



A new study investigates the long-term risks of poststroke epilepsy after primary intracerebral haemorrhage

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Provenance: This is an invited Editorial commissioned by Section Editor Rui Liu (Department of Neurology, Jinling Hospital, Nanjing, China).

Comment on: Lahti AM, Saloheimo P, Huhtakangas J, *et al.* Poststroke epilepsy in long-term survivors of primary intracerebral hemorrhage. *Neurology* 2017;88:2169-75.

Received: 16 August 2017; Accepted: 21 August 2017; Published: 13 September 2017.

doi: 10.21037/amj.2017.08.26

View this article at: <http://dx.doi.org/10.21037/amj.2017.08.26>

Epilepsy can be genetic, but also acquired after brain insults. Cerebrovascular disease is the most common cause of epilepsy after middle age and accounts for 14–21% of all cases of epilepsy in developed countries (1). Exactly how stroke causes seizures is not known, but the risk of poststroke epilepsy (PSE) seems to vary with lesion characteristics. Hemorrhage carries a higher risk of epilepsy than infarctions, as do larger strokes and strokes near the brain cortex (2).

Acquired epilepsy typically arises some time after the insult. For PSE, this latent phase is typically a few months up to two years (3,4). During this time, the brain is believed to undergo a process called epileptogenesis, during which inflammation, remodeling of neuronal networks, and other poorly understood mechanisms give rise to an abnormal enduring tendency for seizures. Clinically, the concept of epileptogenesis is mirrored in the important distinction between seizures that occur at the onset or within the first week of a stroke and seizures that occur later. Early seizures are called acute symptomatic or provoked, and believed to reflect an acute derangement of normal brain function. In theory, epileptogenesis has not yet occurred at this point in time, and the acute brain disturbance may not cause an enduring predisposition for seizures.

In keeping with this notion, seizures within a week after stroke carry a smaller risk of PSE than seizures that occur later (5). The model of epileptogenesis is theoretically appealing, but probably an oversimplification. In reality the neurobiology of PSE is poorly understood and acute symptomatic seizures increase the risk of epilepsy

substantially compared to patients that have not suffered any seizures during the early phase (2).

Currently, there is no way of preventing PSE. Trials with AEDs have been unsuccessful or terminated because of recruitment difficulties (6,7). Interestingly, retrospective data has started to accumulate on statins, that seem to indicate that this drug class may reduce the risk of PSE (3,8). In one study, this effect was seen only in patients with early seizures, which may be a statistical effect since these patients probably run a greater risk of later PSE.

Over the last years, there has been an increased research interest in PSE. Two large epidemiological studies have demonstrated that PSE occurs more often than previously appreciated after stroke, with ten-year risks in some cases exceeding 10% (9,10). In most studies with mixed stroke types, the risk of PSE after intracerebral hemorrhage (ICH) is approximately two-fold that seen after infarctions (2,4,11).

The long-term risk of PSE after ICH has been less extensively studied than that after cerebral infarctions, presumably because fewer patients suffer ICH than infarctions. Epidemiological data from a Swedish register-based cohort study undertaken by our group showed that out of 10,195 patients with ICH during 2005–2010, a total of 12.4% had developed epilepsy after 4.8 years, in comparison to 6.4% of patients with infarctions (4). Other shorter studies have demonstrated similar results. The literature has mainly consisted of register-based investigations, which have the shortcomings of not assessing first-hand data such as medical records, and single center

studies, where selection bias is probably substantial. The recent publication of the results from a large cohort study by Lahti and co-workers is therefore a very welcome addition to the literature (12).

In the article by Lahti and co-workers entitled *Poststroke epilepsy in long-term survivors of primary intracerebral haemorrhage*, the authors included 615 long-term survivors, defined as individuals surviving more than 3 months after primary ICH. The study is an investigation of long-term survivors from an original cohort of patients with ICH (13). Over a median follow-up period of 6.4 years, 83 patients (13.5%) developed PSE. The authors found statistically significant risk increases for the well-known risk factors subcortical location of ICH and early seizures, which validates the methodology. As expected, the incidence of PSE was highest at the beginning of the follow-up period. Interestingly, they also found that in the group of patients with subcortical ICH, patients without hypertension were at a greater risk of PSE.

There are several strengths with the study by Lahti and co-workers. First of all, the health-care organization in the region of Finland where the study was undertaken allowed for recruitment of a large cohort in a population-based manner at a single center, since no other hospital in the region treats ICH. This resulted in good access to primary data sources like medical records etc. Complimentary data sources like prescription registers were also used to ensure that all cases of epilepsy were detected. Another great strength of the article is the long follow-up time.

There are some limitations of the study that are important to keep in mind. First, outcome and risk factor detection may not have been optimal, given the retrospective design of the investigation. It is possible that subtle acute symptomatic seizures were missed, since they may have been deemed clinically insignificant and not entered into the medical records in the absence of a study protocol collecting prospective data, and because of the absence of routine EEG-monitoring. Regarding outcome, the authors state that in rare instances patients may only have been treated for PSE in primary care and thereby escaped detection, but measures were put in place to avoid this problem, such as scrutiny of prescription registers. Somewhat unfortunately, the authors decided on a conservative definition of acute symptomatic seizures as seizures occurring within 14 days of the ICH. The current definition from the International League Against Epilepsy (ILAE) defines acute symptomatic seizures as those occurring within 7 days of a cerebrovascular insult (14), and this time period is also recommended by the epidemiology

commission of the ILAE (15). As a consequence, some patients classified by Lahti and co-workers as having early seizures may not have been included in this category by other investigators. This reduces comparability.

Another limitation is the possibility of confounding factors that may have caused seizures, other than PSE. The authors defined PSE as a single seizure occurring after the specified time interval for early seizures. This is a common pragmatic approach, which is reasonable. It does however expose the study to the risk of classifying patients as having PSE after single seizures that may have been acute symptomatic seizure due to reversible causes such as alcohol withdrawal or other substance abuse. The authors recognize this limitation, and interestingly speculate that advice on alcohol consumption may have confounded the inverse association found between PSE and hypertension. The latter observation is a new one in the field and should be replicated. Overall, the results are well in line with the 12.4% of PSE detected in our register-based investigation in Sweden, indicating that 12–13% is the approximate long-term risk of PSE after ICH in Scandinavian countries (4).

The article by Lahti and co-workers constitutes a very valuable addition to the literature on PSE after ICH. The large study size, population-based recruitment, and access to primary data sources are major advantages. The authors demonstrate that more than one in ten patients with primary ICH will develop epilepsy, making PSE after ICH an important area for future research.

Over the last decade there has been a great accumulation on the epidemiology of PSE. Such information is important for counseling of patients, recognition of PSE, and early diagnosis. Hopefully, the field is soon ready to translate the information on risk factors into studies on how to prevent PSE. As mentioned above, trials with AEDs have not been successful in the past, but encouraging data is starting to accumulate on other classes of drugs, such as statins. Information such as that provided by Lahti and co-workers will hopefully assist in selecting patients for trials of preventive medication in the future.

Acknowledgements

None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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doi: 10.21037/amj.2017.08.26

Cite this article as: Zelano J. A new study investigates the long-term risks of poststroke epilepsy after primary intracerebral haemorrhage. *AME Med J* 2017;2:137.