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Enuresis, sleep and desmopressin treatment

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Aim: To detect effects of desmopressin on sleep in enuretic children and to look for polysomnographical differences between responders and non-responders to desmopressin treatment. *Methods:* Twenty-one children with primary nocturnal enuresis were examined polysomnographically before treatment. All but one of the children then received treatment with desmopressin in standard dosage, and the response was documented. Seven of the children underwent a second polysomnographic registration while on treatment. *Results:* The time interval (±1 SD) between sleep onset and the enuretic episode was 92 ± 67 min without medication and 372 ± 157 min when desmopressin was given ($p = 0.003$). Standard polysomnographic variables were not affected by the drug. Ten children were desmopressin responders and 10 were non-responders. The total sleep time was 455 ± 56 min in the former and 408 ± 31 min in the latter group ($p = 0.04$). The responders spent 27.4 ± 5.5% of their total sleep time in rapid eye movement sleep, compared with 18.2 ± 6.5% in the non-responder group ($p = 0.004$).

Conclusion: Desmopressin has no major effects on sleep as such but does delay bladder emptying. Enuretic children responding to desmopressin treatment have more rapid eye movement sleep than therapy-resistant children.

Key words: *Desmopressin enuresis, polysomnography, sleep*

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Enuresis is one of the most common nocturnal problems in childhood, with a prevalence of approximately 10% among 7-y-olds (1). There are several causes of enuresis, with high arousal thresholds (2), nocturnal polyuria (3) and nocturnal detrusor hyperactivity (4) playing major pathogenetic roles.

The vasopressin analogue desmopressin, one of the two principal antienuretic treatment modalities in use today (the other is the enuresis alarm treatment), has been shown to be beneficial for approximately two-thirds of patients (5). The reason for the therapeutic success of the drug is supposedly its antidiuretic properties (6). However, conflicting views have been expressed based on the clinical observation that a child with non-functioning renal vasopressin receptors still had a positive response to desmopressin treatment (7), and animal experiments have indicated the possibility that desmopressin may also possess central nervous system-stimulating properties (8). Unfortunately, despite the widespread use of desmopressin against enuresis—a problem occurring only during sleep—there has been almost no examination on its effects on sleep as such.

It is becoming increasingly clear that enuretic children who respond to desmopressin treatment differ from therapy-resistant children regarding both urine production and bladder function (9). It is not yet known whether the sleep of these two groups also differs.

Consequently, this study was performed with two aims in mind: first, to examine the effects of desmopressin medication on sleep, as monitored with standard polysomnography; and secondly, to look at polysomnographical differences between responders and non-responders to desmopressin antienuretic treatment. This study focused on desmopressin and sleep. Methodological data and comparisons with dry controls will be published separately.

Patients and methods

Twenty-one children (18M, 3F) aged 8–16 y (mean 11 y), suffering from severe primary nocturnal enuresis, were included. A detailed case history, with emphasis on micturition habits, was taken. To encourage compliance, the families were not required to measure fluid intake and output, or to fill in micturition diaries. All families stated that the children wet their beds during most nights, and that dry nights only occurred occasionally. None had any urological or neurological abnormality as a cause for their enuresis. The wetting was mainly nocturnal, although two children experi-

Table 1. Polysomnographic data comparison between recordings before and during desmopressin medication.

	Night without medication	Night with desmopressin	*p* (paired *t*-test)
Sleep latency (min)	13 ± 12	26 ± 22	0.23
REM latency (min)	130 ± 85	117 ± 40	0.74
Latency to NREM sleep stage 1 and 2 (min)	12 ± 13	27 ± 22	0.22
Latency to delta sleep (min)	23 ± 13	37 ± 22	0.19
Time in bed (min)	625 ± 132	568 ± 66	0.07
Sleep period time (min)	470 ± 52	477 ± 73	0.82
Total sleep time (min)	418 ± 33	457 ± 64	0.21
Sleep efficiency (%)[a]	89.6 ± 9.1	96.0 ± 1.9	0.10
No. of awakenings after sleep onset	27.3 ± 12.6	27.3 ± 12.4	1.00
Average duration of waking episodes (min)	1.9 ± 1.2	0.7 ± 0.2	0.03
Awake (%)[b]	10.4 ± 9.1	4.1 ± 2.0	0.11
REM sleep (%)[c]	17.6 ± 3.4	19.1 ± 5.2	0.51
NREM sleep stages 1 and 2 (%)[a]	36.0 ± 18.7	34.6 ± 10.4	0.78
Delta sleep (%)[c]	21.7 ± 9.5	25.6 ± 6.2	0.15
Movement episodes per night	273 ± 147	264 ± 135	0.87
Movement episodes per hour	27 ± 16	28 ± 12	0.92
Movement time in percentage of total sleep time (%)	4.1 ± 3.4	2.7 ± 1.7	0.28
Micturition latency (min)	92 ± 67	372 ± 157	0.003

Data are means ISD.
Only children who provided both kinds of recording are included.
[a] Percentage of sleep period time spent asleep.
[b] Percentage of sleep period time spent awake.
[c] Percentage of total sleep time spent in the sleep stages indicated.
REM: rapid eye movement; NREM: non-REM.

enced infrequent isolated episodes of daytime incontinence as well.

Polysomnographic investigations were performed in the patients' homes, using a portable system (SleepBox, Biosys AB) recording electroencephalography (EEG), submental electromyography (EMG), electrooculography (EOG) and finger pulse oximetry. Body movements were recorded using a sensor pad placed under the sheets. The signal from the pad was filtered and differentiated into body, respiratory and cardiac movements (ballistocardiography), allowing assessment of respiration and cardiac rate. Bedwetting episodes were documented with a urine detector connected to the sleepbox. Sleep analysis and scoring were done visually (20 s epoch length). All children drank 250 ml of water immediately before bedtime on the recording night, to achieve semi-standardized conditions without obliging the families to record fluid intake. No medication or other antienuretic treatment was allowed during the recording night. For three of the children EEG records were limited to the first 6–8 h of the night, owing to technical problems, although sleep staging could still be done for the whole recording time using data from the other channels, including the movement detector.

After this first polysomnographic investigation the children were offered treatment with desmopressin 0.2–0.4 mg once daily taken orally at bedtime; the higher dose was used if the response was insufficient on 0.2 mg. Seven patients (6M, 1F) underwent a second similar polysomnographic investigation after approximately 10 wk, while they were still taking desmopressin. Those children who were not re-examined either did not want to repeat the examination, had moved away from town or were presently dry without medication. The seven children examined twice thus constituted a selected subgroup and were not compared with the group as a whole.

One child did not want to take the medication and was not followed further. All the other children were treated for more than 3 m. If the child experienced a reduction in the bedwetting frequency of at least 50% he or she was considered a desmopressin responder (R), while the children with less favourable treatment results were defined as desmopressin non-responders (NR).

The study was approved by the university ethics committee and informed consent was obtained from all participating families.

Statistics

When comparing polysomnographic data from the recordings with and without medication, paired *t*-tests were used and only data from the seven children providing both kinds of recording were included. Children with partial and full desmopressin response were treated as one group in the comparisons, since there were very few full responders. Comparisons between R and NR to desmopressin medication were made using unpaired *t*-tests (or χ^2-tests in the case of dichotomized variables) and including data only from the recording without medication. The analyses were repeated with the polysomnograms with incomplete EEG data removed. A statistical significance level of 95% ($p < 0.05$) was chosen. Numbers shown are the mean ±1 SD unless otherwise stated.

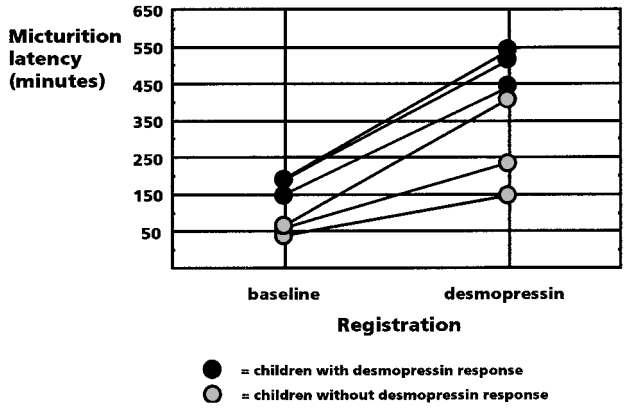

Fig. 1. Micturition latency before and during desmopressin medication.

Results

Of the 20 children taking desmopressin 10 were R and 10 were NR. It should be noted, however, that the R consisted mostly of partial responders: only three children stated that they never experienced wet nights when taking the drug. Of the two children with minor daytime incontinence, one belonged to each group. Eight children experienced daytime urgency symptoms; two of these were R. One child, belonging to the R group, exhibited sleep apnoeas and snoring. Three of the seven children with two recordings were R. The families of the NR families all stated that their child experienced no reduction in the number of wet nights when given desmopressin.

Five children were dry during the first recording night, whereas the remaining 16 wet their beds. Bedwetting occurred during the second recording night for six of seven children. The dry child belonged to the R.

Polysomnographic data compared between recordings with and without desmopressin medication are shown in Table 1. The only differences that showed statistical significance were the average duration of nocturnal waking episodes, which decreased slightly during medication nights, and micturition latency (i.e. the time elapsed between falling asleep and wetting the bed), which was much greater when desmopressin was given. The micturition latency of the children who were recorded with and without medication is further illustrated in Fig. 1, where the values of individual patients can be discerned.

Some tendencies that did not reach statistical significance could also be noted: the sleep recordings while the child was on medication showed a shorter time spent in bed but a longer total sleep time and a better sleep efficiency. Delta sleep was increased and body movement time as a percentage of total sleep time was decreased during medication.

Comparisons between the R and NR groups are depicted in Table 2. The NR children were found to spend somewhat less of their time in bed asleep than the R. In addition, the NR tended to fall asleep later, although they were not slower to reach delta sleep. The micturition latency was usually shorter in the NR group.

The most striking difference was that the R group was

Table 2. Polysomnographic data: comparison between responders and non-responders to desmopressin treatment.

	Desmopressin responders		Desmopressin non-responders		
	n		*n*		*p* (unpaired *t*-test)
Age (y)	10	11.9 ± 2.4	10	11.1 ± 1.9	0.42
Sleep latency (min)	10	12 ± 16	10	19 ± 16	0.27
REM latency (min)	10	129 ± 71	10	101 ± 47	0.46
Latency to NREM sleep stage 1 and 2 (min)	10	8 ± 9	10	18 ± 15	0.08
Latency to delta sleep (min)	10	29 ± 17	10	32 ± 11	0.61
Time in bed (min)	10	581 ± 94	10	573 ± 97	0.85
Sleep period time (min)	10	509 ± 46	9	454 ± 48	0.02
Total sleep time (min)	10	455 ± 56	9	408 ± 31	0.04
Sleep efficiency (%)[a]	10	90 ± 7.6	9	90 ± 4.7	0.86
No. of awakenings after sleep onset	10	31 ± 7.1	9	26 ± 13.6	0.30
Average duration of waking episodes (min)	10	1.7 ± 1.0	9	1.9 ± 1.0	0.72
Awake (%)[b]	10	10.4 ± 7.6	9	9.9 ± 4.7	0.86
REM sleep (%)[c]	10	27.4 ± 5.5	9	18.2 ± 6.5	0.004
NREM sleep stages 1 and 2 (%)[c]	10	42.5 ± 4.1	9	54.8 ± 16.9	0.04
Delta sleep (%)[c]	10	28.7 ± 6.1	9	30.8 ± 13.4	0.66
Movement episodes per night	10	291 ± 118	10	299 ± 190	0.91
Movement episodes per hour	10	31 ± 13	10	32 ± 21	0.85
Movement time in percentage of total sleep time (%)	10	4.2 ± 2.7	10	3.1 ± 2.0	0.32
Micturition latency (min)	7	241 ± 121	8	120 ± 115	0.06

Data are means ± SD.
[a] Percentage of sleep period time spent asleep.
[b] Percentage of sleep period time spent awake.
[c] Percentage of total sleep time spent in the sleep stages indicated.

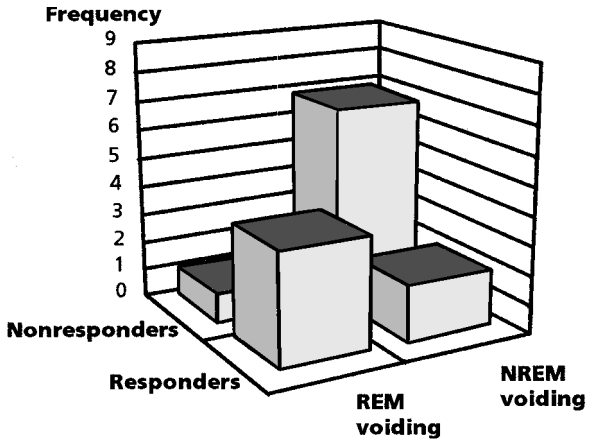

Fig. 2. Occurrence of micturition in responders and non-responders to desmopressin. REM: rapid eye movement sleep; NREM: non-REM sleep.

characterised by a clearly increased percentage of rapid eye movement (REM) sleep, as well as a slightly decreased percentage of non-REM (NREM) sleep, compared with therapy-resistant children. When repeating the analysis with the three children with full desmopressin response as a separate group the differences remained, and the partial responders fell into an intermediate group regarding REM sleep percentage. (The REM sleep percentages of the full responders were 32, 33 and 35%.)

When looking at the sleep stage at micturition it was found that the R were significantly more likely to void during REM sleep than the NR ($\chi^2 = 4.38$, $p = 0.04$) (Fig. 2).

All of the above comparisons were also made after removing the recordings with incomplete EEG data and the recording of the child with sleep apnoeas, but the results were similar and are thus not shown here.

Discussion

Except for the examination of adults with enuresis by Hunsballe (10), to the authors' knowledge this is the first examination of the effects of desmopressin on sleep. The number of children investigated is limited and the results must be interpreted cautiously. There was a slight tendency, although not statistically significant, towards increased sleep efficiency and shorter duration of nocturnal waking episodes when the children were given desmopressin. If the view that desmopressin prevents enuresis via central nervous effects were true the opposite tendency would be expected. The minor polysomnographic differences between the two sleep recording nights may reflect the patients' adaptation to the recording equipment, i.e. "first night effects", although such effects are not pronounced in ambulatory home recodings (11). Central action is rendered still more unlikely by the fact that desmopressin does not cross the blood–brain barrier (12), although peripheral administration of the drug has been shown to increase locomotor activity in rats, supposedly via enhanced dopaminergic neurotransmission (8, 13), and desmopressin-responding enuretic children without any renal effects of the drug have been described (7). The last word has probably not been heard on this matter.

The only clear effect of desmopressin treatment found in this study was that the enuretic episode was delayed. This seems logical, given the drug's antidiuretic properties. The study on therapy-resistant enuretic children by Nevéus et al. (14) is the only previous examination of the effects of desmopressin on the micturition latency. In contrast to the present findings, the enuretic episode was not delayed by desmopressin administration in that study, even though the dosage was increased to 0.8 mg and the micturition latency was examined over several nights. These conflicting results may be explained by two differences between the studies. First, in the present study all children were given extra fluid before going to bed; this would result in extra diuresis during the early part of the night: diuresis that would easily be delayed by concomitant desmopressin medication. Secondly, all children in the earlier study were non-responders to desmopressin treatment (this was part of the inclusion criteria), whereas in the present work more than half of the children were at least partially responsive to the drug. Nocturnal polyuria is a characteristic of desmopressin responders (9). The findings in the work by Hunsballe (10) were largely in accordance with the present results.

An intriguing finding was the higher REM sleep percentage of the desmopressin responders, compared with the therapy-resistant children. This difference was not affected by excluding the children with intermediate desmopressin response, who seem to belong to an intermediate group in this respect. This difference in REM sleep propensity may be caused by differences in vasopressin secretion. Vasopressin in physiological concentrations has been shown to suppress REM sleep in healthy volunteers (15). The vasopressin deficiency that has been demonstrated in enuretic children with polyuria (3) may thus quite neatly explain the increased REM sleep of the R group, since these are the children most likely to have vasopressin deficiency. The failure of desmopressin treatment to suppress REM sleep is not surprising given that the drug, in contrast to vasopressin, does not bind to V1 receptors and does not cross the blood–brain barrier (12). In a recent polysomnographic study, enuretic children were found to spend a surprisingly small part of their night in REM sleep (16). Since mostly therapy-resistant children were included, this fits well with the results of the present study.

It was also found that therapy-resistant children were more likely to void during NREM sleep than the R

group. This difference may at least partly be explained simply by the decreased NREM sleep percentage of these children, and by their tendency to void earlier during the night when NREM sleep predominates. This tendency for early micturition among the NR may reflect differences in pathogenesis: a voiding that is triggered only by bladder filling would probably tend to occur later than a voiding that is also dependent on a hyperactive detrusor.

It has recently become increasingly clear that enuresis is a heterogeneous entity and that the subdivision according to desmopressin response into diuresis-dependent enuresis (desmopressin responders) and detrusor-dependent enuresis (non-responders to desmopressin) is clinically and pathogenetically relevant (9). Urine production and bladder function have been found to differ between these two subgroups. The results of this study provide the first evidence that they also differ regarding sleep mechanisms. This underlines the importance that in future enuresis research the participating subjects should be carefully described and, ideally, subdivided according to treatment response. A greater awareness of the pathogenetic and clinical heterogeneity among enuretic children will reduce the confusion and discord among researchers and lead to individualized and more effective treatment strategies for the children.

In conclusion, desmopressin medication delays nocturnal micturition in enuretic children but does not influence sleep per se. The antienuretic effects of desmopressin probably reside in its antidiuretic properties. Desmopressin-responding children exhibit more REM sleep than therapy-resistant children.

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References

1. Hellström A, Hansson E, Hansson S, Hjälmås K, Jodal U. Incontinence and micturition habits in 7-year-old Swedish school entrants. Eur J Pediatr 1990; 149: 434–7
2. Wolfish NM, Pivik RT, Busby KA. Elevated sleep arousal thresholds in enuretic boys: clinical implications. Acta Paediatr 1997; 86: 381–4
3. Rittig S, Knudsen UB, Nørgaard JP, Pedersen EB, Djurhuus JC. Abnormal diurnal rhythm of plasma vasopressin and urinary output in patients with enuresis. Am J Physiol 1989; 256: F664–71
4. Yeung CK, Chiu HN, Sit FK. Bladder dysfunction in children with refractory monosymptomatic primary nocturnal enuresis. J Urol 1999; 162: 1049–54, 1054–5
5. Chiozza ML, del Gado R, di Toro R, Ferrara P, Fois A, Giorgi P, et al. Italian multicentre open trial on DDAVP spray in nocturnal enuresis. Scand J Urol Nephrol 1999; 33: 42–8
6. Nørgaard JP, Rittig S, Djurhuus JC. Nocturnal enuresis: an approach to treatment based on pathogenesis. J Pediatr 1989; 114 Suppl: 705–10
7. Jonat S, Santer R, Schneppenheim R, Obser T, Eggert P. Effect of DDAVP on nocturnal enuresis in a patient with nephrogenic diabetes insipidus. Arch Dis Child 1999; 81: 57–9
8. DiMichele S, Sillén U, Engel JA, Hjälmås K, Rubenson A, Söderpalm B. Desmopressin and vasopressin increase locomotor activity in the rat via a central mechanism: implications for nocturnal enuresis. J Urol 1996; 156: 1164–8
9. Nevéus T, Tuvemo T, Läckgren G, Stenberg A. Bladder capacity and renal concentrating ability in enuresis—pathogenic implications. J Urol 2001; 165: 2022–5
10. Hunsballe JM. Increased delta component in computerized sleep electroencephalographic analysis suggests abnormally deep sleep in primary monosymptomatic nocturnal enuresis. Scand J Urol Nephrol 2000; 34(5): 294–302
11. Sharpley AL, Solomon RA, Cowen PC. Evaluation of first night effect using ambulatory monitoring and automatic sleep stage analysis. Sleep 1988; 11: 273–6
12. Ang VTY, Jenkins JS. Blood–cerebrospinal fluid barrier to arginine-vasopressin, desmopressin and desglycinamide arginine-vasopressin in the dog. J Endocrinol 1982; 93: 319–25
13. Di Michele S, Ericsson M, Sillén U, Engel JA, Söderpalm B. The role of catecholamines in desmopressin induced locomotor stimulation. J Neural Transm 1998; 105: 1103–15
14. Nevéus T, Läckgren G, Tuvemo T, Olsson U, Stenberg A. Desmopressin-resistant enuresis: pathogenetic and therapeutic considerations. J Urol 1999; 162: 2136–40
15. Born J, Kellner C, Uthgenannt D, Kern W, Fehm HL. Vasopressin regulates human sleep by reducing rapid-eye-movement sleep. Am J Physiol 1992; 262: E295–300
16. Nevéus T, Stenberg A, Läckgren G, Tuvemo T, Hetta J. Sleep of children with enuresis: a polysomnographic study. Pediatrics 1999; 106: 1193–7

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