Case Report
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Clinical Usefulness of Aripiprazole and Lamotrigine in Schizoaffective Presentation of Tuberous Sclerosis

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Tuberous sclerosis is not as rare as once thought and has high psychiatric comorbidities. However, bipolar or psychotic features associated with tuberous sclerosis have been rarely reported. This report first presents a tuberous sclerosis patient, resembling a schizoaffective disorder of bipolar type. A patient with known tuberous sclerosis displayed mood fluctuation and psychotic features. Her symptoms did not remit along with several psychiatric medications. After hospitalization, the patient responded well with lamotrigine and aripiprazole without exacerbation. As demonstrated in this case, tuberous sclerosis may also encompass bipolar affective or psychotic features. We would like to point out the necessity to consider bipolarity in evaluating and treating tuberous sclerosis.

KEY WORDS: Aripiprazole; Lamotrigine; Schizoaffective disorder; Tuberous sclerosis.

INTRODUCTION

Tuberous sclerosis (TSC) can involve almost every organ systems with symptom triads of mental retardation (MR), seizure and facial angiofibroma. It was previously assumed as a rare genetic disorder,[1)] but the incidence of TSC at birth is now reported 1 in 6,000.[2)] TSC is an autosomal dominant disorder involving mutations in TSC1/TSC2 genes, but two-thirds of TSC occur sporadically.[3)] This implies that a patient without a known familial history of TSC could be affected by this hereditary disease and warrants clinical attention not limited to certain pedigrees.

For psychiatric comorbidities of TSC, attention deficit hyperactivity disorder (ADHD; 30-50%) and autism (30-50%) were reported frequent.[4-7)] Depression, anxiety, MR and aggressive behavior were also common.[7-9)] In contrast, manic or psychotic features in TSC have only been described in a number of case reports.

To the best of our knowledge, we present the first case of a patient with TSC, resembling a schizoaffective disorder of bipolar type. After delineating and analyzing the case, review of relevant literature would be provided. The therapeutic utility of aripiprazole and lamotrigine will also be discussed as management options in TSC.

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CASE

The patient was a 19-years-old female with a diagnosis of sporadic TSC made at the age of three after having multiple infantile spasms. She was on vigabatrin 1,500 mg for her recurrent myoclonic seizures (2-3 times/month) throughout her childhood. Her medical records stated intermittent auditory hallucinations during that period. At the age of 13 years, the patient stopped her antiepileptic against medical recommendation. Following a seizure relapse at the age of 16 years, her electroencephalogram (EEG) revealed relatively frequent left occipital spikes. Topiramate 200 mg was started, but she again discontinued it arbitrarily after five months.

Facial angiofibromas developed at the age of 11 years. Although her facial skin lesions became barely noticeable after multiple chemical skin peelings and laser therapies, she was continuously distressed with her appearance. To treat her depressed mood and social withdrawal, the patient received sertraline 50 mg and pimozide 1mg at a private practice. Viewing that she was not fully responsive to

the treatment, she visited our psychiatric outpatient department at Seoul St. Mary's Hospital, Catholic University of Korea.

A brain magnetic resonance imaging, ordered at her first visit, showed multiple non-enhancing cortical tubers and calcifications in both lateral ventricles suggesting subependymal nodules (Fig. 1). The intelligence test revealed borderline intellectual functioning (full-scale intelligence quotient [IQ], 77; verbal IQ, 83; performance IQ, 73).

Diagnosed with psychotic depression, venlafaxine 75 mg and risperidone 1 mg were started. After one month, risperidone was discontinued and venlafaxine was increased to 150 mg as the mood improved. Due to hypomanic features emerged at month 3, venlafaxine was discontinued and valproate 300 mg was added. She displayed somewhat mixed features in mood with 2 months of further treatment. Eventually, loss of follow up occurred before she was hospitalized by her parents. The parents reported hallucinatory behaviors like silly smile and self-talking and their main complaints were irritability and neglect of self-care. The patient's refusal for foods prepared by her mother hinted presence of possible paranoid delusions.

In contrast, the chief complaint of the patient was depressed mood. Her thought process was relatively relevant and coherent. The thought contents were dissatisfaction and preoccupation with her appearance, and feelings of worthlessness. Persecutory delusions and delusions of reference were also displayed. Any forms of hallucinations were denied despite the reported history of hallucinatory behaviors.

While no other laboratory tests showed abnormality, the urine pregnancy test at the admission was tested posi-

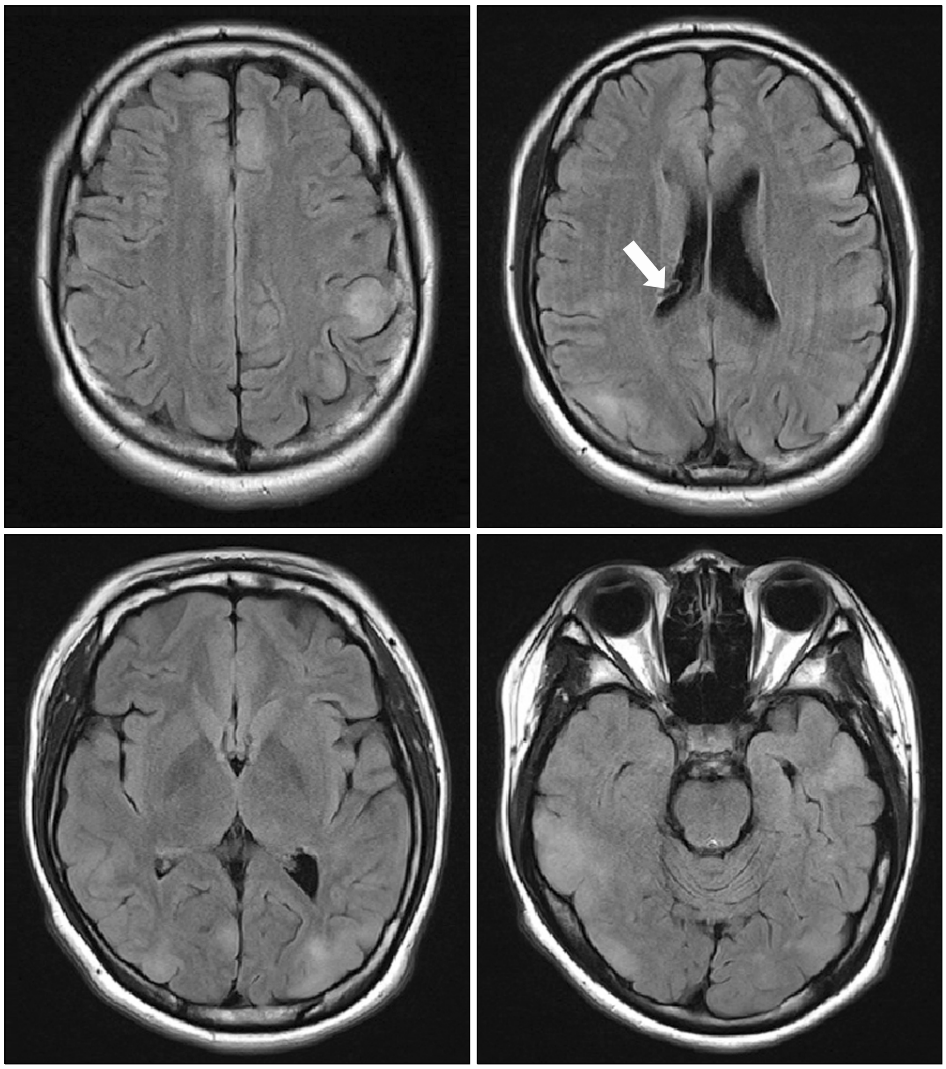

Fig. 1. Brain magnetic resonance imaging (T2- fluid attenuated inversion recovery) showing multiple cortical tubers and subependymal nodule (arrow).

tive. After obstetric consultation, the false-positivity of the initial screening was confirmed. During the 5 days of drug-free period in ruling out pregnancy, worsening of manic symptoms occurred with the emergence of talkativeness and flight of ideas.

As pregnancy was ruled out, aripiprazole 5 mg and valproate 600 mg were started. While increasing aripiprazole and valproate doses to 15 mg and 800 mg respectively, she began to complain akathisia. Propranolol was added for akathisia control. After one week of inpatient treatment, the manic symptoms improved but psychomotor retardation worsened and sudden weight gain of 3 kg occurred. To alleviate the aforementioned side effects, valproate was switched to lamotrigine. An EEG performed at the time of the switch showed no epileptiform discharges.

However, the manic symptoms worsened again after 2 days of valproate discontinuation. Due to her aggravated hostility, regular visit by family members had to be stopped. The patient also admitted auditory hallucinations of criticizing nature. Aripiprazole was increased to 20 mg. Subsequently, the patient's mood and auditory hallucination were improved, but the persecutory delusions persisted. While increasing lamotrigine as scheduled, aripiprazole was increased to 30 mg (Table 1).

During the admission, the patient repeatedly displayed negative perception of herself and others. Altogether with inefficient social skills, they were evaluated as contributing factors to her mood symptoms and paranoia. Therefore, brief cognitive therapy was carried out to improve the distorted self-images in addition to pharmacotherapy. Consequently, the patient's interactions with her family improved. After two successful overnight stay trials at home, she was finally discharged on 50th hospital day. The patient is now being followed up in the outpatients department for over 4 years without exacerbation, currently maintaining aripiprazole 15 mg and lamotrigine 200 mg.

The institutional review board of the hospital approved this report after reviewing that no identifiable personal data were used and checking the presence of consent. Written informed consent was obtained both from the patient and her father for case report (IRB No. KC10EGSI0293).

DISCUSSION

Despite the high psychiatric comorbidities, psychotic or bipolar features of TSC are little known. Hence, it should be considered whether the symptoms are really caused by TSC. As such symptoms could also be caused by a pre-existing mood disorder, secondarily by a seizure disorder, or by antidepressants. However, we concluded that TSC itself directly caused the schizoaffective symptoms for the following reasons.

First of all, no temporal relationship exists to support depression as a cause for the psychotic state. Auditory hallucinations were stated on her medical record many years before the development of facial angiofibromas or depression. As the psychotic symptoms preceded her psychosocial stressor or depression, they can be hardly explained by a pre-existing mood disorder. In addition, the negative familial history of psychiatric illness and the extensive involvement of cortical tubers in the patient's brain all lessened the possibility of primary psychiatric disorder.

Secondly, the chance of a psychiatric disorder secon-

Table 1. Summary of clinical course and medications during hospitalization

Timeline	Clinical course	Medications
Admission day	Urine pregnancy test (+)	Medications were held until false positivity later confirmed
~5 Hospital day	Hypomanic symptoms	ARP 5 mg, VPR 500 mg, LZP 0.5 mg
~8 Hospital day	Akathisia	PPL 20 mg added
~10 Hospital day	Side effects: Psychomotor retardation, Sudden weight gain (53 kg to 56 kg)	VPR switched to LTG ARP 15 mg, LZP 0.5 mg, PPL 40 mg, BZT 0.5 mg
13 Hospital day~	Hypomanic symptoms remerged with increased irritability; Complaint of auditory hallucination	ARP 20 mg, LTG 25 mg, LZP 1 mg, PPL 80 mg, BZT 0.5 mg
21 Hospital day~	Mood stabilized but persistent psychotic symptoms	ARP 30 mg, LTG 25 mg, LZP 1 mg, PPL 80 mg, BZT 0.5 mg
30 Hospital day~	Auditory hallucination : improved Paranoid ideation: remained	ARP 30 mg, LTG 50 mg, LZP 1 mg, PPL 80 mg, BZT 0.5 mg
50 Hospital day	Interpersonal interactions: improved	Discharged with ARP 30 mg, LTG 100 mg, LZP 1 mg, PPL 80 mg, BZT 0.5 mg

ARP, aripiprazole; VPR, valproate; LZP, lorazepam; PPL, propranolol; BZT, benzatropine; LTG, lamotrigine.

dary to seizures, rather than TSC itself, was examined. Because, about 10% of children with complex partial seizures were reported to have a schizophrenia-like psychosis.[10] However, those children displayed poor seizure control. Our patient remained seizure free for three years and her symptoms continued despite no abnormality was found on EEG. Furthermore, positive symptoms like hallucinations and delusions were associated in psychosis with seizures but negative symptoms were not.[10] In contrast, our patient exhibited negative symptoms as well as positive symptoms for substantial period of time, irrespective of the mood status.

Thirdly, an antidepressant-induced mood switch was also considered. However, even after venlafaxine discontinuation for five months, the symptoms remained. Moreover, after the initial stabilization in the absence of an antidepressant, the switch of mood stabilizer from valproate to lamotrigine sufficed the reemergence of manic symptoms. Therefore, the antidepressant cannot be a direct cause of the bipolarity.

Still, we believe that prescribing venlafaxine to TSC patients, whom might be more prone to bipolar disorder, should be done cautiously since venlafaxine was associated with more manic switches.[11]

The literature about psychotic or bipolar disorder in TSC is almost non-existent. Whereas some numbers of cases were reported about psychotic symptoms, only six cases of TCS with mania were found in PubMed literature search until September 2015.[12-17]

The prevalence for seizure, autism and MR are high in TSC with 85%,[18] 30-50%[4,5] and 42-64 %[9,12] respectively. Moreover, those three disorders also demonstrated high comorbidity for psychosis.[19-21] Therefore, TSC may also have an association with psychosis and warrants further investigations.

The highly reported hyperactivity in TSC (56%),[9] also raises the suspicion of under-diagnosed bipolarity. In TSC, ADHD is also prevalent with reported prevalence of 30-50%.[4,6,7] Considering that both ADHD and autism have high comorbidity of bipolar disorder,[22,23] TSC may also encompass high incidence of bipolar disorder. Furthermore, chromosome 16p13.3, where TSC 2 gene is located, was reported to have linkage evidence for bipolar affective disorder.[24] Therefore the risk of bipolarity should be properly assessed in TSC.

The reason for relatively less attention given to psychotic or manic symptoms in TSC may lie in part due to the fact that pediatricians or neurologists, whom TSC patients usually encounter, are not familiar in diagnosing such disorders. In addition, mistaking negative symptom of social withdrawal as a symptom of autism or impulsivity/hallucinatory behaviors as behaviors stemming from MR might have underlain for the under-estimation. Even though 90% of TSC patients display psychiatric problems in life, only 20% of those receive adequate evaluation and management.[25] Additionally to the under-diagnosis due to the overlapping symptoms, we hypothesize that the widespread use of anti-epileptics in TSC may have masked the underlying bipolarity. Considering that the bipolar disorder is not a rare disorder, there is still a chance of co-incidental occurrence of TSC and bipolarity. Still, anticonvulsants already prescribed for seizures might have a protective role against outburst of such manic episode. Therefore, additional caution should be applied when evaluating TSC patients for mood and when anti-epileptics are decided to be discontinued in in TSC.

As literatures on such conditions are scarce, so do the management options. In addition to drawing more clinical attention to TSC, we would like to share our successful treatment experience with aripiprazole and lamotrigine. Although manic symptoms were a major concern, the patient suffered most extensively from depression and psychomotor retardation. Lamotrigine was chosen adjunctively to aripiprazole, as lamotrigine was effective in the depressed phase of bipolar disorder.[26]

Nevertheless, safety and tolerability actually came first before effectiveness in mood stabilizer selection. Valproate and lithium are widely used mood stabilizers. However, the patient was not tolerant to valproate and lithium may increase the risk of seizure.[27] Moreover, lithium usage may become problematic if renal complications occur later by TSC, which is the most common cause of mortality in TSC.[28]

Lamotrigine was chosen not only as a mood stabilizer, but also as a safe measure against possible seizure relapse in the future. In the literature, vigabatrin and topiramate were other frequently prescribed anti-epileptics in TSC. However, they are both not approved as mood stabilizers. Furthermore, vigabatrin may induce peripheral visual field defect in 25-50% of exposed patients.[29] Topiramate may worsen cognitive functions,[30-32] which may negatively impact on already disadvantaged patient's intelligence. On the other hand, lamotrigine was not associated with cognitive impairment.[33,34]

The main purpose for prescribing aripiprazole was to mitigate both the psychotic and manic symptoms. Aripiprazole has partial agonistic activities at dopamine D2 and serotonin 5-HT1A receptors, while also acting as an an-

tagonist at serotonin 5-HT2A receptor. This unique receptor profile of aripiprazole provides some favorable advantages over other antipsychotics in terms of extrapyramidal symptoms, sedation, hyperprolactinemia, and metabolic side effects like weight gain.[35] Thus, aripiprazole was suggested to be both safe and effective for treating pediatric patients with bipolar disorders.[35,36] Improvement of cognitive function was reported in chronic schizophrenia after switching to aripiprazole.[37] Considering the high comorbid intellectual disabilities in TSC, as demonstrated by borderline intellectual funcioning in this case, aripiprazole may have additional value in cognitive domain over other antipsychotics.

In addition to controlling psychotic or behavioral disturbances, aripiprazole can also be useful in dealing with highly prevalent depressive symptoms in TSC, as it is also indicated for adjunctive treatment for major depressive disorder.

In conclusion, aripiprazole and lamotrigine have many potential advantages in treating TSC. While lamotrigine could be a good treatment option in TSC, a combination therapy with an antipsychotic like aripiprazole might be more useful in the acute phase considering the long required build-up time of lamotrigine.

Some promising clinical trial outcomes were reported with mammalian target of rapamycin inhibitors.[38] It should also be assessed whether TSC associated neuropsychiatric disorders (TAND) could also be improved. Even without a disease-modifying treatment option, psychiatric and related behavioral problems may still be managed effectively in TSC. Delayed recognition and management of those problems put the TSC patients and their families in unnecessary suffering. Therefore, TAND should be a major clinical focus when treating TSC patients. Furthermore, whenever encountering symptoms like fluctuation of mood, delusions, sudden changes of behavior, and vegetative functions occur, bipolar/psychotic spectrum disorder should also be evaluated.

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