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Distinct Humoral Immune Profiles in Non-Hospitalized Pediatric Systemic Lupus Erythematosus with Autoimmune Flare versus Bacterial Pneumonia

Ashraf Fadhil Jomah
University of Sumer – College of Medicine

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Annotation: Humoral immune dysfunction plays a pivotal role in the immunopathogenesis of systemic lupus erythematosus (SLE) and serves as a useful tool for differentiating disease activity from infectious processes in pediatric patients. In routine clinical settings the pediatric SLE flares and bacterial infections frequently present with overlapping clinical features and creating diagnostic uncertainty and potentially delaying appropriate treatment. This study evaluated multiple humoral immune indicators that including complement proteins (C3 and C4), total complement activity (CH50), autoantibodies (anti–double-stranded DNA and antinuclear antibodies), and serum immunoglobulins (IgG, IgM, and IgA). The analysis included two groups of ambulatory children aged 5–10 years: one group experiencing SLE disease activity (n = 30) and another with SLE complicated by bacterial pneumonia (n = 30). Laboratory measurements were performed using nephelometric, enzyme-linked immunosorbent assay, and immunoturbidimetric techniques. Children with active SLE exhibited pronounced reductions in C3, C4, and CH50 levels and along with significantly increased anti-dsDNA titers, reflecting active immune complex–driven inflammation. patients diagnosed with bacterial pneumonia demonstrated elevated IgM and IgA

levels which is consistent with an infection-related humoral immune response. Receiver operating characteristic analysis showed that a combined assessment of C3, C4, and anti-dsDNA provided high diagnostic accuracy in distinguishing disease flare from infection (AUC = 0.92). humoral immune marker evaluation represents a practical outpatient tool for differentiating SLE flares from bacterial infections and guiding appropriate therapy in pediatric patients.

Introduction

Systemic lupus erythematosus (SLE) is considered a chronic auto-immune disease characterized by immune dysregulation and autoantibody production also immune complex formation and lastely multisystem involvement. Pediatric onset SLE is often linked with more aggressive disease manifestation compared to adult onset disease including higher disease activity increased organ involvement and greater long term morbidity [1,2]. One of the key component of SLE pathogenesis is the dys-regulation of the humoral immunity particularly B cells hyper-activity excessive auto-antibody production and activations of the complementary system [3–5]. complement consumptions reflected by reduced serum C3 and C4 levels is considered one of the a well-established markers of disease activity and immunity complex mediated inflamation [6–8].

The Humoral immunity has a major role involved in autoimmune mechanisms as well as in protecting the body against any bacterial infections by utiliozing the Complement proteins together with the immunoglobulins to help in opsonization neutralizing pathogen and the immune clearance promotion [9,10]. Children with SLE are more susceptible to infections due to underlying immune abnormalities as well as the effects of immunosuppressive treatments. Bacterial pneumonia in particular is considered one of the most common and clinically serious infectious complications in these patients [11–13].

Differentiating an SLE flare from bacterial infection remains a major clinical challenge especially in pediatric patients managed in outpatient settings. Both conditions may present with similar symptoms such as fever fatigue elevated inflammatory markers and respiratory complaints which can create diagnostic uncertainty [14–16]. Misclassification may lead to inappropriate escalation of immunosuppressive therapy in infected patients or delayed antimicrobial treatment which may increase morbidity and healthcare utilization.

Previous studies have shown that SLE flares are usually associated with low complement levels and elevated anti double stranded DNA (anti dsDNA) titers while bacterial infections are more often characterized by increased immunoglobulin production particularly IgM and IgA [17–20]. However most available data come from adult or hospitalized patient cohorts which limits their applicability to non hospitalized pediatric populations [21–25].

This study aims to evaluate humoral immune profiles in non hospitalized children aged 5–10 years with SLE flare compared to those with bacterial pneumonia. By assessing complement components autoantibodies and immunoglobulin levels we seek to identify objective laboratory markers that can help distinguish autoimmune disease activity from infection in outpatient pediatric SLE. Such differentiation is essential for guiding therapeutic decisions reducing misdiagnosis and improving clinical outcomes [26–35].

Methods

A prospective case control study was conducted between January 2024 and December 2025 among non hospitalised pediatric patients attending a tertiary outpatient clinic. Children aged 5–10 years with a confirmed diagnosis of systemic lupus erythematosus according to the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria were eligible for inclusion.

The study population consisted of two groups the first group included 30 non hospitalised patients experiencing active SLE flare defined by a Systemic Lupus Erythematosus Disease Activity Index (SLEDAI 2K) score ≥6 and absence of clinical radiological or microbiological evidence of infection. The second group comprised 30 non hospitalised patients with SLE complicated by bacterial pneumonia diagnosed based on respiratory symptoms chest imaging findings and microbiological confirmation without the need for inpatient admission at the time of sampling.

Exclusion criteria included viral infections tuberculosis COVID 19 primary immunodeficiency disorders malignancies recent vaccination within four weeks or antibiotic therapy within two weeks prior to enrollment. Peripheral venous blood samples were collected before initiation or modification of immunosuppressive or antimicrobial therapy.

Serum complement components C3 and C4 were measured using Roche Hitachi cobas C311 analyzer while total hemolytic complement activity (CH50) was assessed by standard hemolytic methods. Anti dsDNA antibodies were quantified using enzyme linked immunosorbent assay and antinuclear antibodies were also evaluated. Serum immunoglobulin levels IgG IgM and IgA were measured using immune open system analyzer techniques. Ethical approval was obtained and informed consent was secured from guardians with assent from children when appropriate.

Statistical Methods

Statistical analysis was performed using SPSS version 26. Data distribution was assessed using the Shapiro–Wilk test. Normally distributed variables were expressed as mean ± standard deviation, while non-normally distributed data were presented as median and interquartile range. To compare between the groups the utilizing of independent t-tests or the Mann–whitney u tests as per normality distribution. Categorical variables were analyzed using chi-square or Fisher's exact tests.

Correlations between complement levels, autoantibody titers, and immunoglobulin concentrations were evaluated using Pearson or Spearman correlation coefficients. Multivariate logistic regression analysis was performed to identify independent predictors of bacterial pneumonia, adjusting for age, sex, disease duration, and immunosuppressive therapy.

Receiver operating characteristic (ROC) curve analysis was used to assess the diagnostic performance of humoral immune markers. Area under the curve (AUC), sensitivity, specificity, and optimal cut-off values were calculated. A two-tailed p-value <0.05 was considered statistically significant.

Results & Discussion

A total of sixty non hospitalised children diagnosed with systemic lupus erythematosus (SLE) were enrolled, and they were equally divided into two groups of thirty patients each. Both groups were similar regarding age, gender distribution and duration of illness with no statistically significant variation detected ($p > 0.05$), which reflects proper matching and limits the influence of confounding variables [1,2]. At the time of blood sampling all participants were clinically stable and followed as outpatients, which helped in evaluating humoral immune changes without the effects related to hospital admission.

Patients presenting with SLE flare showed a clear reduction in serum complement levels when compared to those with bacterial pneumonia. The average levels of C3 and C4 were considerably

lower in the flare group (C3: 65 ± 12 mg/dL, C4: 10 ± 3 mg/dL) versus the pneumonia group (C3: 95 ± 15 mg/dL, C4: 22 ± 4 mg/dL, $p < 0.001$). In addition total hemolytic complement activity (CH50) was also significantly reduced among flare patients (35 ± 8%) compared to infected cases (70 ± 10% $p < 0.001$). These results support the concept of complement consumption driven by immune complex formation during active autoimmune disease rather than by infection induced inflammation [6,7].

Table 1: Baseline Characteristics

Characteristic	SLE Flare (n=30)	Pneumonia (n=30)	P-value
Age (years, mean ± SD)	7.6 ± 1.5	7.8 ± 1.4	0.65
Sex (M/F)	12/18	13/17	0.79
Disease Duration (years, mean ± SD)	2.3 ± 0.8	2.4 ± 0.7	0.71

Autoantibody testing showed markedly elevated anti double stranded DNA (anti-dsDNA) levels in non hospitalised patients experiencing SLE flare, with mean values of 210 ± 50 IU/mL compared to 90 ± 35 IU/mL in those diagnosed with bacterial pneumonia ($p < 0.001$). Moreover antinuclear antibody (ANA) fluorescence appeared more intense in the flare group, most commonly at a titer of 1:640, whereas patients with pneumonia generally demonstrated lower titers around 1:320. The results indicates that increased autoimmune activation occures during flare episodes [8–10].

Table 2: Humoral Immune Markers

Marker	SLE Flare (Mean ± SD)	Pneumonia (Mean ± SD)	P-value
C3 (mg/dL)	65 ± 12	95 ± 15	<0.001
C4 (mg/dL)	10 ± 3	22 ± 4	<0.001
CH50 (%)	35 ± 8	70 ± 10	<0.001
Anti-dsDNA (IU/mL)	210 ± 50	90 ± 35	<0.001
ANA (titer/intensity)	1:640 (strong)	1:320 (moderate)	<0.01
IgG (mg/dL)	850 ± 120	800 ± 110	0.12
IgM (mg/dL)	100 ± 25	145 ± 30	<0.01
IgA (mg/dL)	110 ± 20	160 ± 28	<0.01

By contrast patients diagnosed with bacterial pneumonia showed a different pattern of immunoglobulin response. Serum IgM and IgA concentrations were noticeably higher in the pneumonia group (IgM: 145 ± 30 mg/dL and IgA: 160 ± 28 mg/dL) than in patients experiencing disease flare (IgM: 95 ± 25 mg/dL, IgA: 110 ± 20 mg/dL, $p < 0.001$). This pattern likely reflects stimulation of humoral immune defenses against bacterial organisms, even among non hospitalised individuals, and underlines the role of IgM and IgA in the early immune reaction to respiratory infections [11,12]. In contrast IgG levels were comparable between both groups, suggesting that acute infections managed on an outpatient basis mainly provoke IgM and IgA responses rather than sustained IgG production.

Correlation analysis revealed a strong inverse relationship between complement concentrations and anti-dsDNA titers within the flare group ($r = -0.72$, $p < 0.001$), which supports the concept of complement depletion due to immune complex formation. This association was absent in patients with pneumonia, meaning the differing immunopathological processes involved in disease flare compared with infection [13,14].

Table 3: ROC / Diagnostic Performance

Marker / Combination	AUC	Sensitivity (%)	Specificity (%)	Cut-off
C3	0.88	85	82	78 mg/dL
C4	0.85	80	79	12 mg/dL

Anti-dsDNA	0.89	88	85	150 IU/mL
C3 + C4 + Anti-dsDNA	0.92	90	87	Combined
IgM + IgA	0.78	75	70	Combined

Receiver operating characteristic (ROC) curve analysis indicated that the combined evaluation of C3, C4 and anti dsDNA achieved high diagnostic accuracy for distinguishing SLE flare from bacterial pneumonia in non hospitalised patients (AUC = 0.92, sensitivity 90% specificity 87%). When assessed separately, markers including C3, C4 and anti dsDNA showed only moderate performance, however the addition of IgM and IgA measurements increased specificity for detecting bacterial infection [15–25].

The study findings propose that the pediatric patients with SLE clearly display different humoral immune profile during the disease flare compared with bacterial infections pneumonia even when treated out-side the hospital. this distinction carry an important clinical value in outpatient practice where fast and accurate differentiations is essential for appropriate management. Using humoral immune markers may help limit unnecessary hospital admissions and to avoid unwarranted intensification of immunosuppressive therapy in infected patients, and allow earlier initiation of antimicrobial treatment. Results show that the data for complement levels , autoantibody titers, and immunoglobulin patterns are useful and practical in the routine outpatient care for pediatric SLE patients.

Conclusion

In conclution, humoral immune profile can differentiate between SLE flare from bacterial pneumonia in non hospitalized pediatric patient. The disease flares are characterized by the complement consumption and elevated anti dsDNA titer.whereas bacterial pneumonia is associated with preserved complement activites and increased IgM and IgA level. And by Integrating these laboratory markers into outpatient clinical practice offering objective support for therapeutic decision-making, reduces the risk of misdiagnosis and improves patient outcomes. Routine evaluation of humoral immune parameters provides strengthen personalized management strategies and advance precision medicine approaches in pediatric SLE.

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