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Primary nocturnal enuresis: omega-3 fatty acids may be of therapeutic value

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Summary Primary nocturnal enuresis (PNE), or bed-wetting, is a distressing urinary condition which can persist through childhood and beyond. Altered prostaglandin and nitric oxide production have been observed in children with PNE, and prostaglandin inhibitors are known to be of therapeutic value. Omega-3 fatty acids have the potential to influence the symptoms of PNE by inhibition of prostaglandin and renal nitric oxide production. In addition, children with PNE have an inappropriate startle response and an apparent maturational delay of the central nervous system. Research clearly shows that omega-3 fatty acids play a critical role in the development and function of the central nervous system. It is our contention that inadequate omega-3 intake may play a role in the lack of inhibitory input to the startle and micturition centers in PNE.

Introduction

Primary nocturnal enuresis (PNE) is a condition where the involuntary voiding of urine occurs beyond the age of anticipated nocturnal bladder control. While PNE (bed-wetting) can be diagnosed at 5 years old and beyond, clinically it is generally left untreated until 7–8 years old. Although benign, it is clear that PNE can be extremely distressing, with a negative psychological impact on children and their families [1].

Recent research has uncovered physiological abnormalities in children with PNE, including altered prostaglandin and nitric oxide production. In addition, there may be deficits within the central nervous system (CNS) of those with PNE, including an inappropriate startle response. Omega-3 fatty acids, long chain polyunsaturated fatty acids of plant and marine origin, are known to influence these abnormalities described in PNE. The goal of this report is to integrate various branches of research to support our hypothesis, that omega-3 fatty acids may have therapeutic value in PNE.

Prostaglandins in PNE

At least one factor thought to play a role in PNE is an increase in nocturnal diuresis due to elevated solute excretion [2]. Prostaglandin E2 (PGE2) is

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known to decrease the reabsorption of sodium and magnesium in the first part of the distal tubule. Indeed children with PNE have a 44% increase in nocturnal sodium excretion and a 58% increase in magnesium excretion vs. healthy controls [3]. Children with PNE have been shown to have mean serum and urine PGE2 levels that are twice that of healthy controls [4]. Even if levels are normal, there appears to be a relative dominance of prostaglandins acting on the renal tubular cells in PNE vs non-enuretic children [5]. In addition, a number of studies have shown that non-steroidal anti-inflammatory and PGE2 inhibiting medications are valuable in reducing the frequency of bed-wetting [6—8]. Successful pharmacotherapy is correlated with lowered serum and urinary PGE2 levels [4]. PGE2 inhibitors may prevent instability and overcontractility of bladder muscles [9]. Desmopressin, one of the most commonly prescribed medications for PNE is a synthetic analog of natural vasopressin which increases urinary concentration and decreases urine production. Interestingly, enuretic patients who are non-responders to desmopressin have significantly higher PGE2 levels than normal controls and those who respond to the drug [10].

Nitric oxide in PNE

There are two sides to nitric oxide (NO), the beneficial effects of transient low levels produced by endothelial nitric oxide synthase (eNOS) and the negative effects of high concentrations produced by inducible nitric oxide synthase (iNOS) found in renal tubules, fibroblasts and macrophages. Within the urinary system, most of the effects of NO are similar to those of PGE2; NO inhibits sodium and fluid reabsorption and decreases anti-diuretic hormone production. Nitrite is a stable end product of NO, and it has been observed that children with PNE have more than 11 times greater nitrite excretion vs. healthy controls [11]. After administration of the potent prostaglandin inhibitor, indomethacin, the nitrite levels were reduced by almost 50 percent in PNE. The reduction in nitrite levels was correlated with significant reductions in the frequency of bed-wetting. Indomethacin decreased the 24-h urinary volume and increased the day:-night urinary volume ratio by 55% [11].

Startle response in PNE

It has been suggested that PNE represents a functional immaturity of the CNS, with a lack of normal inhibition of the micturition reflex. Research suggests that the inhibitory component of the brain center that regulates micturition is not sufficiently active and/or the signals from the distended bladder are not registered [12]. Indeed the 15% per-year spontaneous resolution rate characteristic of PNE may reflect a slower CNS maturity. Patients with PNE have well-documented deficits in the brain center which normally inhibits the startle response. Briefly, the startle response consists of a contraction of the skeletal and facial muscles, and an eyeblink in response to a sudden, relatively intense stimulus. If, however, an additional weak stimulus (prepulse) is presented immediately before the startle stimulus, there is normally an inhibition of the startle response. The PPI should normally reach maturity between 5 and 8 years old [13].

The prepulse inhibition of startle (PPI) is significantly decreased in PNE, it is a highly specific finding [13,14]. In other words, there is a lack of proper inhibition occurring in an area linked to the micturition center.

The area of the brain which has received considerable attention in regulating the startle response is the nucleus accumbens (NA). An over-activity of dopamine within the NA is thought to promote a decreased PPI [15]. Dopamine agonists can decrease normal PPI, while dopamine antagonists can restore PPI in animals. A direct relationship between dopamine overflow in the NA and a decreased PPI has been observed [16]. The deficiency of inhibitory signal processing within the brain, perhaps mediated by dopamine, appears to be a common thread between PNE and diminished PPI.

Omega-3 and PNE

Omega-3 fatty acids may influence PNE by regulation of PGE2, NO synthesis and brain signaling. The ability of omega-3 fatty acids to inhibit PGE2 synthesis is well-documented, both experimentally and in humans [17,18]. In addition, omega-3 fatty acids from fish have been reported by a number of investigators to markedly lower iNOS and nitric oxide synthesis [19,20]. The advantages of this fish oil-derived NO inhibition within the urinary system have been noted [21]. Clinical trials should be conducted to determine if omega-3 administration can be applied as a monotherapy or perhaps an adjuvant to standard care as a means of lowering the PGE2 and NO influence on nocturnal diuresis.

Omega-3 fatty acids are well-documented to play a critical role in the normal development of the CNS. In omega-3 deficient rats, increases in

dopamine within the NA and decreases within the frontal cortex have been observed [22,23]. The increase in NA dopamine is thought to be a result of the loss of normal inhibitory control by reductions in frontal cortex dopamine [24]. Inadequate omega-3 intake may therefore prolong the delay in normal inhibitory CNS function, including a delayed inhibition of micturition. In omega-3 deficient diets, the pre- and post-synaptic dopamine receptors (DR2) are decreased in the frontal cortex and dramatically increased in the NA, alterations reflective of protein and mRNA expression [25].

Given that PNE has a strong genetic component, these findings in omega-3 deficient diets have tremendous implications in nutritional neuroscience, particularly that related to genetic transcriptions influenced by diet. A recent review found that while genetic factors are the most important in the etiology of PNE, the influence of environmental factors are highly significant [26]. We propose that nutritional factors such as omega-3 intake are one such environmental factor that deserves consideration. It is interesting to note a recent study which described a lower prevalence of PNE in Malaysia, Korea and Taiwan, vs. the United States, United Kingdom, Ireland, Turkey and Australia [27]. A review of the 2002 United Nations Food and Agriculture Organization statistics (FAOSTAT) shows that each of the former nations consume at least more than double the fish/seafood (kg/capita/year) vs. the latter nations. Perhaps nutrition, in the form of omega-3 fatty acids, can influence the genetics of PNE.

Conclusion

PNE is undoubtedly a complex and heterogeneous condition; this is reflected by the non-universal results obtained through pharmacotherapy [12]. Based on the beneficial reports of PGE2 inhibiting medications, and the new research on the influence of iNOS in PNE, it is our contention that omega-3 fatty acids may have therapeutic value. We make this suggestion based on research documenting the ability of omega-3 fatty acids to decrease PGE2 and iNOS production. An additional potential benefit of omega-3 therapy is that it may address a possible root cause of some cases of PNE, namely the delayed development of inhibitory brain pathways.

It would be possible to initially test the hypothesis by laboratory studies examining the influence of dietary lipids on micturition during animal development. Ultimately, clinical trials with omega-3 fatty acids in the treatment of PNE are warranted to determine if they are of value. In the meantime, omega-3 supplements are generally inexpensive and well-tolerated, making them and attractive option to access alone or as an adjuvant to standard care. Given the current excess of omega-6 rich oils in Western countries, all health professionals should at least ensure adequate intake of omega-3 fatty acids in children with PNE.

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