Anti-nucleosome Antibodies: Utility in Diagnosis of SLE and Monitoring Disease Activity

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Systemic lupus erythematosus (SLE) is a complex autoimmune disease of unknown aetiology with heterogeneity in clinical presentation and the course of disease, characterized by a wide range of auto antibodies, immune-complex deposition and end-organ damage. Auto antibodies are present in at least 95% of SLE patients. Presence of auto antibodies is one of the 11 American College of Rheumatology (ACR) Criteria for diagnosis of SLE. Majority of the antibodies are directed against the nuclear antigens (anti-nuclear antibodies [ANA]), cytoplasm or cell surface proteins.1 Anti nuclear antibodies are positive in many other connective tissue disorders like Sjögren’s syndrome, systemic sclerosis, polymyositis, dermatomyositis, etc. They may also be detected in healthy individuals. They have low specificity for the diagnosis of SLE.

Anti-double stranded deoxyribonucleic acid (anti ds-DNA), anti-histone antibodies, anti-Smith (anti-Sm) antibodies are lined up in the diagnostic armamentarium of SLE and considered unique to SLE. Anti-histone antibodies are positive in drug-induced lupus. A rise in the titre of anti ds-DNA antibodies and fall in the complement C3 are the most widely accepted markers that indicate lupus flare. But anti ds-DNA antibodies may be found in only 60% of SLE patients and may not always correlate with disease activity.2-3 For e.g. ds-DNA levels may be elevated without overt renal disease. This can be attributed to the differences in the affinity, specificity and subclass of the antibody; the size, conformation and accessory proteins of the antigen or the test used for detecting the anti-ds-DNA antibodies. Tests like Farr assay detect relatively high-affinity antibodies; whereas tests like ELISA and immunofluorescence also detect low-affinity antibodies. Therefore, the hunt for detection of other auto-antibodies is ongoing which may be useful in the diagnosis of SLE as well as monitoring disease activity in SLE monitoring.

The pathogenesis of SLE consists of B cell activation, immune dysregulation and apoptosis. Pathogenic auto-antibodies produced by hyper-reactive B cells cause tissue damage by complement activation, immune complex formation and direct effect on cells. B cells can cause immune dysregulation by producing cytokines, regulating T cell function and presenting antigens. Defective apoptosis is one of the most accepted mechanism in the pathogenesis of SLE. It is now clear that in SLE there is insufficient removal of apoptotic material which leads to the release of modified auto antigens. These auto antigens are phagocytised by the dendritic cells or the antigen presenting cells (APC) and presented to T cells which become activated and stimulate auto reactive B cells to secrete auto antibodies. Nucleosomes are generated during cell apoptosis by the cleavage of chromatin by endonucleases. Chromatic antigens appear to be a common target of auto antibodies in SLE. Nucleosome is the unit of chromatin and consists of 200 base pairs of DNA wrapped around a protein core.4 The protein core is an octamer consisting of two molecules of each of the histones H2A, H2B, H3 and H4.5 The anti-nucleosome (anti NCS) antibodies can be detected by ELISA. The anti NCS antibodies are also considered to be specific for SLE diagnosis and several studies have reported it to be positive in SLE and its correlation with disease activity.

In a study from Brazil, Sardeo et al have reported a prevalence of antinucleosome antibodies in SLE as 61.9%. However, they did not find any relationship between antinucleosome antibody and any of the clinical features.6 In a study from Taiwan, Hung et al have reported higher levels of antinucleosome antibodies in patients of lupus nephritis as compared to non-renal SLE patients. Their study showed a positive correlation between anti-nucleosome antibodies with British Isles Lupus Assessment Group (BILAG) index, histological activity index of lupus nephritis and negative correlation between complement levels (C3 and C4). There was no significant correlation between serum levels of anti-nucleosome antibodies and histological chronicity index. With their results, it can be concluded that anti-nucleosome antibodies can be considered as a potential biomarker for early recognition of disease activity in SLE.7

In a study by Bigler et al from Switzerland, a high prevalence of anti-NCS has been reported in patients with active severe lupus nephritis 89%. However, these antibodies may be of limited help in distinguishing patients of SLE with and without active renal disease.8

The frequency of anti NCS in SLE varies from 50 – 100 and the specificity for diagnosis of SLE is 90-99%.9-17 Anti NCS antibodies/ Chromatin have been associated with active glomerulonephritis in SLE patients. Anti NCS antibodies could possibly be a sensitive marker in SLE patients who are anti ds DNA negative.

In a study from Mumbai, Pradhan et al18 did not find any statistically significant difference between lupus patients with and without nephropathy for the presence of these antibodies. In the present issue of JAPI, Saigal et al have reported anti NCS in 47.5% of SLE patients and 5% in other systemic autoimmune disorders patients. Anti NCS antibodies were not found in healthy controls, which is an important finding. It was found to be 100% specific for SLE. Anti NCS antibodies could be more sensitive but less specific for the diagnosis of lupus nephropathy. There was a positive correlation between anti NCS and SLE Disease Activity Index (SLEDAI). Anti NCS are probably superior to anti ds DNA in the diagnosis of SLE as it has higher sensitivity and specificity. However, anti NCS are not superior in the assessment of SLE disease activity as its correlation with SLEDAI is weaker than anti ds DNA antibodies.9 Small sample size is the major drawback of this study and more studies all over the country from different geographical distribution are needed to confirm these findings.

This study has shown that anti NCS antibodies are not found in healthy controls and are seen in ds-DNA negative patients; which are the salient highlighting features which will appeal all the readers. With increasing information about the immune
system which upgrades our understanding about autoimmune disorders; it will not be surprising if any therapeutic intervention comes out related to this antibody.

References


