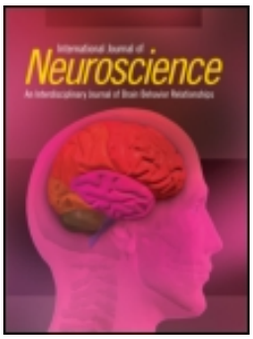

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Reuven Sandyk

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Letter to the Editor

COEXISTING BIPOLAR AFFECTIVE DISORDER AND MULTIPLE SCLEROSIS: THE ROLE OF THE PINEAL GLAND

(Received March 19, 1991)

Keywords: Multiple sclerosis (MS), pineal gland

To The Editor:

Multiple sclerosis (MS), a chronic demyelinating disease of young adults, is characterized clinically by episodes of focal deficits involving the optic nerves, brainstem, cerebellum, and spinal cord, which remit to a varying extent and recur over a period of many years (Adams & Victor, 1985; Winshenker & Ebers, 1987). The clinical manifestations of the disease are protean, being determined by the varied locations and extent of the foci of demyelination. Pathologically, there is an inflammatory response observed in the central nervous system consisting predominantly of activated T-cell lymphocytes and macrophages (Prineas et al., 1978) accompanied by a local immune reaction resulting in the secretion of interleukins and in the synthesis of oligoclonal immunoglobulin (IgG) by plasma cells (Frick & Scheid-Seydel, 1958). Foci of demyelination affect primarily the white matter of the brain and spinal cord. It has been hypothesized that the loss of suppression of or imbalance in the immune system may play a crucial role in the pathophysiology of this disease (Waksman & Reynolds, 1984).

The etiology and pathogenesis of MS are unknown. Epidemiological data suggest that MS is related to some as yet unidentified environmental factor that is encountered in childhood and which, after years of latency, either produces the disease or contributes to its presentation. Research in the past decade suggests that this environmental factor may be of viral origin (McFarlin & McFarland, 1982), triggering an autoimmune process directed against myelin (Weiner & Hauser, 1982; Waksman & Reynolds, 1984). Furthermore, the parallel in histopathological findings and in clinical symptoms of MS to chronic relapsing experimental allergic encephalomyelitis (EAE) (Wisniewski & Keith, 1977), a T cell-mediated autoimmune disease, has led to the concept of MS as being an autoimmune disease (Wisneiwski & Keith, 1977).

The occurrence of psychiatric symptoms in MS, and specifically depression, has been extensively discussed in the neurological and psychiatric literature (Surridge, 1969; Garfield, 1985; Joffe et al., 1987). In one study, depression was found in up to 27% of MS patients (Surridge, 1969). Kahana et al. (1971) reported that 3% of their MS patients committed suicide, a rate 14 times greater than in the general population in Israel. Moreover, several studies have reported an associated between MS and bipolar illness (Kemp et al., 1977; Solomon, 1978; Mapelli & Ramelli, 1981; Peselow et al., 1981; Kellner et al., 1984; Schiffner et al., 1986; Joffe et al., 1987). Kellner et al. (1984) reported two patients with rapidly cycling bipolar disorder who were found to have MS and proposed that the disease should be considered in the differential diagnosis of patients with affective disorder.

In a systematic study involving 100 consecutive patients attending a MS clinic, 13% of patients fulfilled criteria for manic-depressive illness (Joffe et al., 1987). As the prevalence rate of bipolar affective disorder in the general population is approximately 1% (Boyd & Weissman, 1982), the occurrence of bipolar illness in the sample

was approximately *13 times higher* than would be expected. An association between MS and bipolar illness has also been found in one epidemiologic study (Schiffer et al., 1986). In the latter study symptoms of MS appeared in all ten patients at least 1 year before the first manifestation of bipolar illness. In another study, 8 out of 13 MS patients (61.5%) with bipolar illness had the onset of either depression or hypomania more than two years after the onset of motor symptoms, two patients had the onset of psychiatric symptoms more than two years to the onset of MS, and three patients had the onset of the two disorders at approximately the same time.

There are several potential reasons for the relationship between affective disorder and MS. One possibility is that bipolar illness and MS share common neurological and biochemical mechanisms. For instance, lesions in the limbic system, which have been implicated in bipolar illness (Flor Henry, 1969), have been found more frequently in MS patients with bipolar affective illness and other psychiatric disorders (Bigname et al., 1961; Honet et al., 1987). Moreover, diminished serotonin (5-HT) functions has been found in both affective illness and MS (Sonninen et al., 1973; Claveria et al., 1974; Johansson & Roos, 1974; Davidson et al., 1977; Monaco et al., 1979). Alternatively, it is possible that a currently unknown factor, such as an endocrine disorder or a disorder of immune function, may be common to both disorders. In fact, the latter has been implicated in the etiology of both MS and depression (Kronfol, 1985).

In MS pathologic lesions may occur in the hypothalamus (Bignami et al., 1961) and brainstem (Victor & Adams, 1985) and disrupt the activity of the neuronal pathways carrying information about the environment to the pineal gland. Since abnormalities of pineal functions have been linked to the circadian disorganization of manic-depressive illness (Miles & Philbrick, 1988), these lesions may underlie the coexistence of MS with manic-depressive illness. Specifically, since a supersensitive melatonin response to light may be a trait marker of bipolar illness (Lewy et al., 1981; 1985) and since insufficient exposure to light might trigger depression in susceptible individuals (Kripke et al., 1983), I propose that abnormalities of pineal melatonin functions may be one factor underlying the relationship between bipolar affective illness and MS.

This hypothesis is supported further by the observations of diurnal (Goodstein & Ferrell, 1977) and seasonally-dependent variations in the manifestations of MS (Withrich & Rieder, 1970), which may reflect the characteristic diurnal and seasonal variation in the secretion of melatonin. For instance, Wuthrich and Rieder (1970) found that the rate of exacerbation of MS in Switzerland was maximal in the winter months and minimal in the summer time. According to the authors: "consideration of the seasonal variations of bout incidence in different regions could offer an approach to the understanding of the nature of the factors promoting the bouts of MS."

The pineal gland functions as a neuroendocrine "transducer" by translating environmental information (photic, thermic, magnetic) into signals which modulate most neuroendocrine mechanisms (Reiter, 1984). This task is achieved via the circadian synthesis and release of melatonin. It has been shown that immune reactivity and circulating lymphocytes fluctuate according to a circadian rhythm (Abo et al., 1981) and that the circadian release of melatonin modulates immune reactivity (Maesteroni et al., 1987 *a*). For instance, functional (permanent light conditions) or pharmacological inhibition of melatonin synthesis is associated with reduced humoral and cellular immune responses in mice (Maestroni et al., 1987 *b*); This is completely reversed by the administration of exogenous melatonin in the late afternoon (Maestroni et al. 1987 *a*). Furthermore, melatonin has been shown to antagonize corticosteroid partially and cyclophosphamide induced immunosuppression in mice (Maestrone et al., 1987 *a*) and it is possible that the immunosuppressive effects of these agents

in MS (Weiner & Hafler, 1988) may be related to their ability to alter melatonin functions.

Manic-depressive phases are associated with fluctuations in melatonin secretion (Lewy et al., 1979), which, in turn, could influence the course of the neurologic deficit in MS. Thus, the rise in melatonin secretion during manic phases (Lewy et al., 1979) may enhance immune reactivity and potentially exacerbate the neurologic deficits of MS. In contrast, decreased melatonin secretion during the depressive phases of bipolar illness (Lewy et al., 1979), may produce an immunosuppressive effect with resultant attenuation of the neurologic deficits. Hence, alterations in melatonin secretion during the course of manic-depressive illness may in part underlie the spontaneous fluctuations in the severity of motor deficits in MS.

Finally, lithium carbonate, which has been shown to phase delay melatonin secretion (Yocca et al., 1983), is effective in the prophylaxis of manic-depressive illness (Fieve et al., 1975) and affective illness associated with organic brain symptoms (Young et al., 1977). It is therefore possible that the drug, by stabilizing changes in mood, may also be beneficial in preventing neurological exacerbation of MS in patients with coexisting bipolar illness. Further studies investigating the prophylactic effect of lithium in MS are warranted more firmly to substantiate this hypothesis.

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REUVEN SANDYK
Department of Psychiatry,
Albert Einstein College of Medicine,
Montefiore Medical Center,
Bronx, NY 10461, U.S.A.