Journal of Pediatric Urology (xxxx) xxx xxx

The value of case history and early treatment data as predictors of enuresis alarm therapy response

Jens Larsson [a], Malin Borgström [b,c], Birgitta Karanikas [c], Tryggve Nevéus [c,*]

[a]Urotherapy Unit, Section for Pediatric Surgery, Skåne University Hospital, 22185, Lund, Sweden

[b]Center for Clinical Research Dalarna, 791 82, Falun, Sweden

[c]Dept of Women's and Children's Health, Uppsala University, 75185, Uppsala, Sweden

* Correspondence to:
T. Nevéus, Dept of Women's and Children's Health Uppsala University Children's hospital 751 85 Uppsala, Sweden,
Tell.: +46(0)70 6001301
jens.larsson@skane.se (J. Larsson)
malin.borgstrom@region-dalarna.se (M. Borgström)
birgitta.karanikas@gmail.com (B. Karanikas)
tryggve.neveus@kbh.uu.se (T. Nevéus)

Keywords
Nocturnal enuresis; Enuresis alarm treatment; Adherence; Children

Received 10 August 2022
Revised 14 September 2022
Accepted 8 November 2022
Available online xxx

Summary

Background and aim
Two central problems with the enuresis alarm are the family workload and the lack of predictors of therapy response. We wanted to look at predictors of alarm response in a setting reflecting clinical reality.

Methods
An alarm linked to a smartphone app was provided to enuretic children managed at pediatric outpatient wards. Baseline data (sex, age, daytime incontinence, urgency, previous therapies, arousal thresholds and baseline enuresis frequency) were recorded. Further information, such as enuretic episodes and actual alarm use, was gathered via the app during therapy. Therapy was given for 8–12 weeks or until 14 consecutive dry nights had been achieved.

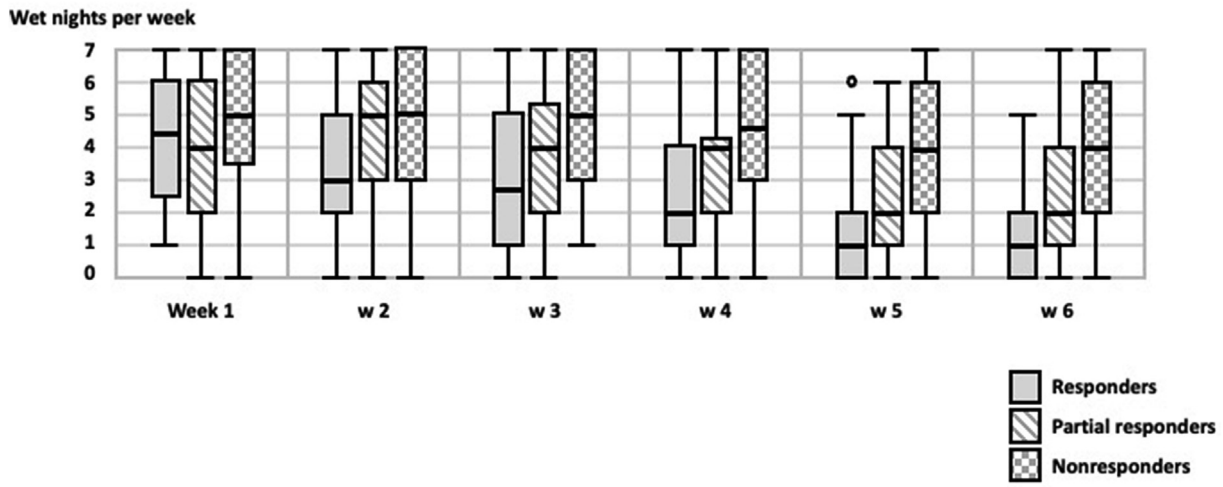
Results
For the 196 recruited children the outcome was as follows: full responders (FR) 18.4%, partial responders (PR) 20.4%, nonresponders (NR) 22.4% and dropouts 38.8%. We found no clear predictors of response or adherence among baseline data. But as treatment progressed responders reduced their enuresis frequency as compared to NR (week two $P = 0.003$, week three and onwards $P < 0.001$). This is further illustrated in the Figure below. Furthermore, the children unable to complete the full treatment had more non-registered nights already from the second week (week two $P = 0.005$, week three $P = 0.002$ and so on).

Discussion
Anamnestic data give little predictive information regarding enuresis alarm response or adherence. Contrary to common belief neither daytime incontinence nor previous alarm attempts influenced treatment success. But after 2–4 weeks of therapy the children with a good chance of treatment success could be discerned by decreasing enuresis frequency, and the families that would not be able to comply with the full treatment showed incomplete adherence already during the first weeks.

Conclusions
Maybe the enuresis alarm strategy should be changed so that the treatment is reassessed after one month and only children with a high chance of success continue. This way, unnecessary frustration for the families of therapy-resistant children may be reduced.

https://doi.org/10.1016/j.jpurol.2022.11.003

Please cite this article as: Larsson J et al., The value of case history and early treatment data as predictors of enuresis alarm therapy response, Journal of Pediatric Urology, https://doi.org/10.1016/j.jpurol.2022.11.003



Summary Figure Numbers of wet nights per week during the first four weeks of therapy, subdivided according to treatment response.

Introduction

The enuresis alarm is an established first-line treatment of enuresis [1]. The mechanism of the therapeutic action of the device is somewhat unclear but it can be assumed to influence sleep and arousal mechanisms. The main asset of the enuresis alarm, as compared to pharmacological alternatives, is that it is more often curative [2—5]. Response rates differ greatly between studies but often approach 80% [3,5—8] but a problem here is that the nature of the therapy makes placebo-controlled studies impossible. And in no study has adherence to the treatment been assessed by any other means than parental self-report.

There are several drawbacks with the enuresis alarm. First, the workload and social disruption imposed on the family are considerable [4]—the guardians must be prepared to wake the child every night and the child must expect to use the alarm for at least 6—8 weeks without interruption [1,9]. Consequently, adherence to treatment is a problem [8], especially if the child has psychological issues [10]. Another drawback is the relative lack of predictors to enuresis alarm success. Some studies indicate infrequent enuresis to be predictive of poor response [11], but other anamnestic and voiding chart data have not so far been found to give any clear predictive information. This is extra problematic for the therapy-resistant children (and their families) who need to work hard for two months only to find that their work and commitment was to no avail.

Our aim was to look for readily available predictors of therapeutic response, as well as therapy adherence, to enuresis alarm therapy, in a real-life sample using a device linked to a smartphone application that records the actual enuresis events. In order to maximize recruitment and get as close as possible to a real-world sample of children with enuresis seeking help for the first time we chose not to include voiding charts or bowel diaries in the evaluation of the children. While doing this, we also took the opportunity of looking at the predictive value of the enuresis latency, i.e., the time elapsed between bedtime and the (first) enuresis event.

Subjects and methods

This was a multi-center study involving nine pediatric outpatient wards in Sweden. All children with enuresis without warning signs suggesting urinary tract infection, urological malformation or other underlying disorders were invited to participate.

The families were provided with a body-worn alarm produced by Pjama Inc (Malmö, Sweden) wirelessly attached to an application that was either downloaded to a parent's smartphone or a tablet that the families borrowed free of charge. When downloading the application, the guardian was asked to provide the following information about the child: age, sex, usual enuresis frequency (wet nights per week), perceived arousal thresholds (low/medium/high/almost impossible to wake up/don't know), urgency (yes/no), daytime incontinence (yes/no), previous alarm use (yes/no), previous desmopressin use (yes/no). During treatment the parent recorded the time when the child went to bed and the device was activated, while the enuretic event was automatically recorded by the application. The enuresis latency was calculated by the application. The parents were asked to indicate in the morning whether the child had awoken by itself to the sound of the alarm or needed parental help, as well as whether (on dry nights) there had been nocturia.

The families were given the following instructions in accordance with international guidelines [1]:

- The parent/guardian should help the child to wake up by the alarm;
- The alarm should only be allowed to go off once per night;
- The alarm should be used continuously (every night) for at least 8 weeks or until 14 consecutive dry nights had been achieved;
- If the child, after 8 weeks, was not completely dry but had experienced a substantial improvement, treatment should continue for four more weeks.

Please cite this article as: Larsson J et al., The value of case history and early treatment data as predictors of enuresis alarm therapy response, Journal of Pediatric Urology, https://doi.org/10.1016/j.jpurol.2022.11.003

Table 1 Baseline characteristics of the patients.

Concomitant daytime incontinence	33/196 (16.8%)
Urgency symptoms	94/196 (48.0%)
Previous alarm treatment	67/196 (34.2%)
Previous desmopressin therapy	129/196 (65.8%)
Difficult or almost impossible to arouse from sleep	127/186 (64.8%)
Baseline wet nights per week	Range 1–7; 5.4 ± 1.8

Table 2 Final outcome.

	Final response	
Full response (100% enuresis reduction)	36 (18.4%)	76 (63.3%)
Partial response (≥50% enuresis reduction	40 (20.4%)	
Nonresponse (<50% enuresis reduction)	44 (22.4%)	44 (36.7%)
Dropout	76 (38.8%)	
Total	196	120

The nurse contacted the family after 2–3 weeks of treatment in order to give encouragement and advice, and again at the end of treatment.

Statistics

Response to therapy, for children completing the full treatment, was determined by comparing the last and the first two weeks of treatment (extrapolating in case of nonregistered nights) and expressed as the percentage reduction of wet nights.

Response was also grouped according to the ICCS definitions [12] into full responders, i.e., 100% enuresis reduction; partial responders, ≥50% enuresis reduction; and nonresponders (<50% enuresis reduction).

Please note that for families that, in spite of the instructions, chose to continue therapy beyond 12 weeks or after 14 consecutive dry nights had been achieved, we still determined response by comparing the last and first two weeks of therapy, since this gave a truer picture of the actual effect of treatment.

When looking for predictors of treatment response the full and partial responders were compared with the nonresponders. All the background information and data acquired during treatment, listed above, were included in the analyses. The following data were recorded for every week during treatment: adherence (recorded nights per week), enuresis frequency (wet nights per week, adjusted for adherence), average enuresis latency, proportion of wet nights when the child awoke by themselves to the alarm, nocturia. At the end of therapy, the following extra data were gathered, in addition to treatment response: length of treatment, overall adherence. Predictors of treatment adherence or nonadherence were made in an analogous fashion. T-tests or nonparametric alternatives were used, depending on the distribution of the data. Dichotomized data were compared using Chi-2 tests. A statistical significance level of 95% ($P < 0.05$) was chosen.

Ethics

The study was approved by the Swedish Regional Ethics Authority (2021-00206) and was performed according to the Helsinki Declaration. The use of the data entered by the patients' guardians in the application was cleared according to the General Data Protection Regulation. Only the patients' treating nurse had access to the identities and patient files.

The alarm unit, including the application, was provided by Pjama® Inc. The researchers did not receive any compensation from the company and none of the researchers have any economic interest in the company.

Results

The population

In total, 196 children were recruited. Their ages varied between 5 and 17 (average 8.3 ± 2.0) and 49 (25.0%) of them were girls. Their baseline characteristics are presented in Table 1.

Table 3 Baseline data in children responding or not responding to therapy.

	Responders		Nonresponders		*P*-value
	n	Number and proportion or average ± 1SD	*n*	Number and proportion or average ± 1SD	
Age (years)	73	8.3 ± 2.1	44	8.5 ± 1.9	0.532
Sex female	79	23 (29.1%)	41	11 (26.2%)	0.733
Wet nights per week before therapy	76	5.1 ± 1.9	44	5.8 ± 1.7	0.026
Daytime incontinence	79	11 (13.1%)	42	9 (21.4%)	0.290
Urgency	79	33 (41.8%)	42	25 (59.5%)	0.063
Previous alarm therapy	79	25 (31.6%)	42	20 (47.6%)	0.084
Previous desmopressin therapy	72	48 (60.8%)	42	30 (71.4%)	0.243
Difficult to arouse from sleep	72	45 (62.5%)	42	31 (73.8%)	0.217

Please cite this article as: Larsson J et al., The value of case history and early treatment data as predictors of enuresis alarm therapy response, Journal of Pediatric Urology, https://doi.org/10.1016/j.jpurol.2022.11.003

Table 4 Data gathered during the first four weeks of alarm therapy in children responding or not responding to therapy. P-values of statistically significant differences in bold typeface.

		Responders		Nonresponders		*P*-value
		N	average ± SD	*n*	Average ± SD	
Treatment duration (days)		76	88.0 ± 57.7	44	100.8 ± 64.8	0.267
Overall adherence (%)		76	97.3 ± 5.6	44	94.6 ± 11.1	0.137
Week 1	Wet nights	76	4.1 ± 2.0	44	4.7 ± 2.2	0.111
	Enuresis latency (hrs)	71	6.4 ± 1.9	41	6.1 ± 1.8	0.369
	Wake up without help (%)	75	58.5 ± 37.6	41	59.4 ± 40.0	0.905
	Nights with nocturia	76	0.6 ± 1.2	43	0.5 ± 1.1	0.685
	Adherence (%)	76	98.5 ± 5.0	44	97.1 ± 8.5	0.314
Week 2	Wet nights	75	4.0 ± 2.1	44	4.6 ± 2.2	0.132
	Enuresis latency (hrs)	68	6.1 ± 1.8	41	6.4 ± 2.0	0.452
	Wake up without help (%)	69	60.3 ± 38.4	42	53.4 ± 40.0	0.368
	Nights with nocturia	76	0.50 ± 1.0	43	0.74 ± 1.4	0.314
	Adherence (%)	76	97.6 ± 8.5	44	96.1 ± 10.9	0.412
Week 3	Wet nights	75	3.5 ± 2.2	43	4.8 ± 2.1	**0.003**
	Enuresis latency (hrs)	63	5.9 ± 2.1	43	6.7 ± 2.0	0.062
	Wake up without help (%)	66	54.5 ± 41.1	44	55.6 ± 41.3	0.892
	Nights with nocturia	76	0.89 ± 1.6	43	0.47 ± 0.8	0.055
	Adherence (%)	75	95.8 ± 12.4	44	95.5 ± 11.8	0.889
Week 4	Wet nights	74	2.9 ± 1.9	44	4.4 ± 2.1	**<0.001**
	Enuresis latency (hrs)	62	6.4 ± 2.2	40	6.0 ± 1.6	0.283
	Wake up without help (%)	67	62.1 ± 40.7	42	53.4 ± 41.2	0.284
	Nights with nocturia	74	0.91 ± 1.4	43	0.65 ± 1.1	0.305
	Adherence (%)	74	97.3 ± 8.8	43	93.5 ± 18.6	0.305

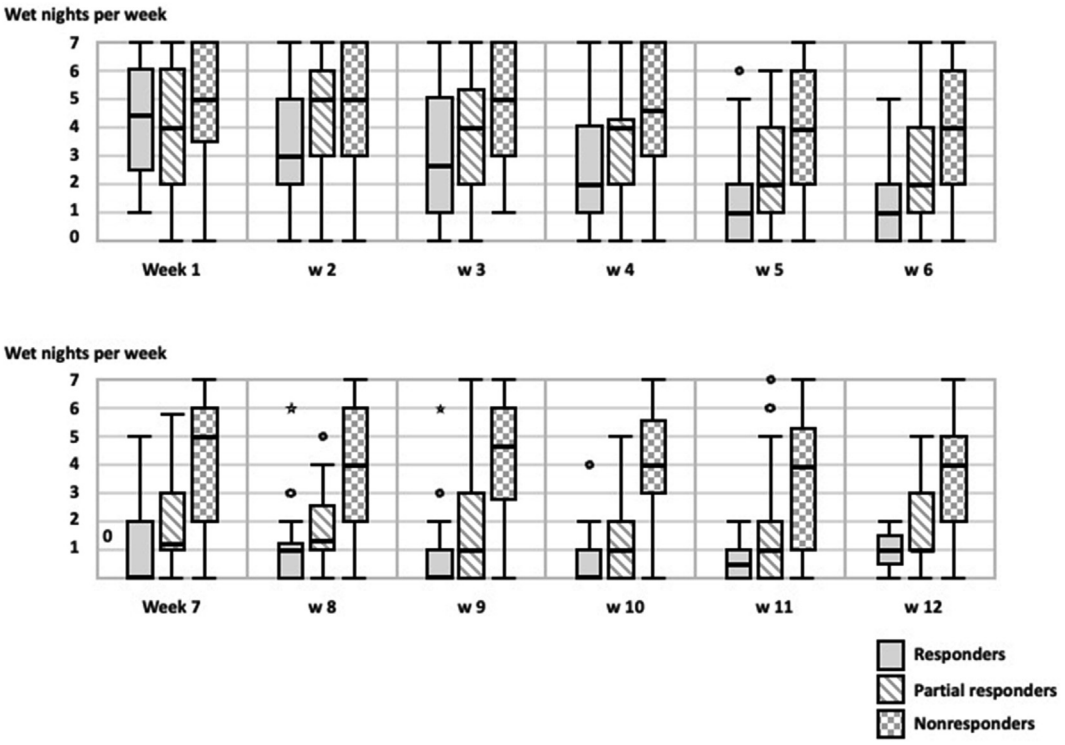


Fig. 1 Numbers of wet nights per week during the first eight weeks of therapy, subdivided according to treatment response.

Please cite this article as: Larsson J et al., The value of case history and early treatment data as predictors of enuresis alarm therapy response, Journal of Pediatric Urology, https://doi.org/10.1016/j.jpurol.2022.11.003

Table 5 Data gathered during the first four weeks of alarm therapy in children or not adhering to the full course of therapy. P-values of statistically significant differences in bold typeface.

		Dropouts		Adherent		*P*-value
		n	Average ± SD	*n*	Average ± SD	
Treatment duration (days)		76	30.9 ± 16.5	120	92.7 ± 60.5	<0.001
Week 1	Wet nights	76	4.1 ± 2.1	120	4.3 ± 2.1	0.596
	Wake up without help (%)	73	54.9 ± 37.4	116	58.8 ± 38.3	0.488
	Adherence (%)	76	94.6 ± 13.8	120	98.0 ± 6.5	**0.045**
Week 2	Wet nights	67	4.7 ± 2.3	119	4.2 ± 2.1	0.171
	Wake up without help (%)	62	46.9 ± 41.5	111	57.7 ± 38.9	0.090
	Adherence (%)	68	88.3 ± 24.0	120	97.0 ± 9.4	**0.005**
Week 3	Wet nights	59	4.2 ± 2.3	118	4.0 ± 2.2	0.535
	Wake up without help (%)	56	48.8 ± 43.5	110	54.9 ± 41.0	0.376
	Adherence (%)	62	83.5 ± 29.2	119	95.7 ± 12.1	**0.002**
Week 4	Wet nights	45	4.0 ± 2.3	118	3.5 ± 2.1	0.149
	Wake up without help (%)	43	46.2 ± 43.2	109	58.7 ± 40.9	0.096
	Adherence (%)	51	82.9 ± 33.4	118	95.9 ± 13.4	**0.010**

Treatment outcome

Overall, 120 children completed therapy, and their reduction of wet nights was 55.4 ± 52.3%, with a range between −200% (i.e., increased enuresis frequency) and 100% (i.e., full response).

The final outcome of the children according to the ICCS classification is presented in Table 2.

Predictors to antienuretic efficacy

The predictive value of baseline data is presented in Table 3 in which only children completing the full treatment course are included. As can be seen, only the estimated enuresis frequency before therapy came out (weakly) statistically significant, the nonresponders having slightly more wet nights per week.

Data gathered during ongoing therapy are presented in Table 4. As can be seen in the table, only the enuresis frequency and only from week three came out statistically significant. This continued to be the case after four weeks of therapy as well (data not shown). Thus, the children who were about to respond to therapy had a clearly decreased number of wet nights after two weeks of therapy. The progression of the enuresis frequency, week by week, is further illustrated in Fig. 1. The enuresis latency gave no predictive information.

Predictors of treatment adherence

Background data for children dropping out of therapy are shown in Appendix 1. When comparing children continuing therapy for the stipulated time with those who dropped out, no differences or even trends were found in demographic data or baseline characteristics (data not shown). The data gathered during treatment are presented in Table 5. As can be seen, the families about to discontinue therapy prematurely could be discerned during the first week by non-optimal adherence.

Discussion

We looked at predictors of enuresis alarm treatment success and/or adherence and found that readily available history data or data acquired at start of treatment were not useful whereas it was clear that already after a few weeks of therapy nonresponders showed an absence of reduction of enuresis frequency and children about to drop out prematurely already at this stage had an incomplete adherence. These findings could serve as grounds for modifying alarm treatment instructions.

One main asset of the study is the reasonably unbiased sample, which probably better than most studies reflect the general population of children with enuresis. The documentation of the enuretic event by the application diminishes recall bias and a true picture is given even regarding children and families who are not able to adhere to the instructions given. This is important, given that alarm treatment is demanding and many children with enuresis have concomitant neuropsychiatric disorders [13].

The main drawbacks of the study are that background data are incomplete and we did not demand that the families complete voiding charts before treatment. However, studies have failed to find consistent support for voiding chart data providing predictive information regarding alarm treatment [7,14] and should we demand voiding charts of the families the dropout rate would have become even higher and the patient sample less representative. We also failed to ask (or have the app ask) the parents regarding daytime incontinence during the treatment. It would have been interesting to see whether treatment of the enuresis had any effect against daytime incontinence.

The purpose of this study was neither to assess the success rate of alarm therapy in general nor the Pjama® alarm in particular. This was not a randomized, controlled clinical trial. Still, the low rate of children becoming completely or partially dry — 18% and 24%, respectively — needs to be commented. The fact that the majority of the

Please cite this article as: Larsson J et al., The value of case history and early treatment data as predictors of enuresis alarm therapy response, Journal of Pediatric Urology, https://doi.org/10.1016/j.jpurol.2022.11.003

patients had already tried desmopressin (and presumably not responded) can be a contributing explanation. All children were supported by dedicated, experienced pediatric nurses, the families were given advice according to established guidelines, and the alarm signal was just as immediate and loud as for other available alarm devices. We do thus not think that the treatment given was substandard. But the population was very unselected and consisted not just of highly motivated families and children who are ready to undergo extensive evaluation and provide detailed treatment documentation. Also, the fact that the enuretic event was documented by the application, not the families, diminished the risk for recall bias (and even cheating). The problem with all studies of the enuresis alarm before the present one is that adherence has not been independently assessed. Thus, we think that our results reflect clinical reality, and the clinical reality is, sadly, that only a minority of children will become reliably dry by the enuresis alarm. We still think that the curative potential of the enuresis alarm warrants it to be considered a first-line therapy.

We found only few predictors of treatment success. Demographic or anamnestic data did not give any clue, not even the presence or absence of concomitant daytime incontinence provided any predictive information. And the response to the alarm was neither clearly better nor worse for children who had tried the therapy earlier. Furthermore, in contrast to earlier studies, the enuresis frequency gave no predictive information. If we had a larger sample, we may have been able to notice differences in these variables, but we believe the number of participants was still large enough not to miss large differences.

What we did find, however, was that alarm responders started to decrease their enuresis frequency already during the first month of therapy. The child who had not reduced enuresis frequency at week four was extremely unlikely to end up responding to the therapy. Likewise, the families who were not able to adhere to the full treatment regime could be discerned already during the first weeks by the appearance of nights without alarm therapy.

If our results are confirmed by more studies future instructions for enuresis alarm therapy may need to be changed in the following way:

- Concomitant daytime incontinence is no contraindication to enuresis alarm treatment;
- If after one month of therapy adherence is not complete treatment should be discontinued;
- If after one month of therapy enuresis frequency has not diminished treatment should be discontinued;
- Otherwise, treatment should be continued until the child has become dry or until further progress has failed to appear after another 2–3 months.

This way, the situation when the family has suffered constant disruption of sleep for several months without any favorable effect, will become less common.

The enuresis latency has only rarely been looked at previously [15–17] and never, to our knowledge, as a potential predictor of alarm treatment response. Before starting the study, we had speculated that this variable might give predictive information and/or change as treatment progressed, at least in children who were about to become dry. We found this not to be the case. The enuresis latency was the same in all outcome groups and did not differ as the weeks progressed.

Conclusions

We found no clear predictors of enuresis alarm treatment response in background data, but after one month of therapy the children who were later to either become dry or drop out of therapy could be discerned with reasonable certainty. We propose that the continuation or interruption of enuresis alarm therapy should be reassessed after one test month. This way the unnecessary burden for the families could be limited.

Author contribution

Jens Larsson took part in the design of the study, collected data and took part in all stages of data analysis and writing of the manuscript.

Malin Borgström took part in the design of the study, collected data and took part in all stages of data analysis and writing of the manuscript.

Birgitta Karanikas took part in the design of the study, collected data and took part in all stages of data analysis and writing of the manuscript.

Tryggve Nevéus conceptualized and designed the study, supervised data collection and analysis and actively participated in the production of the manuscript at all stages.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Funding sources

This study was supported by a grant Sweden's Innovation Agency (2020-04131).

Conflicts of interest

The authors have no conflicts of interest relevant to this article to disclose.

Acknowledgements

We are grateful for the hard work of all nurses taking care of the children at the pediatric outpatient wards.

References

[1] Nevéus T, Eggert P, Evans J, Macedo A, Rittig S, Tekgül S, et al. Evaluation and treatment of monosymptomatic enuresis - a standardisation document from the International Children's Continence Society (ICCS). J Urol 2010;183:441–7.
[2] Keten T, Aslan Y, Balci M, Erkan A, Senel C, Oguz U, et al. Comparison of the efficacy of desmopressin fast-melting

formulation and enuretic alarm in the treatment of monosymptomatic nocturnal enuresis. J Pediatr Urol 2020;16(5):645.e1—7.
[3] Kwak KW, Lee YS, Park KH, Baek M. Efficacy of desmopressin and enuresis alarm as first and second line treatment for primary monosymptomatic nocturnal enuresis: prospective randomized crossover study. J Urol 2010;184(6):2521—6.
[4] Perrin N, Sayer L, While A. The efficacy of alarm therapy versus desmopressin therapy in the treatment of primary mono-symptomatic nocturnal enuresis: a systematic review. Prim Health Care Res Dev 2015;16(1):21—31.
[5] Monda JM, Husmann DA. Primary nocturnal enuresis: a comparison among observation, imipramine, desmopressin acetate and bed-wetting alarm systems. J Urol 1995;154(2 Pt 2):745—8.
[6] Glazener CM, Evans JH. Alarm interventions for nocturnal enuresis in children (Cochrane Review), Issue 1. Oxford: The Cochrane Library; 2007. Update Software.
[7] Berg IB, Forsythe WI, McGuire R. Response of bed wetting to the enuresis alarm: influence of psychiatric disturbance and maximum functional bladder capacity. Arch Dis Child 1982;57:394—6.
[8] Evans J, Malmsten B, Maddocks A, Popli HS, Lottmann H. Randomized comparison of long-term desmopressin and alarm treatment for bedwetting. J Pediatr Urol 2011;7(1):21—9.
[9] Önol FF, Guzel R, Tahra A, Kaya C, Boylu U. Comparison of long-term efficacy of desmopressin lyophilisate and enuretic alarm for monosymptomatic enuresis and assessment of predictive factors for success: a randomized prospective trial. J Urol 2015;193(2):655—61.
[10] Wagner WG, Johnson JT. Childhood nocturnal enuresis: the prediction of premature withdrawal from behavioral conditioning. J Abnorm Child Psychol 1988;16:687—92.
[11] Jensen IN, Kristensen G. Alarm treatment: analyses of response and relapse. Scand J Urol Nephrol 1999;33(Suppl 202):73—5.
[12] Austin P, Bauer S, Bower W, Chase J, Franco I, Hoebeke P, et al. The standardization of terminology of lower urinary tract function in children and adolescents: update report from the standardization committee of the international children's continence society. J Urol 2014;191(6):1863—5.
[13] von Gontard A, Equit M. Comorbidity of ADHD and incontinence in children. Eur J Child Adolesc Psychiatr 2015;24(2):127—40.
[14] Oredsson AF, Jørgensen TM. Changes in nocturnal bladder capacity during treatment with the bell and pad for monosymptomatic nocturnal enuresis. J Urol 1998;160(1):166—9.
[15] Hagstroem S, Kamperis K, Rittig S, Rijkhoff NJ, Djurhuus JC. Monosymptomatic nocturnal enuresis is associated with abnormal nocturnal bladder emptying. J Urol 2004;171(6 Pt 2):2562—6.
[16] Mattsson S, Persson D, Glad Mattsson G, Lindström S. Nighttime diuresis pattern in children with and without primary monosymptomatic nocturnal enuresis. J Pediatr Urol 2019;15(3):229.e1—8.
[17] Nevéus T, Läckgren G, Tuvemo T, Olsson U, Stenberg A. Desmopressin-resistant enuresis: pathogenetic and therapeutic considerations. J Urol 1999;162:2136—40.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpurol.2022.11.003.

Please cite this article as: Larsson J et al., The value of case history and early treatment data as predictors of enuresis alarm therapy response, Journal of Pediatric Urology, https://doi.org/10.1016/j.jpurol.2022.11.003