REVIEW PAPER

DOI: https://doi.org/10.20883/medical.e18

Thin basement membrane disease – literature review

Jakub Żurawski

Chair of Biology and Environmental Protection, Department of Immunobiochemistry
Poznan University of Medical Sciences, Poland

ABSTRACT
Initially, the thin glomerular basement membrane disease was called "a gentle and curable hemorrhagic nephritis". The thin basement membrane disease has been finally characterized at the beginning of 1970s. This is when the connection between previously clinically described gentle microhematuria and significant thinning of glomerular basement membrane discovered during examination under the electron-microscope has been established. Ultimately, the disease has been described as a condition characterized with a diverse clinical course, usually mild, but sometimes progressive. It is a family conditioned disease, but it also appears sporadically and concerns at least 1% of the population. It has also been stated that it is one of the most frequent renal diseases, enumerated directly after changes caused by infections, hypertension and renal lithiasis. This particular disease is diagnosed more often than IgA nephropathy and Alport syndrome, which are also associated with haematuria or microhematuria.

Keywords: thin basement membrane disease.

Introduction

Initially, the thin glomerular basement membrane disease was called "a gentle and curable hemorrhagic nephritis". G. Baehr presented this name in 1926 [1]. The author described this disease in 14 young adults, who temporarily suffered from painless microhematuria. The course of this condition did not reveal hypertension or oedemas. The author concluded that prognosis concerning such cases are clearly optimistic. In 1966 McConville and McAdams reported occurrence of mild haematuria, which was conditioned not only by family factors, but also by factors not related with family. In case of occurrence associated with genetic conditions, they proved that this condition reveals an autosomal dominant inheritance pattern [2].

The thin basement membrane disease has been finally characterized at the beginning of 1970s [3]. This is when the connection between previously clinically described gentle microhematuria and significant thinning of glomerular basement membrane discovered during examination under the electron-microscope has been established. Some authors initially believed that this disease does not stand as the final reason underlying renal insufficiency. What is more, medical inquiries did not reveal any information on the occurrence of uraemia among patients' family members [4]. There were descriptions of cases, where haematuria was present along with proteinuria. Some patients suffered from renal insufficiency [5].

Ultimately, the disease has been described as a condition characterized with a diverse clinical course, usually mild, but sometimes progressive. It is a family conditioned disease, but it also appears sporadically and concerns at least 1% of the population [6]. It has also been stated that it is one of the most frequent renal diseases, enumerated directly after changes caused by infections, hypertension and renal lithiasis [7]. This particular disease is diagnosed more often than IgA nephropathy and Alport syndrome, which are also associated with haematuria or microhematuria [8].

Clinical symptoms

In children, this condition is usually recognized at the age of about 7, whereas in adults, it is diagnosed at

the age of about 37. There are, however, many cases in which the disease appears at a later age. Some authors declare the lack of differences in the frequency of occurrence depending on the gender [8]. Others state that women tend to dominate among patients suffering from this disease [9]. In more than 30% of patients no family history of the disease can be stated [8]. Microhematuria is the most often observed symptom, sometimes episodes of haematuria are also reported. It usually occurs after physical exercises, and also as a result of infection. Slight or moderate proteinuria can also appear during the course of the disease. Nephritic syndrome is very rare in this case.

Histological image

Histological image does not reveal any characteristic features. Glomerular changes are usually imperceptible [10]. Presence of erythrocytes in the tubule lumen is a quite frequently described lesion [11]. It is impossible to present thinning of basement membranes under optical microscope. However, in some cases it is possible to observe their decreased silver absorption [8, 12–15]. What can also be observed is the increased number of mesangial cells with matrix expansion.

Biopsies performed in children rarely do reveal chronic lesions. Whereas, as far as adults are concerned, it is possible to diagnose various degrees of sclerosing glomerular lesions, as well as focuses of interstitial fibrosis and changes in interstitial blood vessels [16]. These changes are most often associated with hypertension or senile age of patients. Nevertheless, in some patients the focal segmental glomerulosclerosis appears prior to the occurrence of hypertension and proteinuria. It has been assumed that such premature glomerulosclerosis may indicate the risk of disease progression [17].

In majority of patients, immunofluorescent examinations do not reveal presence of concrements [17, 18, 19, 20]. Sometimes small, single IgG, IgM, IgG or C3 concrements can be visible [17, 20].

Electron-microscopic image

Thin basement membrane disease is diagnosed when examination under the electron-microscope reveals thinning of lamina densa in the basement membrane, which also extensively covers the glomerulus. The diagnosis seems apparently easy, but we can face certain problems at this stage [14]. One of them is the fact that there are no common criteria for evaluating proper thickness of the basement membrane. Some authors [13] have assumed that the thickness of glomerular basement membrane in an infant equals 150 nm and in one-year-old child it reaches 200 nm. Whilst in children between the 1st and the 6th year of age it ranges between 208 and 245 nm, and between the age of 6 and 11 it is only slightly thicker, reaching 244–307 nm. In adult women this value reaches 320 ± 50 nm, whereas in adult men it can reach 370 ± 50 nm.

It has been assumed that the lower margin of proper basement membrane among adults should not be less than 200–265 nm. Steffes et al. [21] assessed that up to the age of three the basement membrane has not more than 200 nm, in adult females it has 323 ± 45 nm, and in adult males it reaches 373 ± 42 nm. According to guidelines elaborated by the World Heath Organisation helping to diagnose the thin basement membrane disease, it is essential to assume the 250 nm threshold for adults and the 180 nm threshold for children between 2 and 11 years of age [22]. A certain group of authors report that the membrane thickness in the course of this disease ranges between 100 and 250 nm. Other authors believe that this disease can be diagnosed when membrane thickness does not exceed 200 nm [23]. It has been shown that the thickness of membranes increases during the first 2 years of life of a healthy child and reaches 200–300 nm [24, 25]. There are authors [26] who confirmed the data above, but they also simultaneously observed that the lamina densa itself takes much longer to form, as it is not fully formed until the age of four. In the light of this information, all statements calling for exclusion of morphological tests in children under the age of 10 seem entirely groundless [18].

In order to evaluate the thickness of basement membranes, laboratories tend to use various measuring methods. Most authors take advantage of data derived from multiple measures, which are performed on peripheral parts of the loop of capillary vessels. Usually the measurement of basement membrane is taken from basement cell membrane of part in podocytes to the cell membrane in the endothelium. During such measurement the thickness of the whole basement membrane is assessed. Some authors recommend limiting measures only to the thickness of lamina densa. Decreased thickness of lamina densa is of crucial significance in diagnosing thin basement membrane disease [4, 27]. There is no definite opinion on the topic of the assessment of the extent of these changes. It is assumed that the diagnosis of thin basement membrane disease depends on the discovery of extensive thinning involving the globeruli in electron-microscopic examinations. It has not been clearly defined, however,

how the term „extensive" is to be understood. Sue et al. [28] define thin basement membrane disease as a uniform thinning including at least 50% of the membranes. Monnens [29], who confirms that the thinning of the membranes is extensive, says that the thinning can sometimes be focal, but must concern at least 50% of the membranes present in the submitted material. Savige et al. [7] assume that the thinning of the membranes must concern the majority of the capillaries and in each capillary 50% of the length of the membranes.

Apart from significant thinning of membranes, sometimes a change in its structures can also be observed, or even their discontinuation. These changes facilitate migration of red blood cells into the ultrafiltrate [30, 31].

Genetic origin of the thin basement membrane disease

Lemmink et al. [32] were the first ones to describe the mutation in COL4A3/COL4A4 genes in patients with mild forms of microhematuria, and then described mutation in locus COL4A4, which is responsible for changes in glycine substitution in the place of glutamic acid within the collagen area of the gene. They suggested that patients with family mild microhematuria could be heterozygous carriers of the autosomal recessive Alport syndrome (ARAS) [32]. These particular mutations concern the same places that are responsible for autosomal inheritance of the Alport syndrome. They are point sites, and they concern the coding region. Until now no mutation within the region of COL4A3/COL4A4 gene promoter in thin basement membrane disease has been described. Nonetheless, such mutations have been documented in case of the Alport syndrome [13].

Apart from the research on the genetic differences between Alport syndrome and thin basement membrane disease, the subject literature gives only minor attention to the differentiation of these two diseases. In morphological research, though, Alport syndrome itself and the diagnostic difficulties, especially in the early development stage, are often emphasised. The depletions of the structure of the lamina densa typical for Alport syndrome occur also in thin basement membrane disease, but Alport syndrome is sometimes characterized by a lasting thinning of the lamina densa without the characteristic stratification with granulocytic inclusions between the layers [33].

Thin membranes in different glomerulopathies

The presence of thin basement membranes is observed in different glomerulopathies, such as IgA nephropathy, membranoproliferative glomerulonephritis, membranous glomerulonephritis, lupus nephritis, acute endocapillary proliferative glomerulonephritis, extracapillary glomerulonephritis, diabetic nephropathies, tubulointerstitial nephritis, Fabry disease and FSGS [34–43].

Taking the data presented above into consideration, diagnosis concerning thin basement membrane disease cannot be described as an easy procedure. This disease is not usually considered during clinical consideration and not widely accounted for in morphological diagnostics.

Acknowledgements

KBN nr N N402 482037

Conflict of interest statement
The authors declare that there is no conflict of interest in the authorship or publication of contribution.

Funding sources
There are no sources of funding to declare.

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Acceptance for editing: 2015-02-10
Acceptance for publication: 2015-03-30

Correspondence address:
Jakub Żurawski
8 Rokietnicka Str., 60-806 Poznańn, Poland
phone: +48 61 8547652
email: zibc@ump.edu.pl