

Research Article

Validation of 'Kozhikode Criteria' for Diagnosing SLE as a Hematological Disorder

Sasidharan PK*, Arathi N and Geetha P

Department of Medicine & Hematology, Government Medical College Calicut, India

***Corresponding author:** Sasidharan PK, Department of Medicine & Hematology, Government Medical College, Calicut, Kerala, Parijatham, Pipeline road, Patteri, Kozhikode, 673016, India**Received:** November 05, 2015; **Accepted:** December 15, 2015; **Published:** December 16, 2015**Abstract**

Systemic Lupus Erythematosus (SLE) is an autoimmune disease in which cells and tissues undergo damage mediated by tissue binding auto antibodies. At its onset it may involve one organ or tissue alone or more than one organ simultaneously; over a time additional manifestations due to involvement of other tissues and organs may occur. The observations made by us have confirmed that hematological manifestations are the commonest initial presentation in SLE. The criteria used for diagnosis till 2012 were the American College of Rheumatology (ACR) Criteria. If we rely on these criteria, diagnosis is not possible or is often delayed, because the disease could be confined to one organ or tissue alone. Time required for satisfying all 4 of the 11 criteria is variable and prolonged. Moreover hematological manifestations are underrepresented in the ACR criteria. Based on the clinical observations made on patients evaluated in our tertiary center in North Kerala, an alternate diagnostic criteria named the "Kozhikode Criteria" was proposed, especially for the diagnosis of SLE when it presents with Hematological manifestations alone. The present study was an attempt to validate the same and to look for any association of diet and lifestyle to the disease.

Keywords: SLE; Kozhikode criteria; Lifestyle; Diet; Hematological

Introduction

Systemic Lupus Erythematosus (SLE) is a chronic recurrent multisystem disorder, which is difficult to diagnose [1,2]. There is no single diagnostic marker. It is diagnosed with the help of a set of clinical and laboratory criteria [3]. Accurate diagnosis of this disease is important because early diagnosis and appropriate treatment reduces morbidity and mortality [4-12]. SLE is considered to be a rheumatologic disorder, the logic of which is questionable too. Blood and blood vessels contain more variety of antigens than all the other organs and naturally therefore the clinical manifestations should be more often hematological [13].

The criteria used till 2012 for the diagnosis of SLE were the American College of Rheumatology (ACR) criteria. It is useful only in classifying the disease as SLE because four out of the 11 components have to be there to satisfy the criteria. Most cases do not satisfy all these at presentation and if one depends on ACR criteria for diagnosis, it takes several years to confirm the disease as SLE and hence the prompt diagnosis and treatment is delayed in almost all the cases. Another pitfall of the ACR criteria is that it does not give adequate weight age for hematological manifestations. In spite of the fact that hematological manifestations are the commonest; it is not represented adequately, leading to missing the diagnosis of SLE.

Based upon the observations made in our tertiary care center in North Kerala, it was found that hematological manifestations are the commonest and rheumatologic manifestations are rather late at least in our set of population [13]. Most of the cases that presented to our institution were diagnostic problems rather than fully established cases and early diagnosis could be made only with high index of suspicion. Based on these observations, we proposed the need for

a practical guideline to diagnose SLE and framed new criteria and named it "The Kozhikode Criteria" [13].

The kozhikode criteria

Major/Essential criteria

1. Presence of an unresolved autoimmune disorder, which is known to occur with SLE. (Chronic ITP, Autoimmune Hemolytic Anemia, Autoimmune Hypothyroidism, Autoimmune Hepatitis)
2. No other causes other than autoimmunity for the said clinical problem by clinical reasoning and investigations

Minor criteria

1. Another coexisting autoimmune disorder/any other evidence of autoimmunity
2. Positive ANA
3. Positive Anti Ds DNA
4. Sustained and definitive response to steroid and immunosuppressant even after six months of follow up.

If the patient has two essential and two or more minor criteria, they can be diagnosed as SLE.

Materials and Methods

The study was an observational one with a prospective study design. Role of life style and diet was assessed by a case control study.

The ACR criteria and the Kozhikode Criteria were applied to all the diagnosed cases of SLE. All the newly diagnosed cases of SLE using the Kozhikode criteria were subjected to the ACR criteria also.

They were reviewed after a period of 6 months and ACR criteria was applied again to see if they satisfied the ACR criteria and thereby to prove if the Kozhikode Criteria helps in early diagnosis of SLE.

Also those who were already under follow up were studied by reviewing their clinical features and treatment details and whether or not they satisfied the ACR criteria at the beginning and the average time required for them to satisfy the ACR criteria.

For assessing the influence of diet and lifestyle, healthy bystanders of patient's in general medical ward were taken who were matched to cases on age and gender. One control per case was recruited. They were normal by physical examination and had normal routine laboratory investigations and were not on any kind of medications.

Data collection was done by personalized interview including presenting complaints, demographic information, reproductive history, environmental exposure, diet, lifestyle, and medications. Dietary information of patients was estimated using the semi quantitative food frequency questionnaire derived from the IDSP (Integrated Disease Surveillance Project) non communicable disease survey questionnaire for risk assessment. There were 6 possible responses regarding the food frequency. The data was entered using Microsoft Excel and was analyzed using SPSS software.

Results

There were 71 patients diagnosed as SLE. Of them 30 patients were new cases and 41 patients were previously diagnosed as SLE and were under follow up. The male to female ratio was 1: 9. Majority of females were in the age group of 20-40 years, male subjects were equally distributed in all the age groups. All these 41 patients were diagnosed as SLE using Kozhikode criteria, which we had been using for the past two decades and the patient with longest period of follow up included in the study was diagnosed as SLE 12 years back, who presented as isolated thrombocytopenia, who later developed multiple infarcts and was having secondary APLA syndrome. She was ANA negative at the time of presentation and did not satisfy the ACR criteria and only after 12 years she became ANA positive and satisfied the ACR criteria.

Of the 71 patients, 45 satisfied Kozhikode criteria alone, 22 satisfied both ACR and Kozhikode criteria and 4 with suspected autoimmune disease did not satisfy either criterion. There was no such group of patients who satisfied the ACR criteria but not the Kozhikode criteria. Both these observations are highlighting the utility of the new criteria. Altogether 67 patients satisfied the Kozhikode criteria at the beginning of the study (94%). Of the 30 new cases only six were satisfying the ACR criteria whereas 26 individuals satisfied Kozhikode criteria. Among this, 67 patients there was no patient who satisfied the ACR criteria alone but not satisfying the Kozhikode Criteria. Among the 30 new cases there were four individuals with suspected SLE who did not satisfy either criterion. The 26 newly diagnosed cases, which satisfied the Kozhikode criteria alone, were followed up for a period of 6 months and it was observed that only two of them satisfied the ACR criteria even after six months (Figure 1).

The four individuals who did not satisfy either of the criteria were kept under follow up due to strong clinical suspicion of

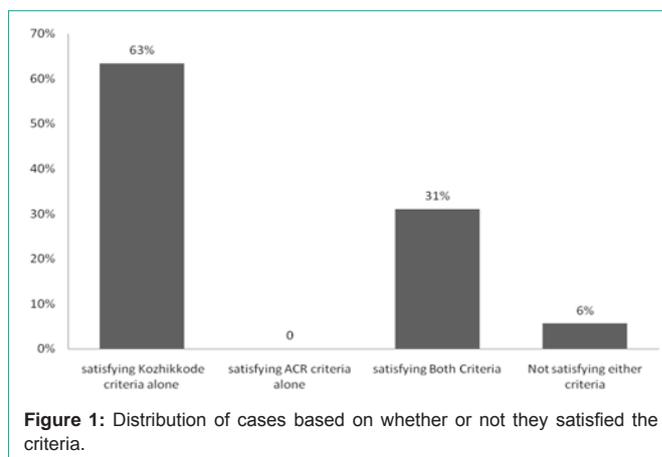


Table 1: Average time required to satisfy the ACR criteria among the cases.

SERIAL NUMBER	DIAGNOSIS	AVERAGE TIME FROM DIAGNOSIS TO SATISFYING ACR CRITERIA
1	ITP	32 MONTHS
2	ITP	72 MONTHS
3	ITP, HYPOTHYROIDISM	40 MONTHS
4	AIHA	7 MONTHS
5	AIHA, NEPHROTIC SYNDROME	64 MONTHS
6	POLYARTHRALGIA	4 MONTHS
7	APLA, HIGH ESR	14 MONTHS
8	CVA, ITP, HIGH ESR	144 MONTHS
9	ANEMIA, SPLENOMEGALY	6 MONTHS
10	SECONDARY SJOGRENS SYNDROME	4 MONTHS
11	THYROTOXICOSIS	11 MONTHS
12	POLYARTHRALGIA	8 MONTHS
13	POLYARTHRALGIA	4 MONTHS
14	ANEMIA, HIGH ESR	12 MONTHS
15	PANCYTOPENIA	12 MONTHS
16	MDS	60 MONTHS

ITP: Immune Thrombocytopenic Purpura; AIHA: Autoimmune Hemolytic Anemia; CVA: Cerebrovascular Accident; ESR: Erythrocyte Sedimentation Rate; MDS: Myelodysplastic Syndrome

autoimmunity. On follow up after six months two of the four became ANA positive and satisfied the Kozhikode Criteria but not the ACR criteria, validating the utility of the former. Of these four cases one of them had refractory oral ulcer and became ANA positive and responded well to steroids. The other patient was a case of alopecia and ITP, which responded to steroids and later became ANA positive. None of these four patients satisfied the ACR criteria even at the end of six months. The two patients who did not satisfy both of the criteria, one patient had refractory oral ulcers and the other patient was lost for follow up.

Of the 30 new patients included in the study, 26 satisfied the Kozhikode criteria and of which only 6 had satisfied the ACR criteria; in this group also there were no such patient who did not satisfy the Kozhikode criteria but the ACR criteria validating the new criteria.

Among the 30 new cases, only 12 were ANA positive at the time of initial clinical presentation. They were diagnosed and treated as SLE due to strong index of suspicion. Those who were ANA positive were also positive for Anti ds DNA. Of the ANA negative patients among the new cases, only 2 became ANA positive at 6 months follow up.

Of the 41 old cases that were already under follow up, all satisfied the Kozhikode criteria at the onset itself but 16 did not satisfy the ACR criteria validating the usefulness of the Kozhikode Criteria. Those 16 patients who did not satisfy the ACR criteria initially, satisfied the ACR criteria subsequently during follow up. The maximum time taken to satisfy the ACR criteria was 144 months highlighting the inability of ACR criteria in diagnosis (Table 1).

The most common clinical manifestation was hematological and it was unusual to see any joint symptoms in this subset. Arthritis was seen in combination with other symptoms but not alone as the initial manifestation. Fever was an unusual presentation seen in our set of population.

Majority of the patients belonged to moderate socioeconomic status. Among those diagnosed as SLE, most of them had a sedentary life style. (P value <0.05) Of the 64 females, consistent use of cosmetics or nail polishes was not seen in any individuals. The patients with coetaneous or oral manifestations also did not use any cosmetics. Comparison of diet among cases and controls showed statistically significant decrease in intake of pulses, green leafy vegetables, legumes and fruits (P value <0.001). The intake of junk food and canned food were significantly higher among cases than controls (P value <0.001).

Discussion

The study was undertaken to validate the Kozhikode Criteria as an alternative to the ACR criteria, since for the last three decades we had been observing that majority of the patients were presenting with hematological manifestations and most of them did not satisfy the existing criteria at the point of presentation. The Kozhikode criteria were developed and we were diagnosing and managing all these based on these criteria and we wanted to share this information with others who are interested in SLE. It became essential to validate the new criteria and hence the study was undertaken.

The observations of the study has shown the utility of the Kozhikode Criteria for early diagnosis of SLE and the observations mentioned are supporting the superiority of the Kozhikode Criteria over the ACR criteria for early diagnosis of SLE. The study has thus validated the Kozhikode Criteria as a useful tool for early diagnosis of SLE

In this study, hematological manifestations were found to be the most common initial presentation of SLE. Hematological manifestations were the presenting complaints in 61% of individuals. This observation made in our tertiary center in Kerala was contradictory to the description of the disease in most Indian and Western text books [14-16]. And majority of the previously conducted studies [17,18]. However a multi centric French study on the initial presentation of childhood lupus showed that the most common presentation was hematological [19]. The Indian study supporting this observation was reported from our own institution [14].

We had observed that several of these patients were ANA negative

at the time of diagnosis and they become ANA positive during follow up only. All these patients were clinically diagnosed as SLE or evolving SLE and all of them had satisfied the Kozhikode Criteria and not the ACR criteria again highlighting the usefulness of this for early diagnosis.

In 1982 Mc Hardy, Horne and Rennie, investigating a cohort of SLE patients in Aberdeen shire, demonstrated an 8.9% ANA negative SLE [20]. Galdman et al., and Feerreiro et al., in two separate studies found a prevalence of 5% cases of SLE which were ANA negative at the time of diagnosis [21,22]. All these cases could have been diagnosed as SLE, had we applied the Kozhikode criteria.

None of the patients were doing any kind of exercise on a regular basis. The level of daily physical activity of newly diagnosed cases when compared with controls showed statistically significant decrease in physical activity among cases. Although there were studies establishing the role of lack of regular exercise and sedentary life style increasing the mortality in SLE [23,24], there were no studies relating physical activity as etiological factor in SLE.

The comparison between diets of cases and controls showed statistically significant difference showing poor intake of pulses, green leafy vegetables and fruits. The intake of junk food, fried food, meat and canned food was high among cases than controls and the p values were statistically significant.

The study also observed the following pitfalls of the ACR criteria. Hematological manifestations are underestimated and not given adequate representation in the ACR criteria. The dietary, life style and the ethnic factors may be responsible for the more hematological manifestations of SLE in our part of the world and ACR criteria, which were validated on the western population, cannot be applied to our population.

SLE can be diagnosed by applying ACR criteria only when more than one organ is involved and it will usually take years for patients to satisfy 4 out of the 11 criteria and these results in undue delay in diagnosis and initiation of treatment. The study has highlighted the inadequacy of the ACR criteria in diagnosing SLE. If these patients were categorically diagnosed as SLE, they could have received definitive therapy. The observations undoubtedly prove that early diagnosis is not possible with the ACR Criteria, but is possible with the Kozhikode criteria.

Conclusion

All diagnosed cases of SLE during the period of January 2013 to December 2013 were included. The cases included were newly diagnosed patients as well as cases already under follow up from the department of Medicine, Rheumatology and Dermatology of the Government Medical College Calicut. Clinical diagnosis of SLE was considered in those presenting with unsettled clinical problems and conditions which were autoimmune in nature like Chronic ITP, Hypothyroidism, Autoimmune Hemolytic anemia, vitiligo and alopecia with clinical and laboratory evidence of autoimmunity.

References

1. Edworthy SM. Clinical manifestations of Systemic Lupus Erythematosus. In: Ruddy S, Harris ED, Sledge CB, editors. Kelley's Textbook of rheumatology. 6th edition. Philadelphia: Saunders. 2001: 1105-1119.

2. Guidelines for referral and management of systemic lupus erythematosus in adults. American College of Rheumatology Ad Hoc Committee on Systemic Lupus Erythematosus Guidelines. *Arthritis Rheum.* 1999; 42: 1785-1796.
3. Petri M. Treatment of systemic lupus erythematosus: an update. *Am Fam Physician.* 1998; 57: 2753-2760.
4. Meinão IM, Sato EI, Andrade LE, Ferraz MB, Atra E. Controlled trial with chloroquine diphosphate in systemic lupus erythematosus. *Lupus.* 1996; 5: 237-241.
5. Molina JF, McGrath H Jr. Longterm ultraviolet-A1 irradiation therapy in systemic lupus erythematosus. *J Rheumatol.* 1997; 24: 1072-1074.
6. McGrath H, Martínez-Osuna P, Lee FA. Ultraviolet-A1 (340-400 nm) irradiation therapy in systemic lupus erythematosus. *Lupus.* 1996; 5: 269-274.
7. Dammacco F, Alberighi ODC, Ferraccioli G, Racanelli V, Casatta L, Bartoli E. Cyclosporine-Aplus steroids versus steroids alone in the 12-month treatment of Systemic Lupus Erythematosus. *IntJ Clin Lab Res.* 2000; 30: 67-73.
8. Carneiro JR, Sato EI. Double blind, randomized, placebo controlled clinical trial of methotrexate in systemic lupus erythematosus. *J Rheumatol.* 1999; 26: 1275-1279.
9. Alvarez-Nemegyei J, Cobarrubias-Cobos A, Escalante-Triay F, Sosa-Muñoz J, Miranda JM, Jara LJ. Bromocriptine in systemic lupus erythematosus: a double-blind, randomized, placebo-controlled study. *Lupus.* 1998; 7: 414-419.
10. Pollak VE, Pirani CL, Kark RM. Effect of large doses of prednisone on the renal lesions of and life span of patients with lupus glomerulonephritis. *J Lab Clin Med.* 1961; 57: 495-511.
11. Bansal VK, Beto JA. Treatment of lupus nephritis: a meta-analysis of clinical trials. *Am J Kidney Dis.* 1997; 29: 193-199.
12. Bellomio V, Spindler A, Lucero E, Berman A, Santana M, Moreno C, et al. Systemic Lupus Erythematosus: mortality and survival in Argentina. A multicenter study. *Lupus.* 2000; 9: 377-381.
13. Sasidharan PK. SLE as a hematological problem. *Hematology* 2010; MB Agarwal, Vikas Publications Mumbai. 2010; 953-966.
14. Sasidharan PK, Bindya M, Sajeeth Kumar KG. Hematological Manifestations of SLE at Initial Presentation: Is It Underestimated? *ISRN Hematology Volume.* 2012; Article ID 961872, 5 pages.
15. Hahn BH, Harrison's principles of internal medicine. 17th Edition. Anthony S, Fauci, Stephen L, Hauser, Dan L, Longo et al, editor. New York: Mc-Graw Hill. 2008; 2075-2083.
16. Dubois' Lupus erythematosus 7th edition Philadelphia, Lippincott Williams and Wilkins. 2006.
17. Von Feldt JM. Systemic lupus erythematosus. Recognizing its various presentations. *Postgrad Med.* 1995; 97: 79, 83, 86 passim.
18. Villamin CA, Navara SV. Clinical manifestations and clinical syndromes of Filipino patients with Systemic Lupus Erythematosus. *Mod rheumatol.* 2008; 18: 161-164.
19. Bader-Meunier B, Armengaud JB, Haddad E, Salomon R, Deschênes G, Koné-Paut I, Leblanc T. Initial presentation of childhood-onset systemic lupus erythematosus: a French multicenter study. *J Pediatr.* 2005; 146: 648-653.
20. McHardy KC, Horne CH, Rennie J. Antinuclear antibody-negative systemic lupus erythematosus-how common? *J Clin Pathol.* 1982; 35: 1118-1121.
21. Gladman DD, Chalmers A, Urowitz MB. Systemic lupus erythematosus with negative LE cells and antinuclear factor. *J Rheumatol.* 1978; 5: 142-147.
22. Ferreira JE, Reiter WM, Saldana MJ. Systemic lupus erythematosus presenting as chronic serositis with no demonstrable antinuclear antibodies. *Am J Med.* 1984; 76: 1100-1105.
23. Joyce K, Berkebile C, Hastings C, Yarboro C, Yocum D. Health status and disease activity in SLE. *Arthritis and rheumatism.* 1989; 2: 65-69.
24. Minami Y, Sasaki T, Arai Y, Kurisu Y, Hisamichi S. Diet and systemic lupus erythematosus: a 4 year prospective study of Japanese patients. *J Rheumatol.* 2003; 30: 747-754.