Risk of Bacterial Infection in Acquired Complement Deficiencies

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Research article

Keywords: Acquired complement deficiency, pediatrics, autoimmune syndromes

Posted Date: February 19th, 2020

DOI: https://doi.org/10.21203/rs.2.23978/v1

Version of Record: A version of this preprint was published on September 24th, 2020. See the published version at https://doi.org/10.1186/s12969-020-00467-0.

Abstract

Background: Acquired complement deficiency can occur in the setting of autoimmune syndromes, such as systemic lupus erythematosus (SLE), with very low or, occasionally, undetectable C3 levels. Based on data from patients with inherited complement defects, a perceived risk for serious bacterial infection exists amongst patients with transiently low complement, but the degree of risk related to C3 level is unknown.

Methods: We performed a retrospective study of all pediatric patients with an undetectable total complement activity or absent individual complement components measured at our institution from 2002 to 2018. We assessed annual rate of serious bacterial infection (SBI) defined as requiring hospitalization and/or parenteral antibiotics. Among included SLE patients, we assessed the 30-day probability of SBI for given C3 measurements using a logistic regression model to determine risk.

Results: Acquired complement deficiency secondary to SLE-related disease [n=44] was the most common underlying diagnosis associated with depressed complement levels. While controlling for immunosuppression level and lupus nephritis diagnosis, our logistic regression analysis of pediatric patients with SLE showed low C3 level was temporally associated with having an SBI event. Even in patients with equivalent immunosuppression, patients with an SBI were found to have lower C3 levels preceding the infection relative to patients without SBI.

Conclusion: Pediatric patients with the diagnosis of SLE can develop very low C3 levels that are independently associated with risk of serious bacterial infection. Patients prone to complement consumption may particularly be at risk.

Background

Primary complement deficiencies are rare genetic conditions associated with clear susceptibility to encapsulated bacterial infections [1]. Secondary complement defects from an acquired disease process, such as systemic lupus erythematosus (SLE) or connective tissue disease (CTD), are usually partial and transient from immune complex formation and deposition. Temporary hypocomplementemia has been proposed to be a significant risk of infection among patients with SLE [2–3]. Although rarely do patients with SLE demonstrate undetectable complement activity and roughly half of patients with active lupus have normal complement levels [4]. With infections still ranking as one of the highest causes for mortality in patients with SLE, understanding the risk factors is critical [5–7].

In this study, we utilized a large catchment area as one of the sole centers with combined Pediatric Rheumatology and Immunology expertise in the greater Pacific Northwest. Here we describe the longitudinal infectious risk among patients with SLE/CTD-related disorders with a history of complement consumption including detailed clinical history to account for kidney disease, immune suppression and types of infection. We compared the risk of infectious complications in the secondary defect group to that of an established cohort of primary complement deficient patients.

Methods

Seattle Children's Hospital institutional review board waived consent due to the study not involving greater than minimal risk (IRB Approval STUDY00001067). A convenience cohort was identified through retrospective review of institutional electronic medical records. Pediatric patients tested for complement activity between 2002 to 2018 were screened. Included subjects had undetectable total complement activity (CH50 or AH50) or undetectable individual complement component(s) at any timepoint. C3 and C4 complement levels were tested by nephelometry method performed at Seattle Children's Hospital. CH50 and AH50 testing were performed by hemolytic methodology. Charts were manually reviewed for included patients extracting patient gender, date of birth, diagnosis, number and date of infections, immunosuppressive medications, treatment setting (inpatient versus outpatient), underlying microorganism(s), and any receipt of parenteral antibiotics and all individual complement protein measurements. Patients were then categorized as primary complement deficiency based upon clinical diagnosis, family history and/or individual factor deficiency. Infections requiring hospitalization or parenteral antibiotics were included. Minor sinopulmonary infections, urinary tract infections or common skin infections not requiring parenteral antibiotics were excluded to limit analysis to clear life-threatening infectious risk. Serum samples drawn on the same day as SBI diagnosis were excluded. Levels of immunosuppression (LOI) were categorized by expert experience: Level 0, hydroxychloroquine only; Level 1, oral prednisone or methotrexate; Level 2, azathioprine or mycophenolate; Level 3, pulsed methylprednisolone and Level 4, cyclophosphamide, tacrolimus or rituximab [8]. Oral prednisone dose was not quantified due to lack of clarity in the medical records. Washington State Immunization Information System (IIS) database verified immunization status. Statistical analysis: Differences in annual rates of bacterial infections were assessed using Kruskal Wallis test (GraphPad Prism 8.0). Multivariable logistic regression was performed to determine the odds of SBI in patients in relation to C3 levels controlling for level of immunosuppression and lupus nephritis diagnosis performed using STATA v16.0.

Results

Study Participants: We performed an unbiased review of all complement levels measured at our hospital from 2002–2018 (n = 5876, from 1643 total patients). Patients clinically diagnosed with SLE or CTD were captured in our pediatric dataset as quarterly complement testing is usual standard practice at our center. A total of 70 subjects met inclusion criteria, based on an undetectable complement measurement during the observation period. Both patients with primary complement deficiency (n = 18) and those with acquired complement deficiency (n = 52) were included in the cohort (Table 1). Manual chart review identified total number of subjects with each diagnosis screened in our dataset. Primary complement deficiencies in this cohort included C1q deficiency (n = 3), C2 deficiency (n = 11), C6 deficiency (n = 3), and C8 deficiency (n = 1). Acquired complement deficiencies included SLE/CTD-related disorders (n = 45), which represented 27% of the SLE patients [n = 43 of 155], 11% of pediatric Sjögren's [n = 1 of 9] and 3.7% of MCTD patients [n = 1 of 27]. Two patients had C3 and/or C5 nephritic factors and 5 patients had

infection-related complement consumption. Median period of observation was 10.83 years (IQR, 4.12–16.12) for primary complement deficiency followed from date of birth and 4.33 years (IQR, 2.7–6.5) for secondary complement disorders followed from diagnosis. Demographic characteristics and diagnoses are summarized in Table 1.

Table 1
Demographic and Clinical Characteristics

Variable[†]	SLE/CTD	PCD
Total	45	18
Female, n. (%)	42 (93)	4 (22)
Age[§] (year)	14.7 (IQR: 12.8–16.4)	10.8 (IQR: 4.1–16.1)
Observation Period (year)	4.8 (IQR: 2.7–6.5)	10.8 (IQR: 4.1–16.1)
SLE + Nephritis,n	23	
SLE, n	20	
Other CTDs, n	2	
LOI [‡]		
LOI 0 n. (%)	1 (2)	
LOI 1 n. (%)	6 (13)	
LOI 2 n. (%)	10 (22)	
LOI 3 n. (%)	5 (11)	
LOI 4 n. (%)	23 (51)	
Rate of SBI/yr	0.06 (IQR: 0-0.40)	0.15 (IQR: 0.07–0.48)
PCD, primary complement deficiency; SLE/CTD, systemic lupus erythematosus/ connective tissue disease (SLEwN: with nephritis; SLE: without nephritis); LOI, level of immunosuppression.		
[†] For interval variables, the medians and interquartile ranges are presented. For categorical variables, the total number and percentages are presented.		
[‡] LOI is the level of immunosuppression: 0 (HCQ) 1: Prednisone and/or methotrexate, 2: Azathioprine, and/or mycophenolate, 3: Methylprednisolone, 4: Rituximab, cyclophosphamide and/or tacrolimus.		

Serious Bacterial Infections: To examine the risk of SBI among patients with acquired complement deficiency, we first established the rate of SBI in our cohort of primary complement deficiencies with a known risk for encapsulated bacterial infections: annual rate of approximately 0.15 SBI/year (IQR, 0.07–

0.48). The annual rate of SBI in patients with SLE/CTD diagnoses used the lowest C3 recorded for each patient as the starting point of their observation period. SLE/CTD patients had a lower median annual rate of SBI of 0.06 (IQR, 0-0.40) following lowest C3 level, although severe hypocomplementemia was transient. Overall, 27 SBIs were recorded in our SLE/CTD cohort with 14 of 43 SLE/CTD patients (32%) having at least one SBI event during their observation period including pneumonia (33%), bacteremia (22%), sepsis (11%), intraabdominal infection (11%) and soft tissue infections requiring parenteral antibiotics (7%). Streptococcus pneumoniae and Staphylococcus aureus were the most frequently isolated microorganisms. Equivalent rates of vaccination for PCV13 and MCV4 were observed in the subjects with or without SBI, as well as rates of PPVS23 (albeit only roughly 40% of the SLE/CTD patients were fully immunized).

Complement Levels: A total of 1197 serum measurements were collected over the observation period for the SLE/CTD cohort with a median of 5.32 separate serum measurements (IQR 3.73–6.35) per year collected per patient with a vast majority of the serum measurements reporting both C3 and C4 levels. Patients with the diagnosis of SLE/CTD all had either an undetectable (89%) or low C4 level (range, 2–6 mg/dL) (11%), at some point during their disease course. C3 levels were normal in 9% (n = 4) of the SLE/CTD cohort. We found trough C3 levels were lower in patients with SBI (35 mg/dL +/- 21) compared with patients without SBI (55 mg/dL +/- 24) (P = 0.01).

We then utilized every C3 measurement for the SLE/CTD patients as a new observation (n = 1,150) and assessed the 30-day probability of having an SBI based upon level. Lupus nephritis and immunosuppression has been associated with SBI in SLE cohorts, thus these were included as covariates. We excluded C3 levels drawn on the same day as the SBI diagnosis. We also categorically examined the risk of an infection in patients with low C3 (C3 < 83 mg/dL per reference range) compared to those with a normal C3 level. In our cohort of SLE/CTD patients with a history of at least one measurement with undetectable complement, we found a correlation between a low C3 level and the probability of being diagnosed with an SBI within 30 days (Fig. 1). Further, our model suggests that patients with a very low to undetectable C3 level have an approximately 15% chance of being diagnosed with an SBI within 30 days. Logistic regression showed that patients with a low C3 measurement have a significantly higher risk of infection than those with a normal C3 level (OR 5.34 [95% CI, 1.88–15.16]) (Table 2). Given that infection itself may be a causal event for undetectable complement, a secondary analysis excluded any C3 levels drawn within 30 days following an SBI and we found similar results.

Table 2
Logistic Regression Analysis of SLE/CTD-related Secondary Complement Deficiency: Odds of SBI following trough C3 level in patients with SCD

Serious Bacterial Infection (SBI)	Odds Ratio	Std. Err.	Z	P>|z|	95% Conf. Interval
C3 (Low)	5.34	2.84	3.15	0.002	(1.88–15.16)
LOI	3.60	2.43	1.89	0.059	(0.95–13.57)
LN Present	1.51	0.81	0.77	0.44	(0.53–4.32)
LOI, level of immunosuppression; LN, lupus nephritis.					

Discussion

Here, we demonstrate that severe C3 insufficiency is associated with a significant risk for serious bacterial infection within 30 days in pediatric SLE/CTD patients, even while adjusting for immunosuppression level and lupus nephritis diagnosis. The increased infection risk among SLE patients is likely multifactorial [9]. From these analyses, it is not possible to ascertain if the observed association between low C3 and infection in our SLE/CTD cohort is truly causative or a marker of other underlying mechanisms for infectious risk. Our findings are consistent with previous studies that found suboptimal C3 levels at time of SLE diagnosis or decreased total complement activity (CH50 < 30 U/mL) to be associated with higher infection risk [2, 10]. Although clinicians generally appreciate that patients with low complement levels predispose for bacterial infections, the degree of complement depletion and duration of deficiency remains hard to quantify the risk. Pediatric SLE/CTD with a tendency to consume complement may benefit from hyperimmunization and rapid receipt of empiric antibiotics similar to primary complement deficient patients [11]. Thus far, physicians are failing to recommend vaccines for SLE patients [12].

A major strength of the study is the large catchment area and lack of other local centers with expertise for these patients, making it less likely that referral bias has affected our results. It is routine care to screen patients with SLE and CTD at our institution with quarterly C3 and C4 complement levels at our center, which lessens the ascertainment bias. The study also benefited from the long observation period to provide a window into longitudinal risk. Being at single referral center permitted normalization of the testing and serum handling methods known to be critical in complement assessment. A sub-analysis excluding complement levels drawn shortly after an SBI did not affect our results, which supports the association of hypocomplementemia and SBI rather than hypocomplementemia being secondary to SBI. Lastly, we made efforts to normalize for confounding variables including immunosuppressive agents, lupus nephritis diagnosis and vaccination status of our cohort.

Our study has several limitations. Our retrospective analysis was limited by missing data, as some of the recorded infections lacked corresponding C3 levels in the preceding 30 days. Due to the lack of a well-established consensus, the grading of immunosuppression level in our cohort was based on expert clinical experience alone. Further prospective studies may be needed to control for these limitations and

better examine the risk of infection in patients with complement defects due to C3 consumption as SLE patients are high risk for infections [13].

Conclusion

Pediatric patients with severe C3 consumption represent a population with significant infectious risk comparable to that of patients with primary complement deficiency, even while adjusting for immunosuppression level and lupus nephritis diagnosis. Prospective validation is thus warranted as the identification of these at risk patients may allow preventative interventions such as hyperimmunization and a lower threshold for antibiotic initiation.

Abbreviations

SLE, systemic lupus erythematosus

CTD, connective tissue disease

SBI, serious bacterial infection

LOI, levels of immunosuppression

Declarations

Ethics approval and consent to participate: Seattle Children's Hospital institutional review board waived consent due to the study not involving greater than minimal risk (IRB Approval STUDY00001067)

Consent for publication: Not applicable; no individual data displayed.

Availability of data and materials: Not applicable

Competing interests: The authors declare that they have no competing interests

Funding: No funding was obtained for this study.

Authors' contributions: TA performed detailed chart review and performed data collection. TA, MB and EA performed data analysis wrote the manuscript. KH and EA reviewed clinical data and KH reviewed manuscript. MB performed statistical analysis of the data. All authors read and approved the final manuscript.

Acknowledgements: We thank Tara Bumgarner for assistance with the Institutional Review Board submission and continued renewal.

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Figures

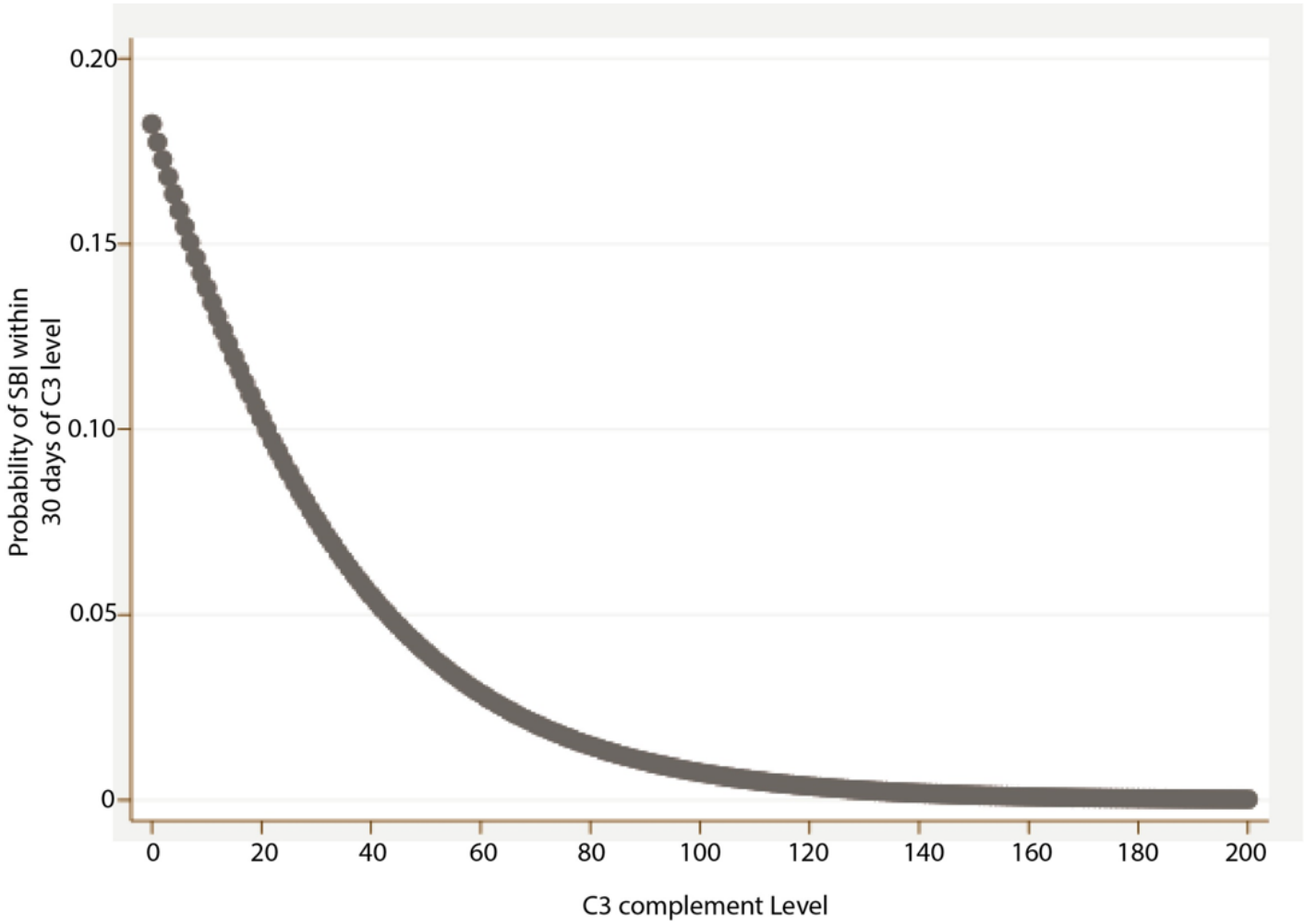

Figure 1

Logistic Regression analysis of C3 level in SLE/CTD patients Logistic regression analysis examining C3 level as a predictor of the 30-day odds of having a serious bacterial infection adjusted for level of immunosuppression and lupus nephritis diagnosis in patients with SLE/CTD.