Correlates of posttraumatic epilepsy 35 years following combat brain injury

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ABSTRACT

Background: The Vietnam Head Injury Study (VHIS) is a prospective, longitudinal follow-up of 1,221 Vietnam War veterans with mostly penetrating head injuries (PHIs). The high prevalence (45%–53%) of posttraumatic epilepsy (PTE) in this unique cohort makes it valuable for study.

Methods: A standardized multidisciplinary neurologic, cognitive, behavioral, and brain imaging evaluation was conducted on 199 VHIS veterans plus uninjured controls, some 30 to 35 years after injury, as part of phase 3 of this study.

Results: The prevalence of seizures (87 patients, 43.7%) was similar to that found during phase 2 evaluations 20 years earlier, but 11 of 87 (12.6%) reported very late onset of PTE after phase 2 (more than 14 years after injury). Those patients were not different from patients with earlier-onset PTE in any of the measures studied. Within the phase 3 cohort, the most common seizure type last experienced was complex partial seizures (31.0%), with increasing frequency after injury. Of subjects with PTE, 88% were receiving anticonvulsants. Left parietal lobe lesions and retained ferric metal fragments were associated with PTE in a logistic regression model. Total brain volume loss predicted seizure frequency.

Conclusions: Patients with PHI carry a high risk of PTE decades after their injury, and so require long-term medical follow-up. Lesion location, lesion size, and lesion type were predictors of PTE.
Neurology® 2010;75:224–229

GLOSSARY

ABLe = Analysis of Brain Lesions; **AFQT** = Armed Forces Qualification Test; **AIR** = Automated Image Registration; **CHI** = closed head injury; **GAD** = glutamic acid decarboxylase; **PH1** = phase 1; **PH2** = phase 2; **PH3** = phase 3; **PHI** = penetrating head injury; **PTE** = posttraumatic epilepsy; **TBI** = traumatic brain injury; **VHIS** = Vietnam Head Injury Study; **WAIS** = Wechsler Adult Intelligence Scale.

Posttraumatic epilepsy (PTE) is the most common cause of new-onset epilepsy in young adults, with up to 30,000 new cases per year in the United States,[1,2] and has been linked to region, type, and severity of injury.[3] The high incidence of postcombat PTE, compared with civilian populations,[4] makes these populations particularly valuable for study.[5] The Vietnam Head Injury Study originally included 1,221 Vietnam veterans with head injuries.[6] Phase 1 (PH1) of the study was a review of subjects' medical records 5 years after injury.[6-8]

Phase 2 (PH2) evaluated 520 subjects with head injuries from the original registry and 85 normal volunteers. Ninety-two percent had penetrating head injuries.[9-12] The prevalence of PTE was 53%, and was associated with total brain volume loss and presence of hematoma or retained metal fragments.[13] PTE onset was predominantly in the first year after injury (table 1). Of those with persistent seizures, 66% were taking anticonvulsant medication. Only 5 brain areas significantly predicted seizure occurrence: right vertex gray matter, left convexity cortex, left temporal gray matter, right frontal white matter, and right corona radiate. Lesions in the

Editorial, page 202

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Disclosure: Author disclosures are provided at the end of the article.

The views expressed in this article are those of the author and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or US Government.

Table 1 Onset latency and duration of seizures					
Onset latency	<12 mo	1-5 y	5-10 y	10-15 y	15-35 y
n	133	49	22	13	14
Mean duration, mo	98.5	103	46	8	32.9

left hippocampus correlated with increased seizure frequency, whereas insula and splenium lesions correlated with lower seizure frequency. Lesions of the posterior callosum and caudate nucleus were associated with less persistent seizures.

Cognitive performance was generally not associated with PTE after compensating for brain volume loss and preinjury intelligence. Exceptions were nonverbal intelligence, verbal learning, memory, motor speed, and control.[13]

We reviewed this population to assess the longer-term associations of traumatic brain injury (TBI) and PTE.

METHODS Of the 520 subjects with head injuries assessed at PH2, 484 were still alive, and 182 attended phase 3 (PH3), 35 years after injury. Additionally, 17 subjects with head injuries identified in PH1 who did not attend PH2 were assessed. Of the original 80 control subjects recruited in PH2 (uninjured Vietnam veterans, matched by age), 32 attended and a further 23 were recruited through advertisements in veteran publications. Subjects were assessed over 5 to 7 days at the National Naval Medical Center, Bethesda, Maryland. This included a history and examination by a neurologist experienced with this population (A.M.S.). PTE diagnosis was based solely on a semistructured interview. Testing included 2 measures of intelligence, the Armed Forces Qualification Test (AFQT)[14] and the Wechsler Adult Intelligence Scale (WAIS) III.[15]

Standard protocol approvals, registrations, and patient consents. We received approval from an institutional ethical standards committee. Written informed consent was obtained from all subjects.

CT scan analysis. Brain lesions were identified by CT scan, and the data were reconstructed with 1-mm overlapping slice thickness and 1-mm interval. Lesions were evaluated by a radiologist and processed by using Analysis of Brain Lesions (ABLe) software.[16,17] ABLe is an interactive program run via MEDx medical imaging software (Medical Numerics Inc., Sterling, VA). Within ABLe, the lesions were drawn manually in native space by V.R. and reviewed by J.G., enabling a consensus decision to be reached regarding the limits of each lesion. Lesion volume was calculated and the brain images automatically registered to a template brain in Talairach space.[18] The template image was derived from a CT scan of a 27-year-old man, conformed to Talairach dimensions in MEDx by using an affine 12-parameter transformation derived from the Automated Image Registration (AIR) software within MEDx.[15] Computerized graphics of Brodmann areas were derived by mapping onto a resliced version of the CT image. Thus the intersection of lesions with Brodmann areas could be determined by using the VOTL database within ABLe. This procedure allowed the measurement of normalized lesion volume and percentage of brain regions involved. Three measurements of atrophy were made via a consensus decision between A.M.S. and V.R.: corpus callosum width (based on 3 measurements: genu, midsection, and splenium), a rating of global brain atrophy, and atrophy in each lobe. Third ventricle width has previously been shown to correlate with other measures of atrophy.[19] We found third ventricle width correlated with corpus callosum width ($r = 0.416$, $p < 0.001$; $r = 0.296$, $p = 0.001$; $r = 0.352$, $p < 0.001$), as well as global atrophy ($r = 0.377$, $p < 0.001$).

Genetic analysis. Because both single and multiple gene mutations have been associated with epilepsy,[20-22] we screened for a number of genetic markers. These included *APOE* ε4, glutamic acid decarboxylase (GAD), catechol-*O*-methyltransferase, GRIN (a glutamate receptor and a subunit of the NMDA), brain-derived neurotrophic factor, and dopamine β-hydroxylase.

Genomic DNA was isolated from blood leukocytes by using a Nucleon™ BACC2 kit according to the manufacturer's protocol (Amersham Life Science, Piscataway, NJ). Quality and quantity of genomic DNA was determined spectrophotometrically by using the absorbance reading 260 and 280 nm. Some DNA samples were repurified by incorporating an additional phenol-chloroform (24:1 vol/vol) extraction before recovery by ethanol precipitation. DNA concentrations were measured by using a NanoDrop ND-1000 spectrophotometer (NanoDrop Technologies, Wilmington, DE). The completion rate of each assay was >99%, with an error rate of <1%.

See appendix e-1, table e-1, and table e-2 on the *Neurology*® Web site at www.neurology.org for additional details.

Statistical analysis. A variety of parametric procedures were used in this study. Analysis of variances and linear logistic and stepwise multiple-regression procedures were performed to assess the impact of preinjury intelligence, change in or current intelligence, brain volume loss, lesion location, wound characteristics, and genetic markers on history of PTE, seizure duration, frequency, or type. A significance level of $p = 0.05$ or less was required to enter and remain in the stepwise regression procedures.

RESULTS **Seizure prevalence and characteristics.** The overall prevalence of PTE in the group with head injuries was 43.7% (87 of 199 subjects). This compares with 53% in the cohort reported in PH2.[13] The mean duration of the last seizure period (time from first to last reported seizure) was 33 months. In the most recent year of reported seizures, the most common frequency was 2 to 10 seizures per year. Complex partial seizures occurred in 31%, and simple partial seizures evolving to generalized seizures occurred in 25%. In contrast, the most commonly reported first seizure type was simple partial seizures evolving to generalized seizures (33.3%), followed by generalized (20.7%; as diagnosis was based solely on subject history, we could not determine whether these were primary or secondary). As at PH2, there was an association between the duration and frequency of seizures during the first reported seizure period ($r = 0.320$, $p = 0.008$).

Figure Prevalence of posttraumatic epilepsy in years after traumatic brain injury

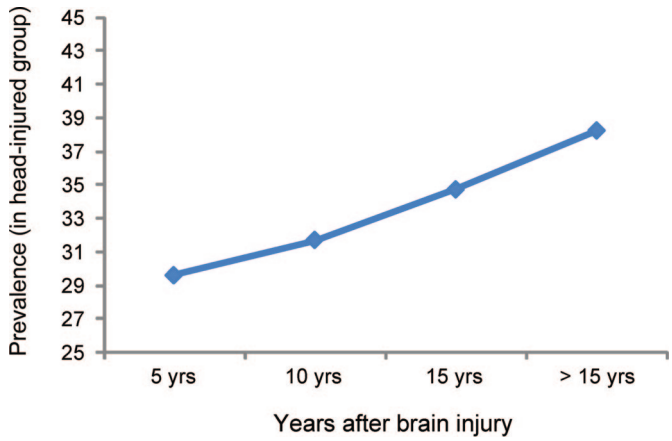

Table 2 Differences between phase 3 attendees and nonattendees[a]

	Phase 2 attendees	Phase 3 attendees	p Value
Years of education	12.98 (5.26)	14.16 (2.28)	0.004
Preinjury AFQT	50.56 (24.48)	60.87 (25.11)	0.000
Last recorded AFQT	48.28 (26.53)	63.14 (25.15)	0.000
Right hemisphere loss, cc	19.04 (30.76)	18.95 (29.02)	0.976
Left hemisphere loss, cc	20.47 (34.60)	14.33 (26.44)	0.044
Total brain volume loss, cc	42.51 (45.94)	35.45 (38.87)	0.089

Abbreviation: AFQT = Armed Forces Qualification Test.
[a] Data are presented as mean (SD).

Eleven patients (12.6% of those with PTE; 5.5% overall) reported onset of seizures since PH2 (figure). There was no association between onset latency and history of cardiovascular disease, preinjury intelligence, change in intelligence, presence of bone or metal fragments, or lesion size.

For those with onset of PTE before PH3, 73.8% described no change in seizure type, 3.2% reported a change from simple partial to generalized seizures, and 4.7% changed from generalized to simple partial or complex partial seizures. Two control subjects also reported a history of seizures, both in the 13 years before PH3.

Of the 520 patients assessed at PH2, 336 did not attend PH3. When we examined the subjects with head injuries who attended both P2 and P3, the prevalence of PTE at PH3 was 45.1% (82 of 182 subjects), compared with 39.6% at PH2. 19.2% reported having a seizure in the year before P3. As in the whole sample with PTE, in the most recent year of subject-reported seizures the most common seizure frequency was 2 to 10 seizures per year, and complex partial seizures were the most common type, occurring in 15.1%. In the 17 subjects who attended P3 but not P2, the prevalence of PTE was 29.4%. Three subjects reported onset of seizures since P2, and 4 had had a seizure in the year before P3. Veterans who did not attend PH3 had significantly lower preinjury and PH2 intelligence scores (table 2), and also a tendency to greater brain volume loss, whereas there were no significant differences in terms of seizure type or frequency. Of those subjects with head injuries who attended PH2 but not PH3, 43.9% had a positive seizure history at PH2. At the time of PH2, 28.0% of these subjects had generalized seizures, compared with 21.7% of those who went on to attend at PH3, indicating that there was no difference in terms of seizure type in PH3 attendees and nonattendees ($p = 0.486$).

Treatment of PTE. More than 88% (n = 77) of the subjects with a history of PTE at PH3 were using medication at the time of their last seizure. Seventy percent were prescribed phenytoin, the second most common medication being phenobarbital (14.5%). Less common therapeutic choices were carbamazepine (4.5%) and sodium valproate (4.5%). Newer anticonvulsants were prescribed less frequently. However, 53% of the subjects (n = 41) reported having seizures in the year before PH3, which may represent a high level of refractoriness or noncompliance, but we were unable to assess which factor was responsible in this study.

Associations with brain lesions. As in PH2, brain volume loss at PH3 was associated with PTE ($t = 3.758$, $df = 186$, $p = 0.000$). There was a correlation between size of lesion and seizure frequency in the first year ($r = -0.203$, $p = 0.005$) and last year of recorded seizures ($r = -0.274$, $p = 0.000$), as well as in duration of seizure history ($r = -0.179$, $p = 0.014$). However, in contrast to the results from PH2, we found that those with parietal lesions ($\chi^2 = 13.603$, $df = 2$, $p = 0.001$) and left insula involvement ($\chi^2 = 12.845$, $df = 2$, $p = 0.002$) were more likely to report a history of seizures. There were no other significant associations between lesion location and seizures. However, there was a correlation between number of lobes involved and PTE ($r = 0.196$, $p = 0.006$), and complex partial seizures were more common in those with multiple lobe involvement. There was no significant association between atrophy and PTE.

Associations with genetic markers. We looked for association between several candidate genes and PTE (table e-3). There was an association between the presence of *GRIN*2A rs11074504 and seizures

Table 3 Characteristics of patients with and without posttraumatic epilepsy[a]

	Subjects without PTE (n = 112)	Subjects with PTE (n = 87)	p Value
Mean age, y	58.8 (3.5)	57.8 (2.3)	0.007[b]
Mean preinjury AFQT	62.8 (25.1)	57.2 (25.9)	0.151
Mean PH2 AFQT	69.7 (23.0)	54.6 (25.9)	0.000[b]
Mean PH3 AFQT	59.7 (24.5)	44.3 (23.1)	0.000[b]
Mean PH3 WAIS full-scale IQ	106.2 (14.3)	98.0 (14.4)	0.000[b]
AFQT change, preinjury to PH3	−4.3 (17.9)	−13.3 (20.0)	0.002[b]
AFQT change, PH2 to PH3	−8.0 (11.2)	−11.0 (12.9)	0.131
CT right volume loss, cc	17.4 (29.8)	24.8 (32.8)	0.111
CT left volume loss, cc	12.2 (17.6)	27.7 (46.2)	0.004[b]
CT total volume loss, cc	29.6 (31.9)	52.5 (50.6)	0.000[b]
Positive cardiovascular history, n (%)	45 (40.2)	39 (44.8)	0.942
Presence of metal/bone fragments on CT scan, n (%)	59 (52.7)	67 (77.0)	0.001[b]

Abbreviations: AFQT = Armed Forces Qualification Test; PTE = posttraumatic epilepsy; WAIS = Wechsler Adult Intelligence Scale.
[a]Data are presented as mean (SD) unless noted as n (%).
[b]Statistically significant.

present at PH3 ($\chi^2 = 14.126$, $df = 4$, $p = 0.007$) and *GAD*2 rs1330582 and PTE at PH2 ($\chi^2 = 11.779$, $df = 4$, $p = 0.019$). There was also a marginal association between *GAD*1 rs769395 and seizures at PH2 ($\chi^2 = 9.351$, $df = 4$, $p = 0.053$), but no association between PTE and the presence of the *APOE* ε4 allele. However, when the p values were corrected for multiple comparisons, these values did not reach significance.

Associations with intelligence. There was no significant difference in preinjury AFQT scores between subjects with and without PTE (table 3), whereas there were significant differences between these groups in their PH2 and PH3 AFQT scores and change in scores from PH2 to PH3 (with those with PTE showing a greater level of decline).

There was an association between the frequency of last reported seizures and PH3 AFQT score ($F = 5.876$, $df = 6$, $p = 0.000$), and change in AFQT scores from preinjury to PH3 ($F = 4.140$, $df = 6$, $p = 0.001$), with those with more frequent seizures having lower AFQT scores and greater decline in intelligence. Similarly, there was also an association between the type of last seizure and PH3 AFQT score ($F = 6.010$, $df = 5$, $p = 0.000$), and change in AFQT scores from preinjury to PH3 ($F = 4.140$, $df = 6$, $p = 0.000$). Those with partial seizures evolving to generalized seizures had the lowest AFQT scores at PH3 and the greatest level of decline from preinjury to PH3, whereas those with simple partial seizures had the highest AFQT scores at PH3 and the least level of decline.

Using a linear regression model, we examined seizure history, duration, frequency, and type vs change in and current intelligence. Unlike at PH2, PTE was predictive of current intelligence, even when allowances for brain volume loss and preinjury intelligence were introduced into the model ($F = 4.102$, $df = 2$, $p = 0.018$). Presence of PTE was also predictive of decline in AFQT score from preinjury to PH3 ($F = 4.102$, $df = 2$, $p = 0.018$). Duration of PTE was a predictor of decline in full-scale IQ from PH2 to PH3 ($F = 4.559$, $df = 1$, $p = 0.034$), as well as decline in intelligence from preinjury to PH2 ($F = 6.883$, $df = 1$, $p = 0.010$).

Overall possible predictors of PTE. We performed a linear logistic regression analysis to assess the predictability of PTE occurrence and frequency at PH3 by total volume loss, lesion location, wound characteristics, and the 3 genetic markers that had been found to be associated with PTE. PTE was predicted by both presence of *GRIN*2A rs11074504 ($F = 3.944$, $df = 2$, $p = 0.021$) and left parietal involvement ($F = 5.931$, $df = 1$, $p = 0.041$). As at PH2, the presence of metal fragments was predictive of PTE ($F = 5.522$, $df = 1$, $p = 0.020$), and its inclusion in the analysis reduced the impact of both *GRIN*2A rs11074504 ($F = 8.091$, $df = 2$, $p = 0.059$) and left parietal involvement ($F = 0.737$ $df = 1$, $p = 0.609$). Total lesion volume loss ($F = 7.230$, $df = 1$, $p = 0.008$) was the only predictor of frequency of seizures. None of these predictors remained significant when the analysis was repeated for very late-onset PTE (>14 years after injury) only. However, given the small numbers involved, this analysis can only be viewed as exploratory.

DISCUSSION

Studies of PTE in military populations have reported higher rates than civilian studies (32%–43%),[5,7,22] likely because the injuries more often involve dural penetration and bleeding, which are associated with increased risk for PTE.[23,24] In our cohort, the incidence of PTE was 53% within 15 years, but some 18% did not manifest their epilepsy until 10 or more years after TBI.

These results seem to confirm the high incidence of seizures in this cohort, with the risk of both PTE and higher seizure frequency being greater in those with large brain lesions. Our data suggest the incidence is greater than after previous conflicts, probably because of improved survival and longer follow-up.[13] However, despite us finding a similar pattern of seizures in both PH3 attendees and nonattendees, we are aware that we were unable to include 65% of the sample from PH2 in this evaluation. Additionally, because the participants with head injuries who had the lowest preinjury intelligence and largest

lesions tended not to attend PH3, this may have caused a significant selection bias, although it may explain the reduced prevalence of PTE at PH3 compared with PH2.

To date, genetic studies have primarily focused on the molecular events that contribute to epileptogenesis after traumatic injury.[25,26] *APO*E ε4 has been associated with an increased PTE in the 6 months after TBI,[2] independent of other functional outcomes. Other genetic candidates have included γ-aminobutyric acid receptor genes[27,28] and haptoglobin HPh2–2 allele.[29] Recent studies have also suggested that TBI results in alterations in glutamatergic transmission[30,31] and that there is a temporal window vital in terms of subsequent epileptogenesis. So whereas initial cellular response has previously been a focus of study, we hypothesize that longer-term events may also have specific molecular triggers, which in turn could be linked to specific genotypes. When corrections were made to our analyses for multiple comparisons, we did not find any significant results in the genetic analyses. Nevertheless, the trends suggest that genetic factors may influence tendency to develop PTE, and as such warrant further study.

The association between long-term cognitive outcome and PTE remains debated,[32,33] as does the long-term use of anticonvulsants.[34] Our data showed an association between PTE, intelligence, and cognitive decline in later life.

Our findings differ slightly from those in PH2 in terms of associations between PTE and lesion site. While we did find that those with left parietal lesions and retained metal fragments were more likely to have a history of seizures, this was also the case in those with lesions involving the left insula. The evidence in the literature regarding the association between brain lesion site and tendency to PTE mainly consists of penetrating head injury (PHI) studies and is conflicting. However, in a recent prospective study of both closed head injury (CHI) and PHI, an association was also found between frontal and parietal lesions on CT scan and PTE.[35] This is consistent with other observations in PHI.[3] Other PHI studies have found an association between frontal and temporal lesions and PTE.[36,37] Conversely, one study of CHI and PHI found no correlation between lesion site and PTE.[38] There have been reports of an increased incidence of later-onset PTE in those with bilateral parietal lesions, suggesting a possible time-dependent process occurring in certain subtypes of PTE.[35] As in other studies, we found a correlation between diffuse brain injury and tendency to PTE, and that complex partial seizures were more common in those with multiple lobe involvement.[39] Although we found no link between atrophy and tendency to PTE, it is possible that iatrogenic effects, such as prolonged treatment with phenytoin, may have contributed to any atrophic changes, because most subjects were receiving long-term treatment with traditional anticonvulsants.

The pathogenesis of later-onset PTE and, more specifically, how characteristics such as clinical outcome and lesion site may impact on the time of onset remain unclear.[21] However, our data suggest that the onset of seizures may be delayed more than 30 years after TBI. The most common seizure type also changed over time, with an increased tendency to complex partial seizures in the later years subsequent to TBI.

Remission rates in PTE have been found to be lower in those with later onset of seizures,[40] although the previous phase of our study did not find any such association.[12] However, this possibility, combined with the severity of injury often found in military populations, suggests that veterans in particular may require long-term neurologic follow-up. Our cohort was the first set of veterans that have been followed up over such an extensive period, partly as a result of their increased survival compared with previous studies. Given the even greater survival rates in present conflicts, together with the high incidence of traumatic brain injury, we suggest that screening for PTE should be a vital component of the long-term care of veterans with penetrating TBI.

DISCLOSURE

Dr. Raymont was supported by a project grant from the United States Army Medical Research and Material Command and administered by the Henry M. Jackson Foundation (DAMD17-01-1-0675). Dr. Salazar is CEO and Chairman of Oncovir, Inc., in which he owns stock; serves on the editorial board of the *Journal of Neurology Neurosurgery & Psychiatry*; and may accrue revenue on a patent re: Method for Preparation of large batches of Poly-ICLC. Dr. Lipsky serves as a field editor for *Amino Acids* and on the editorial board of *CNS and Neurological Disorders—Drug Targets*; may accrue revenue on a patents re: A Missense Variant (P10L) of the Melanopsin (OPN4) Gene in Seasonal Affective Disorder and re: Methods for detecting nucleic acid sequence variation; was supported by the National Institute on Alcohol Abuse and Alcoholism intramural research program; and receives research support from the UD Department of Defense. Dr. Goldman is supported by the National Institute on Alcohol Abuse and Alcoholism intramural research program. Ms. Tasick was supported by a project grant from the US Army Medical Research and Material Command and administered by the Henry M. Jackson Foundation (DAMD17-01-1-0675). Dr. Grafman is supported by the National Institute of Neurological Disorders and Stroke intramural research program; and serves as Coeditor of *Cortex*.

Received August 10, 2009. Accepted in final form March 1, 2010.

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