



Parallels between Post-Polio Fatigue and Chronic Fatigue Syndrome: A Common Pathophysiology?

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Abstract

Fatigue is the most commonly reported and most debilitating Post-Polio Sequelae (PPS) affecting the more than 10 million worldwide polio survivors. Post-polio fatigue is characterized by subjective reports of difficulty with attention, cognition and maintaining wakefulness, symptoms reminiscent of nearly two dozen outbreaks during this century of post-viral fatigue syndromes (PVFS) that are related clinically, historically, anatomically or physiologically to poliovirus infections. Recent studies that relate the symptoms of post-polio fatigue and Chronic Fatigue Syndrome (CFS) to clinically significant deficits on neuropsychological tests of attention, histopathologic and neuroradiologic evidence of brain lesions, impaired activation of the hypothalamic-pituitary-adrenal axis, increased prolactin secretion and EEG slow wave activity are reviewed. Described will be a possible common pathophysiology for post-polio fatigue and CFS, based on the Brain Fatigue Generator Model of PVFS, and a possibility pharmacotherapy for PVFS based on the replacement of brain dopamine.

Fatigue is the most commonly reported and most debilitating Post-Polio Sequelae (PPS).

In two US national surveys, 91% of polio survivors reported new or increased fatigue, 41% reported fatigue significantly interfering with performing or completing work and 25% reported fatigue interfering with self-care activities (1,2).

Fatigue was reported to be triggered or exacerbated by physical overexertion in 92% and by emotional stress in 61%. Importantly, polio survivors differentiate between the physical tiredness and decreased endurance they associate with new muscle weakness and a "brain fatigue" that is characterized by problems with attention and cognition. Between 70% and 96% of polio survivors reporting fatigue complained of difficulty with concentration, memory, attention, word-finding, maintaining wakefulness and thinking clearly, with 77% percent reporting moderate to severe difficulty with these symptoms (3).

These reports are reminiscent of the symptoms associated with nearly two-dozen outbreaks during this century of Myalgic Encephalomyelitis (ME) and Chronic Fatigue Syndrome (CFS), conditions that can be related historically, clinically, anatomically or physiologically to poliovirus infections. These relationships will be described in an attempt to suggest a possible common pathophysiology for all post viral fatigue syndromes (PVFS).

Polioencephalitis and Fatigue

Neither the acute nor late-onset problems with attention and cognition in polio survivors can be explained by poliovirus-induced damaged to spinal motor neurons (4). Postmortem histopathology performed in the 1940s demonstrated the consistent presence of poliovirus lesions in specific brain areas. Brain stem centers were found to be "involved in even mild cases" of polio. (5) The midbrain reticular formation was "always severely altered" (6), being "heavily peppered throughout" (7-11) with lesions that were "very common and often severe." (7) Hypothalamic, thalamic and caudate nuclei, the putamen and globus pallidus were also lesioned by the poliovirus. (11,12) Neurons in the periaqueductal gray, locus ceruleus, median raphe nuclei and especially the substantia nigra were also damaged or destroyed by poliovirus infection. (5, 8-11)

These findings indicate that poliovirus consistently and often severely damaged the brain areas responsible for cortical activation -- the reticular formation, hypothalamus, thalamus, substantia nigra and locus ceruleus -- i.e., the reticular activating system. (RAS) (13-20) And, clinical reports written during the polio epidemics corroborate the pathological evidence of poliovirus damage to the RAS since "drowsiness," lethargy, prolonged somnolence, rousable stupor and even coma were described as sequelae of the acute poliovirus infection. (7,12,21,22) Holmgren (23) reported that 34% of 258 patients with acute spinal, spinal/bulbar and non-paralytic poliomyelitis demonstrated "mental changes" such as "disorientation, apathy, pronounced sleep disorder (and) irritability." These changes were significantly correlated with abnormal slowing of the electroencephalogram (EEG) ("the emergence of theta and some delta activity") in 42% of those with clinically diagnosed spinal or spinal and bulbar symptoms, as well as in 33% of those with non-paralytic poliomyelitis. Meyer (24) reported that a "high percentage of children clinically recovered from poliomyelitis insofar as motor disability is concerned, reveal qualitative difficulties in mental functioning (such as) fatigability (sic) and fleeting attention" for months after the acute episode.

Late-onset post-polio fatigue, ME and CFS can now be compared using techniques that were unavailable during the 1940s and 1950s. (25-28) However, the historical parallels between the poliovirus and chronic fatigue should not be overlooked, since history provides its own lessons as well as a context in which new empirical data can more meaningfully be interpreted.

Historical Parallels

"Attenuated" Type II Poliovirus Infection and Impaired Cortical Activation. During the polio epidemics of the 1950's, a syndrome of impaired cortical activation and parkinsonism was attributed to the poliovirus. In 1951, three cases of "drowsiness" and rousable stupor with marked slowing of the EEG, "bulbar signs" and parkinsonism were reported. (29) While these symptoms were atypical of polio their occurrence in an area where poliomyelitis had become a "serious problem," and the pathologic evidence that "the main brunt of the disorder was borne by the midbrain," prompted the authors to suggest that the syndrome might be caused by a poliovirus with "attenuated virulence." In 1952 eight additional patients were described having an encephalitis whose dominant features were again somnolence and extrapyramidal symptoms. (30) Type II poliovirus was isolated from half of these patients and the two fatal cases that came to autopsy had lesions in the reticular formation, hypothalamus and substantia nigra.

The association of poliovirus-induced somnolence with extrapyramidal symptoms highlights the prominence of poliovirus lesions in the basal ganglia and importance of the basal ganglia (BG) in maintaining cortical activation. (31,32) The BG are thought to gate "sensory input" to the thalamus (32) with the putamen said to control the "mechanisms that contribute to selective attention." (33) Putamen-lesioned animals are "insensitive to quite gross visual stimuli" and "clearly (demonstrate) difficulty transferring attention from one object to another." (34) In humans, BG lesions and impairment of dopaminergic input to the striatum decrease both the diffuse activation of the cortex (35) and the ability to "maintain targeted attention." (36)

What's more, Parkinson's disease (PD) patients demonstrate not only an impaired ability to "transfer attention" (37) but also marked fatigue. (38) In one survey 33% of PD patients reported that fatigue was their "most disabling symptom." (39) "Excessive fatigue" was reported in another study by 48% of PD patients (40), fatigue that was associated with abnormal glucose metabolism or blood flow in the putamen and supplementary motor area (cf. the Brain Fatigue Generator Model, below). It is noteworthy that one of the first descriptions of cognitive dysfunction in PD (41) could serve as a definition for PVFS, i.e., syndromes "characterized by a diminution of voluntary attention, spontaneous interest, initiative and the capacity for effort and work, with significant and objective fatigability and a slight diminution of memory."

"Atypical" Poliomyelitis and Chronic Fatigue. Beginning in Los Angeles in 1934 and continuing for more than twenty years, there were more than a dozen outbreaks of a disease that was at first

diagnosed as poliomyelitis, then as "abortive" or "atypical" poliomyelitis and finally named "Myalgic Encephalomyelitis." (ME) (26,42) Like poliomyelitis, initial symptoms of ME included headache, neck pain, low-grade fever and myalgia that were often followed by paresis. Irritability and anxiety, symptoms typical of the encephalitis accompanying bulbar polio (cf. 22), and even a few cases of post-acute Parkinsonism (42) were noted. Patients demonstrated hyper-somnolence and "conspicuous changes in their levels of concentration" that persisted for months after the acute illness. (26) Slowing of the EEG with the emergence of theta activity, similar to that documented in polio survivors, was also noted. (44-46, cf. 23)

Unlike poliomyelitis, there were frequent complaints of numbness or parasthesias, usually no respiratory involvement, infrequent paralysis or muscle atrophy and almost invariably no fatalities. CSF protein was usually normal and poliovirus was never isolated from ME patients. Also unlike poliomyelitis, recovery from the acute symptoms of ME sometimes required months or years. (43) Most patients were left with a marked "exhaustion and fatigability" that were "always made worse by exercise (and) emotional stress." (26) Patients continued to demonstrate fatigue, hyper-somnolence, impaired concentration, reported "an inordinate desire to sleep," anomia, that they were "not as quick or incisive in thought as before, (had) a decreased ability to learn and a decline in their short-term memory" for years after the acute episode. (26)

Despite the differences between poliomyelitis and ME, an association with the poliovirus was suggested by the fact that, of the more than one dozen ME outbreaks before the introduction of the Salk vaccine, nine occurred during or immediately after outbreaks of polio and several involved hospital staff who cared for polio patients. (42,47-53)

Type III Poliovirus and Iceland Disease. A more direct association between the poliovirus and ME was seen following a 1948 epidemic in Akureyri, Iceland. Two patients presented with fever, myalgia and paresis and were at first diagnosed as having poliomyelitis. This diagnosis was quickly discarded as many more patients reported symptoms atypical of polio, including parasthesias, numbness, "nervousness" and "general tiredness" both acutely and for months after the acute episode. Also unlike poliomyelitis, there was a case fatality ratio of zero, versus a minimum of 2.0% for polio in Iceland (54), and poliovirus was never isolated from any of these patients. When patients were reexamined six years after the original outbreak, 72% reported chronic "nervousness and general tiredness" and 21% complained of "loss of memory." (55)

Sigurdsson, et al (54) suggested two alternatives for the cause of this constellation of symptoms that he called "Akureyri Disease" but has been more commonly referred to as "Iceland Disease" (ID): "Either a strain of poliomyelitis virus with unusual pathologic properties and of low virulence was responsible for this epidemic or...some unknown neurotropic virus has been present." Support for an "unusual" poliovirus as the cause came from Sigurdsson himself. (56) There was an "extensive epidemic" of poliomyelitis caused by Type I poliovirus in Iceland during 1955 that coincided with and was followed by outbreaks of ID. Remarkably, two cities in which ID outbreaks were reported in 1955, as well as the area affected by the 1948 "Akureyri Disease" epidemic, were untouched by poliomyelitis. None of the children tested in the two cities newly-affected by ID and only 13% of the children in Akureyri, showed antibodies to Type I poliovirus as opposed to 86% of the children tested in the polio epidemic areas. Further, following poliovirus immunization, children in one of the ID affected cities demonstrated antibody titres to Type II and Type III poliovirus that were four and twenty-five times higher, respectively, than titers in a city where ID had not been reported. The authors concluded that Type I poliovirus was not related to the occurrence of ID but that inhabitants of the ID-affected areas had previously been exposed to an agent immunologically similar to Type III poliovirus.

An interesting coda to these findings is the report that when an American airman who had contracted polio in the 1955 Iceland epidemic returned to Massachusetts, a small outbreak of ID and polio occurred. (57,58) More recent support for a relationship between poliovirus and ME came in 1989 when a "dangerously rising titre" to Type III poliovirus was documented in a patient who did not have polio but who had been diagnosed with ME. (59)

Post-Polio Fatigue and Chronic Fatigue Syndrome. A constellation of symptoms resembling ME was termed "Chronic Fatigue Syndrome" (CFS) following a Nevada outbreak in 1984. (27) Like ME and post-polio fatigue, CFS is characterized by complaints of chronic fatigue and impaired concentration that are triggered or exacerbated by physical exertion and emotional stress. (59) Both CFS patients (59,60) and polio survivors (3) report subjective memory impairment and word finding difficulty, while 85% of patients with CFS demonstrated "an excess of irregular slow wave activity" on EEG (61) similar to that seen following ME and polio. (cf. 23,44-46) And although polio survivors are different from CFS patients, being on average 16 years older and having had more years of schooling, subjective difficulty with concentration is marked in both groups and the incidence of fatigue, physical and psychological symptoms are elevated and significantly higher than in the general population. (2,27)

The recent emergence of CFS has allowed it to be studied using techniques that were unavailable during the polio, ME and ID epidemics and that now allow neuropsychological, neuroanatomic, neuroendocrine and electrophysiological comparisons between this most recent putative PVFS and post-polio fatigue.

Empirical Parallels

Neuropsychological Parallels. Some of the subjective difficulties with attention and cognition in CFS patients and polio survivors have been corroborated by the documentation of clinical abnormalities on neuropsychological testing. CFS patients (62,63) and polio survivors with severe fatigue (25) have been shown to have clinical impairments of attention and information processing speed. In spite of these marked impairments of attention, CFS patients (60) and polio survivors (2,25,64) have been shown to be within the high normal or superior range on measures of higher-level cognitive processes and I.Q., as well as having higher than average levels of professional achievement. Further, despite the high frequency of subjective complaints of memory impairment in CFS patients (65) and in 87% of polio survivors reporting fatigue (25), verbal memory has been shown to be intact on testing in both groups. (25,63,66)

These findings indicate that fatigue is associated with impairments of attention and information processing speed but not of verbal memory or higher-level cognitive processes both in patients with CFS and in polio survivors. Given the histopathologic documentation of frequent and severe poliovirus lesions in the brain's activating system, it was hypothesized that damage to the RAS and BG is responsible for both fatigue and impaired attention in polio survivors.

Neuroanatomic Parallels. To test this hypothesis, magnetic resonance imaging (MRI) of the brain was performed in hope of documenting poliovirus lesions in the RAS and BG. Carefully selected polio survivors who had unequivocal histories of polio and were free from comorbidities that could have caused fatigue or cognitive problems were imaged. (67) Areas of hyper intense signal in gray and white matter were imaged in 55% of subjects who rated their daily fatigue as moderate or higher but were not seen in any of the subjects reporting no or mild daily fatigue. Small discrete areas of HS were imaged in the putamen and rostral reticular formation. Multiple punctate areas of HS were imaged in the periventricular and deep white matter and discrete areas of HS were seen in the centrum semiovale that were as large as 24.0 mm². Subjects with and without HS were equal in terms of age, years of education, age at polio and the severity of acute polio. The presence of HS was significantly correlated with fatigue severity, year of acute polio and years since polio, but not with depressive symptoms, new respiratory problems or difficulty sleeping. The presence of HS was also significantly correlated with the frequency or severity of subjective difficulty with recent memory, thinking clearly, mind wandering, attention and concentration. The daily fatigue severity rating was significantly correlated with the frequency and severity of all of these cognitive symptoms.

These data support the hypothesis that areas of hyperintense signal are associated with late-onset fatigue and subjective problems with attention in polio survivors and may represent poliovirus damage within the brain activating system. Damage to the putamen and caudate nucleus (16,17,18)

and especially the reticular formation (69) has been shown in other populations to cause deficits in attention. The HS imaged in the reticular formation and BG most likely indicate areas of necrosis where neurons were destroyed by the acute poliovirus infection. This conclusion is supported by a recent case of vaccine related poliomyelitis in which HS in the midbrain and medulla on antemortem MRI corresponded with histopathological findings of necrosis in the substantia nigra and reticular formation. (68)

HS imaged along white matter tracts that have been implicated in the centrifugal spread of the poliovirus (70,71) may have resulted from damage to the brain parenchyma by a local, tissue toxic effect of the poliovirus causing enlarged, fluid-filled spaces around arterioles (7), local neuronal atrophy (71; cf. 72) and possibly axonal demyelination. (10,11) Diffuse atrophy and demyelination of axons within corticofugal white matter tracts could conceivably impair transmission, decrease cortical activation and cause attention deficits and other symptoms of fatigue.

This notion is supported by studies that have documented a relationship between HS, impaired attention and fatigue. First, periventricular and deep white (but not gray) matter HS have been imaged in 27% to 100% of CFS patients and have been suggested to represent either enlarged, fluid-filled spaces around arterioles or demyelination. (27,72,73) Second, white matter HS imaged in both demented (74,75) and non-demented (76-78) elderly adults have also been associated with impairments of attention and information processing speed similar to those documented in CFS patients and polio survivors with fatigue. Third, patients with fatigue secondary to multiple sclerosis have been found to have more brain stem and midbrain white matter HS as well as decreased glucose metabolism on PET in cortical premotor and supplementary motor areas and in the putamen (79), findings are similar to abnormalities in the supplementary motor area and putamen in PD patients with fatigue. (40) Taken together, these findings implicate both damage to the RAS and BG, as well as a partial disconnection between the RAS, BG, thalamus and cortex, underlying the symptoms of fatigue.

Neuroendocrine Parallels. The correlation of HS on MRI with the symptoms of post-polio fatigue suggested that the effects of poliovirus on other brain centers might also be evident. The documentation of hypothalamic lesions on autopsy following poliovirus infection suggested that neuroendocrine abnormalities may also be present. Gupta, et al. (80) reported a marked decrease in growth hormone (GH) secretion in polio survivors reporting late-onset muscle weakness. Since poliovirus lesions have been described in the growth hormone releasing hormone- (GHRH) and dopamine-secreting neurons of the arcuate nucleus it is possible that damage to these neurons could result in a GHRH-induced GH "menopause" with aging in polio survivors. (81) In addition, lesions in the paraventricular nucleus (PVN) were frequently documented following poliovirus infection (70) and could impair the PVN's ability to secrete corticotrophin-releasing hormone (CRH) (82) and thereby decrease ACTH release (see 83).

To examine the relationship between hypothalamic-pituitary-adrenal (HPA) axis activity and the symptoms of post-polio fatigue, polio survivors who underwent neuropsychological testing (25) had their plasma concentrations of ACTH measured using radioimmunoassay following a mild stressor (an overnight fast) which is known to stimulate the HPA axis. (84) Mean plasma ACTH was elevated and outside of the normal range in the mild fatigue subjects (26.7 ± 3.2 ng/ml) as it should be following a fast. In contrast, there was no ACTH elevation in subjects reporting severe daily fatigue (14.3 ± 0.6 ng/ml). These findings suggested that the HPA axis had been activated by the fasting stressor in the mild fatigue subjects but not in those with severe daily fatigue who subsequently were found to have clinical impairments of attention and information processing speed on neuropsychologic testing. (25)

These pilot data lead to the measurement of plasma ACTH in polio survivors following an overnight fast. (85) Patients with conditions that could have altered HPA axis activity were excluded. Again, mean plasma ACTH was significantly elevated and outside of the normal range in subjects reporting mild daily fatigue (28.5 ± 17.7 ng/ml) but not in those reporting moderate or greater fatigue (19.7 ± 10.7 ng/ml) ($t=2.02$; $p<0.05$). Further, plasma ACTH was significantly negatively correlated with

the daily fatigue severity rating, the frequency of problems with recent memory, word finding and muscle weakness and the severity of problems with recent memory and staying awake during the day, but notably not with the Beck Depression Inventory score.

These data suggest that the HPA axis response to a fasting stressor is blunted in polio survivors reporting fatigue. This finding, coupled with histopathologic evidence of poliovirus lesions in the PVN, suggested that the hyposecretion of ACTH may be secondary to decreased production of the hypothalamic secretalogs CRH and vasopressin whose cell bodies are located in the PVN (82) Further, the significant negative correlations between ACTH level and fatigue severity, cognitive problems and difficulty staying awake suggest that a diminution in HPA hormones may contribute to the symptoms of post-polio fatigue.

An existing literature demonstrates that reduced levels of CRH and ACTH are associated with fatigue and impaired attention, since both peptides exert "stimulatory effects on biochemical and electrophysiological parameters of the brain" (83,86) In man, administration of ACTH fragments lacking adrenal stimulating activity were associated with improved memory and alertness, "EEG arousal response patterns," increased sustained attention that was "resistant to attentional fatigue" (87) and a "statistically significant fall in fatigue" (88) These results were attributed to the direct activation of ACTH receptors on neurons in the hypothalamus, midbrain (89) and "the brain stem, particularly the non-specific reticular-thalamic system" (89,90) Thus, post-polio fatigue may be attributable to poliovirus lesions not only in the RAS and BG but also in the PVN which reduce the secretion of peptides that stimulate the cortex. Decreased HPA activity has already been documented in patients with CFS and the reduced secretion of "activating" peptides such as CRH and ACTH has been implicated in its pathophysiology. (91,92)

THE BRAIN FATIGUE GENERATOR MODEL OF PVFS

Taken together, the clinical, historical and empirical findings presented above suggested the "Brain Fatigue Generator" (BFG) model of post-polio fatigue and PVFS. The BFG model postulates that viral damage to the reticular formation, lenticular, hypothalamic and thalamic nuclei, cortical motor areas -- and especially dopaminergic neurons in the substantia nigra and arcuate nucleus -- decreases cortical activation, not only impairing attention and slowing information processing speed, but also inhibiting motor activity and generating the disabling "visceral" feelings of fatigue: exhaustion, passivity and an aversion to effort. (93) (The operation and survival value of a hard-wired, autonomous and "normal" Brain Fatigue Generator that inhibits motor activity when cortical activation, attention and information processing speed are impaired is described fully in 93.)

Recent studies have lent support to the BFG model as an explanation for PVFS. Two studies using SPECT have documented that decreased brain stem metabolism, and by inference decreased activity of RAS neurons, was the only physiological finding differentiating subjects with CFS from healthy controls and subjects with depression or neurological disease. (94,95) Other studies have provided additional support for the BFG model as an explanation for post-polio fatigue well as suggesting that reduced dopamine secretion may play an important role in the generation of fatigue symptoms.

Fainting and Fatigue. Reports of neurally mediated hypotension (NMH) and symptomatic orthostatic tachycardia syndrome (SOTS) in CFS patients suggest that there may be an association between fainting and chronic fatigue. (96-98) The BFG model predicts such an association, not just in CFS patients but especially in polio survivors. The brain stem area most frequently and severely lesioned by the poliovirus and other viral encephalitides, the reticular formation (RF), is not only responsible for cortical activation, waking and focusing attention, but also contains the cardio-depressor center whose outflow slows the heart via stimulation of the vagus nerve. (99,100) Near the RF in the brain stem lie other cardiovascular control centers, all of which were also damaged by the poliovirus: the dorsal vagal nucleus, responsible for slowing the heart and activating the gut, and the nucleus ambiguus and solitary tract nuclei that regulate blood pressure. Acutely, patients with "bulbar polio," in which damage to brain stem neurons was most severe, demonstrated not only respiratory

impairment, rousable stupor, somnolence and even coma, but also cardiovascular abnormalities. Cardio depressor center abnormalities were the more frequent symptoms, with 73% demonstrating hypertension and tachycardia that led to cardiovascular collapse and death in 6%. (22, 101)

To test the hypothesis that fatigue is associated with fainting, the 1995 International Post-Polio Survey asked 1,047 polio survivors and 419 non-disabled control subjects about the frequency and cause of faints during their lifetimes and to rate their current typical daily fatigue severity. (99) Fatigue severity was not only significantly higher in polio survivors as compared to controls, but also in polio survivors and controls who had fainted even once, as compared to those who had never fainted. Daily fatigue severity also increased in both groups as the number of lifetime faints increased. Fatigue was significantly higher in controls who fainted one time and three times as compared to controls who had never fainted. Daily fatigue severity was significantly higher in polio survivors who had fainted three, four and five times as compared to those who had never fainted. These findings suggest a physiological relationship between fatigue and fainting, possibly attributable to the close proximity of cardiovascular regulation and brain activation centers within the brain stem. Fatigue and hypotension in patients with CFS and in polio survivors with late-onset fatigue may be a symptom of damage to RAS neurons and not a primary cause of fatigue.

Hypothalamic abnormalities in polio survivors and CFS patients may also contribute to a relationship between fatigue and fainting. CRH release may be impaired secondary to PVN damage in polio survivors and CFS patients. (85, 92) Since the PVN also produces vasopressin, the secretion of which is also impaired in CFS (102), PVN damage in polio survivors and CFS patients may reduce both brain activating and blood pressure regulating hormones, thereby reinforcing RAS and BFG abnormalities and predisposing these patients to both fatigue and fainting.

EEG Slowing, Prolactin and Fatigue. The postmortem documentation of RAS and dopaminergic neuron lesions in polio survivors, SPECT findings of decreased brain stem neuron activation in CFS, and impaired attention in post-polio fatigue and CFS all suggest that decreased cortical activation and a dopamine deficiency should underlie the symptoms of chronic fatigue. If there is a dopamine deficiency in polio survivors it should be physiologically evidenced by elevated levels of prolactin, since dopaminergic neurons in the arcuate nucleus were damaged by the poliovirus and arcuate dopamine secretion inhibits prolactin release via dopamine 2 (D2) receptor stimulation. (103) Therefore, elevated prolactin should be associated with impaired cortical activation as evidenced by slowing of the electroencephalogram (EEG). Even in healthy subjects, EEG slowing is indicative of impaired cortical activation and has been associated with decreased arousal, "drowsiness" and impaired performance on neuropsychological tests of attention. (104-105) As many as 85% of CFS patients have been shown to have "an excess of irregular slow wave activity" on EEG (44-46,61) similar to the theta and delta activity seen in patients with acute paralytic and non-paralytic polio. (23)

To test the hypothesis that fatigue, plasma prolactin and EEG slowing are associated with post-polio fatigue, polio survivors without medical or psychologic comorbidities were studied. (106) Subjects were administered the Post-Polio Fatigue Questionnaire (PFQ), which asked about cognitive symptoms of fatigue, and had resting measurements of plasma prolactin and power across the EEG frequency spectrum using bilateral temporal-occipital electrode placements. Plasma prolactin levels were within the normal range and 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 ($r=.37$; $p \text{ value} < .05$), and prolactin was significantly correlated ($r=.39$; $p \text{ value} < .05$) with daily fatigue severity.

These data suggest that EEG slowing is related to the severity of post-polio fatigue symptoms, findings similar to those in patients with acute polio and CFS. An important role is also suggested for a dopamine deficiency, implied by the correlation of EEG power and fatigue symptoms with prolactin. A more recent study further supported the putative relationship between decreased dopamine secretion, impaired attention and symptoms of post-polio fatigue. An objective measure of word finding difficulty (animal naming) was significantly correlated not only with subjective word finding difficulty on the PFQ ($r=-.41$; $p \text{ value} < .05$) but also with plasma prolactin ($r=-.36$; $p \text{ value} < .05$) and

scores on four neuropsychological tests of attention. (107) Notably, the animal naming score in polio survivors with fatigue was nearly identical to that measured in patients with CFS. (108)

Bromocriptine and Fatigue. To test the hypothesis that treating the putative dopamine deficiency will decrease the symptoms of post-polio fatigue, a double blind, placebo controlled pilot study of bromocriptine mesylate, a direct acting, post synaptic D2 receptor agonist, was performed in polio survivors disabled by severe, chronic fatigue. (109) Patients were placed on placebo for 28 days and then on an increasing dose of bromocriptine (from 1.25 to 12.5 mg/day) for 28 days. Days on bromocriptine, but not days on placebo, were significantly negatively correlated with subjective difficulty with fatigue on awakening, attention, cognition, word finding, memory and staying awake during the day. 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 MRI, a blunted ACTH response to an overnight fast and a baseline plasma prolactin level nearly double that of the drug non-responders.

That reduced dopamine secretion contributes to the symptoms of chronic fatigue is supported by a placebo-controlled study of healthy subjects who were administered remoxipride, a potent and selective D2 receptor antagonist. (110) The most frequently reported effects of D2 receptor blockade were "moderate fatigue," "mild somnolence" and "difficulty concentrating." Statistically significant, dose-related increases in subjective "drowsiness" and impairment on neuropsychological tests of auditory vigilance, continuous attention and critical flicker fusion were also found following D2 receptor blockade.

CONCLUSION

These data suggest that the polioviruses may be the prototypes for chronic fatigue-producing agents, since they routinely and often preferentially damage neurons responsible for brain activation within the BFG. Post-polio fatigue may provide a complete model for a post-viral fatigue syndrome, since the causative agent is known, the damage done by the agent to the brain has been demonstrated histopathologically and the signs of that damage -- neuroanatomic, neuropsychologic, neuroendocrinologic and electroencephalographic -- have been documented and correlated with the symptoms of fatigue.

However, polioviruses are not the only agents for which the brain's activating system is the "favorite location." Lesions in the reticular formation, putamen, thalamus, hypothalamus and white matter have been associated with a variety of viral encephalitides whose symptoms include markedly impaired cortical activation and fatigue (e.g., Australian X, Coxsackie B1-6, Equine, Enterovirus 71, Japanese B and St. Louis infections) (26-28,111-114) Some viral encephalitides are histopathologically and clinically similar to, or actually indistinguishable from, poliovirus infection (e.g., Central European Encephalomyelitis and Coxsackie A9, Coxsackie B1-6, ECHO, Enteroviruses 70 and 71 infections), the Coxsackie A7 virus producing a paralytic syndrome so similar to that caused by the polioviruses it has been named "Poliovirus IV." (26-28,111-117)

So, while post-polio fatigue may present a "neat and complete" pathophysiological model for PVFS, clinicians and researchers must remember that the polioviruses are neither alone nor unique in their ability to damage the spinal cord and brain, impair the RAS and BG, disrupt the BFG and generate chronic fatigue symptoms. Given the ubiquity of viruses that can impair brain activation the existence of PVFS should be expected. Yet, clinicians and researchers often refuse to "believe" that there could be a syndrome with a physiological basis that has fatigue as its principal symptom. Those of us in the disparate disciplines who are studying PVFS should focus less on who is "right" about the etiology of chronic fatigue and focus both ourselves and front line clinicians on what may be "wrong" in the brain, and how brain abnormalities causing fatigue symptoms may be able to be treated.

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