Original Article

Microscopic Evidence of Prostatic Stromal and Epithelial Hyperplasia: A Post- Mortem Study

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Abstract

Background: The natural history of prostatic nodular hyperplasia (PNH) begins from the pathological phase. This may progress to the clinical phase. The clinical phase is a subset of macroscopic PNH, while the latter is a subset of pathological phase of PNH. The aim of this study is, therefore, to determine the pathological phase of PNH as a prelude to the clinical phase. **Subjects and Methods:** The prostate glands from adult males who died from nonprostate related cause at the University of Benin Teaching Hospital, Benin City were studied. Their glands were obtained during the autopsy, weighed, and the respective weight recorded. Sections were assessed for microscopic evidence of prostatic stromal and epithelial hyperplasia. The clinical case note of each male patient as well as the mortuary/autopsy register was consulted for details of the age and clinical diagnosis. **Results:** The population under study was 86 cases. Of these, 67 (77.9%) cases were in the pathological phase of PNH and their ages ranged from 31 to 78 years. Their mean age was 52.60 ± 12.02 years, while their median and modal ages were 53 and 50 years, respectively. The most common cause of death in these patients was accident/unnatural cause (24%). Nearly 49% (33 cases) had macroscopic PNH with a mean weight of 38.64 ± 8.59 g at a mean age of 59.64 ± 9.73 years. Fifty-one percent (34 cases) had microscopic PNH. Their mean age and mean weight were 45.76 ± 9.97 years and 21.32 g ± 4.13, respectively. There was a significant increase in the mean weight of the prostate gland with age ($P < 0.001$). Cystic change (73%), chronic inflammation (51%), and acute inflammation (5%) in decreasing frequency were associated with the pathological phase of nodular hyperplasia. **Conclusion:** The natural history of nodular hyperplasia of the prostate is age-dependent, whereas the actual pathogenesis is largely undetermined, although various postulates exist. Of these, chronic inflammation may play a role as observed in this study.

Keywords: Clinical phase of prostatic nodular hyperplasia, macroscopic prostatic nodular hyperplasia, microscopic prostatic nodular hyperplasia, pathological phase of prostatic nodular hyperplasia

Introduction

The natural history of prostatic nodular hyperplasia (PNH) is a spectrum that encompasses an initial pathological phase, which may progress, to terminate in a clinical phase.[1-3] The pathological phase is devoid of any clinical symptom, and it is divided into two stages, the microscopic and macroscopic stages of PNH.[2,3] Microscopic PNH denotes microscopic confirmation of stromal and epithelial hyperplasia, while, macroscopic PNH, signify the increase in the size of the prostate gland secondary to stromal and epithelial proliferation.[3,4] Previous studies have documented that, it is only in about one-half (50%) of men with microscopic PNH will the macroscopic form develop, while, in about one-half (50%) of the latter, will gross enlargement of the prostate gland progress to clinical symptoms.[1-3,5,6] The aim of this study is, therefore, to determine the pathological phase of PNH as a prelude to the clinical phase.

Subjects and Methods

The prostate glands were obtained from adult males who died from nonprostate related cause at the University of Benin Teaching Hospital, Benin City, over a 15-month period.

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Their glands were removed undamaged, cleaned of any nonprostate tissue, weighed and fixed in 10% neutral buffered formalin. The partial sampling method of the prostate gland as documented by Bostwick and Meiers was employed in this study.[7] Hematoxylin and eosin was used to stain the paraffin-embedded sections. These sections were assessed for microscopic evidence of prostatic stromal and epithelial hyperplasia. The clinical case note of each male patient as well as the mortuary/autopsy register was consulted for details of the age and clinical diagnosis. The data obtained was analyzed using the Statistical Package for Social Sciences, version 16 (SPSS 16, SPSS Inc. Chicago, Illinois, United States of America).

Results

Eighty-six cases were studied. Of these, sixty-seven cases were in the pathological phase of PNH and their ages ranged from 31 to 78 years. Their mean age was 52.60 ± 12.02 years [Table 1], whereas their median and modal ages, were 53 and 50 years, respectively. The most common cause of death in these patients was accident/unnatural cause (24%). This was closely followed by Cardiac diseases (21%) and then infectious diseases (10.4%). Other causes of death are as shown in Table 2.

The weight of the prostate gland in those in the pathological phase of PNH ranged from 15 to 60 g. Their mean weight was 29.85 ± 10.97 g [Table 1], and the maximum mean weight (39 g) was seen in the 7th decade [Figure 1].

Of the 67 patients in the pathological phase of PNH, 33 (49%) of them, each with a weight of the prostate gland >25 g, had macroscopic benign prostatic hyperplasia (BPH). Their ages ranged from 37 to 78 years. Their mean age was 59.64 ± 9.73 years, while their median and modal ages were 60 and 50 years, respectively. The weight of the prostate gland in those patients with macroscopic PNH ranged from 30 to 60 g. Their mean weight was 38.64 ± 8.59 g [Table 1], and the maximum mean weight (42 g) was seen in the 8th decade [Figure 2]. Patients with microscopic PNH, each with a prostate weight of less than ≤25 g, were 34 cases (51%). They had a significantly less mean age (45.76 ± 9.97 years) than those with macroscopic nodular hyperplasia (>25 g/33 cases) whose mean age was 59.64 ± 9.73 years ($P < 0.001$). Their ages ranged from 31 to 70 years. Their median and modal ages were 47.50 and 32 years, respectively. The weight of their prostate glands ranged from 15 to 25 g. Their mean weight was 21.32 g ± 4.13 [Table 1], while the maximum mean weight (23.18 g) was seen in the 5th decade, [Table 3]. There were six cases with normal prostatic glands in this study. Their ages were from 31 to 48 years. Their mean, median, and modal ages were 39.17 (standard deviation [SD] = 7.63), 39.5, and 45 years, respectively. Their weight ranged from 10 to 25 g, with a maximum mean weight in the 5th decade, [Tables 1 and 3]. There was a significant increase in the mean weight of the prostate gland with age ($P < 0.001$).

The cystic change was the most common histological change seen. It was seen in 73% of PNH. Chronic inflammation (34 cases) and acute inflammation (3 cases) were also seen in association with nodular hyperplasia. There was a significant difference at $P = 0.003$ between the mean weight of those cases associated with chronic inflammation (35.44 ± 10.83 g) and those not associated with it (24.09 ± 7.75 g), [Table 4]. There was no significant difference at $P = 0.27$ between the mean weight of those cases associated with acute inflammation and those not associated with it [Table 4].

Discussion

There is a gradual increase in the size of the prostate gland from neonatal life to puberty. Subsequently, there is a speedy

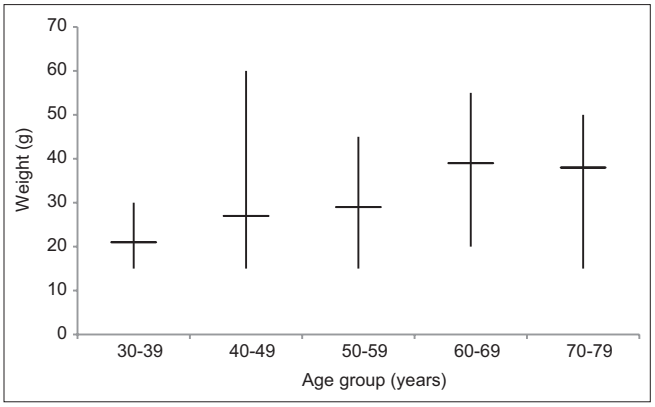

Figure 1: A graph showing the distribution of mean weight of prostate gland in those in pathological phase of prostatic nodular hyperplasia (y axis) with age group (x axis). The mean weight of the prostate gland increases with age. The highest mean weight (39 g) is seen in the 7th decade of life

Table 1: The frequency, age (minimum, maximum, and mean age [years]) and weight (minimum, maximum, and mean weight [g]) of pathological prostatic nodular hyperplasia, macroscopic stage, microscopic stage and normal prostate gland

	Frequency	Minimum age (years)	Maximum age (years)	Mean age±SD (years)	Minimum weight (g)	Maximum weight (g)	Mean weight±SD (g)
Pathological phase	67	31	78	52.60±12.02	15	60	29.85±10.97
Macroscopic stage	33	37	78	59.64±9.73	30	60	38.64±8.59
Microscopic stage	34	31	70	45.76±9.97	15	25	21.32±4.13
Normal prostate gland	6	31	48	39.17±7.63	10	25	18.33±6.06

SD: Standard deviation

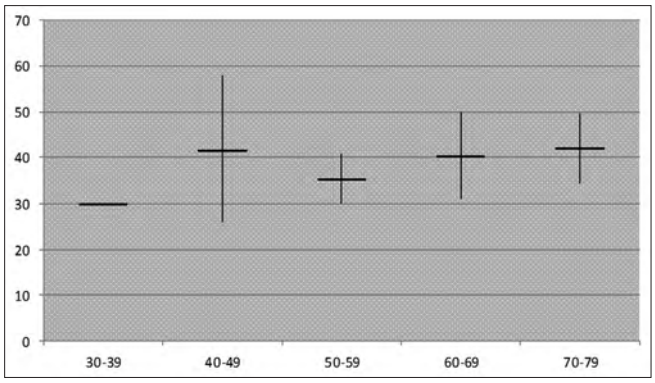

Figure 2: A graph showing the distribution of mean weight of prostate gland (y axis) in patients with macroscopic prostatic nodular hyperplasia with age group (x axis). The mean weight of the prostate gland increases with age. The highest mean weight (42 g) is seen in the 8th decade of life

Table 2: The cause of death in patients in pathological phase of prostatic nodular hyperplasia

Cause of death	Frequency (%)
Accident/unnatural	24 (35.8)
Cardiovascular disease	21 (31.3)
Infectious disease	7 (10.4)
Malignancy	5 (7.5)
Gastrointestinal disease	5 (7.5)
Endocrine disease	3 (4.4)
Renal disease	1 (1.5)
Haematological disease	1 (1.5)
Total	67 (100)

Table 3: The age distribution of the mean weight in those cases with microscopic prostatic nodular hyperplasia's, and normal prostate glands

Age group	Mean age±SD (years)	
	Microscopic PNH	Normal prostate gland
30-39	20.00±4.71	13.33±2.89
40-49	23.18±3.37	22.33±2.87
50-59	21.36±3.93	-
60-69	20.00±0.00	-
70-79	15.00±0.00	-
Total	21.31±4.14	18.33±6.06

SD: Standard deviation, PNH: Prostatic nodular hyperplasia

increase in the dimensions of the prostate up to the 3rd decade and the first year of the 4th decade, at which point the mean weight of the prostate gland is 20 g.[8] This is comparatively similar to the observation in the index study that noted a mean weight of the normal prostate gland of 18.33 g at a mean age in the 4th decade. At autopsy, the mean weight of a prostate gland affected by nodular prostatic hyperplasia has been documented to be 33 g (SD= ±16 g).[9] This is comparatively similar to a mean weight of 29.85 g (SD = ±10.97 g) observed in this study. Of the 67 cases in the pathological phase of nodular prostatic hyperplasia in this study, 51% (34 cases) had microscopic epithelial and stromal hyperplasia in the setting of relatively normal weights of the prostate glands (≤25 g). This group of patients is said to have microscopic BPH (microscopic nodular prostatic hyperplasia).[2-4] The remaining 49% (33 cases) had microscopic epithelial and stromal hyperplasia that has grown to produce enlargement of the prostate glands with weights (>25 g) above the highest value of the weight range of normal prostate glands in this study (mean weight ± SD = 18.33 ± 6.06 g = 12.27–24.39 g). This group of patients are said to have macroscopic BPH (macroscopic nodular prostatic hyperplasia);[2-4] although, there is no consensus establishing the degree of prostate enlargement required to support the diagnosis of macroscopic nodular hyperplasia,[4] despite the fact that the average weight of the prostate gland in an adult has been documented to be 20 g.[6,10]

The natural history of development of pathologic phase of nodular hyperplasia is consistent with this study because macroscopic hyperplasia was seen in about one-half (49%) of those who developed microscopic nodular hyperplasia and none of the patients in the study population had clinical manifestations attributed to the enlarged prostate prior to their death, hence a criterion for enlisting into this study. This study noted an increase in the weight of the prostate gland with age ($P < 0.001$). Hence, it stands to reason that a man that live long enough will in no doubt develop some histological features in keeping with nodular prostatic hyperplasia.[11] The clinical phase of nodular prostatic hyperplasia is, therefore, heralded by the onset of lower urinary tract symptoms (LUTS).[4] Clinical symptoms occur in only about 50% of persons with macroscopic nodular prostatic hyperplasia.[1-3,5,6] It, therefore, follows that macroscopic nodular prostatic hyperplasia is a subset of microscopic nodular prostatic hyperplasia by about one-half, while the clinical phase is a subset of the macroscopic stage of the pathological phase by about one-half.[1-6]

The exact cause of nodular prostatic hyperplasia has not been fully elucidated,[4,12,13] The proposed theories reasonably offer a logical explanation to the pathogenesis of nodular hyperplasia, in an overlapping, yet complementary manner, however, prostatic epithelial-stromal interactions on a background of hormonal stimulation is key to its pathogenesis.[4] It originates in the transitional and periurethral zones.[6,13] The microscopic or histologically recognizable nodular prostatic hyperplasia has been documented to occur as early as the third decade of life.[14]

Aging and hormonal stimulation are key to the development of microscopic nodular prostatic hyperplasia.[13,15] The hormone that drives this development is derived from testosterone which is the male sex anabolic hormone.[5,16,17] The enzyme, 5α-reductase Type 2 converts testosterone to dihydrotestosterone (DHT), this, in turn, stimulates the growth of the prostate gland that leads to the development of microscopic and macroscopic nodular prostatic hyperplasia.[5,17] In emphasizing the importance of these hormones, it is important to note that, factors that can cause the nonproduction of testosterone or inability of the prostate to convert

Table 4: The *P* value, frequency and weight distribution of those cases associated with inflammation

	Frequency	Mean weight (g)±SD	Median weight	Minimum weight (g)	Maximum weight (g)
Acute inflammation (*P*=0.26)					
Yes	3	21.67±11.55	15	15	35
No	64	30.23±10.89	27	15	60
Chronic inflammation (*P*=0.003)					
Yes	34	35.44±10.83	35	20	35
No	33	24.09±7.75	25	15	25

SD: Standard deviation

testosterone to DHT, can result in lack of prostatic growth, and failure to develop nodular hyperplasia. These factors include the castration of a male early in his lifetime,[15] the prolonged use of the drug, 5α-reductase inhibitors such as dutasteride and finasteride,[18,19] and 5α-reductase deficiency syndrome that can occur in some males.[17] Contrary to the central role of DHT in the development of nodular hyperplasia, is the observation that the growth of the prostate gland is not directly proportional to the availability of DHT.[20] This gives the impression that, other factors in synergy with DHT are responsible for the progressive growth and development of the prostate gland that leads to the formation of macroscopic nodular hyperplasia.[4] This, in turn, can progress to clinical nodular hyperplasia with time, moreso that the weight of the prostate gland increases with age as seen in this study, as well as documented by previous studies[4,9,13] The bladder outlet obstruction, is one of LUTS of clinical nodular prostatic hyperplasia. It is viewed as having a dynamic and static component.[4] The dynamic component is the active contraction of the prostatic smooth muscle, while the static component is the hyperplasia of the epithelial glandular component. These views are supported by the clinical observations that LUTS are abated by alpha-blockers that tend to relax the contraction of the prostatic smooth muscle,[21] and the hormonal therapy that selectively reduces the volume of the prostatic epithelium.[22] Interestingly, Lepor *et al*.[23] have documented that the improvement in LUTS is through an unknown mechanism that excludes the reduction of prostate volume by 5α-reductase inhibitors, as well as the relaxation of prostate smooth muscle by α-blockers.

It has also been postulated that DHT binds to the androgen receptor that is located in the nucleus of the stromal (predominantly) and epithelial cells (less predominantly in the basal cells) of the prostate gland. This binding generates signals that activate transcription of androgen-dependent genes. The resultant effect is the up-regulation of several growth factors and their receptors, notable amongst which is the fibroblast growth factor family (FGF), especially FGF-7 produced by stromal cells. It also acts principally on a stromal cell in a paracrine signaling pathway. This postulate holds the view that DHT-induced growth factors cause nodular hyperplasia by decreasing the death of epithelial cells, while, simultaneously stimulating hyperplasia of the stroma.[5]

Another postulate[12] emphasized the role of chronic inflammation as contributing risk factor to the development of nodular prostatic hyperplasia. Many infiltrates of chronic inflammatory cells are present microscopically, their primary role is to identify and neutralize the offending agent for which they were attracted to the inflammatory focus in the prostate. These cells release cytokines and growth factors that aid in the modulation of their immune function, while at the same time, provide the stimulus for the growth of stromal and epithelial cells. The stimulating effect is augmented when prostatic cells begin to secrete their own inflammatory mediators. An overwhelmed feedback control of the mediators of inflammation can lead to a vicious cycle of continuous synthesis and release of these mediators, thus leading to an increase in the size of the prostate gland. Interestingly, this study noted the presence of acute and chronic inflammation in association with PNH in 3 cases (5%) and 34 cases (51%), respectively, thus, giving credence on the role of inflammation in the pathogenesis of PNH, moreso that a significant difference was noted between the mean weight of those cases associated with chronic inflammation and those not associated with it in this study.

Conclusion

The natural history of nodular hyperplasia of the prostate is age-dependent, while the actual pathogenesis is largely undetermined, although various postulates exist. Of these, chronic inflammation may play a role as observed in this study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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