

Some Immunological Changes in Major Depression with Melancholia

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In this study on 29 melancholic patients and 12 healthy volunteers as a control, circulating lymphocytes and their subsets were studied and also serum immunoglobulins and complement. The results showed lower percentage of T and T₄ cells and their absolute count and lower both absolute count and percentage of T₈ cells than controls. There was also higher levels of immunoglobulins and complement 3 and 4 than control group. These findings may be consistent with the studies which found immunological changes in melancholic patients.

(Egypt.J.Psychiat., 1998, 21 :143 - 149).

INTRODUCTION

Since the report by Bartrop et al. (1977) demonstrating reduced lymphoproliferative responses to mitogens in the recently bereaved, extensive work has been done investigating cellular immune function in stress and depression. To date, however, considerable lack of agreement exists as to what specific immune alterations are associated with major depression. In particular some studies have found reduced lymphoproliferative responses to mitogens in patients with major depression (Schleif et al., 1984 and 1985; Evans et al., 1988 and 1992; Stein et al., 1991; Dorko et al., 1992; Marazziti et al., 1992; Hickie et al., 1994; Maes et al 1994; Bauer et al., 1995), while other studies have found no such relationship (Albrecht et al., 1985; Schleifer et al., 1985; Schleifer et al., 1989; Maes et al., 1994), others found enhanced responses in major depression (Schleifer et al., 1996; Maes et al., 1996). Also, some

authors found changes in immunoglobulins mainly beta and gamma globulin in major depression. Van-Hunsel et al., (1996) found that the percentage and concentration of serum albumin beta and gamma globulin fractions were significantly lower in major depression than normal controls. Some authors found that severity of depression and age may be two important variables associated with depression related immune reduced responses (Schleifer et al., 1989; Hickie et al., 1993). Many studies have suggested that patients with melancholia demonstrate differentially impaired cell mediated immunity when compared with other depressives (Cosyns et al., 1989; Maes et al., 1990; Mickie et al., 1993).

Considerable basis and clinical research substantiates a possible link between depression and cell mediated immunity (Evans et al., 1989) ; Reichlin et al., 1993). If such a link is operative in persons with clinical diseases such as AIDS, depression may have a potentially negative effect on their immune response and ultimate health outcome (Evans et al., 1995). The demonstration of impaired cell mediated immunity in patients with melancholia may help to explain an observed increase in physical morbidity and mortality among depressed patients (Murphy et al., 1989).

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Evans et al. (1992) found reduced cell mediated immunity in men with major depression but not in women. This study was restricted to males to avoid the difficulties in studying females as certain factors may affect the results as the stage of the menstrual cycle, oral contraceptives, etc... as it is difficult to match such factors.

SUBJECTS AND METHODS

Two groups of subjects were recruited according to their consent. The first group included 29 men diagnosed as major depression with melancholia using structured interview of DSM-III-R (1987). The second group included 12 healthy men as a control group. No subjects had history of recent medical illness nor had taken over the previous 3 months any drugs as a regular use. Also the blood samples were drawn before the start of antidepressant treatment. The mean age of the depressed group was 39.39 ± 4.3 and of the control group was 41.58 ± 4.58 . Six of the depressed group were smokers. Twelve healthy volunteers were recruited as a control group for the assay method. They were not depressed nor had any psychiatric disorder and reported no stressful life events. Five of them were smokers.

Weight changes underwent many factors: (1) As all the patients started their illness so near but more than 2 weeks (diagnostic criteria) there is no chance for recording weight change (2) Most of the patients did not record their weight as a routine. All patients started their antidepressant measures after the blood sample aspiration.

All lymphocyte assays were carried out at the same day as venipuncture. Total white blood cells and differential counts were performed from EDTA

blood sample on Coulter counter STKS.

Lymphocytes were separated from heparinized blood sample by centrifugation on a Ficoll-Hypaque gradient (Boyum, 1968). Viability was assessed by trypan blue dye exclusion. The concentration of the mononuclear suspension was adjusted to $2-4 \times 10^6$ /ml by Hanks buffered salt solution (HBSS). Aliquots of these lymphocytes were used for in vitro assay of T_4 (CD_4^+) and T_8 (CD_8^+) by monoclonal antibody technique, where 1×10^6 mononuclear cells were incubated with 50 μ l of the specific monoclonal antibody in two polyethylene round bottom tubes for CD_4^+ and CD_8^+ cells, after incubation for 30 minutes in ice-bath the cells were washed 3 times, each for 10 minutes at 1200 r.p.m. with HBSS. After the last wash, the cell pellet was mixed with diluted antimouse IgG F(ab)₂ (diluted 1 to 50 in phosphate buffered saline (PBS), mixed well then incubated for 30 minutes in ice-bath. The cells were washed 3 times, each for 10 minutes at 1200 r.p.m. with HBSS. the cell pellet was resuspended in 50 μ l of washing solution, lastly, one drop was spread over an area of 20 mm square area and covered with a coverslip, 300 lymphocytes were evaluated using X40 phase objective by fluorescent microscope.

A serum sample was used for assay of immunoglobulins (IgG, IgA and IgM) by single radial immunodiffusion (Mansini, 1965). Complement 3 (C3) and complement 4 (C4) were determined by immunoturbidimetric method, performed on Hitachi 911 (Thomas, 1992).

RESULTS

Table (1) shows the comparison of circulating lymphocytes and their sub-

sets between patients with major depression and healthy controls. T and T₄ cells percentages had statistically significant lower percentages in depression patients than in healthy controls. While the absolute count is lower in depressed patients than controls but statistically nonsignificant. T₈ cells percentage and absolute count were lower in depressed patients but did not reach statistical significance.

Table (2) shows serum immunoglobulins and complement in patients with depression and controls. The IgG serum level was higher in depressed ($P < 0.001$) than in control group. The other two immunoglobulins, IgM and IgA, showed statistically nonsignificant higher levels in depressed group. The table shows also that complements 3 and 4 had high-

er serum levels in depressed group but statistically non significant.

DISCUSSION

An association between depression and altered immunity has been suggested by many studies, although the findings have not been consistently demonstrated (Stein et al., 1991; Herbert et al., 1993). Differences between studies may relate to the patient subgroups investigated (Schleifer et al., 1996). Severity of depressive symptoms have been found to be associated with immune change in patients with major depression (Herbert et al., 1993). Patients with melancholia demonstrate differentially impaired cell mediated immunity when compared with other depressives (Cosyns et al., 1989; Maes et al., 1990; Hickie et al., 1993).

In the present study, the percentages of T- and T₄ cells were lower in depressed than in control group. Evans et al. (1992) found that patients with major depression were 27.4% lower in percentage of Leu-11 lymphocytes compared with normal controls and found that peripheral blood Leu-7 cell counts were lower in the depressed group but statistically nonsignificant. Schleifer et al. (1985) found a decrease in the number of T cells in patients with depression. Maes et al. (1994) found that there were significant correlations between urinary cortisol excretion and the absolute number and percentage of lymphocytes, monocytes, CD₄ and CD₈ T cells (negatively) and neutrophils (positively). These findings may be consistent with the present findings with some variation in the finding between the present study and the other studies which maybe related to differences between patient subgroups investigated. With increasing age

Table (1)
Comparison of Circulating Lymphocytes and Their Subsets between Patients with Major Depression and Controls.

Parameter	Controls (N=12)	Depressed Patients (N=29)	P
Lymphocyte (mm ³)	2577.0 ± 824.3	2439.0 ± 666.60	NS
T-cells (%)	66.3 ± 3.30	56.0 ± 4.60	<0.001
T-cells (mm ³)	1451.3 ± 412.2	1349.50 ± 521.3	NS
T4-cells (%)	41.84 ± 5.20	34.20 ± 4.10	<0.001
T4-cells (mm ³)	547.2 ± 201.2	468.30 ± 221.0	NS
T8-cells (%)	22.15 ± 3.07	21.1 ± 4.54	NS
T8-cells (mm ³)	904.1 ± 211.0	881.2 ± 300.3	NS

Table (2)
Serum immunoglobulins and Complement in Patients and Controls.

Parameter	Patients (N=29)	control (N=12)	P value
IgG mg/dL	1739.4 ± 350.6	1327 ± 250.5	p=0.001
IgA mg/dL	251.4 ± 90.2	239.6 ± 80.2	p=0.704
IgM mg/dL	250.1 ± 90.2	199.9 ± 79.1	p=0.1130
C3 mg/dL	111.3 ± 30.2	96.67 ± 20.9	p=0.1464
C4 mg/dL	34.2 ± 2.3	33.7 ± 10.2	p=0.8098

in the middle and later years, the depressed patients had specific CD₄ cell deficits (Rabkin et al., 1991; Scheifer et al., 1989) which is consistent with the findings of the present study as the age of the patients were in the middle age. Strong evidence has recently been reported that major depression is accompanied by an acute phase response, characterized by elevated levels of positive acute phase proteins and decreased levels of negative acute phase proteins (Van-Hunsel et al., 1996). Also, recently several authors have reported that immunoglobulin IgM, complement C₃, complement C₄ and positive acute phase proteins (e.g. haptoglobin, alpha-1 and acid glycoprotein and alpha 1-antitrypsin) were significantly increased, while negative acute phase proteins (e.g. albumin and transferrin) were depressed in depressed patients. The acute phase response in unipolar depression is possibly caused by changes in cytokines and corticosteroid secretion in depressed patients (Song et al., 1994). This is in agreement with the findings of this study, where IgG was increased ($p=0.001$), and also IgA, IgM and C₃ and C₄ were increased but statistically nonsignificant.

Van-Hunsel et al. (1996) found that the percentage and concentration of serum albumin and gamma globulin fractions were significantly lower in major depression than in normal controls. There was a significant increase in percentage of the gamma-globulin fraction after subchronic treatment with antidepressants the results support the hypothesis that major depression is accompanied by an acute phase response.

The demonstration of impaired cell mediated immunity in patients with melancholia may help to explain an observed increase in physical morbidity and mortality among depressed patients

(Murphy et al., 1989). Further, it may help to explain an apparent increased rate of malignancies in a population with depressive symptoms who have been studied prospectively (Shekelle & Raynor, 1981). The significance of such immunological disturbances, however, lies not only in their capacity to predict physical health outcomes in patients with certain depressive disorders. Immune disturbances, like other neuroendocrine markers, may provide an avenue for further investigation of depressive related dysregulation of higher CNS centers which are known to modulate peripheral cell mediated immunity responses directly and indirectly (Jankovic, 1985; Hall et al., 1985; Besedovsky, 1985). The potential importance of studying certain depressive subtypes such as melancholia, is that links may be made between immune dysfunction and other biological parameters (Cortisol, Catecholamine and/or neuropeptide metabolism) which may provide a better understanding of the central mechanisms underlying particular forms of depression (Hickie et al., 1993). There is considerable evidence from basic and clinical studies to suggest that neural modulators, e.g. Catecholamines, as well as neuroendocrine modulators (e.g., corticotropin releasing factor, ACTH, cortisol), are involved in the neurobiology of stress and major depression. These factors and others may regulate stress related changes in immune function. For example, several cytokines can affect Natural Killer cell (NK) populations, and interleukin-2 has been shown to increase NK cytotoxicity and NK cell population (Trinchieri et al., 1984; Condon et al., 1986).

Psychiatric disorder, including depression and schizophrenia, also have been viewed from a neuroimmunologic conceptual frame of reference. Viral in-

fection and autoimmune disorders of the brain have long been considered in the pathogenesis of these disorders. These areas of research are highly controversial and have many methodologic problems, and the failure to replicate findings is commonplace. With the availability of increasingly sophisticated molecular and biochemical methods specifically designed to investigate viral and autoimmune processes, neuro-immunologic research may yield meaningful results for our understanding of psychiatric disorders (Stein et al., 1991).

Conclusion and Recommendation

In conclusion, this study has suggested a relationship between immune response and degree of depression which may indicate a specific hypothesis to be tested in future studies. A larger sample size is required, although difficult to achieve if all relevant factors which might affect immune tests (e.g. drug free, non smoking, constant level of exertion, age matched groups) are considered. Longitudinal measures on the same patients are desirable to correlate changes in clinical and immune variables. Measures of coping and hopelessness would also appear to be indicated, in addition to measures of clinical depression. This assessment of immunosuppression was limited to enumerative measures - other research designs, including direct cell function assays, may prove fruitful in the elucidation of a connection between depression and immune response. Gender may affect specific factors of cellular immunity in depression (Evans et al., 1992), this may suggest that future studies should assess the effect of gender on regulatory processes that mediate immune functions in depression.

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Lis elian gemeuts ivam unologigues

Chez lis malades me'lanclouics ayant la depression majeure

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Aussi, une élévation guifaute dut téux immunoglobuli er du complément daus les seuims des mélan cliolics 3 ov 4 fois plus que le groupe contrôle.

بعض التغيرات المناعية في مرض الاكتئاب الجسيم

أجريت هذه الدراسة على ٢٩ مريضاً مصاباً بالاكتئاب الجسيم مع الأعراض الميلانخولية و١٢ شخصاً سليماً، وقد أوضحت الدراسة وجود نقص في عدد ونسبة الخلايا الليمفاوية وبعض أنواعها مقارنة بالأصحاء، وكذلك وجد ارتفاع في مستوى الجلوبيولينات المناعية مقارنة بالأصحاء.