

## 8. Risk factors associated with primary monosymptomatic nocturnal enuresis

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Many factors related to enuresis have been described in the literature<sup>41,42</sup>. Each one has been individually reviewed and the existing evidence as to their association with PMNE has been identified (table II).

### 8.1 Chronic headache

There is an association between chronic headache and nocturnal enuresis, albeit none of the studies is specific to PMNE. Enuresis is approximately twice as frequent in children with chronic headache (headaches that are so frequent as to interfere with their daily activities for a period of at least 6 months) than it is in controls (OR = 1.8; 95% CI: 1.1-2.9)<sup>43</sup> [IIb]. In another Spanish study, the risk of suffering enuresis was greater (OR = 3.12; 95% CI: 1.14-8.54)<sup>44</sup> [IIIb].

Despite this association, it is not known if enuresis was cured or if it improved after successful treatment of chronic headache in these children. There is no evidence of studies on enuretic children that investigate chronic headache and it is not

known if the presence of chronic headache would have any prognostic or therapeutic implications.

It is recommended inquiring about chronic headache in children with nocturnal enuresis [B].

### 8.2 Epilepsy

Despite the fact that wetting incidents have been described as the manifestation of nocturnal epileptic fits, no evidence has been found of epilepsy as an associated factor to nocturnal enuresis [IIIb]. Most of the documentation found has to do with treatment complications: convulsions secondary to hyponatremia due to the use of intranasal desmopressin and intoxication from tricyclic antidepressants.

There were no or minimal differences in electroencephalogram recordings between children with/without enuresis, and epilepsy was not diagnosed in any case. In case-control studies, when rea-



central nervous system stimulants typically used to treat this syndrome improved their enuresis<sup>52,53</sup>.

This ADHD/enuresis association has also been demonstrated in the opposite direction in studies of children with enuresis. A high prevalence of ADHD was found (40%), especially of the inattentive subtype, in a pediatric hospital outpatient sample with enuresis aged 6-12 years<sup>54</sup> [IIIb].

Fergusson demonstrated that children in whom nocturnal enuresis persists after 10 years of age present a higher association of ADHD, behavior disorders, and anxiety than non-enuretics<sup>55</sup>. In the same line, another case-control study<sup>52</sup> with adolescents found a small, but significant association between nocturnal enuresis and ADHD and vice versa.

Given the high prevalence of these two conditions and their association, it is clinically important to know if there is concomitant ADHD in enuretic children. Hence, ADHD symptoms in children that present enuresis should be investigated [B].

#### 8.4 Other psychological problems

There is no association between psychological problems in general and

PMNE, although there is with secondary NE [IIb]. However, children with PMNE seeking treatment, who have had previous failures, or have been referred to hospital have low self-esteem [IIIa]. Treatment of enuresis enhances the child's self-esteem in the short term regardless of outcome [Ib].

It is currently accepted that certain psychological and social problems can cause secondary enuresis but not PMNE. Although enuresis has been related to behavioral problems, anxiety, depressive tendencies and failure at school, when PMNE is analyzed, these children do not have behavioral problems. In a cohort of children followed up from birth to 15 years of age, the presence of primary enuresis was not associated with prior stressful situations, whereas family conflicts, money or health problems in the family occurred in children with secondary enuresis<sup>55,56</sup> [IIb]. In a case-control study that related PMNE and behavioral problems or emotional disorders, the association disappeared when the socio-economic level was controlled for<sup>57</sup> [IIIb]; i.e., it seems that this would be a confounding factor that should always be analyzed whenever looking for the aforementioned associations.

Although there are many studies that show that children with enuresis suffer from low self-esteem, there are some biases in the analyses that make it impossible to claim that children with enuresis who present in Primary Care have lower self-esteem. The studies associated lower self-esteem in children treated in hospital, those with more than one treatment failure, and those who seek treatment<sup>58</sup> [IIIa].

Merely receiving treatment for enuresis improves the child's self-esteem and behavior in the short term, regardless of clinical response and the type of treatment administered (alarm, desmopressin, or placebo)<sup>59</sup> [Ib].

Early treatment of enuresis is recommended in Primary Care to improve [A] or prevent low self-esteem [D].

## 8.5 Sleep/arousal disorders

PMNE is not associated with any sleep disorder, although there are signs indicating that these children find it more difficult to wake up, at least as a result of acoustic stimuli [IIIb].

In the pathogenesis of enuresis, it has been reported that bed-wetters have greater difficulties in awakening, at

least in response to the urge to void, this being an essential factor for enuresis to exist.

Several polysomnographic studies have been performed with results that do not reveal much and that may indicate thalamic immaturity<sup>60</sup>. Parents have been asked about difficulties in arousing children, and an affirmative response is more common in children with enuresis<sup>61,62</sup>.

The only conclusive study was conducted by Wolfish et al<sup>63</sup> [IIIb], in which they assessed the ability to awaken in response to a sound stimulus in two groups of children: one group was enuretic and the other was not. They put earphones on the children while they slept and transmitted increasingly loud sounds, up to 120 dB, every 10 minutes until the child awoke and responded to an order. The percentage of children that woke up was lower in the enuretic group (9.3% as opposed to 39.7%). It is likely that this difficulty in arousal is greater in the group of children with enuresis via usual attempts at arousal. It is of interest to note that 60% of the control group also failed to awaken.

There are no studies that clearly associate PMNE with other sleep disorders: parasomnia, dysomnia, etc.

Although waking up plays an important role in the pathogenesis of enuresis, no clinical implications have been found. Sleep patterns need not be studied as part of the clinical history of a child with enuresis [B].

It is recommended obtaining a history of sleep apnoea symptoms in children with PMNE, despite the fact that the level of evidence is low [C]. It should always be ruled out in cases of secondary enuresis [A].

## 8.6 Sleep apnoea syndrome

Only cases and case series have been described of the association of sleep apnoea syndrome and nocturnal enuresis [IV]. None of them evaluate PMNE specifically. An association has been demonstrated with secondary enuresis [Ib].

These studies<sup>64</sup> were carried out in sleep clinics, where the patients are referred for apnoea. No cohort or case-control studies have been conducted in children with enuresis to estimate the association with sleep apnoea disorders.

In a sleep clinic, Weider et al<sup>65</sup> showed that twelve months after surgery to clear the airway in 115 subjects with ages 3 to 19 years, the number of wet nights decreased by 77%. In all the cases with secondary enuresis (onset together with clinical symptoms of obstruction), the enuresis remitted at 6 months and patients remained dry at 12 months [Ic].

## 8.7 Asthma/allergy

The association between asthma/allergy and enuresis is not conclusive. Existing studies are of poor quality and contradictory, and none of them are specific to PMNE [IV].

In a case-control study, Rawashdeh et al<sup>66</sup> detected a higher incidence of bronchial asthma and confirmed allergy in the group of enuretics, although other studies did not find that this relationship<sup>67</sup>. Kaplan et al<sup>68</sup> also fail to detect differences in serum IgE levels between children with enuresis and controls. They report that the prevalence of allergic problems in their group of enuretic children is no different from that of the general population. Evidence has not been found that treating asthmatic children improves enuresis.

It is possible that the relationship between asthma/allergy and enuresis is due to the administration of theophylline, which was standard practice in these patients years ago. Due to its diuretic

action, like all methylxanthine-based drugs, theophylline has been considered a causative factor and a reason for treatment failure in enuresis<sup>42,69</sup> [V]. Perhaps because it is considered a confounding factor, the Cochrane library excludes children with asthma from its systematic review of treatments for enuresis<sup>70</sup>.

It is not recommended specifically investigating the presence of asthma/allergy in children with PMNE [C].

## 8.8 Caffeine

Although it has never been studied, it is reasonable to recommend that caffeine-containing beverages be avoided late in the evening given their diuretic effect [D].

## 8.9 Encopresis/constipation

Questions regarding constipation/encopresis are included in reviews and most protocols and guidelines on enuresis. Constipation is considered to be fewer than 3 bowel movements per week<sup>71</sup>.

Although there is a clear association between constipation/encopresis and secondary enuresis, its relationship to PMNE is not well established [IV]. The data obtained in cross-sectional surveys are contradictory; some authors find no association<sup>16</sup>, while others do (OR = 5.75; 95% CI: 3.90-8.47), although they do not distinguish between primary and secondary enuresis<sup>71</sup>, or alternatively relate basically to secondary enuresis<sup>3</sup>. In a single case-control study there is no association<sup>66</sup> [IIIb]. When children with encopresis are studied, 34% have enuresis (no distinction is made between primary and secondary enuresis), which disappears in half of the cases when encopresis is treated (NNT = 6.1)<sup>72</sup> [IV].

The presence/absence of constipation or encopresis is worth investigating in all patients with enuresis; if present, treat the constipation first [C], since constipation is easy to diagnose on clinical grounds (fewer than 3 bowel movements per week), and given the possibility that constipation can be the cause of enuresis.

## 8.10 Pinworm infestation

There is insufficient evidence available to confirm that pinworm infestation is

associated with NE [IV]. Some reviews mention it as a cause of enuresis in light of the fact that it disappears once oxyuriasis is treated<sup>42</sup>. The best evidence found on the subject is a low quality case-control study<sup>73</sup> [IV] in which a higher prevalence rate of enuresis is detected in children infested with pinworm versus the control group (OR = 3.43; 95% CI: 1.14-10.34). They do not mention whether the type of enuresis is primary or secondary. The study was carried out in Latin America in a country where the prevalence of parasite infestation is high.

At present, and in our setting, Graham's technique is not justified in all children with PMNE [C].

### 8.11 Urinary tract infection/bacteriuria

Most protocols or guidelines recommend ruling out urinary tract infection or bacteriuria in children with enuresis<sup>74</sup>. However, there is evidence that PMNE is not associated with urinary tract infection/bacteriuria [IIc].

Undoubtedly, if we are dealing with a child with a history of urinary tract infections, especially if they are recurrent, or any functional abnormality of

the urinary tract, we are almost surely dealing with a patient with non-monosymptomatic enuresis, who should undergo more diagnostic tests. In contrast, the PMNE patient is asymptomatic from the micturition/urinary point of view, and if we detect bacteria in urine it would be a case of asymptomatic bacteriuria.

The best evidence of the prevalence of bacteriuria in children with monosymptomatic nocturnal enuresis is by Hanson, who carried out an epidemiological study of urinary tract infection in a population of 3553 schoolchildren; he found no association with monosymptomatic nocturnal enuresis<sup>75</sup> [IIc]. There are other studies that, although they have a lower level of evidence, are consistent with Hanson's findings and have not detected a higher rate of bacteriuria in children with enuresis<sup>76</sup> [IIIb] or a higher rate of nocturnal enuresis among children with urinary tract infection than in the general population<sup>67</sup> [IV].

In PMNE, it is recommended adopting the same attitude to urinary tract infection/bacteriuria as in the general population [B].

### 8.12 Diabetes mellitus

Juvenile diabetes mellitus is not associated with PMNE although it is associated with secondary enuresis [IV].

The evidence that exists of an association between enuresis and diabetes mellitus is low (the odd clinical case and case series). In a retrospective study of a series of 66 cases on the mode of presentation of juvenile diabetes, none was seen to present primary nocturnal enuresis, although secondary enuresis was present in 25 children (28%)<sup>77</sup> [IV].

It can be stated that diabetes is diagnosed sooner thanks to the clinical manifestations of the illness than by means of dipstick urinalysis in a child with enuresis.

It is not recommended routine testing to rule out diabetes mellitus in children with PMNE [C].

### 8.13 Diabetes insipidus

There is no evidence of an association between diabetes insipidus and NE.

This association was sought as a result of the theoretical physiopathological relationship (described in the literature) between nocturnal enuresis and diabetes insipidus, which share poor functioning of the vasopressin-adiuretine

system, leading some authors to recommend performing a urine density dipstick analysis. In a Spanish review, the overall prevalence (children and adults) of diabetes insipidus is 1/100,000 (60% males)<sup>78</sup>. In Finland, the estimated annual incidence in children of 0-14 years of age is 5 cases/1,000,000; of these, 1/3 are due to tumors of the central nervous system (some of these cases are diagnosed after the tumor) and 23% correspond to an idiopathic deficit and congenital renal diabetes<sup>79</sup> [IIIb].

No study has been found that shows an association between diabetes insipidus and PMNE.

It is not recommended routine testing to rule out diabetes insipidus in children with PMNE [D].

### 8.14 Detrusor overactivity

There is evidence that bladder hyperactivity is associated with PMNE, particularly in cases where treatment with desmopressin or alarm fails [IV].

In order to diagnose PMNE, is required no loss of urine or major daytime urgency, although a certain degree of urgency and frequency in children is normal and should not be considered pathological. Urodynamic detrusor ove-



ractivity is found in 15% of healthy children and is not considered clinically relevant if it is not very intense or if it doesn't produce clear clinical manifestations such as urgency or incontinence. It is possible that there is clinically significant detrusor overactivity in some children with PMNE; consequently it may be of benefit to treat it.

Two series of consecutive cases of 33 and 11 children who consulted for PMNE in hospital underwent functional studies that revealed detrusor overactivity in 49%<sup>80</sup> and 63%<sup>81</sup>. In line with this, another study in 18 cases in which PMNE persisted into adulthood (20-42 years of age) daytime detrusor overactivity was observed in 45%<sup>82</sup> [IV].

Another qualitative important study evaluated nocturnal bladder activity in 33 children with PMNE in which treat-

ment with desmopressin failed, with or without alarm treatment. There were two remarkable aspects. The first one was that 90% of the children had bladder hyperactivity. The second that functional bladder activity can differ when a person is awake and when he/she is asleep, given that in 49% of the cases bladder hyperactivity was only manifested while the patient was asleep<sup>83</sup> [IV].

In one series of enuretics who were resistant to treatment with high doses of desmopressin, the observation that most (20 of 28 children) responded to anticholinergics<sup>84</sup> leads one to consider the clinical importance of bladder overactivity [IV].

The usefulness of anticholinergics in PMNE should be evaluated in clinical trials. [C].