Selective IgA deficiency associated with glomerulonephritis and oligoarthritis

J P Camilleri, R H Moore, D F R Griffiths, B D Williams

Abstract
A 59 year old woman with selective IgA deficiency associated with oligoarthritis and glomerulonephritis is described. She was seropositive for rheumatoid factor and renal histological examination showed a focal glomerulonephritis. High titre rheumatoid factor and a focal glomerulonephritis were also present in the only other well documented report of selective IgA deficiency and renal disease. Histological examination of the kidney suggested that the glomerulonephritis was mediated by immune complexes.

Selective IgA deficiency is common, affecting 1:400 to 1:700 of the general population.\(^1\)\(^-\)\(^3\) Most subjects are healthy,\(^2\)\(^-\)\(^3\) but there is an increased incidence of recurrent upper and lower respiratory tract infection,\(^4\)\(^-\)\(^5\) atopic disease,\(^2\)\(^-\)\(^4\) gastrointestinal disease,\(^2\) and malignancy.\(^5\) There is also a high incidence of selective IgA deficiency associated with connective tissue diseases, including rheumatoid arthritis, systemic lupus erythematosus, Sjögren’s syndrome, and dermatomyositis.\(^4\)\(^-\)\(^8\) About 4% of patients with systemic lupus erythematosus and juvenile rheumatoid arthritis have selective IgA deficiency.\(^6\)\(^-\)\(^7\)

Previous reports linking IgA deficiency with glomerulonephritis are rare.\(^9\)\(^-\)\(^10\) In this paper we describe a patient with focal glomerulonephritis and inflammatory oligoarthritis associated with IgA deficiency.

Case history
A 59 year old woman was referred to the rheumatology department at the University Hospital of Wales in 1989 with a history of an exquisitely painful swollen right first metacarpophalangeal joint. She had had similar symptoms in her left thumb one year earlier, which had settled spontaneously. She had tenosynovitis of the flexor tendon sheaths of the thumbs associated with each episode of joint pain but no other joint symptoms and no history of morning stiffness. There was no family history of joint or skin disease. Details of her past history showed that 22 years earlier she had presented to the dermatology department with an eczematous rash affecting her arms and legs. At that time she was noted to have a raised erythrocyte sedimentation rate with a polyclonal increase in IgG. The lupus erythematosus cell test was negative and cryoglobulins were not detected. In 1986 she had been referred with a history of diarrhoea: a rectal biopsy had shown a mild non-specific colitis and the symptom settled without specific treatment. Dipstick testing of her urine at that time showed 2+ protein without haematuria. Relevant findings on examination in the rheumatology clinic were a tender nodule on the flexor tendon of the right thumb and a non-tender nodule on the left thumb. There was no evidence of widespread synovitis or joint swelling. She was hypertensive with a blood pressure of 224/126 mm Hg. The salivary glands were not enlarged and a Schirmer’s test was negative.

Laboratory investigations showed normal haematology, serum urea was 11·5 mmol/l, and creatinine 141 \(\mu\)mol/l with a creatinine clearance of 50 ml/min and a 24 hour protein excretion of 1·78 g/24 h. No haematuria was detected. Serum immune complex and serum complement concentrations were normal, but C3 and C4 locus allotyping showed one null allele at the C4A locus. Her erythrocyte sedimentation rate was 50 mm/h and C reactive protein 43 mg/l. Rheumatoid factor as measured by the differential agglutination test was positive at a titre of 1/2048. Thyroid microsomal antibodies were weakly positive and gastric parietal cell antibodies were positive. Antimitochondrial and antinuclear antibodies were negative as were antibodies to the non-histone nuclear antigens SSA (Ro) and SSB (La). The serum IgA concentration was less than 0·07 g/l (normal range 0·7–4·0), there was a polyclonal increase in the IgG concentration of 30·1 g/l (normal range 6·0–13·0), and IgM concentration was normal. Radiographic examination of the hands showed soft tissue swelling of the right thumb.
The glomerulosclerosis, but the impairment renal a with renal complexes. This report describes the association of selective IgA deficiency with a focal glomerulonephritis. The patient also had organ specific autoantibodies, a high titre of rheumatoid factor, and oligoarthritis.

A search of published reports disclosed only two associations of selective IgA deficiency with renal disease. The first was a 14 year old boy with chronic nephritis and a raised blood urea.6 No details of the renal lesion are given in this brief report. The second was a 10 year old girl with a focal glomerulonephritis, chronic active hepatitis, haemolytic anaemia, and thrombocytopenic purpura.10 This patient also had positive thyroid mitochondrial and microsomal antibodies and a high titre of rheumatoid factor but without evidence of joint disease. The renal histology described and illustrated in this latter case report was a focal glomerulonephritis that appears similar to the glomerular lesion present in our case.

In the case reported here it seems that the renal impairment is secondary to hypertensive glomerulosclerosis, but the hypertension itself may be secondary to the background focal glomerulonephritis. The presence of immune deposits on the glomerular basement membrane at immunofluorescence suggests that the glomerular disease is mediated by immune complexes. This may be related to the high titre of rheumatoid factor present in our patient and, interestingly, the case previously described with a focal glomerulonephritis also had a high titre of rheumatoid factor. The glomerulonephritis seen here differs from the glomerulonephritis most commonly seen in rheumatoid arthritis, which is a diffuse membranous type.

About 9% of asymptomatic subjects with IgA deficiency are found to have a positive rheumatoid factor,11 and the incidence of connective tissue diseases, including rheumatoid arthritis, is increased.6–8 Despite the finding of a high titre of rheumatoid factor associated with joint symptoms and signs our patient did not fulfill the clinical criteria for rheumatoid arthritis, systemic lupus erythematosus, or Sjögren’s syndrome.

The association of non-organ specific and organ specific disease with selective IgA deficiency may be coincidental, but the greater than expected concurrence of IgA deficiency with antibody mediated autoimmune disease raises the possibility of a process or defect linking these findings. Selective IgA deficiency is a congenital condition which usually occurs sporadically but is also found with variable inheritance patterns, suggesting that more than one genetic defect may cause the condition.14 The deficiency is linked to particular combinations of MHC alleles, and an increased prevalence of HLA, A1, B8, C4AQ0, DR3 is found. This haplotype is also associated with antibody mediated immune disease, such as systemic lupus erythematosus, myasthenia gravis, and insulin dependent diabetes mellitus.12 13 One group has shown a strong association of IgA deficiency with C4 locus null alleles,14 and there is also evidence that the presence of null alleles of C4A and C4B may be responsible for conferring susceptibility to systemic lupus erythematosus.15 C4A is known to play an essential part in the processing and elimination of immune complexes.14 In our patient the null allele at the C4A locus might be responsible for defective processing of immune complexes and hence might have predisposed her to the development of renal disease.

There is evidence that even healthy IgA deficient subjects have a defective gut absorption mechanism, which allows foreign antigenic material to enter the circulation.11 This increased load of potentially cross reactive antigenic material in the presence of null alleles at the C4A locus may overload the ability of the complement system to clear immune complexes.

It seems strange to us that selective IgA deficiency, with its diverse autoimmune and immune complex associations, has not been more frequently reported with glomerulonephritis. More careful observation of the glomerular function in selective IgA deficiency may help to elucidate the true relation between this common immunodeficiency and renal disease.

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