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Elevated plasma prolactin and EEG slow wave power in post-polio fatigue: Implications for a dopamine deficiency underlying post-viral fatigue syndromes.

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ABSTRACT

To test the hypothesis that plasma prolactin and electroencephalographic (EEG) slow wave activity are correlated with fatigue, 33 polio survivors without medical or psychologic comorbidities were studied. Subjects were administered the Post-Polio Fatigue Questionnaire (PFQ) and had resting

measurement of both plasma prolactin and bilateral temporal-occipital power across the EEG frequency spectrum. Typical daily fatigue severity on the PFQ was significantly correlated with daily difficulty with attention, staying awake and motivation, but not with measures of acute polio severity or the number of limbs affected by late-onset Post-Polio Sequelae symptoms. Prolactin was significantly correlated with daily fatigue severity on the PFQ ($r=.39$; $p<.05$). EEG power was equal between the two hemispheres across all frequency bands. However, EEG slow wave power in the right hemisphere was significantly correlated with daily fatigue severity and prolactin level ($r=.37$; $p<.05$). Using multiple linear regression, age at acute polio, frequency of difficulty with attention on the PFQ, prolactin and right hemisphere slow wave power predicted 72% of the variance of the daily fatigue severity rating ($r=.85$; $p<.0001$). These data suggest that increased prolactin secretion and EEG slowing are related to the severity of post-polio fatigue, findings similar to those in patients with acute paralytic and non-paralytic poliomyelitis and with chronic fatigue syndrome. A primary role is suggested for a dopamine deficiency (versus serotonergic receptor supersensitivity) underlying impaired cortical activation and the symptoms associated with putative post-viral fatigue syndromes.

INTRODUCTION

Fatigue is the most commonly reported and most debilitating of Post-Polio Sequelae (PPS), the unexpected, late-onset symptoms affecting the more than 1.8 million North American polio survivors (1). In the 1985 National Survey of polio survivors, 91% reported new or increased fatigue, 41% reported fatigue significantly interfering with performing or completing their work and 25% reported fatigue interfering with self-care activities (2).

Importantly, polio survivors differentiate between physical tiredness and what they describe as "brain fatigue" that is associated with cognitive difficulties. In the 1990 National Survey, between 70% and 96% of polio survivors with fatigue reported concomitant problems with concentration,

memory, attention, word-finding, maintaining wakefulness and thinking clearly, with 77% percent reporting moderate to severe difficulty with these problems (3). Despite their multiple cognitive complaints, the only clinically significant deficits on formal neuropsychologic testing in severely fatigued polio survivors were in attention and information processing speed (4).

Postmortem studies performed during the polio epidemics of 50 years ago demonstrated the consistent presence of poliovirus lesions in the midbrain reticular formation, hypothalamus, thalamus, putamen and globus pallidus, i.e. the reticular activating system (RAS) (3,5). RAS lesions have been hypothesized to cause late-onset fatigue and attention impairments in polio survivors (6). This hypothesis is supported by studies in which magnetic resonance imaging of the brain has revealed small discrete or multiple punctate areas of hyperintense signal in the reticular formation, thalamus, putamen, and white matter tracts only in those polio survivors reporting fatigue (3,7).

Postmortem histopathology also documented that neurons secreting neurotransmitters known to activate the brain, especially dopaminergic neurons in the substantia nigra and arcuate nucleus, were also damaged or destroyed by the poliovirus (5-7). The inability of polio survivors' damaged RAS to adequately activate the cortex, thereby impairing attention and concentration and generating the subjective symptoms of fatigue, has been hypothesized to result in part from reduced secretion of dopamine (3,6,8). This hypothesis is supported by a double-blind, placebo-controlled pilot study of bromocriptine mesylate, a direct-acting, post-synaptic dopamine 2 (D2) receptor agonist (9). An increasing daily dose of bromocriptine was significantly negatively correlated with subjective reports of fatigue on awakening as well as difficulty with staying awake during the day, attention, cognition, word finding and memory. It is notable that bromocriptine was effective only in the most neurophysiologically impaired subjects, i.e., those with more than twice as many lesions on brain MRI, a blunted ACTH response to an overnight fast and a baseline plasma prolactin level nearly double that of the drug non-responders.

If there is a dopamine deficiency in polio survivors it should be physiologically evident. Resting plasma levels of prolactin should be elevated since dopaminergic neurons in the arcuate nucleus were damaged by the poliovirus and arcuate dopamine secretion inhibits prolactin release via D2 receptor stimulation (10). If a dopamine deficiency is preventing brain activation and causing fatigue, elevated prolactin should be associated with impaired cortical activation as evidenced by slowing of the electroencephalogram (EEG). This study was undertaken to test the hypothesis that fatigue, plasma prolactin and EEG slowing are significantly correlated in polio survivors with fatigue.

METHODS

Subjects. Subjects were recruited from patients treated by the Post-Polio Service and from post-polio support groups. Potential subjects completed and mailed to the laboratory a polio and medical history form and the Post-Polio Fatigue Questionnaire (PFQ) which rates typical daily fatigue severity on a six-point scale from "none" through "severe" (3). The PFQ also rates the severity and the frequency (on a four-point scale from "never" through "always") of difficulty with motivation, attention, mind wandering, thinking clearly, concentration, word finding, memory, muscle weakness and staying awake during the day. A phone interview was conducted and individuals were excluded if they were over 59 years of age, had any medical or psychological condition that could cause fatigue or cognitive impairment (e.g., major depressive episode, thyroid, cerebrovascular or cardiac disease, anemia, respiratory insufficiency, sleep apnea or hypopneas, lupus or diabetes) or if they were taking medications that could cause fatigue or cognitive impairment (e.g., anti-depressants, benzodiazepines). Subjects were interviewed when they reported for testing and their medical and psychiatric symptoms and history were confirmed. Thirty-three subjects were selected, giving a power of .80 at a two-tailed alpha level of $p<0.05$.

Power analysis of the EEG frequency spectrum using fast Fourier transformations was performed using the Dantec NEUROSCOPE (Dantec, Inc.). Electrodes were placed at T5-Oz (left hemisphere) and T6-Oz (right hemisphere) with reference placed at FPZ of the International 10/20 System. These placements have been found to be the most sensitive for identifying EEG activity associated with decreased attention and the least affected by eye movement and eye blink artifact (11,12). Scalp skin was wiped with isopropyl alcohol and scrubbed with an abrasive pad; 1.0 cm. diameter silver/silver chloride EEG electrodes were then attached with Ten20© EEG electrode paste to achieve an impedance of <5K ohms. EEG was sampled at 128 Hz during 4 consecutive 4 second epochs with filters (having a 6dB roll-off) set at 1.0 Hz and 32.0 Hz. Power in the delta (1-4 Hz), theta (4-8 Hz), alpha (8-13 Hz) and beta (13-30 Hz) frequency bands was quantified in real time and printed every 30 seconds. The percentage of power for each band was calculated and power in delta and theta bands summed to calculate EEG slow wave power.

Procedure. Subjects were asked to eat their usual morning meal and limit themselves to only two 8 oz. cups of a caffeine-containing beverage on the day of testing. On arriving at the Institute, the experimental procedure was described to the subjects who gave written informed consent. Subjects were then taken to the hospital's hematology laboratory where venous blood was drawn. Plasma prolactin was assayed by a commercial laboratory using CIBA-Corning ACS immunochemiluminometric kits. Pre-menopausal women were studied during their luteal phase to control for the effects of ovulation on prolactin. Blood was also drawn by finger-stick for a simultaneous study of blood glucose and post-polio fatigue (data to be presented elsewhere). Subjects were then escorted to the psychophysiology laboratory where EEG electrodes were attached over the course of approximately 20 minutes. The subjects were then requested to sit facing a white wall that was one meter away, with their eyes open and their muscles relaxed, and to refrain from talking or moving. Muscle (EMG) activity was monitored both visually and via the NEUROSCOPE's EMG artifact rejection software. After one minute of sitting, the subjects' first 16 seconds

of artifact-free EEG was recorded. Subjects then began taking neuropsychologic tests of attention and word finding during which EEG was also recorded (data to be presented elsewhere).

Data analysis. Statview 4.5 was used to perform statistical analyses. Descriptive statistics were calculated for all variables as were product-moment intercorrelations. The p value for correlations of daily fatigue severity with subjective symptoms on the PFQ was corrected for multiple comparisons using the Bonferroni inequality. Multiple linear regression was performed to determine if the daily fatigue severity rating could be predicted on the basis of the prolactin value and the demographic item, PFQ subjective symptom of fatigue and EEG frequency band power most significantly correlated with daily fatigue severity.

RESULTS

Eighteen females and 15 males participated, ages 38 to 59 years, having a mean educational level of 16 years (Table 1). On average, the patients contracted polio in 1951 when they were 5 years old, were hospitalized at polio onset and had one limb permanently affected. This sample is typical of the population of American polio survivors (2). Subjects were tested between 8:15 and 14:45 (x = 11:00).

Subjects had resting plasma prolactin values ranging from 2.7 to 16.3 ng/ml ($x = 6.9 \pm 3.7$), typical of the resting prolactin levels measured in both healthy controls and CFS patients and within the normal range (13-17). As opposed to other studies, there were no significant correlations between prolactin and time of blood drawing, age or gender (17). Prolactin was significantly correlated with daily fatigue severity on the PFQ ($r=.39$; $p<.05$). Daily fatigue severity was also significantly correlated with age at acute polio ($r=.39$; $p<.05$), the severity of difficulty with attention, mind wandering,

muscle weakness, concentration, staying awake and motivation, and the frequency of difficulty with attention and mind wandering (Table 2). Fatigue severity was not correlated with measures of acute polio severity or the number of limbs affected by current PPS symptoms (e.g., muscle weakness and pain). These relationships are consistent with the symptom profile of polio survivors with fatigue seen in the 1990 National Post-Polio Survey (3).

EEG power was equal between the two hemispheres across all frequency bands. However, EEG power in the right hemisphere was significantly correlated with daily fatigue severity (slow wave and delta power) and prolactin (slow wave and theta power) (Table 3).

Using multiple linear regression, the age when polio was contracted, frequency of difficulty with attention on the PFQ, plasma prolactin and right hemisphere slow wave power predicted 72% of the variance of the daily fatigue severity rating ($p<.0001$) (Table 4).

DISCUSSION

These findings suggest the hypothesis should be accepted: there are significant correlations between fatigue, plasma prolactin and slowing of the EEG in polio survivors. The correlation of fatigue and prolactin with EEG slow wave power only in the right hemisphere may be related to the important role ascribed to the right hemisphere in cortical activation (18). Since polio survivors have impaired visual memory, a function also ascribed to the right hemisphere, they may have an as yet unexplained tendency toward right hemisphere damage and therefore a predisposition to impaired cortical activation and fatigue (4,19). The correlation of age at polio onset with fatigue severity may be indicative of the brain's decreased ability to compensate for poliovirus-induced damage inflicted at an older age because of decreased neural plasticity as the brain develops.

EEG slowing and fatigue. Slowing of the EEG has already been documented following the acute episode of polio. Holmgren reported that 34% of 258 patients with acute spinal, spinal/bulbar and even non-paralytic polio demonstrated "mental changes" such as "disorientation, apathy, (and) irritability" (20). These changes were significantly correlated with abnormal slowing of the EEG (i.e., the emergence of theta and delta activity) in 42% of those with spinal or bulbar symptoms as well as in 33% of those with non-paralytic polio.

Even in healthy subjects, EEG slowing is indicative of impaired cortical activation and has been associated with decreased arousal, "drowsiness" and impaired performance on neuropsychologic tests of attention (11, 21-23). Since EEG slowing similar to that documented in polio survivors and controls has also been noted in patients with putative post-viral fatigue syndromes (PVFS), and since 85% of CFS patients demonstrated "an excess of irregular slow wave activity" on EEG, decreased cortical activation may be a common substrate of impaired attention and fatigue (24-27).

Dopamine and fatigue. The correlations of prolactin with daily fatigue severity and EEG slow wave power suggest that a reduction in central dopaminergic activity may underlie reduced cortical activation and the symptoms of post-polio fatigue. This suggestion is supported by the finding that D2 receptor antagonists increase EEG slow wave power, cause subjective fatigue and difficulty concentrating, and produce dose-related increases in subjective "drowsiness" and impairments on neuropsychologic tests of attention (28,29).

Buspirone, a D2 receptor antagonist that is an even more potent serotonin (5-HT) 1A receptor agonist, was also found to increase EEG slow wave power, decrease subjective alertness, impair performance on

neuropsychologic tests of attention and cause a nearly two-fold increase in prolactin release in healthy subjects (30). Identifying whether these psychophysiological effects are caused by D2 receptor blockade or 5-HT1A receptor stimulation is important since buspirone and other 5-HT mimetic agents have been employed to study the pathophysiology of CFS. Buspirone has been found to produce at least a twofold greater release of prolactin in CFS patients as compared to healthy controls and to generate "excessive fatigue" in CFS patients (13,16,31). Bakheit et al. concluded that the prolactin elevation resulted from "increased sensitivity" of hypothalamic 5-HT1A receptors in CFS patients (13).

A 5-HT releasing and reuptake blocking agent, d-Fenfluramine, was found in one study to produce a 130% increase in prolactin in CFS patients as compared to controls (14). Although the same researchers did not find a d-fenfluramine-induced increase in prolactin in a second study of CFS patients, they did find a significantly attenuated prolactin response to hypoglycemia (15). The authors concluded that while impaired prolactin release during hypoglycemia could have resulted from "subsensitivity" of hypothalamic 5-HT1A receptors, the patients' intact ACTH/cortisol response to hypoglycemia failed "to support a role for altered 5-HT neurotransmission" in CFS. Further, when the authors compared their failure to elicit a prolactin increase with d-fenfluramine to buspirone's ability to release prolactin, they concluded that buspirone's D2 antagonist properties may be "confounding the serotonergic effects on prolactin secretion."

A neurotransmitter of fatigue? Buspirone's combined 5-HT1A agonist and D2 antagonist properties confound any conclusions about altered central 5-HT1A receptor sensitivity in CFS, since buspirone's blockade of D2 receptor is the more likely cause of prolactin increases (32). But an additional confound exists when using prolactin as an indicator of central 5-HT receptor sensitivity following administration of 5-HT mimetics. In animals, 5-HT itself can directly inhibit dopaminergic neurons, reducing tyrosine hydroxylase activity and dopamine release, suppressing nearly 70% of the

dopaminergic prolactin-inhibiting neurons in the arcuate nucleus and lowering dopamine concentrations in portal blood (10,33,34).

In humans, a 5-HT mimetic drug (fluoxetine) has been seen to produce Parkinsonian rigidity, akathisia and dystonia, while buspirone itself has been shown to exacerbate Parkinsonian symptoms (34-39). These findings suggest that the ability of 5-HT mimetics to trigger prolactin secretion, increase EEG slow wave power, impair attention and alertness, and trigger symptoms of fatigue is more likely due to 5-HT's "inhibitory influence on central dopamine mechanism and functions" within an already dopamine-depleted RAS, rather than an unspecified effect of unexplained increases in 5-HT1A receptor sensitivity (34; cf 3,6,7). This conclusion would explain the failure of one 5-HT mimetic agent (fluoxetine) to ameliorate symptoms of CFS in a randomized, double-blind, placebo-controlled controlled study, and suggests that serotonin reuptake blocking agents could actually reduce cortical arousal, decrease alertness and induce fatigue via serotoninÕs inhibition of central dopamine mechanism and functions (13,34,40,41).

In this context it is noteworthy that Parkinson's patients, with their profound dopamine depletion, demonstrate impaired attention and marked fatigue (42,43). "Excessive fatigue" was reported by 48% of Parkinson's patients while nearly one-third reported that fatigue was their "most disabling symptom" (43,44). Indeed, one of the first descriptions of cognitive dysfunction in Parkinson's disease (PD) could serve as a description of post-polio fatigue or chronic fatigue syndrome, i.e., a syndrome "characterized by a diminution of voluntary attention, spontaneous interest, initiative and the capacity for effort and work, with significant and objective fatiguability, and a slight diminution of memory" (45).

However, if low central dopaminergic tone underlies the symptoms of chronic fatigue, why was baseline prolactin found not to be related to chronic fatigue in any of the buspirone and fenfluramine stimulation studies? One possibility is that dopaminergic neurons are more severely

damaged by the poliovirus than by other putative PVFS-inducing agents, thus allowing a prolactin/fatigue relationship to be more readily detected in polio survivors. While PD symptoms were seen acutely during poliovirus infection, the extent and severity of brain stem damage in these patients proved fatal in nearly all of the reported cases (46-50). In contrast, survivable parkinsonism was noted during PVFS outbreaks earlier in this century and has even been documented recently in PVFS patients, suggesting that dopaminergic neurons are damaged - albeit less severely - in PVFS (Behan, Lapp, and Richardson, personal communications) (50,51).

A more readily testable explanation for the lack of elevated baseline prolactin values in CFS patients is that the assayed blood was drawn following an overnight fast. Although hypoglycemia is known to increase prolactin secretion, this effect is significantly attenuated in CFS patients (15,17). Fasting may increase only the control subjects' baseline prolactin values and thereby obscure an elevated baseline prolactin in CFS patients. This explanation is supported by a study of circadian hormonal variations, in which non-fasting prolactin levels were significantly higher in CFS patients, and a report that 25% of one group of PVFS patients had "high basal prolactin levels" (51, 52).

Future research. These findings provide a rationale for further study of the role played by the brain stem's reticular activating system and dopaminergic neurons, especially within D2 receptor-mediated systems, in the genesis of fatigue and other fatigue-related cognitive symptoms (cf 53,54). For example, the word finding difficulty reported by 82% of polio survivors with fatigue, which appears similar both to the "tip-of-the-tongue" phenomenon in PD patients and word finding problems reported by CFS patients, may be related to impaired dopaminergic neurotransmission (3,55,56, cf 57). For example, the number of animals polio survivors could name in 60 seconds was significantly positively correlated with their score on a neuropsychologic test of vigilance but significantly negatively correlated with plasma prolactin (-.36; $p<.05$) (58).

Further, recent research suggests that the emerging relationship between chronic fatigue and fainting in CFS patients, polio survivors and even in healthy subjects may have a dopaminergic component that is related to RAS damage (cf 9, 59-62). However, the interactions of many brain neurotransmitter systems - peptidergic, cholinergic, glutaminergic, as well as monoaminergic - need to be considered and studied simultaneously to determine whether neurotransmitter abnormalities underlie any of the symptoms of fatigue in polio survivors, in those with CFS or with other putative PVFS (3,6,8,62).

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