

A CASE OF OBSESSIVENESS INDUCED BY LEVETIRACETAM IN A PATIENT WITH EPILEPSY, INTELLECTUAL DISABILITY AND PERVASIVE DEVELOPMENTAL DISORDER

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We describe an individual with mild intellectual disability, pervasive developmental disorder, and childhood-onset epilepsy with primary generalized seizures. In the period following initiation of treatment with levetiracetam, one of the newer anticonvulsant medications, this individual experienced the onset of symptoms of obsessiveness. Following our speculation regarding a possible association between the symptoms and the medication, the levetiracetam was tapered and eventually discontinued. The symptoms dissipated as the levetiracetam was reduced and discontinued. We believe that this is the first demonstration of an association between levetiracetam and symptoms related to obsessive-compulsive disorder.

Keywords: intellectual disability, levetiracetam, mental retardation, seizures, obsessive-compulsive disorder, pervasive developmental disability, psychiatric disorder

Levetiracetam (Keppra) is one of the newer anticonvulsant medications. It has gained wide acceptance due to its broad-spectrum efficacy, convenient dosing schedule, lack of significant drug-drug interactions, and a relatively benign side effect profile.^{8,9} Nonetheless, levetiracetam is occasionally associated with a variety of adverse psychiatric reactions. These include anxiety, irritability, hostility, depression, and even hallucinations and other manifestations of psychosis.^{3,7,11,19} To our knowledge, however, levetiracetam has not been reported to have an association with symptoms of obsessiveness or stereotypy. We report here on a patient we observed and treated, in whom we believe levetiracetam was associated with the apparent induction of obsessive preoccupation.

CASE REPORT

The patient was a 21-year-old Asian American male diagnosed with intellectual disability, pervasive developmental disorder, and childhood onset epilepsy. The patient's seizures were characterized as generalized tonic-clonic, and they were typically associated with post ictal confusion. No abnormalities were noted on CT and MRI studies. EEG studies showed spike and wave discharges over the left hemisphere, leading to a presumption that the seizure generalization was secondary. The patient had not been diagnosed at any time with a psychiatric disorder other than pervasive developmental disorder, although there was a maternal history for major depression with

psychotic features. The symptoms of the patient's pervasive developmental disorder included both language and socialization difficulties and a preference for sameness and structure, but did not include a history of overt stereotypy or repetitive behaviors. The patient lived in a community residence and required some support for his epilepsy. Described by his care providers as outgoing and gregarious, he was considered a good student and had successfully participated in several "enclave" type work-settings in the community. He participated in several group social activities, was comfortable with females, but did not express an interest in dating.

For several years prior to July 2004, the patient's seizures had been well controlled with topiramate monotherapy. During the first part of 2004 the patient experienced six seizures, despite therapeutic serum levels of topiramate. In response, his neurologist decided to transition the patient from topiramate to levetiracetam, which was titrated up to a dose of 1500 mg./day. In the period following the change in medication, caretakers noted that the patient had developed a new interest in what he termed "girlfriends." The patient explained to staff that he had a number of girlfriends, and that he had made an index card for each one. Each card contained the name of a woman the patient had met in some social or vocational setting, along with a minimal amount of personal information that he was able to obtain, such as the person's birthdate. The explanations provided by the patient were not sexual in nature

and focused instead on the number of cards he had created, and on the ways that he could arrange and display them on a table or other surface. Until he had done so, he seemed unable to move on to other activities. Over a period of months the patient became more and more preoccupied with his lists of cards. The number of cards gradually increased, as did the intensity of his insistence on displaying and discussing the card collection. In a corresponding manner, the patient gradually withdrew from other activities of interest or opted not to engage in required activities, focusing instead on the cards. These preferences gradually came to interfere more and more with his functioning in varying settings, including home and school. The difficulties persisted and in October 2005 the patient was referred for neuropsychiatric consultation to address the issue of the "girlfriends."

On mental status examination, the consultant (MS) found the patient to have a clear sensorium, a euthymic mood and a responsive affect. The examination was remarkable for a variety of oddities in the patient's language structure and language, although these were subsequently found to be longstanding in nature and were attributed to the pervasive developmental disorder. During the examination, the patient had a strong preference to direct the conversation toward his cards; by the time of the consultation, the number of cards had reached close to one hundred and fifty and the patient seemed eager to display and discuss each one. The patient was not able to provide insight into the reasons for his excessive focus on the card list, and he could not comment meaningfully on his disregard of other areas of interest. Questions by the consultant regarding details about his personal behavior and interests, including sex, evoked volleys of rehearsed utterances about his "girlfriends;" these appeared to have the purpose of keeping the examiner at a distance. The patient showed no signs of overt disturbances in reality testing or other symptoms of a thought disorder. Neurological exam was also performed and was unremarkable.

A comprehensive review of available information suggested a possible association of levetiracetam and the behavioral symptoms. Following consultation with the attending neurologist, a decision was made to change anticonvulsants again, this time to lamotrigine. Since seizure control had been good with levetiracetam and since the association of

levetiracetam with the behavioral symptoms was speculative, the transition from levetiracetam to lamotrigine was deliberately done in a slow and cautious manner. (see Table 1) Per data in chart, levetiracetam was first tapered from 1500 mg./day to 1250 mg./day and 100 mg./day of lamotrigine was added. In February 2006 the patient stated during psychiatric follow up that he had "fewer" girlfriends and cards. In March 2006 levetiracetam was decreased to 1000 mg./day and lamotrigine was increased to 200 mg./day; in April 2006 lamotrigine was increased further to 300 mg./day. During his May 2006 psychiatric appointment the patient reported that the number of cards had decreased to fifty, and residential staff reported improved behavior and some reengagement with community activities. In June 2006 levetiracetam was tapered to 500 mg./day, in July 2006 it was tapered further to 250 mg./day, and in August 2006 levetiracetam was discontinued. During the August 2006 psychiatric visit the patient stated that he had only twelve to twenty four cards left. He did not have the cards with him, and he shared that he no longer carried them around. During the fall of 2006 the patient had a number of breakthrough seizures and lamotrigine was increased to 400 and then 450 mg./day. In November 2006 the client mentioned that still had ten girlfriends, but he did so only in response to a question. By January and February 2007 the patient acknowledged only two girlfriends, both peers. By that time residential and vocational counselors reported that the patient was back to his usual self.

DISCUSSION

Levetiracetam is an anticonvulsant that has been related to a number of adverse psychiatric effects. These include new onset mood and anxiety symptoms, as well as occasional overt psychosis.^{3,7,11,19} We are not aware of any prior reports of an association between levetiracetam and obsessive symptoms, even though these are listed by the DSM-IV-TR of the American Psychiatric Association¹ as one of the anxiety disorders. Our observations suggest that in this case there was a temporal association between our patient's use of levetiracetam and his obsessive symptoms. This is supported not only by the proximity between the start of treatment with levetiracetam and the development of symptoms, but also by the fact that the symptoms dissipated in a seemingly dose related manner during the withdrawal of the medication. The addition of

TABLE 1. TRANSITION FROM LEVETIRACETAM TO LAMOTRIGINE AND CLINICAL DATA

Date	Dosage		Number of Seizures	No. of Girlfriends
	Levetiracetam	Lamotrigine		
Oct-05	1500 mg./day		0	148
Nov-05	1250 mg./day	100 mg./day	0	x
Feb-06			0	“fewer”
Mar-06	1000 mg./day	200 mg./day	0	x
Apr-06		300 mg./day	0	x
May-06			0	50
Jun-06	500 mg./day		0	x
Jul-06	250 mg./day		0	x
Aug-06	0		1	12-24
Sep-06	0	400 mg./day ^a	2	x
Oct-06	0	400 mg./day	0	x
Nov-06	0	450 mg./day	1	10
Dec-06	0	450 mg./day ^b	0	x
Jan-07				2
Feb-07	0		0	2

^alevel = 15.9 mcg/ml
^blevel = 11.6 mcg/ml
x = No information available

lamotrigine could conceivably also be associated with the reductions in symptoms, but we note that the symptoms had not been present prior to the use of levetiracetam.

Although our patient had not previously experienced any of the described obsessive symptoms, we note that he was diagnosed with pervasive developmental disorder, a condition in which repetitive behaviors and stereotypy are common. Perhaps this disorder made him more vulnerable to the induction of the reported symptoms by levetiracetam. The patient was obviously also diagnosed with epilepsy, and epilepsy itself has also been associated with an increased incidence of both repetitive behaviors and overt obsessive-compulsive disorder.^{2,12,17} Various anticonvulsant medications including valproic acid, carbamazepine, and phenytoin have been reported as potentially helpful in the treatment of these disorders.^{5,6,13,22} Conversely, the anticonvulsants zonisamide and topiramate have been reported to induce or exacerbate obsessive-compulsive disorder.^{10,18,21} If the patient was vulnerable to obsessive symptoms due to his

epilepsy, however, we cannot explain why such vulnerability would have manifested in this particular patient, on this particular drug. We did examine our patient's seizure records to see whether there had been a change in his seizure control, since frequency of seizures is potentially related to behavioral changes.³ No such association was noted. Our patient had good seizure control with both levetiracetam and lamotrigine, but obsessiveness was associated only with levetiracetam.

One can, of course, speculate on possible neurochemical underpinnings of an association between an anticonvulsant and obsessive-compulsive disorder. Several neurochemicals—for example, glutamate—have been implicated as having roles in the pathophysiology of both obsessive-compulsive disorder¹⁵ and epilepsy.^{4,16} Unfortunately, the mechanism of action of levetiracetam (a piracetam derivative) is not well understood generally, and exploration of the obvious neurochemical links has not proven productive.^{14,20} In sum, we note that levetiracetam remains a very useful and highly effective

anticonvulsant medication. Its behavioral side effects can be significant, however, and the development of obsessive symptoms may be one of those possible adverse effects.

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