Combined Dietary Recommendations, Desmopressin, and Behavioral Interventions May Be Effective First-Line Treatment in Resolution of Enuresis

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Purpose: Nocturnal enuresis (NE) is a very common multifactorial pediatric disorder and in children without any other lower urinary tract symptoms is defined as monosymptomatic NE (MNE). Pharmacological, psychological/behavioral, and alternative interventions are commonly used and the first-line drug therapy for patients with MNE is desmopressin (dDAVP) but the response rate is less than 40-60% and the relapse rate is about 50-80% after treatment. Many studies show that some foods and beverages can promote diuresis or bladder irritability, which in some people can exacerbate bladder symptoms and NE. The present study aimed to compare the efficacy of combined specific dietary advices and dDAVP vs dDAVP alone.

Materials and Methods: We enrolled in the study 172 patients affected by MNE between January 2013 and May 2014, of these 35 were excluded. The inclusion criterion was primary MNE and exclusion criteria included non-MNE, secondary MNE and lactose intolerance. Children were treated with dDAVP at a dose of 120 µg a day and were randomized to receive dietary recommendations. They were asked to fill out a charter depicting their wet and dry nights for the period of treatment. Sixty-seven patients were randomly assigned to receive dDAVP and dietary advices (group A) and 70 patients to receive dDAVP alone (group B).

Results: We included in our study 137 children, 102 (74.5%) male, and 35 (25.5%) female, aged between 5 and 14 years. Our results show a higher response rate and a lower number of relapse in group A vs group B with 67.2% of responders in group A vs 58.6% in group B, after 3 months of therapy and 31.1% of relapse in group A vs 46.3% in group B one month, after the end of treatment.

Conclusion: Our results show the effectiveness of specific dietary advices in the management of primary MNE. However further studies are needed to determine whether the difference between therapy with combined dietary recommendations and dDAVP vs dDAVP alone.

Keywords: nocturnal enuresis; therapy; treatment outcome; deamino arginine vasopressin; drug therapy; remission; diet; nutrition policy.

INTRODUCTION

Nocturnal enuresis (NE) is a very common pediatric disorder. The estimated prevalence of NE is highly variable be¬cause there is a heterogeneity in diagnostic criteria. It is estimated to be approximately 10-15% at 5-year old, 5-10% at 7-year old, 3-8% at 10-year old children and 1-4% in adolescents with 0.5-2% in the untreated adults.[1] A multicenter Italian study shown an overall prevalence of 3.8%, which progressively decreased from 8.1% in males and 9.6% in females at age 6 years to 1.2% at age 13 years.[2] According to recent International Children's Continence Society (ICCS), NE is defined as intermittent incontinence occurs exclusively during sleeping periods. NE should not be used to refer to daytime incontinence.[3] In children without any other lower urinary tract symptoms and without a history of bladder dysfunction is defined as monosymptomatic NE (MNE). According to Diagnostic and Statistical Manual of Mental Disorders (DSM) 5 NE is defined as repeated voiding of urine into bed or cloche while asleep in children older than 5 years.

NE is a multifactorial disorder with a genetic underpinning. It has 3 main pathophysiological determinants that are nocturnal polyuria, detrusor overactivity and failure to awaken in response to bladder sensations (high arousal thresholds).[3-7] Otherwise rectal distension due to fecal retention in chronic functional constipation causes bladder distortion and may cause stimulation of detrusor stretch receptors resulting in detrusor overactivity. So constipation is another cause of detrusor overactivity.[8] When organic disease is not suspected, and children suffer from MNE that they consider a significant problem it should be treated.[9]

Pharmacological, psychological/behavioral and other interventions such as homotoxicology are commonly used.[10] Simple behavioral interventions are often used as a first attempt to improve NE and include reward systems such as star charts given for dry nights, lifting or waking the children at night to urinate and to involve the child in cleaning up after wetting, so that they can share the responsibility.[11] Many studies show that some foods and beverages can promote diuresis or

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Received February 2015 & Accepted June 2015

Table. List of dietary advises in children with nocturnal enuresis.

Recommended Food	Not Recommended Food at Evening	Not Recommended Food
Vegetables	**Yogurt**	**Salt**
(spinach, chard, cauliflower, chicory, cabbage, legumes,	**Water**	**Chocolate, cocoa**
tomatoes, eggplant, peppers, beans, cucumbers, asparagus,	**Fruit**	**Carbonated drinks**
celery, peas, beans, lettuce, kale)	(pineapple, melon, apples, watermelon,	**Tea**
	apricot, banana)	**Fruit juice**
Fish	**Milk**	(specially grapefruit and orange)
(tuna, salmon, sardines, sea bream, sole, sea bass)	**Cheese**	
Seafood	(mozzarella, cottage cheese, soft cheese, chartreuse)	
Dried fruits		
Cereals		
(gems of oats, wheat buds, puffed rice, corn flakes, wheat bran, muesli)		
Eggs		

detrusor over-activity, which in some people can exacerbate overactive bladder symptoms and NE. These findings explain how behavioral therapy by reducing the consumption of foods and drinks containing caffeine, carbonated drinks and fluid intake after 6 p.m. (or approximately 3-4 h before bedtime) can often promote continence.[12-14]

The first-line drug therapy for patients with MNE associated with nocturnal polyuria and normal bladder function is desmopressin (dDAVP) for a period of 3 months following by withdrawal.[15]

dDAVP is associated with a response rate of about 40-60% however its effect may not be maintained on discontinuing treatment, and symptoms have been found to recur in about 50-80% after stopping treatment.[9,15,16]

The present study aimed to compare the efficacy of combined specific dietary advices and dDAVP vs dDAVP alone in these patients.

MATERIALS AND METHODS

Study Participants

According to the ICCS classification, we enrolled 172 children with NE referred to the Pediatric ambulatory, 'Campus Bio-Medico' University of Rome, from January 2013 to May 2014, of these 35 were excluded. The inclusion criterion was primary MNE and exclusion criteria included non-MNE, secondary MNE and lactose intolerance, in order to avoid bias, secondary to the exclusion of lactose-containing foods: fresh dairy products with the preference of ripened cheeses whose lactose content is almost zero. The children and their families were asked to participate in the study at the end of the clinical evaluation and, after a 3 months observation period.

Treatment Protocols

Eligible children were randomly divided into 2 groups assigned to receive combined dDAVP and dietary recommendations (group A) or to receive dDAVP alone (group B). Children were treated for a period of 3 months with dDAVP at a dose of 120 µg a day and were open randomized to receive dietary recommendations or nonspecific dietary advices such as reducing fluid intake after 6 p.m. The list of dietary advices have been made reviewing literature and consisted in a list of recommended food, not recommended food at evening and not recommended food (**Table**). Nonspecific advices consisted in simple advices given to the child and to the parents such as to reduce the fluid intake at evening and to treat constipation if present. The parents were asked to fill out a charter depicting their wet and dry nights and an alimentary diary. During the 3 months follow up we called families to verify their adherence to alimentary recommendation and to the therapy and their response.

Outcome Measures

According to the ICCS classification for initial success, the children were classified as non-responders if there was no or less than 50% decrease in wet nights compared to baseline; partial responders if there was 50% or more, but less than 99% decrease in wet nights compared to baseline; responders if there was a 100% of reduction.[3]

Statistical Analysis

Data are presented as frequency and percentage. Paired-samples *t* test and independent-samples t test were used for continuous variables; the χ^2 test was used for categorical variables. The significance level was set at $P < .05$.

RESULTS

We enrolled 172 patients with bedwetting. Of these 35 (20.3%) were excluded for the following reasons: 19 because of presence of daytime symptoms, 11 were lost to follow up, 3 had undergone therapy with dDAVP in the last 6 months, 1 patient was diagnosed with diabetes insipidus, and 1 patient had secondary NE. So we included in our study 137 children, 102 (74.5%) male and 35 (25.5%) female, aged between 5 and 14 years (mean age 8.8 years). Sixty-seven patients were randomly assigned to receive combined dDAVP and dietary recommendations (group A) and 70 patients to receive dDAVP alone (group B).

There were no differences in gender, age, or number of wet nights/week between groups. The baseline severity of MNE was similar in the two groups (mean 6/7 wet night in both groups). After the first 3 months of thera-

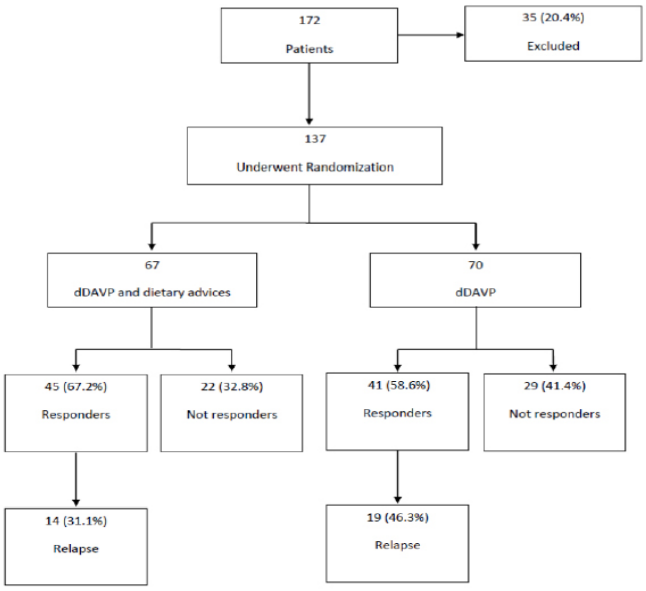

Figure. Study Flow Chart.

py a response was achieved in 45/67 (67.2%) in group A vs. 41/70 (58.6%) in group B ($P > .05$). In group A there was a full response in 40/45 (88.9%) and a partial response in 5/45 (11.1%). Partial responders had a mean reduction of wet night of 75%. In group B there was a full response in 37/41 (90.2%) and a partial response in 4/41 (9.8%). Partial responders had a mean reduction of wet night of 80%.

One month after the end of treatment, relapse, defined as bedwetting occurring more than 2 night per month after the 1-month treatment-free period, occurred in 14/45 (31.1%) of group A vs. 19/41 (46.3%) of group B ($P > .05$) (**Figure**).

DISCUSSION

Many studies showed that some foods and beverages can promote diuresis or detrusor overactivity and have suggested that absorptive nocturnal hypercalciuria might be responsible for NE in some patients.[12-14,17] Therefore diet changes and behavioral interventions are usually recommended in MNE to reduce fluid intake before bedtime, to reduce the consumption of carbonate drinks and to treat constipation. However most provided dietary advices to treat MNE are non-specific and provided before the beginning of therapy.

Excessive fluid intake can cause polyuria and exacerbate overactive bladder symptoms and incontinence. Fluid restriction reduces the total overnight urine production which reduces the child's need to void overnight. Otherwise carbonated drinks may contribute to overactive bladder symptoms and there are evidences that eliminating this kind of fluid from the diet may promote continence.[14] Caffeine in particular has been shown to have a diuretic effect and may increase overactive bladder symptoms by increasing detrusor pressure and by promoting detrusor muscle excitability, so it should be avoided in MNE.[12-14] Caffeine is a constituent of variety of beverages and foods such as coffee, tea, cocoa and chocolate and we advised against them.[14,17] There is also evidence to suggest that aspartame and other artificial sweeteners induce detrusor contraction, so we recommended avoiding these bladder irritants.[14,18]

Fresh fruit also contributes to fluid intake because contains lot of water, but it also contains important vitamins, so we recommended to take it during daytime (and to avoid it at evening).

As far as other dietary factors are concerned hypercalciuria has been considered as an important pathogenic factor of NE. High levels of calcium in the urine seem to decrease the amount of aquaporin-2 (AQP2) detectable in the urine and urinary excretion of AQP2 in humans has been proposed to be a potential marker of collecting-duct responsiveness to vasopressin, indeed studies report that urinary AQP2 correlates with the severity of NE in children.[19] Moreover several studies demonstrated a strong association between dDAVP resistance and hypercalciuria, with dDAVP responsiveness increasing when a calcium restricted diet was implemented.[19,20] However an adequate calcium intake is important for healthy growth. For these reasons we recommended fresh cheese such as mozzarella and ricotta (Italian soft cheese) especially during daytime, and advised against ripened cheese, such as parmesan cheese, grana padano and pecorino (Italian sheep cheese) at every meal because aged cheese are too rich in calcium. To advise against milk would be unhealthy so we recommended taking it before 6 p.m. We also recommended drinking a bottle of water with lower calcium level. In order to low calcium intake we also recommended vegetables rich in oxalate and phytate, such as spinach, chard, legumes, tomatoes, eggplants and peppers, because they have been reported to inhibit bowel calcium absorption in association with fresh cheese.[21]

Otherwise in a recent study vitamin B12 and folate levels were found significantly lower in enuretic children compared with the control group.[22] Vitamin B12 and folate are effective on the neurogenic maturation and lack of them could cause maturational delay of the central nervous system connections necessary for nocturnal bladder control. According to this hypothesis the most commonly emphasized pathophysiologic theory of NE proposes a delayed functional maturation of the central nervous system control on the bladder at night. Basing on this possible lack of vitamin B12 and folate in enuretic children we recommended foods rich in them such as meat (entrails, above all), fish (pilchard, mackerel, salmon), albumen and yolk, seafood (mussel) and cheese, which all supply vitamin B12; wheat germ, wheat bran, corn flakes, crisped rice, asparagus, turnip greens, chickpeas, spinach, muesli, chard which all supply folate.

Another recent study suggests omega-3 fatty acids may influence NE by regulation of prostaglandin E2 (PGE2), nitric oxide (NO) synthesis and brain signaling.[23] It is important, because children with NE have been shown to have higher mean serum and urine PGE2 levels and higher nitrite excretion compared with healthy controls. In fact PGE2 and NO (nitrite is a stable end product of NO) inhibit sodium and fluid reabsorption and decrease anti-diuretic hormone production. Effects on brain signaling are important because it has been suggested that NE represents a functional immaturity of the CNS. Basing on this study we recommended foods rich in omega-3 fatty acids such as fish, especially tuna, salmon, trout, bass, sea bream, better if caught in their natural environment rather than from fish breeding, dried fruit and cereals as germ of oats and wheat.

Finally NE often occurs concomitantly with constipation defined in accord to Roma III criteria. This association is probably due to the close anatomical communication between bladder and rectum, which share muscular structures of the pelvic floor: the distension of the rectum by stool impaction in constipated children presses on the bladder wall, causing bladder outflow obstruction as well as inducing detrusor over-activity. For this reason it is necessary treat constipation if present, in fact constipated children with NE often become dry when successfully treated for their constipation. Standard treatment of constipation includes advice regarding sufficient fluid and dietary fiber intake and regular toilet habits (e.g., defecation every morning after breakfast).[24]

Therefore we advised to improve fiber intake by recommending wheat bran and vegetables.

We can summarize our dietary recommendations in three groups: recommended food, not recommended food at evening, not recommended food.

We evaluated the effectiveness of these specific dietary advices comparing the response rate to therapy with dDAVP and dietary recommendations (group A) vs. response rate to dDAVP alone (group B). Our results show a higher rate response and a lower number of relapse in group A vs. group B (67.2% of responders - full and partial - in group A vs. 58.6% in group B and 31.1% of relapse in group A vs 46.3% in group B).

Also if our preliminary results aren't statistically significant we suppose it's due to the small sample size and is possible that specific dietary recommendations are effectiveness in the management of primary MNE. It suggests the effectiveness of specific dietary advices in the management of primary MNE. Strength of our study is to advice healthy diet regardless NE. Our diet advices, indeed, can be followed by every child because they respect healthy diet principles and this is mainly important for parents since they are able to cook the same food for the whole family, even for those who do not have health problems and this is a strength point which improves parent's adherence to our advices. Another strength point is to propose dietary advices instead diet which is considered too restrictive for children (it need to know exact quantity of food and complete adherence and has to be customized) and too difficult to follow for parents.

CONCLUSIONS

In conclusion MNE is a common pediatric condition and, despite several treatment options, a group of children remain not responders to pharmacological therapy and it can be inconvenient and distressing to both the child and their family and recent studies shown persistence of NE can have medical consequences.[25-27] Because behavioral modifications in association with pharmacological therapy can be superior to pharmacological therapy alone in treatment of MNE we believe that further studies with a larger sample size are needed to determine whether the difference between therapy with dDAVP used alone and dDAVP plus dietary recommendations may become statistically significant.

CONFLICT OF INTEREST

None declared.

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