THE NEUROPSYCHOLOGY OF POST-POLIO FATIGUE

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Short Title: Neuropsychology of Post-Polio Fatigue

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ABSTRACT

To test the hypothesis that post-polio fatigue and its concomitant cognitive deficits are associated with an impairment of attention and not of higher-level cognitive processes, six carefully screened polio survivors were administered a battery of neuropsychological tests. Only subjects reporting severe fatigue, and not those with mild fatigue, demonstrated clinically significant deficits on all tests of attention, concentration and information processing speed while showing no impairments of cognitive ability or verbal memory. These findings suggest that an impaired ability to maintain attention and rapidly process complex information appears to be a characteristic in polio survivors reporting severe fatigue, since these deficits were documented even when their subjective rating of fatigue was low. This finding supports the hypothesis that a polio-related impairment of selective attention underlies polio survivors' subjective experience of fatigue and cognitive problems.

Polio; Post-Polio Sequelae; Fatigue; Attention

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Fatigue is the most commonly reported, most debilitating and most poorly understood Post-Polio Sequelae (PPS) affecting the more than 1.63 million polio survivors *(1)*. In national surveys 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 *(2,3)*. Importantly, polio survivors differentiate between physical tiredness, that is associated with muscles being weak or easily fatigued, and "brain fatigue" that is characterized by problems with attention and cognition. 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 problems with these functions *(3)*.

It has been suggested that post-polio fatigue is caused by poliovirus-induced damage to the neurons of the Reticular Activating System (RAS) *(3)*. Such damage would impair the ability of the RAS to maintain attention, activate the cortex and would generate the subjective problems with attention, concentration and maintaining wakefulness that polio survivors described as "brain fatigue." For this hypothesis to be supported, post-polio fatigue would have to be associated with impaired functioning on neuropsychological tests measuring attention and not on those assessing memory, abstraction and intellectual ability.

Freidenberg, et al. *(4)* did administer a battery of neuropsychological tests to polio survivors with and without "progressive weakness, pain and fatigue." Their findings did not support the hypothesis since both groups were found to have marked impairments of non-verbal memory and performance on tests of attention was significantly lower in the subjects without symptoms. However, this study did not adequately test the hypothesis since the severity of fatigue was not assessed and fatigue was not measured during testing.

This study was an initial attempt to test the hypothesis that post-polio fatigue is associated with impaired functioning on neuropsychological tests measuring attention - the Paced Auditory Serial-Addition Test, the Double Letter Cancellation Test and the Trail Making Test - and not on tests assessing memory and higher-level cognitive processes.

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 subjectively rate their daily level of fatigue and cognitive problems occurring with fatigue on a six-point scale from "none" through "severe." They were also asked to give a complete medical history, including descriptions of the effects of the acute poliovirus infection and their PPS.

Exclusion criteria were established to eliminate subjects whose fatigue could have been caused by factors other than PPS. One-hundred (108) volunteers were excluded as a result of co-morbidities that could cause fatigue and cognitive problems, e.g. psychiatric diagnoses including a major depressive episode, thyroid, cerebrovascular or cardiac disease, anemia, lupus or diabetes. Volunteers were also excluded if they were above 65 years of age, were taking sedating medications, including antidepressants and benzodiazepines for sleep, or if they had a been diagnosed with respiratory problems or had a history of breathing problems associated with the acute poliovirus infection *(4)*.

Of the 38 volunteers remaining, only the 5 reporting "severe fatigue" and the 16 reporting "no fatigue" or "mild fatigue" were asked to participate in order to create two groups that were maximally different in terms of fatigue. Six volunteers agreed to be studied; three reporting "no fatigue" or "mild fatigue" were assigned to the mild fatigue group and three reporting severe fatigue were assigned to the severe fatigue group.

Procedure. After subjects gave written informed consent, they recorded their daily subjective levels of fatigue, emotional stress, motivation, sleep quality and cognitive problems for 14 days, rating them on a six-point scale from "none" through "severe" (Figure 1). On the 15th day, fasting blood was drawn at 11:00 AM to measure hypothalamic-pituitary-adrenal functioning (neuroendocrine data will be presented elsewhere). Subjects then completed the Beck Depression Inventory *(5)* and brief Type A questionnaire *(6)* to quantify symptoms of depression and Type A behavior that have both been associated with fatigue and cognitive problems in polio survivors *(3)*. Over the next hour subjects ate lunch and rested.

Beginning at 1:00 PM, a three-hour battery of neuropsychological tests was administered to assess higher-level cognitive processes and to repeatedly assess attention, concentration and fatigue. Four tests were administered to assess attention and a subjective rating of fatigue on a six-point scale from "none" through "severe" was elicited prior to beginning testing and after each of three, 45 minute testing periods. The Paced Auditory Serial-Addition Test (PASAT) *(7)* assessed complex attention by requiring subjects to sequentially add a series of 60 digits presented by a tape recording at three presentation speeds: one every 1.6, 2.0 and 2.4 seconds. The Double Letter Cancellation Test *(8)* required subjects to cross-out two specified letters on a sheet filled with similar letters in the shortest possible time to assess selective and sustained attention. The Trail Making Test *(9)* assessed visual scanning and visual motor speed by requiring subjects to draw a line to sequentially connect circles containing 25 ascending numbers (Parts A) or sequentially but alternately connect circles containing ascending numbers and the letters of the alphabet (Part B) in the shortest possible time.

During the first testing period four tests were administered. The Vocabulary subtest of the Wechsler Adult Intelligence Scales-Revised (WAIS-R) *(10)* required subjects to give correct definitions of increasingly difficult words to assess verbal intelligence. The Block Design subtest of the WAIS-R assessed visuo-constructive ability and non-verbal reasoning by requiring subjects to correctly reproduce two-dimensional colored designs using colored blocks. The Logical Memory I subtest of the Wechsler Memory Scale-Revised (WMS-R) *(11)* required subjects to recall two paragraph-length passages

immediately after each reading to assess immediate verbal memory. The Visual Memory I subtest of the WMS-R assessed immediate visual memory by requiring subjects to reproduce several drawings from memory after a 10 second exposure.

During the second testing period three tests were administered. The Token Test *(12)* required subjects to manipulate plastic tokens in response to a series of hierarchally-ordered commands to assess language comprehension. The Ravens Progressive Matrices *(13)* assessed visual-spatial analysis and non-verbal reasoning by requiring subjects to select a small patterned insert to complete a large pattern that had a portion omitted. The Visual Form Discrimination Test *(14)* required subjects to select a match for a complex graphic design from a group of designs to assess visual-spatial analysis.

During the third testing period three tests were administered. The Short Form Category Test *(15)* assessed abstract reasoning and problem solving by requiring subjects to develop a classification scheme for a series of pictures grouped by conceptual similarity. The Logical Memory II and Visual Memory II subtests of the WMS-R required subjects to recall the passages and reproduce the designs to which they had been exposed during the first testing period to measure delayed verbal and visual memory.

Neuropsychological tests were administered and scored according to accepted procedures. Since the small sample size prevented statistical analysis, the means of the test scores were calculated for the two groups and compared to established clinical norms to determine whether group performance was clinically impaired.

RESULTS

Demographics. Subjects in both groups were essentially equal on demographic variables (Table 1). Subjects in both groups had elevated Type A scores (i.e. >50) *(6)* and were equally affected by polio and PPS as measured by the number of limbs originally paralyzed or affected by new muscle weakness and pain. No subject had a clinically elevated score (i.e ., >17) on the Beck Depression Inventory *(5)*. Those with severe fatigue were on average younger and had polio at a slightly younger age later in the century than those in the mild fatigue group. Two subjects with severe fatigue had retired on Social Security disability income as a result of fatigue preventing continued employment. The remaining subjects in both groups were working full-time outside or inside the home.

Symptom Logs. Mild fatigue subjects' mean daily fatigue and functional problems were rated between "none" and "mild" (Figure 1). Severe fatigue subjects rated mean daily fatigue above "moderate" while other functional problems were rated as "mild to moderate" or above. Difficulty with sleeping and emotional stress were rated between "mild" and "mild to moderate" by both groups, suggesting that these symptoms, which have been shown to be related to post-polio fatigue, did not differentially affect the severe fatigue subjects *(3)*.

Neuropsychological Testing. Scores on tests of verbal and non-verbal intellectual abilities (WAIS-R Vocabulary Test, Ravens Progressive Matrices and Short Form Category Test) revealed that subjects in both groups had at least average intellectual ability (Table 2). Although subjects with mild fatigue scored slightly higher on all of these measures, the elevations were not clinically significant. The equivalence of intellectual ability was supported by the mean estimated full-scale intelligence quotient of 111 for both groups (Table 1). Language abilities were also intact in both groups and there was no evidence of deficits in the comprehension of simple or complex verbal material as demonstrated by equivalent mean scores on the Token Test in the two groups.

Tests of immediate memory (WMS-R Logical Memory I and Visual Reproduction I) revealed no

difference between severe and mild fatigue groups in their ability to learn and recall verbal and non-verbal (visual) material. Additionally, both groups demonstrated a normal capacity for delayed recall of verbal information as shown by their scores on WMS-R Logical Memory II. However, both the severe and mild fatigue groups were similarly impaired in their ability to recall visual information after a delay as shown by their scores on WMS-R Visual Reproduction II.

Visuospatial perception and organization and visuopraxis were average or higher for both groups as shown by the nearly equivalent Visual Form Discrimination Test scores and their accuracy of construction on the WAIS-R Block Design Test. Notably, severe fatigue subjects' slower psychomotor speed prevented them from obtaining higher scaled scores on the Block Design Test.

Clinically significant differences were seen between the two groups on measures of attention and information processing speed. Subjects with severe fatigue required 23% and 67% more time, respectively, to complete the initial presentation of Double Letter Cancellation and Trail Making Tests (Part A), tasks requiring sustained attention and vigilance (Figure 2). In the severe fatigue group, the time required for completion of the first three trials of the Double Letter Cancellation Test was clinically abnormally elevated (i.e., >100 seconds) *(7)*, as was the completion time for the first three trials of the Trail Making Test (Part A) (i.e., >30 seconds) *(8)*. Practice and learning effects were demonstrated by decreased completion times in both groups even though the mean fatigue ratings increased to "severe" for the severe fatigue subjects and "mild to moderate" for the mild fatigue group by the last testing period. However, even with practice, the completion times for the last presentation of these tests for the severe fatigue subjects was still longer than those for the initial presentation in the mild fatigue group. Notably, the number of errors on the Double Letter Cancellation Test was essentially equal and decreased with practice in both groups (Table 2).

Subjects with severe fatigue also demonstrated deficits in their ability to rapidly process complex information and sustain divided attention as measured by the Paced Auditory Serial-Addition Test (PASAT)(Figure 3). In the severe fatigue group, the mean percentage of correct responses was clinically abnormally decreased at the 1.6 second (<66% correct), 2.0 second (<73% correct) and 2.4 second presentation rates (<82% correct) during each of the four testing periods. Again, practice and learning effects were demonstrated by the increase in the percentage of correct responses in both groups across testing periods despite an increase in the fatigue rating during testing. However, the percentage of correct responses for the last testing period in the severe fatigue subjects was still lower than that for the first testing period in the mild fatigue group.

DISCUSSION

These findings provide preliminary support for the hypothesis that post-polio fatigue is associated with impaired functioning on neuropsychological tests that assess attention and not on those assessing higher-level cognitive processes. An impaired ability to maintain attention and rapidly process complex information appears to be a characteristic of these polio survivors reporting severe fatigue, since the deficits were documented during the first testing period when the subjective rating of fatigue was still low.

The impairment of delayed recall of non-verbal information in both groups of polio survivors was also reported by Freidenberg, et al. *(4)*. These data suggest a right hemisphere information processing deficit in polio survivors that is unrelated to fatigue. As yet there is no empirical or theoretical explanation for a polio-related, lateralized impairment of hemispheric functioning.

It is noteworthy that the severe fatigue subjects' subjective ratings of cognitive problems on their 14-day

logs were not associated with comparable impairments of cognition and verbal memory on neuropsychological testing. It is possible that these Type A individuals, whose cognitive abilities equaled or exceeded the norms, perceived even small decrements in their cognitive functioning as significant problems. It is also possible that subjects' continuous expenditure of effort, to compensate for fatigue, impaired attention and maintain a generally high level of cognitive functioning, creates the subjective impression that they are having problems with cognition and memory.

A strength of this study, the careful selection of subjects to rule out causes of fatigue other than polio, is also a weakness since the small sample size limits the generalizability of its findings. If these findings do apply in general to polio survivors with fatigue, they have important implications. Despite their subjective reports of cognitive impairment and documented deficits in attention and information processing speed, polio survivors reporting severe fatigue were able to maintain their ability to learn and perform high-level cognitive tasks even as their fatigue during testing increased. Thus, although the work performance of polio survivors may be impaired if they are required to rapidly process multiple sources of complex information, tasks requiring even high-level cognitive abilities (e.g., accounting, copy editing, computer programming) may be performed accurately with reasonable accommodations that allow increased time for task completion and minimize distractions.

Unfortunately, these job modifications alone will not affect problems such as word-finding or maintaining wakefulness, effort and motivation in the face of increased fatigue. Reducing physical and emotional stress, energy conservation, adequate rest and the pacing of activities remain the treatments of choice for post-polio fatigue *(16,17,18)*. We continue to study the neuroanatomy and neuroendocrinology of post-polio fatigue to identify its cause and are developing pharmacological treatments for fatigue and its associated attention deficits.

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FIGURE LEGENDS

Figure 1.

Fourteen-day mean ratings of fatigue and functional problems.

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Figure 2.

Double letter cancellation and trail making test scores.

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Figure 3.

Paced auditory serial addition (PASAT) test scores.

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