

## Do Seizures Promote Epileptogenesis and Cause Cognitive Decline?

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### Abstract

The assumption that repeated seizures may induce a progression of epilepsies towards an intractable condition and a cognitive decline does not hold true for idiopathic epilepsies but can only be considered for mesial temporal lobe epilepsy and epileptic encephalopathies. The available evidence leads to the conclusion that in most cases the epilepsy worsening and cognitive decline are due to the progression of the underlying pathology or to its interference with the developmental programme, the notable exception being the epileptic encephalopathies with continuous epileptic activity during sleep.

### Keywords

Epilepsy progression, epileptogenesis, temporal lobe epilepsy, epileptic encephalopathies.

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William Gower's statement that seizures beget seizures<sup>1</sup> is often quoted as a first recognition of seizure-dependent progressive character of epilepsies. It is worth saying that this assumption has by no means a general value as it does not apply to many types of epilepsies, namely to the idiopathic ones. A progressive course towards drug refractoriness and cognitive decline is seen only in epileptic encephalopathies (EES) and in some focal epilepsies whose prototype is the mesial temporal lobe epilepsy (MTLE) that substantially contribute to 30–40 % of patients with epilepsy who show drug resistance.<sup>2</sup>

Here the evidence supporting a role of repeated seizures for inducing progressive alterations in neural circuits, resulting in progression of epilepsy severity and neurological deterioration will be discussed.

### Progression of Mesial Temporal Lobe Epilepsy

In several instances, the natural history of MTLE indicates an initial precipitating event followed after a variable latent interval by chronic epilepsy.<sup>3</sup> The initial event (trauma, infection, autoimmune process) is often associated with repeated seizures/status epilepticus (SE), which may be themselves the initial event in the form of complex febrile seizures or febrile SE.<sup>4</sup> During the latent period, several changes occur in hippocampal structures (axonal sprouting, synaptic reorganisation, gene and protein expression, neurogenesis, gliosis, inflammation and angiogenesis) that are associated with alteration of excitability and neuronal synchronisation.<sup>5</sup> These changes can also be found in tissue samples from patients operated on for drug-refractory MTLE with hippocampal sclerosis.<sup>6</sup> A crucial role is attributed to the epileptic activity associated with the initial event, less substantiated is the claim that seizure occurring during the chronic phase are responsible for further progression of epilepsy. Indeed little, if any, evidence of further progression of structural damage has been documented by imaging studies.<sup>7</sup>

Animal models of MTLE based on acute induction of SE fail to demonstrate any seizure-related progression.<sup>8</sup> In pilocarpine and kainic acid models, once the spontaneous recurrent seizures have fully developed in the late chronic period, they do not tend to worsen. In an animal model of post-traumatic epilepsy, spontaneous seizures maintain a fairly constant frequency and severity over an extended time period<sup>9</sup> and in a tetanus toxin model the spontaneous seizures even tend to subside after about 6 weeks.<sup>10</sup>

### Progression of Epileptic Encephalopathies

EES are defined as conditions in which seizures or interictal electroencephalographic (EEG) discharges themselves can induce a progression towards more severe epilepsy and a regression of brain function.<sup>11</sup> The definition applies to early myoclonic encephalopathy, Ohtahara syndrome, epilepsy of infancy with migrating focal seizures, West syndrome (WS), Dravet syndrome (DS), myoclonic encephalopathy in non-progressive disorders, Lennox-Gastaut syndrome, epileptic encephalopathy with continuous spike-and-wave during slow sleep (CSWSS) and Landau-Kleffner syndrome (LKS). These disorders are age related and occur at different stages of post-natal development thus raising the question of whether an apparent regression of brain functions can be accounted for by the interference of the underlying aetiological factors with the brain development. This is the case of DS that is due to a gene mutation resulting in a the loss of Na<sup>+</sup> channel function<sup>12</sup> and in which the longitudinal analysis supports the conclusion that the apparent intellectual deterioration is rather due to an arrest of cognitive development in the early stages.<sup>13</sup> Different interpretations have been proposed for WS, which is due to brain malformations or perinatal insults that may interact with epigenetic control of development thus determining a progressive psychomotor deterioration. The contribution of epileptic activity in its progression is difficult to assess because of the difficulty of defining the EEG and clinical manifestations (hypsarrhythmia

and spasms) as interictal or ictal phenomena in WS. Whichever is the interpretation, it can be logically expected that the dysfunction of the widespread cortico-subcortical system underlying the epileptic activity accounts for the failure to acquire new developmental milestones.<sup>14</sup> Quite special is the situation of CSWSS/LKs in which cognitive, motor and behavioral deterioration are thought to depend on the disruption of the sleep architecture, thereby interfering with memory consolidation taking place during slow wave sleep.<sup>15</sup>

The reviewed evidences lead to the conclusion that a progressive aggravation of epilepsy is by no means a general phenomenon and that its occurrence can be hypothesised only in a limited number of epilepsy types. Moreover in some epilepsy types, namely MTLE, the positive correlation between high seizure frequency and bad outcome is not unequivocally documented and even if it is in future, it would

not necessarily demonstrate a cause–effect relationship, rather high seizure frequency and bad outcomes can both depend on a particularly aggressive epileptogenic process. Whereas clinical and experimental data concur in indicating prolonged seizures/SE as a risky initial event in MTLE, the role of subsequent seizures in sustaining progression is much less clear and requires further prospective controlled studies.

As for EEs, whose natural history is proposed as a typical example of seizure-dependent progression towards seizure severity and cognitive deterioration, the insufficient knowledge of their pathogenesis does not allow a definite conclusion. A persistent epileptic activity/SE during sleep may be responsible for cognitive deterioration in CSWSS/LKs but not in other EEs and the available information makes questionable the search for a common seizure-dependent mechanism that may account for epilepsy progression and intellectual decline. ■

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