
FLASH Syndrome: Tapping into the Root of Chronic Illness

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To cite this article:

Michael Raymond Binder. FLASH Syndrome: Tapping into the Root of Chronic Illness. *American Journal of Clinical and Experimental Medicine*. Vol. 8, No. 6, 2020, pp. 95-103. doi: 10.11648/j.ajcem.20200806.11

Received: November 3, 2020; **Accepted:** November 13, 2020; **Published:** November 23, 2020

Abstract: It has now been established that persons with higher resting heart rates are at increased risk of morbidity and mortality from a plethora of mental and physical illnesses. However, the mechanism underlying the predictive value of this core vital sign remains obscure. This seminal report will integrate clinical, neuropsychological, physiological, and genetic evidence to assert that an inherent hyperexcitability of the neurological system is at the heart of the connection between resting heart rate and disease. Hypothetically, neuronal hyperexcitability can cause multiple circuits in the brain to overfire, including cognitive circuits, limbic circuits, and autonomic circuits, thereby dysregulating the associated systems of the body and allowing the aberration to be detected through standard vital signs and related measures of autonomic activity. Because the cognitive-emotional system is exquisitely sensitive to neuronal excitation, the aberration could also manifest as psychiatric symptomatology, thus suggesting that psychiatric symptoms may be the first subjective markers of the abnormality. Based on the well-recognized link between mental illness, autonomic dysregulation, and systemic disease together with mounting evidence that the related illnesses are associated with gene variants whose protein products fail to adequately regulate the firing of neurons, the vulnerability trait could aptly be called Familial Limbic Autonomic System Hyperexcitability or “FLASH.” Because the trait appears to be so common, its effects so pervasive, and its expression so modifiable, its identification is of critical importance to every medical specialty. FLASH could give clinicians the first comprehensive biological target through which to treat and prevent a plethora of mental, emotional, and physical illnesses.

Keywords: Prognostic Indicators, Heart Rate, Heart Rate Variability, Heart Rate Recovery, Respiratory Rate, Neuronal Hyperexcitability, Molecular Genetics, Ion Channelopathies

1. Introduction

It is now clear that persons with higher resting heart rates (RHRs) are at significantly increased risk of developing a wide range of physical illnesses including high blood pressure [1-4], type-2 diabetes [5-7], cardiovascular disease [8-13], cerebrovascular disease [14-16], kidney disease [17], cancer [16, 18, 19], dementia [20], and sudden death [21]. Higher RHRs have also been associated with a wide range of mental and emotional illnesses, including major depressive disorder, generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder, and psychotic disorders [22-26]. Although less well-studied in relation to RHR, psychiatric disorders have long been associated with autonomic dysregulation [27-29], and most persons with severe mental illness die of the same kinds of diseases as the general population [27, 30]. However, for

unclear reasons, they die at a much earlier age [27, 30].

This seminal report will examine the connection between RHR and vulnerability to illness. From there, it will posit the underlying abnormality, trace its origin, and discuss the means by which the abnormality can be identified and modified so as to improve the long-term health and well-being of those affected by it.

2. Examining the Mechanism of the Connection

The RHRs that have been linked to an increased vulnerability to illness are not necessarily outside the accepted range of “normal” but rather on the upper end of normal, with most studies reporting a significant increase in disease risk with RHRs above 70 beats/min [2-22]. Other measures that have been linked to an increased vulnerability

to illness include resting respiratory rate (RRR) [31-33], resting blood pressure (RBP) [22, 34, 35], blood pressure variability [34, 36], heart rate variability [4, 36-38], and heart rate recovery [21, 39]. The increased risk of morbidly and mortality associated with these indices can be more than two-fold [21, 31, 37, 40]. This is particularly concerning because it includes the world's leading cause of death—heart disease. What's more, the actual risk of illness, as will be discussed, is often much greater than statistically indicated, thus making it all the more important to get to the heart of the connection between constitutionally-elevated vital signs and disease.

Because all three vital signs—RHR, RRR, and RBP—are regulated by the autonomic nervous system (ANS), all three (and their correlates) reflect on the activity of the ANS. The ANS has two divisions: the sympathetic division, which is activated when there is a call to action, and the parasympathetic division, which regulates the digestive and recuperative functions of the body. When there is a call to action, the sympathetic nervous system drives an increase in heart rate, heart contractility, and respiratory rate in anticipation of an increased need for oxygen. When the job is done, sympathetic activity decreases, and parasympathetic activity increases [41].

Based on these physiological dynamics, a chronic elevation in the ratio of sympathetic-to-parasympathetic activity, as indicated by higher RHRs and other indices of autonomic function, would maintain the body in a heightened catabolic state—more breaking down than building up. This would naturally tend to accelerate the aging process and hasten the onset and progression of diseases that ultimately lead to the end of life [42, 43]. The pressing question is: what causes the chronic dysregulation of the ANS?

3. Shared Effect on Mental Health

An important clue to what persistently dysregulates the ANS is the increased risk of psychiatric disorders that is associated with constitutionally-elevated vital signs [22, 44]. Although the pathophysiology of mental illness remains unclear, an emerging hypothesis contends that psychiatric symptoms are driven by pathological hyperactivity in symptom-related circuits in the brain. According to the Multi-Circuit Neuronal Hyperexcitability (MCNH) hypothesis of psychiatric disorders, persistent firing in anxiety circuits causes persistent feelings of anxiety; persistent firing in depressive circuits causes persistent feelings of depression; persistent firing in cognitive circuits causes ruminative and obsessive thoughts; etc...[45]. That is not to say that the brain as a whole is pathologically hyperactive. Rather, the pathological hyperactivity is thought to occur in the brain's microcircuitry [45, 46], with hotspots of activity that either remain focal or migrate from one circuit loop to another like a wandering tornado [45]. The theoretical means by which this occurs is that the locus of hyperactivity, like a short-circuit in a wired electrical system, inappropriately fuels activity in circuits that would remain less active were they not themselves hyperexcitable [45, 47].

In addition to increasing activity in the cognitive-emotional system, neuronal hyperexcitability would tend to increase activity in the sensory system, the motor system, the endocrine system, and other systems of the body, including the ANS [42, 45, 47-50]. These systems must be tightly regulated to maintain optimal health, and any lack thereof would heighten the risk of both acute symptoms and long-term illness. Thus, in addition to explaining both the production of symptoms and the migration of symptoms in psychiatric disorders, an inherent hyperexcitability of the neurological system could explain the various functional symptoms that are associated with psychiatric disorders; it could explain the chronic dysregulation of the ANS that is associated with psychiatric disorders; and it could explain the early onset of disease that is associated with psychiatric disorders [27, 30]. Such broad explanatory power would hypothetically place neuronal hyperexcitability at the heart of the connection between constitutionally-elevated vital signs and chronic disease.

The excitability of neurons is governed by electrical gradients across neuronal membranes and the flow of ions through their respective channels. Consistent with the MCNH hypothesis, drugs that influence these channels—specifically benzodiazepine and non-benzodiazepine anticonvulsants—have been used for decades in the treatment of psychiatric disorders, and the anticonvulsant-like drug lithium was the first to be used [51-53]. Then again, reducing excitation in overactive cognitive and dysphoria-related circuits is not, from the perspective of the MCNH hypothesis, the only means by which psychiatric symptoms could be reduced. Symptoms could also be reduced by increasing excitation in pleasure-related circuits (as with tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and psychostimulants) and by modulating activity in these circuits (as with selective serotonin reuptake inhibitors) [46, 54-56]. Note, however, that any associated increase in the excitatory/inhibitory balance would tend to further dysregulate the system, thus increasing the risk of aberrant circuit induction. This is demonstrated by the potential of these drugs to cause paradoxical effects, rapid cycling, and conversion to mania [57-61]. It is also demonstrated by their overall tendency, even when used successfully to treat anxiety and depression, to adversely affect RHR, heart rate variability, and other novel markers of disease risk [62-69]. Although a complete discussion of the MCNH hypothesis is beyond the scope of this article, it should be noted that there is strong biological, pharmacological, psychophysiological, neuropsychiatric, radiologic, medical, experimental, electrophysiological, observational, behavioral, and explanatory evidence for the hypothesis [45, 47].

Persons with psychiatric disorders are quick to react [70] and slow to recover [43] from stressful events. Even in the absence of specific stressors, they tend to be stressed by abstract worries and fears [43, 71]. During that time, the sympathetic nervous system, which is tightly integrated with the cognitive-emotional system [72], would be activated beyond its already elevated basal activity [42, 43]. It would

also be activated more steeply [70] and more robustly than normal (Figure 1A) [42, 43, 70]. In addition, the prolonged recovery time would increase the likelihood that the autonomic responses to repeated stressors would coalesce or even summate (Figure 1B) [42]. Were this to occur, it would create a chronic allosteric load that would markedly accelerate the aging process and hasten the onset of illness [42, 43, 70]. In addition to amplifying stress, an inherent

hyperexcitability of the neurological system could, through maladaptive behavior, drive the development of the stressors themselves, thus orchestrating a vicious cycle of pathological stress and reasons to be stressed [42]. This neuropsychological dynamic would again place neuronal hyperexcitability at the heart of the connection between constitutionally-elevated vital signs and disease.

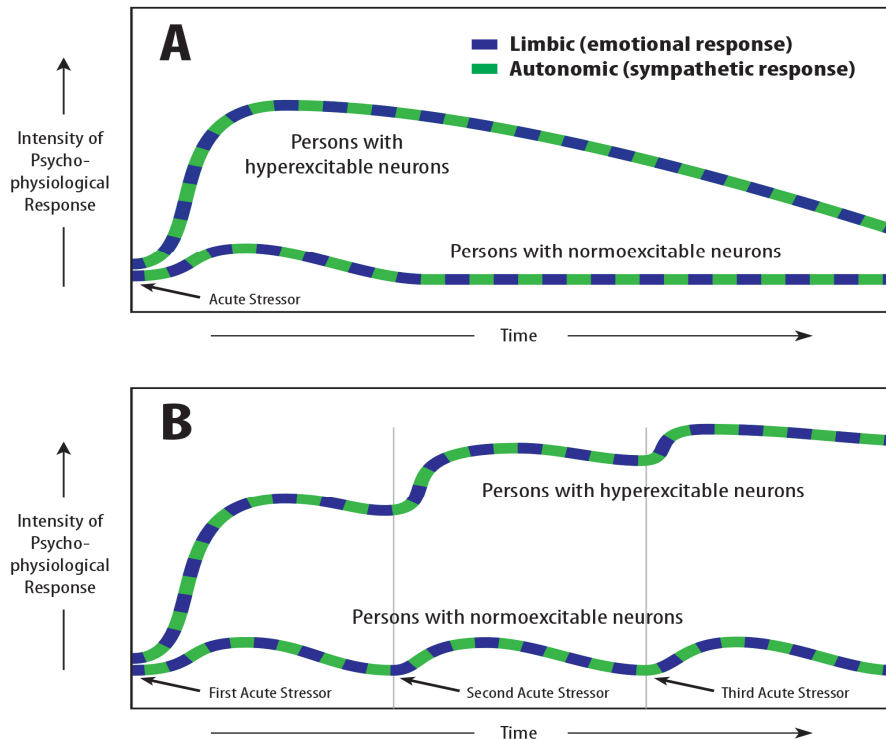


Figure 1. Schematic illustration of the stress-response curves in persons with hyperexcitable neurons compared to those with normoexcitable neurons A) when there is a single stressor; B) when there is a rapid series of stressors. Note: color variegation depicts the limbic and autonomic responses tracking together.

Figure 1 schematically illustrates how dramatically the response to stress can be amplified by hyperexcitable neurons: A) in response to a single stressor; B) in response to a rapid series of stressors. Hypothetically, this pathological amplification of neural signaling is what increases an affected person's risk of developing any illness that could be brought on by severe or persistent stress.

4. The Many Faces of Neuronal Hyperexcitability

That leads to another question: if neuronal hyperexcitability were at the heart of the connection between vital signs and disease, why is it that only some persons with constitutionally-elevated vital signs develop psychiatric disorders?

The answer lies in the same set of factors that would determine which, among many possible psychiatric disorders, if any, a person with hyperexcitable neurons would develop; namely, the complex dynamic between trait severity, brain architecture, developmental factors, situational factors, and the coping skills of the individual [42, 73, 74]. The idea of a

shared diathesis with variable expression is supported by the high degree of genetic correlation among many psychiatric disorders and by the high correlation of the personality trait of neuroticism with almost every psychiatric disorder [71]. Also, it is not uncommon for various combinations of psychiatric symptoms to come and go or wax and wane in severity over the course of an affected person's lifetime. Although the severity of symptoms is largely determined by one's perceived level of stress, the constellation of symptoms that will develop during a given psychiatric episode is more difficult to predict, even in the same individual [73, 74]. What is predictable is that symptoms will tend to resolve or completely disappear during low-stress periods [70, 73]. Hypothetically, the reduction in stress reduces intrapsychic tension, thus allowing the pathological hyperactivity in the hyperexcitable brain to dissipate [45, 47].

Then again, because the excitation-to-inhibition balance in the hyperexcitable brain would be tonically elevated, the dissipation of pathological hyperactivity consequent to stress reduction would not necessarily leave an affected person symptom-free. Any persistent symptomatology would, however, be more likely to fall short of one of the currently accepted DSM-5 psychiatric disorders [43]. Such

subsyndromal symptomatology could include excessive worry, excessive fear, obsessive thoughts, moodiness, irritability, impatience, inattentiveness, and trouble sleeping. Although generally perceived as extremes of normal, these symptoms, like upper-end-of-normal vital signs, are both associated with psychiatric disorders [44, 71] and predictive of their development [22, 43, 74]. Also, many of these symptoms, having been variably described as “neurotic” [22], “ruminative” [43], “Type A” [75], or “Type D” [76] personality, have been independently linked to autonomic dysregulation and the development of cardiovascular disease [43, 75, 76]. Other seemingly non-psychiatric ways that neuronal hyperexcitability could manifest include hypersensitivity to sound or light, recurrent headaches, fibromyalgia, irritable bowel, chronic pain, and somatoform disorders [45, 48]. There are also some persons who, for cultural reasons or to avoid social stigma, unconsciously “convert” their emotional pain into physical symptoms. Finally, some persons may mask, distort, or temporarily quell their symptoms through the use of alcohol and other psychoactive substances. Notably, the two most commonly used substances—alcohol and cannabis—are potent anticonvulsants, an observation that could explain the high frequency with which they are used to self-medicate. For all of these reasons, the absence of overt psychiatric symptoms would not necessarily mean that a person did not have hyperexcitable neurons.

5. Probing the Cause of Neuronal Hyperexcitability

Although there are many state-dependent factors that could cause the neurological system to become pathologically hyperexcitable, such as metabolic disturbances, inflammatory states, and stimulant-type drugs, these would not explain the hyperexcitability that is hypothetically at the root of constitutionally-elevated vital signs. The cause of the abnormality would have to be something more fundamental and more deeply rooted than that.

An important clue to what that abnormality might be comes from gene association studies for common psychiatric, neurologic, and general medical conditions. The most robust and consistent outcome of these studies has been the identification of gene variants whose protein products fail to adequately regulate the excitability of neurons [71, 77-89]. Consistent with the wide distribution of neurons (and other excitable cells) throughout the body, ion channelopathies have been linked to a plethora of illnesses including anxiety [74, 83, 87], depression [74, 79, 80, 87], bipolar disorder [74, 77-81, 87], schizophrenia [74, 79, 84-87], autism [74], epilepsy [78, 88, 89], migraine headache [88], irritable bowel syndrome [88], diabetes mellitus [88], high blood pressure [88], cardiac conduction abnormalities [88, 89], renal abnormalities [88], asthma [88], cystic fibrosis [88], peripheral pain syndromes [89, 90], and cancer [88]. That the genetic underpinnings of these disorders would cause a

hyperexcitability of the neurological system would once again place neuronal hyperexcitability at the heart of the connection between constitutionally-elevated vital signs and disease. It would also reveal the probable source of the abnormality.

6. How to Identify the Vulnerability Trait

In contrast to the gradual erosive effects that neuronal hyperexcitability would have on physical health, its effects on mental health would be more readily apparent due to the exquisite sensitivity of the cognitive-emotional system to neuronal excitation [46]. Every time an emotional stressor were experienced, the hyperexcitable brain would abnormally amplify the stress, thus increasing the potential for psychiatric and related functional symptoms to emerge [42, 43]. Moreover, the severity of the symptoms and magnitude of the stress-induced adverse effects on general health would be proportionate to the severity of the neuronal hyperexcitability trait. That could explain why persons with the most severe psychiatric symptoms have the shortest lifespans [27, 30]. It could also explain why they die of the same kinds of illnesses as the general population [27, 30]. From this perspective, psychiatric symptoms could be reconceptualized as the first subjective markers of a chronic dysregulation of the ANS and, hypothetically, of an underlying hyperexcitability of the neurological system. Then again, as previously discussed, the behavior of hyperexcitable neurons tends to normalize during low-stress periods, thus allowing psychiatric symptoms to remit during those times. In addition, social stigma and lack of clarity about the cause of mental illness lead many persons to rationalize, self-medicate, or deny their symptoms even when they are overtly present. These factors could potentially reduce the reliability of psychiatric symptoms as markers of neuronal hyperexcitability. However, the well-established connection between RHR, autonomic dysregulation, and the development a wide range of mental and physical illnesses strongly suggests that RHR continues to flag the trait of neuronal hyperexcitability whether or not a person is symptomatic. Moreover, in all of the RRR studies, which include RRR in relation to either autonomic function, current illness, or risk of illness, the relationship was not linear but rather dichotomized, with RRRs above 15 breaths/min being independently associated with an elevation in sympathetic drive [49], emotional disorders [44], and all-cause morbidity and mortality [31-33]. This dichotomization suggests that there is a gene-related difference between the two groups and, hence, that RRR may be a more reliable marker of the trait of neuronal hyperexcitability and its underlying channelopathies. Although RHRs likewise showed some tendency to dichotomize (mainly above 75 beats/min) [4, 9, 11, 15, 18, 19, 21] the pattern with RRRs was more distinct, a finding that may be explained by the superior long-term stability of RRR in comparison to RHR and other novel markers of disease risk [91].

Based on evidence that neuronal hyperexcitability has a

genetic origin and would most readily be expressed clinically through perturbations in the limbic and autonomic nervous systems, the trait could aptly be called Familial Limbic Autonomic System Hyperexcitability, or FLASH. The acronym “FLASH” fittingly recapitulates the fundamental abnormality that it describes; namely, a hyperexcitability of the neurological system that causes circuit-specific electrical storms in the brain. What would distinguish FLASH storms from seizure activity is that in FLASH the involved neurons would be fewer in number, circuit-specific, and synchronous rather than hypersynchronous in their activity [45, 47]. Consequently, they would not induce the large magnetic fields that are associated with seizure activity [47]. This conceptualization is supported by multiple lines of evidence including the long-recognized connection between seizure disorders and psychiatric disorders [47], the well-recognized benefits of anticonvulsant drugs in psychiatry [92, 93], and the ability of anticonvulsant drugs to improve heart rate variability [94], a well-recognized index of autonomic activity [37, 62, 63].

7. Discussion

The evidence base for the prognostic potential of RHR and other indices of autonomic activity is exploding, yet the mechanism of their connection to long-term health remains obscure. Elucidating the mechanism of the connection is of critical importance because it could reveal a modifiable risk factor, assist in illness detection, and help guide treatment.

Based on a confluence of clinical, neuropsychological, physiological, and genetic evidence, I propose that an inherent hyperexcitability of the neurological system is at the heart of the connection between constitutionally-elevated vital signs and vulnerability to illness. Hypothetically, a failure of the neurological system to self-regulate not only increases the baseline activity of every physiological function, but it also causes a heightened reactivity and slowness to recover that manifests physiologically as a perseveration of the stress response, and cognitive-emotionally as a perseveration of thoughts, feelings, and behaviors [42, 43]. The associated sympathetic overdrive hastens the development and progression of various disease processes [42, 43], thus explaining how a subtle elevation in vital signs, which is reflective of that overdrive [27, 49], can be predictive of long-term health [21, 27, 30, 31, 36, 40]. Neuronal hyperexcitability could also explain why severe mental illness, which is known to identify those with the most severe autonomic dysregulation, is associated with such a shortened lifespan [27].

Although the impact of the proposed abnormality, even after adjusting for confounding factors, such as physical fitness, alcohol use, and cigarette smoking, is highly significant, its effects are severely underestimated because most of the so-called “confounding factors” are hypothetically driven by neuronal hyperexcitability. The amplification of stress that is driven by neuronal hyperexcitability can rob affected persons of the motivation

to exercise; it can cause them to make poor dietary choices; it can cause them to smoke excessively, drink excessively, and use addictive drugs; it can cause them to be impulsive, contentious, and take unnecessary risks; and it can cause them to become emotionally exhausted, lose hope, and, in extreme cases, take their own lives. The association of these behaviors with neuronal hyperexcitability is supported by the comparatively high frequency with which they occur in persons with psychiatric disorders [45]. When the aforementioned effects are factored in, it becomes apparent that the behavioral consequences of neuronal hyperexcitability can be even more destructive than the abnormality itself and that the external consequences are, in essence, an outward expression of the dysregulation that the abnormality is causing within [42]. This has profound implications because neuronal hyperexcitability is a readily modifiable risk factor. Any habit, food, or chemical that calms the brain could potentially help mitigate the trait of neuronal hyperexcitability [45]. Examples include judicious stress management, maintaining an early sleep schedule, exercising in moderation, enjoying a relaxing hobby, avoiding caffeine and other psychostimulants, minimizing refined sugar, and leaning toward a plant-based diet [45]. Although the benefits of these interventions are widely known, the trait of neuronal hyperexcitability could help explain why some persons fail to implement them, and others remain at high risk even if they do implement them. Hypothetically, such persons, when presenting with upper-end-of-normal vital signs, would benefit from treatment with neuroregulators [93] (i.e., anticonvulsants and other brain-calming medications).

8. Conclusion

The proposed identification of a readily modifiable, easy to detect, predisposing factor for a wide range of mental and physical illnesses has enormous implications in the field of medicine. Recognition of the FLASH trait as the underlying driver of the connection between constitutionally-elevated vital signs and disease risk could give healthcare professionals the ability to better educate high-risk patients and more accurately guide them on how to reduce their risk regardless of their clinical status. FLASH could also provide the first objective, quantifiable, physiological basis for the development of psychiatric symptoms, an advance that would circumvent diagnostic ambiguity, provide a consistent target for treatment, and reduce the stigma of mental illness. Also, by reconceptualizing psychiatric symptoms as the first subjective markers of systemic disease, FLASH could help dispel long-held misconceptions about mental illness, encourage patients to be more forthcoming about their symptoms, and curtail discriminatory practices that limit insurance coverage for mental health services. Finally, the ease of identifying the FLASH trait could prompt otherwise unsuspecting persons to become more aware of their health and seek formal evaluation early on, as it would afford them the ability to assess their own genetic vulnerability as well as

their progress in treatment.

Disclosure Statement

The author declares that this article was conceived and written in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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