A case report: a patient with IgA nephropathy and coeliac disease. Complete clinical remission following gluten-free diet

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Background

IgA nephropathy (IgAN) presents usually as a primary disease. However, secondary forms of IgAN have been described, most commonly associated with liver disease [1]. The presence of high levels of IgA against food antigens including gliadin and IgG and IgA antiendomysial antibodies in some patients with IgAN has raised the possibility of a pathophysiological link between IgAN and coeliac disease (CD) [2]. Experimental IgAN can be induced by dietary gluten or gliadin [3]. Furthermore, a favourable outcome of gluten-free diet on IgAN has been described [4].

Case report

We report a 46-year-old male with IgAN who presented at autumn 2001 with incidental hypertension [blood pressure (BP) level 180/105 mmHg] during routine health examination. In further examinations, proteinuria and haematuria were detected. Despite nephrotic range of proteinuria (daily urinary protein excretion 11.5 g) and hypoaluminaemia (plasma albumin 20 g/l), plasma creatinine was normal, 70 μmol/l, and he had only minor peripheral oedema. There had not been any periods of macroscopic haematuria. Antinuclear and antineutrophil antibodies were negative. Serum immunoglobulins and complement levels were normal.

A renal biopsy revealed a typical IgAN. In light microscopy, a focal proliferative glomerulonephritis with mesangial segmental hypercellularity and increase in the mesangial matrix was seen in almost all glomeruli. Immunofluorescense microscopy demonstrated mesangial, granular IgA deposits and lesser amounts of C3 and kappa (Figure 1). Electron microscopy at that point was not studied.

At first, the patient was treated with enalapril. Since the BP remained above the recommended levels, 140–157/80–94 mmHg, the dose was increased to 30 mg/day. Furthermore, in March 2006 valsartan was added with a dose of 160 mg/day.

Proteinuria persisted but renal function remained normal. Prednisone (40 mg/daily at start and tapering down) and azathioprine (1 mg/kg/day) were started. Proteinuria, ranging from 1.5 to 7 g/day, persisted. In 2005, azathioprine was temporarily changed to mycophenolate for 6 months without any avail. In May 2007, azathioprine was also stopped. More accurate description of clinical course and immunosuppression is presented in Figure 2.

In January 2007, the plasma haemoglobin level had decreased from 140 (August 2005) to 110 (January 2007) g/l. Plasma iron and serum ferritin were low. In further studies, high levels of serum IgA-endomysial and IgA-anti-tissue transglutaminase antibodies were detected. Gastroscopy revealed macroscopic and microscopic subtotal villous...
atrophy in duodenum. The decline in haemoglobin level was the only clinical manifestation of CD. A gluten-free diet was introduced for CD in April 2007. At the beginning of diet, the amount of proteinuria was 6.8 g/day. After 4 months of gluten-free diet, plasma albumin was normal 38 g/l, plasma haemoglobin 141 g/l and urine protein excretion had dropped down to 0.2 g/day. In November 2007, no proteinuria or haematuria was seen.

On a repeat renal biopsy in February 2008, IgA was still moderately present in mesangium cells in IF. In light microscopy, somewhat less mesangial changes were detected in comparison to the first biopsy. Electron microscopy showed mesangial hypercellularity and electron-dense deposits corresponding to the mesangial IgA (Figure 3). Podocyte foot processes were mainly separate, but areas of fusion were also detected.

Discussion

CD affects up to 1% of the population in the Western world according to recent screening studies [5]. Furthermore, IgAN is the most common form of primary glomerulonephritis in all countries where renal biopsy is widely practised. There is also a relatively high frequency of subclinical IgAN in supposedly healthy populations. This may be as high as 16% in certain Asian populations, implicating that the chances of occurrence of a clinical IgAN and another pathophysiologically unrelated medical condition are high [6].

CD is characterized by malabsorption, chronic mucosal inflammation and villous atrophy affecting the small intestine. In IgAN, there is evidence of normal intestinal morphology but an increase in permeability has been described [7]. Disordered mucosal permeability barrier can enhance antigen access to the immune system that further drives the production of pathogenic IgA and mesangial IgA deposits. Not all mesangial IgA deposition is associated with the development of glomerular inflammation. IgA deposition may also be reversible. Mesangial IgA deposits have disappeared when kidneys with subclinical IgAN have been inadvertently transplanted into recipients who originally did not have IgAN. Sequential biopsy studies have shown that clinical remission is not always related to disappearance of IgA as was seen in our case [8]. This concept is not surprising because IgA deposits have been observed in the mesangium in individuals without urinary abnormalities. Pasternack et al. evaluated a fine needle biopsy in 25 newly diagnosed CD patients without any clinical evidence of renal disease [9]. In eight of them, mesangial IgA deposits were detected. This suggests that mesangial deposition of IgA may be common in CD, but does not usually cause clinically apparent glomerulonephritis.
The detection of high titres of antigliadin antibodies in the sera of IgAN patients has drawn attention of many authors to the possible relationship between IgAN and CD. However, controversial data of the presence of antigliadin antibodies in patients with IgAN have been reported, probably because of different techniques used whereas IgA-endomysial antibodies have been absent in patients with IgAN at all times [2]. Moreover, there is a lack of correlation between jejunal mucosal atrophy and gliadin, reticulin and endomysial antibodies in IgAN, suggesting that most of these patients do not have CD [7]. These data indicate that routine screening of antigliadin antibodies from IgAN patients is not useful.

In experimental models in mice, it has been demonstrated that gluten and gliadin were able to induce IgAN [3]. Based on these findings, Coppo et al. [10] carried out a study of gluten-free diet in 29 IgAN patients. After 6 months of diet, proteinuria significantly decreased. As some of the patients continued a gluten-free diet, the decrease in proteinuria remained significant after 1 year, but after 2–4 years it did not attain the level of statistical significance. However, the progression of renal failure was observed. Since this was not a controlled study, no comparison could be made with patients on a gluten-containing diet. The progression of renal disease may indicate that immunological factors may play a role early in the development of mesangial deposits, but the disease progresses by different mechanisms.

The genetic influence in the pathogenesis of CD is indicated by its familial occurrence. CD does not develop unless a person has HLA alleles DQ2 or DQ8 [5]. In one of the largest case series reported, 233 adults with IgAN, 8 patients (3.6%, CI = 1.6–7.0%) were found to have CD and all of them had the HLA-DQ2 or DQ8 haplotype. However, the prevalence of HLA-DQ2/8 was the same in IgAN patients than in controls [11]. Thus, the HLA type is an unlikely explanation of the association between CD and IgAN.

We report here a patient with IgAN and nephrotic syndrome who responded to a gluten-free diet. As treatment of IgAN remains controversial, an extensive study of the effect of gluten-free diet on the course of IgAN might be warranted. Taking into account the natural history of IgAN, the follow-up time should be extended.

Conflict of interest statement. None declared.

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