A comparative study of Vitamin D serum levels in monosymptomatic enuretic children and non-enuretic children

INTRODUCTION

Nocturnal enuresis is a widely prevalent problem. It occurs in up to 15% of 5-year-old children and 10% of 10-year-old, with a spontaneous remission rate of 14% per year. Bedwetting can have a considerably distressing social impact on children and subsequently their families, affecting children's self-esteem and interpersonal relationships, and their scholastic achievement. [0]

Nocturnal enuresis is classified into monosymptomatic (MNE) and non-monosymptomatic (NMNE), depending on whether it is associated with voiding or storage symptoms or not. It can also be categorized into primary, which is since birth, and secondary enuresis, which is newly onset after at least 6 months of a previous asymptomatic state. [2]

Primary monosymptomatic nocturnal enuresis (PMNE) is the most frequent urologic complaint among pediatric patients; however, the pathology and etiology of this problem have not been clearly determined. [3]

Nocturnal bladder control is a matter of developmental delay. At 1 year of age, the conscious sensation of urinary bladder fullness starts to evolve and this physiological turning point allows the beginning of the development of voluntary control of voiding by the age of 2 years. [4] By the age of 4 years, full daytime and nighttime urinary control is obtained by most children. [5]

The idea that enuresis is related to the immaturity of the central nervous system is supported by the finding that premature and/or low-birth-weight children experienced bed-wetting more often than normal-birth-weight children. [6]

Low nocturnal anti diuretic hormone (ADH) and urine osmolality play a role in MNE associated with Nocturnal Polyuria (NP), which doesn't occur as an isolated abnormality but is also linked to children who also suffer of arousal abnormality [7]. We have proved this in our previous study in which we stated that Nocturnal polyuria and decreased nocturnal urine osmolality were key factors in pathogenesis of nocturnal enuresis [7].

There are many clinical observations that link nocturnal enuresis with developmental delay in language and physical growth [8] and skeletal maturation. [9] Nocturnal enuresis could be linked with sleep disorders as well. [10]

Vitamin D is important for bone growth and regulation of calcium homeostasis. It not only plays a vital role in skeletal growth but also has other critical biological actions in neural development and function. [11]

The source of vitamin D is primarily sunlight; it is also found in few foods as oily fish and fortified margarine. Vitamin D consists of a cholesterol backbone and has steroid-like effects. It is the fat-soluble hormone that plays an essential role in brain health. [12]

Studies claim that vitamin D may have an essential role in sleep regulation [13].

Vitamin D deficiency is linked with Obstructive Sleep Apnea (OSA) [14] and nocturnal polyuria is one of the main adverse outcomes of OSA. [15]

Vitamin D deficiency could cause excessive urine production directly. This was shown in a study done on mice which showed that vitamin D deficiency leads to activation of the Renin Angiotensin system. Eventually the augmentation of renin synthesis leads to increased

plasma Ang II production from angiotensinogen, which drives mice to increase water intake and intestinal salt absorption, since Ang II is a very potent thirst-inducing agent that acts on the central nervous system, as well as a potent stimulator of intestinal sodium absorption. As a result, the mice must excrete more urine and salt to maintain volume and electrolyte homeostasis. *(16)*

AIM OF THE STUDY

To evaluate the relationship between Vitamin D deficiency and nocturnal enuresis, and to study the correlation between vitamin D deficiency and urine osmolality which is an indirect indicator of ADH deficiency.

PATIENTS AND METHODS

This is a case control study which was performed in Ain Shams University Hospitals. It was conducted in the period between February 2021 and August 2021.

Patient group: Sixty children aged from 5 to 15 with primary mono-symptomatic nocturnal enuresis were included and selected randomly.

Inclusion criteria: Patients with PMNE which was defined as bedwetting frequency of 3 or more nights per week for at least 2 weeks of observation, and who didn't receive any previous treatment for enuresis.

Exclusion criteria: Patients with non-monosymptomatic enuresis (associated with storage and/or voiding symptoms), anatomical abnormalities (Meatal stenosis, Hypospadias, Epispadias, etc.), neurological diseases, renal impairment, previous pelvic, urological or brain and spinal cord surgery, chronic constipation and irritable bowel habits, active urinary tract infection and patients who are on vitamin D supplements.

Control group: Sixty healthy children were included as a control group whose ages ranged from 5 to 15 years old, and they were chosen from apparently healthy non-enuretic children.

Written informed consent was obtained from patients' legal guardians, and the study was approved by Ain Shams University Ethical Committee.

Methods:

All children included in the study were subject for detailed medical and surgical history to rule out the presence of organic or psychological diseases. Physical examination including focused neurological examination to exclude neurological diseases, especially (neural tube defects) and local urological examination to check for any genital or external urethral meatus anomalies. Also urine analysis was done to exclude urinary tract infection.

Frequency Volume chart and nocturnal urine osmolality.

Volume Frequency chart was recorded for both enuretic and control groups, to evaluate frequency, average voided volume, and to exclude or confirm the presence of nocturnal polyuria.

Nocturnal polyuria is defined in children and adolescent age group as, urine production during the period of sleep which equals to or more than 130% of estimated bladder volume for age (EBV). *(17)*

Estimated bladder capacity for age is calculated by the formula [30 X (age in years + 2)] in ml. The amount of urine last voided before sleep is discarded and first morning voiding volume is

added to the calculated nocturnal urine volume. Clear instructions for mothers were to let the child void before sleep and every two hours till 8 am. Short intervals were meant to avoid enuretic episodes during calculation of nocturnal urine volume, and if occurred it mandates the repeat of chart on another day.

Nocturnal urine collected over the night was tested for osmolality, it was measured in mOsm/kg.

Serum Vitamin D level.

Vitamin D serum level was measures using the ELISA technique. The Cal Biotech Vitamin D Kit (Mannheim, Germany) was used, which is a solid phase enzyme linked immunoassay (ELISA), based on the principal of competitive binding. Vitamin D deficiency was defined as serum Vit. D below 20 ng/ml.

Sensitivity:

The sensitivity of this test kit is 0.67ng/ml. Sensitivity was determined by calculating the mean plus 2SD of the standard zero point tested 20 times in the same Statistical Methods run.

Statistical methods

The collected data were coded, tabulated, and statistically analyzed using IBM SPSS statistics (Statistical Package for Social Sciences) software version 28.0, IBM Corp., Chicago, USA, 2021. Quantitative data tested for normality using Shapiro-Wilk test, then described as mean±SD (standard deviation), and then compared using independent t-test. Qualitative data described as number and percentage and compared using Chi square test. Pearson test was used for correlations. ROC curve was used to evaluate the performance of variables to differentiate between conditions. The level of significance was taken at p-value <0.050 was significant, otherwise was non-significant.

Diagnostic characteristics was calculated as follows:

- Sensitivity = (True positive test / Total positive golden) x 100
- Specificity = (True negative test / Total negative golden) x 100
- Diagnostic accuracy = ([True positive test + True negative test] / Total cases) x 100
- Youden's index = sensitivity + specificity – 1
- Predictive positive value = (True positive test / Total positive test) x 100
- Predictive negative value = (True negative test / Total negative test) x 100
- Likelihood ratio positive (LR+) = (sensitivity/ 1-specificity)
- Likelihood ratio negative (LR-) = (1- sensitivity / specificity)

Diagnostic odds ratio (DOR)= LR+/ LR-

Serum level of vitamin D, in monosymptomatic enuretic children and non-enuretic children: a comparative study

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Informed consent was obtained from all patients or their legal gaurdians before recruitment in the study.

Cover letter

Dear editorial Board:

We are group of researchers interested in causes and management of nocturnal enuresis, we embarked on this research last year and we reached promising results regarding the role of vitamin D in management of monosymptomatic enuresis.

This research was conducted in Ain Shams university hospitals after approval of our university ethical committee, no external funds whatsoever was received for this study, and no conflict of interest to be declared.

This study was continuation of our previously published study about the etiology of monosymptomatic nocturnal enuresis.

Title was "Nocturnal polyuria and nocturnal arginine vasopressin (AVP): A key factor in the pathophysiology of monosymptomatic nocturnal enuresis.

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Thanks, and much obliged.

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