Does Electron Microscopy Change the View of the Diagnosis of IgA Nephropathy?

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Abstract: Our study is aimed to reveal the frequency and clinical significance of the coincidence of two widely spread entities, e.g. minimal change disease (MCD) and IgA nephropathy (IgAN), claimed to be found in an overwhelming number in some Asian regions. We retrospectively analyzed clinical and histological data from 627 renal biopsies, performed in our department from January 2002 to January 2005 and completed electron microscopy in 112 specimens diagnosed as IgAN. The coincidence of IgAN and MCD was found in 8 patients (7.1 %). The coincidence of IgAN and minimal change nephrotic syndrome (MCNS) clinically – especially presence of nephrotic syndrome and the response to drug therapy (with corticosteroids) – behaves as "pure" MCN. Our data from Czech Republic seem to suggest that the combination of IgAN with MCNS can be found relatively frequently not only in Asian patients (as stressed by some authors of Asian origin) but also in European inhabitants. The pathogenesis of the coincidence of IgAN and MCD needs to be elucidated by further studies.

Introduction

Minimal change disease (MCD) and IgA nephropathy (IgAN) belong to the major primary glomerulonephritides. The combination of the two entities seems to be observed more frequently in some Asian countries than in Europe. This difference could be partly explained by different renal biopsy policy.

IgAN is a mesangial proliferative glomerulonephritis characterized by diffuse mesangial deposition of immunoglobulin A (IgA). It is the most common nephropathy in the world among adult patients undergoing renal biopsy (RB). However, there is a striking geographic variation. IgAN was first described in 1968 by a Parisian pathologist, Jean Berger. Although its most common clinical presentation is macroscopic hematuria provoked by upper respiratory tract infection, predominantly in the second and third decades of life, this is neither universal nor necessary for the diagnosis. Asymptomatic urine testing – microscopic hematuria with or without proteinuria (usually < 2g/24 h) – identifies 30–40% of patients (pts) with IgAN. Nephrotic syndrome (NS) occurs in only 5 % of all pts with IgAN. Severe immune injury with necrotizing GN and crescent formation leading to acute renal failure is uncommon in IgAN. Some patients already have renal impairment and hypertension at presentation [1]. The main diagnostic sign is mesangial positivity of IgA in immunofluorescence microscopy.

Minimal change disease (MCD, also called nil disease or lipoid nephrosis) is the most common cause of the NS in children, accounting for 90 percent of cases under the age of 10 years and more than 50 percent in older children [2]. It also accounts for 20 percent of cases in adults of all ages [2]. The plasma creatinine concentration is usually normal, but in adults it is often slightly elevated at presentation. Infrequently acute renal failure can also occur.

The diagnosis of MCD is necessary to establish by RB in adults. Light microscopy in this disorder is either normal or reveals only mild mesangial cell proliferation. Immunofluorescence typically shows no evidence of immune complex deposition. The characteristic histological finding in MCD is diffuse effacement of the epithelial cell foot processes on electron microscopy (Figure 1).

The aim of the study was to determine the coincidence of IgAN and MCD in the pts with histologically proven diagnosis of IgAN and to find out typical clinical features of this specific nosologic entity.

Materials and methods

Patients: We analyzed histological and clinical data from all pts, in whom the diagnosis of IgAN was confirmed by RB findings between January 2002 and January 2005 in the Dept. of Nephrology of the First Faculty of Medicine in Prague [12]. The patients with the diagnosis of Henoch-Schonlein purpura as well as with liver cirrhosis were not included.

Diagnosis of IgAN was established by renal biopsy. Immunofluorescence studies were performed (IgG, IgA, IgM, C3, light chain kappa and lambda in all cases, and

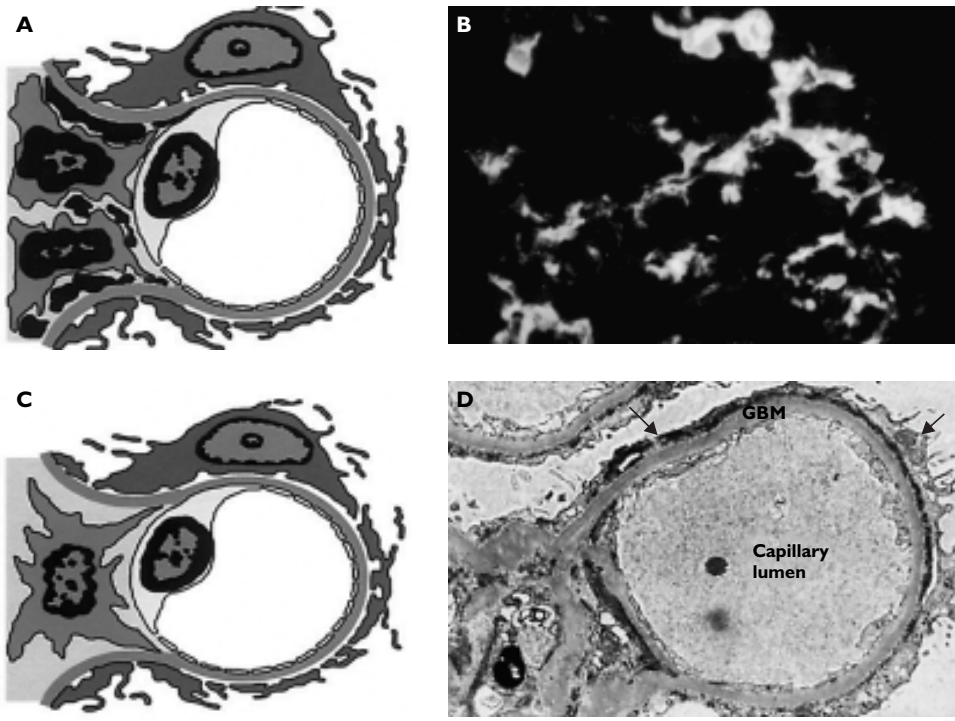

Figure 1 – Histologic patterns of IgAN and MCD. ***A****) IgAN Mesangioproliferative GN.* ***B****) IgAN Typical immunofluorescence.* ***C****) MCN Foot process effacement.* ***D****) MCN Typical electron microscopy. GBM: glomerular basement membrane. Arrow: foot process effacement.*

C1q in the majority of cases) and showed at least 1+ (on a scale from 0 to 3+) mesangial deposition of IgA, with IgA being the dominant immunoglobulin deposited in the glomeruli. Ultrastructural studies were performed, and mesangial electron-dense deposits were found. Each case was assigned to one of the four groups (I–IV, florid, sclerosing, pure mesangioproliferative, and marginal sample) according to morphological features in light microscopy. The presence of one or more cellular or fibrocellular crescents characterized group I, florid. Biopsy specimens showing segmental glomerular sclerosis with proliferative GN were assigned to group II, sclerosing. Group III represented pure mesangioproliferative GN. In group IV, marginal sample, there were cases with IgA positive deposits in the mesangium and less than 4 glomeruli in light microscopy.

Cases with IgA deposits in mesangium and diffuse effacement of foot processes of the podocytes were considered as IgAN and MCNS.

Clinical data: In all pts, in which the coincidence of IgAN and MCN was found out, the following clinical data and therapy were analyzed (initial data at the time of RB and the data at the end of the follow up) – serum creatinine (μmol/L), proteinuria (g/24h), serum albumin (g/L), microscopic hematuria (positive or negative according to the urine sediment), arterial hypertension (according to WHO criteria), antihypertensive therapy (inhibitors of angiotensin converting enzyme – ACEI, angiotensin II receptor blockers – ARB), time to achievement of remission, number of relapses and the duration of the follow up.

Definition of remission: decrease of proteinuria under 1g/24h and stable levels of serum creatinine.

Definition of relapse: increase of proteinuria more than 1g/24h, or elevation of creatinine > 25% from baseline or more than 50 μmol/l.

Therapy with corticosteroids: initially 1mg/1kg of body weight/day till the achievement of the remission.

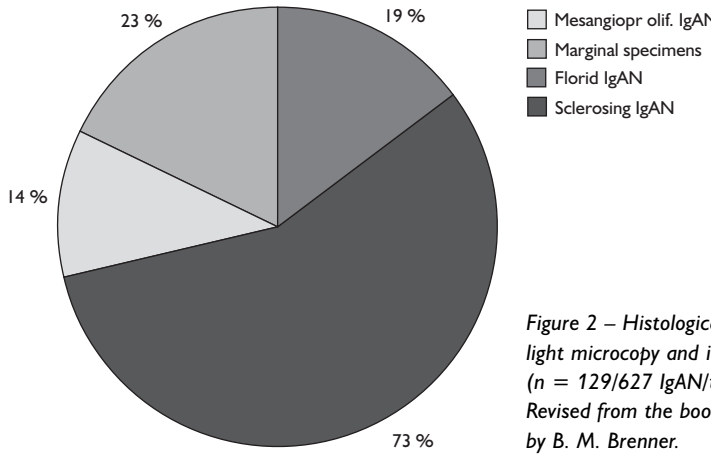

Figure 2 – Histological types of IgAN – according light microcopy and immunofluorescence (n = 129/627 IgAN/total RB). Revised from the book The Kidney by B. M. Brenner.

Results

Around 40% of renal biopsies (RB) from native kidneys in Czech Republic are performed in our department of nephrology (that is cca 200 RB per year). We analyzed 627 RB performed from January 2002 to January 2005 and we diagnosed 129 IgAN.

We found out 19 acute florid IgAN, 73 sclerosing IgAN, 14 pure mesangioproliferative GN and 23 biopsies constituted marginal specimens (Figure 2). We implemented electron microscopy examination in 112 pts and diagnosed the coincidence of IgAN and MCD in 8 patients (7,1%). The clinical data are presented in the Table 1.

All these patients were corticoresponsive and after therapy with corticosteroids (two patients used a combination with cyclosporine and one with cyclophosphamide) the remission was achieved.

Discussion

Our study addressed the frequency, clinical picture and prognosis of the coincidence of two glomerular nosological entities, namely IgAN and MCN. The systematic review of serial RB specimens diagnosed as IgAN, completed with ultrastructural examination, revealed that the coincidence of IgAN and MCD could be determined in a non negligible proportion of findings. Our results are very similar to the data published by different authors of Asian origin [7, 8, 10, 11],

Table 1 – Clinical data at the presentation and during the follow up

Variables at histologic diagnosis	Average (± standard deviation) Range (minimum – maximum)	number of patients
Proteinuria (g/24h)	5.01 ± 2.98 (1.6–10)	8
Serum albumin (g/L)	20.25 ± 6.09 (13–30)	8
Microscopic hematuria (n)	positive	4/8
Serum creatinine (μmol/L)	70.88 ± 15.52 (44–90)	8
Variables during the follow up		
Arterial hypertension		8/8
ACEI		8/8
ARB		4/8
Time to remission after the initiation of therapy (in months)	5.13 ± 5.73 (1–19)	8
Therapy with corticosteroids		8
Therapy with cyclosporin		2/8
Therapy with cyclophosphamide		1/8
Number of relapses	0.71 ± 1.70 (0–4)	8

while only exceptionally supported by data published by authors of non-Asian origin [9]. To our knowledge our study is one of the rare studies which unequivocally concludes that the coincidence of IgAN and MCN is a relatively common finding even in European area and should not be considered as "Asian peculiarity". The reason of such a shifting of attitude can be explained by the fact than only a systematic ultrastructural examination of the epithelial structures in the background of IgAN can disclose MCN (and therefore the coincidence of the two entities). The standard policy in most European countries did not include such a complex examination of the histological specimens of IgAN in the past and this policy only gradually changes.

Minimal change nephrotic syndrome (MCNS) associated with mesangial IgA deposition has been regarded as a variant of IgAN and was known to be steroid responsive [6]. However, there also have been several reports that it might be a variant of MCD [7, 8] or an overlap syndrome of MCD and IgAN [9].

These two glomerulonephritides have common and distinct findings in their pathogenesis.

MCD may reflect a disorder of T lymphocytes, which are presumably sensitive to corticosteroids and cyclosporine, and are thought to release a cytokine or cytokines that injure the glomerular epithelial cells [3]. Further data support the role of a circulating glomerular toxin – some data suggest hemopexin, an acute phase reactant [4]. Additional possible factors include interleukin-4, vascular endothelial growth factors, etc. Epithelial cell damage may lead to proteinuria by decreasing the synthesis of polyanions such as heparan sulphate. On the other hand diffuse effacement of the epithelial cell foot processes may result in part because of altered interactions between podocyte adhesion molecules, such as alpha 3-beta 1 integrin, the dystroglycans, and glomerular basement membrane. The expression of beta-dystroglycan is significantly reduced in patients with MCD. Corticosteroid therapy appears to normalize beta-dystroglycan expression in MCD. Corticosteroids are the treatment of choice in MCD, leading to complete remission of proteinuria in over 90 percent of cases.

There is a report of a cadaver transplant donor with active MCD; the diseased kidney was placed in a healthy recipient, proteinuria rapidly fell and remained persistently within the normal range within six weeks. Also immune deposits in a kidney transplanted from a donor with subclinical IgAN to a patient with non-IgAN renal disease clear within several weeks [12], suggesting that the causes of IgAN and MCD are extra renal.

It has recently been shown that mesangial IgA1 in IgAN has the abnormalities of O-glycosylation (abnormal O-linked hinge-region sugars with reduced glycosylation – [15, 16, 17, 18]. In the absence of Gal, the terminal sugar is N-acetylgalactosamine (GalNAc) [13, 14], these sugar moieties or glycopeptides [19, 20] are recognized by antibodies with antiglycan or antihinge region peptide

specificities [14, 20], and CIC are formed [19]. Recent studies showed that the IgAN-CIC, composed of galactose-deficient IgA1 complexed with antiglycan antibodies, is bound to mesangial cells more efficiently than uncomplexed IgA [21, 22]. Thus, likely play a role in the pathogenesis of IgAN. Also familiar forms of IgAN [23] have been described; a linkage of IgAN to chromosome 6q22-q23 has been demonstrated [24].

In our all patients with the coincidence of IgAN and MCD, the clinical course was markedly influenced by heavy proteinuria within fully blown picture of nephrotic syndrome, distinguishing thus within other patients with IgAN. A therapy consisting of standard dosing of corticosteroids enabled to achieve the remission in 6/8 patients. In two patients, in whom monotherapy with corticosteroids failed the addition of either cyclosporine (in patient with mesangioproliferative type in ultrastructural examination) or cyclophosphamide (in patient with sclerosing type) was necessary. The clinical picture, incl. the response to the therapy, observed in the patients with the coincidence of IgAN and MCD was very close to the clinical manifestation of "pure" MCD.

It could be submitted to discussion the proposition to complete in the patients with IgAN, especially in those with nephrotic proteinuria, the full spectrum of histological examinations by electron microscopy. Thus, it could be expected that the initiation of the therapy and especially further management of the patient would be done not only on the basis of clinical findings but also in conjunction with relevant histological changes.

Conclusions

Our data from Czech Republic, based on systematic analysis of electron microscopy of more than 600 RB specimens, diagnosed as IgAN, seem to confirm that the combination of IgAN with MCNS can be found relatively frequently not only in Asian patients (as stressed by some authors of Asian origin) but also in European inhabitants. The pathogenesis of the coincidence of IgAN and MCNS needs to be elucidated by further studies. The coincidence of IgAN and MCNS clinically – especially the response to drug therapy (with corticosteroids) – behaves as "pure" MCN.

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