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The influence of urine osmolality and other easily detected parameters on the response to desmopressin in the management of monosymptomatic nocturnal enuresis in children

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Aim. **The aim of this paper was to examine the early morning spot urine osmolality and some other parameters easily detected from home chart recordings and history as predictive of the therapeutic response to desmopressin in children with monosymptomatic nocturnal enuresis.**

Methods. **Sixty seven monosymptomatic nocturnal enuretic children were included in the study. Age, sex, family history, the number of family members and siblings, existence of urgency symptoms, the history of urinary tract infection, sleep patterns, the number of wet nights per month and bedwetting in the same night were recorded. Additionally, spot morning urine osmolality was examined. All children were given desmopressin for at least 2 months. At the end of the treatment period, patients considered as responders and non-responders were compared in all these parameters.**

Results. **Although there was considerable overlap between groups, lower spot urine osmolality was the only data we found statistically significant as predictive of response to desmopressin. Moreover, male predominance, fewer wet nights per month and bedwetting per night were also associated with a better response.**

Conclusion. **We believe that it is important to characterize such different subgroups that could be used as predictors of a good response to desmopressin.**

Key words: **Child - Enuresis - Desmopressin.**

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Monosymptomatic nocturnal enuresis (MNE) is defined as urine emission during sleep in children older than 5 years, at which age bladder control should have been achieved.[1] MNE is a common problem and, due to its social consequences, many studies have been carried out about the etiology and treatment of this problem. Three of the many causes including nocturnal polyuria, nocturnal detrusor hyperactivity and abnormally deep sleep have been supported by reasonably firm evidence.[2] The finding of insufficient nocturnal vasopressin release, resulting in an increased urine volume which exceeds bladder capacity, has led to the application of desmopressin in the therapy of MNE in children.[3, 4]

Desmopressin, that has been used to treat cranial diabetes insipidus for many years with excellent safety and minimal side-effects, is an analog of the neurohypophyseal hormone arginine vasopressin, exerting antidiuretic effects through receptors on the kidney collecting ducts.[5] Dimson [6] first reported its use in the treatment of enuresis in 1977 and since then it has become a well-established ad-

dition to the treatment options for MNE in children. However, given an enuresis prevalence among 8-year-olds of 7% and the treatment success rate of 60% to 70%, it is clear that there is still a large number of children to whom effective treatment cannot be offered and it still remains unclear which patients are most likely to benefit from desmopressin treatment.

In this study, we aimed to identify a cost effective method of predicting a therapeutic response to desmopressin treatment by determining early morning spot urine osmolality and some other parameters easily detected from home chart recordings and history which are completely noninvasive for children.

Material and methods

Sixty-seven nocturnal enuretic children of at least 6 years old and completely continent during the day were included in the study by one department. No children with urological and neurological abnormalities were included in our analysis.

In the first visit, a detailed history was taken for each case and the children's health was confirmed by a complete physical examination including urine analysis. Based on the history, the age, sex, family history, the number of family members and siblings, the existence of urgency symptoms and the history of urinary tract infection were recorded. Then, a 4-week observation period without any intervention was started. The family kept a diary (home chart recording) for the number of wet nights and number of bedwettings each night for a month. If the child sleeps in the bed until awakened, the child is accepted as a deep sleeper.[7] The family reported and also asked to reveal this during the 4-week observation period.

In the second visit, the number of wet nights per month, number of bedwettings in the same night and the sleep pattern were determined from the home chart recording. Additionally, spot morning urine osmolality determination was carried out in each case of study group, if the child was not wet in the night before examination morning. All children were given a desmopressin dose of a maximum 40 μg for at least 2 months. At the end of the treatment period, patients whose wet nights decreased by 80% compared with baseline were considered responders (Group 1) and otherwise as non-responders (Group 2) to desmopressin.[1]

To examine the differences in groups of responders and non-responders, we subdivided groups into subgroups by the number of family members (less or more than 5), siblings (less or more than 1), wet nights in a month (more or less than 20), bedwetting in a single night (more or less than 1). Children in each group were compared in all the above parameters.

Statistical analysis

SPSS (statistical package for social sciences) for windows 10.0 software package was used for the statistical analysis when the results were being evaluated. During the evaluation of the study data, along with the descriptive statistical methods, parameters without normal distribution (median age among the groups) were evaluated using Kruskall Wallis analysis. The qualitative data were evaluated using χ^2 test. Significance was accepted as $p \leq 0.05$ level.

Results

Urine osmolality was found to be higher than 800 mOsm/kg in 15 (22.38%), and lower than 800 mOsm/kg in 52 (77.62%) children. No significant difference was noted for responders and non-responders of mean age 10.47 and 9.84, respectively. The responses in the high osmolality group and low osmolality group were revealed as responders in 8 (53.3%) and 39 (75%), non-responders in 7 (46.7%) and 13 (25%) respectively (Figure 1). When we compared group 1 and group 2 on the basis of spot urine osmolality <800, we found a statistically significant difference (Table I).

In our study 47 of 67 children (70.1%) were boys. When we examined male predomi-

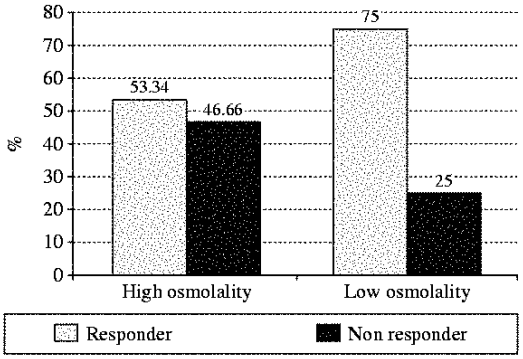

Figure 1.—The percentage of responders and non-responders to desmopressin treatment in low and high osmolality groups (< or > 800 mOsm/kg).

nance as a predictive factor between responders and non-responders, it was 76.5% and 55% respectively. Even though the difference was not significant statistically the p value (0.077) was one of the lowest (Table I). In subgroups of responders and non responders created by urine osmolality, we did not find any obvious difference in response to desmopressin between boys and girls (Table II).

In the present study, a positive family history in first degree relatives was found in 63 % of all children with MNE, 61.7 % for responders and 65 %for non-responders. The difference was not statistically significant.

In families of more than 5 persons living in the same house, the response to desmopressin was found to be lower (Table I). This was statistically significant in the low osmolality group with 16.7 % responders and 50% non reponders (p=0.049) (Table II). Even though no statistical difference was detected, the smaller number of siblings was associated with slightly better response to desmopressin in groups.

The children who did not respond to desmopressin had the most wet nights during the observation period in our study; 95% of non responders had more than 20 wet nights in 1 month (Table I). All of the children in the low osmolality non-responder group were found wet more than 20 nights per month (Table II). Also, the number of bedwettings in one night was observed to

TABELLA I. — *Vie anatomiche del dolore nelle lombosciatalgie.*

	Grou5p 1 Responder n. 47	Group 2 Non-responder n. 20	P values
Osmolality <800	39* 82.9%	13* 65%	P=0.043*
Male predominance	36 76.5%	11 55%	P=0.077
Mean age	10.47±2.95	9.84±2.65	p>0.05
Positive family history	29 61.7%	13 65%	p=0.798
Number of siblings <1	27/38 71%	12/15 80%	p=0.650
Number of family members ? 5	8/38 21%	5/15 33.3%	p=0.609
More than 20 wet nights per month	38 80.8%	19 95%	p=0.137
More than 1 bedwetting in the same night	24/32 75%	16/18 88%	p=0.239
Deep sleep pattern	33 70.2%	13 65%	p=0.674
Positive urge symptoms	7 14.8%	4 20%	p=0.606
Positive history of urinary tract infection	7 14.8%	3 15%	p=0.991

be higher in the non-responder group (Table I). However, these differences were not found to be statistically different.

No difference was found within or among groups regarding urge symptoms, urinary tract infection. The results were very close to those of the subgroups in all these parameters.

Discussion

Since the abnormality of the diurnal rhythm of vasopressin with insufficient nocturnal elevation in plasma increases nocturnal urine production and reduces urine osmolality in some enuretics compared to controls, the investigation of urine osmolality during the night could be a starting point for determining which children are most likely to benefit from desmopressin treatment. We observed better responses in the low osmolality group compared to the high osmolality group. Moreover, the responses in the higher group were also considerable in the success of de-

TABLE II.—*Differences in subgroups based on osmolality. †: statistically significant, p<0.05.*

	High osmolality group (spot urine osmolality >800) No.=15		Low osmolality (spot urine osmolality <800) No.=52	
	Responder No.=8	Nonresponder No.=7	Responder No.=39	Nonresponder No.=13
Sex				
Male	7	4	29	7
	87.5%	57.1%	74.3%	53.8%
Female	1	3	10	5
	12.5%	42.9%	25.7%	46.2%
Age	9±2.2	10±4.28	10.48±2.85	10.16±2.58
Family history	7	5	22	8
	87.5%	71%	56%	61.5%
Number of siblings				
1	3†	7†	24/30	5/8
	37.5%	100%	80%	62.5%
>2	5	0	6/30	3/8
	62.5%		20%	37.5%
Number of Family members				
5	5	6	25/30	4/8
	62.5%	85.7%	83.3%	50%
> 5	3	1	5/30†	4/8†
	37.5%	14.3%	16.7%	50%
Number of wet nights per month				
> 20	6	6	32	13
	75%	86%	82%	100%
< 20	2	1	7	0
	25 %	14 %	18 %	
Number of bedwettings in the same night				
1	3/7†	1	5/25	1/11
	43%	14%	20%	9%
>1	4/7†	6	20/25	10/11
	57%	86%	80%	91%
Sleep pattern				
Normal	1	3	13	4
	12.5%	43%	34%	31%
deep	7	4	26	9
	87.5%	57%	66%	69%
Urge symptoms	3	1	4	3
	37.5%	14 %	10 %	23 %
Urinary tract infection	0	1	6	2
		14 %	15 %	15.5 %

smopressin therapy. The results in previous studies have been conflicting since in some studies desmopressin responders had lower osmolality than non-responders but in most studies no differences were observed.[7-12]

The genetics of NE have been studied by formal genetic methods since the 1930s and it is well demonstrated that there is a significant prevalence of a positive family story in NE patients.[12] In our study, the highest (87.5%) positive family history rate was detected in the high osmolality responder group and the lowest (56%) in the low osmolality responder group (p=0.130). But the difference in the low osmolality group between responders and non responders was not noteworthy. In the study of Hogg and Hussman [13] a poor response was detected in patients with no family history, but many others found no correlation, as in like our study.[14] The failure of a positive family history to predict a good response to desmopressin may lead us to conclude that the only important inherited factor is not a lack of the circadian rhythm of vasopressin.

It is not just genetic factors that are important in the etiology of NE, the psychosocial environment also has a major modulatory effect. A higher prevalence of enuresis among children of larger families was the most substantial of the factors related to the social environment.[15] This was also found to be statistically significant in the low osmolality group in our study.

In 1952, Poulton first reported relative nocturnal polyuria in 69 % of children complaining of MNE.[16] These observations have been confirmed several times since and nocturnal polyuria is now one of the important accepted causes of MNE.[7] Thus, our study also confirms earlier studies that a good response to desmopressin is associated with fewer wet nights per month.[17] Even though differences in these parameters related to night time polyuria could not be detected statistically in our study, we want to point out that we found 95% of non responders and 80.8% of responders had more than 20 wet nights per month.

Finally, we also want to mention that the highest (87.5%) deep sleep pattern was detected in the high osmolality responder group in which a positive family history was also highest (87.5%). Deep sleep pattern is more likely to be hereditary than polyuria. On the other hand, this finding may also agree with the finding of Eggert *et al.*[18] that desmopressin has an influence on the arousability of children with primary nocturnal enuresis.

We believe that it is advantageous to characterize such different subgroups by specific features that could be used as predictors of a positive treatment outcome of NE. Although there is a considerable overlap between groups, spot urine osmolality was the only data we found to be statistically significant as predictive of a response to desmopressin in this study. If we consider low osmolality to be a predictive factor and compare responders and non-responders in this group only, a low number of family member was found to be associated with a statistically significant better response. Male predominance is also associated with better response, but the finding is not statistically significant. High numbers of wet nights and bedwetting on the same night and family history are associated with a worse response in the low osmolality group.

An important limitation of our study was the small number of children in some subgroups which makes statistical analysis hard. We were unable to prove statistically significant percentage differences with this limitation. For the future, more studies are needed to identify the factors which have an influence on the response to desmopressin treatment, particularly with larger numbers of children.

Riassunto

Influenza dell'osmolalità urinaria e di altri parametri facilmente rilevabili sulla risposta ala desmopressina nella gestione dell'enuresi notturna monosintomatica infantile

Obiettivo. L'obiettivo di questo lavoro è stato esaminare l'osmolalità urinaria nelle prime ore del mattino e di valutare alcuni altri parametri facilmente rilevabili da diari e dall'anamnesi, per avere un valore predittivo della risposta terapeutica alla desmopressina in bambini con enuresi notturna monosintomatica.

Metodi. Nello studio sono stati valutati 67 bambini con enuresi notturna monosintomatica. Sono stati considerati l'età, il sesso, la familiarità, il numero di membri della famiglia e di fratelli/sorelle, la presenza di sintomi di urgenza alla minzione, la presenza di infezioni delle vie urinarie, gli aspetti relativi al sonno, il numero di notti/mese nelle quali il bambino è stato enurico e quanti episodi di enuresi nella stessa notte si sono verificati. Inoltre, è stata esaminata l'osmolalità urinaria nelle prime ore del mattino. A tutti i bambini è stata somministrata desmopressina per almeno 2 mesi. Alla fine del periodo di trattamento, la risposta a quest'ultimo è stata giudicata sulla base di tutti questi parametri.

Risultati. Sebbene vi sia stata una notevole sovrapposizione tra i gruppi, la minore osmolalità urinaria è stato l'unico dato che si è dimostrato statisticamente significativo quale fattore predittivo della risposta alla desmopressina. Altri fattori associati alla miglior risposta sono stati il sesso maschile, il minor numero di enuresi notturne al mese e il minor numero di enuresi per singola notte.

Conclusioni. Crediamo che sia importante caratterizzare tali diversi sottogruppi, che potrebbero essere utilizzati per predire una buona risposta alla desmopressina.

Parole chiave: Età pediatrica - Enuresi - Desmopressina.

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