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BRIEF REPORT

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Henoch-Schönlein purpura in Wiskott-Aldrich syndrome

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Abstract Wiskott-Aldrich syndrome (WAS) is a rare immune deficiency disease. Sialophorin glycosylation is defective in WAS. Although it is not very common, renal involvement including IgA nephropathy (IgAN) was reported. Abnormal glycosylation plays a key role in the pathogenesis of IgAN. We present an 8-year-old boy with WAS who had recurrent episodes of Henoch-Schönlein purpura with renal involvement following upper respiratory tract infections. His renal function did not deteriorate. Both IgAN and WAS have glycosylation defects, but there must be some other factors (genetic and environmental) to explain their rare association.

Keywords Abnormal glycosylation · Henoch-Schönlein purpura · IgA nephropathy · Wiskott-Aldrich syndrome

Introduction

The Wiskott-Aldrich syndrome (WAS) is a rare X-linked disorder characterised by the clinical triad of immune deficiency, thrombocytopenia and eczema [1]. Malignancy, asthma, autoimmune haemolytic anaemia, arthritis and glomerulonephritis are other less common manifestations [2]. Renal involvement has a wide spectrum: membranoproliferative, mesangial proliferation, interstitial nephritis, as well as IgA nephropathy (IgAN) have been shown in both WAS patients and in families with attenuated variants and no immune deficiency [3, 4, 5, 6].

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In IgAN, IgA1 subclass is deposited in the mesangium. Allen et al. suggested that abnormal glycosylation might play a role in the pathogenesis of IgAN [7]. On the other hand, defective glycosylation of sialophorin (CD43) may also have a role in the immune deficiency in WAS patients [8, 9]. We report on an 8-year-old boy with WAS who developed Henoch-Schönlein purpura (HSP), and discuss the association of the two diseases.

Case report

A 16-month-old boy was admitted to Hacettepe University Ihsan Dogramacı Children's Hospital in 1991 with petechiae. He had had frequent episodes of petechiae and otitis media from 2 months of age. His 3.5-year-old brother was healthy. There was no consanguinity between parents, and no similar complaints were noticed among relatives. Physical examination was normal. Laboratory investigations revealed haemoglobin 9.8 g/dl, leukocytes 11,200/mm^3 and platelets 44,000/mm^3, and a peripheral blood smear showed small platelets. Blood group was A Rh (+), and anti-B was 1/16 (+). The immunoglobulin levels were IgM 51.5 mg/dl (normal: 116±34.9), IgA 172 mg/dl (normal: 56.6±23), IgG 894 mg/dl (normal: 894±233.2), and IgE 34 IU/ml. On repeated analysis the IgM level was always subnormal. Mutation analysis revealed C to T nucleotide change at position 290, leading to R86C amino acid change. According to the scoring system proposed by Nonoyama and Ochs [10], the patient was classic WAS and his score was 2–3. He was put on intravenous immunoglobulin therapy (400 mg/kg every 4–6 weeks). He had no serious infection until 8 years of age.

In February 1998, he suffered from macroscopic haematuria. A physical examination was normal, and laboratory investigations revealed haemoglobin 9.4 g/dl, leukocytes 13,900/mm^3, platelets 60,000/mm^3. Liver and renal function tests were normal, and urinalysis showed 3+ proteinuria and many erythrocytes. Urinary protein/creatinine ratio was 3.0, C3 122 mg/dl (normal: 90–180), C4 30 mg/dl (normal: 10–40), antinuclear antibody, anti-double-stranded DNA antibody, ANCA, hepatitis-B serology were all negative, and the stool was guaiac negative. IgAN or type II membranoproliferative glomerulonephritis was suspected. One month later he had purpuric lesions on his buttocks, thigh and calves compatible with HSP. No significant changes happened in laboratory findings. A skin biopsy revealed a leucocytoclastic vasculitis with IgA deposition. A course of oral prednisolone (2 mg/kg per day, tapered to 1 mg/kg per day) was started. At the end of 1 month there was no clinical improvement. Proteinuria persisted and occult blood in stools became positive. Bolus methylprednisolone (MP) was given (500 mg/day for 3 consecutive days, month-

ly), and 10 mg/day oral prednisolone in between bolus MP. The patient received a total of five courses of bolus MP. Proteinuria and haematuria ceased after the third course of bolus MP. He was in complete remission during the following 2 months, while he was on treatment. After stopping the low-dose prednisolone (10 mg every other day), following an upper respiratory tract infection (URTI), his haematuria and purpuric lesions relapsed, but his renal function remained normal. He was restarted on oral low-dose prednisolone.

Discussion

In 1966 Ter Bensel reported a nephrotic syndrome in a patient with WAS, but none of the 14 patients reported by Blaese et al. had renal involvement [11, 12]. Renal involvement had been thought to be uncommon in WAS before Spitler et al. (1980) reported occurrence of nephropathy in 6 of 32 patients with WAS [4]. All 6 patients reported by Spitler et al. presented with haematuria and proteinuria, one with nephrotic syndrome and five with impaired renal functions [4]. It was not possible to obtain renal biopsies in the majority of patients due to thrombocytopenia similar to our case. The limited number of renal biopsies had shown variable renal histological features, membranoproliferative, mesangial proliferation, interstitial nephritis and IgAN [3, 4, 5, 6]. There are several speculative mechanisms concerning mesangial IgA deposition in WAS. Although De Santo suggested that immune complex deposition and insufficient immune complex clearance occur after recurrent respiratory infections, IgAN has also been described in variant forms of WAS without immune deficiency [6].

Deposition of the IgA1 molecules in the glomerular mesangium is the characteristic of IgAN. Several studies suggested that the key abnormality is a reduction in the terminal galactosylation of the *O*-linked sugar moiety of IgA1 [13, 14, 15, 16]. All immunoglobulins have numerous *N*-glycosylation sites, but *O*-glycosylation is exclusive for IgA1. *O*-linked sugars lie in the hinge region (17 amino acids, of which five are *O*-linked glycosylation sites) of the IgA1 molecule between the CH1 and CH2 [16]. *O*-linked sugars are composed of *N*-acetylgalactosamine (GalNac) *O*-linked to serine or threonine residues. The chain may be extended with the addition of galactose to GalNac and may carry one or two sialic acid. β1,3 galactose transferase is responsible for the addition of galactose to GalNac. Defective galactosylation of IgA1 results in increased exposure of GalNac. Tomana et al. have reported that IgG-IgA1 and IgA1-IgA1 circulating complexes occur, with IgA1 hinge region *O*-glycans acting as the antigen [20]. They have also shown that there is a significant correlation between IgG binding to the hinge region of IgA1 and the absence of galactose in the GalNac region (defective galactosylation of IgA1) [17]. Degalactosylated IgA1 may serve as ligand to a lectin and may facilitate deposition of IgA1. Although concrete evidence concerning IgA deposition is lacking, it is known that altered glycosylation may promote direct interaction with matrix proteins and interaction with C3 [18, 19, 20].

In WAS patients, increased activity of β1,6-*N*-acetylglucosamine transferase (an *O*-linked glycosyltransferase) results in the expression of highly *O*-glycosylated sialophorin [21]. Sialophorin has a functional role in T-cell activation; the defective glycosylation of sialophorin may have a role in the immune deficiency in WAS patients. Recently Huang et al. have shown that the transduction by the retroviral vector carrying WAS protein partially restored abnormal glycosylation and decreased the activity of β1,6-*N*-acetylglucosamine transferase [8]. Furthermore, Lasseur et al. showed abnormal glycosylation of serum IgA1 in a WAS carrier patient with HSP [22]. This abnormal glycosylation of IgA1 was as prominent as in IgAN.

In our patient, the diagnosis of WAS was proven by mutation analysis. The diagnosis of HSP was based on characteristic clinical presentation and the skin biopsy which revealed leucocytoclastic vasculitis with IgA deposition. Skin lesions and haematuria recurred following URTIs. Although a renal biopsy could not be performed due to thrombocytopenia and renal manifestation occurred prior to the typical skin lesions which could rarely be seen [23], we think that our patient might have HSP nephritis.

Although the glycosylation disorders are not the same in IgAN and WAS, both diseases have an altered *O*-glycan pattern. In WAS the exposed sugar moiety is GlcNac whereas, on the other hand, in IgAN it is GalNac. Since there is an abnormal *O*-glycosylation in both IgAN and WAS, one would expect to see more renal involvement in WAS patients. Host and environmental factors must also have an important role in the pathogenesis. We think that further studies focusing on IgA1 characteristics and comparing normal patients with WAS only and WAS plus HSP or IgAN will help to clarify the pathogenesis of IgAN in WAS patients.

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LITERATURE ABSTRACT

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Autosomal recessive distal renal tubular acidosis associated with Southeast Asian ovalocytosis

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Background A defect in the anion exchanger 1 (AE1) of the basolateral membrane of type A intercalated cells in the renal collecting duct may result in a failure to maintain a cell-to-lumen H+ gradient, leading to distal renal tubular acidosis (dRTA). Thus, dRTA may occur in Southeast Asian ovalocytosis (SAO), a common AE1 gene abnormality observed in Southeast Asia and Melanesia. Our study investigated whether or not this renal acidification defect exists in individuals with SAO.
Methods Short and three-day NH4Cl loading tests were performed in 20 individuals with SAO and in two subjects, including their families, with both SAO and dRTA. Mutations of AE1 gene in individuals with SAO and members of the two families were also studied.
Results Renal acidification in the 20 individuals with SAO and in the parents of the two families was normal. However, the two clinically affected individuals with SAO and dRTA had compound heterozygosity of 27 bp deletion in exon 11 and missense mutation G701D resulting from a CGG→CAG substitution in exon 17 of the AE1 gene. Red cells of the two subjects with dRTA and SAO and the family members with SAO showed an approximate 40% reduction in sulfate influx with normal 4,4′-di-isothiocyanato-stilbene-2,2′-disulfonic acid sensitivity and pH dependence.
Conclusion These findings suggest that compound heterozygosity of abnormal AE1 genes causes autosomal recessive dRTA in SAO.