IgA Nephropathy in Patients with HLA Dq2 Positive Celiac Disease

A Report of Two Cases

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ABSTRACT

Background: Two reported siblings cases have linked IgA Nephropathy (Berger's disease) to Celiac disease.

Case Summary: We describe here two cases of IgA nephropathy for whom the initial diagnosis was celiac disease. The diagnosis was established. In fact, Anti tissue trans-glutaminase IgA and IgG antibodies were detected in serum of the patient and the endoscopic biopsy of the duodenum revealed celiac disease. HLA molecular PCR (SSO) alleles for celiac disease DQB1*02 was identified in both of them. Percutaneous kidney biopsy was also performed and IgAN was diagnosed. Gluten-free diet, ACE inhibitor and oral iron were introduced to the patients. The improvement of clinical and laboratory disorders of celiac disease as well as gradual remission of the nephrotic range proteinuria were observed. Prior ethical approval was obtained from the patients' parents and permission was obtained for publishing their cases.

Keywords: Celiac disease, IgA nephropathy (Berger's disease), HLADQ2, Gluten free diet.

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Both Celiac disease and IgA nephropathy are autoimmune diseases are IgA mediated and share many clinical, pathophysiological, genetic, nutritional and immunological aspects[1].

Celiac disease occurs in genetically predisposed people, class II human leukocyte antigens (HLA), such as HLA-DQ2 or, much less commonly, HLA-DQ8, are expressed in the majority of patients with celiac disease[2], patients negative for both types are unlikely to suffer from celiac disease[3].

IgA nephropathy presents as primary disease. However, secondary forms of IgA nephropathy have been described. Celiac disease is an autoimmune inflammatory disorder of the small intestine, triggered by the ingestion of prolamins contained in wheat, barley or rye, in genetically susceptible individuals[4].

The presence of high level of IgA against food antigens including wheat gluten, have been proposed as potential contributing environmental factors[5].

The detection of high titers of antigliadin antibodies in the sera of IgA nephropathy patients has drawn attention of many authors to the possible relationship between IgA Nephropathy and celiac disease[6].

Several tests for gluten free diet for IgAN were described in literatures. The diet was associated with decrease in the circulating IgA complexes and proteinuria but not reverse the progression of the disease[7].

Several diets were investigated and suggested for patient with IgAN as Mediterranean diet, low antigen diet (a diet free of foods likely to cause an allergic reaction) and fish oil (KDIGO recommendations)[8].

We report here two siblings with celiac disease who presented in autumn 2017. Both attended the consulting clinic of the Central Teaching Hospital of pediatrics in Baghdad, Iraq. They presented with atypical presentation of celiac disease as IgA nephropathy.

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——————————Case One

A 13-year old male, presented two years ago as pallor, easy fatigability, failure to gain weight and recurrent diarrhea with abdominal distension.

Diagnosis of iron deficiency anemia was confirmed by complete blood count and blood film which revealed hypochromic, microcytic RBCs with leucocytosis/neutrophilia. Platelet count was increased. G6PD enzyme level was normal.

Iron study showed low transferrin, low plasma Iron and serum ferritin, with high total iron binding capacity. He was treated as a case of iron deficiency anemia with oral iron and folic acid.

Anti-tissue transglutaminase Ab IgG: 150 U/ml (normal up to 15). Anti-tissue transglutaminase Ab IgA: 120 U/ml (normal up to 15) which was decreased to 3.8 U/ml after gluten free diet for six months. Anti Gliadin (IgG) was: 9.3 u (positive more than 30 u/ml) after gluten free diet for six months.

HLA molecular PCR (SSO) alleles for Celiac disease DQB1*02 was identified which was performed in the histopathology laboratory in Al-Karama Teaching Hospital in Baghdad, Iraq. Thyroid function test was normal.

Duodenal biopsy was performed at time of presentation in the Hepatology and Gasrtoenterology center and it was tested in histopathology laboratories of Baghdad teaching hospital in the Medical City in Baghdad, Iraq. It showed leaf- like appearance with severe to partial blunting in height subtotal villous atrophy, expansion of lamina propria by mononuclear cells and increased in intraepithelial lymphocytes. No Giardia trophozoites were seen. No malignancy. At that point, a gluten-free diet had been introduced but with poor compliance of the patient.

One year later, patient developed eye puffiness and generalized body edema macroscopic haematuria and mild hypertension. Laboratory analysis showed urine with red appearance, Albumin: +++, RBC: ++, Leishman stain for RBC morphology in urine: isomorphic RBC. No growth of any uropathogenic bacteria seen.

The 24-hours urinary protein: 8.3 g/1.73 m^2 /day (nephrotic range). Urinary protein / creatinine ratio: 7.46 g (nephrotic range). Then dropped down with time to less than 0.2 g with more restriction on gluten free diet.

Serum immunoglobulin and complements were normal. Renal function test and blood urea nitrogen was normal and serum creatinine was elevated for age and gender at the time of diagnosis as nephrotic range proteinurea then returned to the base line within a week of starting steroid.

Percutaneous renal biopsy was performed in the Central Teaching Hospital of Pediatrics in Baghdad and tested in a private histopathology laboratory. It was consistent with IgA nephropathy with (Hass class 1) with mild segmentally accentuated mesengial hypercellularity with a mild increase in mesengial matrix. RBCs were found in some tubular lumens. There was mild interstitial fibrosis with no demonstrable tubular atrophy. Arteries and arterioles are unremarkable. Immunostain showed IgG: glomeruli negative ± tubular resorption droplets. IgA: glomeruli moderate 2+ positive, granular staining ±tubular resorption droplets. IgM: glomeruli weak 1+ positive, granular mesengial pattern. C3: glomeruli weak 1+ positive, granular mesengial pattern. 1+ tubular protein resorption droplets. C1q: negative. Electron microscopic examination was not done at that point because it was not available.

Gluten-free diet was advised to be much more restricted. Enalapril and oral iron were introduced to the patient[8]. Gradual remission of the nephrotic syndrome was observed. Patient was treated as a case of IgA N with nephrotic range proteinurea (8.3 g/1.73 m^2 /day) by 3 courses of 3 pulses of methylprednisolone (10mg/kg) for 3 days on alternative three months followed by oral prednisolon 2 mg/kg/day for 2 months

followed by reduced doses for total six months[8,9]. Fish oil as Omega 3 fatty acid cap orally 1000 mg daily had been given from the start daily[8,10].

——————————Case Two

A 9-year old female, presented six months later than her older brother (case one) with recurrent diarrhea with abdominal distension.

At time of presentation, her growth parameters were normal for age and gender. Pallor (congenctiva and mucous membrane). Flat nails, no clubbing. laboratory investigations revealed also celiac disease with iron deficiency anemia as the following: Blood film morphology showed hypochromic, microcytic anemia. Iron study revealed iron deficiency.

Anti-tissue transglutaminase Ab IgG:21.1 U/ml (normal up to 15). Anti-tissue transglutaminase Ab IgA : 120 U/ml (normal up to 15) which decrease to 2.1 U/ml after gluten free diet for six months.

Duodenal biopsy was performed at time of presentation in the Hepatology and Gasrtoenterology center and it was tested in histopathology laboratories of Baghdad teaching hospital in the Medical City in Baghdad, Iraq. It showed focal villous branching and widening with mucosal inflammation, mild focal increased intra-epithelial lymphocytes and moderately lymphocyte infiltrate in lamina properia. No Giardia trophozoites were seen. No malignancy. No granuloma. HLA molecular PCR (SSO) alleles for celiac disease DQB1*02 was identified which was performed in the histopathology laboratory in Al-Karama Teaching Hospital in Baghdad, Iraq. Thyroid function test was normal. Renal functions and liver functions were normal. A gluten-free diet was recommended at that point but unfortunately with poor compliance.

One year later: The patient developed eye puffiness and generalized body edema and there had not been any periods of macroscopic hematuria but her urine analysis showed microscopic hematuria with isomorphic morphology on Leishman stain.

Blood pressure was normal. The 24-hour urinary protein was 6.4 g (nephrotic range). Urinary protein / creatinine ratio: 5.46 g (nephrotic range). Serum immunoglobulin and complements were normal.

Percutaneous renal biopsy was also performed in the Central Teaching Hospital of Pediatrics in Baghdad and tested in a private histopathology laboratory. It was consistent also with IgA nephropathy with focal segmental glomerulosclerosis (Hass class II). In light microscopy, the glomeruli have basement membranes of normal thickness and show mild segmentally accentuated mesangial hypercellularity with no appreciable increase in mesangial matrix with segmental sclerosis and adhesion to Bowman's capsule, and few globally sclerotic glomeruli were present. Many tubules contain granular casts. There was no evidence of interstitial fibrosis and tubular atrophy. Arteries and arterioles were unremarkable.

Immunostain : IgG: glomeruli negative ± tubular resorption droplets. IgA : glomeruli moderate 2+ positive, granular staining ±tubular resorption droplets. IgM : glomeruli weak 1+ positive , granular mesengial pattern. C3: glomeruli moderate 2+ positive, granular mesengial pattern. 1+ tubular protein resorption droplets. C1q : negative.

Enalapril was started with oral iron, and prednisolone of 2mg/kg/day as a starting dose for four weeks with gradual tapering over the following 8 weeks and then small doses for about six monthes according to the patient's response[8,9]. Fish oil as Omega 3 fatty acid orally 1000 mg daily had been given from the start[8,10]. Restricted gluten-free diet has been advised too.

Patient responded well to that regimen but relapsed frequently with non-compliance to regarding gluten-free diet. Six months later, high dose of prednisolone 2mg/kg/day had been started again for four weeks with gradual tapering over the following 8 weeks and then on small doses combined with mycophenolate mofetil.

Although the effectiveness of mycophenolate mofetil is still debated, it had been given in a dose of 360 mg pill twice daily for more than six months with good remission achievement[8,9,11].

Discussion

Two similar cases (siblings) were previously described in the literature. They presented with CD associated with biopsy proven nephrotic syndrome due to IgAN.

Both represented proteinuria about one year following the diagnosis of CD. The introduction of a gluten-free diet and ACE inhibitor resulted in remission of nephropathy and improvement of clinical and laboratory disorders of CD. Frequent relapsing need the starting of prednisolone. The pathogenic link between CD and IgAN involves increased permeability of the mucosal barrier to pathogens that can stimulate the production and further deposition of pathogenic IgA in the glomerular mesangium[2].

Koivuviita et al reported a case of a male patient with nephrotic syndrome and IgAN in whom the treatment with prednisone and immunosuppressive drugs was ineffective. Also, in this case introduction of a gluten free diet after the diagnosis of CD was established resulted in complete remission of kidney disease[7].

Both cases had the HLA DQ2. Celiac disease is strongly associated with the HLA DQ2 and DQ8 haplotypes, which might explain the potential risk of patients to contract various autoimmune conditions. It can be hypothesized that the increased intestinal permeability in IgA nephropathy may predispose genetically susceptible patients to celiac disease[12].

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[7].

There are many case reports associating IgAN with many other conditions as Rheumatoid arthritis and other autoimmune diseases, gastrointestinal disease like ulcerative colitis and rarely Crohn's disease[13].

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