IgG subclass distribution of autoantibodies differs between renal and extra-renal relapses in patients with systemic lupus erythematosus

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Abstract

Background. IgG subclasses of autoantibodies differ in their potential to induce an inflammatory response as they interact differentially with complement and Fcγ receptors.

Methods. The IgG subclass distribution of anti-nucleohistone and anti-dsDNA antibodies was analysed longitudinally in patients with systemic lupus erythematosus before and at the moment of an extra-renal (n = 23) or a renal relapse (n = 17). Kidney biopsy specimens of patients with a renal relapse were analysed for IgG subclass deposition.

Results. IgG1 anti-nucleohistone and IgG1 anti-dsDNA antibodies were present in plasma of 39 out of 40 patients. At the moment of a relapse, IgG2 and IgG3 anti-nucleohistone and IgG2 anti-dsDNA antibodies were more frequently present in patients with renal disease compared with those with extra-renal disease. Increases in levels of IgG1 anti-dsDNA were observed in 10 out of 11 patients prior to a renal relapse but only 10 out of 22 patients with an extra-renal relapse (91 vs 45%, P = 0.02). Rises in IgG2 anti-dsDNA occurred at an equally low rate prior to both renal and extra-renal relapses. A rise in IgG2 anti-nucleohistone antibodies preceded a renal relapse in eight of 11 patients and an extra-renal relapse in only four out of 22 patients (73 vs 18%, P = 0.006). In kidney biopsies all IgG subclasses could be detected. IgG1 and IgG2 subclass antibodies to nucleohistone and to dsDNA are the predominant subclasses found in plasma of lupus patients with renal disease.

Conclusions. The frequent occurrence of a rise in IgG2 anti-nucleohistone and IgG1 anti-dsDNA in patients prior to a renal relapse suggests that, besides IgG1 subclass autoantibodies, IgG2 subclass antibodies to nucleohistone have a particular pathophysiological role in lupus nephritis.

Key words: Autoantibodies, IgG subclasses, SLE.

Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease associated with a multitude of autoantibodies. The kidneys are frequently involved, presumably due to autoantibody deposition at the glomerular basement membrane (GBM), which results in complement activation and attraction and influx of inflammatory cells [1]. Deposition of antibodies at the GBM can occur via trapping of circulating immune complexes within the glomerulus, via nucleosomes that bind to the GBM and act as a substrate for autoantibody binding, or through cross-reactivity of antinuclear antibodies with glomerular structures [1]. Antibodies most closely associated with lupus nephritis are anti-dsDNA antibodies [1]. In addition, there is accumulating evidence for an important role of nucleosomes and anti-nucleosome antibodies in the pathogenesis of SLE. Nucleosome-specific antibodies emerge before anti-dsDNA antibodies in lupus-prone mice. Antibodies to dsDNA as well as to nucleosomes can be eluted from kidney specimens of lupus mice with overt glomerulonephritis [2]. IgG class antibodies seem
most relevant as there is a close relationship between levels of IgG anti-dsDNA and histological activity scores in patients with lupus nephritis [3]. Furthermore, in the majority of patients, a renal relapse is preceded by a significant rise in IgG anti-dsDNA as detected by enzyme-linked immunosorbent assay (ELISA) [4].

All IgG subclasses can be found in kidney biopsies [5]. Of the different subclasses, IgG1 and IgG3 activate complement more efficiently than IgG2 while IgG4 does not activate complement at all [6]. The IgG subclass distribution of autoantibodies could therefore be of relevance in the pathogenesis of lupus nephritis. To evaluate their possible nephritogenic role, we monitored levels of total IgG and IgG subclasses of antibodies to nucleohistone and to dsDNA in patients who suffered a renal relapse. The IgG subclass distribution in kidney biopsies of patients with a renal relapse was also assessed. Serological data obtained from patients with renal relapses were compared with those of lupus patients who developed an extra-renal relapse in order to evaluate the specificity of the findings for lupus nephritis.

Patients and methods

Patients fulfilling at least four revised American College of Rheumatology (ACR) criteria for the diagnosis of SLE [7] were eligible for participation in this study. Patients originated from the cohorts of SLE patients (n = 156) who participated in a prospective study at the University Hospitals of Groningen and Utrecht, the Netherlands. Patients belonging to this cohort are seen at the outpatient department at least every 3–4 months for clinical evaluation. At every visit disease activity is scored and the SLE Disease Activity Index (SLEDAI) is calculated [8]. Attention is paid to the occurrence of infections. For all patients who developed a relapse of the disease in the period between September 1991 and September 1997 (University Hospital, Groningen) and between September 1991 and January 1995 (University Hospital, Utrecht), data from their first relapse were included. Criteria for a relapse were predefined [9]. Patients were classified into those with a renal relapse, defined as biopsy-proven WHO class III, IV or Vd lupus nephritis according to the World Health Organization criteria [10], with or without extra-renal symptoms, and those with an extra-renal relapse of the disease. Blood samples were drawn monthly in EDTA (ethylene-diamine tetraacetic acid) (Vacutainer; Becton Dickinson, Mountain View, CA, USA) during the study period. Plasma was stored at −80°C until needed.

Measurement of anti-dsDNA and anti-nucleohistone antibodies

Anti-dsDNA antibodies were detected by the Farr assay using 125I-labelled recombinant dsDNA (Diagnostic Products Corporation, Los Angeles, CA, USA), which is free of contamination with ssDNA. The Farr assay was performed according to the manufacturer’s instructions and positive samples were measured at different dilutions to obtain measurements within the range of the assay. Results of this assay were expressed in IU/ml using W/o as the ultimate standard [11]. The normal value of the Farr assay in our laboratory is <10 IU/ml; intra- and interassay variations are both less than 10%.

Antibodies to dsDNA were also detected by ELISA as described [9]. For detection of IgG subclasses, microtitre plates (Nunc-Immuno plate Maxisorb; Nunc, Roskild, Denmark) were precoated with 100 µl well protamine sulphate (500 µg/ml in millipore water) at 4°C for 45 min. Plates were washed with Millipore water. Coating was performed with DNA [10 µg/ml DNA (Sigma, St Louis, MO, USA) in 10 mM Tris, pH 8.0, 0.15 M NaCl overnight at 4°C. After washing with washing buffer (0.01 M Tris, pH 8.0, 0.15 M NaCl, 0.05% Tween 20), plasma samples (diluted 1:60 in phosphate-buffered saline (PBS, pH 8.0) with 0.05% Tween 20, 0.2% bovine serum albumin) were added and plates were incubated for 1 h at 37°C and subsequently for 2 h at 4°C. Plates were washed and mouse anti-human monoclonal antibodies in dilution buffer were added (anti-IgG 1:6000, clone HP6017; anti-IgG1 1:1000, clone 8c/6-39; anti-IgG2 1:6000, clone HP6014; anti-IgG3 1:5000, clone HP6050; anti-IgG4 1:6000, clone HP6025; Sigma). After incubation for 1 h at room temperature, plates were washed and alkaline phosphatase-labelled sheep anti-mouse IgG (Sigma; 1:3000 dilution buffer) was added. After final incubation for 1 h at room temperature, plates were washed and p-nitrophenyl phosphate [Sigma 104-40T; 1 tablet suspended in 40 ml 10% (w/v) diethanolamine, buffer pH 9.8] was added for development. After 30 min of incubation in the dark at room temperature, the reaction was stopped with NaOH.

Total IgG and IgG subclasses of anti-nucleohistone antibodies were also detected by ELISA. Microtitre plates (Nunc Maxisorb) were coated with 10 µg/ml nucleohistone (Sigma; in 0.15 M NaCl, 0.15 M trisodium citrate, pH 7.0) for 1 h. This nucleohistone preparation contains only the core histone subcomponents and H1 [12]. After washing, plasma was added (diluted 1:60 in PBS, 0.05% Tween 20, 0.2% BSA) for incubation at room temperature for 1 h. Further development of the ELISA was similar to the anti-DNA ELISA described above.

For both assays, normal values were below the detection threshold. Values were expressed as arbitrary units. To prevent interassay variation, serial samples of individual patients as well as all exacerbation samples were analysed in one assay. Intra-assay variation was less than 10%. Based on the intra-assay variation and previous studies [9], a rise in antibody level of at least 25% within a period of 4 months was arbitrarily considered significant.

Biopsies

Renal biopsy specimens from lupus patients with a renal relapse obtained in the study period were used. Tissue specimens were available from 10 patients with renal
relapse. Cryosections (4 μm) were defrosted and fixed in 100% acetone. After preincubation with 10% v/v 
normal goat serum (Dako, Glostrup, Denmark) in PBS, 
sections were incubated for 3 h at room temperature 
with the same monoclonal mouse anti-human anti-
bodies as used in the ELISA. Anti-human total IgG 
(1:3000), anti-human IgG1 (1:600), anti-human IgG2 
(1:600), anti-human IgG3 (1:250) and anti-human 
IgG4 (1:1000) were diluted in PBS. Specimens of lupus 
nephritis class IV were used as positive control. Renal 
biopsy specimens from patients with minimal change 
nephropathy and acute transplant rejection served as 
negative control. Possible endogenous peroxidase 
activity was blocked by incubation for 15 min with 
0.1% NaN₃ and 0.3% H₂O₂ in PBS. After washing, 
sections were incubated with horseradish peroxidase 
(HRP)-conjugated goat anti-mouse IgG1 (Southern 
Biotechnology Associates, Birmingham, AL, USA) 
or HRP-conjugated goat anti- mouse IgG2a (Southern 
Biotechnology Associates). All goat anti-mouse mono-
clonal antibodies were used at 1:100 dilution in PBS 
enriched with 10% normal human serum (CLB, 
Amsterdam, The Netherlands) to block cross-reactivity 
with human IgG in the biopsies. HRP activity was 
detected by the addition of 3-aminoethylcarbazole. 
Finally, specimens were counterstained with haemato-
xoylin. Staining was scored by two independent 
observers on a semi-quantitative scale of 0 (no staining), 
1+ (weak or scarce, but unmistakably present) to 6+ 
(diffuse and global, strong intensity). Discrepancies 
between observers were resolved by scoring specimens 
together, thereby reaching consensus.

Statistics

GraphPad Instat (GraphPad Software, San Diego, CA, 
USA) was used for statistical calculations. Differences in 
parameters between groups were evaluated with the 
unpaired t-test when the normal distribution could be 
assumed, otherwise the Mann–Whitney U-test was used. 
Fisher’s exact test was used for comparison of differ-
ences in prevalence. Spearman’s test was used to detect 
correlations between different study parameters. 
A P value < 0.05 was considered significant.

Results

In the study period, 40 relapses were encountered. Char-
acteristics of the patients and the relapses are shown in 
Table 1. Seventeen relapses were classified as renal, all 
with biopsy-proven proliferative lupus nephritis (WHO 
class III, IV or Vd). In a minority of patients the renal 
relapse was accompanied by other manifestations of the 
disease, among which haematological abnormalities 
were seen most frequently (29%). The relapses without 
renal involvement were classified as extra-renal. Seven 
patients were included at the moment of relapse (six 
renal, one extra-renal); therefore antibody levels of these 
patients could not be monitored prior to the relapse.

Plasma anti-nucleohistone antibodies

Total IgG as well as IgG1-subclass antibodies to 
nucleohistone could be detected in all but one of the 
patients (Table 1). Antibodies of the IgG2 subclass were 
more frequently present in patients with a renal relapse 
than in those with extra-renal relapses (76 vs 35%, 
P = 0.01). Also, IgG3 anti-nucleohistone antibodies 
could be detected at a higher frequency in patients 
with a renal relapse (29 vs 0%, P = 0.009). A weak 
correlation was found between levels of total IgG anti-
nucleohistone antibodies and anti-dsDNA, as measured 
by the Farr assay (r = 0.44, P = 0.02). Furthermore, 
a correlation was found between levels of total IgG 
anti-nucleohistone antibodies and anti-nucleohistone 
antibody levels of the IgG1 (r = 0.87, P < 0.001) and 
the IgG2 subclass (r = 0.69, P < 0.001). Evaluation of 
the presence of the various anti-nucleohistone IgG 
subclasses in particular disease manifestations revealed 
no associations, although IgG2 anti-nucleohistone 
antibodies were present in most patients with nephritis, 
serositis or haematological abnormalities. Serial plasma 
samples were available in 11 patients with a renal relapse 
and in 22 patients with an extra-renal relapse. A rise in 
IgG2 anti-nucleohistone antibodies occurred more fre-
quently in patients with a renal relapse than in those 
with an extra-renal relapse (73 vs 18%, P = 0.006). With 
respect to the other subclasses, no differences could be 
found (Table 2).

Table 1. Clinical and serological characteristics of 40 SLE patients at the moment of relapse of the disease

<table>
<thead>
<tr>
<th>Clinical manifestation</th>
<th>Renal relapse</th>
<th>Extra-renal relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>17</td>
<td>23</td>
</tr>
<tr>
<td>Male/female</td>
<td>3/14</td>
<td>1/22</td>
</tr>
<tr>
<td>SLEDAI score (IU/l)</td>
<td>15.5 (6–25)***</td>
<td>9.6 (3–16)</td>
</tr>
<tr>
<td>Anti-nucleohistone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>antibodies: presence of IgG</td>
<td>IgG1</td>
<td>17 (100%)</td>
</tr>
<tr>
<td>subclasses</td>
<td>IgG2</td>
<td>13 (76%)#</td>
</tr>
<tr>
<td></td>
<td>IgG3</td>
<td>5 (29%)##</td>
</tr>
<tr>
<td></td>
<td>IgG4</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Anti-dsDNA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>antibodies: presence of IgG</td>
<td>IgG1</td>
<td>17 (100%)</td>
</tr>
<tr>
<td>subclasses</td>
<td>IgG2</td>
<td>13 (76%)#</td>
</tr>
<tr>
<td></td>
<td>IgG3</td>
<td>7 (41%)</td>
</tr>
<tr>
<td></td>
<td>IgG4</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are expressed as mean (range). ***P < 0.001, unpaired t-test; #P < 0.05, ##P < 0.01, Fisher’s exact test.
Table 2. Significant rises of anti-nucleohistone and anti-dsDNA antibodies occurring in a period of 6 months prior to a relapse of the disease

<table>
<thead>
<tr>
<th></th>
<th>Patients with renal flares (n = 11)</th>
<th>Patients with extrarenal flares (n = 22)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anti-nucleohistone</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total IgG</td>
<td>9 (82%)</td>
<td>9 (41%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>IgG1</td>
<td>8 (73%)</td>
<td>14 (64%)</td>
<td></td>
</tr>
<tr>
<td>IgG2</td>
<td>8 (73%)</td>
<td>4 (18%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>IgG3</td>
<td>2 (18%)</td>
<td>3 (14%)</td>
<td></td>
</tr>
<tr>
<td><strong>Anti-dsDNA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total IgG</td>
<td>9 (82%)</td>
<td>10 (45%)</td>
<td></td>
</tr>
<tr>
<td>IgG1</td>
<td>10 (91%)</td>
<td>10 (45%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>IgG2</td>
<td>4 (36%)</td>
<td>6 (27%)</td>
<td></td>
</tr>
<tr>
<td>IgG3</td>
<td>3 (27%)</td>
<td>2 (10%)</td>
<td></td>
</tr>
</tbody>
</table>

A significant rise was defined as a rise in antibody level of at least 25% within a period of 4 months.

Plasma anti-dsDNA antibodies

In patients with a renal relapse, levels of antibodies to dsDNA, as measured by the Farr assay, tended to be higher than in patients with an extra-renal relapse (P = 0.08, Table 2). Levels of IgG class antibodies to dsDNA, as measured by ELISA, showed a similar trend (P = 0.07) and correlated with the results of the Farr assay (r = 0.63, P < 0.0001). All but one of the patients had antibodies to dsDNA of the IgG1 subclass. The patient without IgG1 antibodies had an extra-renal relapse. Antibodies to dsDNA of the IgG2 subclass were found at increased frequency in patients with a renal relapse compared with those with an extra-renal relapse (76 vs 39%, P = 0.02). In fewer than half of the patients, anti-dsDNA antibodies of the IgG3 subclass were present (Table 1), showing a similar trend of a higher frequency in patients with renal disease (41 vs 17%, P = 0.07). None of the patients had IgG4 anti-dsDNA antibodies. The level of total IgG anti-dsDNA correlated with that of the IgG1 subclass (r = 0.88, P < 0.0001) as well as with that of IgG2 anti-dsDNA (r = 0.86, P < 0.0001). Longitudinal studies revealed that nine out of 11 (82%) of the patients with a renal relapse and 13 out of 22 (67%) with an extra-renal relapse had a significant rise in antibodies to dsDNA by the Farr assay, preceding the clinical relapse by a median period of 3 months (range 1–5). Table 2 shows the presence of significant rises in total IgG and IgG subclasses of anti-dsDNA, as measured by ELISA, in relation to relapses. The majority (91%) of renal relapses were preceded by a significant rise in antibodies to dsDNA of the IgG1 subclass. In contrast, only 45% of patients with an extra-renal relapse had a significant rise in IgG1 anti-dsDNA antibodies preceding their relapse (P = 0.02). Significant rises in the other IgG subclasses of anti-dsDNA before disease exacerbation occurred in a minority of patients.

Renal deposition of total IgG and IgG subclasses

In all biopsies, immunoglobulins of each IgG subclass were detected. Notably, in contrast to subclass analysis of plasma samples, IgG3 and IgG4 were detected in every kidney specimen. No correlation was found between the relative amount of any of the IgG subclasses in the kidney biopsy and plasma levels of IgG antibody subclasses to anti-dsDNA or anti-nucleohistone (data not shown).

Discussion

In this study we cross-sectionally and longitudinally analysed plasma IgG subclass levels of antibodies to nucleohistone and to dsDNA as well as the IgG subclass distribution in kidney biopsies from SLE patients. We performed this study in order to obtain more insight into the different roles of these autoantibodies and their IgG subclasses in the pathogenesis of SLE. Antibodies to nucleohistone as well as to dsDNA were found in plasma of 39 of 40 patients. These antibodies were mainly of the IgG1 subclass, and less frequently of the IgG2 subclass. Antibodies of the IgG3 subclass directed to nucleohistone or to dsDNA could be detected in fewer than half of the patients. Finally, antibodies of the IgG4 subclass directed to nucleohistone were present in only one out of 40 patients analysed, whereas those directed to dsDNA were not found at all.

We found that anti-nucleohistone antibodies can be detected in most of our lupus patients. Interestingly, IgG2 and IgG3 anti-nucleohistone antibodies were present more often in lupus patients with a renal relapse than in patients with an extra-renal manifestation of the disease only. Furthermore, a significant rise in IgG2 anti-nucleohistone preceded 78% of the renal relapses, in contrast to the extra-renal relapses, in which only 18% were preceded by a significant rise in IgG2 anti-nucleohistone antibodies. These data support the hypothesis that antibodies to nucleohistone are involved in the pathogenesis of lupus nephritis. In addition, our results suggest that anti-nucleohistone antibodies of the IgG2 subclass play a particular role. The predominance of IgG2 in autoantibody subclass distribution has been described for other autoantibodies in lupus patients. Indeed, antibodies of the IgG2 subclass to C1q are over-represented in lupus nephritis patients [13, 14]. Furthermore, we observed that antibodies to dsDNA of the IgG2 subclass were also over-represented in nephritis patients. It should be stated that the specific epitopes to which antibodies to nucleohistones and those to dsDNA are directed are unknown and that the reactivity of SLE serum to nuclear antigens is complex. Our nucleohistone ELISA not only measures antibodies specific for the conformational structure of nucleohistones but probably also antibodies to the individual components of nucleohistones, i.e. DNA and histones. This might explain why the subclass distribution of anti-dsDNA antibodies was comparable with that of anti-nucleohistone antibodies, i.e. IgG1 being present in the majority of patients, both with renal and extra-renal relapses, and a skewed distribution of IgG2 in patients with a renal relapse. Also, epitope spreading may,
in part, account for the overlap in subclass distribution of the autoantibodies measured [15].

In cross-sectional studies, others have also reported a restriction in subclass distribution of antibodies to dsDNA. In accordance with the present study, IgG1 has been demonstrated to be the anti-dsDNA antibody subclass most frequently encountered [16–20]. In addition, in support of a pathophysiological role for the IgG1 subclass, we observed that a significant rise in IgG1 anti-dsDNA occurred in 91% of the patients prior to a renal relapse. In contrast to our results, next to IgG1, the IgG3 isotype of anti-dsDNA as well as of antinucleohistone has been reported to be present most frequently in patients with renal disease [19–21]. These discrepancies might, at least in part, be explained by differences in the affinity of the monoclonal antibodies to IgG subclasses used in the various studies [22].

The longitudinal data on the IgG subclass distribution of anti-nucleohistone and anti-dsDNA antibodies obtained in this study are unique and are therefore difficult to compare with those of previous studies. Several others have reported stable isotype profiles of anti-dsDNA as well as anti-nucleohistone antibodies independent of antibody fluctuations (as measured by the Farr assay) and independent of disease activity [18]. Winkler et al. [18] analysed the IgG subclass pattern of antibodies to dsDNA in 22 SLE patients over a period of 1–3 yr. Data concerning disease activity were not provided. Furthermore, the time interval between blood sampling for all patients was not explicitly reported and ranged up to 8 months for the four selected patients for whom data were shown. In the period analysed, no switch in IgG subclass was found. In contrast, Devey et al. [20] found increases in the IgG1- and IgG3-subclasses, but not of the IgG2 anti-dsDNA antibody subclass with increased disease severity in patients with renal disease. Because the intervals between blood sampling in all of the studies mentioned above were much longer than the monthly period that we have used consistently, the possibility cannot be excluded that rises in levels of IgG subclasses prior to a relapse have been missed in these studies. We found a subclass-specific rise in levels of anti-nucleohistone and anti-dsDNA occurring over a period ranging from 1 to 5 months preceding a relapse, which is comparable with a previous study from our group, in which total levels of anti-dsDNA were evaluated [9].

Also in other studies, all IgG subclasses could be detected in renal biopsies from lupus patients [5, 23, 24]. Imai et al. [5] analysed glomerular immunofluorescence intensity of IgG subclasses in patients with membranoproliferative glomerulonephritis, membranous nephropathy and lupus nephritis and demonstrated increased intraglomerular deposition of IgG1 and IgG2 in lupus nephritis. This might reflect the predominance of the IgG1 and IgG2 subclasses of anti-nucleohistone and anti-dsDNA antibodies that we found in plasma of patients with a renal relapse. Others, however, found IgG3 to be the dominant isotype in kidney biopsies of patients with class IV lupus nephritis [24]. Interestingly, IgG4 was detected in all kidney specimens of our patients with a renal relapse, while in plasma IgG4 anti-nucleohistone antibodies were found in only one patient. The lack of correlation between levels of the measured autoantibodies in the serum and their deposition in renal tissue suggest that the autoantibodies deposited in the kidney may include antigenic specificities other than those measured in sera. The deposition of antibodies might also be dependent on factors other than their serum concentration, such as their affinity to their respective antigen, the degree of presence of the antigen along the basement membrane, and epitope specificity.

For many years, attention has been paid to IgG subclasses in SLE. Each IgG isotype has different biological and functional properties. The subclass distribution might therefore influence the course of SLE [6]. Recently, the role of Fcγ-receptor IIa (FcγRIIa) has renewed interest in IgG subclasses. First, the important role of FcγR in the mediation of an inflammatory reaction by immune complexes has been shown in NZB/NZW mice. These mice spontaneously develop glomerulonephritis. Deficiency of the χ chain of the FcγR protected them from severe nephritis, although immune complex deposition and complement activation were unaltered [25]. Secondly, polymorphisms of FcγR can influence the interaction with IgG subclasses, in particular with IgG2 [26]. This is highly relevant for the second Fcγ receptor (FcγRIIa), in which the presence of either arginine or histidine at position 131 (FcγRIIa-R131 and FcγRII-H131 respectively) determines the interaction with IgG2 and, to a lesser extent, IgG3. In contrast to FcγRIIa-H131, the FcγRIIa-R131 isoform cannot interact with IgG2 and has less affinity for IgG3. It has been suggested that patients homozygous for FcγRIIa-R131 will be prone to the development of lupus nephritis because of decreased clearance of complexed IgG2 and IgG3 subclass antibodies. Indeed, in several studies the FcγRIIa-R131 genotype was significantly more frequent in patients with proliferative lupus nephritis. However, there is still controversy, as in most studies no skewing of FcγRIIa-R131 was observed in lupus patients with nephritis compared with those without nephritis [27].

In conclusion, IgG1 and IgG2 subclass antibodies to nucleohistone and to dsDNA are the predominant subclasses found in plasma of lupus patients with renal disease. The frequent occurrence of a rise in IgG2 anti-nucleohistone and IgG1 anti-dsDNA in patients prior to a renal relapse suggests that, besides IgG1 subclass autoantibodies, IgG2 subclass antibodies to nucleohistone have a particular pathophysiological role in lupus nephritis. Therefore, the autoantibody constellation and changes in the subclass distribution in time may be a risk factor for the development of a renal flare. A prospective study is needed to support this hypothesis and to determine whether the immunosuppressive therapy of SLE patients should be modified according to (changes in) their autoantibody profile.
Acknowledgements
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References