The Neuroanatomy of Post-Polio Fatigue

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ABSTRACT

Fatigue is the most commonly reported, most debilitating and most poorly understood Post-Polio Sequelae (PPS). Postmortem studies of fifty years ago documented frequent and severe poliovirus-induced lesions within the reticular activating system (RAS). Recently, neuropsychological testing has documented marked attention deficits in polio survivors reporting severe fatigue. However, neither of these findings has been related to the pathophysiology of post-polio fatigue. Magnetic resonance imaging of the brain was performed in 22 polio survivors carefully screened to eliminate the effect of comorbidities. Subjects rated the severity of their daily fatigue and subjective problems with attention, cognition and memory. Small discrete or multiple punctate areas of hyperintense signal (HS) in the reticular formation, putamen, medial lemniscus or white matter tracts were imaged in 55% of the subjects reporting high fatigue and in none those reporting low fatigue. The presence of HS significantly correlated with fatigue severity and subjective problems in attention, concentration, staying awake, recent memory and thinking clearly. The lack of significant correlations between HS or fatigue severity and age, severity of the acute polio, depressive symptoms or difficulty sleeping militates against these factors as either causing HS or producing fatigue. These preliminary findings suggest that poliovirus-induced lesions in the RAS may underlie the subjective fatigue and attention deficits associated with PPS fatigue.

INTRODUCTION

Fatigue is the most commonly reported, most debilitating and most poorly understood Post-Polio Sequelae (PPS) affecting the more than 1.63 million American polio survivors (1). In the 1985 National Survey of 676 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, that they associate with new muscles weakness and decreased physical endurance, and brain fatigue that is characterized by problems with attention and cognition. In the 1990 National Survey of 373 polio survivors, between 70% and 96% of respondents reported that fatigue was accompanied by problems with concentration, memory, attention, word-finding, maintaining wakefulness and thinking clearly, with 77% reporting moderate to severe difficulty with these functions (3). These problems with attention and cognition suggest that the symptoms of post-polio fatigue cannot be explained merely by poliovirus induced damage to anterior horn motor neurons (4). Postmortem histopathology from the 1940s demonstrated the consistent presence of poliovirus lesions in specific brain areas. Brainstem centers were found to be involved in even mild cases of polio (5), with Guizetti (6) stating in 1933 that “only one area is always severely altered (by the poliovirus): the so-called substantia reticularis, i.e. the midbrain reticular formation.” This conclusion was supported by others (7,8,9,10) who found the reticular formation to be heavily peppered throughout with lesions that were very common and often severe (7), with Luhan stating that it was the brain area most uniformly involved (11) following poliovirus infection.

In addition to the reticular formation, neurosecretory neurons were damaged or destroyed by the poliovirus, including the periaqueductal gray (5,8), locus ceruleus (11), median raphe nuclei (10) and substantia nigra (5,9,10,11). Hypothalamic lesions were also documented in both the

paraventricular nucleus and preoptic area, with the posterior region thought to be the most severely damaged (11). Lesions were also noted in lateral, median and midline thalamic nuclei as well as in the putamen, caudate and septal nuclei (12) Cortical lesions, while frequent and severe, were limited only to the motor and pre-motor areas (7,12).

These findings indicate that the poliovirus consistently and often severely damaged brain areas responsible for cortical activation and attention - the reticular formation (13, 14), posterior hypothalamus (15) and thalamus (16), as well as the putamen, caudate (16, 17, 18), locus ceruleus and substantia nigra (17,19,20,21) - which comprise the Reticular Activating System (RAS). Clinical reports written during the polio epidemics seem to corroborate the pathological evidence of poliovirus damage to the RAS since drowsiness and even coma were described as sequelae of the *acute* poliovirus infection (7,12,22). Even months after the acute episode, Meyer (23) noted 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 and fleeting attention."

Poliovirus-induced damage to the RAS impairing cortical activation has also been hypothesized as a cause of late-onset fatigue and subjective problems with attention in polio survivors (3). This hypothesis has received some empirical support. Clinically significant deficits on neuropsychological tests measuring attention, concentration and information processing speed were documented only in polio survivors reporting severe fatigue and not in subjects reporting mild fatigue (24). Importantly, no impairment of higher-order cognitive ability or verbal memory was seen in any of the post-polio subjects.

In additional, small discrete and multiple punctate areas of hyper intense signal (HS) were imaged in the thalamus, caudate nucleus, centrum semiovale, deep and periventricular white matter in eleven of twelve polio survivors who underwent magnetic resonance imaging of the brain (3). These areas of HS were interpreted as evidence of damage to the RAS and its associated corticofugal white matter tracts caused by the original poliovirus infection. However, no attempt was made to correlate HS with reports of fatigue severity nor were variables controlled for that have been associated with HS, e.g. advanced age, hypertension and depression (25,26).

The purpose of this study was to test the hypothesis that areas of hyperintense signal on MRI of the brain are associated with late-onset fatigue and subjective problems with attention in polio survivors.

METHODS

Subjects. Volunteer subjects were recruited through the media, post-polio support groups and by direct mail over two years. One-hundred forty six (146) polio survivors requested and returned survey forms on which they were asked to rate their usual daily level of fatigue on a six point scale from "none" to "severe" and to list their complete medical history, including a description of the effects of the original poliovirus infection.

One-hundred (108) volunteers were excluded as a result of comorbidities that could have caused HS, fatigue or cognitive problems, e.g., a major depressive episode, hypertension, anemia, lupus, diabetes, traumatic brain injury, or thyroid, respiratory, cerebrovascular or cardiac disease. Volunteers were also excluded if they were above 65 years of age or were taking sedating medications for sleep, including antidepressants or benzodiazepines. Of the 38 remaining volunteers, 22 agreed to have an MRI of the brain. All had unequivocal histories of polio and none had received treatment for post-polio fatigue.

Procedure. Subjects completed the Post-Polio Fatigue Questionnaire (3) that requested subjective ratings of their usual daily level of fatigue and the frequency and severity of problems with attention,

concentration, staying awake during the day, thinking clearly, sleeping and muscle weakness on a six-point scale from “none” through “severe”. They also completed the brief Type A questionnaire (27) since Type A behavior has been associated with fatigue and cognitive problems in polio survivors (2,3).

After giving written informed consent, an MRI of the brain was performed on a Diasonics MT/S system operating at 0.35 Tesla. A quadrature head coil was employed with spin echo technique. Imaging consisted of sagital and coronal T1 sections with TR=500-600 msec and TE=25/30 msec. Ten millimeter slices were obtained with a 256 x 256 matrix and 0.95 x 0.95 mm resolution. T2 images were performed in the transaxial and coronal planes with a TR=3,000 msec and TE=30 and 80 msec. Five millimeter T2 sections were obtained with a 256 x 256 matrix and 1.0 mm x 1.0 mm resolution. MRI films were read by one of us (JMC) who was blind to the patients symptoms.

Data Analysis. Descriptive statistics, product-moment correlations, linear regression and independent-groups tests were performed using the Macintosh version of Statview (28). Since a daily fatigue severity rating of moderate is considered clinically significant, subjects who reported no or mild fatigue were classified has having low fatigue while those reporting fatigue as moderate or higher were classified has having high fatigue.

Although none of the subjects met DSM-IIIR criteria for an affective disorder, ten subjects reported “frequent low mood” and seven reported that they had been diagnosed in the past as “depressed”. These subjects were all classified as having “depressive symptoms” to control for the possible effect of “low mood” on subjective symptoms of fatigue and because HS have been imaged in elderly patients with depression (26).

RESULTS

MRI Findings. Areas of hyperintense signal in gray and white matter were imaged in eight of the subjects. This 36% incidence of HS is significantly greater ($p<0.05$) than the 24% incidence that would be expected to occur in a healthy sample with a mean age of 46.7 years drawn from the general population.

All eight subjects with HS reported high fatigue. No areas of HS were seen in subjects reporting low fatigue. However, HS was not imaged in seven (45%) of the subjects reporting high fatigue. In four subjects multiple punctate areas of HS were imaged in the periventricular and deep white matter. In one of these subjects a small discrete area of HS was also imaged in the right putamen. A single discrete area of HS was imaged in the rostral reticular formation in one subject and in the right medial lemniscus in another. A seventh subject demonstrated three discrete areas of HS in the centrum semiovale, each approximately 5.0 mm2 in area. In an eight subject, one discrete area of HS was imaged in the left putamen and a 4.0 x 6.0 mm2 area of HS was seen in the centrum semiovale.

Demographics. Subjects with and without HS were equal in terms of age, years of education, year of polio, age at polio and the severity of acute polio as measured by the number of limbs originally paralyzed and being hospitalized by polio. Subjects with HS were six years further from the acute polio as well as having a clinically and statistically significant elevation in mean Type A score as compared to those without HS.

Problem Severity. The presence of HS was significantly correlated with fatigue severity, year of acute polio, years since polio and Type A score. The presence of HS and fatigue severity were also significantly correlated with the frequency of problems with thinking clearly, mind wandering, staying awake and recent memory, and the severity of problems with thinking clearly, mind wandering, attention, concentration and recent memory. It is noteworthy that the severity of problems

with attention was highly correlated with the severity problems with thinking clearly (product-moment r = 0.79), mind wandering (product-moment r = 0.76) and concentration (product moment r = 0.70). Problem severity was compared between subjects with and without HS who reported high fatigue. Subjects with HS had elevated ratings for all problems (except with sleeping) although only the between-groups difference for the problems with mind wandering (independent groups t-test = 2.39; p = 0.033), attention (independent groups t-test =2.30; p = 0.039) and thinking clearly (independent groups t-test = 2.25; p = 0.044) were statistically significant.

DISCUSSION

The findings of this preliminary study support the hypothesis that areas of hyperintense signal on MRI of the brain are associated with late-onset fatigue and subjective problems with attention in polio survivors. The correlation of HS imaged in the RAS with fatigue severity and problems in attention, concentration and staying awake, in addition to the significantly elevated severity of attention problems in high fatigue subjects with HS, suggest that HS are related to the pathophysiology of post-polio fatigue (24). The lack of correlation between HS or fatigue severity with age, severity of the acute polio, depressive symptoms or difficulty sleeping militates against these factors as either causing HS or producing symptoms of fatigue.

The significant correlation of fatigue severity and HS with problems in thinking clearly and recent memory indicate that subject's quantification of fatigue depends on more than just subjective problems with attention. However, subjective problems with cognition and memory in polio survivors may be more perceived than real. Cognition and memory were found to be intact on neuropsychological testing even in post-polio subjects reporting severe fatigue; however, attention and information processing speed in these subjects were significantly impaired (24). Problems with thinking clearly were highly correlated with the severity of problems in attention. Thus, subjective problems in information processing and short-term memory may be the result of impaired attention.

Clinical Correlation of Gray Matter HS. The correlations between HS and the symptoms of post-polio fatigue can only be explained by understanding the pathogenesis of HS. HS imaged in the putamen and reticular formation most likely represent areas where astroglia have replaced neurons destroyed during the acute poliovirus infection, since gliosis has been correlated with HS in postmortem examinations of the brains of healthy elderly adults (35). Since damage to the putamen and caudate nucleus (16,17,18) and especially the reticular formation (36) has been shown to cause deficits in attention, poliovirus damage to these areas could conceivably impair attention and produce the symptoms of post-polio fatigue.

The size and distribution of poliovirus lesions in the reticular formation may also explain the absence of HS in 50% of the high fatigue subjects. Bodian stated, "In most of our material and that described by others the lesions in the reticular formation (even) in fatal bulbar cases were heavily peppered throughout this region rather than being predominately composed of large discrete areas of destruction" (5). Furthermore, he stated that only "In a few instances clearly delimited areas of complete neuronal destruction were seen, as large as 1 or 3 mm. in diameter" (5). Since the limit of MRI resolution is 1 mm, HS resulting from poliovirus lesions will only infrequently be large enough to be imaged by MRI and will be seen only in those polio survivors having both severe and confluent damage.

If HS are indicative of reticular formation damage that dates from the original poliovirus infection, the emergence of symptoms of fatigue more than thirty years later must be explained. The acute poliovirus infection is thought to have destroyed as many as 50% of spinal motor neurons in infected individuals (37). Even if a similar percentage of reticular formation neurons was also destroyed, persistent fatigue and attention deficits may have been prevented by inherent neuronal redundancy and the sprouting of axons such as that which was seen in motor neurons following

poliomyelitis (4). With aging, the cell bodies of reticular formation neurons may become distorted and dendritic shafts may be lost, changes seen in animal reticular formation neurons that resemble degenerative changes in aging human cortex (38). Thus, the age-related degeneration and possibly attrition of reticular formation neurons, combined with an already diminished neuronal pool, may degrade RAS functioning sufficiently to impair attention and produce symptoms of fatigue as polio survivors reach midlife.

Clinical Correlation of White Matter HS. Bodian has suggested that damage to other than gray neurons may result from a local reaction of tissue to the passage of the poliovirus. For example, lymphocytic infiltrations following the acute poliovirus infection were said to "sometimes reach massive proportions" and be "present diffusely in the tissue for two or three weeks, but persist as perivascular accumulations as late as the second month" (39). Bodian suggested that the combination of this "severe reaction to virus and local circulatory embarrassment" may be the cause of local tissue damage. Since HS were imaged along white matter tracts that have been implicated in the centrifugal spread of the poliovirus (40,41), it is conceivable that poliovirus may have damaged the brain parenchyma and produced both enlarged, fluid-filled spaces around arterioles and the local atrophy and degeneration of myelinated axons that have been correlated with HS in postmortem examinations of the brains of healthy elderly adults (35,42).

Diffuse atrophy and degeneration of myelinated axons within corticofugal white matter tracts could conceivably impair transmission, decrease cortical activation and thereby cause the attention deficits and symptoms of fatigue. This notion is supported by a number of other studies that have documented a relationship between HS, impaired attention and fatigue. Periventricular and deep white matter HS have been associated with impairments of attention and information processing speed in demented (43,44) and non-demented (34,45,46,47) elderly adults, impairments similar to those documented in polio survivors reporting severe fatigue (24). In addition, 82% of patients with Chronic Fatigue Syndrome (CFS) reported subjective problems in attention (29) with impaired attention being the "most pronounced and frequent deficit" seen on neuropsychological testing (30). Between 40% and 100% of CFS patients demonstrate periventricular and deep white matter HS on MRI (29,30). Thus, there may be a common pathophysiology for attention deficits and putative "postviral" fatigue syndromes.

Conclusion. The imaging of HS in brain areas severely and frequently affected by the poliovirus suggests that a poliovirus-damaged RAS is responsible for the documented attention deficits (24) and subjective symptoms of "brain fatigue" reported by polio survivors.

However, there are several caveats. First, only the correlation of fatigue, subjective problems and impaired attention documented by neuropsychological testing with postmortem histopathology will provide an adequate test of this hypothesis. Since postmortem histopathology is difficult to obtain, the correlation of symptoms and neuropsychological test results with the results of imaging techniques that quantify brain functioning (e.g., measurement of local cerebral blood flow or positron emition tomography) might be an interim methodology.

Second, these preliminary findings need to be replicated on a larger sample that represents a cross-section of the post-polio population. Participants in all studies of PPS are likely to have more severe symptoms than are non-participants. Thus, polio survivors without symptoms will be under represented. A larger sample would likely reveal HS in some percentage of polio survivors who do not report fatigue or problems with attention. This percentage would have to equal that of controls of similar age and be significantly lower than the percentage of HS in polio survivors with fatigue for the hypothesis to be accepted.

Although preliminary, these findings do have clinical implications. First, polio survivors need reassurance that their "brain fatigue" is not hysterical or hypocondriacal, as they have frequently been told, but is real and may have a physiological basis. Second, the current treatments for

post-polio fatigue are limiting and only partially effective. Reducing physical and emotional stress (3), energy conservation (48), adequate rest and the pacing of activities (49) do reduce the symptoms of fatigue. Unfortunately, these treatments require polio survivors to significantly reduce their activities. Further, there is a subgroup of polio survivors who report severe and malignant fatigue that is refractory to any of these treatments. Understanding the physiological basis for post-polio fatigue may allow the development of a pharmacological treatment.

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