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Monoclonal gammopathy in patients with HIV infection and aids patients

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ABSTRACT

Two hundred and twenty two HIV positive serum specimens from different stages of HIV infection and from different high risk groups were subjected to electrophoresis on conventional agar gel by zone electrophoresis and analyzed in Davis Polyacrylamide Gel Disc electrophoresis (PAGDE). 52(23.42%) had shown monoclonal immunoglobulin components in their serum samples. Monoclonal immunoglobulins were typed by immunoelectrophoresis (IEP) using monospecific antisera. 50 (22.52%) had IgG type and 2(0.99%) were of IgA type. Monoclonal Gammopathy (MG) occurs in a much higher frequency in full blown AIDS cases (42.85%) as compared to asymptomatic (27.64%),Lymphadenopathy syndrome (LAS) (16.6%) and AIDS Related Complex (ARC) (16.2%) patients. The percentage of monoclonal gammopathy ranged from 16.2% to 42.85% in different stages of HIV infection and from 12.5% to 33.33% in different other high risk groups. The findings indicate a monoclonal or oligoclonal B cell activation in patients with HIV infection and AIDS.

1. Introduction

Monoclonal Gammopathy (MG) is defined as an excessive secretion of immunoglobulin (Ig) that results from abnormal clonal proliferation of plasma cells or B lymphocytes. The abnormal secretory product is termed as paraprotein and the resulting disease state as either Paraproteinemia, Monoclonal Gammopathy or Plasma Cell Dyscrasia (PCD). The clinical spectrum of diseases that are associated with MG includes monoclonal gammopathy of undetermined myeloma and amyloidosis as allied disorders.1,2,3

Several abnormalities of the immune system have been reported in patients with Human immunodeficiency virus infection (HIV) and AIDS. These abnormalities include lymphocytopenia, T lymphocyte dysfunction, polyclonal B – cell activation and elevated levels of serum immunoglobulin and circulating immune complexes4,5.

A high prevalence of monoclonal gammopathy was reported in serum from the patients with AIDS or Lymphadenopathy syndrome (LAS)6. Monoclonal gammopathy was also reported in asymptomatic HIV- Seropositive patients.7 Papadopolous et al8 reported monoclonal gammopathy in AIDS patients with kaposis sarcoma and with opportunistic infections.

There are very few reports describing monoclonal gammopathy in patients with HIV infection and AIDS and the data from the developing countries is fragmentary. Therefore an attempt is made to study the monoclonal gammopathy in different stages and in different high risk groups of patients suffering from HIV infection and AIDS.

This study reports the result observed in analysis of 222 serum specimens from HIV infected and AIDS Patients.

2. Material and methods

(A) Cases - Serum Samples from 222 patients from different high risk groups of HIV infection were tested and confirmed for HIV antibodies by different ELISA and Western blot techniques using standard criteria.9,10

1.These 222 Patients includes 63 blood donors, 42 sexually transmitted Diseases (STD) Patients, 15 contacts of HIV Positive patients, 28 patients with AIDS related illness, 8 hetrosexuals, 6 Patients with persistent generalized lymphadenopathy (PGL), 5 Patients with Hepatitis, 48 Patients with Pulmonary Tuberculosis and 7 from other high risk groups.

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2. These patients were classified according to CDC criteria11 into Asymptomatic (123 Patients), PGL (6 Patients), AIDS related complex (86 Patients) and AIDS (7 Patients).

Controls: 300 Age and Sex matched normal healthy HIV Negative individuals were included as controls.

B) Immunological Studies:

1. Agar Gel Electrophoresis: Electrophoresis of 222 serum samples was done on conventional agar gel electrophoresis12 A compact, dense and distinct M band resolving anywhere between gamma to alpha -2 region was noted. The electrophoretic pattern of test sample was compared with the simultaneously run normal human serum under identical electrophoretic conditions.

2. Disc electrophoresis: Electrophoresis of all 222 serum specimens were also done in Davis Polyacrylamide Gel Disc electrophoresis under optimized conditions13. A compact, dense disc with sharp margins resolving at the cathodic region was noted as a M band on Polyacrylamide gel. The protein profile of the test sample was compared with that of the normal human serum under identical electrophoretic conditions.

3. Immunological typing:- A total of 52 serum samples showings M band by conventional agar gel electrophoresis and polyacrylamide Gel Disc electrophoresis were further tested in the Immunoelectrophoresis (IEP) against the locally raised monospecific anti IgG, and anti IgA antibody14. The structural abnormality of the affected class of immunoglobulin was identified with the deviation in the shape, the density and the configuration of the arc. The abnormal arc was compared with the normal arc of the normal human serum run on the same gel as a control.

4.) Estimation of Serum Immunoglobulins:- All the 52 serum samples showing M band were subjected for estimation of serum immunoglobulin IgG, and IgA by Mancini's single Radial Immnodiffusion (SRID).15 Suitable standards of the known concentration were employed. The diameter of the ring was directly proportional to the immunoglobulin concentration and the values were derived from the Precalibrated reference graph. A total of 100 normal human serum were employed as controls.

3. Results

Out of 222 patients with Human Immunodeficiency Virus infection, 52 (23.42%) patients had shown Monoclonal gammopathy in their serum samples. 50 (22.5%) had IgG type and 2 (0.99%) were of IgA type. A compact , dense and distinct M Band was detected at α-2, β & γ position by serum electrophoresis with conventional Agar gel electrophoresis (Fig.1) Also a compact dense disc with sharp margins as a M Band was detected at cathodic region by serum electrophoresis with Davis polyacrylamide gel disc electrophoresis (Fig . 2).

The different patterns of the IgG monoclonal gammopathy observed in this study were heavy precipitation, scoop formation, Duplication, Crossing of the arcs, crossing with heavy precipitation and bulging toward antibody and forking of the arcs (Fig 3). In case of IgA monoclonal gammopathy, broad line of heavy precipitate bulging towards antibody trough was observed (Fig 4).

The mean level of serum IgG monoclonal gammopathy was 3500 mg/dl (3000 mg/dl to 6800 mg/dl) and in the IgA monoclonal gammopathy, the mean level of serum IgA was 880 mg/dl (648 mg/dl to 1112 mg/dl) (Fig 5)

This study shows overall incidence of 23.42% MG in HIV infected patients.As high as 42.85% monoclonal gammopathy was detected in AIDS patients (3 out of 7) followed by 27.64% in Asymptomatic patients (34 out of 123), 16.6% in LAS (1 out of 6) and 16.26% in AIDS related complex patients (14 out of 86), The percentage of monoclonal gammopathy was ranged from 16.26% to 42.85% in Patients from ARC to AIDS as classified by CDC criteria.

As per high risk groups categories of HIV infection, as high as 33.33% monoclonal gammopathy was detected in blood donors followed by 28.57% in STD patients, 20% in Hepatitis, 17.85% in patients with AIDS related symptoms, 16.66% with pulmonary tuberculosis, 16.66% in PGL, 14.28% with other bacterial infection, 13.33% in contacts HIV positive patients and 12.5% in Hetrosexuals. The percentage of monoclonal gammopathy was ranged from 12.5% to 33.33% in different high risk groups of HIV infection.

Monoclonal gammopathy was detected in 45 males and 7 females. The age ranged from 16 to 50 years. The males (45) outnumbered the females (7) in frequency however the disease manifested at the mean age of 30 years.

Monoclonal gammopathy was not detected in 300 Age & sex Matched normal healthy individual controls

4.Discussion

The presence of Monoclonal gammopathy in response to antigenic stimulus is well established in both animals and man. Dictor et at 16 found an IgG lambda paraprotein in a three year old child with combined immunodeficiency. Axelsson et al 17reported 2% MG in Swedish population. Fine et al18 reported 0.15% MG in healthy French blood donors. Monoclonal gammopathy was also reported from primary, secondary and combined immunodeficiency states.15,19

Heriot et al6 reported 53.33% MG in AIDS patients and 66.66% in LAS patients. Papadopoulos N.M et al8 reported 89% paraproteinemia in AIDS patients with kaposis sarcoma and 13% in patients with opportunistic infections. Kandle et al20 reported 13.65% MG in three asymptomatic HIV seropositive blood donors. Jean et al7 reported 2.5% MG in 243 asymptomatic HIV seropositive blood donors.

This study shows overall incidence of 23.42% MG (52 out of 222 patients) in HIV infected patients. Monoclonal paraproteins detected from all the stages of HIV infection and also associated with other infections like Hepatitis,Herpes which may be the contributory factors for B cell expansion and ultimately to Monoclonal gammopathy..

In this study, a majority of 50 cases of monoclonal gammopathy were of IgG and 2 were of IgA.Geha et al21 reported an IgG paraprotien in patients with severe combined immunodeficiency syndrome. HOJ et al 22 reported a monoclonal B Cell proliferation of IgG kappa on the membrane surface in AIDS patients.

It is observed that there were maximum chances of missing the M band by zone electrophoresis or PAGDE as it is difficult to distinguish the paraprotein in a background of generalized hypergammaglobulinemia unless it is a clear oligoclonal band. Therefore it is emphasised that the serum samples should be subjected to zone electrophoresis, PAGDE and immunoelectrophoresis to yield a maximum result as it is done in this study.

An important finding of this study is that MG detected at a mean age of 30 yrs, which shows that MG occurs at a younger age and is also associated with infections like STD, tuberculosis and hepatitis in HIV seropositive patients. It is not clear whether these monoclonal proteins are detected against a specific antigen or antigens.

This study shows a high incidece of MG in AIDS and asymptomatic groups as compared to other high risk groups in HIV infected patients. This study also shows an increased abnormal immunoglobulin of serum IgG ranged from 3000 mg/dl to 6800 mg/dl and serum IgA ranged from 648 mg/dl to 1112 mg/dl.

There are many mechanisms to explain emergence of Monoclonal gammopathy in HIV infected patients. The abnormal B cell activation have been described in HIV infected patients.4 B cell activation is an inherent component of HIV infection and is induced by HIV itself as well as by other antigens,,mitogens and additional infecting microorganisms.23 The clonal expansion of B lymphocytes results in the florid follicular hyperplasia seen in reactive lymph nodes.24 Apart from B cell expansion,HIV infection may also be associated with an intrinsic impairement in B cell maturation.25 The mechanism of emergence of monoclonal proteins may be due to monoclonal or oligoclonal B cell activation,due to HIV infection, deficiency of T4 cells or as a direct effect of the virus on B cell lineage.4,23

The existence of Monoclonal gammopathy indicates immunodysfunction which ultimately precedes to immunodeficiency and AIDS .It is necessary to follow up these patients for many years to determine whether these patients leads towards a malignant process or to a benign essential Monoclonal gammopathy..

5. Conclusion

Fifty Two (23.42%) HIV infected patients in our study were characterised by the detection of monoclonal proteins. Monoclonal Gammopathy was detected in all the stages of HIV infection.Majority of 50 patients shows IgG type of MG and 2 patients with IgA type of MG. The detection of monoclonal proteins in this study is possibly due to oligoclonal or monoclonal abnormal activation of B cells. Long term follow-up of these patients is needed to know whether these patients progress to B cell malignancies or multiple myeloma or benign essential monoclonal gammopathy.

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