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Commentary

Towards a Biopsychosocial Model of Gulf War Illness?

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In this issue of *EBioMedicine*, Georgopoulos et al. report significant differences in the frequency of six HLA alleles in a sample of 66 US Gulf War illness (GWI) veterans and 16 healthy veteran controls (Georgopoulos et al., 2016). Their interpretation is that these alleles conferred a protective effect, as evidenced by the negative association between GWI symptom severity and allele counts, such that higher allele counts were associated with lower symptom severity in the whole sampled population.

GWI is a chronic multi-symptom illness reported by soldiers returning from the Gulf War of 1990–1991. As many as one in four of 700,000 US soldiers reported such symptoms, which included cognitive and mood disturbance, fatigue, musculoskeletal and other non-specific complaints (Steele, 2000). It also affected other armies serving in that war. For example, 17% of almost 3000 UK veterans reported having GWI (Chalder et al., 2001).

The etiology of these chronic symptoms has been difficult to elucidate despite extensive, if retrospective, research and investment. Suggested mechanisms have included multiple vaccinations, chemical exposure in theater, the use of pyridostigmine bromide as a prophylactic against nerve gas attacks and other exposures such as depleted uranium used in weaponry. GWI has also been viewed as a chronic medically unexplained illness comparable to chronic fatigue syndrome (CFS) (Iversen et al., 2007). Indeed, the US Institute of Medicine uses the term chronic multi-symptom illness rather than GWI in reference to this topic. Immunological models of pathophysiology have been explored, particularly with respect to the impact of multiple vaccinations in a stressful environment, and it is here that the reported finding may add evidence if replicated. However, it is important to note that not all forces carried out such extensive immunization programs, such as Denmark, whose soldiers have similarly suffered illness following the Gulf War. Furthermore, history shows that war makes soldiers ill, with different presentations predominating during different campaigns in the nineteenth and twentieth centuries. For example, a review and cluster analysis of post-combat syndromes from a random sample of more than 1800 records in British veterans from the Boer War to the Gulf War demonstrated the rise and fall of different chronic syndromes, including disordered activity of the heart, non-ulcer dyspepsia, shell shock and neurasthenia, as well as those of contemporary records of GWI (Jones et al., 2002).

Complex, poorly understood conditions demand consideration from multiple non-exclusive perspectives (Lawrie et al., 1997). Biopsychosocial approaches are well established in optimizing treatment of several chronic conditions, regardless of etiology — be it heart disease, diabetes or CFS. In particular, cognitive behavioral therapy (CBT) and a graded approach to increasing activity have been found to improve outcomes in CFS. However, a randomized controlled trial (RCT) of exactly this approach (CBT and graded exercise) in GWI demonstrated only modest benefit, in a sample of 1092 US GWI sufferers with 11% improving at 1 year with usual care, 18% with CBT (OR = 1.7) and the exercise intervention having a minimal impact (Donta et al., 2003). Differences between soldiers and the general population these interventions were developed for (in baseline activity levels for example), may have limited the effectiveness of the intervention. Psychological or functional interventions for chronic illness may have low acceptability amongst young fit soldiers and their superiors. Clearly this leaves a need to explore other treatments to benefit ill veterans.

The plight of GWI sufferers, many of whom remain chronically symptomatic, has driven funding and research into approaches to better support soldiers following deployment. In the US for example, a resilience program ('Battlemind') has been developed which appeared to reduce the burden of stress related and post-traumatic symptoms. However, a UK RCT failed to demonstrate its effectiveness in a British Army population (Mulligan et al., 2012). Meanwhile, active service continues to induce a somewhat lower but still significant incidence of similar symptoms following deployment in Iraq and Afghanistan.

There remains scope for immune and genetic hypotheses to inform our understanding of GWI and similar syndromes. One hypothesis has been that a stress-induced modulation of circulating pro-inflammatory factors may have primed soldiers to have an exaggerated response to insults, be they chemical exposure, vaccination post-deployment or other medication, thus precipitating GWI. Recent reports include that of greater cytokine variability in veterans with GWI compared to controls (Parkitny et al., 2015), and of a mouse model of increased corticosterone (consistent with a physiological stress state) priming a pro-inflammatory

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response to a substance analogous to some of the postulated exposures in GWI (O'Callaghan et al., 2015). Such findings are not specific to GWI, but if replicated they do at least offer the possibility of new hope and treatments. We note that recruitment is underway in Minnesota for a trial of prednisone, a steroid with anti-inflammatory properties, in GWI. To date, large-scale replication of immunological mechanisms in the etiology of GWI has remained elusive and the heterogeneity of exposures (e.g. vaccinations) across different armies remains a challenge to rigorously testing this hypothesis.

The findings reported by Georgopoulos et al. suggest that a genetic immunological factor may have played a protective role against GWI in soldiers. Scientific caution demands, as the authors suggest, replication in other and much larger samples. One cannot help exercise a degree of healthy skepticism in a field so extensively studied with such little obvious advance in treatment in the past two decades, but any potentially robust means of a step forward can only be welcomed.

Disclosure

The authors declared no conflicts of interest.

References

Chalder, T., et al., 2001. Prevalence of Gulf war veterans who believe they have Gulf war syndrome: questionnaire study. BMJ 323, 473–476.
Donta, S.T., et al., 2003. Cognitive behavioral therapy and aerobic exercise for Gulf War veterans' illnesses: a randomized controlled trial. JAMA 289, 1396–1404.
Georgopoulos, A.P., et al., 2016. Reduced human leukocyte antigen (HLA) protection in Gulf War Illness (GWI). EBioMedicine 3, 79–85.
Iversen, A., Chalder, T., Wessely, S., 2007. Gulf War Illness: lessons from medically unexplained symptoms. Clin. Psychol. Rev. 27, 842–854.
Jones, E., et al., 2002. Post-combat syndromes from the Boer war to the Gulf war: a cluster analysis of their nature and attribution. BMJ 324, 321–324.
Lawrie, S.M., MacHale, S.M., Power, M.J., Goodwin, G.M., 1997. Is the chronic fatigue syndrome best understood as a primary disturbance of the sense of effort. Psychol. Med. 27, 995–999.
Mulligan, K., et al., 2012. Postdeployment Battlemind training for the U.K. armed forces: a cluster randomized controlled trial. J. Consult. Clin. Psychol. 80, 331–341.
O'Callaghan, J.P., Kelly, K.A., Locker, A.R., Miller, D.B., Lasley, S.M., 2015. Corticosterone primes the neuroinflammatory response to DFP in mice: potential animal model of Gulf War Illness. J. Neurochem. 133, 708–721.
Parkitny, L., Middleton, S., Baker, K., Younger, J., 2015. Evidence for abnormal cytokine expression in Gulf War Illness: a preliminary analysis of daily immune monitoring data. BMC Immunol. 16, 57.
Steele, L., 2000. Prevalence and patterns of Gulf War illness in Kansas veterans: association of symptoms with characteristics of person, place, and time of military service. Am. J. Epidemiol. 152, 992–1002.