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REVIEW

Comorbidity of ADHD and incontinence in children

Alexander von Gontard · Monika Equit

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Abstract ADHD and incontinence are common childhood disorders which co-occur at much higher rates than expected by chance. The aim of this review was to provide an overview both of the comorbidity of nocturnal enuresis (NE), daytime urinary incontinence (DUI) and faecal incontinence (FI) in children with ADHD; and, vice versa, of the co-occurrence of ADHD in children with NE, DUI and FI. Most clinical studies have focussed on the association of ADHD and NE. Population-based studies have shown that children with DUI have an even greater risk for ADHD than those with NE. While children with FI have the highest overall comorbidity rates of psychological disorders, these are heterogeneous with a wide range of internalising and externalising disorders—not necessarily of ADHD. Genetic studies indicate that ADHD and NE, DUI and FI do not share the same genetic basis. The comorbidity is conferred by non-genetic factors. Possible aetiological and pathogenetic links between ADHD and incontinence are provided by neurophysiological, imaging and pharmacological studies. The co-occurrence has clinical implications: children with ADHD and NE, DUI and FI are more difficult to treat, show lower compliance and have less favourable treatment outcomes for incontinence. Therefore, both groups of disorders have to be assessed and treated specifically.

Keywords ADHD · Nocturnal enuresis · Daytime urinary incontinence · Faecal incontinence · Enuresis · Comorbidity

A. von Gontard · M. Equit (✉)
Department of Child and Adolescent Psychiatry,
Saarland University Hospital, 66421 Homburg, Germany
e-mail: monika.equit@uks.eu

Abbreviations

ACC	Anterior cingulated cortex
ADHD	Attention-deficit/hyperactivity disorder
CBCL	Child behaviour checklist
CNS	Central nervous system
DSM-IV/5	Diagnostic and statistical manual IV/5
DUI	Daytime urinary incontinence
ENS	Enteric nervous system
FI	Faecal incontinence or encopresis
HKD	Hyperkinetic disorder
ICCS	International children's continence society
ICD-10	International classification of diseases
MPH	Methylphenidate
NE	Nocturnal enuresis
ODD	Oppositional defiant disorder
OR	Odds ratio
PAG	Periaqueductal grey
PFC	Prefrontal cortex
PMC	Pontine micturition centre
PPI	Prepulse inhibition
TCA	Tricyclic antidepressant

Introduction

Attention-deficit/hyperactivity disorder (ADHD) and incontinence are not only common disorders in childhood, but also co-exist and interact with each other. Among 7-year-old children, 10 % have nocturnal enuresis (NE), 2–3 % daytime urinary incontinence (DUI) and 1–3 % faecal incontinence or encopresis (FI), while 5–10 % are affected by ADHD [1, 2]. Under the most conservative assumptions (i.e. not considering the co-occurrence of

different types of incontinence), the maximal expected comorbidity would be 16 % (incontinence) × 10 % (ADHD) = 1.6 % (for both together). Based on a growing research base, the actual comorbidity rates are far higher and cannot be explained by chance alone. Compared to other typical comorbid disorders such as conduct, depressive and anxiety disorders, the specific relevance of ADHD and incontinence is often neglected in research and in clinical practice.

The aim of this review is to provide an up-to-date, critical overview of the association of ADHD and incontinence. Specifically, this article will focus on:

- Classification of NE, DUI and FI.
- Prevalence of incontinence among children with ADHD.
- Prevalence of ADHD among children with incontinence.
- Aetiological and pathogenetic associations.
- Pharmacology.
- Consequences for clinical practice when children are affected by both disorders.

Method

A Scopus/PubMed search was conducted entering the terms enuresis, urinary incontinence, faecal incontinence, encopresis combined with the term ADHD from 1990 onwards. A total of 154 publications were identified, of which those applicable to this review were selected. After reading the abstracts, all publications were excluded, that were not in line with the topic of this review; e.g. publications, in which NE and ADHD were mentioned as comorbid disorders in other psychological disorders such as autism. Additional studies not identified by this search, but relevant to the topic were also included. Only one review on the association of ADHD and NE was identified [3], but other comorbid disorders in addition to ADHD were included in this overview.

Classification of NE, DUI and FI

Incontinence comprises a heterogeneous group of functional disorders (i.e. organic causes have to be ruled out) which can be diagnosed from the age of 5 years onwards for urinary and 4 years for faecal incontinence. They can broadly be divided into NE, DUI and FI. For comprehensive overviews on incontinence the readers are referred to von Gontard and Neveus [1] and von Gontard [4, 5]. In the context of this paper, only a short summary on current classification can be given to be able to interpret the different terminology used in studies on incontinence and ADHD.

The criteria for the traditional classification systems ICD-10 [6] and DSM-5 [7] do not reflect current research standards [8, 9]. Therefore, newer systems such as those of the International Children's Continence Society (ICCS) for NE and DUI [10, 11] and of Rome-III for FI [12] are needed.

In ICD-10 and DSM-5, the category enuresis is used for both NE and DUI. No subtypes of NE or DUI are differentiated. In DSM-5, the frequency of two times per week is too restrictive; with such a criterion many children needing treatment are excluded. Regarding the classification of encopresis, in DSM-5 the term constipation is not defined precisely. In contrast, these aspects are considered in the ICCS or Rome-III classifications. For a complete comparison between DSM-5 and ICCS criteria/Rome-III criteria, please see von Gontard [9].

According to the ICCS, urinary incontinence is the general term for any 'uncontrollable leakage of urine', which can be continuous (rare) or intermittent (common) [10]. In the current revision, a duration of 3 months, a minimum frequency of one episode per month and a minimum chronological age of 5.0 years are required [11]. In functional forms of enuresis and incontinence, organic factors have to be ruled out. Enuresis (or nocturnal enuresis—NE) means any intermittent incontinence while sleeping (at night or during daytime naps). Four subtypes can be differentiated: In primary NE, the child has been dry for less than 6 months; in secondary NE, a relapse after a dry period of at least 6 months has occurred. Children with NE who do not have daytime signs and symptoms of bladder dysfunction have monosymptomatic and those with bladder symptoms during the day non-monosymptomatic NE. Daytime urinary incontinence (DUI) is mainly functional—the term 'diurnal enuresis' is obsolete. Children with combined daytime and nighttime wetting have dual diagnoses: the subtype of DUI and NE. Overactive bladder or urge incontinence, voiding postponement and dysfunctional voiding are the most common subtypes of DUI.

In ICD-10 and DSM-5, the term encopresis is used for involuntary or voluntary passage of stool in any inappropriate place. A minimum age of 4.0 years and the exclusion of organic factors are needed [6, 7]. According to the Rome-III criteria [12], two subtypes of FI can be differentiated: functional constipation which can, but does not necessarily co-exist with FI; and non-retentive FI without any sign of constipation. In contrast to encopresis, FI is assumed to be involuntary. FI is also used in the ICCS nomenclature [11]. Many providers in clinical practice use FI and encopresis interchangeably, and none of the studies described in this review differentiates these subtle differences. Therefore, in the present review, the term FI is used for any form of passage of stool in inappropriate places.

NE, DUI and FI, themselves, can co-exist. In addition, other comorbid psychological disorders are associated with incontinence. In total, 20–30 % of children with NE, 20–40 % with DUI and 30–50 % with FI have a comorbid behavioural or emotional disorder [13]. Although ADHD is the most common one, both internalising and externalising disorders can co-exist [13].

Classification of ADHD

Attention-deficit/hyperactivity disorder (ADHD) is defined by the presence of persistent, incapacitating symptoms of inattention, hyperactivity and impulsivity. According to DSM-5, these symptoms have to present before the age of 12 years. Combined, predominantly inattentive and predominantly hyperactive/impulsive presentations (formerly subtypes according to DSM-IV) are differentiated [7]. The ICD-10 diagnosis of a Hyperkinetic disorder (HKD) is a more stringent diagnosis requiring symptoms of all three domains of inattention, hyperactivity and impulsivity [6].

Clinical studies

Prevalence of incontinence among children with ADHD

Few clinical studies have focussed on the occurrence of incontinence in children with ADHD. In a series of 112 children with ADHD and 112 controls (aged 3–12 years), 28.6 % of those with ADHD had NE, but only 5.2 % of controls [14]. In another early study of 140 children with ADHD, 32 % wetted (78 % of these with NE) compared to 14 % of 120 controls (77 % of these with NE) [15]. A retrospective study analysed 153 patients with ADHD and 152 controls. The odds ratios (OR) for NE were 2.7 times higher for NE (20.9 vs. 7.8 %) and 4.5 times higher for DUI (6.5 vs. 2.1 %) in children with ADHD at the age of 6 years. At the age of 10−11 years, the OR were 2.6 times increased for NE (3.9 vs. 2.9 %) and even 11.7 for DUI (13.1 vs. 1.4 %) [16].

In a small study, 28 children with ADHD (mean age 9.4 years) had significantly more NE, DUI, constipation, urgency and infrequent voiding than controls ($N = 22$) assessed with a standardised questionnaire [17]. In another clinical study, all 75 children with ADHD (median age of 7.8 years) had DUI and urgency, 88 % a frequency of >10 voids per day and 87 % additional NE [18]. In this sample, signs indicative of overactive bladder (or urge incontinence) predominate. In a large study of 344 children aged 6–12 years, 286 had ADHD alone and 58 both ADHD and NE (16.9 %). The NE group had a higher likelihood of inattentive symptoms than the 'pure' ADHD group [19]. In a very small sample of a tertiary care hospital, 100 % of the children with inattentive ADHD ($N = 3$) but 0 % of combined ADHD ($N = 4$) were affected by NE [20].

A Turkish study revealed a rate of 23.5 % for NE in children with ADHD. The rate of FI was 3.2 % among 153 children with ADHD (mean age 9.0 years) [21]. In a recent study, 28.3 % of 53 children with ADHD (aged 6–10 years) had NE. In addition, these children had a higher dysfunctional voiding score compared to the continent children with ADHD [22]. Smith et al. [23] reported a rate of 9.1 % for NE among 242 children and adolescents with ADHD (aged 3–17 years). Other clinical studies revealed prevalence rates of 11.7–17.1 % for NE among children with ADHD [24, 25].

In summary, clinical studies of selected groups of children have shown consistently that children with ADHD have high rates of NE. The differences in comorbidity rates are most likely due to methodological factors such as selection effects of recruiting institutions, as well as differences in definition. All studies do not adhere to ICCS recommendations. Many do not report exact definitions (such as incontinence frequency) or assessment procedures of both incontinence and ADHD. Much less data are available on DUI and FI in children with ADHD. Far more studies have analysed the occurrence of ADHD among children with incontinence.

Prevalence of ADHD among children with incontinence

Prevalence of ADHD among children with NE

In clinical studies, the rates of ADHD among children with NE ranged from 9.1 to 53.2 % (e.g. [26–29]).

High rates of ADHD among 6- to 12-year-old children with NE were reported by Baeyens et al. [28], possibly due to selection effects. A total of 40 % were affected by ADHD; 15 % had a combined, 22.5 % an inattentive and 2.5 % a hyperactive type of ADHD. In addition, the authors [30] compared the comorbidity rate for ADHD among children with NE between a sample of a university clinic setting and a population-based sample of children with NE. According to a multi-informant method, the rate of ADHD among enuretic children of the clinical setting was 28.3 % compared to only 10.3 % in the population-based sample. ADHD continued to be present in 72.5 % of the children with NE in a two-year follow-up at the university setting indicating a highly stable rate [31] Children with ADHD continued to wet at follow-up much more often (65 %) than children without ADHD (37 %) (OR 3.2) [31]. At a 4-year follow-up, 64 % still had ADHD. Of these, 42 % continued to wet at night compared to 39 % of the children without ADHD [32].

In a sample of 363 children and adolescents (aged 6–16 years) referred to an outpatient mental health clinic, 16 % had NE. Of these children with NE, 33 % had comorbid ADHD [33]. Even higher rates of ADHD among children with monosymptomatic NE were reported by Okur et al. [29]. 64 children with monosymptomatic NE were compared to 42 controls. 53.2 % of the children with NE (26.6 % predominantly inattentive type, 14.1 % predominantly hyperactive-impulse type and 4.8 % combined type), but only 12 % of the controls (4.8 % predominantly inattentive type, 4.8 % predominantly hyperactive-impulse type and 2.4 % combined type) were affected by ADHD.

Prevalence of ADHD among children with DUI

In a clinical study, 10.5 % of 53 children with DUI referred to a tertiary outpatient psychiatric clinic were affected by ADHD [34]. An even higher prevalence rate of 21 % for ADHD among children with DUI without urinary tract infections (aged 5–17 years) was reported by Kodman-Jones et al. [35] (compared to 0 % of ADHD among children with DUI and urinary tract infections). Zink et al. [36] assessed 166 5 16-year-old children with NE or DUI and found highest rates of psychological comorbidity for children with voiding postponement. 29 % of the children with DUI and 18 % of the children with NE were affected by externalising disorders according to ICD-10. Kuhn et al. [37] showed significant associations between DUI (voiding postponement or urge incontinence) and psychological symptoms among 5- to 13-year-old children referred to a tertiary clinic.

Prevalence of ADHD among children with FI

Studies on the prevalence rates of ADHD or attention problems among children with FI in clinical settings are rare. In general, the rate of psychological comorbidity in children with FI is high (30–50 %) [13]. The rates of psychological problems in the clinical range were similar between children with constipation and children with non-retentive FI (37 and 39 %, respectively) [38, 39]. Children with combined FI and UI showed even higher rates of comorbid disorders [34].

Johnston and Wright [40] assessed the association of FI and attentional dysfunction among 167 children with FI (mean age 8.4 years) referred to a tertiary care facility. 23.4 % of these children had increased *T* values (>70) on the hyperactive subscale of the child behaviour checklist [41]. Similar results were found by Cox et al. [42] that children with FI had more attention problems than controls (20 vs. 3 %). Van Everdingen-Faasen et al. [43] assessed the effects of psychosocial comorbidity on treatment outcome in 141 children with FI (mean age 9.6 years). With the published data of this study, prevalence rates of 17 % for ADHD among these children could be calculated [43].

In summary, these clinical, cross-sectional studies show that children with incontinence have higher rates of ADHD. Most studies have focussed on NE, which seems to persist for a longer time in children with dual diagnoses (of NE and ADHD). The database for DUI and FI is rudimentary. Definitions of incontinence, as well as methodology in assessing ADHD can differ between the studies. These clinical studies are not population-based and therefore not representative.

Population-based studies

Prevalence of incontinence among children with ADHD

Two recent population-based studies demonstrated increased rates of NE and FI in children with ADHD. No studies on DUI in children with ADHD have been published, so far.

In the cohort study of Mellon et al. [44], children with ADHD (mean age 6.7 years) showed a 2.1 times higher risk for NE than children without ADHD. The relative risk for children with ADHD to meet the DSM-IV criteria for encopresis was 1.8, but did not reach statistical significance. However, the relative risk of 2.0 became significant, if a less stringent definition of encopresis was used [44].

In another retrospective cohort study performed using a database of the military health system in the United States, children with ADHD had an increased prevalence rate of constipation (4.1 vs. 1.5 %) and FI (0.9 vs. 0.15 %) compared with children without ADHD [45].

Prevalence of ADHD among children with incontinence

Prevalence of ADHD among children with NE

In the large sample of the Avon Longitudinal Study of Parent and Children (ALSPAC study) [46], the overall prevalence of NE was 15.5 % among 8,269 7 ½-year-old children. 2.6 % wetted two or more times per week [47]. In the same population-based study, ADHD was the most common parent-reported disorder with a prevalence of 17.6 % in children with NE alone—and even 23.1 % among children with combined NE and DUI—compared to 11.9 % among continent children [48]. Therefore, additional DUI increases the risk for ADHD. Similar results for NE were found in a German population-based study with 1,379 6-year-old children. The rate of ADHD symptoms was 9.4 % in children with NE compared to 3.4 % of continent children [49].

In a representative US sample of 1,136 children (aged 8–11 years), the overall prevalence of NE was 4.45 % and for ADHD 9.9 %. 12.5 % of children with NE had ADHD, compared to 3.6 % of the continent controls (OR 2.9) [50].

Data of the Seoul Child and Adolescent Mental Health Survey emphasised the association between NE and ADHD, too [51]. From a representative sample of 1,645 students (age 6–12 years), 1.8 % had NE. Among these children, the risk for ADHD was increased (OR 2.6).

Prevalence of ADHD among children with DUI

In the ALSPAC study, DUI was assessed in a cohort of 8,213 children (aged 7 ½–9 years), as well. Children with DUI had significantly increased rates of DSM-IV disorders [52]. Again, ADHD symptoms were most common in children with DUI (24.8 %) compared to continent children (13.8 %). The association of ADHD and DUI remained significant even after adjusting for developmental delay, gender and socioeconomic factors. In the cohort of the ALSPAC study, especially children with a high voiding frequency (≥10 times/day; urge incontinence) showed signs of hyperactivity (36 %) and conduct problems (24 %) [53].

In a large German population-based study of children with DUI, children with DUI even had significantly more ADHD symptoms (37 %) than children with NE (9.4 %) (OR 5.49). If confounding factors were controlled for, only DUI but not NE was significantly associated with ADHD (OR 4.4) [49].

Prevalence of ADHD among children with FI

In the large ALSPAC study of 8,242 children aged 7–8 years, 4.0 % of the children with occasional FI (<2 times/week) had ADHD and 9.2 % of those with frequent soiling (≥2 times per week) compared to 1.9 % of the continent children [54]. However, both internalising and externalising disorders are significantly more prevalent (in frequent soiling) such as separation anxiety (4.3 %), specific phobias (4.3 %), generalised anxiety (3.4 %) and ODD (11.9 %) [54]. Overall, symptoms of activity and attention problems were much more common than full diagnoses of ADHD. They also increased with the frequency of soiling: while 13.9 % of continent children had activity and attention problems, this rate rose to 21.3 % in those with infrequent (< once per week) and to 38.6 % with frequent soiling (≥ once/week) [54].

In another population-based study of 3,500 children with a mean age of 7.1 years, 'complaints of bowel and colon' were associated with hyperactivity and inattention in boys (OR 3.7), but not in girls (OR 1.3) [55].

In summary, most representative, population-based studies have focussed on the comorbid prevalence of ADHD among children with different types of incontinence. ADHD is a common, but not an exclusive disorder to concur with incontinence, i.e. the behavioural comorbidity is heterogeneous including both externalising and internalising disorders. Furthermore, ADHD is most common among children with DUI, only then followed by NE. Children with FI are least affected by ADHD, but have a high risk for many other behavioural and emotional disorders.

Aetiological and pathogenetic associations

Genetics

Aetiologically, NE can be considered to be a genetically determined maturation disorder of the central nervous system (CNS) [56]. Only a third of cases of NE are sporadic, in 60–70 % other relatives are affected. The heritability is 0.7 and molecular genetic studies have demonstrated highly significant linkage to chromosomes 12, 13 and 22. The genetic disposition is the same in all types of NE, which can be modulated by environmental factors.

Genetic factors have not been studied in such detail in DUI. Urge incontinence is the subtype with the greatest genetic disposition. One linkage analysis identified a gene region on chromosome 17 [57]. Voiding postponement and dysfunctional voiding are mainly acquired disorders in which genetic factors presumably play a minor role.

In the aetiology of FI, but especially of constipation, genetic factors may play an important role. In 234 children with FI with constipation, 15 % of the relatives suffered from FI and 26 % from constipation [58]. Benninga et al. [38] reported even higher rates: 42 % of children with FI with constipation had relatives who had constipation, as well. In children with FI without constipation this rate was only 15 % [38]. Hence, genetic factors seem to mainly affect the phenotype of constipation and the phenotype of FI secondarily. This was also shown in the twin study of Bakwin and Davidson [59]. The authors could demonstrate that the concordance rate of constipation was 70 % in monozygotic and only 18 % in dizygotic twins.

No genome-wide association studies on either of the incontinence forms have been conducted.

Both genetic and environmental factors, as well as their interactions contribute towards the aetiology of ADHD. Family, twin and adoption studies showed a heritability of 0.6–0.9 [60, 61]. Molecular genetic studies suggest a complex genetic architecture of ADHD. Linkage on chromosomes 2q24, 5p13, 6q12, 14p13, 17p11 has been demonstrated [62], but results were heterogeneous [61]. Several candidate genes (dopaminergic genes: DRD4, DRD5, DAT1; serotonergic genes: 5HTT, HTR1B; other genes:

SNAP-25) were likely to be involved. However, effect size of each candidate gene is small (for a review see [63]). Again, results on the genetic contribution to different subtypes of ADHD are mixed [60].

Bailey et al. [64] examined the transmission of primary NE in relatives of primary NE and controls with or without ADHD to determine if primary NE and ADHD share a genetic basis. As suggested, primary NE was shown to be highly familial, but the rate of primary NE in first-degree relatives was independent of the presence of comorbid ADHD. Of children with NE, 40 % of parents wetted and of those with NE and ADHD 38 %. However, the rate of parental wetting was not different if children had ADHD alone (11 %) compared to healthy controls (6 %). Therefore, the authors concluded that ADHD and primary NE were transmitted independently and did not share a genetic basis.

Only one molecular genetic study has addressed the comorbidity of ADHD and NE. Of 344 children at age of 6–12 years, association studies of 51 trios with ADHD and NE showed non-significant associations with previously defined loci on chromosomes 8, 12, 13 and 22 (transmission disequilibrium test) [19]. These studies need to be replicated with large number of probands.

In summary, there is evidence that genetic factors play an important role in the aetiology of NE and ADHD, to a lesser degree for constipation. The heritability of NE and ADHD as individual disorders is high (around 0.7). However, the only formal and molecular genetic study on both disorders indicates that NE and ADHD are genetically independent, separate entities which do not share a common genetic basis.

Up to date, genetics alone cannot explain the high co-occurrence of NE and ADHD, much less the even higher comorbidity of ADHD and DUI. This means that other, non-genetic factors must play a major role in the joint pathogenesis of the combined disorders.

Neurophysiology

In the aetiology of NE, two main functional deficits in the CNS were proposed: First, stimuli from the bladder are not registered during sleep and do not lead to arousal. Second, the micturition reflex is not inhibited during sleep and so wetting occurs. Both developmental delays are mediated by nuclei of the brainstem: the locus coeruleus (arousal deficit) and the lateral region of the pontine micturition centre (PMC) (micturition inhibition deficit) [65]. Several studies support these assumptions of a developmental delay of brainstem centres. In a study with 37 children with NE and 40 control children, children with NE showed longer interpeak I–III and I–V latencies in brainstem auditory-evoked potentials [66]. The study of Wolfish et al. [67] provides evidence of arousal deficits. Only 9.3 % of the children with NE (compared to 39.7 % of the healthy controls) could be aroused successfully with volumes of up to 120 dB. Moreover, P300 abnormalities in children with NE such as longer P300 latencies [68] or a reduction of P300 amplitude in the parietal (Pz) recording site [69] provide evidence of maturation deficits even of higher cortical structures, especially of the motor cortex circuitry in NE. These findings could not be replicated in another study, in which visual-evoked potentials and event-related late acoustic-evoked potentials were assessed in children with NE [66]. There were no differences in both measures between children with NE and controls.

In addition, some studies revealed decreased prepulse inhibition (PPI) in children with NE. While children with NE showed differences in PPI at baseline, they did not differ from controls at a 2-year follow-up, indicating brainstem maturation over the course of time [70]. Eggert et al. [71] identified two subgroups of children with NE: one subgroup with reduced prepulse inhibition and good desmopressin response and another group with normal prepulse inhibition and nonresponse. A recent combined PPI and functional magnetic resonance imaging study demonstrated a pronounced prefrontal activation in healthy controls compared to children with monosymptomatic NE [72]. The authors concluded that high cortical mechanisms are relevant in PPI and so play a role in the pathogenesis of NE.

Compared to NE, studies assessing neurophysiologic processes in DUI are rare. In adult patients with urgency, anterior cingulated cortex (ACC) activity is increased and activation in the orbitofrontal cortex is decreased [73]. No electrophysiologic studies could be identified assessing brain activity in children with DUI.

Neurophysiologic studies on children with FI are rare, too. Some studies focused on early somatosensory-evoked potential, which reflect neural pathways from the rectum to the cortex. Somatosensory-evoked potentials triggered by electric or pressure stimulation in the rectum were abnormal [74, 75]. Becker et al. [76] showed altered emotion processing through event-related potentials in children with FI—in contrast to controls and children with ADHD. Children with FI with constipation had the most intense reactions in event-related potentials onwards emotional stimuli.

Numerous neurophysiologic studies show alterations in brain activity in children with ADHD. However, the reports on the affected functions and areas are quite heterogeneous. Williams et al. [77] showed reduced ERP activity in children with ADHD while viewing facial expressions and a normalisation of neural activity with methylphenidate. In contrast, in the above-mentioned study of Becker et al. [76], children with ADHD did not differ in their CNS processing of emotions in comparison to healthy controls.

Another study assessing event-related potentials in children with ADHD during a go/no go-task, showed an association of a steeper increase in reaction time and P3s in the parietal region [78]. PPI was also reduced after attended prestimuli in children with ADHD [79]. Methylphenidate enhanced PPI during attended stimuli in children with ADHD [80].

A few studies focussed on CNS processing in children with NE and ADHD. Ornitz et al. [81] found greatest deficits in PPI in children with NE and ADHD. With the association of NE and ADHD, the severity of PPI deficit was increased. This interaction was not replicated by Baeyens et al. [70]: children with NE had decreased PPI compared to controls and children with ADHD, while no pronounced PPI deficits were found for children with NE and ADHD. Although PPI is a theoretically interesting paradigm, it is not a robust and not a specific electrophysiological measurement neither for NE, nor for ADHD [82].

Carefully selected groups of children with NE alone, NE and ADHD, ADHD alone and healthy controls were compared using event-related potentials following the presentation of emotional visual stimuli [83]. Children with NE and ADHD showed the most intense central processing of emotions compared to healthy controls and children with ADHD. They form a special group with CNS interaction effects that cannot be explained by each disorder alone (i.e. NE or ADHD), presumably due to complex neural networks.

A few other studies also identify children with ADHD and NE as a special group. In a recent study, attentional performance was assessed in children with ADHD and NE compared to children with ADHD only [22]. Different aspects of attentional performance (e.g. alertness, auditory sustained attention, inhibitory control) were tested. The results showed shorter reaction times (i.e. lower inhibitory control) in children with ADHD and NE compared to children with ADHD only, whereas accuracy was similar between the two groups, suggesting different patterns of attentional functions in children with ADHD with and without NE.

Neurophysiologic studies focussing on the association between ADHD and DUI or FI are not known to the authors.

Functional imaging

Griffith and Tadic [84] define a simplified model of normal bladder control: Afferent signals of the bladder received in the periaqueductal grey (PAG), are mapped in the insula, forming the basis of sensations. The ACC is responsible for monitoring and control. During storage phase, efferent inhibitory signals are provided via the PAG to the pontine micturition centre (PMC). The prefrontal cortex (PFC) is responsible for conscious attention and voluntary voiding decisions. It sends efferent signals to disinhibit the PMC (and so to void) or to continue to inhibit. Thereby insula, PAG, PMC, ACC and PFC are connected brain regions that are active in bladder control.

The number of studies focussing on bladder control assessed with functional imaging is limited [85], especially in children.

In a functional magnetic resonance imaging study of working memory, children with NE showed significantly reduced activity in the left posterior cerebellum compared to controls [86]. Another imaging study showed an underactivation in the right prefrontal cortex and an overactivation in the left hemisphere in children with primary NE compared to healthy controls during motor response inhibition, indicating an abnormal network of brain areas during response inhibition in children with primary NE [87]. In a resting-state imaging study investigating spontaneous brain activity, children with primary monosymptomatic NE showed decreased amplitudes of low-frequency fluctuation in the left inferior frontal and medial frontal gyri compared to healthy controls. Increased amplitudes of low-frequency fluctuation were shown in the posterior cingulate gyrus, the middle temporal gyrus and in the left middle temporal gyrus [88].

Structural changes in the brains of children with primary monosymptomatic NE compared to healthy controls were assessed in a diffusion tensor study [89]. Children with NE showed a decrease in fractional anisotropy and an increase in mean diffusivity in the thalamus. Additionally, mean diffusivity was increased in the frontal lobe, the ACC and the insula. These microstructure abnormalities could indicate developmental delay in these areas and may be the cause of NE.

According to the systematic Scopus/PubMed search, there exist no functional imaging studies in children with DUI.

Functional imaging could demonstrate an activation of the CNS by local intestinal factors in adults with irritable bowel syndrome [90].

Imaging studies identified abnormalities in the following brain regions in ADHD: dorsal anterior midcingulate cortex, dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, parietal cortex as well as striatum, premotor areas, thalamus and cerebellum [91].

For a review of structural brain imaging in children with ADHD see Seidman et al. [92].

There exist no functional imaging studies focussing on the association between incontinence and ADHD.

Neurophysiologic and functional imaging studies show alterations of CNS activity in different forms of incontinence, as well as in ADHD alone.

In summary, PAG, insula, PMC are regions involved in inhibition of micturition reflex and bladder control. The locus coeruleus is involved in arousal processes, which are relevant in NE, as well. In addition, ACC and regions of

the prefrontal cortex are responsible for monitoring and control functions, emotion regulation and conscious attention. These areas are involved in NE, DUI, FI and ADHD. Dysfunctions of other cortical structures such as several regions of prefrontal and parietal cortex are present in ADHD, responsible for executive function and integration of sensory information. Furthermore, thalamus and cerebellum are involved in ADHD as well as NE.

Main functions of the thalamus are the relaying of sensory and motor signals to the cortex and the regulation of consciousness, sleep, and alertness. After receiving information from sensory systems of the spinal cord and from other parts of the brain, the cerebellum integrates them into motor activity.

Therefore, there is a great overlap of brain structures being involved in ADHD and NE (and to a smaller degree in DUI, FI). Possible interaction effects between functional brain activity in combined incontinence and ADHD have not been studied, so far. It is therefore not known why and how joint ADHD and incontinence affect CNS functioning. From the few studies on ADHD and NE, it can be speculated that complex neural networks including cortical, subcortical and brainstem regions will most likely be responsible for the clinically evident interaction effects.

Environmental or psychosocial factors

Genetic factors contribute to the aetiology of NE, FI and ADHD to a significant and to DUI to a lesser extent. In addition, environmental or psychosocial factors play a role in the aetiology of incontinence and ADHD to a varying degree [1, 63].

Whereas psychosocial or environmental risk factors play a minor role in primary NE, the rates of psychological disorders and stressful life events (e.g. parental separation) are increased in secondary NE [93, 94]. In DUI, especially in voiding postponement, psychosocial factors (comorbid externalising behaviour problems, rigid modes of family adaptability, etc.) are predominant [95]. Among all types of incontinence, psychological risk factors are highest in children with encopresis [13]. Difficult temperament and maternal depression/anxiety were found to be risk factor for incontinence [96].

Several studies have shown associations between ADHD, environmental adversity, parental mental illness and early attachment deficits (see [97]). Studies evaluating prenatal substance exposure (such as tobacco, alcohol, heroin) as risk factors for ADHD have shown divergent results [98].

Epigenetics

Studies on gene–environment interaction revealed an association between tobacco smoke exposure and executive function disorders in children with specific gene variants [99]. Children with specific gene variants in the DAT1, DRD4, CHRNA4, who experienced prenatal smoke exposure showed an increased risk of ADHD (e.g. [100–104]).

There exist no studies on epigenetics in children with incontinence.

Pharmacology

Stimulants

Stimulants are the most effective pharmacological treatment option for ADHD, leading to effect sizes up to 1.0 or more [2]. Stimulants do not have an anti-enuretic effect and are thus not indicated in children with NE without ADHD [105].

There are two small case series of children with ADHD and comorbid NE showing a resolution of NE with stimulant treatment. In the first series of three children and adolescents aged 9, 11 and 15 years, stimulant treatment of ADHD (methylphenidate HCl, dexmethylphenidate HCl, amphetamine–dextroamphetamine) was sufficient to resolve NE [106]. In two of the children, NE ceased immediately after taking stimulants. In the third, NE occurred only when the child did not take the medication. The authors hypothesised that stimulants might decrease the sleep arousal threshold, thus allowing the child to awaken. However, it is not clear if this result was due to possible pharmacological effects of the stimulants or to indirect, secondary effect such as increased compliance, self-esteem, and attention-span or positive interactions. In the case of a 7-year-old girl with ADHD, treatment with methylphenidate HCl resulted in a cessation of NE immediately, while she experienced only minimal improvement of ADHD symptoms and lost weight. For this reason, atomoxetine was prescribed instead of methylphenidate, resulting in a considerable improvement of ADHD symptoms. In addition, NE disappeared completely and occurred only when she had forgotten to take the medication [107].

Most children with dual diagnoses will need a more rigorous treatment for both their ADHD and incontinence. In a clinical sample of 75 children with ADHD (mean age 7.8 years), 60 were on medication for ADHD (unfortunately not specified), all had DUI, 87 % NE and 88 % frequency. Individualised treatment with behaviour modification, anticholinergics and biofeedback led to treatment success in 83.9 % of patients [18].

A rare form of DUI (giggle incontinence) is characterised by a complete bladder emptying evoked by laughing, but not by other forms of increased intraabdominal pressure as in stress incontinence. Due to the overlap with

cataplexy (which in turn is associated with narcolepsy), stimulant treatment was shown to be effective in case series. The doses required are much higher than in the treatment of ADHD: thus, 0.3–0.5 mg of methylphenidate (MPH) per kg bodyweight every 4–5 h during the day is prescribed. In addition, 5–20 mg of MPH is taken before engaging in social activities which might induce laughing. Despite these high doses, side effects were not typical and all children remained dry even 1–5 years later [108]. Of 15 patients with giggle incontinence (mean age 12.4 years), 80 % reported complete cessation of wetting on 0.2–0.5 mg/kg/day of MPH [109]. In the newest study, even low doses of MPH (only 5 mg/day) lead to continence in all nine females with giggle incontinence (mean age 16.2 years) [110]. Unfortunately, none of the studies reports if the children had comorbid ADHD or not.

In three case reports, the effects of methylphenidate on FI in children with ADHD were described [111, 112]. In the first report, the FI of one of the two boys (aged 9 and 10 years) stopped in the first week of MPH treatment, in the second boy FI was ameliorated within 3 weeks [112]. In the second case report, two boys (age 8 and 13 years) with ADHD and comorbid FI experienced a complete resolution of FI with MPH treatment. In one boy, ADHD symptoms decreased markedly with 27 mg MPH daily; in the second case, impulsivity and hyperactivity decreased with 20 mg MPH per day, but attention symptoms did not improve [111]. The third case report described a 12-year-old boy with FI and obsessive–compulsive disorder. With a combination of imipramine 25 mg/day and sertraline 25 mg/day the obsessive compulsive symptoms decreased, but FI was unchanged. After 1 year, treatment with imipramine and sertraline was discontinued. Although ADHD criteria were not met, treatment with methylphenidate (27 mg/day) was started based on study results showing the effectiveness of methylphenidate on FI in children with ADHD symptoms. Under MPH treatment FI disappeared [113].

Antidepressants

Tricyclic antidepressants (TCAs) are no longer indicated for the treatment of ADHD, but are known to have positive effects [114]. TCAs are third- or fourth-line treatment options reserved to children with treatment-resistant NE. Gepertz and Nevéus [115] reported that quite a few enuretic children report that they become calmer and more focused when taking the drug.

Other antidepressants such as reboxetine, a selective Noradrenaline reuptake inhibitor, has been shown to be effective in therapy-resistant NE. Similar to the positive side effects of imipramine [115], children were calmer and had less difficulty focusing under the treatment with reboxetine [116].

Treatment success of FI with sertraline was shown in a case report of an 11-year-old girl with ADHD and FI in an on–off–on treatment sequence. With sertraline (50 mg/d), frequency of FI decreased. Following discontinuation of sertraline after 45 days, FI recurred within 7 days. Hence, treatment with sertraline was restated and FI stopped immediately. No changes in ADHD were noticed [117].

Other medication

Desmopressin, which is the second-line treatment for NE, has hyperactivity as a rare side effect [118]. The Swedish Enuresis Trial, in which the long-term safety and efficacy of intranasal desmopressin treatment in 399 children (aged 6–12 years) with different forms of NE were evaluated, showed some psychological reactions such as nervousness (4 %) and aggressive reactions (4 %) as possible adverse events [119].

Anticholinergics such as oxybutynin, which are indicated in children with overactive bladder (urge incontinence) can evoke hyperactivity and attention problems comparable to ADHD as side effects [120].

Atomoxetine

Atomoxetine, a selective Noradrenaline reuptake inhibitor, is effective in the treatment of ADHD. In a first series of four cases, anti-enuretic effects could be demonstrated [121]. In a randomised-controlled trial of 87 children with NE (mean age 10.2 years), a reduction of wet nights could be achieved [122]. The doses of atomoxetine were increased from 0.5 mg/kg/day to 1.5 mg/kg/day. Dry nights per week increased by 1.47 in the atomoxetine—compared to 0.60 in the placebo group. There were no significant differences of adverse effects. The authors conclude that drugs with noradrenergic agonist effects may be useful in the treatment of NE. As mentioned above, in the case of a girl aged 7 years with ADHD, treatment with atomoxetine resolved NE [107]. Although the effects of atomoxetine is not sufficient to warrant a recommendation for the treatment of NE alone, it will most likely not aggravate, but will have a positive effect in a child with ADHD who is still affected by NE.

In a recent case series of children with ADHD and comorbid FI, two boys (aged 8 and 10 years) showed amelioration and cessation of FI under the treatment with atomoxetine (40 mg/day) [123].

In summary, these studies show that ADHD medication (such as MPH and atomoxetine) can have positive effects on the resolution of NE—and to a lesser degree on DUI and FI. On the other hand, NE medication such as desmopressin can aggravate ADHD symptoms, while TCAs can reduce hyperactivity and inattention. These studies are

mostly anecdotal reports or clinical series. It can therefore be speculated that, in addition to unspecific effects on motivation and compliance, dopaminergic (MPH) and noradrenergic (TCA, atomoxetine) neurotransmitter systems are involved in joint ADHD/NE diagnoses.

Consequences for clinical practice when children are affected by both disorders

In clinical practice, children with dual diagnoses of ADHD and NE are more difficult to treat. In a retrospective study, 113 children with ADHD and nocturnal enuresis had a far worse outcome on alarm treatment than controls (with nocturnal enuresis only): 43 % (vs. 69 %) were dry at 6 months and 19 % (vs. 66 %) at 12 months. There was no difference if they were treated with medication, which does not require active cooperation. Non-compliance was reported in 38 % of the children with ADHD, but only in 22 % of the controls [124]. Therefore, the comorbid diagnoses of both enuresis and ADHD require special treatment approaches—and both need to be dealt with separately.

In a retrospective analysis of 671 children with NE and/or DUI (mean age of 8.6 years), 130 had ADHD. Of these, 99 % had NE and 43 % DUI; additionally, 39 % had signs of frequency and 56 % urgency, indicative of overactive bladder. Patients were treated with desmopressin and anticholinergics. Those with ADHD had a worse outcome than those without, defined by a minimum of 3 consecutive months without wetting (vs. 61 %) [27].

With ADHD, treatment outcome is worse in DUI, as well. In a retrospective analysis, 68 % of day wetting children with DUI and ADHD became dry compared to 91 % of controls with DUI alone. Non-compliance was much higher for timed voiding [124].

Children with FI and behavioural maladjustment are also less compliant than children without psychological disorders (71 vs. 38 % were non-compliant) [125].

In summary, identification of ADHD in children with incontinence (and vice versa) is of great clinical relevance. When these disorders co-exist, both require evidence-based, symptom-oriented treatment. In mild to moderate cases, this can take place at the same time. In severe cases, ADHD needs to be tackled first to ensure sufficient compliance and cooperation for a successful incontinence treatment.

Conclusions

Children with incontinence have a higher risk of behavioural problems [13]. Although most studies have focused on the association between NE and ADHD, ADHD is much more common in children with DUI. ADHD is also one of many possible comorbid disorders in FI. In future research, more studies are needed to clarify the specific neurobiological associations of all types of incontinence and ADHD.

In clinical practice, children with all types of incontinence should be screened for psychological symptoms (especially ADHD) routinely [13] and vice versa [50]. Practical recommendations could be found in von Gontard et al. [13]. If incontinence and ADHD (or other psychological disorders) are present, treatment of both disorders is recommended, following evidence-based treatment guidelines.

Conflict of interest The authors have no conflicts of interest to declare.

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