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PREMENSTRUAL EXACERBATION OF SYMPTOMS IN MULTIPLE SCLEROSIS IS ATTENUATED BY TREATMENT WITH WEAK ELECTROMAGNETIC FIELDS

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It has been suspected that hormonal factors contribute to the etiology and pathogenesis of multiple sclerosis (MS). A direct relationship between MS and endocrine functions is suggested by changes in disease activity during the phases of the menstrual cycle. A subset of women with MS experience premenstrual worsening of symptoms which improve dramatically with the onset of menstruation. The biological mechanisms underlying these changes in disease activity are unexplained but may be related to cyclical fluctuations in gonadal sex steroid hormones, abrupt changes in the activity of the endogenous opioid peptides and fluctuations in plasma melatonin levels which affect neuronal excitability and immune functions. Extracerebral application of weak electromagnetic fields (EMFs) in the picotesla range intensity has been reported efficacious in the treatment of MS with patients experiencing sustained improvement in motor, sensory, autonomic, affective and cognitive functions. The present report concerns two women with chronic progressive stage MS who experienced, coincident with increasing functional disability, regular worsening of their symptoms beginning about a week before menstruation and abating with the onset of menstruation. These symptoms resolved two months after the initiation of treatment with EMFs. The report supports the association between the endocrine system and MS and indicates that brief, extracranial applications of these magnetic fields modifies the activity of neuroendocrine systems which precipitate worsening of MS symptoms premenstrually.

Keywords: electromagnetic fields; multiple sclerosis; menstrual cycle; premenstrual syndrome; endorphins; pineal gland; melatonin; immune responses

Hormonal factors have been suspected to contribute both directly and indirectly to the etiology and pathogenesis of multiple sclerosis (MS) (Birner, 1945; Tillman, 1950; Sweeney, 1955; Millar et al., 1959; Schapira et al., 1966; Fischman, 1981; Poser & Poser, 1983; Korn-Lubetzki et al., 1984; Birk & Rudick, 1986; Birk et al., 1990; Sandyk, 1993; Sandyk & Awerbuch, 1991; 1994 *a*; Duquette et al., 1992; Duquette & Girard, 1993). For instance, the susceptibility of MS is higher in women than men and women are even more susceptible when onset occurs at an early or delayed age (Wainerdi, 1961; Fischman, 1981; McCall et al., 1969; Duquette & Girard, 1993). Also, parent-child transmission is clearly more frequent when the mother rather than the father is affected (Duquette et al., 1992) Men, on the other hand, may experience a more rapid progression to a nonambulatory status (Detels et al., 1982). The association between MS and hormonal factors is supported further by the observations that: (a) pregnancy has both a short and long-term favorable effect on the

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course of the disease (Ghezzi & Caputo, 1981; Korn-Lubetzki et al., 1984; Birk & Rudick, 1986; Davis & Maslow, 1992); (b) there is an increased rate of relapse during the postpartum period (Millar et al., 1959; Schapira et al., 1966; Korn-Lubetzki et al., 1984; Birk et al., 1990); (c) the course of MS is influenced by the menstrual cycle (Francis et al., 1990); and (d) there is an association between puberty and the timing of onset of the clinical manifestations MS (Fischman, 1981; Wainerdi, 1961; Sandyk, 1993).

A direct relationship between MS and endocrine functions in women is more clearly illustrated by changes in disease activity during the phases of the menstrual cycle. In my experience a substantial number of women experience exacerbation of MS symptoms premenstrually i.e. during the luteal phase and spontaneous symptomatic improvement coincident with the onset of menses. These patients report premenstrual exacerbation of symptoms starting at an early stage of the disease but with progression and overall decline in motor and mental functioning these exacerbations became more accentuated and debilitating. The occurrence of premenstrual reactivation of symptoms may be related to one or a combination of the following factors: (a) changes in gonadal steroid hormone plasma levels particularly estrogen and progesterone which increase during the luteal phase and then fall abruptly at the onset of menstruation (Junquiera & Carneiro, 1983; Magos & Studd, 1985); (b) changes in the levels of circulating opioid peptides which peak during the luteal phase and fall to undetectable levels at the onset of menstruation (Wehrenberg et al., 1982; Ferin, 1984; Reid, 1983); and (c) changes in melatonin plasma levels which rise during the luteal phase and reach a peak at menstruation (Wetterberg et al., 1976; Hariharasubramanian et al., 1985; Webley & Leidenberger, 1986; Brun et al., 1987; Parry et al., 1990; Sandyk, 1992 *a*).

Several recent reports have demonstrated that extracranial application of weak electromagnetic fields (EMFs) in the picotesla (pT) range of low frequency is an efficacious, safe, nonpharmacologic modality for symptomatic therapy of MS patients (Sandyk, 1992 *b*; *c* 1994 *a*; *b*; Sandyk & Derpapas, 1993 *a*; *b* ; Sandyk & Iacono, 1993; 1994 *a*; *b*). These case studies have shown that extracranial application of pT EMFs is efficacious in ameliorating motor, sensory, autonomic, and cognitive functions in patients diagnosed with either relapsing-remitting or chronic progressive MS. This procedure has also been shown efficacious in rapidly resolving an acute relapse of MS (Sandyk & Derpapas, 1993 *a*). In addition, my experience over the past three years indicates that this treatment modality also stabilizes the course of the disease including in those patients classified with a chronic progressive course. I now report on two patients with MS who experienced regular exacerbations of symptoms premenstrually which were attenuated during the course of treatment with EMFs.

Case Reports

Case I. This 41 year old right-handed woman was well until the age of 19 when she first experienced an attack of left-sided optic neuritis resulting in blindness. Her vision in the left eye returned to normal after several months and she remained clinically asymptomatic until about 8 years ago when, after the birth of her third child, she developed fatigue, paresthesias and numbness in the fingertips of both hands, and weakness of her left leg. Over the ensuing years she experienced gradual progression of symptoms with increased weakness and spasticity in the legs and difficulties with her balance. In 1991 she became dependent on a walker for ambulation. By 1992 she was using ankle braces and in late 1993

she stopped driving a car and by the end of the year became confined to a wheelchair. Approximately six months prior to presentation she began to experience intermittent difficulties with swallowing and increasing weakness in the left arm and hand. Her medical and gynecological history were unremarkable.

The patient recalled that she noted some degree of premenstrual worsening of her symptoms, particularly in fatigue, early in the course of the disease. But as of 1991, when she began ambulating with a walker, she started to experience distinct premenstrual exacerbation of symptoms which included increased weakness and spasticity in the lower extremities, increasing difficulties with swallowing, more frequent episodes of daytime urinary urgency, deterioration of axial balance, difficulties rising from a chair, and generalized weakness with fatigue, mild mental depression, poor concentration and impaired short-term memory functions. On the day of menstruation she experienced abrupt improvement in motor and mental symptoms with a burst of energy, mood elevation and improved ambulation and reported to function physically and mentally best during the 3–4 days of menstruation.

The patient began treatment with EMFs in April of 1994. Using the Sandyk Electromagnetic Stimulator she received an average of 3 treatment sessions per week over the following 2 months and thereafter 1–2 sessions per week during the following 12 months. A session was comprised of two magnetic treatments each of 45 minutes duration separated by a 15 minute break. The frequency of stimulation ranged from 2–4 Hz using a sinusoidal wave in the first treatment and a trapezoidal wave in the second treatment. Since the introduction of treatment with EMFs the patient experienced improvement in a variety of symptoms including increased level of energy, improvement in mood, short-term memory and concentration span, increased strength in the upper limbs especially the left arm and hand, resolution of the dysphagia, improved balance especially trunk control, diminished spasticity in the lower limbs and reduction of nocturia to an average of once per night. The patient also recalled that as early as 2 months after the introduction of magnetic treatment she ceased to experience distinctive episodes of premenstrual reactivation of symptoms noting that her symptoms remained fairly even throughout the menstrual cycle although during some cycles she continued to experience a burst of energy on the day of menstruation.

Case II. This 50 year old right-handed woman was well until the age of 41 when in 1986, after returning from a trip to Florida, she developed an acute attack of optic neuritis on the right and a week later on the left with blurring of vision lasting about 4 weeks. After undergoing a spinal tap she was diagnosed with MS. Four months later, she experienced recurrence of bilateral optic neuritis with visual impairment lasting almost 8 months. She was hospitalized and after receiving a course of intravenous corticosteroids her vision improved immediately and returned to normal 6 weeks later. An MRI scan and visual evoked potential studies which were performed at the same time were abnormal and supportive of the diagnosis of MS. Over the ensuing 5 years she experienced intermittent episodes of urinary urgency and incontinence, difficulties with balance, fatigue, numbness and paresthesias in the feet, dizziness, and weakness in the left leg. Three years prior to presentation she began to use a cane due to increasing weakness in the left leg and additional difficulties with balance. She also experienced paresthesias in the feet, daytime urinary urgency with nocturia 2–3 times, increasing fatigue and heat intolerance, increased sensitivity to light, attacks of daytime sleepiness, episodes of urinary incontinence, constipation, and depression. Over the past year there has been marked deterioration in her balance and after falling sev-

eral times she confined herself to her house. At the time of presentation the patient was taking 4-aminopyridine (45 mg/d) for about 1 1/2 years and fluoxetine 40 mg/d for the past two years.

The patient recalled that about 3 years ago she began to experience regular and predictable exacerbation of symptoms beginning the week prior to menstruation which, at that time, were mild consisting mainly of increased fatigue with intermittent blurring of vision. However, about a year prior to presentation premenstrual exacerbation of symptoms became more intense and disabling and she often felt as though she is having an attack of MS. She began to experience intolerable fatigue forcing her to spend 5–6 hours a day confined to bed. Other symptoms included blurring of vision, increased weakness in the legs, deterioration of balance, marked intolerance to heat with profuse attacks of sweating, increased sensitivity to light, abdominal cramping, increasing constipation and occasional migraneous headaches all of which improved dramatically with the onset of menstruation.

In March of 1995 the patient began experimental treatment with EMFs using the Sandyk Electromagnetic Stimulator which emits an alternating current (AC) EMF of an amplitude of 7.5 picotesla. The patient received 3 magnetic treatment sessions per week. Each treatment session, which was applied in a quiet and artificially illuminated room that was magnetically unshielded, comprised two successive treatments each of 25 minutes duration separated by a break of 15 minutes. The frequency of stimulation used in this patient was 4 Hz for the first AC pulse and 4.5 Hz for the second pulse using sinusoidal and trapezoidal waves, respectively. The patient's eyes were shielded during each treatment. On this regimen the patient made a dramatic recovery during the following four months with improvement in balance, level of energy and mood, resolution of daytime sleepiness, improved strength in the left leg, diminished heat and light sensitivity and diminished daytime and nocturnal urinary frequency. After two months of magnetic therapy the patient ceased to experience worsening of her symptoms premenstrually and reported that her symptoms remained fairly even throughout the cycle. She continued, however, to experience a burst of energy with the onset of menstruation.

DISCUSSION

In the presence of normal menstrual cycles both patients experienced regular exacerbation of their MS symptoms beginning about a week before menstruation and spontaneous improvement in symptoms coincident with the onset of menstruation thus supporting the notion that the course of MS is influenced by fluctuations in gonadal sex steroid hormone levels (Birk & Rudick, 1986; Birk et al., 1990; Francis et al., 1990; Davis & Maslow, 1992; Duquette & Girard, 1993). Both patients, who at the time of presentation were classified as having a chronic progressive MS, noted during the course of the disease worsening of their symptoms premenstrually. However, with progression of the disease and increasing level of disability these exacerbations predictably became more accentuated and debilitating suggesting that in some women premenstrual worsening of symptoms may parallel deterioration of MS disability and may serve as a useful clinical marker of increased disease activity including in patients with chronic progressive MS. In both patients periodic, brief extracerebral applications of EMFs resulted, within two months, in resolution of the premenstrual reactivation of symptoms which occurred along with improvement in motor and mental functions. These findings clearly suggest that in patients with MS application of

EMFs in the picotesla range intensity is capable of attenuating premenstrual reactivation of symptoms conceivably by modifying the activity of neuroendocrine system which ultimately are responsible for exacerbation of the disease premenstrually.

The menstrual cycle reflects the expression of a cyclical process involving the interaction between the hypothalamic-pituitary axis and the ovaries. These interactions, which require integrated neural control mechanisms governed by a hypothalamic "transducer" located within the medial basal hypothalamus (Yen, 1986), are central to the sexual differentiation of the brain, to control of brain-pituitary-gonadal axis, and to the establishment of normal patterns of sexual and aggressive behavior in both sexes (Schipper, 1986). The potent influences exerted by sex steroids on catecholamine and serotonin (5-HT) turnover (Algeri et al., 1977) and the colocalization of labeled estradiol within catecholaminergic luteinizing hormone-releasing hormone (LHRH) positive perikarya (Stumpf & Sar, 1977) suggest that many of the physiologic effects of sex steroids are mediated by modulation of specific monoaminergic and peptidergic pathways. The impact of gonadal sex steroids on monoaminergic and peptidergic neuronal systems may explain the influence of the menstrual cycle on the course of diverse neurological disorders such as migraine, Parkinsonism, chorea, myoclonus, Tourette's syndrome and MS (Schipper, 1986; Quinn & Marsden, 1986; Sandyk et al., 1987; Francis et al., 1990; Davis & Maslow, 1992).

Premenstrual exacerbation of MS symptoms may be considered part of the broader manifestations of the premenstrual syndrome (PMS). PMS, which lately has been defined more rigorously as late luteal-phase dysphoric disorder (American Psychiatric Association, 1987), is a complex psychoneuroendocrine disorder which temporarily disrupts the personal and professional lives of 10%–30% of women throughout their reproductive years (Coppen & Kessel, 1963; Yen, 1986). There's increasing evidence indicating a relationship between PMS and major depressive disorder (Halbreich & Endicott, 1985; Hallman, 1986). PMS patients often have a lifetime history of major depressive disorder (Halbreich & Endicott, 1985) and a subgroup may develop major depressive disorder at a later stage (Schuckit et al., 1975). Features often experienced with PMS include fatigue, irritability, anxiety, overeating, sleep disturbances, disordered temperature regulation, carbohydrate craving, constipation, and lethargy (Dalton, 1964; Reid, 1983). These symptoms are also common in patients with seasonal affective disorder (SAD), a condition characterised by seasonal cyclical mood changes with characteristic symptoms of hypersomnia, fatigue, increase in appetite and weight, and carbohydrate craving occurring in the winter months (Rosenthal et al., 1985; Garvey et al., 1988; Wehr & Rosenthal, 1989).

The pathophysiology of PMS remains unexplained. The popular neuroendocrine hypothesis proposed in 1938 by Israel that PMS results from gonadal steroid hormonal disequilibrium remains controversial (Reid, 1983; Rubinow et al., 1987). Patients with PMS have no abnormalities in secretion or in blood levels of estrogen, progesterone, or prolactin suggesting that the syndrome may involve an abnormal response to physiological levels of sex steroid hormones (Martin & Reichlin, 1987). Nevertheless, menstrual-related fluctuations in sex steroid hormone plasma levels with an abrupt decline in estrogen and progesterone concentrations in the late luteal phase is relevant to the clinical manifestations of MS since estrogens have been shown to influence immune responses (Schuurs & Verheul, 1990; Duquette & Girard, 1993). For instance, estrogen receptors have been demonstrated on macrophages (Gulshan et al., 1990) and estradiol has been shown to increase phagocytic activity in macrophage and the production of interleukin-1 in vivo by mouse peritoneal macrophages (Duquette & Girard, 1993). In women, interleukin-1 activity is con-

sistently higher in plasma during the luteal phase (Duquette & Girard, 1993) and natural killer cell activity is decreased during the peri-ovulatory period (Duquette et al., 1992). In addition, estrogens influence the activity of the pineal gland (Semm et al., 1983) and that of 5-HT neurons (Pranzatelli & Snodgrass, 1985), which have been ascribed neuroimmunomodulatory functions (Roszman et al., 1985) and a pathogenetic role in MS (Claveria et al., 1974; Davidson et al., 1977; Sonninen et al., 1973; Tabaddor et al., 1978; Luca & Hategan, 1986; Kisser & Harrer, 1974; Lenon & Carnegie, 1971; Hyyppa et al., 1975; Markianos & Sfagos, 1988; Sandyk & Awerbuch, 1991; 1994 *b*).

Reid and Yen (1981; 1983) proposed that cyclical gonadal steroid-induced changes in endogenous opioid peptide activity might be the central neuroendocrine event that precipitates the varied manifestations of PMS. As levels of circulating opioid peptides in primates peak during the luteal phase and subsequently fall to undetectable levels at the onset of menstruation (Wehrenberg et al., 1982; Reid, 1983; Ferin, 1984), it was suggested that opioid withdrawal premenstrually, which may lead to rebound hyperactivity of noradrenergc neural pathways owing to slowly acquired receptor supersensitivity (Walker et al., 1984), might precipitate in susceptible individuals the development of the mental changes of PMS (Reid, 1983; Halbreich et al., 1988). This hypothesis is supported by the observation that in humans opiate withdrawal is associated with depression, irritability, a low threshold for stressful stimuli, altered appetite and disturbances of temperature regulation (Halbreich et al., 1986).

Changes in the activity of endogenous opioid peptides have been demonstrated in patients with MS (Rosenberg & Appenzeller, 1988; Gusev et al., 1994), but it remains unknown whether these are related causally to the pathogenesis and clinical manifestations of the disease. Circumstantial evidence suggests that the endogenous opioids are involved in the pathophysiology of MS since: (a) stress, which causes the release of beta-endorphins (Cohen et al., 1982), adversely affects the symptoms and course of the disease (Walton, 1977; Warren et al., 1982; Grant et al., 1989), (b) chronic pain, which is associated with disruption of opioid peptide activity (Terentus, 1982), is a common feature of MS occurring in a range 20% to 80% of patients at some point during the course of the disease (Albert, 1969; Shibasaki & Kuroiwa, 1974; Clifford & Trotter, 1984) (c) MS patients who experienced diminished fatigability during treatment with amantadine (Symmetrel^{R}) were found to have higher plasma beta-endorphin levels compared to patients whose fatigue was unaffected by the drug (Rosenberg & Appenzeller, 1988); (d) beta endorphins are known to exert a neuroimmunomodulatory function and therefore may be involved in some pathogenetic aspects of the disease (Weber & Pert, 1984; Gusev et al., 1994); and (e) opioid peptides and opiates influence the propagation of action potential discharges of single neurons by increasing potassium conductance (Williams et al., 1982) which is implicated in impulse transmission in demyelinated fibers (van Diemen et al., 1993; Russell et al., 1995). Thus, the rise in opioid peptide activity during the luteal phase and its rapid decline with the onset of menstruation might be involved in the pathogenesis of premenstrual reactivation of MS symptoms.

PMS also has been proposed to be related causally to changes in pineal melatonin secretion (Clare, 1985; Parry et al., 1987, 1990; Sandyk, 1992 *a*). Plasma melatonin levels are low during ovulation and high premenstrually (Wetterberg et al., 1976; Arendt, 1978; Penny, 1982; Law, 1986; Webley & Leidenberger, 1986; Hariharasubramanian et al., 1985; Brun et al., 1987). Wetterberg et al. (1976) found plasma melatonin levels during men-

struation to be 45 times higher than during ovulation. In addition, altered circadian nocturnal melatonin secretion was reported in women with PMS and evening administration of bright light, which inhibits melatonin secretion (Lewy et al., 1980) and resets its circadian secretion, has shown beneficial effects in patients with premenstrual depression (Parry et al., 1987, 1989). On the other hand, melatonin may cause worsening of dysphoric mood in depressed patients and exacerbation of symptoms in MS patients (Carman et al., 1976; Sandyk, 1992 *b*). Since nocturnal melatonin plasma levels are diminished in MS patients during periods of symptom exacerbation and in those with a history of mental depression (Sandyk & Awerbuch, 1992; Sandyk & Awerbuch, 1993 *a*, *b*; and since melatonin is a neuroimmunomodulator (Maestroni et al., 1987 *a*; *b*; Cardarelli, 1990; Pierpaoli & Maestroni, 1987, 1988; Fraschin & Reiter 1990; Guerrero & Reiter, 1992), it is conceivable that abnormal circadian melatonin secretion premenstrually may contribute to the development of premenstrual reactivation of symptoms in these patients.

The mechanisms by which treatment with EMFs attenuate premenstrual exacerbation of symptoms in these patients remain unexplained. The neuroendocrine system, particularly the hypothalamus and pineal gland, are sensitive to the influences of the geomagnetic field and to exposure to artificial EMFs (Jakovleva, 1975; Kholodov, 1966; Semm, 1983; Semm et al., 1980; Free et al., 1981; Stoupel et al., 1983, Michaelson & Lu, 1992; Wilson et al., 1992) For instance, in rats chronic exposure to electric fields has been reported to produce changes in corticosteroids, testosterone, and growth hormone levels (Hackman & Graves, 1981; Free et al., 1981) which in part involve the mediation of the endogenous opioid peptides and melatonin (Kavaliers & Ossenkopp, 1992). That EMFs alter opioid functions is suggested by observations in experimental animal studies which have shown magnetic stimuli to: (a) suppress the analgesic and locomotor effects of morphine (Kavaliers et al., 1984; Kavaliers & Ossenkopp, 1986 *a*; *b*), (b) modify the rate of tolerance development to morphine-induced analgesia (Kavaliers & Ossenkopp, 1985), and (c) reduce stress-induced opioid analgesia (Kavaliers & Ossenkopp, 1986 *c*). Magnetic stimuli also have been shown to alter the circadian secretion of pineal melatonin (Semm et al., 1980; Welker et al., 1983; Rudolph et al., 1988) which is altered in women with premenstrual depression (Parry et al., 1990). Melatonin in turn, has been shown to modify immune responses (Jankovic et al., 1970; Rella & Lapin, 1976; Maestroni et al., 1987 *a*; *b*; Pierpaoli & Maestroni, 1987, 1988; Angeli et al., 1988; Maestroni et al., 1988; Guerrero & Reiter, 1992), inhibit the activity of endogenous opioid peptides (Lissoni et al., 1986), affect the release of gonadotropin (Reiter, 1991), and increase 5-HT functions (Anton-Tay et al., 1968; Moszkowska et al., 1971; Aldegunde et al., 1985) which are thought to participate in the pathogenesis of PMS symptoms (Halbreich et al., 1988; Pies, 1990; Rickels et al., 1990; Stone et al., 1991).

In conclusion I have presented two women with MS who experienced regular premenstrual reactivation of symptoms which became increasingly more disabling in temporal association with overall deterioration in disability. Since all ovulating women have cyclical hormonal fluctuations, it remains unclear why only a subset of women develop PMS and with respect to MS patient, why some experience premenstrual reactivation of the disease followed by spontaneous improvement of symptoms with the onset of menstruation. Nevertheless, the observation that periodic applications EMFs led to attenuation of premenstrual exacerbation of symptoms in these patients adds an additional facet in support of the unique efficacy of this treatment modality in the management of MS.

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