A Retrospective, Epidemiological Review of Hemiplegic Migraines in a Military Population

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INTRODUCTION
Prior to joining the US military, every potential service member must meet the minimum fitness standards for induction, enlistment, or appointment in the US Armed Forces. Individuals with certain prior or existing medical conditions are disqualified from entry into the military. As a result, those entering the military represent a healthier cross section of the populace than the general American public. Once in service, however, military personnel are often exposed to various occupational hazards throughout their military careers that place them at increased risk for the development of a number of psychological health and medical conditions relative to their initial health status upon entry onto active duty. Some of these conditions are readily intuitive, such as the development of combat-related posttraumatic stress disorder (PTSD) or experiencing a traumatic brain injury (TBI) as a consequence of combat deployments. Other conditions that are not so apparently related to military service also emerge within this population. Headaches represent one such condition that, given their unpredictability and debilitating nature, may cause significant disruptions to operational readiness.

Headache disorders are classified in the International Classification of Headache Disorders 3rd edition (ICHD-3) as primary and secondary type headaches. Primary headaches are symptom-based and include tension-type headaches, migraine headaches, trigeminal autonomic cephalalgias, and other headaches (i.e., cough and exercise headache). The vast majority of headaches are tension-type headaches (46-78%) and migraine headaches (14-15%). Together, tension-type and migraine headaches comprise between 60-93% of reportable headaches. In
addition, tension-type and migraine headaches are ranked globally as the number two and three most burdensome health conditions in the 2010 Global Burden of Disease Study.6

Migraine headaches have two major types: migraine without aura (ICHD-3 code: 1.1) and migraine with aura (ICHD-3 code: 1.2).4 In the general population, migraine primarily affects women (3:1 over men).5 Migraine without aura occurs in around 15% of the general population, and they are more common in females (about 20%) than males (about 10%). Migraine with aura occurs in around 8%.5,7 and often lasts for about 30–75 minutes.8 Classic aura consists of any number of symptoms to include: hemispheric emanations of headache, nausea, phonophobia, photophobia. Clinically, the two are often treated in a similar manner2,9–11 however, instances of more severe phenotypes (i.e., hemiplegic migraine) may present unique challenges both for military providers as well as force readiness.

Hemiplegic migraine (ICHD-3 code: 1.2.3) specifically is a particularly rare but temporarily disabling headache subtype of migraine with aura. The ICHD-3 diagnostic criteria for hemiplegic migraine are listed in Table I. Hemiplegic migraine is further subdivided into familial hemiplegic migraine (ICHD-3 code 1.2.3.1) and sporadic hemiplegic migraine (ICHD-3 code: 1.2.3.2). Migraineurs with familial hemiplegic migraine have a first or second-degree family member with hemiplegic migraine and a defined genetic cause (i.e., missense mutations in genes that encode proteins involved in ion transportation),8 while persons with sporadic hemiplegic migraine do not have an affected family member (See Table I).4 Sporadic and Familial hemiplegic migraine are clinically identical to familial hemiplegic migraine and the two occur in the general populace with approximately the same frequency.4,12 There have not been any recent prevalence estimates completed but in the late 1990s, a population prevalence of hemiplegic migraine, in Denmark found hemiplegic migraine to occur in approximately 0.01% of the population.13 The same study found the gender ratio (M:F) of Familial hemiplegic migraine to be 1:2.5 and Sporadic hemiplegic migraine to be 1:4.5.13 Conversely, there have been no published incidence rates on hemiplegic migraine.

An episode of hemiplegic migraine may include all the classic migraine with aura symptoms as well those associated with migraine with brainstem aura (i.e., hemispheric or brainstem emanations of migraine with aura symptoms). Hemiplegic migraines often present with a progressive feeling of motor aura (i.e., tingling or numbness in the hand, face, leg, or chest) and may eventually lead to actual loss of motor control.14 Patients with hemiplegic migraine may present with symptoms such as: aphasia (~80%), comprehension impairment (~10%), vertigo, tinnitus, confusion, or loss of consciousness (up to 70%) as well as searing head pain, confusion, and increased white blood cell counts in the cerebrospinal fluid.8 Episodes of motor aura (i.e., weakness to or complete loss of mobility in: the face/tongue, hand/arm, foot/leg, and body), are unique to hemiplegic migraine and typically last between 5.5 to 7 hours.8 Aphasic aura (i.e., paraphasia, impaired language production, and impaired comprehension) typically lasts four times longer in individuals with hemiplegic migraine than is commonly seen in individuals with other types of migraine.8

Hemiplegic migraine also adds unique aspects of motor aura in the form of acute neurological symptoms akin to stroke that may last extended periods of time.4,12,15 The aura associated with hemiplegic migraine may last for several weeks4 and, in severe circumstances, cause coma or neuronal death.16,17 Hemiplegic migraine presentation often mimics transient ischemic stroke or may be mistaken as an epileptic seizure. Treatment for hemiplegic migraine may require advanced medical procedures and tests that are not readily

<table>
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<tr>
<td>1.2.3</td>
<td>Hemiplegic migraine</td>
<td>Attacks fulfilling criteria for 1.2 Migraine with aura and Aura consisting of both of the following: Fully reversible motor weakness Fully reversible visual, sensory and/or speech/language symptoms</td>
</tr>
<tr>
<td>1.2.3.1</td>
<td>Familial hemiplegic migraine</td>
<td>Attacks fulfilling criteria for 1.2.3 Hemiplegic migraine At least one first- or second-degree relative has had attacks fulfilling criteria for 1.2.3 Hemiplegic migraine.</td>
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<tr>
<td>1.2.3.1.1</td>
<td>Familial hemiplegic migraine type 1</td>
<td>Attacks fulfilling criteria for 1.2.3.1 Familial hemiplegic migraine A mutation on the CACNA1A gene has been demonstrated.</td>
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<td>1.2.3.1.2</td>
<td>Familial hemiplegic migraine type 2</td>
<td>Attacks fulfilling criteria for 1.2.3.1 Familial hemiplegic migraine A mutation on the ATP1A2 gene has been demonstrated.</td>
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<td>Familial hemiplegic migraine type 3</td>
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<td>Familial hemiplegic migraine, other loci</td>
<td>Attacks fulfilling criteria for 1.2.3.1 Familial hemiplegic migraine Genetic testing has demonstrated no mutation on the CACNA1A, ATP1A2, or SCN1A gene.</td>
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<td>1.2.3.2</td>
<td>Sporadic hemiplegic migraine</td>
<td>Attacks fulfilling criteria for 1.2.3 Hemiplegic migraine No first- or second-degree relative fulfills criteria for 1.2.3 Hemiplegic migraine.</td>
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available in contemporary operating environments (i.e., neuroimaging). There is a paucity of research in the existing literature to date on the etiology of hemiplegic migraine within the general population and no published research on active duty service members or veterans. What little research exists suggests that hemiplegic migraine may be related to minor head trauma in the general population, but this research is limited as much of the work conducted thus far has focused on case studies, largely amongst children. In line with many commonly observed headache precipitators (i.e., physical and psychological stressors, exertion, dehydration, bright light, and sleep disruptions), Additionally, they are often exposed to increased instances of head trauma, a suspected precipitator of hemiplegic migraine. In fact, in the post 9/11 force, headache disorders have been recorded as one of the top ten conditions for which active duty service members receive an involuntary, medical discharge. In line with many commonly observed post 9/11 disorders (i.e., PTSD and TBI) the Veterans Health Administration (VHA) has also recently started to see a large increase in migraine diagnoses (nearly 1:5 in some demographics) among veterans.

Due to the limited research available on hemiplegic migraine, and with consideration to the prevalence of head injuries in post 9/11 service members and veterans, we hypothesized there would be increasing incidence of hemiplegic migraine amongst active duty service members over time. The primary objective of the current study was to examine incidence rates of hemiplegic migraine in military personnel over the past 20 years and to determine whether the incidence of hemiplegic migraines within a variety of key demographic characteristics differs from the military population at large.

**METHODS**

To determine hemiplegic migraine occurrence within the military, we analyzed data stored in the Defense Medical Epidemiological Database (DMED). The DMED is a subset database of the Defense Medical Surveillance System. It records longitudinal data relevant to medical events and diseases for US military service personnel data and are further stratified by: Race, Gender, Age, Service Component, Military Pay Grade, Location, Duty type, and Marital Status. Medical diagnosis information is available through both International Classification of Disorders (ICD) codes 9 or 10. Cohort data for hemiplegic migraine were retrievable from 1990 through 2017. Extracted DMED data are group-level counts, which only allows for comparison at the population level.

Data was accessed February 25, 2018 and was filtered for initial diagnoses of hemiplegic migraine (ICD-9 – 346.3; ICD-10 – G43.4). We examined hemiplegic migraine incidence within each available demographic (i.e., gender, age, marital status, military pay grade, branch of service, military occupational specialty, and race; see Table II) and conducted one sample one sample Chi-Square goodness of fit tests to determine whether any demographic subgroups were over- or under-represented with regards to hemiplegic migraine diagnoses relative to their respective percentages in the entire military. The one sample Chi-Square test is a nonparametric test that...
is used to determine whether the distribution of cases (e.g., participants) in a single categorical variable (e.g., gender of new onset hemiplegic migraine cases) follows a known or hypothesized distribution (e.g., gender distribution in the military). Significance of these tests indicates that the observed proportions differ significantly from those in the known or hypothesized distributions. The data distributions for each military composition variable used to derive expected values for each test were provided with the DMED data at time of data extraction. Chi-square results are reported with the appropriate degrees of freedom and number of subjects (i.e., \(X^2(1, 597)\)) per test. Distributions for each demographic variable used in this study for the entire military force were obtained from the DMED (See Table II). Based on DMED data, the mean population of service members each year was calculated to be 1,359,819 service members, with a low of 1,283,682 in 2017 and a high of 1,418,896 in 2010. All demographic variables reported in this manuscript are reported based on the pre-designated cohort groups as defined by and stored in the DMED (i.e., Age: <20, 20-24, 25-29, 30-34, 35-39, 40+). The present project was reviewed by the Institutional Review Board at the University of Texas Health Science Center at San Antonio and was deemed to be not human research (protocol number: HSC20190028N).

RESULTS

Hemiplegic migraine received an ICD code in 1988, but no cases were recorded in the DMED between 1990 and 2007. From 2008 to 2017, 597 service members were diagnosed for the first time with hemiplegic migraine (see Fig. 1). In 2008, four cases were identified. In 2009, the Department of Defense recorded a greater than 1,400% increase (\(n = 61\)) in hemiplegic migraine first-time diagnoses. In subsequent years, the number of first-time diagnoses fluctuated, but not substantially. In 2016, diagnoses peaked (\(n = 101\)) with a greater than 2,400% increase over the first-year diagnoses were recorded (2008; Fig. 1).

The incidence rates of hemiplegic migraine (per 1,000) in the US military ranged between 0.04 to 0.05 (i.e., 4 or 5 per 100,000). In the present sample, those most often diagnosed with hemiplegic migraine (see Table II) were white (65%), married (63%), male (60%), in the enlisted pay grade of E-5 to E-9 (52%), serving in combat support roles (37%), in the Army (41%), and were between the ages of 25-29 (24%).

One sample Chi-square tests showed the observed and expected frequencies differed significantly for five of the six demographic variables tested. Gender (Supplementary Figure 1) exhibited a significant discrepancy between observed and expected frequencies \(X^2(1, 597) = 297.37, p = 0.001\), with females presenting with 2.66 times as many more cases (\(n = 240\)) than expected (\(n = 90\)). Military Pay Grade (Supplementary Figure 2) likewise was found to be significant \(X^2(3, 597) = 57.96, p < .001\), with individuals in the pay grade of E-5 to E-9 presenting with 1.34 times as many more cases (\(n = 313\)) than expected (\(n = 234\)). E-1 to E-4 and all commissioned officers presented with fewer cases than expected.

A significant Chi-square was also found for Service Component (Supplementary Figure 3), \(X^2(3, 597) = 31.48, p < .001\). Both the Army and Air Force presented with significantly more new cases (\(n = 246\) and 181, respectively) than expected (\(n = 222\) and 142, respectively), whereas the Marines and Navy were both underrepresented in number of new cases (\(n = 67\) and 103, respectively) compared to expected values (\(n = 86\) and 147, respectively). Additionally,
significant differences between observed and expected frequencies were observed for Race (Supplementary Figure 4), $X^2 (2, 597) = 37.32, p < .001$. Both white and black service members presented with more new cases of hemiplegic migraine ($n = 390$ and $130$, respectively) than expected ($n = 358$ and $101$, respectively), whereas individuals with a race other than white or black presented with fewer new cases ($n = 77$) than expected ($n = 137$). Hemiplegic migraine incidence differed from expectations with respect to the age categories we tested as well (Supplementary Figure 5), $X^2 (5, 597) = 62.60, p < .001$, with the most extreme discrepancies from expected values existing for service members <25 years of age and for those >34 years of age. Marital status (Supplementary Figure 6) proportions did not differ from expected values $X^2 (1, 597) = 2.57, p > .05$. Due to ambiguity in the DMED database with regards to population densities and military occupational specialties (MOS), we were unable to test statistical differences among the varied MOSs.

**DISCUSSION**

Reporting of hemiplegic migraine has increased significantly in recent years. To date, the prevalence rates of hemiplegic migraine in the military population have not been established. Data presented in this paper, however, show increasing incidence rates of hemiplegic migraine in service members. The increasing incidence rates discovered in this study indicate extant prevalence estimates may be outdated. The recent increases of recognition may be due to increased awareness amongst military medical providers, however a more likely explanation is the causal relationship between traumatic brain injury and hemiplegic migraine onset. At the present the DMED does not allow for multiple ICD codes to be searched at once thereby limiting our ability to discuss this prospect with certainty, though this is certainly a recommendation for future research.

In the general population, females are overrepresented in most forms of headache to include hemiplegic migraine. Among civilians, sporadic hemiplegic migraine has been recorded between 3:1 and 4:5:1 between females and males. However, when considering the ratio of females to males ($1:5.67$) in the military, we expected males to be overrepresented with hemiplegic migraine diagnoses, which was not the case. In fact, females comprised significantly more new onset hemiplegic migraine cases than expected given the gender distribution of the military, though the observed distribution was far less than that seen in civilians. This is likely due to the interplay of biologic considerations with migraine triggers common to all service members.

With consideration to most common migraine triggers among military service members (namely: environmental factors [74%], stress [67%], fatigue [57%], and exertion/activity [32%]), the role of the Army in the contemporary operating environment, it was not surprising to see Soldiers account for the majority of hemiplegic migraine diagnoses (41%). Interestingly, the Air Force comprises only 23% of the Armed Forces but Airmen represented 30% of the total diagnoses ($N = 181$). Flying military aircraft could be an occupational factor related to the higher rate amongst Airmen. Recent reports have found that occupational exposure to hypobaria in U-2 pilots can lead to increased incidence of white matter hyperintensities. It is also possible that Air Force medical providers have a greater emphasis during their graduate medical education training (e.g., neurology residency programs) on the differential diagnosis of headaches that results in an increased detection of hemiplegic migraines. Additional research is warranted to examine the factors unique to the service components that are contributing to greater or fewer diagnoses than expected based on service component densities.

The finding that black service members were found to be over represented in this sample (observed: $n = 130$; expected: $n = 101.5$) is noteworthy in that there is limited research on race and migraine prevalence, specifically within the military context. Social determinants of health risk such as socioeconomic status are known to increase the risk for developing migraines. Differences in socioeconomic status prior to joining the military could explain some of the observed disparity. Alternatively, hemiplegic migraine is known to be sensitive to genetic pre-morbidities. Future studies of hemiplegic migraines in military personnel should assess for family history of migraine conditions to elucidate the phenotypes present in this cross-section of the population.

Despite comprising 38% of the military, service members between 17-24 years of age only accounted for 27% of the hemiplegic migraine diagnoses in the present study. Conversely, service members aged >35 were over represented by nearly 50%. This is directly in line with previous findings that show migraines are most common among those aged 35-44. Additionally, we offer tentative speculation that the increased instances of hemiplegic migraine among service members aged >35 may be related to a higher likelihood of combat exposure sequelae as well as the potentially long lead time that it may take for hemiplegic migraine to be diagnosed.

In the broader military, enlisted service members outnumbered commissioned officers by greater than a 4:1 ratio. Therefore, we expected to find more enlisted service members with hemiplegic migraine diagnoses. Enlisted were in fact overrepresented amongst service members with hemiplegic migraine by nearly a 6:1 ratio. This may reflect the fact that enlisted service members conduct a broader array of duties and experience more occupational hazards that may expose them to triggers for this condition. Future research should investigate this more closely by examining whether enlisted service members with specific roles or jobs constitute a sizeable proportion of new onset cases. Though we were only able to qualitatively describe the impacts of hemiplegic migraine by MOS, the finding that hemiplegic
migraine is most commonly diagnosed amongst those with a combat service support MOS is not surprising as the majority of the US military is comprised of non-combat arms personnel. Future studies that are not reliant solely on cohort data should examine MOS and pay grade to see if duty or probable duty position has a relation to hemiplegic migraine diagnosis.

This study has a number of limitations. It is based on retrospective data that does not include where hemiplegic migraine diagnoses occurred (i.e., deployed or stateside) or at what time in a service member’s career the diagnosis was made. While causal relationships (i.e., between hemiplegic migraine instance and increases in head trauma) cannot be established from this data, there appears to be a correlation between exigencies associated with military service and hemiplegic migraine diagnoses. Though there is a clear rise in hemiplegic migraine diagnoses over the past decade, it is unclear why there were no cases diagnosed or recorded prior to 2007. Due to the rarity of hemiplegic migraine presentation, it is possible there was a general lack of knowledge or awareness of hemiplegic migraine among military medical providers. Therefore, the temporal increase in hemiplegic migraine diagnoses in the military could be because of increased diagnostic awareness and specificity in military medical providers rather than a true increase in incidence. Similarly, differences in hemiplegic migraine incidence between service branches may be a reflection of differences between medical education and training programs across the services rather than a true difference in occurrence within individual branches.

An additional explanation for the increased incidence of hemiplegic migraine is that during the study timeframe, annual military recruitment quotas were increased, and medical waivers were increased. Therefore, more service members may have received medical waivers for migraine headaches, thereby contributing to the increased incidence in the military. Finally, the DMED is populated by cohort data. As a result, the analysis was limited to descriptive statistics and weighted frequency distributions. Also due to the ICDs for hemiplegic migraine, it was not possible to assess severity or frequency based solely on the information available. The sudden rise of hemiplegic migraine in the US military over the past decade, however, provides interesting challenges to the currently held prevalence rates while providing ancillary support for the need to re-examine what is currently known about the prevalence of hemiplegic migraine.

CONCLUSIONS

Despite its limitations, the current study has a number of strengths. First, the DMED has provided what may be the largest cohort of population based hemiplegic migraine data in the world. To the best of our knowledge, few population-based studies of human subjects with hemiplegic migraine exist in the extant scientific literature, and to the best of our knowledge this is the first study to report incidence data. Thomsen and colleagues identified a population prevalence of 0.01% for familial and sporadic hemiplegic migraine. In the present study, our findings are slightly higher (0.04 to 0.05) than the previously recorded prevalence rates in civilians. Additionally, the present study is the only one to address hemiplegic migraine in a military population. Here we provide scientific evidence to justify further research into the prevalence and impact of migraine, specifically unusual phenotypes in the military population. Due to the noted increase in incidence rates over the past decade, future research should re-evaluate known prevalence rates. Though it appears that awareness among military medical providers has increased in recent years, the limited number of published manuscripts in this area coupled with the data presented should serve to increase hemiplegic migraine awareness among military healthcare providers. This may, in turn, may allow for a better understanding of hemiplegic migraine and facilitation of referrals to military neurologists and other health care specialists.

In the general population, the impact of migraine on individuals is substantial. Work productivity has been reported to be reduced by at least 50% in many migraineurs. In uniquely demanding military environments, migraines and hemiplegic migraines in particular can be detrimental to medical readiness and mission accomplishment. If the upward trend in hemiplegic migraine diagnoses continues, it may result in a significant drain on the resources of both the military healthcare system and the Department of Veterans Affairs.

Due to the remarkable nature of the psychological and physical injuries seen in post 9/11 veterans, it is reasonable to expect a continued rise in headache conditions such as hemiplegic migraine in active duty and veteran populations. There is also a need to increase our understanding of potential comorbidities, such as traumatic brain injury and post-traumatic stress disorders, in these populations. As the US military continues into nearly the third decade of continuous combat operations, additional research is warranted to reassess the prevalence and impact of migraine phenotypes among active duty service members and veterans.

SUPPLEMENTARY MATERIAL

Supplementary material is available at Military Medicine online.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

REFERENCES


