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Chronic fatigue, fainting and autonomic dysfunction: Further similarities between Post-Polio Fatigue and Chronic Fatigue Syndrome?

To test the hypothesis that fatigue and fainting occur together, 1,047 polio survivors and 419 non-disabled control subjects were asked about the frequency and cause of fainting and asked to rate their typical daily fatigue severity. Fatigue severity was significantly higher in polio survivors as compared to controls, and in both polio survivors and controls who had fainted, as compared to those who had not. 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 chronic fatigue syndrome and in polio survivors with late-onset fatigue may result from damage to brain stem and hypothalamic neurons.

Fatigue is the most commonly reported and most debilitating of Post-Polio Sequelae (PPS), the unexpected, late-onset symptoms affecting the 1.8 million North American polio survivors. A number of clinical and physiological similarities between chronic fatigue in polio survivors and

Chronic Fatigue Syndrome (CFS) have been documented, including brain lesions on MRI, slowing of the EEG and clinical impairment of attention and hypothalamic-pituitary-adrenal (HPA) axis functioning. 1-3 Reports of neurally mediated hypotension (NMH) and symptomatic orthostatic tachycardia syndrome (SOTS) in CFS patients suggests that there may be an association between fainting and chronic fatigue. This association may represent yet another similarity between post-polio fatigue and CFS, and may help to explain the pathophysiology of these putative post-viral fatigue syndromes. 4-6

Autonomic dysfunction and the poliovirus. Damage to the autonomic nervous system (ANS) has long been associated with poliovirus infection. Postmortem histopathology from the 1940's demonstrated that the poliovirus routinely damaged the brain stem, the so-called "bulb" of the brain, whether or not there was spinal cord damage or paralysis. 7 The brain stem area most frequently and severely lesioned by the poliovirus was the reticular formation (RF). The RF is part of the reticular activating system (RAS), responsible for cortical activation, waking and focusing attention, and contains the cardiodepressor center whose outflow slows the heart via stimulation of the vagus nerve. 8-9

Near the RF lie the other brain stem 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 which regulate blood pressure by sensing and altering the force and rate of the cardiac contraction via the vagus nerve and sympathetic efferents. 7, 10-11

Between 27% and 56% of polio survivors had symptoms of abnormal vagal functioning, including nausea, vomiting and constipation, that persisted after the acute poliovirus infection "for some weeks whether paralysis was present or not." 10 So-called "bulbar polio," in which damage to brain stem neurons was most severe, was associated not only with respiratory impairment,

rousable stupor, somnolence and even coma, but also with ANS abnormalities. More patients (55%) had signs of vagus nerve impairment (e.g., dysphagia) than respiratory center involvement (36%). 11 Cardiodepressor center abnormalities were even more frequent, with 73% demonstrating hypertension and tachycardia which led to cardiovascular collapse and death in 6%. 11

The poliovirus has also been associated with damage to the sympathetic nervous system. Polio survivors' cold intolerance and typically cold and violet-colored feet have been attributed to poliovirus damage to both intermediolateral column and post-ganglionic sympathetic neurons paralyzing vascular smooth muscle. 12 This paralysis allows passive dilatation and engorgement of cutaneous venous capacitance beds and the loss of heat from warm blood that pools near the skin's surface. Further, the poliovirus damaged the posterior hypothalamus, which modulates sympathetic activity and participates in brain activation, as well as the preoptic hypothalamus, responsible for the central control of peripheral thermoregulatory responses. 8

Considering the severity and extent of damage to neurons throughout the ANS, many of which are either part of or lie close to the RAS, it would be surprising if symptoms of impaired brain activation in polio survivors (e.g., fatigue) did not co-occur with some symptom of cardiovascular dysregulation (e.g., fainting). Such a co-occurrence did become evident when two post-polio patients presented with vasovagal syncope. 13 One patient, who had been disabled for a decade by severe chronic fatigue, reported episodes of fainting since childhood that were triggered by vomiting, suggesting a life-long association between increased vagal efferent activity and fainting.

METHODS

To test the hypothesis that there is a relationship between fatigue and fainting in polio survivors, the 1995 International Post-Polio Survey included questions about the lifetime number of faints, subjects' beliefs as to the cause of faints, as well as requesting a rating of typical daily fatigue severity using a six point scale from none through severe. 8 The survey also asked about other physically and emotionally traumatic experiences during childhood and was distributed in November, 1994 to all post-polio support groups throughout North America. Polio survivors were asked to complete the survey and give a similar survey to a non-disabled individual of the same sex, similar age and socioeconomic status. The chi squared (X²) statistic and independent groups t-tests were used to compare polio survivors to controls and fainters to non-fainters.

RESULTS

Completed surveys were received from 1,047 polio survivors and 419 controls who were equivalent in terms of age, number of fainting episodes and causes of faints (Table). Significantly more female polio survivors fainted (X²=15.8;p=.0001), most likely because there were 13% more female respondents among the polio survivors. A higher female response rate is typical in surveys of polio survivors. 8 The percentage of fainters did parallel the gender distribution in both groups.

Daily fatigue severity was significantly higher in polio survivors (rated as "moderate") as compared to controls (rated as "mild")(t=22.9;p=.001). Daily fatigue severity was statistically (although not clinically) significantly higher both in polio survivors (t=2.7;p=.01) and in controls (t=3.3;p=.01) who had fainted as compared to those who had not.

Daily fatigue severity was statistically and clinically significantly increased in

both groups as the number of lifetime faints increased (Figure). This increase in fatigue severity was variable in the controls. Fatigue was significantly higher (approaching "mild to moderate") in controls who fainted one time ($t=3.6$; $p=.001$) and three times ($t=2.7$; $p=.01$) as compared to respondents who had never fainted. Daily fatigue severity was significantly higher in polio survivors who had fainted three ($t=2.0$; $p=.04$), four ($t=2.1$; $p=.04$) and five times ($t=2.3$; $p=.02$) as compared to those who had never fainted, with fatigue severity rating increasing to "moderate to severe" in the last group. Neither fatigue severity nor fainting was related to chronological age or severity of polio (i.e., age or hospitalization at acute polio, length of hospitalization, or number of limbs affected). A lack of association between the severity of the acute polio episode and late-onset fatigue has been documented previously. 8

DISCUSSION

These findings suggest that there may be a relationship between fatigue and fainting that causes non-disabled individuals who have fainted to experience more daily fatigue (albeit only "mild to moderate" in severity) than those who have never fainted. This relationship between between fatigue and fainting may be attributable to the close proximity of cardiovascular regulation and brain activation centers within the RF and brain stem. Some individuals may have abnormalities of brain stem neurons that predispose them both to cardiovascular dysregulation that promotes fainting and impairment of brain activating neurons that promotes fatigue.

However, polio survivors' clinically and statistically significantly elevated fatigue severity ratings, as well as the incremental increase in fatigue severity as the number of lifetime fainting episodes increased, suggest that the process underlying fatigue and fainting covaries in polio survivors and is superimposed on a pathological fatigue generating mechanism that is related to poliovirus damage to the brain. (see 14)

A relationship between pathological fatigue and fainting in polio survivors is of special interest in light of the reports of NMH and SOTS in patients with CFS. 4-6 Since viruses other than the poliovirus (e.g., the Coxsackie, St. Louis, Japanese B, Equine, Australian X and Central European Encephalomyelitis viruses) frequently and preferentially damage brain stem neurons, putative post-viral fatigue syndromes may be associated with damage to both cardio regulatory and brain activation centers. 3 This suggestion is supported by the finding of brain stem lesions on MRI only in polio survivors reporting fatigue and studies showing that decreased perfusion of the brain stem using SPECT was the only physiological finding differentiating subjects with CFS from healthy controls and subjects with depression or neurological disease. 15,16

In addition, hypothalamic abnormalities in polio survivors and CFS patients may contribute to the putative relationship between fatigue and fainting. A marked blunting of fasting adrenocorticotrophic hormone (ACTH) release in polio survivors was correlated with their daily fatigue severity rating. 3 Both fasting ACTH and the secretion of corticotropin releasing hormone (CRH), which stimulates ACTH release, have been found to be decreased in patients with CFS. 17,18 Since both ACTH and CRH can directly activate the brain, their decreased secretion has been implicated in the pathophysiology of CFS. 19

CRH is secreted by the paraventricular nucleus (PVN) of the hypothalamus, which is known to have been damaged by the poliovirus 7 The PVN also produces vasopressin, the secretion of which is also impaired in people with CFS. 20 Thus, PVN damage in polio survivors and CFS patients may reduce both brain activating and blood pressure regulating hormones, thereby reinforcing brain stem abnormalities that may predispose to both fatigue and fainting.

A question remains as to whether hypotension associated with NMH and SOT actually causes fatigue or if hypotension and even fainting are merely coincidental in those who have post-viral fatigue syndromes. In the approximately 50% of NMH patients who had "complete or near complete resolution of all symptoms" after receiving blood pressure elevating therapies, did fatigue decrease as a result of elevated blood pressure directly increasing perfusion and activation of the brain, or by increased brain stem perfusion indirectly increasing RAS neuronal firing which then activated the brain? 4,5 And in the nearly 50% percent of NMH and 65% of SOTS patients whose fatigue did not decrease or was only "somewhat better" after blood pressure elevation, was hypotension merely coincidental evidence of damage to brain stem and hypothalamic cardioresgulatory centers which accompanies the RAS damage that may be the fundamental cause of fatigue? 4-6

These important questions about the pathophysiology of fatigue and fainting will only be answered by double-blind, placebo-controlled trials of treatments for fatigue-related hypotension, combined with brain perfusion and SPECT studies and the simultaneous dynamic assessment of the functioning of the individual sympathetic and parasympathetic effector pathways, measurement of blood volume in specific vascular beds (especially the splancnic), and assays of plasma catecholamines and peptides. cf. 21

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