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MEETING NEWS: DO SEIZURES DAMAGE THE BRAIN?

Jack M. Parent, M.D.

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*U-M Comprehensive Epilepsy Center
Department of Neurology
University of Michigan Medical Center*

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Commentary from the Editor-in-Chief of epilepsy.com:

This important conference examined the scientific evidence about whether isolated, brief seizures have a negative effect on brain function. The evidence suggests that these seizures do have a negative effect and possibly result in loss of specific brain cells. However, the evidence also indicates that this is not true for all forms of epilepsy. We also do not yet know the consequences of these effects for thinking, memory, mood, and other aspects of daily life.

As was true before this conference, people with epilepsy are well advised to work with their doctors to achieve the best possible seizure control.

Steven C. Schachter, MD

Harvard Medical School

(Rovaniemi, Finland, June 2001)

Epilepsy researchers from around the world gathered in Rovaniemi, Finland, at the edge of the Arctic Circle, in June 2001 for a workshop aimed at addressing the question: "Do seizures damage the brain?" The workshop was organized by Dr. Tom Sutula, Chairman of Neurology at the University of Wisconsin, and Professor Asla Pitkänen, Director of Epilepsy Research at the A.I. Virtanen institute of Kuopio, Finland. The meeting was supported by the American Epilepsy Society and Elan Pharmaceuticals. Over 35 scientists from eight countries attended. Among them were specialists in both clinical and laboratory epilepsy research, as well as basic neuroscience. Presentations from the meeting were published in book form in 2002. (See details at end of this report.)

This workshop was aimed at discussing the question of whether isolated, brief seizures damage the brain. Although scientists and clinicians have long known that prolonged seizures, a condition referred to as "status epilepticus," kill brain cells, surprisingly little scientific evidence exists to support the notion that individual seizures do damage. This is not to say that individual seizures cause no harm to the brain, but proof of such damage is difficult to obtain for a number of reasons:

- It is often hard to separate the underlying brain injury that produces seizures from the effects of the seizures themselves.
- Most of the animal models used to study epilepsy involve prolonged seizures.
- Patients with epilepsy often are studied only after they have had seizures for many years, and clinicians do not have information, such as MRI scans, of the same individuals before their epilepsy developed.

However, scientific data are slowly accumulating to suggest that recurring seizures may contribute to nerve cell injury in the brain, and this may be associated with declines in cognitive function and quality of life.

Animal models of epilepsy

On the first day, investigators discussed experimental studies using animal models of epilepsy, typically laboratory rodents (rats and mice) in which seizures are induced and subsequent changes in the brain are measured. One way to assess whether seizures cause damage is to see if epileptic animals have fewer nerve cells in specific brain areas. Researchers count the cells using sophisticated computerized statistical analyses, a technique known as unbiased stereology. This technique presents significant technical challenges, however, because the brain (unlike other organs) contains irregularly shaped structures that have many different cell types.

In some experiments, electrical stimulation is used to induce seizures in rats (referred to as "electrical kindling"). These studies have shown that certain populations of brain cells may die after single or repeated brief seizures. Molecular signals inside nerve cells lead to their death. Researchers have identified many of the chemical pathways where this occurs. As a result, it may be possible to develop "neuroprotective" medical treatments specifically to prevent this kind of injury.

These studies have also shown that certain genes may protect the brain or make it more susceptible to injury after seizures. By comparing strains of mice in which many brain cells die after seizures with other strains of mice in which the same nerve cells survive, scientists are now on the trail of a number of these important genes.

Epileptic seizures adversely alter brain function in other ways besides killing cells. Rewiring of brain circuitry and the birth of new brain cells (neurons and glia) both may lead to seizures. The discussion at the end of the first day concentrated on definitions of damage and potential improvements in animal models used to study epileptic brain injury.

Studies in humans

The second day was focused on studies of epilepsy in individuals or populations. Many of the presentations concentrated on the use of brain MRI to measure injury after recurrent seizures. By using new MRI techniques, such as MRI volumetry or magnetic resonance spectroscopy (MRS), researchers can measure changes in the brain over time during the course of epilepsy.

Others discussed the role of prolonged seizures in early life as a risk factor for the later development of epilepsy. An important study being carried out at Duke University Medical Center is identifying infants and young children with prolonged seizures induced by fever (febrile status epilepticus). The researchers are performing a series of MRI scans on each of these children over a number of years, trying to find out whether brain damage is already present and whether those who go on to develop recurrent seizures will have further nerve cell injury.

Some presentations described studies of epileptic human brain tissue removed during surgery to treat focal epilepsy (mainly temporal lobe epilepsy). For many years we have known that in epilepsy certain nerve cells are lost in specific areas of the brain, such as the hippocampus, but these studies are showing that the amount of damage may depend upon the age at which the epilepsy began. The researchers discussed the importance of correlating findings in animal studies with research on human epilepsies.

Exciting new research is aimed at simultaneously measuring changes in the expression (the amount of protein a gene produces) of hundreds of genes after seizures. This new technology, referred to as genetic microarrays, or "gene chips," offers great potential for providing insight into the effects of epilepsy on the brain at the level of individual molecules.

The effects of seizures during early life

The third day of the workshop was devoted to animal models of childhood epilepsy and changes in the brain caused by seizures during early development. Research performed over several decades suggests that seizure-induced brain injury is highly dependent upon developmental age, with the juvenile and adult brain being more susceptible to damage and rewiring after seizures than the brain of the newborn.

Recent animal studies indicate that seizures early in life adversely affect learning and memory performance during adulthood. Experiments using animal models of prolonged febrile seizures in infancy (seizures induced by high fevers) have found that this type of seizure may lead to changes in brain structure and function that persist for many months.

Group discussions focused on the importance of studying the effects of seizures during early life, and determining why

epilepsy affects the brain differently at different ages.

Cognitive effects

Presentations during the final day covered neuropsychological research into cognitive changes caused by epilepsy in children and adults. The talks focused on the effects of epilepsy on learning, memory, speech, and other higher brain functions. It was emphasized that researchers need to begin studying patients soon after diagnosis, monitoring their course with carefully chosen neuropsychological tests and brain imaging studies. Ongoing research is aimed at determining whether alterations in cognitive function after recurrent seizures correlate with changes in brain structure or function found on neuroimaging (for example, brain MRI or PET scans). Functional MRI (fMRI) is a new technique that measures changes in blood oxygen to indicate when a specific brain area is being activated (in use). This method is an extremely promising tool that eventually may allow doctors to determine the specific locations of brain functions and seizure development non-invasively, without injecting drugs into brain arteries or putting EEG electrodes directly over the brain, for instance, as we do now.

The discussion was directed at the difficulties of distinguishing the direct effects of seizures on neuropsychological measures from the effects of the underlying brain abnormalities. Attention was also focused on the idea that various types of epilepsy affect cognitive function differently, so further research concentrating on specific forms of epilepsy is needed.

Conclusions and future directions

The workshop provided an important forum for discussion among epilepsy researchers from a variety of disciplines, each with a different approach to understanding how seizures affect the brain. Many research controversies remain, but the meeting did lead to a number of important preliminary conclusions and directions for future study:

- Prolonged seizures are clearly capable of injuring the brain.
- Isolated, brief seizures are likely to cause negative changes in brain function and possibly loss of specific brain cells. This is not true for all forms of epilepsy, however, and is likely to be highly dependent upon the type of seizure and the specific cause of the epilepsy.
- Increased collaboration between clinicians and laboratory researchers is essential.
- Better experimental epilepsy models of relevance to many different, specific forms of human epilepsy are badly needed.
- New and better ways to image brain function in patients with epilepsy would be valuable.
- More long-term studies of the course of epilepsy are required. Such research should begin as soon as the person starts having seizures, and should include repeated neuroimaging and neuropsychological tests to look for evidence of ongoing brain injury due to epileptic seizures.

Details of this meeting have been published as Sutula T and Pitkänen A. Do seizures injure the brain. Progress in Brain Research 135. New York: Elsevier Science; 2002.