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THE CAUSE AND TREATMENT OF POST-POLIO FATIGUE. Richard L. Bruno, Nancy M. Frick, Susan J. Creange, Todd Lewis, and Terry Molzen.

Fatigue is the most commonly reported, most debilitating and least studied Post-Polio Sequelae (PPS) affecting the nearly 2 million North American polio survivors. Among polio survivors, 91% 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 increased by physical overexertion in 92% and by emotional stress in 61%. Importantly, polio survivors distinguish between the physical tiredness and decreased endurance they associate with new muscles weakness, and a "brain fatigue" that is characterized by problems with attention and thinking. Between 70% and 96% of polio survivors reporting fatigue complained of problems with concentration, memory, attention, word-finding, maintaining wakefulness and thinking clearly, with 77% percent reporting moderate to severe difficulty with these functions (3).

Problems with attention, memory and thinking suggest that the symptoms of post-polio fatigue cannot be explained merely by the poliovirus damaging anterior horn motor neurons (4). Autopsies performed fifty years ago on people who died after having had polio, whether they had paralysis or not, showed that the poliovirus almost always damaged specific areas in the brain (Figure 1). These damaged areas include the brain's activating system that keeps you awake and allows you to focus your attention. The poliovirus also damaged neurons that produce neurotransmitters, including the enkephalins and endorphins (called the "body's own morphine") as well as dopamine and ACTH which activate the brain.

With poliovirus damaging the brain's activating system, you would expect that the original polio infection should cause brain activating problems. And, reports written during the polio epidemics did describe "drowsiness," lethargy, prolonged sleeping and even coma during the acute polio infection (7,12,21,22). One-third of patients with acute spinal, spinal and bulbar and even non-paralytic polio showed "disorientation, apathy, pronounced sleep disorder (and) irritability" (4). These mental changes were associated with the abnormal slowing of brain wave activity on the electroencephalogram (EEG). Further, a high percentage of children clinically recovered from poliomyelitis insofar as motor disability is concerned, had qualitative difficulties in mental functioning such as "fatiguability and fleeting attention" for months after the acute polio (5).

These reports of persistent drowsiness, fatigue and fleeting attention following the acute poliovirus infection are similar to polio survivors' recent complaints of late-onset fatigue and impaired attention (25). And, both acute and late-onset post-polio fatigue are reminiscent of nearly two dozen outbreaks during this century of post-viral fatigue syndromes (PFS) that are related clinically, historically or anatomically to poliovirus infections (26-28). These relationships and recent studies comparing post-polio fatigue and chronic fatigue syndrome will be described in an attempt to understand the cause and treatment of post-polio fatigue.

CAN THE POLIOVIRUS CAUSE FATIGUE?

Type II Poliovirus and Decreased Brain Activation. During the polio epidemics of the 1950s, there were several small outbreaks of patients having drowsiness, prolonged sleeping, slowing of brain waves, as well as some of the symptoms of both bulbar polio and Parkinson's disease (e.g., tremor and rigidity) (29-30). In 1952, Type II poliovirus was isolated from one group of patients having these symptoms and it was found that the neurons in their brain activating system had been damaged.

The association of decreased brain activation and Parkinson's disease symptoms remind Dr. Oliver Sacks of the "sleeping sickness" patients with Parkinson's disease he described in his book *Awakenings*. The relationship between

"sleeping sickness," Parkinson's disease and polio may be important for understanding post-polio fatigue, since all of these conditions are associated with damage to a part of the brain activating system called the basal ganglia. For example, Parkinson's disease (PD) patients have severe damage to one of the basal ganglia, the substantia nigra (sub-STAN-sha NYE-gra), which produces the neurotransmitter dopamine (doe-PAH-mean). PD patients often describe fatigue. "Excessive fatigue" was reported by 48% of PD patients in one study (40) while nearly one-third of PD patients reported that fatigue was their "most disabling symptom" (39). As a matter of fact, one of the first descriptions of Parkinson's disease (41) could serve as a definition of post-polio fatigue, 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" (38).

Figure 1. Brain areas lesioned by the polio virus as seen in 158 human autopsies. Severe lesions: Reticular formation (RF); vestibular nuclei (V); cerebellar roof nuclei (R); periaquiductal gray (PG). Moderate lesions: Paraventricular hypothalamic nucleus (PV); posterior hypothalamic nuclei (P); substantia nigra (SN). Mild lesions: Globus pallidus and putamen (GP); locus ceruleus (LC); median raphe nuclei (MR); preoptic hypothalamic nuclei (PO); thalamic nuclei (T).

"Atypical Poliomyelitis" and Chronic Fatigue. Beginning in Los Angeles in 1934 and continuing for more than twenty years, there were over a dozen outbreaks of a disease that was at first thought to be poliomyelitis, was then called "abortive" or "atypical" poliomyelitis and finally named "Myalgic Encephalomyelitis" (ME) (6). Like poliomyelitis, initial symptoms of ME included headache, neck pain, low-grade fever and muscle pain that were often followed by muscle weakness. Patients were excessively sleepy and had "conspicuous changes in their levels of concentration" that lasted for months after the initial illness. Slowing of the EEG similar to that seen in acute polio was also noted.

Unlike poliomyelitis, there were frequent complaints of numbness or tingling, usually no breathing problems, paralysis or muscle wasting and almost invariably no deaths. Also unlike poliomyelitis, recovery from the initial symptoms of ME sometimes required months with most patients being left with a marked "exhaustion and fatiguability" that were "always made worse by exercise (and) emotional stress." Patients continued to have fatigue, excessive sleepiness, trouble concentrating, difficulty with word finding, memory and thinking for years after the acute episode.

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 (7).

Type III Poliovirus and Chronic Fatigue in Iceland. A more direct association between the poliovirus and ME was seen in 1948 in Akureyri, Iceland. Patients there presented with fever, muscle pain and weakness and were at first diagnosed as having poliomyelitis. After about a month, this diagnosis was discarded as patients reported additional symptoms not typical of polio, including tingling, numbness, "nervousness" and "general tiredness." Also unlike poliomyelitis, no deaths were reported and poliovirus was never isolated from any of these patients. When patients were reexamined six years after their original illness, 72% still had chronic "nervousness and general tiredness" and 21% reported a of "loss of memory."

It was suggested that either an "unusual" and mild poliovirus or some unknown virus caused these symptoms that were called "Akureyri Disease" but are more commonly referred to as "Iceland Disease" (ID). Support for an "unusual" poliovirus as the cause came in 1955 (10). There was an extensive epidemic of poliomyelitis in Iceland caused by Type I poliovirus 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 ID-affected cities and only 13% of the children in Akureyri had 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 than titres in a city where ID had not been reported. It was concluded that Type I poliovirus was not the cause of ID, but the citizens of the ID-affected areas had previously been exposed to something that was 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 (11). 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 had been diagnosed with ME (12).

Post-Polio Fatigue and Chronic Fatigue Syndrome. A group of symptoms resembling ME was termed "Chronic Fatigue Syndrome" (CFS) following a Nevada outbreak in 1984 (13). Like ME and post-polio fatigue, CFS is characterized by complaints of chronic fatigue and trouble with concentration, memory and word finding that are triggered or exacerbated by physical exertion and emotional stress. And, although polio survivors are on average at least ten years older than patients with CFS, the years of education, sex distribution, frequency of difficulty with concentration

and psychological symptoms are nearly identical in the two groups (Table 1)(17,18,19). However, unlike ME and PPS, CFS patients report recurring sore throat, swollen glands and fever, suggesting to some that CFS is caused by a recurring or chronic viral infection. It is important to keep in mind that there is no evidence that PPS is caused by a persistent infection by any virus, including poliovirus (14,15).

The recent occurrence of CFS has allowed it to be studied using techniques that were not available during the polio, ME and ID epidemics and now allow neuropsychologic, neuroanatomic and neuroendocrine comparisons between this newest PFS and post-polio fatigue.

COMPARISONS OF POST-POLIO FATIGUE AND CFS

Neuropsychologic Studies. Some of the subjective difficulties with attention and cognition in CFS patients and polio survivors have been confirmed with neuropsychologic testing. CFS patients and polio survivors with severe fatigue have been shown to have clinical impairments of attention and information processing speed (Table 1)(16,19). Polio survivors reporting severe fatigue required 23% to 67% more time to complete tasks requiring sustained attention and vigilance than did polio survivors with no or mild fatigue. In spite of these marked impairments of attention, CFS patients and polio survivors have been shown to have I.Q.s within the high normal or superior range and have higher than average levels of educational and professional

achievement (Table 1)(17). Further, despite the high frequency of subjective complaints of memory impairment in CFS patients and in 87% of polio survivors reporting fatigue, verbal memory has been shown to be intact on testing in both groups (16,19,20). However, polio survivors have twice been shown to have trouble recalling visual information whether or not they report fatigue (7,16).

These findings indicate that fatigue in CFS patients and polio survivors is associated with impairment of attention and information processing speed but not of memory or thinking ability. Given the findings of frequent and severe poliovirus lesions in the brain's activating system, it was hypothesized that damage to the brain's activating system is responsible for both fatigue and impaired attention in polio survivors.

Brain Scan Studies. To test this hypothesis, magnetic resonance imaging (MRI) of the brain was performed to look for evidence of poliovirus lesions in the brain's activating system. In a first study, small areas of hyperintense signal (which look like white spots) on MRI were seen in the brain's activating system and in the myelinated (insulated) neurons that connect the brain stem (at the bottom of the brain) to the cortex (the "supercomputer" at the very top of the brain) in eleven of twelve polio survivors (1). In a second study, white spots were seen in 55% of polio survivors with fatigue but were not seen in any of the subjects without fatigue (Figure 2)(21).

The presence of the white spots were not only related to increased fatigue severity, but also to problems with memory, thinking clearly, mind wandering, attention and concentration.

Finding white spots on MRI supports the theory that fatigue and problems with attention in polio survivors may be related to damage the poliovirus did to the brain activating system. This conclusions is supported by a number of other studies that have shown a relationship between white spots on MRI, fatigue and problems with attention. Notably, white spots have been seen in between 40% and 100% of CFS patients (13) and even in healthy elderly adults who have problems with attention similar to those seen in CFS patients and polio survivors (22).

Figure 2. A 24 mm² focus of hyperintense signal (arrow) in the centrum semiovale in a 50 year old female polio survivor reporting moderate daily fatigue and frequent problems with concentration, thinking clearly, short term memory and staying awake (putamen lesion not seen in this view).

Hormonal Studies. The association of white spots in the brain activating system with the symptoms of post-polio fatigue suggested that the effects of poliovirus on other brain areas might also be evident in polio survivors. For example, poliovirus lesions were often seen on autopsy in the hypothalamus (hypo-THAL-ah-mus), the brain area that automatically controls the body's internal environment and its response to stress.

To test the functioning of the hypothalamus, we measured polio survivors' blood concentrations of ACTH (a-DRE-no-cor-ti-co-TRO-pick hormone), one of the body's stress hormones whose release is triggered by the hypothalamus. ACTH was measured following an overnight fast, which is a mild stress known to cause the release of ACTH (7). ACTH was increased outside of the normal range (as it should be following stress) in polio survivors who reported mild fatigue. However, there was no ACTH increase in subjects reporting severe daily fatigue. Further, the higher the ACTH level, the lower the subjects' reported fatigue and the less the difficulty with memory, word finding, muscle weakness and staying awake during the day.

These findings indicate that the hypothalamus had not been activated in the subjects with post-polio fatigue and that ACTH production is reduced in these individuals. This conclusion is interesting for two reasons. First, ACTH has been found in humans to promote alertness, increase attention and decrease fatigue by directly stimulating the brain activating system. Thus, a decrease in ACTH production may prevent brain activation and contribute to the symptoms of post-polio fatigue. Decreased activation of the hypothalamus has already been found in patients with CFS and a decrease in ACTH stimulation of the brain has been suggested as a cause of CFS (23).

Second, a decrease in ACTH production may be caused by a

decrease in production of its parent molecule, POMC. POMC also produces beta-endorphin (BAY-ta en-DOOR-fin) which along with the enkephalins (en-KEF-ah-lins) are "the body's own morphine." Since poliovirus also damaged the brain area that produces enkephalins, both beta-endorphin and enkephalin production may be reduced in polio survivors. A reduction in the body's own morphine would help to explain why polio survivors have a nearly doubled sensitivity to pain (1).

A MODEL FOR POST-POLIO AND CHRONIC FATIGUE

Taken together, these findings suggest a model for the cause of post-polio fatigue:

- * Poliovirus damaged the brain activating system;**
- * MRI and hormonal findings suggest that damage to the brain activating system is present today in polio survivors;**
- * Neuropsychological testing shows impaired attention in patients with post- polio fatigue;**
- * Therefore, poliovirus damage to the brain's activating system may cause decreased brain activation, impair attention and generate the symptoms of post-polio fatigue.**

While poliovirus damage to the brain activating system would be expected to cause the sleepiness, inattention and fatigue reported during the original polio infection, it is the

recurrence of these symptoms, or their appearance decades after the acute infection, that are more difficult to explain. The emergence of fatigue decades after the acute polio may result from normal age-related changes in and loss of brain activating system neurons that had survived the acute polio infection, combined with an already decreased number of neurons as a result of the original poliovirus infection. Eventually, the loss of brain activating system neurons would decrease cortical activation, reduce attention and produce the symptoms of fatigue as polio survivors reach mid-life (1). The occurrence of these symptoms during physical or emotional stress in polio survivors may reflect the ability of stressors to uncover otherwise unseen damage in the brain activating system.

IS FATIGUE "HARD WIRED" INTO THE BRAIN?

The findings presented above describe an intimate relationship between impaired attention and fatigue. However, difficulty with attention is not fatigue's only symptom. Even more disabling is the physical experience of fatigue: feelings of exhaustion, "passivity and an aversion to continued effort" that generate an aversion to both mental and physical activity. However unpleasant these feelings are in man, passivity and aversion to activity have clear survival value, especially in organisms without conscious awareness that their attention and thinking speed are impaired. For example, an animal that continues to explore its environment even though its attention is impaired would be less able to

direct attention on the goal of its exploration (e.g., searching for food) and would thereby waste already diminishing energy stores. More importantly, impaired attention could also render the animal unaware of dangers in its environment (e.g., a predator stalking the animal in search of its food). Thus, there would be survival value in a brain mechanism that monitors cortical activation, biases an animal toward stopping motor behavior and promotes rest when attention and thinking speed are impaired.

The Brain "Listens" to Itself. Groups of neurons near the bottom of brain called the basal ganglia are in an ideal location to monitor the level of brain activation and stop an animal when it has too little attention to allow efficient and safe activity in its environment. All parts of the cortex connect to one of the basal ganglia, called the putamen (pew-TAY-men), which "listens" to the activity level of the brain (24). If the brain is awake enough, the putamen allows us to focus attention, to move and to act. When the brain activating system turns down, the putamen stops the cortex from allowing us to move. Damage to the putamen in animals has been shown to slow movement, while damage to another of the basal ganglia, the substantia nigra, decreases or even stops movement and prevents us from focusing attention (7).

The importance of the basal ganglia - and especially the neurotransmitter dopamine - in focusing attention and allowing us to move is most evident in patients with

Parkinson's disease (PD). PD patients, whose damaged substantia nigra neurons produce too little dopamine, show not only slowed movement and an inability to focus attention but also excessive and disabling fatigue (7, 38-41). And, remember Oliver Sacks' Awakenings patients whose damaged basal ganglia caused both Parkinson's disease and "sleeping sickness."

The Brain Fatigue Generator. It appears that the basal ganglia could produce the mental and physical symptoms of both normal and pathological fatigue. In normal fatigue, a long and hard day of work would slow the firing of brain activating system neurons. This decreased activity would impair attention and information processing ability (recognized by humans as symptoms of fatigue) and produce a decrease in cortical activation that would slow the firing of putamen neurons, prevent the release learned motor behaviors and slow or stop activity (Figure 3). Humans would notice problems with focusing attention, feel an aversion to activity and would be able to move only with significant conscious effort. Animals would slow or even stop their activity. In both man and animals, rest or sleep would increase the firing of brain activating system neurons, restore cortical activation, increase the firing of putamen neurons and once again allow the release of motor behavior.

Figure 3. A model for the brain fatigue generator. Fatigue would be produced by a reduction in reticular activating system (RAS) activity that would directly decrease cortical

activation, impair attention and cognition and prevent the firing of putamen neurons (dark lines). The reduction in putamen activity would then inhibit the release of motor behavior, further decrease attention and produce the visceral feelings of "exhaustion" and aversion to effort that accompany fatigue (stippled lines).

Pathological states such as chronic fatigue syndromes could be produced by viral damage to the brain activating system, putamen and/or dopamine-producing neurons. This damage would chronically reduce the firing of brain activating system and putamen neurons, decrease cortical activation and produce the symptoms of fatigue. Poliovirus would be expected to cause fatigue, impaired cortical activation and decreased attention since it damages all of these brain areas.

CLINICAL IMPLICATIONS

This description of the basal ganglia as the brain fatigue generator suggests that increasing brain levels of dopamine (the neurotransmitter that stimulates the basal ganglia) might "turn on" the brain activating system, increase cortical activation and attention, release motor behaviors and reduce the symptoms of chronic fatigue. We are currently studying the use of a drug that stimulates dopamine receptors on brain neurons to treat post-polio patients whose fatigue has not responded to the current treatments of choice, i.e., adequate rest, energy conservation, the pacing of activities and reducing physical and emotional stress (2,17,27,28). Preliminary results show that fatigue,

impaired attention and difficulty staying awake during the day decrease as the dose of the drug increases.

However, there is the very real danger that taking a drug that reduces fatigue will allow polio survivors to resume their hyperactive, Type A lifestyles (as they do now when they feel better following physical, occupational and psychological therapy for PPS) and further stress poliovirus-damaged, "metabolically vulnerable" neurons in the brain and spinal cord. Decreasing "overuse abuse" will always be necessary to treat PPS, regardless of whether a drug is found that decreases the symptoms of fatigue.

It is also possible that damage to the basal ganglia and a lack of dopamine may be related to other PPS symptoms. Word finding difficulties, reported by 82% of polio survivors with fatigue, appear similar both to word finding problems reported by CFS patients and the "tip-of-the-tongue" phenomena seen in PD patients (Table 1)(1,7). And, in a study we have just completed, polio survivors with severe fatigue had low scores on a test of word finding ability - scores that were identical to those in Parkinson's patients.

In addition, 63% of polio survivors report Generalized Random Myoclonus (GRM), the slow contraction or rapid twitching of hand, arm, trunk and leg muscles at night that disturb sleep in 33% of polio survivors (2). GRM may provide more evidence that polio survivors have a brain dopamine shortage, since GRM are similar to "periodic

movements in sleep'' seen in PD patients.

We continue to examine the possible role of the basal ganglia and dopamine in PPS to help identify the cause and treatment of not only post-polio fatigue, but also other PPS, CFS and to understand the neurophysiology of fatigue itself.

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