Original Article

Definite Cutoff Point to Diagnose "Nutcracker Syndrome": An Ignored Cause of Microscopic Hematuria

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Background: One of the causes of gross hematuria is nutcracker syndrome or renal vein entrapment. The computerized tomography (CT) scan can demonstrate the precise left renal vein (LRV) compression between the aorta and the superior mesenteric artery. These modalities are usually applied for initial investigations. At present, there is no definite cutoff point to diagnose nutcracker syndrome in patients who present with asymptomatic microscopic hematuria (AMH).

Objective: To study whether the nutcracker syndrome might be associated with AMH and to determine the definite cutoff point to diagnose nutcracker syndrome.

Materials and Methods: The authors retrospectively reviewed the CT scans of patients diagnosed with AMH and had no abnormal urological findings from standard investigations compared with patients in a control group who had normal urine exams and no urological abnormalities from CT scans. CT scan assessment included the diameter ratio of the LRV at the aortomesenteric angle and the renal hilar, the aortomesenteric distance, and the aortomesenteric angle.

Results: Forty-eight patients diagnosed with AMH were included in the present study. The diameter ratio of the LRV at the aortomesenteric angle and the renal hilar in the AMH group was 0.7 compared to 0.9 for the control group (p=0.001). The mean aortomesenteric angle in patients with AMH was 45.9 degrees compared to 54.8 degrees in the control group (p=0.004). The mean aortomesenteric distance in patients with AMH was 1.36 cm compared to 1.56 cm in the control group (p=0.032).

Conclusion: These data showed the significant difference in the diameter ratio of the LRV at the aortomesenteric angle and the renal hilar, the aortomesenteric angle, and the aortomesenteric distance between patients with AMH and the normal population. Therefore, the nutcracker syndrome may be associated with AMH.

Keywords: Microscopic hematuria, Nutcracker, Left renal vein

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The diagnosis of patients with microscopic hematuria is by detection of red blood cells in the urine at more than three cells per high-power field. The prevalence of microscopic hematuria varies from 0.19% to 21%[1]. The treatment of microscopic hematuria should begin with a history of risk factors, a physical examination, cystoscopy, and diagnostic radiology[1,2].

One of the causes of gross hematuria is nutcracker syndrome or renal vein entrapment. This phenomenon results in left renal venous hypertension, which leads to left renal vein (LRV) and left gonadal vein varices and unilateral hematuria[3]. The computerized tomography (CT) scan can precisely demonstrate the LRV compression between the aorta and the superior mesenteric artery (SMA). CT scans are usually applied for initial investigations. At present, there is no definite cutoff point to diagnose nutcracker syndrome in patients present with asymptomatic microscopic hematuria (AMH)[4].

Materials and Methods

Between January 2007 and December 2016,

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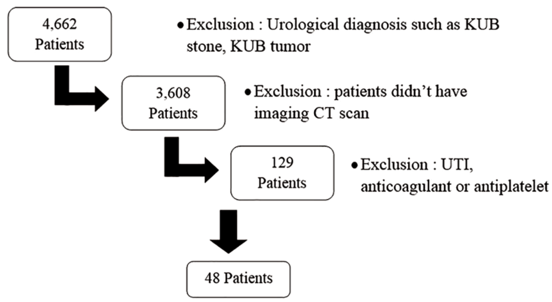

Figure 1. Inclusion and exclusion criteria flowchart.

4,662 patients in Ramathibodi Hospital (Thailand), were diagnosed with hematuria, identified by searching from ICD-10. Inclusion criteria were patients aged 18 to 70 years old diagnosed with AMH that had a CT scan and did not have abnormal symptoms associated with the urinary tract such as dysuria, flank pain, or gross hematuria. Exclusion criteria were patients who had a known cause of microscopic hematuria, such as a tumor or stone, and patients who were taking antiplatelet or anticoagulant drugs. By these criteria, 3,608 patients were excluded from the study because they had urological diseases. Another 129 patients were excluded because they did not have CT scan. After reviewing the patient medical records to exclude other causes of microscopic hematuria, such as infection or history of antiplatelet or anticoagulant drug used, 48 patients were enrolled in the present study (Figure 1). The control group was 50 patients, randomly selected, who did not have microscopic hematuria but had a CT scan performed for other conditions.

Demographic data consisted of age, gender, body mass index (BMI), and underlying diseases. Urological investigation included urinalysis, creatinine level, cystoscopy, and ultrasound or magnetic resonance imaging (MRI).

The parameters focused on CT scans were the aortomesenteric distance, aortomesenteric angle, and the ratio of the diameter of the LRV at the aortomesenteric part and the hilar renal vein part. The definition of the aortomesenteric distance is the maximum distance between the anterior margin of the aorta and the posterior aspect of the SMA at a level where the duodenum is crossing. The aortomesenteric angle was measured on reformatted sagittal plane images at the same level of aortomesenteric distance, which the line was drawn between the root of the SMA and an imaginary point on the SMA, where the SMA began to descend parallel to the abdominal aorta[5-7].

Continuous data were presented as mean ± standard deviation (SD) or median (interquartile range [IQR]) and compared by independent sample t-test or the Mann-Whitney U test. Categorical variables were presented as frequency (%) and compared by chi-square or Fisher's exact test. All analyses were calculated using Stata, version 14 (StataCorp LP, College Station, TX, USA). Statistical significance was defined as a p-value of less than 0.05. The receiver operating characteristic (ROC) curve was used for explaining correlations among parameters from CT scans for both the AMH group and the control group.

Results

There were no statistically significant differences between the two groups in terms of gender, BMI, underlying disease, and glomerular filtration rate (GFR). Age was the only parameter in the demographic data that was statistically significant different between the two groups. The median age in the control group was 61.0 years and in the AMH group was 66.5 years ($p<0.05$) (Table 1).

Eight of the 48 patients in the AMH group and none in the control group underwent cystoscopy. Six patients in the control group and 23 patients in the AMH group had kidneys, ureters, or bladder (KUB) ultrasonography. Three patients in the AMH group had abnormal findings from the ultrasound, but the abnormalities were simple renal cortex cysts. There were only two patients in control group who had MRI scans, and no abnormalities from the KUB ultrasound were found for the control group (Table 2).

Three parameters from the CT scans showed statistically significant differences between the two groups, 1) the mean aortomesenteric angle in the control group was 54.8 degrees and in the AMH group was 45.9 degrees ($p<0.05$), 2) the mean of aortomesenteric distance for the control group was 1.56 cm and for the AMH group was 1.36 cm ($p<0.05$), and 3) the median value of the aortomesenteric-hilar ratio for the control group was 0.9 and for the AMH group was 0.7 ($p<0.05$) (Table 3).

The data were further described by the ROC curve. For the parameters aortomesenteric angle, aortomesenteric distance, and aortomesenteric-hilar diameter ratio, the area under the curve was 0.7113. Only three parameters were used for ROC curve analysis to produce the maximum ratio of the area under the curve with the maximum power of statistical data (Figure 2).

Discussion

Nutcracker syndrome refers to LRV entrapment

Table 1. Characteristics data

Variable	Total (n=100) n (%)	Normal (n=52) n (%)	Hematuria (n=48) n (%)	p-value	95% CI
Sex					
Male	34 (34.00)	21 (40.38)	13 (27.08)	0.161	
Female	66 (66.00)	31 (59.62)	35 (72.92)		
Age (year); median (range)	62.5 (16 to 86)	61.0 (16 to 86)	66.5 (18 to 85)	0.017	59.45 to 64.92
Weight (kg); mean±SD	58.3 (10.94)	59.9 (10.28)	56.5 (11.45)	0.119	56.14 to 60.48
High (cm); mean±SD	157.5 (8.50)	157.9 (8.44)	157.1 (8.63)	0.640	155.83 to 159.21
BMI (kg/m^2); mean±SD	23.5 (3.91)	24.0 (3.68)	22.8 (4.10)	0.134	22.69 to 24.24
Underlying					
DM	22 (22.00)	11 (21.15)	11 (22.92)	0.832	
HT	48 (48.00)	21 (40.38)	27 (56.25)	0.113	
DLP	19 (19.00)	11 (21.15)	8 (16.67)	0.568	
COPD	3 (3.00)	2 (3.85)	1 (2.08)	0.999	
IHD	2 (2.00)	1 (1.92)	1 (2.08)	0.999	
Creatinine; median (range)	0.8 (0.3 to 6.8)	0.8 (0.4 to 6.8)	0.8 (0.3 to 1.5)	0.961	0.77 to 1.10
GFR; mean±SD	84.1 (25.22)	85.6 (24.33)	82.5 (26.32)	0.542	79.09 to 89.10

CI=confidence interval; SD=standard deviation; BMI=body mass index; DM=diabetes mellitus; HT=hypertension; DLP=dyslipidemia; COPD= chronic obstructive pulmonary disease; IHD=ischemic heart disease; GFR=glomerular filtration rate

Table 2. Others investigation

Variable	Total (n=100) n (%)	Normal (n=52) n (%)	Hematuria (n=48) n (%)	p-value
Cystoscope (n=8)				
Normal	7 (87.50)	-	8 (100)	-
Abnormal	1 (12.50)	-	0 (0.00)	
Ultrasound KUB (n=29)				
Normal	26 (89.66)	6 (100)	20 (86.96)	0.999
Abnormal	3 (10.34)	0 (0.00)	3 (13.04)	
MRI (n=2)				
Normal	2 (100)	2 (100)	-	-
Abnormal	-	-	-	

KUB=kidneys/ureters/bladder; MRI=magnetic resonance imaging

Table 3. Measurement parameter from CT scan

Variable	Total (n=100) Mean±SD	Normal (n=52) Mean±SD	Hematuria (n=48) Mean±SD	p-value	95% CI
Aortomesenteric angle (degree)	50.6±15.96	54.8±15.16	45.9±15.64	0.004	47.39 to 53.73
Aortomesenteric distance (cm)	1.47±0.49	1.56±0.49	1.36±0.47	0.032	1.37 to 1.56
Hilar portion diameter (cm)	0.98±0.20	0.98±0.18	0.99±0.21	0.807	0.95 to 1.03
Aortomesenteric-hilar diameter ratio; median (range)	0.8 (0.6 to 1.4)	0.9 (0.5 to 1.4)	0.7 (0.6 to 1.0)	0.001	0.79 to 0.85

CI=confidence interval; SD=standard deviation

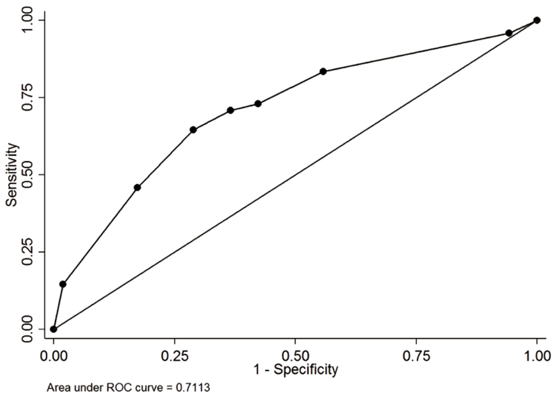

Figure 2. ROC curve for predicting "nutcracker phenomenon" in patient with AMH.

between the abdominal aorta and the SMA. The exact prevalence is unknown(3,8,9). Limited data are available on the prevalence or incidence of nutcracker syndrome in the general population, and it is thought to be underdiagnosed because of non-specific urine analysis findings and complaints(10,11). The present study used CT scans to detect an association in two different populations with a diagnosis of nutcracker syndrome. However, the results did not provide sensitivity and specificity because there was no gold standard diagnosis for this syndrome(10,12,13). Ideally, nutcracker syndrome must be a left side unilateral hematuria, but in practice, as in the present study, it was difficult to diagnose it as such.

According to the results, there are two appropriate cutoff values that could be used for diagnosis of nutcracker syndrome from CT imaging. First, the degree of the aortomesenteric angle should be 48.50 degrees, with the ROC=0.6687 (sensitivity 68.75% and specificity 53.85%). Second, the aortomesenteric-hilar diameter ratio should be 0.82, with the ROC=0.7019 (sensitivity 72.62% and specificity 59.62%).

There was no standard cutoff point for diagnosing nutcracker syndrome in terms of aortomesenteric angle, aortomesenteric distance, and aortomesenteric-hilar diameter ratio. Instead, the authors used area under the ROC curve (Figure 2) to show the maximum power to separate the AMH patients from the normal population.

The present study was a retrospective study, so there were some limitations on collected data, such as cystoscopy to evaluate microscopic hematuria. In the opinion of the researcher, patients with no symptoms other than only microscopic hematuria often refuse to have a cystoscopy performed. Another limitation to the study is that some of the patient were not referred to the urologist and there were fewer patients who had had laparoscopies. A prospective study may be helpful to address the limitations.

The CT scan parameters in the present study were measured by a single physician and confirmed by a single radiologist. This method can reduce observer bias in study.

Several methods have been used to diagnose hematuria. Most cases are diagnosed by exclusion, because LRV compression is usually deducted after discarding other possible causes compatible with the clinical presentation of the patient(14).

Conclusion

Nutcracker syndrome may be associated with AMH. The CT scan is a safe and reliable tool for diagnosing nutcracker syndrome. From the present study, the significant differences between the AMH patients and the normal population were the aortomesenteric-hilar diameter ratio, the aortomesenteric angle, and the aortomesenteric distance.

What is already known on this topic?

Previous case reports show that the nutcracker syndrome can cause gross hematuria. The CT scan can show the LRV being compressed between the aorta and the SMA, but there is no definite cutoff point to diagnose nutcracker syndrome.

What this study adds?

The findings support the hypothesis that the nutcracker syndrome may be associated with AMH. The authors show the cutoff point to diagnose nutcracker syndrome by using the aortomesenteric angle, the aortomesenteric distance, and the aorto-mesenteric-hilar ratio.

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Conflicts of interest

The authors declare no conflict of interest.

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