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Hypothesis: disrupted regulation of the intracranial vascular and cerebrospinal fluid circulations causes nocturia

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Abstract

Nocturia is a prevalent condition and may result from nocturnal polyuria, where overnight urine production is excessive. Anecdotal cases of idiopathic nocturnal polyuria in which cerebrospinal fluid (CSF) disorders were identified suggests a potential mechanism. The skull constrains three circulations, the CSF, interstitial fluid and vascular supply. For each, the fluid dynamics (pressure, volume, flow) are closely regulated, and adapt to changes such as recumbency or circadian variation. Pathologies disrupting the regulation, and thus impairing intracranial fluid dynamics, will place the brain environment at risk. Hence, compensatory responses are needed to maintain safe limits and prevent neurological deficits. We hypothesise that change in the fluid dynamics of an intracranial circulation (CSF, interstitial or vascular) means that positional or circadian changes of sleep trigger compensatory hormonal responses to protect the brain, but also causing nocturnal polyuria. Natriuretic hormones are candidate mediators to protect against excess intracranial pressure or volume.

Article

Background

The rate of urine production normally slows during sleep, mainly due to increased secretion of antidiuretic hormone (ADH). This ensures that nocturnal urinary volume does not exceed bladder storage capacity, hence avoiding sleep disturbance. Nocturia is experienced where the rate of urine production increases or bladder storage function is impaired.[1] Nocturia is a common issue, that negatively affects quality of life and is associated with increased mortality.[2]

Systemic conditions raising urine production rate are key aetiological factors,[3] either increasing it continuously (24-hour polyuria) or selectively during sleep (nocturnal polyuria).[4] For example, obstructive sleep apnoea (OSA) generates increased atrial natriuretic peptide (ANP), hence causing nocturnal polyuria.[5] Factors linking increased urine production to sleep include:

1. Disrupted circadian regulation, with impaired hormonal control of urine production.
2. Postural/positional changes, such as exaggerated fluid shifts caused by recumbency for oedematous patients.

Clinical assessment of nocturia requires assessment of behavioural factors (e.g. evening fluid intake) and co-morbid causes (cardiovascular, endocrine, renal, biochemical, urological and sleep disorders).[3,6] However, evaluation may not find a causative explanation (idiopathic nocturnal polyuria), suggesting there are unidentified causes. We have seen several cases of idiopathic nocturnal polyuria where cerebrospinal fluid (CSF) disorders were identified [Box 1].

Hypothesis

The skull encloses a constrained volume housing the brain, and accommodates circulations in the CSF, interstitial fluid and vascular supply. Circulatory variables are closely regulated in each to protect the brain and maintain its essential supplies. This regulation has to deal with a range of circumstances. Sleep is an important example, as it requires responses to fluid shifts that could raise intracranial volume and hydrostatic pressure when lying down (recumbency), cerebrovascular fluctuations with different sleep stages,[7] and physiological CO_2 retention. Regulating the dynamics of the intracranial circulations ensures appropriate pressure, volume and flow for each fluid compartment, to maintain a safe environment in healthy individuals [Figure 1].

A problem affecting any of the circulations may disrupt this regulation, impairing the intracranial fluid dynamics. Hence, compensatory responses become necessary to back up regulatory mechanisms, in order to stay within safe limits and protect the brain. The physical and physiological influences of sleep increase fluid dynamic stresses in the intracranial environment. Hence, the challenge to ordinary regulatory processes is greater, and the possible need for protective compensatory responses is enhanced. Up to a point, regulation and compensation could prevent the emergence of neurological symptoms. However, further progression could mean that these processes fail to keep the pressure or volume within safe limits, leading to clinical problems such as intracranial hypertension or hydrocephalus.

Water and salt levels are crucial variables determining dynamics of a physiological compartment, and for transferring volume between compartments. Accordingly, their hormonal control could counteract situations where ordinary regulation of an intracranial circulation is insufficient to maintain the safe environment. Hence, natriuretic hormones are candidate mediators of a compensatory protective effect against excess intracranial pressure or volume. In the systemic circulation, these hormones powerfully affect rate of urine production by controlling urinary salt (natriuresis).

We hypothesise that change in the fluid dynamics of an intracranial circulation (CSF, interstitial or vascular) means that positional or circadian changes of sleep trigger compensatory hormonal responses to protect the brain, but also causing nocturnal polyuria.

Functioning normally, regulation of the fluid dynamic variables in each intracranial circulation successfully maintains safe parameters in all circumstances. Our hypothesis suggests that onset of dysfunction leads to an additional compensation mechanism, with natriuretic peptides as candidate mediators. This is more likely to be needed during sleep, due to the additional challenges to the intracranial circulations. The compensatory process maintains safe limits and so prevents neurological symptoms (subclinical), but causes nocturia [Figure 2]. Progression of the predisposing cause could mean that compensatory processes are present but insufficient, so this subgroup of patients with apparently idiopathic nocturia may later develop neurological symptoms.

Nocturnal changes in intracranial circulatory dynamics

Night-time variations in intracranial pressure (ICP) occur in health, influenced by recumbency, sleep stage[7] and CO_2 retention.[8] The intracranial volume of CSF (production and inflow into the cranial cavity) varies over the circadian cycle, peaking nocturnally [9]. Brain interstitial space expansion also occurs during sleep[10] and is associated with enhanced clearance of metabolic waste products via glymphatic drainage, which itself shows strong circadian rhythmicity,[10,11] and can be impaired in neurodegenerative conditions.[12] In individuals with pre-existing disorders of intracranial CSF pathways, night-time ICP fluctuations are more marked than in healthy individuals.[13] Abnormalities of these dynamic nocturnal processes were proposed in disorders with impaired intracranial circulation,[14] potentially including idiopathic intracranial hypertension (IIH), normal pressure hydrocephalus, traumatic brain injury and subarachnoid haemorrhage (SAH).

Hormonal effects of intracranial circulatory dynamics

Our hypothesis suggests a link between intracranial circulatory variables (volume, pressure or flow) and rate of urine production in circumstances where ordinary regulatory processes are insufficient to maintain a controlled environment. ANP and brain natriuretic peptide (BNP) increase in cranial conditions associated with elevated ICP. Increased plasma BNP associated with raised urine output is seen following SAH,[15] while ANP and BNP are both elevated following ischaemic stroke.[16] Furthermore, compensatory modulation of choroid plexus function by ANP may down-regulate ICP in hydrocephalus,[17] by reducing CSF production. ANP rises in association with increasing ICP, and is particularly enhanced at higher ICPs.[18] This non-linear relationship suggests a "threshold" at which standard pressure regulation is insufficient, and secondary protection becomes prominent. ICP can empirically be reduced by administration of exogenous ANP, as demonstrated in a rodent model[19] further suggesting a protective role. Plasma BNP levels correlate with nocturnal polyuria in elderly patients;[20] this was attributed to latent heart failure, but protection of intracranial circulations may be an alternative or additional explanation. Indirectly, modest elevations in ICP activate the sympathetic nervous system [21,22], that can trigger systemic release of ANP and BNP.[23] Sympathetic activation with modest ICP elevation ("intracranial baroreflex") is seen in humans when ICP is elevated from 8 to 15mmHg during lumbar infusion,[21] a comparable rise to that seen with lying down from standing.[24]

In principle, an altered rate of urine production in the context of intracranial pathology could also be mediated by changes in ADH secretion. The most clearly recognised links are to increased ADH release or to central diabetes insipidus, reducing or increasing urine output respectively, which may arise in severe or acute situations with evident increase in ICP, such as traumatic brain injury.

Exploring the hypothesis further

In health, a safe intracranial environment is maintained during sleep, with reduced urine production. Disrupted intracranial fluid dynamics necessitates compensatory mechanisms to protect the brain. Natriuresis, or perhaps diuresis, may protect the intracranial environment, for example by reducing CSF production, and by offloading volume and salt from the systemic circulation. Recumbency and the circadian changes of sleep may elicit the need for intracranial protection, hence nocturnal polyuria.

Key indicators will be changes to relevant hormones in idiopathic nocturnal polyuria, for example increased overnight ANP/ BNP. The greater challenge comes from identifying the underlying triggers that lead to endocrine responses. Our hypothesis recognises the potential relevance of any one of three intracranial circulations. Indeed, it may be that the issue is localised to a particular region within one of these circulations, which may differ from person to person. Yet further complexity comes from the fluid dynamics, since a healthy intracranial environment requires that volumes, flow rates and fluid compositions all stay within acceptable ranges, alongside pressures. Evaluating these in a subclinical population is particularly challenging.

Case series and anecdotal evidence could support an association between disrupted intracranial fluid dynamics and nocturia. Several groups can be considered across a spectrum of severity for clinical features, for example;

1. Idiopathic nocturnal polyuria. This group would constitute people who are compensating for inadequate regulation of intracranial fluid dynamics, and thereby remain subclinical. Here, finding increased natriuretic peptides would be suggestive. Affected people could be screened for undiagnosed intracranial problems, such as raised ICP or normal pressure hydrocephalus.
2. Asymptomatic papilloedema caused by raised ICP (commonly referred urgently after detection at optician appointments). Here, screening for nocturnal polyuria should be undertaken- ideally before intervention such as lumbar puncture. This would be simple to undertake using a bladder diary.
3. IIH. Anecdotal observation suggests a higher prevalence of nocturia than expected for age in IIH patients; widespread use of bladder diaries would enable this to be catalogued systematically.
4. Common brain neurodegenerative conditions. In many, notably Parkinson's disease and Alzheimer's disease, there is eventual brain atrophy with expanded CSF spaces. Nocturia is prevalent in neurodegenerative disorders, and a compensatory response for inadequate regulation of intracranial fluid dynamics could be a factor.

For all groups, screening for confounding causes of nocturnal polyuria, notably OSA, would be important.

Unfortunately, case series are insufficient to identify the complex relative influences of the intracranial circulations (CSF, blood and interstitial space), the fluid dynamics (pressure, volume and flow), the precipitating circumstances (recumbency or circadian variation) and the potential co-existence of other causes of nocturnal polyuria. Accordingly, understanding the pathophysiology requires evaluation in animal models, where individual factors can be more easily manipulated to explore the complex interplay of influences.

Conclusions

The intracranial CSF, interstitial and vascular circulations are regulated to adapt to variations in position and the circadian cycle. Impairment of intracranial fluid dynamics necessitates compensatory processes. The compensation may include natriuretic hormones to delay onset of neurological symptoms, but leading to nocturnal polyuria. Exploring this hypothesis may explain idiopathic nocturnal polyuria and allow the development of new treatments, while simultaneously improving our understanding of cerebral physiology.

Author contributions

All authors contributed to the conceptualisation of the hypothesis. Roy and Smith undertook literature reviews. Blaber prepared the illustrations. Roy, Smith and Drake wrote the manuscript. Blaber, Pereira and Fry reviewed and edited the manuscript. All authors approved the submitted version.

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References

1. Hashim H, Blanker MH, Drake MJ, et al. International Continence Society (ICS) report on the terminology for nocturia and nocturnal lower urinary tract function. *Neurourol Urodyn* 2019; **38**(2): 499-508.
2. Funada S, Tabara Y, Setoh K, et al. Impact of Nocturia on Mortality: The Nagahama Study. *J Urol* 2020; **204**(5): 996-1002.
3. Cornu JN, Abrams P, Chapple CR, et al. A contemporary assessment of nocturia: definition, epidemiology, pathophysiology, and management--a systematic review and meta-analysis. *Eur Urol* 2012; **62**(5): 877-90.
4. Hashim H, Drake MJ. Basic concepts in nocturia, based on international continence society standards in nocturnal lower urinary tract function. *Neurourol Urodyn* 2018; **37**(S6): S20-S4.
5. Umlauf MG, Chasens ER, Greevy RA, Arnold J, Burgio KL, Pillion DJ. Obstructive sleep apnea, nocturia and polyuria in older adults. *Sleep* 2004; **27**(1): 139-44.
6. Everaert K, Herve F, Bosch R, et al. International Continence Society consensus on the diagnosis and treatment of nocturia. *Neurourol Urodyn* 2019; **38**(2): 478-98.
7. Wayenberg JL, Hasaerts D, Franco P, Valente F, Massager N. Anterior fontanelle pressure variations during sleep in healthy infants. *Sleep* 1995; **18**(4): 223-8.
8. Fultz NE, Bonmassar G, Setsompop K, et al. Coupled electrophysiological, hemodynamic, and cerebrospinal fluid oscillations in human sleep. *Science* 2019; **366**(6465): 628-31.
9. Nilsson C, Stahlberg F, Thomsen C, Henriksen O, Herning M, Owman C. Circadian variation in human cerebrospinal fluid production measured by magnetic resonance imaging. *Am J Physiol* 1992; **262**(1 Pt 2): R20-4.
10. Xie L, Kang H, Xu Q, et al. Sleep drives metabolite clearance from the adult brain. *Science* 2013; **342**(6156): 373-7.
11. Hablitz LM, Pla V, Giannetto M, et al. Circadian control of brain glymphatic and lymphatic fluid flow. *Nat Commun* 2020; **11**(1): 4411.
12. Harrison IF, Ismail O, Machhada A, et al. Impaired glymphatic function and clearance of tau in an Alzheimer's disease model. *Brain* 2020; **143**(8): 2576-93.
13. Yokota A, Matsuoka S, Ishikawa T, Kohshi K, Kajiwara H. Overnight recordings of intracranial pressure and electroencephalography in neurosurgical patients. Part II: Changes in intracranial pressure during sleep. *J UOEH* 1989; **11**(4): 383-91.

14. Rasmussen MK, Mestre H, Nedergaard M. The glymphatic pathway in neurological disorders. *Lancet Neurol* 2018; **17**(11): 1016-24.
15. Berendes E, Walter M, Cullen P, et al. Secretion of brain natriuretic peptide in patients with aneurysmal subarachnoid haemorrhage. *Lancet* 1997; **349**(9047): 245-9.
16. Makikallio AM, Makikallio TH, Korpelainen JT, et al. Natriuretic peptides and mortality after stroke. *Stroke* 2005; **36**(5): 1016-20.
17. Johanson CE, Donahue JE, Spangenberger A, Stopa EG, Duncan JA, Sharma HS. Atrial natriuretic peptide: its putative role in modulating the choroid plexus-CSF system for intracranial pressure regulation. *Acta Neurochir Suppl* 2006; **96**: 451-6.
18. Yamasaki H, Sugino M, Ohsawa N. Possible regulation of intracranial pressure by human atrial natriuretic peptide in cerebrospinal fluid. *Eur Neurol* 1997; **38**(2): 88-93.
19. Akdemir G, Luer MS, Dujovny M, Misra M. Intraventricular atrial natriuretic peptide for acute intracranial hypertension. *Neurol Res* 1997; **19**(5): 515-20.
20. Sone A, Kondo N, Kobayashi T, et al. [Association with relative nocturnal polyuria using BNP (brain natriuretic peptide) in eldely patients with nocturia]. *Nihon Hinyokika Gakkai Zasshi* 2007; **98**(3): 558-64.
21. Schmidt EA, Despas F, Pavy-Le Traon A, et al. Intracranial Pressure Is a Determinant of Sympathetic Activity. *Front Physiol* 2018; **9**: 11.
22. Guild SJ, Saxena UA, McBryde FD, Malpas SC, Ramchandra R. Intracranial pressure influences the level of sympathetic tone. *Am J Physiol Regul Integr Comp Physiol* 2018; **315**(5): R1049-R53.
23. Luchner A, Schunkert H. Interactions between the sympathetic nervous system and the cardiac natriuretic peptide system. *Cardiovasc Res* 2004; **63**(3): 443-9.
24. Magnaes B. Body position and cerebrospinal fluid pressure. Part 2: clinical studies on orthostatic pressure and the hydrostatic indifferent point. *J Neurosurg* 1976; **44**(6): 698-705.

Box 1 Case studies

An 81-year old woman with severe nocturnal polyuria. Her nocturnal polyuria index (NPI), the overnight urine production as a proportion of the overall daily urine volume, was 74%; the normal NPI at this age is <33%. She had no medical history of note, took no regular medications, had no signs of cardiac failure and her blood pressure was normal. Investigations established normal renal function and absence of obstructive sleep apnoea (OSA) on overnight oximetry. Nocturia was refractory to antimuscarinic and diuretic agents, and desmopressin was contraindicated on grounds of age. She was found on screening to have normal pressure hydrocephalus.

A 26-year old man initially with no urinary symptoms or nocturia. He underwent surgical management of a Chiari-I malformation which was complicated by hydrocephalus, managed conservatively. Concurrently, he developed urinary symptoms, including urgency, and nocturia. His bladder diary confirmed nocturnal polyuria, with an NPI of 58%; the normal NPI at this age is <20%. There was no other medical history of note.

A 17-year old woman with idiopathic intracranial hypertension and extreme bedwetting. There was no other medical history of note, and OSA was excluded. She used intermittent self-catheterisation in the daytime, but at night she used an indwelling catheter. Overnight, a 2-litre urine bag would overfill and she would develop bypassing around the catheter whilst remaining asleep.

Figure 1 *Within the intracranial cavity, fluid dynamics of the vascular supply (red and blue arrows), cerebrospinal fluid (CSF; yellow arrows) and the interstitium (green arrows) are all crucial. The importance of pressure, volume and flow rate necessitate complex regulatory control, due to potential for rapid deterioration in the confined space enclosing the brain.*

Figure 2 *In health, regulation (green arrow) of each parameter in the overall intracranial fluid dynamics keeps them all within appropriate levels under differing conditions, for example safely enabling change of posture from upright to recumbent. Pathology affecting one of the intracranial circulations may mean that aspects of the fluid dynamics encroach on unsafe levels (dotted brown arrow). Hence, compensatory processes (purple arrow) are needed to ameliorate the effects; release of a natriuretic peptide to compensate for potentially dangerous fluid dynamics when recumbent will lead to nocturnal polyuria. Progression of the dysfunction in the intracranial fluid dynamics leads to neurological symptoms.*