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Occasional Survey

What Do We Know About Childhood Nocturnal Enuresis ?

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Abstract Primary nocturnal enuresis refers to persistent bedwetting beyond the age of five years. It is a common problem. Its exact causation is unknown but is believed to involve bladder dysfunction, nocturnal polyuria and impaired sleep arousal. Most resolve spontaneously with age. However, children with PNE may have psycho-behavioural problems and their parents experience greater stress. Treatment should be individualised depending on patient and family preference, presence of daytime symptoms or nocturnal polyuria. Recent meta-analysis suggested that alarm therapy, if properly used, has the best long term success. Desmopressin given intranasally or orally provides good symptomatic relief, giving it a role in gaining initial confidence of the family, ensuring dry nights when sleeping out, or when alarms therapy is not successful or contraindicated, or perhaps for those with nocturnal polyuria. Tricyclic antidepressants are as effective as desmopressin but best avoided because of potential risk of fatal poisoning to patients and siblings.

Key words Desmopressin; Enuretic alarm therapy; Primary nocturnal enuresis; Tricyclic antidepressant

Introduction

Nocturnal Enuresis refers to persistent bedwetting with a frequency of two or more times per week for at least 3 months in a child aged 5 years or more (DSM-IV classification).[1] If the child has never been dry for six months, primary nocturnal enuresis (PNE) is diagnosed. Usually no organic diseases are associated. It should be distinguished from continuous dribbling of urine, or diurnal enuresis (both day and night wetting) because these latter conditions strongly suggest organic disorders such as ectopic ureters or neurogenic bladders.

There has been intense interest in this subject recently in both the medical profession as well as the public. This is because the Student Health Screening Programme has picked up a large number of these children whom we have to manage, and because of the recent controversy in its cause and significance.

This review attempts to discuss the updated understanding on the aetiology, psychological effect, and treatment options of PNE.

What is the size of this problem? Epidemiological studies in the United Kingdom suggested that it is a common problem – affecting 15% to 20% of the five years old and 1% to 2% of 15 years old.[2] Yeung et al have reported that the prevalence in HK was much lower, with an overall prevalence of 3.5% for children aged four to 12 years.[3] Even then, with an estimated total childhood population of 820,000 between five to 15 years in 1996, we are still facing about 28,000 children with this problem.

Aetiology of Primary Nocturnal Enuresis

What causes enuresis? Is it a bladder problem, a neurological problem or hormonal problem? Equally important, is it a permanent disability or a developmental delay that will resolve with time?

Until now, the exact cause of nocturnal enuresis is unknown. However most believe that it is multifactorial in causation. Genetic factors are implicated. Firstly, the risk

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of having enuresis in the child was increased 7-fold if the father had enuresis or 5-fold if the mother had enuresis in their childhood.[4] Secondly, linkage studies have identified possible genetic loci for enuresis, on chromosomes 8q, 12q, 13q and 22q11.[5,6] Thirdly, the concordance rates for monozygotic twins were 0.43 to 0.68 which were higher than those for dizygotic twins (0.19 to 0.36).[6,7] However the concordance rate was at most 68%, indicating that genetics is not the entire explanation.

Three basic pathogenetic mechanisms have been extensively studied. They include: dysfunctional bladder, nocturnal polyuria, and sleep dysfunction.

Bladder abnormalities was inferred from the observation that some 20% of PNE children also had daytime symptoms of frequency, urgency, or infrequent voiding. Some studies found reduced maximal functional bladder capacities[8-12] while others had not.[13] Some studies found evidence of unstable bladder contractions while others found normal urodynamics.[14]

There are local studies in this aspect as well. Yeung CK et al performed continuous urodynamic and sleep studies in 33 boys and eight girls who had monosymptomatic PNE that was refractory to conventional treatment.[15] He could distinguish five different patterns of abnormal bladder functions: Patterns 1 and 2 showed normal daytime urodynamics, but significant bladder instability at night with either normal or low volume voidings. Patterns 3 to 5 showed abnormal bladder function even during daytime. Of particular importance is pattern 4 which showed marked detrusor hypercontractility and high bladder pressure, signifying the presence of obstruction and he found urethral membranes in some patients. The findings are different from the majority of studies which found no urethral obstruction in children with PNE. Although the report suffers from the limitations of the small number of patients studied, possible selection bias, and the lack of a control group, it deserves our attention and further study.

Nocturnal polyuria was postulated to be the cause of PNE because: firstly enuretic children were found to have reduced ratios of day to night urine volumes.[16] Secondly there should be a rise in Arginine-Vasopressin level during sleep in normal children but this expected rise was absent in enuretic children.[17] These observations suggested that enuretic children continue to produce large urine volume during sleep which exceed the bladder storage capacity, thus causing the bedwetting. These theories form the basis for using Desmopressin as its treatment. Moreover more recent studies have also identified AVP insensitivity[18] and excessive urine sodium loss[19] as possible mechanisms of the nocturnal polyuria, especially in enuretic adults.

Even though there is urine production exceeding the bladder capacity, why do enuretic children not wake up and go to the toilet as many normal children do? It is logical to consider sleep abnormalities as a cause of bedwetting. Indeed, most parents would comment that their enuretic children are deep-sleepers. However, sleep studies have not shown consistent results. Some researchers have found increased arousal threshold[20] or more sleep problems such as onset insomnia, confusion when awoken or nightmares in enuretics.[21]

Of interest was a report from Watanabe's group in Japan, showing three patterns of abnormal arousal responses in enuretic children.[22] In the normal children, bladder sensation caused them to shift from deep sleep to light sleep and then awakening. In type 1 enuretics, there was lightening of sleep but no actual awakening. In type II there was no shifting to light sleep. The authors postulated that an immaturity in subcortical centers may affect the arousal response so that the full bladder causes contraction without awakening.

On the other hand, other authors had found no difference in the sleep patterns in enuretic compared to normal children[23] or between the wet and dry nights in enuretic children.[24]

Probably there is no single cause for enuresis, but it is the result of the interaction of these three factors plus other unknown factors. Is PNE due to a delay in maturation or a permanent abnormality in these children? If we look at the prevalence of PNE in different populations, there is always a decreasing prevalence with increasing age. The most widely quoted data came from a UK study by Forsythe in 1974 in which they reported a spontaneous resolution rate of about 15% per year.[25] The prevalence data from HK also showed a decreasing prevalence with age.[3] These epidemiological data favoured the concept of a delay in maturation of whatever mechanism responsible for the bedwetting. Nevertheless about 1% of children did have the problem that persisted into adulthood, and it is possible that this subgroup of patients have a permanent abnormality leading to their bedwetting.

Psychological Significance of PNE

What adverse effect does it have for the child and the family? Does it lead to psychiatric illness? Western studies have suggested that bedwetting confers a bad social and emotional stigma, stress and inconvenience to the child and family.[26] Most studies confirmed that enuretic children had

lower self-esteem, secondary to parental disapproval, teasing by others and repeated treatment failures.[27-29] They tend to be immature, less self-reliant, less ambitious or secure. They are less motivated for achievements, or less adaptable to different environments. They are also at increased risk of emotional or physical abuse.[28]

Studies also found an increased incidence of behaviour problems in enuretic children: They have more aggressive behaviour, greater motor hyperactivity; conduct problems, attention-deficit behaviours, anxiety or withdrawal symptoms than control groups. However most studies did not find any formal psychiatric disturbances in enuretic children.[27]

We should be aware that cultural or ethnic differences may exist so that Western psychological studies may not apply locally. A recent study by the Hong Kong Childhood Enuresis Study Group also confirmed that our local enuretic children and their parents also have worse scores in the Childhood Behaviour Checklist, Parenting Stress Index and Global Assessment of Functioning scales, indicating that they had problems of anxiety, depression, attention deficit, delinquency and aggressiveness. They had inferior social and school competence. Their parents felt greater stress in child rearing and more social isolation.[30]

Furthermore in a review of the literature by Moffatt on the psychologic implications of treatment and nontreatment, he concluded that self-concept appears to improve with successful treatment, and that there was no definite evidence that the behaviour of children who failed treatment will deteriorate.[27] Therefore treatment is beneficial and is justified.

Treatment Options of PNE

The fact that many treatment have been tried suggests that none have proven to be the best. There are several good quality meta-analysis in this topic recently. The NHS Center for Reviews and Dissemination published its analysis of 62 good quality RCTs up to Spring 1997.[31] The Cochrane Collaboration published three reviews with updates in January 2000.[32-34] The July 2000 issue of Current Evidence also had a section on this topic.[35]

Desmopressin (or DDAVP) works by reducing the nocturnal urine production. It is given as intranasal spray (in doses of 20 to 40 mcg nocte) or as oral tablets (in doses from 200 to 400 mcg nocte). The smallest dose that is effective should be used. The electrolytes should be checked if use for more than seven days or during intercurrent illness. The parents and child must be warned of the risk of water intoxication and to limit fluid intake to 240 ml in the evening and night of taking desmopressin. If they experience nausea, vomiting, cramps, headache or apathy, they should stop the drug and seek medical consultation. Desmorpressin treatment should be avoided in diseases associated with fluid imbalance such as renal failure or cardiac failure.

The effect of desmopressin on enuresis is immediate but relapses were common. It is not certain what is the optimal duration of treatment. One study did not find any difference between one and three months treatment. Some authors suggested to give it for six months or even longer. Therapy should be stopped every three months to assess whether spontaneous remission has occurred. In a meta-analysis of 18 RCTs by Moffatt in 1993, the average complete cure rate was 24.5% but long term dryness was unusual, being 21% after three months off treatment in one study and 6% after six months in three other studies.[36]

The Cochrane Reviews also confirmed that, compared with placebo and while treatment is being given, desmopressin can reduce the number of wet-night per week by 1.56, and increase the chance of complete cure by an odds ratio of 4.6. However when off treatment and on follow-up, there was no difference between treatment and placebo group.[32]

Another commonly used drug is Tricyclic antidepressants such as imipramine. Its postulated action is on the central nervous system, and it has additional anticholinergic and antispasmodic effects. It is given in doses of 25 to 50 mg before bedtime. It should not be given to children younger than six years, or in doses greater than 75 mg or for treatment courses of more than three months.[31] The response is also immediate. The response rate varied between zero percent to 69% and relapse rate was high.[33] The main problem is its serious toxicity to patients and accidentally to siblings.

The Cochrane review concluded that compared with placebo, imipramine was effective during treatment. The mean weighted reduction in wet nights per week was 1.04, and odds ratio of achieving 14 consecutive dry nights was 7.23. However after stopping treatment, there was no difference between treatment and placebo group. Another TCA called viloxazine may be better with sustained reduction in wet nights on follow up. But they needed further study.[33]

The modern enuretic alarm is a wearable mini-alarm that consists of a wetness sensor which triggers a bell. The enuretic alarms works by the principle of conditioning: it converts the meaning of full bladder sensation from a signal to urinate to a signal to inhibit urination and waken. It

probably works by increasing bladder capacity and/or the arousal response.

Combined data from 34 case series showed an initial success rate of 68%.[37] The Cochrane review of controlled trials concluded that alarms resulted in a reduction of 2.5 wet nights per week compared with controls.[34] The NHS Centre for Reviews and Dissemination reported a relative risk of 13.3 in achieving complete dryness when alarm is compared to control.[31]

The effect of alarm therapy is also sustained. In one case series of 275 patients, 60% showed initial response. Of these, 49% did not relapse, while 10% relapsed within six months after therapy. In this latter group, 80% will respond to a second treatment course.[38] In another controlled trial, the alarm group had a lower chance of relapse with a relative risk of 0.38 (95% CI: 0.2 to 0.7) compared to controls.[39]

What about the comparative efficacy of different therapies? The Cochrane review suggested that desmopressin and imipramine had similar effects both during and off treatment. When desmopressin was compared to alarms, desmopressin was better during the first week of treatment, with 1.7 wet nights fewer; but by the last week of therapy, it was worse than alarm group, with 1.4 more wet nights per week. More importantly, the chance of relapse with desmopressin was 7.36 times higher compared with alarms after stopping treatment.[32]

Of some interest are the combination of alarm plus desmopressin. In three controlled trials, including one in Hong Kong, combination therapy resulted in one to two less wet nights per week compared with alarm alone. However, there was no difference after treatment was stopped.[40-42]

In the July 2000 issue of Current Evidence, Bosson and Lyth have compared the common treatment options for PNE: Desmopressin has short term efficacy, no long term benefit (unless you give it long term). Its advantages are immediate effect and convenience to the family. Its main disadvantages are its high cost and the risk of water intoxication. Imipramine is similar in efficacy to desmopressin. It is certainly cheaper but the potentially lethal poisoning to patient and siblings have made it out of favour now when other options are available. Alarms therapy has proven to have short and long term benefit, better than that of drug therapy. Its main disadvantages are its slower action, the need for high motivation from the child and disturbance to other family members. There are also some evidence to suggest that combining alarm and desmopressin improves short term success.[35,41]

Table 1 shows the comparative cost of treatment options in public hospitals, and it is evident that imipramine and alarms are much less expensive than either the nasal or oral form of desmopressin. In discussing treatment options with parents, cost must also be taken into consideration.

However, we should note a word of caution on interpreting meta-analysis: They have the limitation of pooling patients together, and hence heterogeneous groups of patients may be considered the same when in fact they are different. It is possible that enuresis as a symptom is the manifestation of a heterogeneous group of patients that should be treated in different ways. In fact Djurhuus have proposed to distinguish the following subtypes of PNE which have important implications on treatment.[43] Firstly, there are those children with daytime urinary symptoms that suggest bladder instability. They should respond well to anticholinergics and bladder training exercises. Secondly, those without daytime symptoms (called monosymptomatic PNE) have uncertain etiology. Among them are those children who have large nocturnal urine production. They lack the normal rise of vasopressin during sleep. They are expected to have good response to desmopressin. Other children in this group have slightly increased micturition frequency during daytime, small bladder capacity, normal nocturnal urine production but wets several times a night. They are expected to respond well to alarms therapy. Lastly, there are the rarer types of PNE associated with natriuresis, hypercalciuria, and upper airway obstruction whose treatment are uncertain.

Table 1 Comparison of cost of different treatment options for childhood primary nocturnal enuresis

Treatment options	Max. dose	Daily cost*(HK$)	Total cost for six months (HK$)
Imipramine	50 mg nocte	0.28	50.4
Desmopressin (nasal)	40 mcg nocte	33.28	5990.4
Desmopressin (oral)	400 mcg nocte	20.54	3697.2
Alarms			350-750

* data obtained from a public hospital pharmacy as at October, 2000.

Some Suggested Management Strategies
(Figures 1 and 2)

Organic causes should be ruled out, especially urinary tract infection, diseases causing polyuria and structural bladder problems. Secondly, those with daytime dysfunctional voiding symptoms should be identified for urodynamic workup and treated as bladder instability. Thirdly, proper counseling and general advice are to be given to child and parents.

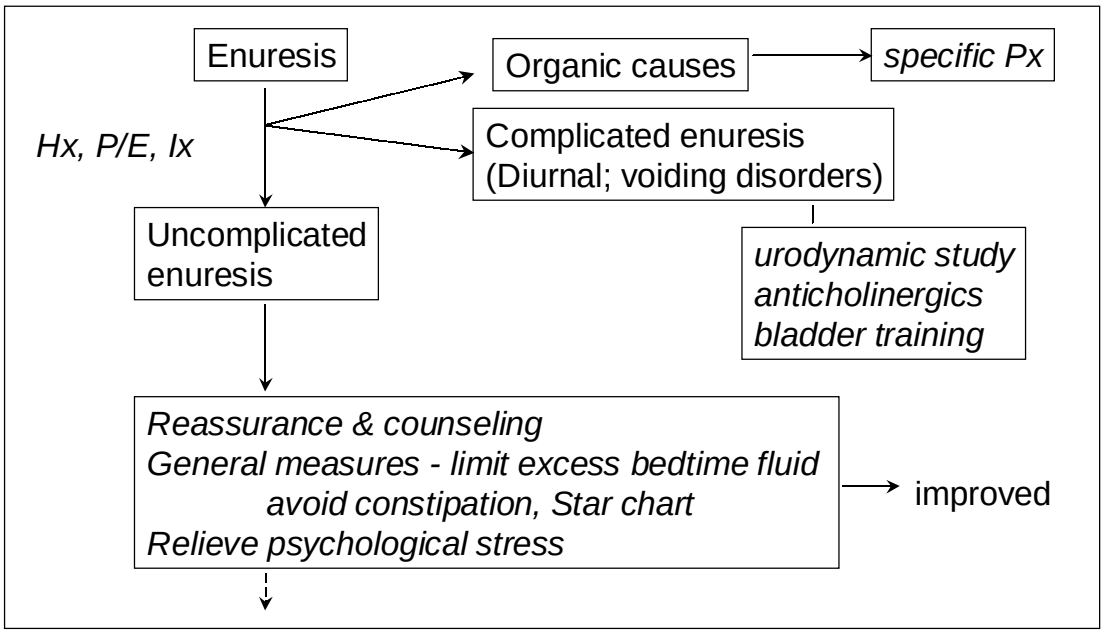

Figure 1 Suggested management strategies for childhood nocturnal enuresis (Part 1).

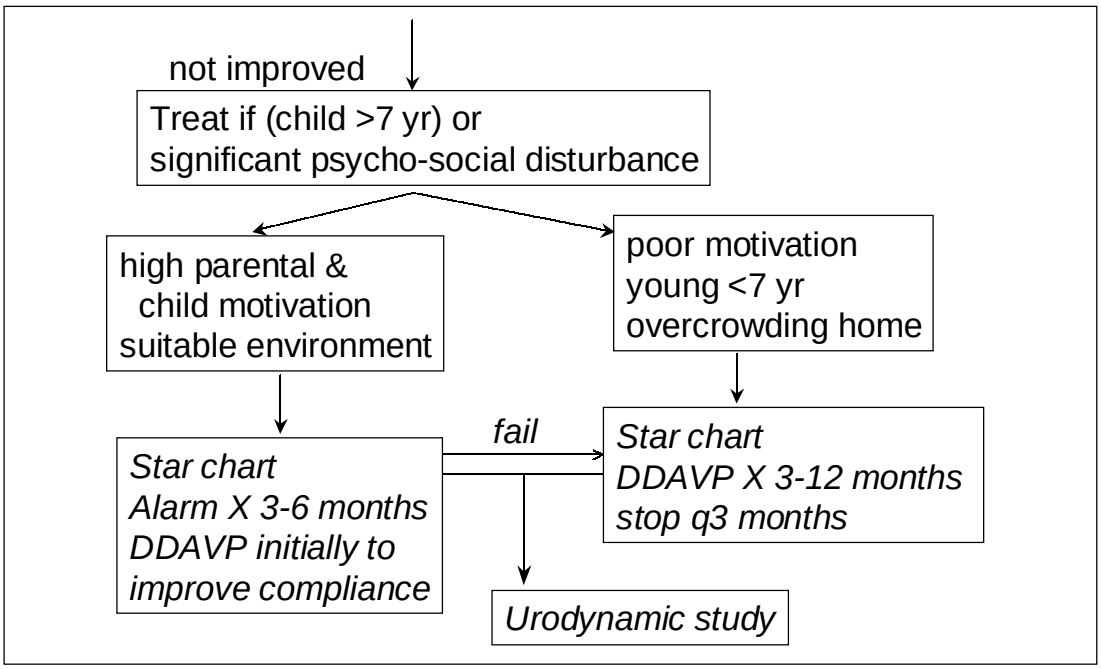

Figure 2 Suggested management strategies for childhood nocturnal enuresis (Part 2).

They should be reassured that PNE is not an organic disease of the kidneys or the brain, and that they stand a high chance of getting rid of the problem in future. We should relieve the guilty feeling of the parents, advise them not to punish their child for wet nights but praise them for dry nights. The child should be motivated to improve and develop his self-confidence. The possibility of the bedwetting as a manifestation of underlying stress or conflict in the family should be explored and dealt with appropriately. Often this simple counseling already leads to significant improvement or even resolution. The child should also be encouraged to keep a star chart as a reward and record of the progress of further treatment.

If there is no resolution and child is over seven years old, or earlier if the enuresis has caused significant psycho-social disturbance, specific treatment is advised. The first-line treatment is alarms therapy. Desmopressin has a role as an adjunct to improve compliance if it can be afforded, or when patients are too young or poorly motivated to comply with alarms, or when alarms are contra-indicated because of home environment. If these therapies fail, it may be worthwhile to proceed to invasive urodynamic studies to uncover any voiding dysfunction.

Conclusion

PNE has multifactorial causation. Children with PNE have a high chance of resolution, either spontaneously or with treatment. PNE may lead to parental stress and psycho-behavioural problems in the child, but not psychiatric diseases. Treatment should be individualised because there may be different subtypes of patients, and because of patient and family preference. From the evidence so far, alarms therapy, if properly used, has the best long term success. Desmopressin has good symptomatic relief and, for those who can afford it, desmopressin has a role as short term therapy in gaining the initial confidence of the family, or ensuring dry nights in outings, or as longer term therapy when alarms are contraindicated or have failed, or perhaps for those who have large nocturnal urine production. Imipramine is as effective as desmopressin, but best avoided because of potential risk of fatal poisoning.

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