FAINTING AND FATIGUE: Causation or Coincidence

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As the former autonomic nervous system fellow at New York's Columbia-Presbyterian Medical Center, and in my current incarnation studying chronic fatigue in polio survivors, I have read with special interest the reports from Johns Hopkins University describing neurally mediated hypotension (NMH) in adults and adolescents with CFIDS.*[1]* In June 1995, we presented a paper to the American Congress of Rehabilitation Medicine describing several of our post-polio patients who have had episodes of vasovagal syncope.*[2]* One patient with a 10-year history of severe, chronic and disabling post-polio fatigue had a history of frequent fainting 35 years before she ever experienced fatigue.

The 1995 North American Post-Polio Survey

Because of fainting episodes in our patients, we included questions about fainting and late-onset fatigue in the 1995 North American Survey of Polio Survivors conducted last Fall. We have recently analyzed data from the first 1,000 respondents to the survey. As was seen in our two previous National Post-Polio Surveys, chronic fatigue was the most frequent symptom in polio survivors; the daily fatigue rating was reported as "moderate" or higher in 76 percent of the 665 polio survivors, versus 29 percent of the 406 non-disabled controls.

An equal number of polio survivors and controls (44%) reported at least one fainting episode during their lifetimes. The causes of fainting - from physical trauma to emotional stress - were identical in polio survivors and controls. However, the occurrence of even one fainting episode was significantly related to having a daily fatigue rating of moderate or greater in both polio survivors ($X^2=7.46$; $p=.0063$) and in

controls (X2=7.74; p=.005). Polio survivors who passed out at least twice in their lives had a 14 percent higher daily fatigue rating (p=0.0014) and controls had a 31 percent higher daily fatigue rating (p=0.019) as compared to those who never had fainted. These finding suggest that there may be a relationship between fainting and fatigue in polio survivors and the general population, as well as in people with CFIDS.

Physiology of Fainting and NMH

The question raised by our data and those from Johns Hopkins is: why do fainting, NMH and fatigue appear to go together? The answer may lie in the physiological mechanisms that regulate blood pressure and actually trigger NMH.

NMH has been said to result from a "miscommunication between the heart and the brain which causes blood pressure to lower when it should rise."*[3]* Actually, NMH is a survival mechanism, hard-wired into the brain, that turns on when the autonomic nervous system (ANS) is unable to stop blood pressure (BP) from falling. If BP falls for any reason (e.g., loss of blood from a cut artery) pressure detectors in the carotid arteries of the neck (the baroreceptors)stop firing.*[4]* (Figure 1) The silence of the baroreceptors is "heard" by BP regulation centers in the solitary tract and dorsal vagal nuclei, which release the brake on heart rate that is normally provided by the cardiodepressor center of the reticular formation. The BP regulation centers also trigger the release of vasopressin and norepinephrine, neurochemicals that constrict blood vessels and make the heart beat harder and faster, and should help to increase BP.

However, if these measures cannot stop BP from falling, the amount of blood returning to the heart will decrease. If the heart continues beating hard and fast even though it is nearly empty, the heart muscle will be damaged. Stretch receptors in the heart detect that it is "beating on empty," and send a signal to the dorsal vagal nucleus to protect the heart by stopping its beating for a few seconds. With the heart stopped, BP falls to zero and causes the faint of NMH.

But, even fainting has a protective function (if you don't knock yourself out falling to the ground). Lying flat, your brain will be at the same level as your heart. Without gravity pulling blood toward your feet, the heart will have an easier time increasing BP, pumping your remaining blood to your brain and (hopefully) waking you up again.

A Physiological Link Between Fainting and Fatigue.

If we assume that the heart itself is normal, there must be something wrong with the BP regulation centers in the brainstem that causes fainting in our post-polio patients and NMH in people with CFIDS. In the case of polio survivors, damage done by the poliovirus to the brain suggests that fainting should be expected.

The poliovirus frequently and severely damaged the brainstem, especially the reticular formation (RF).*[5]* The RF contains the cardiodepressor center that is responsible for "putting the brake" on heart rate. Of those with acute "bulbar" polio ("bulbar" meaning associated with the brainstem) 73 percent had hypertension and rapid heart rate and five percent died of cardiovascular collapse.*[6]*

Importantly, the RF is not only responsible for heart regulation, but also brain activation, keeping us awake and allowing us to focus attention. Using MRI of the brain, we have found lesions of the RF and its connections to the cortex, as well as clinically impaired attention on neuropsychological tests, in polio survivors with chronic fatigue.*[7]* Recently, Costa, et al. found that decreased perfusion of the brainstem

on SPECT was the ***only*** *physiological finding that differentiated people with CFIDS from patients with depression, neurological disease and controls.[8] These data support our hypothesis that damage to the brainstem "reticular activating system" may be a cause of chronic fatigue in polio survivors and in patients with post-viral fatigue.[7]*

Outside of the RF, but in the same area of the brainstem, lie the other cardiovascular control centers. The dorsal vagal nucleus, responsible for activating the stomach and slowing the heart, was damaged in 55 percent of those who had bulbar polio, as were the vestibular nuclei. Nausea, reported by 70 percent of those who have NMH, was seen in 27 percent of those with acute polio and attributed to poliovirus lesions in the vestibular nuclei.*[1,5,6]*

Also outside the RF but damaged by the poliovirus, were the nucleus ambiguus and solitary tract nuclei, the main centers for blood pressure regulation. These nuclei "communicate" with the heart via the vagus nerve, regulating blood pressure by sensing and altering the force and rate of the heart's contraction.*[4]*

The Chemistry of Fatigue, Fainting and NMH.

Recent research has also found chemical abnormalities that may be related to fatigue and fainting in polio survivors and CFIDS and NMH. We found a marked blunting of adrenocorticotropic hormone (ACTH) release in polio survivors that was correlated with daily fatigue severity.*[7]* The secretion of corticotropin releasing hormone (CRH), which stimulates ACTH release, had already been found to be decreased in patients with CFIDS.*[9]* CRH is secreted by the paraventricular nucleus (PVN) of the hypothalamus, which is known to be damaged by the poliovirus.*[5]* Both ACTH and CRH are brain activating hormones, and their decreased secretion could cause symptoms of fatigue.*[7]*

The PVN of the hypothalamus also produces the vasoconstrictor neurochemical vasopressin, the secretion of which is also impaired in people with CFIDS.*[10]* Thus, the PVN may be damaged in polio survivors and people with CFIDS, causing impaired brain activation and faulty BP regulation in both groups.

The Coincidence of Fainting and Fatigue

Taken together, these findings suggest that polio survivors may be predisposed to fainting because of poliovirus damage to their brainstem cardiodepressor and blood pressure regulation centers and PVN. However, it is important to note that many viruses besides polioviruses (e.g., the Coxsackie viruses) are also known to frequently and preferentially damage the brainstem, especially the reticular formation. *[7,11]* People with post-viral fatigue may have similar brainstem and hypothalamic damage as is seen following poliovirus infection, as Costa's finding of decreased brainstem perfusion in CFIDS suggests. Thus, damage to cardioregulatory centers could be responsible for NMH in people with CFIDS. But what of the coincidence of fainting and fatigue?

Since the cardioregulatory centers are either part of or lie close to the reticular activating system, it would be surprising if fainting and fatigue did not occur together. Damage to the RF alone could both decrease brain activation and impair BP regulation. The question that remains is whether NMH is the "cause" of chronic fatigue or if it is just coincidental in those who have chronic fatigue. At this early stage in the research, the answer to both of these questions appears to be "yes."

The Johns Hopkins team reported that 47 percent of their adult CIFDS patients and 57 percent of their adolescent patients with NMH had "complete or near complete resolution of all symptoms" after receiving blood pressure elevating therapies. Could the resolution of fatigue symptoms in CFIDS patients whose

NMH was treated have resulted from elevated BP increasing brainstem perfusion, thereby enhancing the functioning of the reticular activating system, or by elevated BP directly increasing perfusion of the brain? SPECT scans in people with CFIDS whose symptoms disappear when their BP is increased could answer these question.

But what of the nearly 50 percent of patients whose CFIDS symptoms did not respond or were only "somewhat better" after NMH treatment? Could NMH in these individuals just be a coincidence of generalized damage to the brainstem, including the BP regulation centers? Could fatigue symptoms in these individuals actually result from damage to the brainstem's reticular activating system, or the hypothalamus or the immune system? Only blinded, placebo-controlled trials of treatments for NMH, combined with SPECT scans of the brainstem, measurement of CRH, norepinephrine, and vasopressin, and assessment of the individual blood pressure and heart rate regulation pathways to and from the brain stem will provide answers to these important questions.

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Figure 1.

Brain stem centers damaged by the poliovirus involved in brain activation and blood pressure and heart rate regulation.

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Figure 2.

Brain areas damaged by the poliovirus involved in brain activation and blood pressure and heart rate regulation. PVN: Paraventricular nucleus of the hypothalamus; ACTH: Adrenocorticotropic hormone produced by the pituitary; CRH: Corticotropin releasing hormone, produced by PVN, that

releases ACTH; VP: Vasopressin, produced by PVN, and released from the pituitary.

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Figure 3.

Possible mechanisms of fatigue symptom generation. Damaged reticular formation neurons may decrease reticular activating system (RAS) stimulation of the brain, in combination with reduced CRH and ACTH secretion. Damaged blood pressure regulation centers, in combination with reduced vasopressin secretion, may produce NMH, decrease blood pressure, and reduce the perfusion of the RAS and brain, resulting in decreased brain activation

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