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Effects of antiseizure medications on alternative psychosis and strategies for their application

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Abstract

Forced normalization (FN) is a unique phenomenon that is often seen in the treatment of epilepsy. FN is characterized by abnormal mental behavior and disordered emotions in epilepsy patients despite a significantly improved electroencephalogram and successful seizure control; the occurrence of FN seriously affects patients' quality of life. The causes of FN include antiseizure medications (ASMs), epilepsy surgery and vagus nerve stimulation, with ASMs being the most common cause. However, with the timely reduction or discontinuation of ASMs and the use of antipsychotic drugs, the overall prognosis is good. Here, we perform an extensive review of the literature pertaining to FN, including its epidemiology, possible mechanisms, clinical features, treatment and prognosis.

Key Words: Forced normalization; Antiseizure medications; Neurotransmitter; Antipsychotic drugs; Electroshock

Core Tip: Forced normalization (FN) is often seen in the treatment of epilepsy. FN is characterized by abnormal behavior and disordered emotions in epilepsy patients despite a significantly improved electroencephalogram and successful seizure control; the occurrence of FN seriously affects patients' quality of life. However, with timely recognition and treatment, the overall prognosis is good.

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INTRODUCTION

Alternative psychosis is also known as forced normalization (FN). This phenomenon is characterized by abnormal mental behavior and disordered emotions after the seizures of active epilepsy patients are controlled and their electroencephalograms (EEGs) have significantly improved. FN is unique to the pharmacotherapy of epilepsy and often leads to the failure of epilepsy treatment. Although FN is still an entity with uncertain pathophysiology, it has received extensive clinical attention in recent years, and significant progress has been made regarding its pathogenesis and treatment strategies[1-5]. Recently, Calle-López *et al*[5] conducted a study on 193 FN episodes and found that the causes included antiseizure medications (ASMs), epilepsy surgery and vagus nerve stimulation (VNS), with ASMs being the most common cause. This article aims to describe the clinical features and possible mechanisms of FN induced by ASMs and to explore strategies for its treatment.

HISTORICAL EVOLUTION OF FN

FN was first described by Landolt[6] in the 1950s. They noticed that after active epilepsy was well controlled and the EEG signals returned more or less to normal, the patients developed episodic behavioral abnormalities and mood disorders. They could not reasonably explain this clinical phenomenon and thought it might be a unique phenomenon in epilepsy patients. In 1965, De Jorio *et al*[7] summarized the clinical manifestations of this "Landolt FN". At the same time, Tellenbach[8] published a study on the electrophysiological characteristics of Landolt FN and began to explore its possible mechanism; since then, this unique phenomenon in the treatment of epilepsy has received more extensive attention.

The first discovery regarding the cause of FN was the influence of a type of herbal ingredient. Later, with the widespread use of ethosuximide (ESM) in clinical practice, it was found that the number of patients with FN gradually increased[9]. In 2005, Clemens[10] reported that FN could be caused by lamotrigine (LTG). There were also reports of FN caused by valproic acid (VPA), phenytoin (PHT), and zonisamide (ZNS)[4,5,9]. In recent years, studies on the relationships between FN and ASMs have focused more on levetiracetam (LEV)[11,12]. In 2018, Esang *et al*[12] systematically discussed the clinical features and treatment strategies for FN and explored its relationship with ASMs, which made the clinical diagnosis and treatment of FN more rational.

EPIDEMIOLOGICAL CHARACTERISTICS OF FN

Carazo Barrios *et al*[3] found that 10 patients met the criteria for FN in a cohort analysis of 4468 patients with epilepsy; Wolf *et al*[13] reported that the prevalence of FN in epilepsy patients was 7.8%. Calle-López *et al*[5] used the MEDLINE, Embase, Cochrane and Scielo databases to collect clinical data, electrophysiological characteristics and imaging data of patients with FN for a systematic analysis. They found that 48.5% of cases of FN were caused by ASMs, 31.8% by epileptic surgery, and 13.6% by VNS.

PATHOGENESIS OF FN

The pathogenesis of FN is unclear and lacks a solid experimental basis. It is difficult to establish a suitable animal model. Therefore, the current understanding and various hypotheses regarding the mechanism of FN are mainly based on the observation of responses to three clinical treatments: Epilepsy surgery, VNS and ASMs[3,9,14-17].

Human behavioral changes associated with FN are related to the midbrain limbic system, which has a wide range of connections with the cortex. After surgical removal of brain tissue from patients with epilepsy, the epileptic seizures stopped, but FN occurred, which indicated that the mental behavior abnormalities associated with FN have an anatomical basis[9]. On this basis, Wolf[18] proposed that the formation of FN may be the result of epileptic discharges that are not fully suppressed and spread along specific channels under the cortex after epileptic seizures are controlled, but the specific location is not clear.

Although the surgical methods and excision sites of patients undergoing epilepsy surgery are different, they can all develop FN, indicating that its anatomical basis is likely very extensive, and electrical ignition can activate these neuronal activities. The most obvious feature of FN is that when epileptic seizures are effectively controlled, abnormal mental behavior and emotional disorders appear. Electroshock can not only relieve the mental symptoms of patients with FN but also cause the occurrence of epilepsy, so it has effects on these mutually antagonistic outcomes, which indicates that it may participate in the formation of FN. After VNS, FN will occur with the reduction or cessation of seizures, which supports the hypothesis that electric ignition participates in the formation of FN and

plays an important role in FN[3,9,19].

FN caused by ASMs is related to "pharmacological kindling". It has long been known that certain drugs that selectively activate the limbic system can cause behavioral abnormalities, which are similar to the electrical activation of the limbic system; accordingly, this drug-induced activation is called pharmacological kindling. Many drugs can cause epilepsy, which supports the existence of pharmacological kindling. Existing studies have found that electrical kindling can effectively induce seizures, but pharmacological kindling can result in behavioral changes[9].

Pharmacological kindling is related to neurotransmitters. Brigo *et al*[20] reported on two patients with tuberous sclerosis with FN who had used VPA, LTG, rufinamide, carbamazepine (CBZ), topiramate (TPM), ZNS, and LEV. It has been found that all the drugs that can cause FN can affect the transmitter glutamate. Subsequent research found that drugs that can induce FN, such as TPM, ZNS, and LEV, can affect α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-mediated excitatory synaptic transmission, and drugs that enhance AMPA-mediated glutamatergic transmission can treat psychosis, which indicates that impaired glutamatergic neurotransmission may be related to FN. Additionally, researchers have found that repeated administration of small doses of dopamine agonists and stimulants will produce increased behavioral responses, while dopamine antagonists can cause seizures while producing antipsychotic effects. The mechanism of electroshock treatment of psychosis is also related to upregulating dopamine and its metabolites, which suggests that dopamine may play an important role in mediating FN, and the hypothesis of "dopamine igniting" has been proposed[9].

CLINICAL FEATURES OF FN

The main clinical manifestations of FN are that patients with active epilepsy have abnormal mental behavior and mood disorders after the seizures are controlled, and most patients have improved or normal EEG synchronization[2-4]. Recently, Calle-López *et al*[5] analyzed 193 FN episodes reported in the literature and found that 69.4% of patients presented with mental disorders; 27.9%, mood disorders; and 10%, dissociation. The clinical features of FN are summarized in Table 1.

FN induced by different ASMs

LEV: LEV is the ASM that most often causes FN, but whether FN occurs during LEV use is related to many factors.

Age of onset: FN induced by LEV, as currently reported in the literature, mostly occurred in patients between 9-56 years old. Kawakami *et al*[21] reported that a 9-year-old girl with idiopathic epilepsy had seizures and EEG results that gradually worsened after taking VPA and benzodiazepines and then was switched to LEV. The epileptic seizures stopped, and the epileptiform discharges on EEG disappeared, but the patient showed anger and violent behavior. The authors suggested that this was FN induced by LEV. Kikuchi *et al*[22] reported a 10-year-old girl with unclassified epileptic encephalopathy, and FN occurred after taking LEV. Topkan *et al*[11] reported that the age of the patient with FN after taking LEV was 56 years old.

Gender: FN often occurs in women. The Calle-López *et al*[5] review on FN found that 60% were women. Of the 10 patients reported by Carazo Barrios *et al*[3], 6 were women. At present, it has been reported in the literature that FN induced by LEV has occurred in females, with the exception of one male[3,11,19-22].

Time of onset: The onset time of FN is not certain. Topkan *et al*[11] reported that a 56-year-old woman was treated with LEV for epileptic seizures. Forty-five days after the seizures ceased, the patient had a personality change accompanied by visual hallucinations. The 24-h EEG examination was also normal. This author believes that this was FN induced by LEV. Kikuchi *et al*[22] reported a patient with epileptic encephalopathy. One day after taking LEV, his tonic and myoclonic seizures as well as the paroxysmal discharge on the EEG disappeared, but there was a slow response and dyskinesia. After the recurrence of myoclonic epilepsy, his psychiatric symptoms also disappeared. This author believes that this was FN caused by the administration of LEV. Green *et al*[19] reported a 14-year-old boy who had a history of mental illness. One month after treatment with olanzapine, he developed tonic-clonic epileptic seizures. LEV was used to prevent the seizures. After 6 mo, he developed FN manifesting as self-harming cutting behavior and auditory and visual hallucinations.

Main clinical manifestations: FN induced by LEV mainly manifests as abnormal mental behavior and dissociative personality. Topkan *et al*[11] reported that a 56-year-old patient had obvious personality changes after the seizures stopped that were accompanied by visual hallucinations and déjà vu, and the mental symptoms disappeared after treatment with quetiapine. Kawakami *et al*[21] reported that after the use of LEV in a patient with epilepsy, the epileptic seizures stopped, but FN occurred. The patient showed episodic anger and violent behavior. The simultaneous EEG examination revealed that the epileptiform discharge had disappeared. Green *et al*[19] reported a 27-year-old female patient with spastic cerebral palsy and febrile convulsions. At the age of 22, she was diagnosed with epilepsy, and treatment with LEV was initiated. Subsequently, FN occurred with many behavioral abnormalities, such as decreased alertness and concentration, confusion, delusions, and auditory and visual hallucinations.

Table 1 Clinical features and treatment of forced normalization

Classification			Ref.
Clinical features	LEV	Abnormal mental behavior and dissociative personality	[11,19,21]
	ESM	Mania; visual and olfactory hallucinations; paranoid psychosis	[9,24,25]
	VPA	Paranoid thoughts, agitation, sleep disturbances, confusion	[26,27]
	LTG	Irritable, inattention, insomnia, paranoid thoughts, and hallucinations appearing	[3,10]
	LCM	Paranoid behavior and psychotic symptoms	[3,28,29]
	TPM	Abnormal mental behavior	[20]
	ZNS	Communication disorders, interpersonal tension and stereotyped behaviors	[20,30]
	VGB	Hallucinations and anxiety	[1,31]
	PHT	Paranoia, restlessness, aggressiveness, command hallucinations, and stereotyped, short-term psychomotor excitement and impulsive violent events, irritability	[3,12,32]
	ESL	Behavioral disturbances, psychosis	[3]
	BRV	Dysthymia, generalized anxiety disorder	[3]
Treatment	Dose reduction or drug withdrawal		[3-5,10,11,15,21]
	Control of mental symptoms (haloperidol, risperidone)		[2,3,5,25,26,33]
	Electroshock		[19]

LEV: Levetiracetam; ESM: Ethosuximide; VPA: Valproate; LTG: Lamotrigine; LCM: Lacosamide; TPM: Topiramate; ZNS: Zonisamide; VGB: Vigabatrin; PHT: Phenytoin; ESL: Eslicarbazepine; BRV: Brivaracetam.

The symptoms continued to worsen until the seizures reappeared; the psychiatric symptoms then began to improve, and the aggressive behavior decreased.

Possible mechanism of the FN induced by LEV: Helmstaedter *et al*[23] conducted genetic polymorphism analysis on 290 patients with mental symptoms taking LEV and found that patients who had dopaminergic genetic variants were prone to irritation and aggressive behavior after taking LEV, suggesting that it may be related to FN. This author believes that the use of pharmacogenomics methods to examine the side effects related to mental behavior may provide a useful tool for the prediction of poor mental outcomes related to ASMs.

ESM: ESM is the main ASM for the treatment of epileptic absence seizures and certain epileptic syndromes. It was also the first drug found to cause FN[9]. Recently, Yamamoto *et al*[24] reported an 11-year-old boy with intractable myoclonic epilepsy and severe psychomotor development delay treated with ESM. After his myoclonic seizures were fully controlled, he had episodic behavior changes (mainly mania), and the EEG examination at this time was almost completely normal. This author believes that this was FN caused by ESM. Apap Mangion *et al*[25] reported a man with drug-resistant epilepsy featuring both focal and generalized seizures. After ESM treatment was started, the seizures stopped, and the EEG was normal; however, 3 wk into the use of this medication, FN occurred and manifested as visual and olfactory hallucinations that rapidly deteriorated into paranoid psychosis. After ESM treatment was stopped and olanzapine was added for one month, his psychiatric symptoms disappeared; he then restarted taking a small dose of ESM without the recurrence of psychiatric symptoms.

VPA: VPA is another of the main drugs causing FN. Banwari *et al*[26] reported a case of an epilepsy patient who had a disease course of 13 years and had not been treated with ASMs. One week after the start of treatment with VPA, the patient's seizures stopped, but FN occurred. With low-dose risperidone treatment, the patient's mental symptoms disappeared. Turan *et al*[27] reported that a patient with epilepsy developed mental symptoms under combined treatment with VPA and LTG. This author believes that there are related underlying mechanisms among ASMs, seizure control and psychosis development.

LTG: Two of the 10 patients reported by Carazo Barrios *et al*[3] were patients with FN induced by LTG. Both of them were male; one of them was 41 years old at the time of FN, and another was 40 years old. The former had focal epilepsy, and the latter had generalized seizures. Clemens *et al*[10] also reported 2 patients with FN induced by LTG. One patient was a 10-year-old girl with normal development and no history of neuropsychiatric disease. At the age of 7 years, paroxysmal and transient clonic movements of

the right arm and hand occurred. She was diagnosed with epilepsy when she was 8 years old, and treatment with CBZ was ineffective. After switching to LTG, the epileptic seizures stopped, the epileptiform discharge of the interictal EEG disappeared, but mental and behavioral disorders appeared. After reducing the daily dose of LTG, the mental symptoms gradually disappeared. Another patient was a 43-year-old woman with temporal epilepsy, complicated partial seizures appeared from the age of 6 years, and treatment with CBZ was ineffective; CBZ was replaced with LTG, and the dose was gradually increased to 100 mg bid. After a few days, the seizures disappeared, but the patient became increasingly irritable with inattention and insomnia and finally paranoid thoughts and hallucinations appearing. At the same time, EEG showed that all paroxysmal activities had completely disappeared, and the diagnosis was FN. The dose of LTG was gradually reduced to 50 mg bid, and the mental symptoms disappeared after haloperidol treatment.

Lacosamide: Lacosamide (LCM) is a new ASM in clinical use in recent years. It is mainly used for the adjuvant treatment of partial seizures. It has a good safety profile with the most common side effects, including dizziness, headache, diplopia, nausea, nasopharyngitis and vomiting. In 2013, Chatzistefanidis *et al*[28] reported that young female patients with drug-resistant partial epilepsy developed FN after treatment with LCM. In 2015, Pinkhasov *et al*[29] reported that after using LCM, a young woman experienced psychiatric symptoms. This author believes that this is the first case report of FN induced by LCM in the United States. Carazo Barrios *et al*[3] reported three patients with FN related to LCM administration. Among them, one patient was a 44-year-old woman with focal seizures caused by cortical dysplasia, and FN occurred after taking LCM. Another patient was a 42-year-old woman with unknown disease etiology and developmental delay, presenting focal or focal secondary generalized seizures. The seizures disappeared after taking LCM, but behavioral abnormalities appeared. The other patient was a 66-year-old man with focal epilepsy caused by meningoencephalitis, and FN occurred after the use of LCM. This author believes that this was FN induced by LCM.

TPM: TPM is another ASM that can cause FN. Brigo *et al*[20] reported a 33-year-old female patient with tuberous sclerosis. The initial treatment with VPA, LTG, and rufinamide was ineffective. After switching to TPM, the patient's seizures stopped, and the epileptiform discharges on the 60-min EEG were reduced by more than 50%, but severe abnormal mental behavior appeared. These mental abnormalities disappeared after stopping the drug, and the patient developed mental abnormalities again after adding TPM. This author believes that this was FN caused by TPM.

ZNS: Hirose *et al*[30] reported a 5-year-old child with refractory epilepsy. After receiving ZNS treatment, the seizures stopped, but FN appeared, manifesting as communication disorders, interpersonal tension and stereotyped behaviors. This situation persisted after ZNS was stopped, and seizures then reappeared. This author believes that although most of the patients with FN are adults and adolescents, ZNS can induce mental disorders even in young children. Brigo *et al*[20] reported a 33-year-old female patient with vascular encephalopathy following cerebral bleeding due to moyamoya disease who had seizures, and VPA treatment was ineffective. After switching to ZNS, the epileptic seizures stopped, but the patient showed obvious mental and behavioral abnormalities. This author believes that this is consistent with a diagnosis of FN and that these contradictory outcomes with treatment are extremely challenging.

Vigabatrin: Vigabatrin (VGB) has also been reported to cause FN. Weber *et al*[31] reported that a young patient had symptomatic and refractory focal seizures due to middle cerebral artery obstruction. After five weeks of treatment with VGB, the seizures stopped, but obvious abnormal mental behavior appeared after two weeks. This author believes that this was FN caused by VGB. To date, there have been more than 13 patients with FN caused by VGB[1].

PHT: Hirashima *et al*[32] reported an 11-year-old girl with FN of occipital epilepsy. This patient had no family history of epilepsy or mental disorders and developed normally. At the age of 11, she developed a fever-free generalized tonic-clonic seizure and was diagnosed with epilepsy. After PHT (37.5 mg bid) was administered, the seizures were controlled. Three days later, she developed mental symptoms, paranoia, restlessness, aggressiveness, command hallucinations (command voices from strangers) and stereotyped, short-term psychomotor excitement and impulsive violent events; recurring, neurological examinations were normal, clinical chemistry and clinical hematology test values were within the normal range, and brain magnetic resonance imaging scanning and analysis also found no abnormalities. After stopping PHT, her mental condition did not improve. Based on the patient's clinical course, this author believes that she developed FN by taking PHT. Esang *et al*[12] reported a 26-year-old female patient with no history of mental illness. Her family members described that she had been diagnosed with epilepsy in 2016 and received LEV treatment, which was initially effective; however, she had frequent seizures 1 year later, and then PHT (0.1 g tid) was added. The epileptic seizures stopped, the EEG and the head CT scan were normal, but FN occurred. There were severe mental abnormalities, severe agitation, irritability, and "all day anger", and the patient was finally hospitalized for impulsive behavior. Carazo Barrios *et al*[3] also reported one patient with FN caused by PHT among 10 FN patients.

Others: Among the 10 patients reported by Carazo Barrios *et al*[3], FN was also caused by eslicarbazepine and brivaracetam.

TREATMENT

De Toffol *et al*[4] advocated that the treatment of FN should be divided into two steps. First, it should be assessed whether the current ASM treatment is reasonable. Second, the appropriate antipsychotic should be selected. The reduction or withdrawal of suspicious ASMs and the addition of antipsychotic drugs are the main management methods of FN. The treatment of FN is summarized in Table 1.

Dose reduction or drug withdrawal

In most cases, the reduction in the dose of the drug inducing FN or the withdrawal of the suspicious drug can effectively alleviate the clinical manifestations of FN. Among the 10 FN patients reported by Carazo Barrios *et al*[3], one patient stopped suspicious ASMs and started using antidepressants, and another patient reduced the dose of suspected ASMs, which relieved the symptoms. Topkan *et al*[11] reported that patients who took LEV had FN, and the symptoms disappeared after switching to PHT. Of the 193 FN episodes studied by Calle-López *et al*[5], 47% of the patients ceased using the suspected ASMs, 25% received a dose reduction, and 28% maintained use of the original drug. In 87% of patients who withdrew their medication, FN was completely in remission, compared with 75% of those who did not discontinue. However, the treatment recommendations across different drugs are not exactly the same. It is necessary for patients receiving LEV to stop the drug when FN occurs. The symptoms of FN caused by LTG will improve by dose reduction[3,10,15,21].

Control of mental symptoms

The mental symptoms of patients with FN are often severe, which affects the quality of life of these patients. In severe cases, it may cause self-injury or other forms of injury, which requires antipsychotic treatment. Carazo Barrios *et al*[3] reported that 5 of 10 FN patients received antipsychotics or increased their antipsychotic doses, and 5 patients started taking antidepressants or increased their antidepressant drug doses. The symptoms of FN were subsequently relieved. In an analysis of 193 FN episodes, Calle-López *et al*[5] found that 73% of patients received antipsychotic treatment; haloperidol (35.4%) was used the most often, followed by risperidone (18.7%). These studies are supported by studies by Banwari *et al*[26] and Apap Mangion *et al*[25]. They also reported that the use of risperidone relieved the symptoms of FN patients. Domzał[33] suggested that haloperidol is a suitable treatment method. Agrawal *et al*[2] advocated a first choice of second-generation antipsychotic drugs, especially risperidone, because there is little interaction between this drug and other drugs, and the risk of side effects is also low.

However, whether antipsychotic treatment is provided does not affect the overall prognosis of patients. The complete remission rate of patients who received antipsychotic treatment was 56.2%, while the complete remission rate of those who did not receive antipsychotics was 92.8%. The reason is not clear[5].

Others

Not all patients with FN can be treated by discontinuing or reducing the dose of suspicious drugs and adding antipsychotic drugs. For those who are unresponsive to drug treatment, Green *et al*[19] suggested that electroshock treatment can be considered; they reported that two patients with FN were treated with electroshock methods and achieved good results. Therefore, they suggested that this method may be a reasonable treatment for FN. Kikuchi *et al*[22] reported a patient with epileptic encephalopathy who developed FN after taking LEV. They did not change the original drug, and the patient subsequently experienced epilepsy; the original mental symptoms completely disappeared.

PROGNOSIS

The overall prognosis for patients with FN induced by ASMs is good. Seven out of 10 patients reported by Carazo Barrios[3] had a good prognosis, with seizures not reappearing after the FN symptoms disappeared, and only 3 patients had a poor prognosis with recurrent attacks. Among the 193 episodes of FN studied by Calle-López *et al*[5], 65% of patients had complete control of their psychiatric symptoms, 27% had mild psychiatric symptoms, and 6% of patients had long-term symptoms. Among them, symptoms in women were more likely to be relieved than those in men, and children (< 14 years) were more likely to experience relief of their symptoms than adults. Seventy-five percent of patients with focal epilepsy experienced complete relief, and 61% of patients with generalized seizures experienced complete relief.

CONCLUSION

In conclusion, FN is a unique and easily overlooked entity. When ASMs such as LEV, ESM, LTG, and VPA are used to control epileptic seizures, if abnormal mental behavior occurs despite successful seizure control and normal EEG results, the possibility of FN should be considered. FN often leads to failure of the treatment of epilepsy and affects the quality of life of the patient. However, if this phenomenon is detected in time and corresponding measures are taken, such as dose reduction or withdrawal of the causative drug and administration of antipsychotic drugs, the overall prognosis is good. Exploring the factors related to FN caused by different ASMs can further improve clinicians' understanding of FN. The specific pathogenesis of FN needs further research in the future.

FOOTNOTES

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