, the dose may be increased by 120 mcg to a maximum dose of 240 mcg.

If effective, it should be used for 3-6 months, and then an attempt should be made to taper the dosage. However, the procedures by which the termination of the therapy has not been fixed to date.

Recently, we performed retrospective analysis of our patients (49 cases) with polyuric monosymptomatic nocturnal enuresis (MNE), who were treated with two different withdrawal protocols of oral desmopressin melt (ODM) tablet, MinirinMelt®, after they responded well to it.

Group A (25 cases): (240 mcg ODM per day →)120mcg ODM per day → 120mcg ODM per alternate day → cessation

Group B (24 cases): (240 mcg ODM per day →)120mcg ODM per day → 60mcg ODM per day → 60mcg ODM per alternate day → cessation

After having obtained the results that 14 patients in Group A (56%) and 4 in Group B (17%) experienced relapses of enuresis after the discontinuation of ODM ($p=0.026$), and we proposed that more gradual withdrawal of desmopressin leads to the better outcomes in the treatment of MNE (Pediatr Int 2015 Mar 1. doi: 10.1111/ped.12614. [Epub ahead of print]).

How to use treatment modalities?

“Treatment aspects of nocturnal enuresis- How to use other treatment modalities focus on the difficult patient”

Johan Vande Walle, M.D.

Chair, Paediatric Nephrology and Rheumatology
Director, Safepedrug Consortium,
Academic chair of Department of Paediatrics and Genetics,
University Hospital Ghent, Belgium

Born in 1957, studies medicine and health sciences university Ghent 1975-1982. Training in pediatrics 1982-1987 University hospital Ghent. 1987-1991 training as pediatric nephrologist in Nijmegen and Utrecht Netherlands. In 1991 initiation of a pediatric nephrology department in Ghent not only with major interest in dialysis, transplantation, renal physiology, acute renal failure and nephrotic syndrome, but also in pediatric drug development program on bladder dysfunction and enuresis in children.

He started in 1992 together with P. Hoebeke, (pediatric urologist) a multidisciplinary enuresis team PUNC (pediatric urology nephrology center). This team covers a multidisciplinary approach in clinical practice as in research, targeting the complexity of pathogenetic mechanisms involved in nocturnal enuresis and bladder dysfunction: the team includes pediatric nephrologists, urologists, urotherapists, physiotherapists, psychologists, sleep specialist, gastroenterologist and pharmacologist.

The tertiary care program targets the 4 major factors, involved in the pathogenesis of refractory enuresis : abnormalities in circadian rhythm of water- and sodium handling in the kidney, bladder dysfunction both in filling and emptying phase, abnormalities in sleep and arousal, as well as comorbidities (constipation, psychology, mental and motoric disabled).

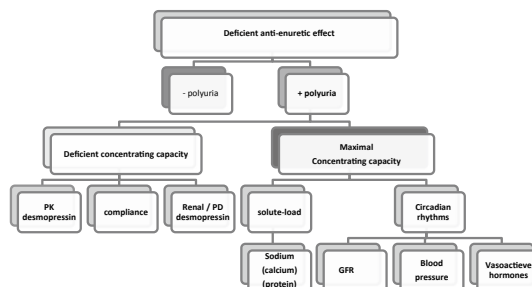
This has resulted in individualised treatment regimens and the organization of voiding camps and the voiding school for refractory cases.

In the past decades research has been concentrating on the interface between nocturia/enuresis, circadian rhythm of renal functions, sleep disturbances and concentration disorders. The center has a leading role in pediatric continence societies and guideline committees. More than 100 abstracts, 40 publications and 8 PhD's on the topic document the scientific work.

Recently he developed a safepedrug consortium on innovative drug research in paediatrics: The consortium is concentrating on antibiotics, antihypertensives, and drugs targeting antidiuresis and bladder dysfunction. The consortium includes research lines in pharmacologic modelling, pediatric animal models, drug studies on intensive care and neonatology as well as innovative ethical approach.

Standard therapy for monosymptomatic enuresis in children according to ICCS guidelines is desmopressin and/or alarm therapy. But up to 30% of patients might be resistant to the initial approach. In therapy resistant patients the following strategy should be followed:

- 1) Redo the full non-invasive screening during normalised fluid intake. The major reason for therapy resistance, is missed diagnosis of underlying bladder dysfunction,
- 2) In the children with persistent enuresis without persisting nocturnal polyuria, consider OAB overnight. Association of anticholinergic therapy is a rational choice but is not EBM
- 3) Identify or exclude comorbidities, known to coincide with therapy resistance, such as
 - a. constipation faecal incontinence, thick bladder wall,
 - b. history of uropathie and/or UTI, abnormal uroflow, residue after micturition, thick bladder wall , suggestive for Non MNE (ICCS standardisation)
 - c. 7/7 days wet
 - d. Sleep disturbances (OSAS, Sleepwalking, restless legs syndrome)
 - e. Mentally and motoric disabled, AD(H)D (D.Baeyens)
 - f. Psychological problems
- 4) Analyse the pathophysiologic mechanism involved in the monosymptomatic nocturnal enuresis with desmopressin resistant nocturnal polyuria
- 5) Use an individualised treatment approach, dependent of the pathophysiologic findings.
 - a. Treat first the constipation
 - b. Maximalise urotherapy advice, including fluid intake and normal sodium and solute load
 - c. Take in the charge if possible or at least in consideration the ADHD, autism and psychological problems , (including familial, social problems like divorce, burden for the parents)
 - d. Treat sleep disturbances
 - i. Sleep hygiene
 - ii. Melatonin for failure of sleep initiation
 - iii. OASAS
 - iv. Restless legs syndrome
- 6) Desmopressin resistant nocturnal polyuria with low osmolality overnight
 - a. Melt is superior to tablet
 - b. Individualise treatment with up titration in specialised enuresis centres, based on PK studies
 - c. Tackle compliance
 - d. Understand desmopressin resistance
- 7) Desmopressin resistant nocturnal polyuria with high osmolality overnight
 - a. Consider to high sodium and osmotic load
 - b. Abnormalities in circadian rhythm of renal functions and hormones (GFR, prostaglandins, blood pressure, solute and sodium excretion)



Abstracts

Day-1 Sunday, June 28

Combination therapy

Shuichiro Fujinaga, M.D.

Director, Division of Nephrology, Saitama Children's Medical Center, Japan

1997-1998 The Fraternity Memorial Hospital, Department of Pediatrics
1998-2003 Juntendo University, Department of Pediatrics
2003- Saitama Children's Medical Center, Division of Nephrology

Desmopressin is an evidence-based first-line medical treatment of primary monosymptomatic nocturnal enuresis (PMNE). In clinical practice, however, we have often encountered unsatisfactory outcomes of the monotherapy. Rushton et al. reported that a decreased functional bladder capacity of 70% or less of predicted functional bladder capacity for age appears to be a predictor of a poor response to desmopressin. Anticholinergic agent is not the first-line treatment option for PMNE. Therefore, this drug is usually used in combination with desmopressin especially for resistant children as the second-line treatment. In a randomized, double-blind, placebo-controlled trial for resistant patients to desmopressin, Austin et al. demonstrated that there was significant 66% decrease in the risk of a wet episode in combination therapy group (desmopressin and long-acting tolterodine), compared with the placebo group (desmopressin and placebo). Recently, Park et al., retrospectively analyzed children with PMNE administered desmopressin alone or combination therapy with desmopressin and plopiverine as the first-line treatment. These results demonstrated that complete response was achieved quicker and at a higher rate in the combination therapy group compared with the desmopressin monotherapy at 1 month of treatment (20.4% vs. 6.1%). Based on these findings, anticholinergic agent in combination with desmopressin may play an important role not only in desmopressin-resistant patients with decreased bladder capacity but also in PMNE children as the beginning of treatment.

The ICCS recommendations for enuresis alarm are based on the highest level of evidence. Although the effect of pharmacological therapy such as desmopressin and anticholinergic agent is usually not sustained after the treatment stopped, enuresis alarm appears to be more effective in the long run. However, a well-known disadvantage of the treatment is the necessity of cooperation and motivation of both child and their families. Furthermore, alarm therapy may take several months to exert this positive effect, resulting in non-compliance and high rate of early withdrawal (10-40%). In a double-blind, placebo controlled study for PMNE, Leebeek-Groenewegen et al. showed a significant greater reduction in number of wet nights in combination therapy group (alarm and desmopressin) compared with placebo group (alarm and placebo) after the first 3 weeks of treatment. They concluded that the initial positive effect of desmopressin may be of clinical use to keep patients motivated for enuresis alarm.

In this presentation, we will show the outcome of PNE patients with small bladder volume who received initial triple combination therapy (enuresis alarm, desmopressin, and long-acting anticholinergic agent) at Saitama Children's Medical Center.

Abstracts

Day-2 Monday, June 29

Nonmonosymptomatic Nocturnal Enuresis (NMNE)

Stephen Shei-Dei Yang, MD, PhD

Taipei Tzu Chi Hospital, New Taipei, Taiwan and Buddhist Tzu Chi University, Hualien, Taiwan

He is a board member and Chairman of Committee of in many domestic and overseas academic organizations (table 1), He is also and editor and reviewer of 11 domestic and international journals. His recent researches focus on establishing nomogram of pediatric lower urinary tract function and the effects of bladder bowel dysfunction (BBD) in children. International Children's Continence Society (ICCS) adopted his publication to establish normal reference values of pediatric LUT function in 2014. BBD has a strong impact on pediatric UTI and VUR. Recognition and Management of BBD to prevent UTI and to enhance resolution of VUR in children is one of the recent missions of ICCS' Standardization Committee in which he is the chairman.

Table 1. Academic services:

Vice president of Asian Association of UTI/STI (AAUS)
Board member of International Children's Continence Society (ICCS)
Board member of Asia Pacific Association of Pediatric Urology (APAPU)
Board member of Taiwan Urological Association (TUA)
Board member of Taiwan Continence Society (TCS)
Board member of Taiwan Andrological Association (TAA)
Chairman of Genital urinary tract infection/ Inflammation, TUA
Chairman of Standardization Committee, ICCS

Field of specialty:

Pediatric urology, Lower Urinary Tract (LUT) dysfunction, and minimally invasive surgery

NMNE means that the child with nocturnal enuresis has daytime lower urinary tract symptoms (LUTS). In addition to the recognition of daytime LUTS, presence of constipation/fecal incontinence and lower urinary tract dysfunction should be recognized. About 30-50% of children with NMNE have psychological comorbidity, adequate consultation should be done. Diagnosis of hidden constipation and LUT dysfunction will be presented in the talk.

ICCS recommendations on the treatment of NMNE are the followings (Franco I, 2013). It is advisable to follow a sequence of steps. 1. Treat any constipation (or fecal incontinence) first, as effective treatment of bowel problems can lead to spontaneous remission of daytime incontinence. 2. Treat the underlying LUTD symptoms first, as effective treatment of an overactive bladder (or postponement, dysfunctional voiding) can lead to cessation of nocturnal enuresis. 3. If comorbid behavioral disorders are present, these often require specific additional treatments (such as stimulants and behavioral therapy in comorbid ADHD). 4. If nocturnal enuresis persists, then standard treatment for monosymptomatic nocturnal enuresis can follow (alarm treatment, desmopressin).

Treatment outcomes of our center will be presented.

Abstracts

Day-2 Monday, June 29

Refractory and adult nocturnal enuresis (NMNE)

Stephen Shei-Dei Yang, MD, PhD

Taipei Tzu Chi Hospital, New Taipei, Taiwan and Buddhist Tzu Chi University, Hualien, Taiwan

He is a board member and Chairman of Committee of in many domestic and overseas academic organizations (table 1), He is also and editor and reviewer of 11 domestic and international journals. His recent researches focus on establishing nomogram of pediatric lower urinary tract function and the effects of bladder bowel dysfunction (BBD) in children. International Children's Continence Society (ICCS) adopted his publication to establish normal reference values of pediatric LUT function in 2014. BBD has a strong impact on pediatric UTI and VUR. Recognition and Management of BBD to prevent UTI and to enhance resolution of VUR in children is one of the recent missions of ICCS' Standardization Committee in which he is the chairman.

Table 1. Academic services:

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Board member of International Children's Continence Society (ICCS)
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Board member of Taiwan Continence Society (TCS)
Board member of Taiwan Andrological Association (TAA)
Chairman of Genital urinary tract infection/ Inflammation, TUA
Chairman of Standardization Committee, ICCS

Field of specialty:

Pediatric urology, Lower Urinary Tract (LUT) dysfunction, and minimally invasive surgery

There are two types of adult nocturnal enuresis: persistent from childhood and new onset.

Not all nocturnal enuresis will grow out with age. There are 0.5% to 1% of adults still suffering from NE. Risk factors of persistent or refractory NE are: severe enuresis (>4 nights per week), associated bladder bowel dysfunction, organic brain or urinary tract disorders. Bowel and lower urinary tract function should be extensively investigated to find out potentially treatable diseases. For example, anterior urethral valve or obstructive posterior urethral membrane can be easily treated by surgical ablation.

Urinary tract infection is one of the frequent causes of new onset of adult NE. Diagnosis and treatment of UTI is mandatory.

Overactive bladder is frequently encountered in adult NE. Overactive bladder may develop with age or relate to BPH. Neurological disease involving CNS is also common in adults, neurogenic detrusor overactivity and sphincter dyscoordination may be present.

Nocturnal polyuria is another important risk factor. It may be associated with global polyuria. Fluid restriction should be done in global polyuria. For genuine nocturnal polyuria without apparent cardiac, neurogenic causes, supplying anti-diuretic hormone can reduce nocturnal polyuria and nocturnal enuresis.

Frequency volume chart and uroflowmetry + PVR are helpful to delineate the change of lower urinary tract function in adults. Invasive urodynamic examinations are usually necessary. Treatment of adult NE should be individualized and no general rule is applicable.

Diagnostic approach to incontinence

Paul Austin, M.D.

St. Luis Children's Hospital, Washington University School of Medicine, USA

Dr. Paul Austin is the Director of Pediatric Urology Research, Director of the Multidisciplinary Spina Bifida Program and Professor of Urologic Surgery at Washington University in St. Louis School of Medicine. Dr. Austin leads a robust basic science research program that is funded by the NIH and investigates the molecular pathways involved with renal injury resulting from obstructive uropathy. In addition to his basic science work, Dr. Austin is also recognized as a leading clinical trial investigator of lower urinary tract function and serves on global advisory panels for national and international urology clinical trials. Dr. Austin is the current General Secretary for the International Children's Continence Society and has served on the Executive Committees for the Society of Pediatric Urology and the Section on Urology of the American Academy of Pediatrics.

The evaluation and diagnosis of urinary incontinence requires a systematic and methodical approach to properly identify the lower urinary tract (LUT) behavior in children with urinary incontinence. A comprehensive elimination history and physical examination are the hallmark diagnostic tools for evaluation of children and adolescents with LUT dysfunction and the first step in the diagnostic approach for urinary incontinence. The nature of the incontinence is important as a child with continuous incontinence implies different etiologies compared to another child with intermittent incontinence. Additionally, intermittent incontinence that occurs during 'awake' periods as opposed to sleeping is managed differently.

It is advisable to inquire if the child exhibits holding maneuvers, expressions of urgency or any behavioral issues that are relevant to the urinary incontinence. Specific tools that aid the evaluation have been published in the ICCS guideline on diagnostic evaluation of children with daytime incontinence. These tools of investigation are categorized into invasive and non-invasive urodynamics. The majority of children with urinary incontinence are able to be successfully diagnosed using non-invasive urodynamics. The key tools within non-invasive urodynamics include the 1) bladder and bowel diaries, 2) questionnaires of LUT function, quality of life and psychology, 3) pelvic ultrasonography and 4) uroflow.

After proper characterization of the LUT function, a tailored, stepwise treatment approach can be employed with confidence.

Abstracts

Day-2 Monday, June 29

Neurogenic bladder and overactive bladder

Paul Austin, M.D.

St. Luis Children's Hospital, Washington University School of Medicine, USA

Dr. Paul Austin is the Director of Pediatric Urology Research, Director of the Multidisciplinary Spina Bifida Program and Professor of Urologic Surgery at Washington University in St. Louis School of Medicine. Dr. Austin leads a robust basic science research program that is funded by the NIH and investigates the molecular pathways involved with renal injury resulting from obstructive uropathy. In addition to his basic science work, Dr. Austin is also recognized as a leading clinical trial investigator of lower urinary tract function and serves on global advisory panels for national and international urology clinical trials. Dr. Austin is the current General Secretary for the International Children's Continence Society and has served on the Executive Committees for the Society of Pediatric Urology and the Section on Urology of the American Academy of Pediatrics.

An overactive bladder (OAB) can occur in neurogenic and non-neurogenic bladders. The clinical hallmark of OAB is urinary urgency, usually accompanied by frequency and nocturia, with or without urinary incontinence, in the absence of urinary tract infection (UTI) or other obvious pathology. Children with OAB usually have detrusor overactivity, but this label can only be applied with cystometric evaluation. Urodynamic studies are not routinely used to evaluate LUT function in neurologically intact children but are employed regularly in children suspected of having a neurogenic bladder.

The principals for efficient and effective measurements of the state of the urinary tract in order to insure normal function on a long-term basis in children with neurogenic bladders will be examined. There are several options regarding therapeutic interventions used for the management of congenital neurogenic bladder. The mainstay of current neurogenic bladder management is non-surgical with anticholinergics and CIC in the majority of children. Other pharmacologic treatments include Beta-3 agonists and Botulinum-A toxin. A small subgroup that fails to respond to treatment may need to undergo surgical reconstruction and is tailored to each individual case, based on careful consideration of urodynamic findings, medical history, age, and presence of other disability.

Bladder bowel dysfunction

Shina Kawai, M.D.

Instructor, Pediatric Urology, Jichi Medical University, Children's Medical Center Tochigi, Japan

Education and Training

- 1992-1998 University of the Ryukyus School of Medicine
- 1998-2000 University of the Ryukyus Hospital, Okinawa, Japan
Residency in Urology
- 2000-2004 University of the Ryukyus School of Medicine, Okinawa, Japan
Fellow in Urology

Field of specialty:

Pediatric urology

The association of bowel dysfunction with lower urinary tract dysfunction is well established recently, with functional constipation having a significant effect on urinary incontinence, lower urinary tract symptoms (LUTS), urinary tract infections (UTIs) and vesicoureteral reflux (VUR). Bladder Bowel Dysfunction (BBD) is the term describing children with "a combination of functional bladder and bowel disturbances, including bladder overactivity (urge), increased or decreased voiding frequency, bladder underactivity or constipation".

Several theories have been proposed as to the mechanism of effect of bowel dysfunction on the lower urinary tract, including mechanical compression of the bladder by rectal distention from stool, neurologically mediated overactivity of the urethral sphincter, or changes in sphincter muscle contractibility resulting from chronic pelvic floor muscle contraction. It is assumed that the close anatomical proximity of the bladder and urethra to the rectum makes it likely that abnormalities within one system will affect the other.

In the initial assessment of a child presenting with LUTS, evaluation of the micturition and bowel habits is mandatory. Dysfunctional Voiding Symptom Score (DVSS) questionnaire is assessment tool of LUTS and bowel habits. It has been tested across cultures, validated and undergone test and re-testing for reliability. A bladder diary is also needed to evaluate LUTS. Clinical inconsistency of LUTS between questionnaire and bladder diary is reported. A questionnaire provides a detailed history and voiding habits but it is a diagnostic tool obtaining subjective answers. The bladder diary is considered an objective diagnostic tool but it may have the limitations of the possibility of intraindividual variation in daytime urine production or storage capacity. In the work up for bowel dysfunction, a bowel diary utilizing the Bristol Stool Form Scale is preferable. The accuracy of the defecation history in children as provided by the child and/or parents can be improved with use of a bowel diary.

The diagnostic criteria and the goal of treatment of bowel dysfunction in the context of BBD are not defined at present. The Roma- III criteria are the most commonly accepted guideline for diagnosis of functional constipation in children but these are originally the diagnostic criteria for the children suffered from chronic gastrointestinal symptom, so even the bowel dysfunction which does not fulfill the Roma- III criteria may cause BBD. Further research into the exact mechanisms of rectal-bladder interactions and pathophysiological connections between bowel dysfunction and lower urinary tract dysfunction in children is needed to resolve this problem.

Abstracts

Day-2 Monday, June 29

Posterior urethral valve and incontinence

Hideo Nakai, MD, PhD

Professor of Pediatric Urology, Jichi Medical University, Children's Medical Center Tochigi, Japan

Education and Training:

- 1975-1981 Keio University School of Medicine
- 1981-1983 Keio University Hospital and Saiseikai Central Hospital,
Residency, general surgery
- 1983-1987 Keio University Hospital and National 2nd Tokyo Hospital,
Residency, general urology
- 1987-1991 Tokyo Metropolitan Kiyose Children's Hospital
Fellowship, department of urology and kidney transplantation
- 1991-1992 Mainz University
Scholarship, department of urology

Field of specialty:

Pediatric Urology

Posterior Urethral Valve is one of the most important clinical entities in the field of pediatric urology. Depending on severity of mechanical obstruction, it causes wide range of symptoms and disturbances in both upper and lower urinary tracts. One extreme is renal insufficiency in perinatal period associated with renal dysplasia. In these clinical settings myogenic bladder may be another sequel in later childhood and adolescence, which causes persistent lower urinary tract dysfunction associated with urge and/or overflow incontinence. The valve bladder syndrome is coined for that. The other extreme is refractory overactive bladder in older children with late-presenting PUV, the exact cause of which has not been clearly elucidated yet. Between these two extremes UTI is sometimes recognized.

Although diagnosis of PUV in infancy is rather simple, straightforward and well established, it is often difficult as well as controversial to diagnose PUV as a cause of refractory incontinence in older children. In this lecture, importance in evaluating urethral anomalies in older children with refractory incontinence will be emphasized and management practice will be reappraised comprehensively.

Dysfunctional voiding

Hidehiro Kakizaki, MD, PhD

Professor and Chairman, Department of Renal and Urologic Surgery,
Asahikawa Medical University, Asahikawa, Japan

Education and Training:

1977-1983 Hokkaido University School of Medicine (Sapporo, Japan)
1994-1996 Research Fellow, Department of Pharmacology
University of Pittsburgh School of Medicine (USA)

Academic appointment:

1998-2003 Assistant Professor, Department of Urology
Hokkaido University Graduate School of Medicine
2003-2005 Associate Professor, Department of Urology
Hokkaido University Graduate School of Medicine
2005~ Current position

Field of specialty:

Neurourology, Pediatric Urology, Reconstructive Urology

Dysfunctional voiding is a urodynamic entity characterized by an intermittent and/or fluctuating uroflow rate due to involuntary intermittent contractions of the striated muscle of the external urethral sphincter (EUS) or pelvic floor during voiding in neurologically normal individuals. Dysfunctional voiding in children is common in clinical practice and predisposes to various urinary problems including lower urinary tract symptoms, recurrent UTI and VUR. Dysfunctional voiding is usually manifested in children who finished toilet training. Pathophysiological reasons why hyperactivity of the striated muscle of the EUS or pelvic floor during voiding is developed after toilet training are not clearly understood. Many but not all children with dysfunctional voiding have involuntary detrusor contraction during urine storage (detrusor overactivity: DO). Children with DO often attempt to overcome DO by voluntarily contracting the striated muscle of the EUS and pelvic floor (so called guarding reflex). If this guarding reflex is overused, then the exaggerated guarding reflex might be sustained even during voiding phase and thus cause overactivity of the EUS or pelvic floor during voiding. However, dysfunctional voiding can occur even in early infancy before toilet training (Jayanthi et al, J. Urol., 158: 1281, 1997). Incoordination between the detrusor and the striated muscle of the EUS or pelvic floor during voiding could induce high pressure voiding and/or incomplete emptying, resulting in structural consequences of the bladder (bladder deformity).

Initial assessment of children with suspected dysfunctional voiding includes careful history taking, urinalysis, physical examination, ultrasound (US) of the kidney and bladder, uroflowmetry (UFM) and postvoid residual urine (PVR) evaluation on US. UFM and PVR evaluation should be repeated because of variability of the results. Voiding and bowel habits should be evaluated using proper questionnaire such as Dysfunctional Voiding Symptom Score (Farhat et al, J. Urol., 164: 1011, 2000). Typical urine holding posture and urgency incontinence suggest the presence of DO. Bladder wall thickness on US suggests high intravesical pressure during urine storage or voiding. Bladder diary would provide valuable information on voiding habits.

Initial treatment of dysfunctional voiding is behavioral therapy including timed voiding, advice for appropriate posture during voiding and correction of bowel habits. Behavioral therapy should be initiated together with patient's and parents' education. If behavioral therapy for at least 6 to 8 weeks fails to improve urinary problems, then medical therapy should be considered. The safety and efficacy of anti-cholinergic medication for DO in children have been reported in the literature. Proper use of laxative would enhance the improvement of dysfunctional voiding in children with concomitant bowel problems. The use of α -blocker for children with refractory dysfunctional voiding may be considered. Biofeedback training, if available, should be a part of treatment protocols for dysfunctional voiding in children.

Abstracts

Day-2 Monday, June 29

Urotherapy

Tryggve Nevéus, M.D., Ph.D.

Uppsala University Children's Hospital, Sweden

Education, clinical

Medical studies at Uppsala University, Uppsala, Sweden. Graduated 1990.

Residency, paediatrics, completed 1999 at Uppsala University Children's Hospital, Sweden.

Postspecialist education in paediatric nephrology at Uppsala University Children's Hospital, Uppsala, and Sahlgrenska University Hospital, Gothenburg, Sweden, completed 2001.

Senior Consultant in Paediatric Nephrology and head of section for Paediatric Nephrology at Uppsala University Children's Hospital, Uppsala, since 2001.

Visiting Consultant in Paediatric Nephrology at Karolinska University Hospital, Stockholm 2008-2010

Society

Secretary General of the International Children's Continence Society (ICCS), from 2006 to 2012. President of the ICCS since 2014.

With urotherapy we roughly mean the part of lower urinary tract (LUT) therapy that involves neither drugs nor surgery. According to the ICCS definition, urotherapy involves

- Information and demystification. Explanation about normal LUT function and how the particular child deviates from normal.
- Instruction in how to resolve LUT dysfunction; i.e. behavioral modification with regular voiding habits, proper voiding posture, avoidance of holding maneuvers, regular bowel habits, etc.
- Life-style advice. Encompasses balanced fluid intake and diet, diminished caffeine, regular bladder and bowel emptying patterns, etc.
- Registration of symptoms and voiding habits, using bladder diaries or frequency-volume charts and potentially mobile apps.
- Support and encouragement via regular follow-up with the caregiver.

Parts of urotherapy, as defined above, can be regarded as general "good doctoring/nursing", and should be part of the practice of every serious healthcare professional. There are, however, also more specific interventions that can be part of the urotherapist's tasks, such as pelvic floor muscle retraining (biofeedback), neuromodulation, intermittent catheterisation or psychological treatments such as cognitive behavioural therapy. The urotherapist may be a specially trained nurse, physiotherapist or physician.

The central instrument in standard urotherapy is the bladder diary or voiding chart. This can be designed in various ways depending on the LUT disturbance of the child. For the child with daytime incontinence the most basic chart includes the timing of daytime voidings and the documentation of incontinence episodes and other LUT symptoms such as urgency. The addition of documentation of fluid intake as well as bowel movements adds to the therapeutic value of the chart, as does the instruction to have the family document the voided volumes during a few days. In the evaluation of the enuretic child the measurement of nocturnal urine production via the weighing of diapers adds prognostic information.

The most prominent role of urotherapy is in the treatment of functional daytime incontinence. Via the institution of regular voiding habits, repeated completion of a bladder diary, elimination of constipation and regular follow-up visits to the healthcare provider many incontinent children will become dry without the need for medication. The most important part of successful therapy in this situation is probably the scheduled voiding at regular time intervals.

The efficacy of urotherapy in the treatment of isolated enuresis, i.e. bedwetting without daytime incontinence, is probably not as good, especially if the child has enuresis every or almost every night.

Persistent urotherapy with biofeedback is a cornerstone in the treatment of children with voiding dysfunction. The biofeedback stimulus in this situation can either be the EMG signal or the uroflow curve.

Nursing care and medical support for incontinence children

Naoko Kamata

Certified Nurse in Wound, Ostomy and Continence Nursing
Hyogo Prefectural Kobe Children's Hospital, Japan

Education:

Nursing, School of Medicine (Faculty of Health Sciences), Kobe University

1999: Completed educational course of Certified Nurse in Wound, Ostomy and Continence

2000: Certified Nurse in Wound, Ostomy and Continence

Elimination disorder in children is mostly due to the congenital disease. Therefore, it is normal for the patients to have the elimination problems, such as urinary incontinence and encopresis, while their families tend to take them as unavoidable conditions by their nature.

If the children fail to be toilet-trained properly, they live in their society without properly mastered toilet etiquettes. They are at high risk of being involved in a serious accident. Childhood is the developing period in their life. We must prepare for the future problems of elimination according to every developmental stage. It is important to manage those problems from the early developmental stage.

Today, I would like to talk about nursing care for children with neurogenic elimination disorders according to each developmental stage.

Abstracts

Day-2 Monday, June 29

Emotional and behavioral disorders associated with enuresis

Yuko Ishizaki, MD, PhD

Department of Pediatrics, Kansai Medical University, Japan

Education:

1989	Kansai Medical University	MD
1995	Tokyo University	PhD

Residencies:

1989-1991	Pediatrics, Kansai Medical University Hospital, Osaka, Japan
1991-1995	Psychosomatic Medicine, LCC Institute of Stress Medicine, Tokyo, Japan

Academic Appointments:

1997-2000	Visiting Assistant Professor, Hamamatsu University School of Medicine Visiting Assistant Professor, Teikyo University School of Medicine
2001-2007	Visiting Assistant Professor of Pediatrics, Kansai Medical University
2007-2012	Assistant Professor of Pediatrics, Kansai Medical University
2012-	Associate Professor of Pediatrics, Kansai Medical University

Field of specialty:

Developmental and behavioral pediatrics, psychosocial problems of children

Enuresis in children is highly comorbid with emotional and behavioral disorders. Previous studies have suggested that one-third of children with nocturnal enuresis and daytime urinary incontinence have coexisting developmental disorders in addition to behavioral and psychological problems. Typical developmental problems associated with enuresis include developmental delays and attention deficit hyperactivity disorder (ADHD), and the primary corresponding psychological issues are depression and anxiety. Generally, developmental disorders are genetic and behavioral and psychological issues are secondary to enuresis.

The most common and significant complication of enuresis is ADHD, a multifactorial disorder, involving genetic factors, an immature central nervous systems, and a dysfunctional lower urinary tract. Enuresis and ADHD are estimated to have a 30% co-occurrence incidence, and children with nocturnal enuresis are more likely to have inattentive than hyperactive symptoms. ADHD is also the disorder most significantly associated with the long-term persistence of enuresis, respectively.

In regard to treatment of children with enuresis with emotional and behavioral disorders, pharmacological and non-pharmacological therapies have combined for resolving both enuresis and ADHD. Treatment specific to just one of these disorders sometimes improve symptoms of both disorders. The first-line non-pharmacological treatment is cognitive-behavioral therapy, which is adapted to the child's level of intelligence. The mainstream pharmacological therapy for enuresis is desmopressin acetate, which is also believed to improve concentration in children with ADHD. Another study has reported atomoxetine as a first-line ADHD treatment that also improves symptoms of enuresis. Several reports propose that methylphenidate, a first-line therapy for ADHD, is also effective for enuresis risoria so called giggle incontinence, which is characterized by involuntary bladder emptying in response to laughter.

The involvement of the central nervous system in the comorbidity of enuresis and ADHD remains unclear; however, it is expected that in future studies, clinical experience will provide important information to help elucidate the comorbid association between enuresis and ADHD.

Relationship between symptoms in children and adults

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Education and Work history

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Recent studies have indicated that adult lower urinary tract symptoms are associated with bladder-related problems during childhood. I conducted a survey parents and grandparents of children with NE. They completed a questionnaire that provided details on their current age, underlying disease, the age when NE resolved and current nocturia and urgency. (I published in *Acta Paediatr.* 2014 103: e410-415)

When I excluded the incomplete questionnaires, I had 3,804 valid responses aged between 30 and 89 years and analysed the frequency of nocturia and urgency based on historical NE in 2,555 responses (30-79years) without underlying disease. I was able to analyse the frequency of nocturia and urgency, based on a precise age at resolution of NE, in 1,300 adults aged between 30 and 49 years without underlying disease. The risk factor analysis for adult nocturia and urgency included all 3,804 respondents by multivariate logistic regression analyses.

In adults aged 30 to 79 years without underlying disease, the frequency of nocturia, urgency and severe nocturia (two or more voids a night) were significantly higher in those with a history of NE than those with no history of NE. When I looked at adults aged 30 to 49 without underlying disease, I found that the frequency of nocturia and urgency was significantly higher in those who were 12- year-of-age or older. In men, history of NE was a risk factor for nocturia (OR, 3.832) and urgency (OR, 2.669) that was at a comparable level to aging and prostatic disease. In women, a history of NE was a risk factor for nocturia (OR, 4.097) and urgency (OR, 3.840) at a comparable level to aging. Thus, a history of NE played a more significant role than underlying diseases such as diabetes mellitus, hypertension.

Delayed NE resolution is considered to be associated with decreases nocturnal urine volume and increases nocturnal bladder capacity during sleeping. The background for adult nocturia and urgency increase may be associated with the effect of an overactive bladder, that develops with age and nocturnal polyuria. The decrease in nocturnal urine volume is thought to be associated with increased antidiuretic hormone secretion during sleep and the increase in nocturnal bladder capacity is thought to be associated with the resolution of an overactive bladder or the development of the autonomic nervous system during sleep. If this circadian rhythm in childhood is delayed, the control of these factors will remain unstable in the person's twenties, during the healthiest time of their life. Then, it is assumed that nocturia and urgency rapidly increase in severity when a person is 50 or older. This trend was particularly noticeable in adults whose NE resolved at the age of 12 or more.