Original Article

Hematological manifestation of Pediatric Systemic Lupus Erythematosus (SLE) – A single centered cross-sectional study

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Abstract

Introduction: Systemic lupus erythematosus (SLE), the commonest type of lupus, is an autoimmune multisystemic disorder that can affect any organ system of the body, especially blood vessels and connective tissues, causing widespread inflammation. Pediatric onset of SLE is a rare condition with more hematological involvement. **Aim:** This study was undertaken to observe various hematological abnormalities and their association with various autoantibodies present in pediatric SLE in Eastern India. **Methodology:** It was a single-centered, cross-sectional, observational, hospital-based study conducted in the Department of Pediatric Medicine in collaboration with the Department of Rheumatology in IPGME and R and SSKM Hospital, Kolkata. The duration of the study was 1.5 years, and a total of 30 children up to 12 years of age of either gender were enrolled. Study participants were evaluated for various parameters like demographic, hematological (anemia, neutropenia, leucopenia, lymphopenia, and thrombocytopenia), biochemical (CRP, Lactate dehydrogenase (LDH), and bilirubin), autoantibodies (anti-dsDNA, anti-Ro 52, and anti-Ribonucleoprotein [RNP]), and SLE related pathologies (Cutaneous, nephritis, serositis). **Results:** In the present study, most of the participants had arthritis, muscle pain (86.66%), and hematological involvement (80%). Among cytopenias, anemia was the commonest. dsDNA autoantibody was positive in most of the patients (83%), and about one-third suffered from autoimmune hemolytic anemia (AIHA). No association was observed between autoantibodies and various hematological manifestations. **Conclusion:** It can be concluded from the present study that anemia is the most common cytopenia in pediatric SLE, but there is no association between autoantibodies and these cytopenias. However, study on larger population may give better results.

Keywords: Anemia, autoantibodies, AIHA, hematological manifestations, leucopenia, lymphopenia, neutropenia, pediatric lupus, SLE, thrombocytopenia ds DNA

Introduction

Systemic lupus erythematosus (SLE) is the most common type of lupus, which is an autoimmune multisystemic inflammatory disorder that affects various systems and organs of the body, especially blood vessels and connective tissues.[1] The severity of the disease ranges from mild manifestations (e.g., skin rash or

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Received: 22-09-2023 **Revised:** 15-12-2023
Accepted: 23-12-2023 **Published:** 24-05-2024

Access this article online

Quick Response Code:

Website: http://journals.lww.com/JFMPC

DOI: 10.4103/jfmpc.jfmpc_1583_23

How to cite this article: Hassan MR, Hossain A, Mahata J, Srivastava V, Sarkar S. Hematological manifestation of Pediatric Systemic Lupus Erythematosus (SLE) – A single centered cross-sectional study. J Family Med Prim Care 2024;13:1787-92.

non-erosive arthritis) to severe disabling or even life-threatening complications like lupus nephritis, neuropsychiatric disorders, etc., Pathogenesis of SLE is characterized by the production of autoantibodies directed against self-antigens, especially nucleic acids. There is an increased level of apoptosis or impaired ability to clear debris, occurring in patients having SLE, leading to prolonged exposure to nucleic antigens in the bloodstream and increased recognition by immune cells, causing B cell autoantibody production.[2]

Pediatric onset of SLE is a rare condition with a prevalence of only 1 to 6 patients per 1,00,000 children.[3] About 20% of all pediatric SLE patients are diagnosed at an early age. Incidence of this disease is higher among black and Asian as compared to whites. It has been observed that SLE presents with a more aggressive form in children than in adults.[4] Children presenting with complaints of fever, rashes, myalgias, and arthralgias under 16 years of age with positive laboratory parameters should be considered as a case of pediatric SLE.[5] The average age of onset of SLE in children is 11-12 years, and it is very rare before 5 years of age. SLE is more common in girls and females than males due to the presence of estrogen which plays an important role in its etiopathogenesis.

The most common manifestations of SLE are hematological abnormalities, which basically occur due to the pathophysiology of the disease itself. Hematological involvement is seen in about 40-50% of adults and 55-77% of pediatric SLE patients.[6,7] There have been multiple studies in this context in adult SLE patients in India, but only few studies are there regarding abnormal hematological parameters in childhood SLE.[8] Hence, this study was taken to note various hematological manifestations in pediatric lupus and their association with different autoantibodies in patients belonging to eastern India.

Objectives

Primary objective

- To detect the various hematological abnormalities in pediatric SLE including leucopenia, thrombocytopenia, and anemia with special reference to autoimmune hemolytic anemia (AIHA)

Secondary objective

- To evaluate if there is any association between detected autoantibodies and various hematological manifestations.
- To detect the frequencies of various clinical manifestations in pediatric SLE.
- To identify the distribution of various autoantibodies and inflammatory markers in pediatric SLE.

Methodology

It was a single-centered, cross-sectional, observational, hospital-based study conducted in the Department of Pediatric Medicine in collaboration with the Department of Rheumatology in IPGME and R and SSKM Hospital, Kolkata. The duration of the study was 1.5 years. Thirty children, up to 12 years of age, attending the outpatient Department of Pediatric Medicine, having SLE as a diagnosis, and fulfilling the inclusion and exclusion criteria were included in the study.

Inclusion criteria

- Children up to 12 years of age of either gender.
- Children diagnosed with SLE by clinical and different laboratory parameters.
- Willing to participate in the study (cooperative patients).

Exclusion criteria

- Children of more than 12 years of age.
- Suffering from various other hematological diseases.
- Other systemic causes of similar hematological abnormalities.
- Not willing to participate (noncooperative patients).

Study technique

After obtaining ethical clearance from the Institutional Ethics Committee (IEC), the study was conducted after obtaining verbal assent (from children <7 years of age) or written assent (from children >7 years of age) along with written informed consent from the parents/legal guardian. During the initial, 21 eligible participants were enrolled. All participants were clinically evaluated properly (with history, clinical examination, investigation findings in past and present medical records, etc., relevant to the present study), and documentation was conducted in an IEC-approved case report form (CRF). For statistical analysis, data was evaluated using SPSS (version 25.0; SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 5.

Study parameters

After obtaining consent, all participants were evaluated, and various relevant study parameters were documented on CRF, which includes

- Demographic details – age and sex.
- Hematological parameters to identify – anemia (Hb < 11.5 mg/dl), leucopenia (total leucocyte count <4000/mm^3), neutropenia (absolute neutrophil count <1000/mm^3), lymphopenia (absolute lymphocyte count <1000/mm^3), thrombocytopenia (platelets count <100000/mm^3) as per SLICC criteria.
- Biochemical parameters – CRP, LDH, and bilirubin.
- Antibodies – anti-dsDNA, anti-Ro 52, anti-RNP.
- SLE-related pathologies the participants are suffering from – nephritis, serositis, distribution, cutaneous, and hematological involvement.

Results

It was a cross-sectional observational study that included 30 participants of 6-12 years. Out of 30 participants, 25 children were above 10 years and 5 were below 10 years; 26 were girls and 4 were boys [Table 1].

Regarding the involvement of various organ systems, most of the participants had arthritis or muscle pain (86.66%) and hematological manifestation (80%). It was followed by nephritis and mucocutaneous involvement. CNS involvement and serositis were rather infrequent among our study participants [Table 2].

In the present study, 83% of SLE participants were positive for anti-dsDNA, whereas frequencies of anti-RNP positive and anti-Ro 52 antibodies positivity were 40% and 33%, respectively [Table 3].

Regarding cytopenia, all participated children having hematological involvement were anemic (100%). Seven children had leucopenia (one had neutropenia and six had lymphopenias), and two had thrombocytopenia; five children had bi-cytopenia, and two had pancytopenia [Table 4].

Analysis of RBC indices was also performed. A low PCV value was seen in all 24 participants with hematological involvement. The MCV value was low in 4 and normal in 20 participants. Regarding MCH value, it was low in 2 and normal in 22 participants. Meanwhile, for MCHC, value 20 was normal, 1 was higher, and the rest 3 had lower-than-normal limits. Fourteen children were reported with high reticulocyte counts, while 2 had low counts [Table 5]. Out of 24 children with hematological involvement, 20 had normocytic normochromic RBC morphology, while 4 had microcytic hypochromic morphology.

Regarding biochemical parameters, in the present study, LDH was elevated in 21 participants; the Coombs test and CRP were positive in 11 and 6 patients, respectively. Hyperbilirubinemia was seen in only six participants [Table 6].

The present study also tried to evaluate if there was any association between antibodies (like dsDNA, Ro52, and anti-RNP) and SLE nephritis with various cytopenia (like anemia, thrombocytopenia, and neutropenia). However, no significant associations were noted among them [Table 7].

Table 1: Showing the demographic details of the study participants

Total number of patients (*n*)=30

Parameters	Frequency, *n* (%)
Age ≥10 years	25 (83.3%)
Age <10 years	5 (16.7%)
Female	26 (86.67%)
Male	4 (13.33%)

Table 2: Showing the distribution of various SLE-related manifestations in the study participants

Total number of patients (*n*)=30

Parameters	Present, *n* (%)	Absent, *n* (%)
Arthritis/muscle pain	26 (86.66)	4 (13.33)
SLE nephritis	17 (56.7%)	13 (43.3%)
SLE mucocutaneous involvement	16 (53.3%)	14 (46.7%)
SLE Serositis	4 (13.33%)	26 (86.67%)
CNS involvement	3 (10.0%)	27 (90.0%)
SLE hematological involvement	24 (80%)	6 (20%)

Table 3: Showing the distribution of various antibodies in the study participants

Total number of patients (*n*)=30

Parameters	Present, *n* (%)	Absent, *n* (%)
Anti-dsDNA antibody	25 (83.3%)	5 (16.7%)
Anti-Ro 52 antibody	10 (33.3%)	20 (66.7%)
Anti-RNP antibody	12 (40.0%)	18 (60.0%)

Table 4: Showing the distribution of various types of cytopenia in the study participants

Total number of patients (*n*)=24

Parameters	Present, *n* (%)	Absent, *n* (%)
Anemia	24 (100%)	0
Leucopenia	7 (29.17%)	17 (70.83%)
Neutropenia	1 (4.17%)	23 (95.83%)
Lymphopenia	6 (25%)	18 (75%)
Thrombocytopenia	2 (8.33%)	22 (91.67%)

Table 5: Showing the distribution of various types of RBC indices in the study participants

Total number of patients (*n*)=24

Parameters	Normal	Low	High	Normal range
PCV	0	24	0	≥34%
MCV	20	4	0	76-95 μm^3
MCH	22	2	0	25-32 pg
MCHC	20	3	1	32-36 g/dl
Reticulocyte count	2	10	12	0.5 – 2.5%

Discussion

The present study was a cross-sectional hospital-based study conducted at the Department of Pediatric Medicine in collaboration with the Department of Rheumatology in IPGME and R and SSKM Hospital, Kolkata. The total duration of the study was 1.5 years, and 30 participants were enrolled. The children included were mostly between 6 and 12 years of age.

SLE is a chronic autoimmune disorder affecting five million people globally. Adolescent girls and women between 14 and 55 years of age are most commonly affected. Pediatric SLE is defined as the onset of SLE below 16 years of age (though, according to some authors, it is below 18).[9] Studies have shown that the prevalence of pediatric SLE is more in girls than boys.[10] In the present study also, among 30 enrolled children, 26 (80%) were girls; this finding was similar to many other previous studies. The development of autoimmunity (SLE) is known to be influenced by both genetic and environmental factors. The X chromosome carries many genes that are directly or indirectly involved in (auto-) immunity; among them, *TLR7* (encodes toll-like receptor 7) on the short arm of the X chromosome is

Table 6: Showing the distribution of various biochemical parameters in the study participants

Total number of patients (*n*)=30		
Parameters	**Present, *n* (%)**	**Absent, *n* (%)**
Direct Coombs test Positive	11 (36.7%)	19 (63.3%)
Hyperbilirubinemia	8 (26.66%)	22 (73.33%)
Elevated LDH	21 (70%)	9 (30%)
CRP positive	6 (20%)	24 (80%)

Table 7: Showing the association of various hematological parameters with the detected antibodies

Parameters	Anti-dsDNA	Anti-Ro 52	Anti-RNP	SLE nephritis
Anemia	*P*: 0.5402	*P*: 0.628	*P*: 0.925	*P*: 0.407
Thrombocytopenia	*P*: 0.853	*P*: 0.465	*P*: 0.800	*P*: 0.389
Leucopenia	*P*: 0.362	*P*: 0.719		

the primary SLE susceptible gene. Evidence also suggests that estrogens influence the survival and function of immune cells involved in SLE.[11] All these make girls (and females) more susceptible to autoimmune disorders including boys (male). The median age of our study participants was approximately 12 years (11.75 years); this finding is also corroborative with "the average age of onset of pediatric SLE is between 12 and 14 years and rarely before the age of 5 years."[12]

The SLE can target almost all body organ systems including skin, joints, blood, and organs like kidneys, heart, lungs, and brain. Pediatric SLE is more severe than its adult counterpart and commonly presents with fever, rashes, arthralgia, myalgia, and cytopenia, which can further progress to nephritis and neuropathy later.[13] In the present study, most of the participants had arthritis, muscle pain (86.66%), and hematological involvement (80%). The other manifestations were SLE nephritis (57%), mucocutaneous involvement (53%), serositis (13%), and CNS involvement (10%). Most of these manifestations are due to the formation of autoantibodies and the deposition of immune complexes in various organ systems. In SLE, many apoptotic cells (antigens) exist against which B-lymphocytes and T-lymphocytes produce excess autoantibodies. This results in immune complex formation and deposition, leading to inflammatory reactions that ultimately result in tissue damage.[14]

The autoantibodies in SLE are directed to nuclear, cytoplasmic, and cellular membrane antigens. These autoantibodies are considered as diagnostic as well as prognostic biomarkers. Anti-nuclear antibodies comprise various autoantibodies with their specific nuclear antigen specificities.[15] These nuclear antigens include single-strand (ss) and double-strand (ds) DNA (deoxyribonucleic acid), histone proteins, nucleosome (histone-DNA complex), centromere proteins, and extractable nuclear antigens [like Smith antigen (Sm), Ro, La, ribonucleoprotein (RNP), etc.]. Among the evaluated autoantibodies, in the present study, anti-dsDNA antibody was found positive in 83.3% of cases. Other autoantibodies like anti-RNP and anti-RO-52 antibodies were positive in 40% and 33% of cases. Autoantibodies like anti-dsDNA and anti-Sm autoantibodies are very particular to SLE disease and cause the formation and deposition of immune complexes that ultimately lead to multiple organ damage.[16] The induction of autoantibodies and their immunological effects are highly heterogeneous in SLE, due to complex interaction among multiple immune cells and antigen molecules. Several evidences demonstrate the pathogenic role of anti-dsDNA antibodies in kidney involvement in SLE. Studies have shown that an increase in serum levels of anti-dsDNA could lead to renal disease exacerbation and relapse of SLE.[17]

Hematological manifestations are common findings in SLE and in our study population (80%), and anemia (100%) was the most common manifestation seen in all patients with hematological abnormalities. This corroborates the finding "in pediatric SLE with anemia being the most common finding."[18] In the present study, RBC indices are also evaluated in all participants with hematological involvement. The present study shows low PCV values in all 24 children, while MCV values were low in 4 patients and normal in 20 children. MCH values were low in 2 and normal in 22 children, while MCHC values were low in 3, high in 1, and normal in 20 children. Out of 24 children with hematological involvement, 20 had normocytic normochromic RBC morphology, while 4 had microcytic hypochromic morphology, and 10 children reported low reticulocyte counts. All these findings corroborate the reported possible causes of anemia in SLE, including the destruction of RBCs due to directed autoantibodies or suppressed erythropoiesis. This suppression of erythropoiesis occurs due to variable reasons like chronic inflammation, bone marrow suppression, impaired erythropoietin production due to lupus nephritis, increased red cell destruction from hypersplenism, recurrent infection, or drug-induced immune phenomenon.[19] In the present study, 20 children had normocytic normochromic anemia and 10 had low reticulocyte counts, possibly due to suppression of erythropoiesis.

Autoimmune hemolytic anemia (AIHA) is considered as one of the diagnostic criteria for SLE by both the American College of Rheumatology and Systemic Lupus International Collaborating Clinics (SLICC). AIHA can be the first manifestation of SLE, and it can appear years before the actual diagnosis of SLE itself.[20] Studies also suggest that the incidence of AIHA is higher in childhood SLE than in adults. It is proposed that AIHA is due to the destruction of RBCs by warm and cold antibodies. AIHA mostly presents with biochemical features of hemolytic anemia and, in severe cases, hepatosplenomegaly, hemoglobinuria, and heart failure. It is diagnosed by a positive direct antiglobulin test (or Coombs test), anemia (low hematological parameters), elevated lactate dehydrogenase, indirect bilirubin, and reticulocyte count.[21] In the present study, the Coombs test was positive in 11 (36.7%) participants, LDH, bilirubin, and reticulocyte counts were elevated in 21, 8, and 12 participants, respectively. So, in the present study, more than one-third of participants

had AIHA. This finding is corroborative with the finding that "AIHA is more common in pediatric SLE and children with AIHA present with variable degree of severity." As mentioned above, the mechanism of AIHA is mediated by autoantibodies directed against red blood cells. Those erythrocytes, coated with immunoglobulin G antibodies, either induce cell lysis or undergo a change in structure (resulting in spherocytes) that are removed by phagocytosis during passage through the spleen.[22] Hemolysis triggers compensatory erythropoietin production that increases erythropoiesis and reticulocyte counts.

Regarding other cytopenia, in the present study, leucopenia (29.17%), lymphopenia (25%), neutropenia (4.17%), and thrombocytopenia (8.33%) were also seen among participants. The potential mechanism of neutropenia in pediatric SLE could be increased peripheral destruction of granulocytes, changes in marginal and splenic pool, and decreased marrow production. The mechanism of lymphopenia is unclear, though antilymphocyte antibodies and apoptosis are suspected of playing a role in decrease the number of lymphocytes. The causes of thrombocytopenia in SLE are defective production of platelets in the bone marrow, segregation of platelets in the spleen, or increased destruction of platelets in the peripheral circulation.[23]

The present also tried to evaluate the association between the present antibodies (anti-dsDNA, anti-RO-52, and anti-RNP) and different hematological parameters (anemia, leukopenia, and thrombocytopenia), but no statistically significant association was noted. This indicates that the causes of various cytopenia are not related to the presence of those autoantibodies but various disease-related pathologies mentioned above.

Conclusion

SLE is a chronic autoimmune disease that involves multiple organs, including the hematopoietic system, with a wide range of disease manifestations. The pediatric form of SLE is more severe and aggressive in comparison to the adult form, affecting girls more than boys. In the present study, most of the pediatric SLE patients suffered from various cytopenias, the commonest being anemia, and others including neutropenia, lymphopenia, leucopenia, and thrombocytopenia. The present study was unable to establish any association between cytopenias and various autoantibodies. There is a scope for further research in this area with a broader population and multiple clinical settings.

Acknowledgment

Staff of Department of Pediatrics, IPGME&R and SSKM Hospital, Kolkata.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Siegel DM, Gewanter HL, Sahai S. Rheumatologic diseases. In: Textbook of Pediatric Care. 2nd ed. Chapter-324. American Academy of Pediatrics. p. 2586-92.
2. Rebecca E, Sadun, Ardoin SP, e Schanberg L. Systemic lupus erythematous. In: Kleigman RM, St Geme JW III, editors. Nelson Textbook of Pediatrics. 21st ed. Elsevier; 2019. p. 1274–80.
3. Levy DM, Kamphuis S. Systemic lupus erythematosus in children and adolescents. Pediatr Clin North Am 2012;59:345–64.
4. Trindade VC, Carneiro-Sampaio M, Bonfa E, Silva CA. An Update on the management of childhood-onset systemic lupus erythematosus. Paediatr Drugs 2021;23:331-47.
5. Kumar V, Abbas AK, Aster JC, editors. Robbins and Cotran Pathologic Basis of Disease. 9th ed. Chapter 6. Elsevier. 2020. p. 218-22.
6. Available from: https://www.uptodate.com/contents/childhood-onset-systemic-lupus-erythematosus-sle-clinical-manifestations-and-diagnosis.
7. Justiz Vaillant AA, Goyal A, Varacallo M. Systemic lupus erythematosus. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2023.
8. Benseler SM, Silverman ED. Systemic lupus erythematosus. Pediatr Clin North Am 2005;52:443–67.
9. Malattia C, Martini A. Paediatric-onset systemic lupus erythematosus. Best Pract Res Clin Rheumatol 2013;27:351-62.
10. Nusbaum JS, Mirza I, Shum J, Freilich RW, Cohen RE, Pillinger MH, *et al.* Sex differences in systemic lupus erythematosus: Epidemiology, clinical considerations, and disease pathogenesis. Mayo Clin Proc 2020;95:384-94.
11. Schwartzman-Morris J, Putterman C. Gender differences in the pathogenesis and outcome of lupus and of lupus nephritis. Clin Dev Immunol 2012;2012:604892.
12. Thakral A, Klein-Gitelman MS. An update on treatment and management of pediatric systemic lupus erythematosus. Rheumatol Ther 2016;3:209-19.
13. Font J, Cervera R, Espinosa G, Pallarés L, Ramos-Casals M, Jiménez S, *et al.* Systemic lupus erythematosus (SLE) in childhood: Analysis of clinical and immunological findings in 34 patients and comparison with SLE characteristics in adults. Ann Rheum Dis 1998;57:456–9.
14. Silva CA, Aikawa NE, Pereira RM, Campos LM. Management considerations for childhood-onset systemic lupus erythematosus patients and implications on therapy. Expert Rev Clin Immunol 2016;12:301–13.
15. Yu H, Nagafuchi Y, Fujio K. Clinical and immunological biomarkers for systemic lupus erythematosus. Biomolecules 2021;11:928.
16. Cozzani E, Drosera M, Gasparini G, Parodi A. Serology of lupus erythematosus: Correlation between immunopathological features and clinical aspects. Autoimmune Dis 2014;2014:321359.
17. Irure-Ventura J, López-Hoyos M. Disease criteria of systemic lupus erythematosus (SLE); The potential role of non-criteria autoantibodies. J Transl Autoimmun 2022;5:100143.
18. Lam SK, Quah TC. Anemia in systemic lupus erythematosus. J Singapore Paediatr Soc 1990;32:132-6.

19. Santacruz JC, Mantilla MJ, Rueda I, Pulido S, Rodriguez-Salas G, Londono J. A Practical perspective of the hematologic manifestations of systemic lupus erythematosus. Cureus 2022;14:e22938. doi: 10.7759/cureus. 22938.
20. Gormezano NW, Kern D, Pereira OL, Esteves GC, Sallum AM, Aikawa NE, *et al*. Autoimmune hemolytic anemia in systemic lupus erythematosus at diagnosis: Differences between pediatric and adult patients. Lupus 2017;26:426-30.
21. Arora S, Dua S, Radhakrishnan N, Singh S, Madan J, Nath D. Autoimmune hemolytic anemia in children: Clinical presentation and treatment outcome. Asian J Transfus Sci 2021;15:160-5.
22. Voulgaridou A, Kalfa TA. Autoimmune hemolytic anemia in the pediatric setting. J Clin Med 2021;10:216.
23. Fayyaz A, Igoe A, Kurien BT, Danda D, James JA, Stafford HA, *et al*. Haematological manifestations of lupus. Lupus Sci Med 2015;2:e000078. doi: 10.1136/lupus-2014-000078.