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ORIGINAL ARTICLE

Anti-C1q autoantibodies as markers of renal involvement in childhood-onset systemic lupus erythematosus

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Abstract
Background Childhood-onset systemic lupus erythematosus (cSLE) is rare, and considered more severe than its adult-onset counterpart. Lupus nephritis (LN) occurs more frequently in children, accounting for higher long-term morbidity and mortality compared with adults. Thus, reliable biological markers are needed to predict disease course. This study aimed to investigate the capacity of anti-C1q autoantibodies (Abs) to predict renal flare and global disease activity in cSLE patients, and association with disease activity and kidney involvement.
Methods Twenty-eight patients with cSLE including 19 patients (68%) with a history of LN were included retrospectively. Anti-C1q Abs were analysed by ELISA at renal flare-up or in the quiescent phase of disease and compared with Farr dsDNA assay.
Results Thirty-one flares occurred during follow-up: anti-C1q Abs were positive in 26 (84%), strongly associated with active disease status ($p < 0.0001$), and correlated with global disease activity score ($p < 0.0001$) and anti-dsDNA Abs presence ($p < 0.0001$). The specificity of anti-C1q Abs was higher than anti-dsDNA (73% vs 19%) in discriminating LN patients, whereas the receiver operating characteristic curves were not statistically different (0.83 ± 0.06 vs 0.78 ± 0.08 respectively), similar to C3 dosage. The presence of anti-C1q Abs at diagnosis was not predictive for global or renal flare. Introduction of a modified SLEDAI score excluding dsDNA Abs, demonstrated a stronger correlation of anti-C1q Abs titres with SLEDAI score in comparison with the Farr test.
Conclusion Anti-C1q Abs seem very specific to flares, including LN in children, and their role in daily practice compared with the Farr dsDNA assay needs to be defined.

Keywords Childhood-onset systemic lupus erythematosus · Anti-C1q antibody · Lupus nephritis · Pediatrics · Biomarker · SLEDAI

Introduction

Systemic lupus erythematosus (SLE) is a prototypical autoimmune disease that occurs at all ages. The pathogenesis is linked to multiple factors, including environmental, immunological, and genetic anomalies. The latter factor probably plays a predominant role in the pediatric forms of the disease, which account for 15–20% of all cases of SLE [1–3]. Childhood-onset SLE (cSLE) has been associated with a more severe phenotype and a higher mortality rate than adult-onset forms [3–5].

Systemic lupus erythematosus is associated with numerous autoantibodies (Abs), including antibodies targeting the classical pathway complement fragment 1 (C1q). Anti-C1q Abs are found in about one third to one half of patients [6]. Complement deficiencies were identified 40 years ago, in

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association with SLE [7], and C1q deficiencies were frequently associated with lupus nephritis (LN) [8, 9]. Interestingly, C1q deficiency is a monogenic form of lupus that is linked to an excess of autoantigens secondary to a defective clearance of immune complexes and apoptotic bodies [1]. Furthermore, C1q displays an immunoregulatory function, as it has been shown to decrease circulating immune complex-induced IFNα production in plasmacytoid dendritic cells [10].

Anti-C1q Abs are supposed to arise in SLE following an antigen-driven immune response as a result of abnormal apoptotic body clearance [8, 11]. They specifically recognise the immunogenic collagen-like region of the molecule C1q and may have a direct impact on tissue injury [8]. These Abs have been reported as being specific to SLE and evocative of renal involvement. The strong association with LN has been shown in adults and mentioned as a marker of renal flares [12–16] during the course of the disease. Furthermore, anti-C1q Abs were recently described as better biomarkers of LN activity than anti-dsDNA Abs [17–19].

As well as in adulthood, a few studies support the association between LN and the positivity of anti-C1q Abs in juvenile SLE [20, 21]. Anti-C1q Abs are still not considered as a biomarker of renal involvement or flares during follow-up and thus are not routinely used in daily practice. Multicentre studies have shown that renal involvement in cSLE patients was more common than in adult patients [3, 22–29]. LN highly impacts on long-term morbidity and mortality, and thus partly explains the poorest prognosis of cSLE. Given all these observations, clinicians need reliable predictive biomarkers of renal flares even more in the paediatric population. Therefore, this single-centre study is aimed at investigating the association of anti-C1q Abs with renal flare at diagnosis and during the follow-up of cSLE, in comparison with anti-dsDNA Abs in children.

Patients and methods

Patients

We retrospectively collected data from patients diagnosed with cSLE who were under 18 years of age, fulfilled at least four of the revised American College of Rheumatology (ACR) criteria for SLE. They were all followed at the Hôpital Femme Mère Enfant in Lyon between 2003 and 2015. To be included in the study, all biological and clinical data had to be available at the time or 15 days before or after anti-C1q Abs measurement for each patient.

Disease activity was assessed retrospectively using the SLE Disease Activity Index (SLEDAI) [30] for each patient on the date of anti-C1q Abs measurement. A flare was defined by a score strictly >4. Nephritis was considered to be active if patients developed proteinuria >0.5 g/24 h after achieving complete remission or doubling to >1 g per day after achieving partial remission, an increase or recurrence of urinary sediment with or without increased proteinuria, or associated with a decline in renal function. Confirmation of LN flare by kidney biopsy was not mandatory. When performed, biopsies were classified according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS).

Laboratory parameters

Anti-C1q Abs levels were all assessed with the same commercial enzyme-linked immunosorbent assay kit (IMTEC, Wiesbaden, Germany) according to the manufacturer's instructions, at different times of disease activity for each patient (diagnosis, flare or quiescent phase). The cut-off for these Abs was routinely fixed at 20 AU/mL. A minimum of two anti-C1q Abs measurements during follow-up was required for cSLE patients presenting with a renal involvement. Anti-dsDNA Abs were determined using a radioimmunological test (Farr assay; Trinity Biotech, Wicklow, Ireland) with a cut-off at 7 IU/mL. Levels of C3 and C4 components were assessed by nephelometric assay (BNII analyser; Dade Behring, Marburg, Germany) and CH50 according to Mayer's method. Urine sediment and creatinine levels were determined by routine laboratory procedures.

Statistical analysis

Distribution normality was assessed using the Kolmogorov–Smirnov test. Comparisons between groups used Spearman's test, Student's *t* test for quantitative variables and the Chi-squared test, or Fisher's exact test, as appropriate, for categorical variables. Sensitivity, specificity, and positive and negative predictive values for flare diagnosis were also determined. The negative (LR− = (1 − test sensitivity) / (specificity)) and positive likelihood ratio (LR+ = (test sensitivity) / (1 − test specificity)) were computed (package epiR for R). A LR− <0.1 was used to rule out the disease. A LR+ >10 was viewed as a strong indicator for ruling-in diagnosis. The areas under the receiver operating characteristic (ROC) curves (AUC) were compared (pROC package for R). ROC analysis combines measures of sensitivity and specificity. The AUC can be interpreted as the probability that a randomly chosen diseased subject is rated or ranked as more likely to be diseased than a randomly chosen non-diseased subject. The AUC value lies between 0.5 and 1, where a value between 0.5 and 0.7 denotes a bad classifier and 0.8–1 denotes a good classifier. Survival was analysed using the log-rank method: survival was calculated between the first anti-C1q Abs testing and SLE relapse. The relationship between anti-C1q Abs levels and continuous variables was tested using a linear mixed model (nlme package for R). Significance was established at the *p*

<0.05 level. Analyses were performed with SPSS version 17.0 (SPSS, Chicago, IL, USA) for Windows and R (R Development Core Team, Vienna, Austria).

Results

Patients

A total of 28 patients were included with a median age at diagnosis of 13.5 years (range 4–17). Among them, there were 24 females and 4 males (ratio F/M = 6), the latter all belonging to the group of patients with renal involvement (Table 1). The median follow-up duration was 55.5 months (range 1–186). Nineteen of the 28 patients (67.8%) had a past medical history of renal involvement, histologically proven during follow-up in 72% of cases ($n = 13$). A total of 80 and 74 serum samples were analysed for anti-C1q and anti-dsDNA Abs respectively. The median of the serum samples included per patient was 3 (range 2–5) or 2 (range 1–3) for patients with and without renal involvement respectively. All patients were positive for antinuclear Abs (ANA) and anti-dsDNA Abs at least once during follow-up. Data for C3, C4 and CH50 were available for 44, 50 and 47 serum samples respectively.

Anti-C1q antibodies exhibited high sensitivity and specificity for renal flares

A total of 31 flares occurred at diagnosis or follow-up, including 18 renal flares. Anti-C1q Abs displayed a sensitivity of 84 or 90% for a disease activity score (SLEDAI) >4 or for renal flare respectively. Anti-C1q Abs were significantly associated with an active disease status ($p < 0.0001$), and especially with renal ($p < 0.0001$) and non-renal flares ($p < 0.0001$; Fig. 1). Eight patients displayed positive anti-C1q Abs concomitantly with a quiescent phase of the disease, but 6 of them (86%) had a history of previous renal flare.

Sensitivity, specificity and AUC of ROC curves for anti-C1q and anti-dsDNA Abs for overall and renal flares are summarised in Tables 2 and 3 respectively. Anti-C1q Abs displayed higher specificity and AUC compared with anti-dsDNA Abs to discriminate patients in an active phase of the disease (Fig. 2; Tables 2, 3) according to the manufacturer's cut-off. However, the AUC of these Abs did not significantly differ ($p = 0.43$ for overall flare, $p = 0.19$ for renal flare). The diagnostic characteristics of anti-C1q were very close to those of the C3 fraction (Tables 2, 3).

Using linear mixed model analysis, we found that anti-C1q Abs were significantly associated with disease activity, as described by SLEDAI score (slope =0.32, $p < 0.0001$; Fig. 3a).

The presence of anti-C1q Abs at diagnosis was not predictive of upcoming lupus flare ($p = 0.20$) or renal flare ($p = 0.92$) at follow-up (Fig. 4 respectively) by using log-rank analysis.

Correlations of anti-C1q antibodies with anti-dsDNA and complement in cSLE

We found a significant relationship between anti-C1q Abs and the following biological parameters: anti-dsDNA Abs (slope 0.8, $p < 0.0001$), C3 (slope −0.09, $p = 0.0003$), C4 (slope −0.023, $p = 0.0001$) and CH50 (slope −6.99, $p = 0.0001$) by mixed linear regression (Fig. 3b–e). Conversely, using this model of mixed linear regression, we found that anti-C1q Abs were not associated with the ratio of proteinuria to creatininuria (slope 1.27, $p = 0.21$).

There were no significant differences in the means of anti-C1q Abs levels between proliferative ISN/RPS histological classes (III or IV) and non-proliferative classes (I, II, V; (157.1 vs 158.2 AU/mL respectively). In addition, no correlation was found between anti-C1q Abs levels and the presence of proliferative LN.

Anti-C1q antibodies are more potently correlated with disease activity than anti-dsDNA antibodies

The SLEDAI includes the presence of anti-dsDNA Abs in the evaluation of SLE activity. To address whether anti-C1q Abs could be a more portent marker linked to SLE activity, we designed a test to compare anti-dsDNA Abs positivity with anti-C1q Abs positivity for a modified SLEDAI, not including

Table 1 Characteristics of patients

	Renal involvement	No renal involvement	Total
Number of patients	19	9	28
Female (%)/male (%)	15 (79)/4 (21)	9 (100)/0 (0)	24 (86)/4 (14)
Age at diagnosis in years, median (range)	13 (4–16)	14 (9–17)	13.5 (4–17)
Follow-up in months, median (range)	70 (11–186)	37 (1–132)	55.5 (1–186)
Number of anti-C1q antibodies measurements	3 (2–5)	2 (1–3)	3 (1–5)
Histological confirmation of renal involvement (%)	13 (68)	0 (0)	13 (50)
Proliferative nephritis (class III or IV)	8	0	8
Non-proliferative nephritis (other classes)	5	0	5

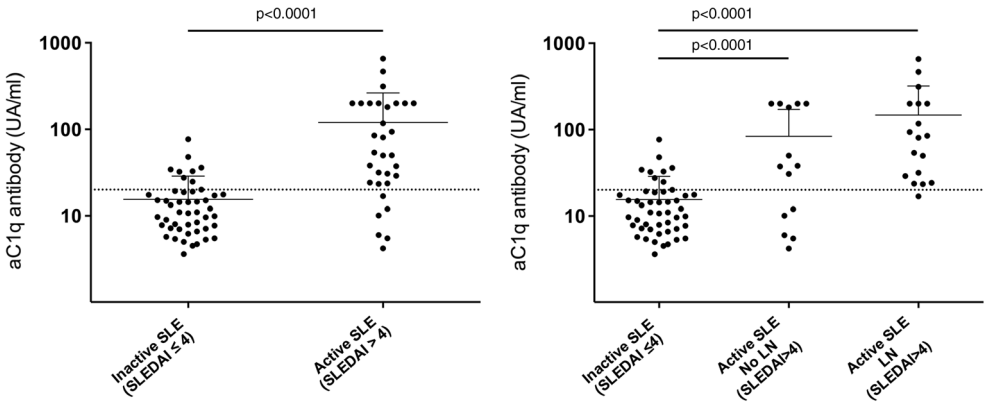

Fig. 1 Titres of anti-C1q antibodies according to systemic lupus erythematosus (*SLE*) activity

anti-dsDNA Abs data. Interestingly, we found a higher correlation of anti-C1q Abs titres compared with anti-dsDNA Abs titres with the SLEDAI score ($p = 0.02$ vs $p = 0.04$ respectively).

Discussion

This retrospective study was performed to assess the value of anti-C1q Abs as a diagnostic and predictive biomarker for LN and global flares during the follow-up of cSLE. Anti-C1q Abs are accurate and reliable biomarkers for adult-onset SLE, and the clinical value of these Abs has recently been demonstrated in this population [31, 32]. Conversely, only a few published studies on the interest of these Abs exist in the setting of cSLE [20, 21, 33, 34]. Remarkably, kidney involvement is a very common feature in cSLE and is a major factor in disease-associated morbidity and mortality [26, 35].

In our study, almost all cSLE patients during active renal flare displayed positive anti-C1q Abs at a high level. Sensitivity and negative predictive values for anti-C1q Abs in active nephritis were strikingly high, supporting the capability of this assay to discriminate LN. Similar to previous results, these Abs demonstrated a low positive predictive value for renal flare [16, 36, 37]. Conversely, negative anti-C1q Abs values were associated with a high negative predictive value for renal flare, thus suggesting that the detection of such Abs could be helpful in the detection of LN. Only one patient had mild positive anti-C1q Abs at the time of active or inactive disease

Table 2 Diagnostic characteristics of anti-C1q, anti-dsDNA antibodies and complement for disease activity defined as systemic lupus erythematosus disease activity index (SLEDAI) >4 according to manufacturer cut-offs

	Anti-C1q *n/N* % (CI)	Anti-dsDNA *n/N* % (CI)	C3 *n/N* % (CI)	C4 *n/N* % (CI)	CH50 *n/N* % (CI)
Sensitivity	26/31 84 (66–95)	27/30 90 (74–99)	19/21 90 (70–99)	19/25 76 (55–90)	17/23 74 (52–90)
Specificity	41/49 84 (70–93)	9/44 21 (10–35)	17/23 74 (52–90)	11/25 44 (35–76)	16/24 67 (45–84)
Positive predictive value	26/34 77 (59–89)	27/62 44 (31–57)	19/25 76 (55–90)	19/30 63 (44–80)	17/25 68 (47–85)
Negative predictive value	41/46 89 (76–96)	9/12 75 (43–95)	17/19 90 (67–99)	14/20 70 (46–88)	16/22 73 (50–89)
Positive likelihood ratio	5.14 (2.68–9.86)	1.13 (0.93–1.37)	3.47 (1.72–6.99)	1.73 (1.05–2.83)	2.22 (1.20–4.10)
Negative likelihood ratio	0.19 (0.09–0.43)	0.49 (0.14–1.65)	0.13 (0.04–0.49)	0.43 (0.20–0.93)	0.39 (0.19–0.82)
AUC ± SD	0.81 ± 0.06[a]	0.74 ± 0.06[a]	0.88 ± 0.06[b]	0.72 ± 0.09[b]	0.78 ± 0.08[b]

AUC area under the curve, *CI* confidence interval, *SD* standard deviation

[a] Analysis performed on 74 samples

[b] Analysis performed on 41 samples

Table 3 Diagnostic characteristics of anti-C1q, anti-dsDNA antibodies, and complement for renal flare according to manufacturer cut-offs

	Anti-C1q *n*/*N* % (CI)	Anti-dsDNA *n*/*N* % (CI)	C3 *n*/*N* % (CI)	C4 *n*/*N* % (CI)	CH50 *n*/*N* % (CI)
Senstiivity	17/18 94 (72–100)	16/17 94 (71–99)	12/13 92 (64–100)	12/16 75 (48–93)	11/14 79 (49–95)
Specificity	45/62 73 (60–83)	11/57 19 (10–32)	18/31 58 (39–76)	16/34 47 (30–65)	19/33 58 (39–75)
Positive predictive value	17/34 50 (32–68)	16/62 26 (15–39)	12/25 48 (28–69)	12/30 40 (23–59)	11/25 44 (24–65)
Negative predictive value	45/46 98 (89–100)	11/12 92 (62–100)	18/19 95 (74–100)	16/20 80 (56–94)	19/22 86 (65–97)
Positive likelihood ratio	3.44 (2.26–5.24)	1.17 (0.98–1.39)	2.20 (1.41–3.42)	1.41 (0.93–2.17)	1.85 (1.14–3.00)
Negative likelihood ratio	0.07 (0.01–0.52)	0.30 (0.04–2.20)	0.13 (0.02–0.89)	0.53 (0.21–1.34)	0.37 (0.13–1.06)
AUC±SD	0.84 ± 0.06[a]	0.78 ± 0.08[a]	0.81 ± 0.07[b]	0.63 ± 0.11[b]	0.73 ± 0.09[b]

[a] Analysis performed on 74 samples

[b] Analysis performed on 41 samples

without any history of renal flare. As this study occurred within a limited follow-up period, we were able to suggest close monitoring for this patient, especially for renal activity parameters.

As previously reported in cSLE patients, a strong association between anti-C1q Abs and disease activity score was found [20]. In this study, we analysed anti-C1q Abs levels over time for each patient, during active and quiescent phases. Hence, we observed in most patients, even without renal involvement, that anti-C1q Abs levels were significantly higher during flares compared with quiescent phase, paralleling the SLEDAI score. Furthermore, a strong association was found between anti-C1q Abs and the presence of flare with or without renal involvement. Few studies investigating these Abs in adult-onset SLE suggest a higher association with global SLE activity than with active LN [38]. A meta-analysis of the capacity of anti-C1q Abs levels to diagnose an LN flare in adults showed variable values across the studies included [39]. Anti-C1q titres fluctuated over time in a single patient and returned to within the normal range when the disease was inactive, supporting the interest in anti-C1q Abs management. Therefore, the repetition of this analysis prospectively in the paediatric population would be helpful, especially considering that pattern of Abs and renal involvement are distinct from adult-onset SLE [27]. Taken together, these findings suggest that anti-C1q Abs screening might represent an alternative method to anti-dsDNA Abs in assessing the disease activity of cSLE.

Regarding correlation with classical biomarkers of LN, a significant positive correlation between anti-C1q and anti-dsDNA Abs levels, in addition to a negative correlation with complement C3, C4 and CH50, was observed. In contrast to previous studies, no significant association was found here between anti-C1q Abs and the proteinuria/creatininuria ratio [20], but this observation may be secondary to the lack of power of this retrospective study. In summary, with the increase of anti-C1q Abs levels during active nephritis demonstrated above, anti-C1q Abs may be a reliable marker in the follow-up of cSLE patients. Some studies have shown that the likelihood of severe proliferative LN (stage III/IV) was low when anti-C1q Abs were lacking [18]. Anti-C1q Abs have been well described as a potential predictor of renal involvement in adult lupus patients [40–42]. We found no differences in anti-C1q Abs prevalence and levels between patients with histological proliferative disease (class III/IV) and patients with mesangial or membranous LN (class I/II/V), similar to what has already been observed in adults [16, 36, 37, 43] and cSLE [20]. We acknowledge here the limited number of patients and subsequent lack of power of this retrospective study. The pathogenic role of anti-C1q Abs in renal injury is now well documented in SLE patients. Renal inflammation allows the deposition of immune complexes and apoptotic bodies on which the component C1q binds, promoting the development of anti-C1q Abs [8, 44, 45]. This binding has been shown to consequently induce the activation and amplification of the classical complement pathway. The global nephritogenic role of anti-C1q Abs is probably followed by other immunological events that lead to a distinct histological pattern, therefore explaining the absence of a correlation with a proliferative or a non-proliferative state on kidney biopsy.

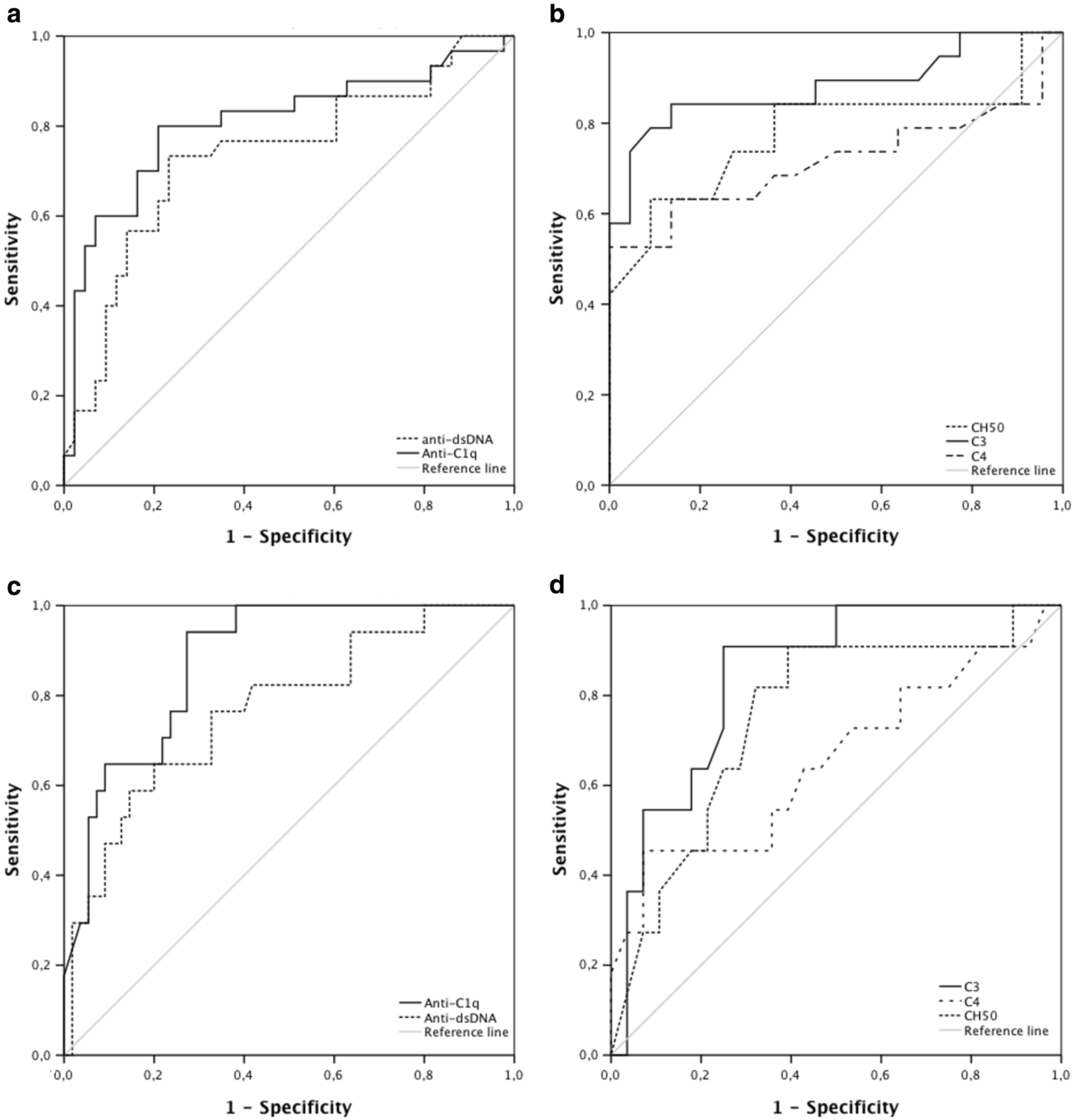

Fig. 2 Receiver operating characteristic (ROC) curves describing anti-C1q, anti-dsDNA, and complement as diagnostic tests of SLE **a**, **b** overall and **c**, **d** renal flare

To our knowledge, this study is the first to investigate the diagnostic and prognostic value of anti-C1q Abs for renal flare and disease activity during the follow-up of cSLE. Patients negative for anti-C1q at diagnosis became positive during the subsequent flare. Here, this biomarker was not predictive of the subsequent flare at follow-up. These Abs represent at least a potent marker of kidney or global flares and this study supports the need to repeat this analysis over time.

Finally, with an original approach based on a modified SLEDAI score, we found that anti-C1q Abs could be a more reliable biomarker of cSLE activity than anti-dsDNA Abs. These latter antibodies are a diagnostic marker for SLE and are routinely used for the follow-up of SLE patients to detect a flare of the disease. However, this biomarker lacks specificity for the detection of the flares and can also rise in the quiescent phase. Furthermore, some previous studies found no

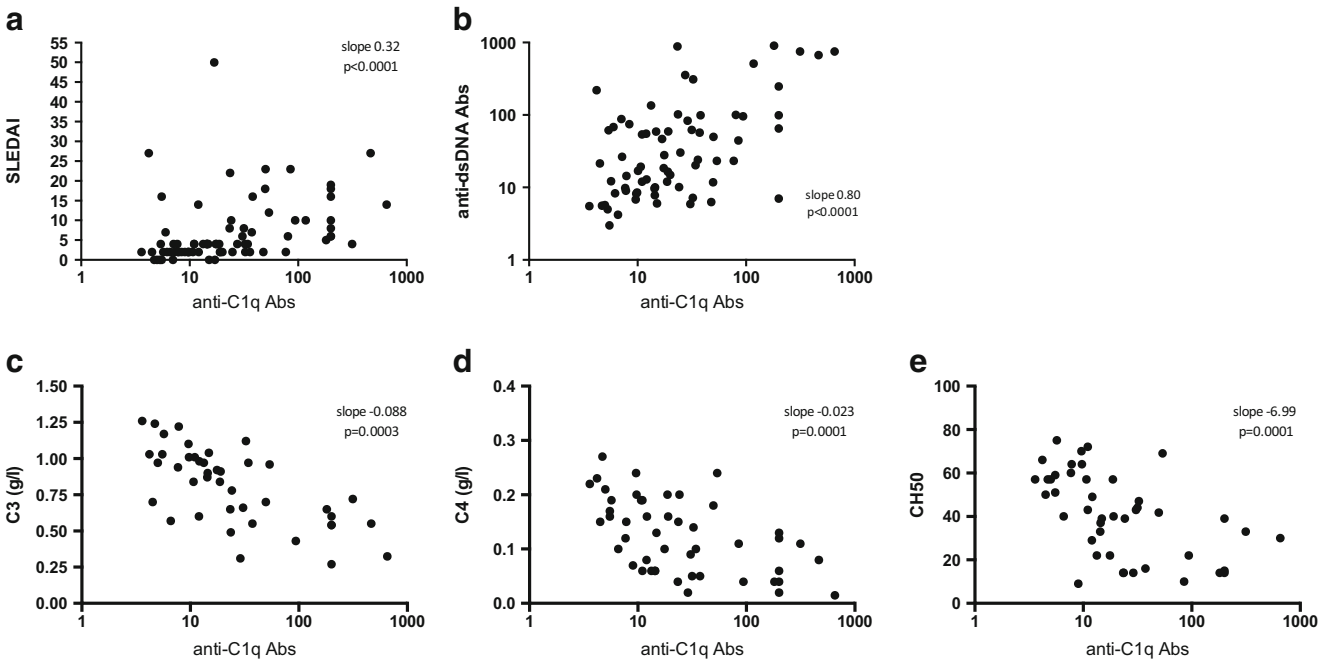

Fig. 3 Correlation between anti-C1q Abs and systemic lupus erythematosus disease activity index (SLEDAI) score, **b** anti-dsDNA antibodies, **c** complement C3, **d** C4, and **e** CH50 for data points of each patient

association between anti-dsDNA Abs and SLE disease activity in a substantial proportion of patients [42, 46, 47]. Few studies showed the association of anti-C1q antibodies with SLE activity and not specifically with LN in adult-onset SLE [32, 38]. Our results indicate that this is also the case in cSLE. Finally, acquired autoimmunity against C1q, together with inherited anomalies of the classical pathway of the complement highlight the importance of early components of this pathway in the maintenance of tolerance and preventing renal flares. It is unclear whether the C5 inhibitor could be helpful or harmful in this setting and clinical trials to modulate complement in this context are essential [48, 49].

Our study has several limitations because of its single-centre and retrospective nature; we had to select a small number of patients given the lack of information concerning some biological data and patient characteristics. In particular,

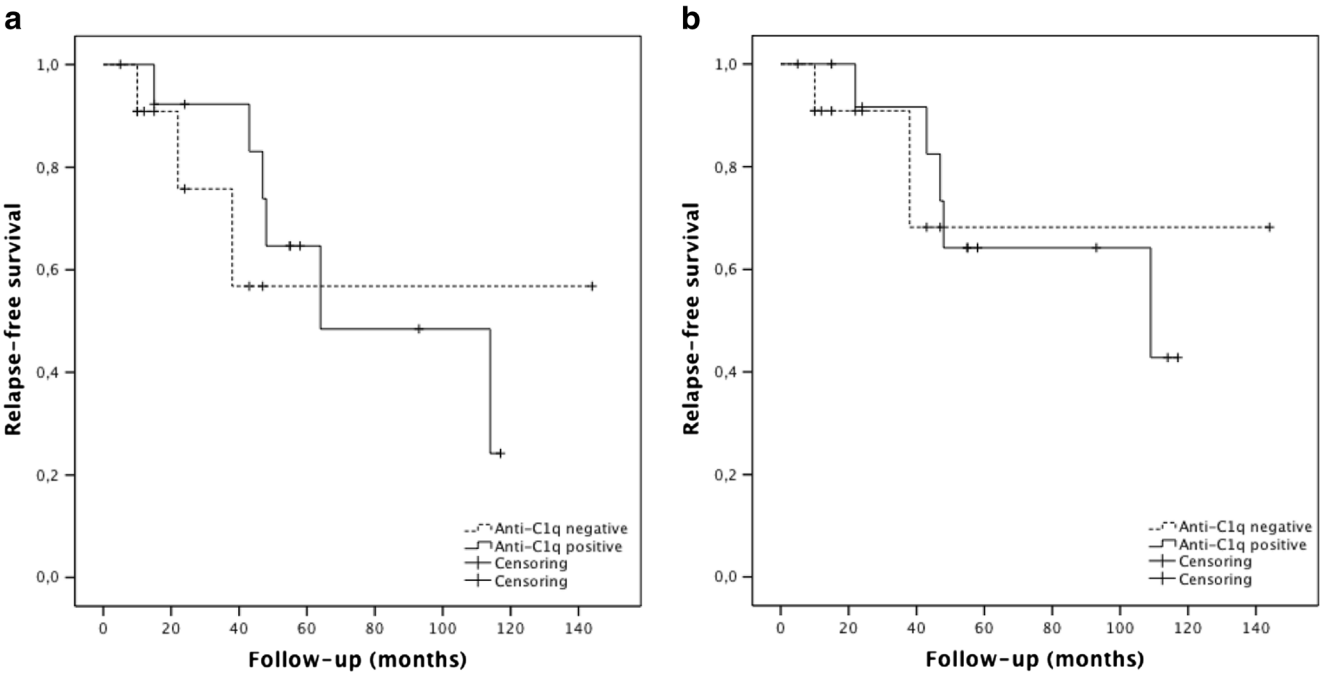

Fig. 4 Kaplan–Meier curve of **a** overall SLE relapse and **b** renal relapse according to the presence of anti-C1q antibodies at diagnosis

this small sample did not allow us to prove the significant capacity of anti-C1q Abs to predict an upcoming flare at follow-up. Conversely, the method of data collection was the same for all patients, in addition to the anti-C1q Abs assessment during the follow-up of all patients. Another point is that the decision to measure anti-C1q Abs in this population was subjective, depending mostly on the clinician's decision and this could have induced a bias in the selection of the population.

In conclusion, we found that anti-C1q Abs constitute a reliable biomarker of cSLE flares and a predictor of renal involvement in children with SLE. The monitoring of anti-C1q Abs could be proposed routinely during the follow-up of cSLE and not exclusively when LN occurs.

Compliance with ethical standards The study was approved by the Research and Ethical Committees of the Hospices Civils de Lyon (24 March 2015). Patient records and information were anonymised and de-identified before analysis.

Conflicts of interest The authors declare that they have no conflicts of interest.

Key messages

- Children with SLE have a severe phenotype, in particular because of the more common occurrence of LN
- Anti-C1q Abs were found to correlate well with SLE global activity and with active LN
- Anti-C1q Abs may be recommended as follow-up biomarkers in cSLE

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