Tamm-Horsfall Protein Determination in Balkan Endemic Nephropathy

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Summary. Data on the excretion of Tamm-Horsfall protein (THP) in subjects living in an area of Balkan endemic nephropathy (BEN) are reported. The study subjects were divided into groups as follows: diseased, suspect, “at risk” and others, according to previously adopted criteria. The THP excretion in “at risk” subjects was found to be significantly higher as compared to control subjects. The difference between these two groups could not be registered by any other clinical or laboratory diagnostic methods. No difference in the excretion of THP was observed between the groups of others and control subjects. According to the results obtained, the excretion of THP may be considered a possibly useful additional diagnostic test for the detection of subjects with the latent, early subclinical phase of BEN. On the other hand, the data obtained shed some more light on the still obscure pathogenesis and natural history of BEN.

Key words: Tamm-Horsfall protein — Endemic (Balkan) nephropathy

Introduction

In the late fifties, the physicians in Bulgaria, Romania and Yugoslavia were faced with an “epidemic” chronic renal disease occurring in particular rural areas. Extensive research work attempted to clarify the nature of the disease [6, 21, 25]. The clinical manifestations of the disease were unlike other common renal diseases such as glomerulonephritis or pyelonephritis or hypertensive kidney disease. Initial studies indicated that BEN had similar clinical and patho-morphological characteristics to chronic interstitial nephritis [14, 15, 27], and the name Balkan Endemic Nephropathy (BEN) was accepted [27]. Since that time, many research studies on the ethiology of BEN have carried out but, unfortunately, the ethiology of BEN has remained obscure.

In the advanced phases of the disease, BEN presents clinically as a chronic tubulo-interstitial syndrome and can be diagnosed with a sufficient reliability on the basis of clinical and morphological criteria [19]. In the advanced phases (azotemia, uremia) it is not difficult to ascertain the existence of a renal disease, but difficulties arise in the differential diagnosis versus other renal diseases, which also present at ‘end stage’. Therefore, much effort has been invested in the search for diagnostic procedures that would allow an early diagnosis to be made during the initial phases of the disease while clinical signs are still scarce or absent. An exact diagnosis is particularly difficult to approach when proteinuria can not be detected [12, 16, 22, 23].

Further advances in the diagnosis of BEN were achieved by the discovery that the tubular pattern of proteinuria was characteristic [10, 12, 16, 23]. Since then, more sophisticated methods of urinary protein multifractionation and determination of individual low molecular weight proteins have been employed in the diagnosis of BEN. The measurement of urinary beta-2-microglobulin excretion has been demonstrated to be a valuable indicator of tubular proteinuria, and recognized as a positive diagnostic sign of the presence of BEN as well as a useful method of the detection of patients suffering from BEN [8, 11, 17]. In an earlier study [2], we summarized the characteristics of proteinuria obtained by means of the available methods of protein separation in urine. Since 1980, when we introduced the method of Tamm-Horsfall protein (THP) determination in urine, urinary THP excretion has been studied in subjects from the endemic area of Slavonski Brod (Yugoslavia). This approach seemed relevant, because the excretion of THP takes place in a limited segment of the nephron, where the thick ascending limb of Henle’s loop turns into the distal convoluted tubule [9]. It appeared reasonable to expect the THP excretion to be elevated in such a tubulo-interstitial disorder, because an increased excretion of THP was also reported on in a condition pathologically very similar to BEN, caused by cadmium poisoning [9].

Since 1980, we have published several reports on the results obtained, along with the description of the methodology [1, 4, 5, 18, 19]. The present paper records the results
Table

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<thead>
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<th></th>
<th>Values</th>
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<th>Median</th>
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<tr>
<td></td>
<td>n</td>
<td>min</td>
<td>max</td>
<td>versus Control</td>
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<tr>
<td>Diseased</td>
<td>34</td>
<td>8.4</td>
<td>153.0</td>
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<tr>
<td>Suspect</td>
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<td>1.8</td>
<td>171.4</td>
<td>21.5</td>
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<td>&quot;At Risk&quot;</td>
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<td>3.6</td>
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<tr>
<td>Others</td>
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<td>73</td>
<td>1.8</td>
<td>52.9</td>
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Fig. 1. Urinary THP excretion in the examined group of subjects, expressed as mg/g creatinine

Fig. 2. Urinary THP excretion presented in Box and Whisker plot, and frequency histogram of subjects "at risk" in the endemic area

Fig. 3. Urinary THP excretion presented in Box and Whisker plot, and frequency histogram of control subjects from a non-endemic area. A difference in THP excretion between the groups of "at risk" (Fig. 2) and control subjects (Fig. 3) is obvious

Results

The results of our recent studies, supplementing those obtained previously, are summarized in Fig. 1. As can be seen from the table, the study subjects from the diseased and suspect groups excreted significantly higher amounts of THP than those belonging to the control group, which is consistent with both our previous findings and our expectations. The group of subjects designated as "at risk" was also found to excrete more THP than the normal control subjects from a non-endemic area. This difference was statistically significant \( (P = 0.0007) \). To illustrate the difference between the "at risk" and control groups, the data are presented on the Box and Whisker Plot and frequency histograms (Fig. 2 and 3). No significant difference was recorded between the groups of others and controls, but was found to exist when these were compared to the groups of diseased, suspect and "at risk" subjects.

Discussion

Our previous studies on the determination of THP in urine of subjects from the endemic area revealed the subjects designated as diseased to excrete more THP than the control subjects. The subjects designated as suspect were also found to excrete higher amounts of THP than the normal control subjects from a non-endemic area. This finding was also consistent with our expectations, because the former were the subjects with clinical signs of a renal disease, most probably BEN, presenting a clinical picture of nephropathy without azotemia. It is known, that any renal disease may result in an increased excretion of THP. During our previous stud-