EBioMedicine 13 (2016) 5–6

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Commentary

Supporting a Neuroimmune Basis of Gulf War Illness

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ARTICLE INFO

Article history:
Received 25 October 2016
Accepted 25 October 2016
Available online 26 October 2016

Gulf War Illness (GWI) is a complex multi-symptom disorder that has proven elusive to understand and treat and it afflicts as many as a quarter of the 700,000 soldiers deployed (Steele, 2000) to the Persian Gulf in the 1991 war. These ill veterans were exposed to a number of agents and conditions, but no specific sets of exposures can explain the persistent symptoms (e.g. headaches, chronic fatigue, memory loss, confusion, skin and gastrointestinal problems) and, not surprisingly, the pathophysiology of GWI has remained unclear (RAC, 2008). However, recent examinations of ill veterans reveal a systemic immune dysfunction that is exacerbated by physiological stress (Broderick et al., 2013). Congruently, animal models now exist that point to a heightened neuroinflammation resulting from several Gulf War-relevant chemical and physiological exposures (O'Callaghan et al., 2015). Neuroinflammation, the elaboration of proinflammatory cytokines and chemokines in the CNS, is known to serve as an underlying cause of sickness behavior, the features of which resemble those associated with GWI. Thus, a convergence of animal and human data now point to a neuroimmune mechanism underlying this disease.

While there is strong evidence suggesting that GWI is the result of exposure to chemical toxicants during the war, there also have been several studies suggesting that this illness is the result of an interaction between exposures and genetics. A prior report in EBioMedicine by Georgopoulos and colleagues (Georgopoulos et al., 2015) provided insight into a basis for a genetic/immune role in GWI by showing that higher counts for six Class II human leukocyte antigen (HLA) alleles conferred protective effects in GW veterans based on lowered symptom severity. In a recent follow-up from this group (Engdahl et al., 2016), a difference in neural synchrony was found between ill and healthy GW veterans. In an important extension of these findings in the current issue, James et al. (2016) integrate these "neuro" and immune components. Using analyses by magnetoencephalography (MEG), they show that the HLA alleles have their action via modulation of neural signaling patterns based on a sophisticated mapping of brain regional neural synchrony. The MEG signatures and their analyses by statistical heat mapping, approaches pioneered by this laboratory, have allowed for the separation of reported symptoms of GWI into distinct HLA and non-HLA related domains. These findings lend further credence to an immune/neuroimmune basis for the symptoms associated with GWI and link them with the concepts of exposure/genetic interactions. However, the non-HLA related cluster also suggests that other mechanisms are at play in the pathophysiology of GWI. The authors present ample speculation as to the roles of both HLA and non-HLA-related factors relevant to GWI, but also provoke many additional questions. For example, what is the next step in understanding the meaning of these HLA and non-HLA domains? Additionally, does the implied autoimmune mechanism provide clear steps to pursue that will lead to treatable targets or provide a path to the discovery of viable treatments for GWI?

As discussed in the commentary of the prior report (Georgopoulos et al., 2015) provided by Wojcik and Lawrie (2015), illness results from war, in general, and the number of studies evaluating the role of stressors in GWI, as well as the implementation of programs to support soldiers both pre- and post-deployment, highlights the impact that stressors have on deployment-related disease. Previously, there has been a tendency to label GWI as a psychological disorder (see discussion by Steele, 2000; RAC, 2004). The overwhelming body of evidence has ruled out a psychological/psychiatric basis of GWI (White et al., 2016) and stressors in theater now are viewed as interacting with neurobiological systems to contribute to GWI symptoms. As such, both human and animal studies have suggested a connection between physiological stress and the immune system, both systemically and in the brain. The findings presented by James et al. (2016) support the notion that GWI is a disease in which genetically-regulated sensitivity of the immune system interacts with exposures that occurred in the Gulf War to reprogram neural functioning. The importance of such studies is highlighted by the emphasis of the Gulf War Illness Research Program of the Department of Defense's Congressionally Directed Medical Research Programs (CDMRP), where the need for research to address the role of neurological and immune dysfunction, as well as genetic predisposition in GWI is a current priority. Not only does the work of James et al. (2016) address all of these areas of interest, but it also supports the expansion of this work into other relevant genetic/immune based studies. Such studies are underway in animal models where genetically defined strains of mice, which combine a toxicologically susceptible mouse strain with a more resistant strain (Jones et al., 2013) can be used to replicate a genetically diverse population to evaluate genetic-based neuroimmune susceptibility to GWI. The combination of studies in both humans and

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2016.10.019.
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http://dx.doi.org/10.1016/j.ebiom.2016.10.037

animals can hopefully lead to a greater understanding of the cause of GWI and the development of specific, targeted therapeutics to aid a population of ill veterans who have been without a successful treatment for nearly three decades.

Disclosure

The authors declared no conflicts of interest.

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