PATHOPHYSIOLOGY OF NOCTURNAL ENURESIS

An Essay
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In Urology

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ARABIC SUMMARY ................................................................—
LIST OF ABREVIATIONS

Ach.........................Acetylcholine
ADH.........................Antiduretic Hormon
CNS.........................Central Nervous System
DDAVP......................Vasopressin
DO.........................Detrusor Overactivity
FBC................. Functional Bladder Capacity
NE.........................Nocturnal Enuresis
MNE.................Monosymptomatic Nocturnal Enuresis
OSA.........Obstructive Sleep Apnea
PGNs.......... preganglionic neurons PGNs
PMC ........pontine micturition centre
PNE.........Primary Nocturnal Enuresis
SNE.........Secondary Nocturnal Enuresis
UTI........Urinary Tract Infection
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INTRODUCTION

Nocturnal enuresis (NE) is a common problem that can cause much distress to affected families.[1]

Nocturnal enuresis is defined as repeated spontaneous voiding of urine during sleep in a child that persists beyond the normative age of maturation of urinary control which is 5 years old.[2]

It is classified as primary or secondary, and monosymptomatic or polysymptomatic. Primary nocturnal enuresis (PNE) is enuresis in a child who has never established urinary continence for more than six months. It accounts for 80% of cases of enuresis. PNE is a common disorder that affects around 15-20% of 5 years old children, 10% of 7-12 years old and up to 2% of adults.[3]

Monosymptomatic or uncomplicated enuresis is enuresis without lower urinary tract symptoms other than nocturnal enuresis and, while polysymptomatic is enuresis with lower urinary tract symptoms. [4]
Introduction

Enuresis has no clear etiology; it is hypothesized to be related to genetics, sleep arousal dysfunction, maturational delay, stress, poor toilet training, bladder dysfunction, and occasionally organic causes.\[^5\]

Positive family history greatly increases the chance of a child wetting the bed, this encourages the idea about genetics and its role in nocturnal enuresis, and when children cannot wake up even the central nervous system (CNS) senses that the bladder is full, this puts sleep arousal dysfunction as an important cause in this condition.

In small functional bladder capacity, children cannot hold the normal amount of urine produced at night. Often associated with frequent daytime voiding.\[^5\]

The maturational delay as a cause of nocturnal enuresis is supported by the fact that 5% of children become dry at night per year without intervention. One theory suggests that development of the CNS recognition of and response to full bladder is delayed.\[^5\]
AIM OF STUDY

The aim of study is to discuss the different theories, causes and mechanisms of action which explain nocturnal enuresis.
Neurophysiology of Micturation

**NEUROPHYSIOLOGY OF MICTURATION**

- Introduction
- Peripheral innervation of the urinary tract
- CNS pathways involved in micturition
- Regulation of bladder filling and voiding
- The guarding reflex
Neurophysiology of Micturation

NEUROPHYSIOLOGY OF MICTURATION

Introduction:

Normal bladder storage and voiding involve low pressure and adequate bladder volume filling followed by a continuous detrusor contraction that results in bladder emptying, associated with adequate relaxation of the sphincter complex. This process requires normal sensation and normal bladder outlet resistance. The neurophysiological mechanisms involved in normal bladder storage and evacuation include a complex integration of sympathetic, parasympathetic and somatic innervation which ultimately controlled by a complex interaction between spinal cord, brain stem, midbrain and higher cortical structures.[6]

In newborns the bladder has been traditionally described as "uninhibited", and it has been assumed that micturition occurs automatically by a simple spinal cord reflex, with little or no mediation by the higher neural centers. However, studies have indicated that even in full-term fetuses and newborns, micturition is
modulated by higher centers and the previous notion that voiding is spontaneous and mediated by a simple spinal reflex is an over simplification.[7]

Peripheral innervation of the urinary tract

The requirement for voluntary control over the lower urinary tract necessitates complex interactions between autonomic (mediated by sympathetic and parasympathetic nerves) and somatic (mediated by pudendal nerves) efferent pathways. The sympathetic innervation arises in the thoracolumbar outflow of the spinal cord, whereas the parasympathetic and somatic innervation originates in the sacral segments of the spinal cord. Afferent axons from the lower urinary tract also travel in these nerves.[8]
Neurophysiology of Micturation

Efferent pathways of the lower urinary tract[^9]

**a** | Innervation of the lower urinary tract. Sympathetic fibres originate in the T11–L2 segments in the spinal cord and run through the inferior mesenteric ganglia (inferior mesenteric plexus, IMP) and the hypogastric nerve (HGN) or through the paravertebral chain to enter the pelvic nerves at the base of the bladder and the urethra. Parasympathetic preganglionic fibres arise from the S2–S4 spinal segments and travel in sacral roots and pelvic nerves to ganglia in the pelvic plexus (PP) and in the bladder wall. Somatic motor nerves that supply the striated muscles of the external urethral sphincter arise from S2–S4 motor neurons and pass through the pudendal nerves.

**b** | Efferent pathways and neurotransmitter mechanisms that regulate the lower urinary tract. Parasympathetic postganglionic axons in the pelvic nerve release acetylcholine (ACh), which produces a bladder contraction by stimulating M3 muscarinic receptors in the bladder smooth muscle. Sympathetic postganglionic neurons release noradrenaline (NA), which activates β3 adrenergic receptors to relax bladder smooth muscle and activates α1 adrenergic receptors to contract urethral smooth muscle. Somatic axons in the pudendal nerve also release ACh, which produces a contraction of the external sphincter striated muscle by activating nicotinic cholinergic receptors. Parasympathetic postganglionic nerves also release ATP, which excites bladder smooth muscle, and nitric oxide, which relaxes urethral smooth muscle. L1, first lumbar root; S1, first sacral root; SHP, superior hypogastric plexus; SN, sciatic nerve; T9, ninth thoracic root.[^9]
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Sympathetic postganglionic nerves — for example, the hypogastric nerve — release noradrenaline, which activates β-adrenergic inhibitory receptors in the detrusor muscle to relax the bladder, α-adrenergic excitatory receptors in the urethra and the bladder.\(^\text{[10]}\)

Parasympathetic postganglionic nerves release both cholinergic (acetylcholine, ACh) and non-adrenergic, non-cholinergic transmitters. Cholinergic transmission is the major excitatory mechanism in the human bladder. It results in detrusor contraction and consequent urinary flow and is mediated principally by the M3 muscarinic receptor, although bladder smooth muscle also expresses M2 receptors. Muscarinic receptors are also present on parasympathetic nerve terminals at the neuromuscular junction and in the parasympathetic ganglia.\(^\text{[11]}\)

Somatic cholinergic motor nerves that supply the striated muscles of the external urethral sphincter arise in S2–S4 motor neurons in Onuf's nucleus and reach the periphery through the pudendal nerves.\(^\text{[8]}\)
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CNS pathways involved in micturition

The regulation of micturition requires connections between many areas in the brain and extensive tracts in the spinal cord that involve sympathetic, parasympathetic and somatic systems. Parasympathetic and sympathetic preganglionic neurons (PGNs) are located in the intermediate grey matter (laminae V–VII) of spinal cord sacral and lumbar segments, respectively.

Parasympathetic PGNs send dendrites into the dorsal commissure and into the lateral dorsal horn of the spinal cord and exhibit an extensive axon collateral system that is distributed bilaterally in the cord. A similar axon collateral system has not been identified in sympathetic preganglionic neurons. The somatic motor neurons that innervate the external urethral sphincter are located in the ventral horn (lamina IX) in Onuf's nucleus, have a similar arrangement of transverse dendrites and have an extensive system of longitudinal dendrites that travel within Onuf's nucleus.[12]

Afferent nerves from the bladder project to regions of the spinal cord that contain interneurons and
Neurophysiology of Micturation

parasympathetic PGN dendrites. Pudendal afferent pathways from the urethra and the urethral sphincter exhibit a similar pattern of termination.\[13\]

In the brain, many neuron populations are involved in the control of the bladder, the urethra and the urethral sphincter. Some, such as the serotonergic neurons of the medullary raphe nuclei and the noradrenergic A5 cell group in the brain stem, are non-specifics. Others are specific for micturition: these include the neurons of Barrington's nucleus (also called the pontine micturition centre (PMC) and those of the periaqueductal grey (PAG), cell groups in the caudal and preoptic hypothalamus, and the neurons of several parts of the cerebral cortex, in particular the medial frontal cortex.\[14\]

**Regulation of bladder filling and voiding**

The neural pathways that control lower urinary tract function are organized as simple on–off switching circuits that maintain a reciprocal relationship between the urinary bladder and the urethral outlet. Storage