Primary bladder neck obstruction in men – what´s new in the pathophysiology of this underestimated problem?

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Article

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Abstract

Primary bladder neck obstruction (PBNO) is a dysfunction of the bladder neck (BN) in which the collum vesicae is narrow or fails to open adequately during voiding, resulting in a bladder outlet obstruction. PBNO causes storage or voiding LUTS often years before a correct diagnosis of PBNO is made. These patients have often been seen by many physicians and misdiagnosed as having psychogenic voiding dysfunction because of a normal prostate on rectal examination, a negligible residual urine volume, and a normal endoscopic bladder and prostate appearance. The cause of PBNO has not yet been clarified and has so far been a clinical differential diagnosis after the exclusion of the usual differential diagnoses of LUTS and bladder emptying disorders. Several publications let assume that PBNO could be induced by inflammatory processes, possibly by the same inflammatory patterns that have been previously described for BPH development, leading to an initially reversiblel and later irreversible remodeling of the connective tissue of the BN. The clinical value of these observations consists of a correct and precise diagnostic framework especially in young men referring pelvic pain and LUTS despite their small prostate volumes. The proper diagnosis could provide a tempestive calculated therapy proposal that can stop illness progression or in same cases reverse inflammation and collagenic deposition, limiting the risk of future obstruction and symtomatic progression.

Introduction

Primary bladder neck obstruction (PBNO) is a dysfunction of the bladder neck (BN) in which the collum vesicae is narrow or fails to open adequately during voiding, resulting in increased urinary obstruction. The precise cause of PBNO has not been clearly elucidated, but has to be clearly separated from of other anatomical or functional bladder outlet obstructions such as benign prostatic enlargement in men or genitourinary prolaps in women, with the typical late-onset manifestations. In men, PBNO was first reported by Guthrie in 1836 [1–3]. Marion described the condition in detail in 1933 as a new syndrome [4]. The diagnosis of PBNO became popular in the 1960s, and surgical therapy was commonly performed in boys with lower urinary tract symptoms (LUTS) and urinary infections [5]. PBNO may present with a variaty of symptoms including voiding and storage symptoms, ejaculation dysfunction and pelvic pain, or a combination of all symptoms. Due to PBNO being a rather unknown urologic disorder, its incidence is may be underestimated, but has been reported in 28–54% of young men with LUTS [6–10] and is mostly diagnosed between the ages of 18–50 years [11, 12]. LUTS in PBNO are frequently not reported by the patients or misdiagnosed by prior treating physiciansas having psychogenic voiding dysfunction because of a normal prostate on rectal examination, a negligible residual urine volume, and a normal endoscopic bladder and prostate appearance. When prostatic enlargement develops in individuals with PBNO, a double obstruction results. These patients often present with a lifelong history of voiding dysfunction, that the patients have to accept as normal even in younger years. Exacerbation of symptoms can occur quickly and at early stages of prostatic enlargement [13]. The cause of PBNO has not yet been clarified and has so far been a clinical differential diagnosis after the exclusion of the usual differential diagnoses of LUTS and bladder emptying disorders. These difficulties led to the controversy

on the very existence of this entity. The term “primary“ implicates an congenital or early aquired condition with an early-onset manifestation and non-iatrogenic or non-traumatic cause of a separate disease complex. A broader awareness of PBNO as a differential diagnosis especially in younger men or men with a lifelong history of voiding disorder is needed. A better understanding of the pathogenesis will enable a more targeted therapy and prevention.

Methods

The following keywords were used to search PubMed and Web of Science databases for literature published before February 2023: ((“Marion`s disease” [title]) or (“primary bladder neck obstruction” [title]) or (“fibroelastosis of the bladder neck” [title]) or (“primary bladder outlet obstruction” [title]) or (“primary bladder neck dysfunction” [title]) or (“bladder neck” [title]) or (“wall of the bladder neck” [title]) or (“internal vesical sphincter” [title]) or (“functional bladder neck obstruction” [title]) or (“bladder neck dyssynergia” [title]) or (bladder neck hypertrophia [title]) or (“dysfunctional bladder neck” [title]” or (“smooth muscle dyssynergia” [title] or (“proximal urethral obstruction” [title]). Several search filters were used during the search including the language and the time filters to include all the types of articles published in English language in the last 20 years. Generally, the search revealed 136 records. After the removal of non referred articles to PBNO and duplicates, the records were screened by the title and abstract to identify all the articles of real interest. Overall, 0 clinical studies were identified (ClinicalTraisl.gov; International Clinical Trials Registry Platform ICTRP of WHO). Publications with small case series or case reports that dealed with no hypotheses were sorted out. We excluded papers regarding PBNO in females and children. Other 27 articles dealing with historical aspects and technological background of PBNO were additionally discussed. We excluded all the papers regarding embriologycal theories on bladder neck dysfuction. In this setting, the current review focuses particularly on the evaluation of physiopathological changes of the BN and its new hypotheses.

Pathophysiology Of Primary Bladder Neck Obstruction (Pbno) – Historical Findings And New Theories

Initially, Marion focused 1933 on structural changes at the BN by fibrous narrowing and hyperplasia [4]. Leadbetter and Leadbetter assumed in 1959 that a remodeling of the BN in nonmuscular connective tissue results in obstructed BN by hypertrophic musculus sphincter vesicae, fibrous contracture and postinflammatoric processes [5]. Turner-Warwick described in 1973 inefficient BN opening due to an abnormal morphologic arrangement of the bladder musculature (detrusor/trigonal) [14]. Awad suggested in 1976 a neurological dysfunction of the sympathic nervous system with a kind of detrusor-sphincter-dyssynergia [15]. Yalla found in 1977 striated muscle components of the urethral sphincter involving the BN and supposed a dysfunction by as an anatomical anomaly or dysfunction of the BN [16]. To date, however, no concrete cause of the PBNO could be justified. Even if PBNO is a frequent condition, several hypotheses have been formulated on its pathogenesis but none of those has reached a good reliability on clinical practice [17]. There is the hypothesis of an impaired dissolution of the BN mesenchyme during

foetal life, others sustained the non compliance of BN musculature; more recent theories support an increase in the density of Neuropeptide Y immunoreactive nerves, stating PBNO is more a functional illness linked to pelvic floor dyssynergia than a structural issue [18].

Over the last 20 years, chronic inflammation has been proposed as a prominent role in the pathogenesis of LUTS and BPH. Although almost all surgical BPH histological specimens show chronic inflammatory infiltrates, most of these patients have neither clinical signs of infection nor any correlation with bacterial or other foreign antigenstherefore an hypotesisis of an autoimmune disease has been proposed [19–22]. The recent literature on this specific pathogenesis theory of PBNO supports two pathogenetic mechanisms: the inflammatory and the non-inflammatory pathways.

Inflammatory Pathway

Compared to patients with typical LUTS related to BPH, PBNO patients are younger, have a lower body mass indexes, lower comorbidity scores, and lower PSA, but worse IPSS scores and smaller prostate volumes [23]. Urodynamicaly, several degrees of urinary obstruction with adequate detrusor function were detected and very often they reported a history of previous or current prostatic inflammation, with a failed treatment. Endoscopically, the features considered suggestive of PBNOare internal urethral sphincter hypercontraction and complete lack of elasticity in the absence of urethral strictures, posterior urethral valves, inflammatory lesions, or foreign bodies [23]. In our opinion the PBNO should be always considered throughout the diagnostic work-up of men presenting with LUTS, especially in the context of younger patients with more severe LUTS, including urethrocystoscopy and video urodynamic assessment with voiding cysto-urethrogram [7].

Several publications let assume that PBNO could be also induced by inflammatory processes. It is well known that there is a relationship between prostatic inflammation and LUTS and that physician-diagnosed prostatitis was associated with a 2.4-fold increase in the likelihood of a later diagnosed BPH. Men with a history of prostatitis were also more likely to receive treatment for BPH compared with men without prostatitis. A diagnosis of prostatitis may be an early marker for later development of BPH [24].

Interestingly, analysing 30 periurethral tissues derived from whole prostates samples (prostate cancer specimen), Cantiello found that 70% had an important periurethral inflammatory infiltration. They found significant differences in terms of severity of IPSS, high collagenic deposition in patients with periurethral inflammation compared with patients without. They speculated that the periurethral fibrosis secondary to inflammation could cause LUTS through decreased urethral flexibility while compromising the ability of the prostatic urethra to enlarge and adequately accommodate urinary flow during micturition [25].

Fibbi in a large review on the role of the prostate as an immunocompetent organ, considered the presence of a bacterial and non-infectious chronic prostatitis the initiating and inciting factors leading to tissue hyperproliferation. This change might be facilitated via the antigen-presenting capacity of prostatic stromal cells, which are to induce and sustain intraglandular immune responses. They supported the idea

that the inflammation-induced damage of the prostatic tissue represents a chronic process of wound healing which activates hyperproliferative programmes resulting in BPH nodules and collagen deposition [26].

Robert highligthed that deep analyses of the inflammatory infiltrates has shown a wide spectrum of antigen-presenting cells, involved in the manteinance of the sterility of the genital environment [27]. However, immune cells could also release cytokines and growth factors that recruit other cells that promote the growth of epithelial and stromal prostatic cells, with an unavoidable prostate volume enlargement and prostatic urethra compression [28].

PBNO-affected patients present symptoms which can be confounded with prostatitis, potentially leading to chronic pelvic pain [6] supporting our idea that PBNO can be a consequence of previous prostatic inflammation. However, there is still a debate on the reversibility of the inflammation linked to reversible causes. Wong examined stability of the newly synthesized collagen in bacterial-induced prostatic inflammation and the reversibility of fibrosis and collagen content after resolution of infection and inflammation. Generating inflammation by injecting E.coli into prostates of mice the authors found the half-life of newly synthesized collagen to be significantly shorter in infected/inflamed prostates than in controls. Moreover authors found antibiotic treatment to reverse collagenic deposition, supporting that fibrosis linked to infectious disease is a reversible process [29]. Moreover, Kim demonstrated that profound epithelial mesenchimal transition is observed in lipopolysaccharide induced prostatitis and that the natural HIF-1α inhibitors ascorbate and curcumin were capable to attenuate prostate enlargement both in vivo and in vitro [30].

Prostatitis is known to be a frequently misdiagnosed condition, as young men who are affected by it, mostly for shaming reasons, don’t seek urological counselling. A sperm culture or Meares Stamey tests are rarely prescribed, and a proper antibiotic or anti-infammatory treatment is rarely proposed. We hypotesized that the presence of all these conditions justify the persistence of a chronic inflammatory intraprostatic status. This lastly represents the promoter of progressive collagenic deposition and decrease of elastic system fibers that determine a sudden and long-term bladder outlet obstruction (due to a more rigid or less elastic BN and prostatic urethra that becomes more difficult to bend or compress) and LUTS progression [31–33].

In other terms we speculate on the possibility that the same inflammatory patterns that have been previously described for BPH development and BOO onset should be taken in consideration for the ethiopathogenetic explanation of PBNO (Fig. 1).

The clinical value of these observations consists of a correct and precise diagnostic framework especially in young people referring pelvic pain, voiding and storage LUTS despite their small prostate volumes. The proper diagnosis could provide a tempestive treatment proposal that can stop illness progression or in same cases reverse inflammation and collagenic deposition, limiting the risk of future obstruction and symtomatic progression.

Non-inflammatory **pathway**s

The data on other, non-inflammatory possible causes of PBNO, are scarse and weak. Like Yalla [16], Billis [34] demonstrated significantly more skeletal striated muscle fibers in TURP resection fragments of the BN in PBNO patients than patients with typical symptomatic BPH. In PBNO patients the fibers were thick, prominent, hypertrophied, and frequently in a parallel distribution; whereas BPH patients showed discrete, thin, and transversally or longitudinally cut fibers. They assumed that in PBNO there is a persistence of the cranial part of the skeletal urethral sphincter, which may interfere in the complex process of voiding, and that may explain why those patients did not have their symptoms relieved with alpha-blocker therapy. According to Yalla and Billis, Zago and Camarota hypothized in a case series a possible role of unbalanced biomechanics of the pelvis on the urethral and vesical sphincter activity by an unknown postural orthopaedic condition with pelvic torsion that causes hypercontraction on the pelvic floor and interfering with the normal micturition [35–36]. Camerota et al. found out that PBNO patients have a high prevalence (76%) of myofascial or articular, mostly nociceptive pain across different regions as a relevant component. They postulated that an interplay of peripheral inflammation, postural imbalance and chronic pain could induce nociceptor activation and sympathetic nervous system hyperactivation which in turn leads to a bladder sphincter dysfunction [35–36] (Fig. 1). Hruz described in 60% of patients with diagnosis of category IIIb chronic pelvic pain syndrome a BN hypertrophy as the primary cause of their symptomatology [37].

Hinata described a correlation between increased prostate volume due to BPH and an increase of collagen fibers and degeneration of muscle bundles in the BN. By progression of prostatic hyperplasia the BN muscles were progressively affected by fibrosis with fragmentation of the smooth muscle sphincter vesicae [38] .

Bolton proved that BN shows a physiological variability around its circumference with a uniform response to noradrenaline of whole circumference, significantly stronger response to alpha-adrenergic agonists compared with cholinergic agonists in the posterior part, where as the anterior part had no significant differential response to these [39]. However, alpha-1-blocker just only have a variable success 30–60% in PBNO. Unfortunately most of these studies are small, uncontrolled and non-randomized, non-placebo-controlled with no consistent type or dosage of drug.

Discussion And Conclusions

A synopsis of the various publications raises the suspicion of a multifactorial pathogenesis of PBNO with the result of infection/inflammation leading to degeneration of the BN and subsequent neuromuscular dysfunction. The differently described morphological characteristics and degrees of manifestation of PBNO and the different therapeutic response rates suggest a non-homogeneous and non-continuous remodeling process of the BN in PBNO. The different theories mentioned above do not necessarily contradict each other. Subacute or chronic prostatitis can be subclinical with no clinical signs of inflammation and no symptoms. LUTS can often be determined with variable characteristics and

subjective perception. Likewise, in the case of pelvic pain syndrome, no clinical correlate can often be determined using conventional examination methods. However, this does not exclude occult inflammation with a corresponding pain reaction. According to clinical understanding, this can be accompanied by reactive changes in posture and movement, which in turn promote pain and stress reactions.

In the context of subclinical pathogen-induced inflammation, the theory of the urinary tract microbiome should be discussed. Based on 16S rDNA sequencing and culture techniques, urine is usually not a sterile body fluid, even in healthy people, contrary to the classic conventional medical-urological view, but has a multifaceted microbiome [40]. Changes of the microbiome have been observed in certain urologic disorders. However, an increased occurrence of various pathogens (bacteria, fungi and viruses) in connection with various urological diseases could be determined [41–42]. The effects of antibacterial treatments must be studied further to help clarify whether changes in the urinary microbiome are primarily causative or correlative with bladder disease.

Currently as of the 01/23/2023, no registered clinical study could be found with the term “Primary Bladder Outlet Obstruction” resp. “PBNO”. The search for “Bladder Outlet Obstruction” revealed 44 studies (ICTRP Search Portal Advanced Search (who.int); Search of: bladder outlet obstruction – List Results – ClinicalTrials.gov), with no study on PBNO or on the pathogenesis of PBNO being registered.

Even if the inflammation models and clinical studies are urgently needed to understand the inflammatory signaling pathway mechanisms and the pathogenesis in the hypothized development of PBNO, new minimally invasive therapies (MIST) are emerging [43–46]. If the MIST treatment options will be a perfect match for men suffering from PBNO should be further evaluated.

In summary, it can be assumed that PBNO is an acquired disease and not a congenital anomaly. The degenerative remodeling process of the BN seems to be based on an inflammatory changes.

Declarations

Conflict of Interest

The authors declare no competing financial interests and no other conflict of interests.

Ethics approval and consent to participate

No ethical approval and no informed consent were needed.

The study was performed in accordance with the Declaration of Helsinki.

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Figures

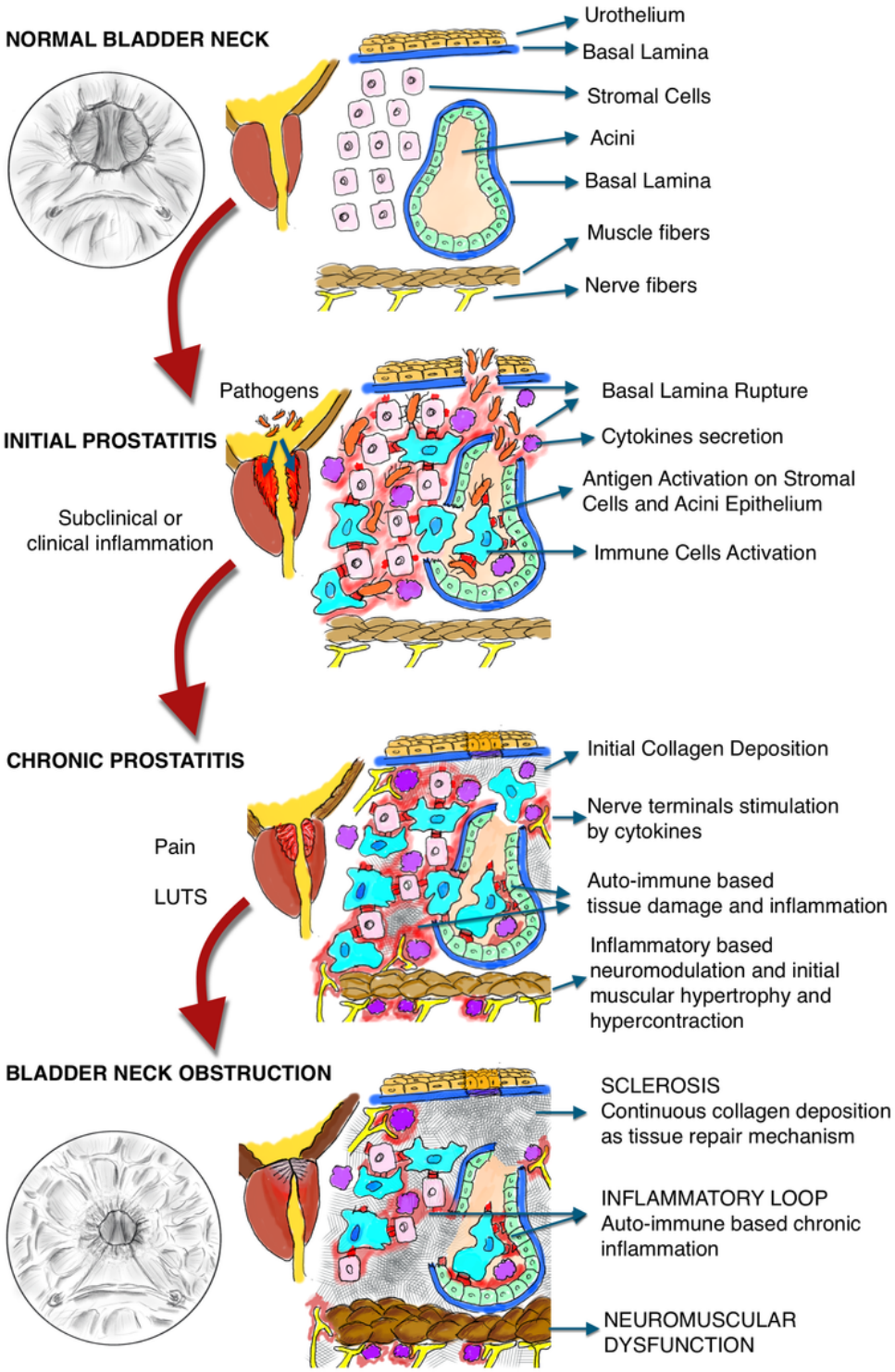

Figure 1

The hypotesized relationship between infection, inflammation and development of primary bladder neck obstruction.