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Topical Review

Forced Normalization: Antagonism Between Epilepsy and Psychosis

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ABSTRACT

The antagonism between epilepsy and psychosis has been discussed for a long time. Landolt coined the term "forced normalization" in the 1950s to describe psychotic episodes associated with the remission of seizures and disappearance of epileptiform activity on electroencephalograms in individuals with epilepsy. Since then, neurologists and psychiatrists have been intrigued by this phenomenon. However, although collaborative clinical studies and basic experimental researches have been performed, the mechanism of forced normalization remains unknown. In this review article, we present a historical overview of the concept of forced normalization, and discuss potential pathogenic mechanisms and clinical diagnosis. We also discuss the role of dopamine, which appears to be a key factor in the mechanism of forced normalization.

Keywords: epilepsy, forced normalization, alternative psychosis, electroencephalogram, kindling, dopamine

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Introduction

The term "forced normalization" was coined in the 1950s by Heinrich Landolt,[1,2] who described the phenomenon as the normalization of electroencephalographic findings and relief of symptoms in patients with epilepsy, accompanied by the emergence of behavioral or psychotic disturbances. The relationship between epilepsy and psychosis had long been a popular topic of debate,[3] but since Landolt's report of forced normalization as a phenomenon closely linking epilepsy and psychosis, the discussion has moved worldwide. Over the years, the concept of forced normalization has undergone the changes described herein.

History of the concept of forced normalization

About 100 years before Landolt coined the term *forced normalization*, Hoffmann[4] summarized his clinical experiences in an extensive monograph containing the first description of what is now taken to have been an example of drug-associated forced normalization: a girl with epileptic seizures (tonic convulsions and shaking spasms) occurring in monthly clusters of up to 50 episodes per day was treated with a herbal compound, which inhibited the seizures; following treatment, however, she developed a paranoid psychosis. Samt[5] later characterized postparoxysmal psychopathologic symptoms (such as aggression, amnesia, anxiety, disturbance of consciousness, and impairment of speech) and developed a classification system for epilepsy composed of 12 categories, with mental disorders having the same diagnostic significance as seizures. He used the term "transformed epilepsy" in reporting on a patient whose epileptic seizures had been replaced by psychosis.

In the 1950s Landolt proposed the term "twilight state" in postictal psychosis[1] and reported on some patients whose electroencephalographs (EEGs) were close to normal or entirely normal but who were productive, excitable (even occasionally screaming uninterruptedly), and lucid with clear thinking. Landolt called this phenomenon "forced normalization."[2] Almost all of the individuals described by Landolt were induced by the administration of antiepileptic drugs (AEDs).

Later, in the 1960s, Tellenbach[6] introduced the term "alternative psychosis," meaning that the attenuation of

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seizures did not mean the disappearance of epilepsy; epilepsy was still active subcortically and still induced psychopathologic symptoms. This concept covered patients without complete electroencephalographic normalization. Since then, the phenomenon of forced normalization has been discussed as a clinical counterpart of alternative psychosis. In the 1980s the phenomenon of psychosis appearing in spite of the remission of epileptic seizures came to be described as "antagonistic correlation."[7,8] Wolf[9] proposed possible mechanisms of forced normalization and used the term "paradoxical normalization" to describe his theory that while epilepsy was still active subcortically, the concurrent activity of the inhibitory system spread electroencephalographic discharges along uncertain pathways, possibly inducing acute psychotic symptoms.

Mechanism of forced normalization

The exact neurobiologic mechanism of forced normalization remains unknown. Proposed mechanisms of forced normalization in previous reports are listed in the following sections.

Electrical factors including kindling phenomenon

The phenomenon of kindling was discovered by Alonso-DeFlorida and Delgado[10] but was first systematically examined by Goddard et al.[11] Since it is recognized in a wide range of species, it has become a major experimental model for epilepsy.[12] The ability of kindling stimuli applied to the mesolimbic system to produce behavioral changes has been demonstrated[13] and may partly explain the gradual development of psychosis in chronic epilepsy.[14] Electroconvulsive therapy (ECT) has been used as an effective treatment for psychosis, especially depressive disorder, since the 1930s,[15] and it has been suggested that ECT might kindle epileptic foci.[16] Interestingly, one study described two patients who developed clinical epileptic seizures after successful electroconvulsive ECT.[17] This study demonstrated bidirectional, rather than directional, mutual antagonism between epilepsy and psychosis. Examples of alternative psychosis secondary to vagus nerve stimulation have also been reported.[18] These findings suggest that electrical stimulation to the brain plays at least a supporting role in the pathophysiology of forced normalization.

Resection

Psychosis developing after dramatic attenuation of seizures by epilepsy surgery has been documented.[19] Although the patients had no personal or family history of psychiatric disorders before surgery, psychiatric symptoms developed after surgery in spite of the dramatic alleviation of their epileptic seizures.[20] In regard to postoperative psychosis, several studies have shown that laterality, type of resection, histopathologic diagnosis, and total tissue resection volume are not significantly associated with postoperative psychiatric morbidity.[21-23] Postoperative psychosis seems to occur after the extratemporal resection in a near incidental ratio after the temporal resection.[22] It seems probable, therefore, that resection of the brain tissue is a potent mechanism of forced normalization.[19] However, because none of these reports provides EEG evidence, psychic symptoms cannot be strictly defined as forced normalization.

Chemical factors

Pharmacologic kindling

In addition to electrical kindling, pharmacologic kindling has been used to develop models to explain the relationship between epilepsy and psychosis. Amphetamine derivatives are reportedly effective agents.[24] In experiments, behavioral responses were observed under selective activation of the limbic structures during drug-induced seizures in a way that resembles the limbic activation occurring during electrical kindling. Given the progressive stepwise alteration, the phenomenon was dubbed "pharmacological kindling."[8] Thus electrical kindling appears effective in inducing seizures, whereas pharmacologic kindling may be effective in controlling behavioral responses.[8]

Neurotransmitters

Clearly, some neurotransmitters are more likely than others to play a role in the development of forced normalization, and dopamine, glutamate, and γ-aminobutyric acid (GABA) have been singled out for attention. Repeated administration of dopamine agonists and stimulants in small doses has been shown to produce an increasing behavioral response that might last for weeks or, on occasion, be relatively permanent.[25] Dopamine antagonists have antipsychotic effects and are known to provoke seizures (so mutual antagonism between epilepsy and psychosis also exists here) while increasing the intensity of psychotic symptoms.[26] On the other hand, it has also been reported that electroconvulsive therapy (mentioned earlier) upregulates dopamine and its metabolites.[27] Taken together, these studies suggest that dopamine plays a significant role in mediating forced normalization, and the term "dopaminergic kindling" has even been proposed.[8] It has been reported that modulations of glutamate or GABA affect behavioral changes,[28,29] which indicates that these neurotransmitters also play a role in the relationship between epilepsy and psychosis.[30]

Antiepileptic drugs

The first agent implicated in drug-associated forced normalization was a herbal compound,[4] but the first drug listed as an essential "anticonvulsant" was the oldest AED, bromide.[31] Landolt[32] himself pointed out that, although in the early years forced normalization was observed only in relatively sensitive people with focal epilepsy, when ethosuximide was introduced in 1954, there was an immediate increase in the occurrence of both forced normalization and psychotic "twilight state" in the absence of epilepsy. Tellenbach[6] also noted this effect of ethosuximide.

Although they have not been in use for long, the occurrence of forced normalization induced by recently approved AEDs (lamotrigine[33] and levetiracetam[34]) has been reported, and forced normalization has been linked to the use of GABAergic materials and related powerful agents such as vigabatrin[35] or topiramate.[36]