



Case report

TREATMENT WITH ZUCLOPENTHIXOL OF A WOMAN WITH PSYCHOSIS AND TUBEROUS SCLEROSIS: A CASE REPORT

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ABSTRACT

This case is about a 20-year-old woman with tuberous sclerosis complex and psychosis admitted to the psychiatry clinic of UMHAT Aleksandrovska and treated with zuclopenthixol. She experienced paranoid delusions and verbal and physical aggression towards her mother. Because of side effects, the treatment with risperidone was changed to zuclopenthixol. We evaluated her condition with BPRS24. The score of BPRS24 in admission to the hospital was 97 points. At discharge, the score of BPRS24 was 54 points. After a month, the BPRS24 score was reduced to 39 points; two months later, it was 37.

Keywords: tuberous sclerosis complex, psychosis, zuclopenthixol,

BACKGROUND

Tuberous sclerosis complex (TSC) is a rare autosomal dominant genetic disease that manifests with a triad, characterized by epileptic seizures, mental retardation, and adenoma sebaceum [1]. There are also de novo mutations in TSC1 (encoding hamartin) or in TSC2 (encoding tuberin) genes. Mutations in these genes lead to extreme activation of the mammalian target of rapamycin (mTOR), which is the main regulator of the body's growth and controls the anabolic and catabolic processes [2]. TSC can affect multiple organs by forming benign tumors of the heart, brain, kidney, skin, liver, and lungs. Treatment with everolimus (mTOR complex inhibitor) does not impact the neuropsychiatric disorders associated with tuberous sclerosis (TAND) [3]. Psychiatric disorders are present in 80% of patients with TSC. The most prevalent are attention deficit hyperactivity disorder (in 30-60%) and autism spectrum disorders (40-50%). Psychosis is found in only 2.3% of cases [4, 5]. Due to the high incidence of psychiatric disorders in TSC, a TAND checklist has been developed to investigate multiple dimensions: behavioral, psychiatric, intellectual, academic, neuropsychological, and psychosocial [2].

In the literature, most of the reported cases of psychosis in TSC are treated with atypical antipsychotics, mainly with risperidone [6, 7, 8]. In our case, the patient was treated with risperidone and quetiapine, but there is data for increased body weight and, subsequently, a relapse of the psychotic symptoms on monotherapy with aripiprazole. In the second admission to the hospital (due to the new psychotic relapse), we decided to treat with zuclopenthixol because of the reported side effects, the registered prolongation in QTc interval at admission, and the opportunity of zuclopenthixol acetate for acute treatment and simultaneous oral application (in tablet form).

CASE REPORT

A 20-year-old woman with TSC and psychosis was admitted for the second time to the psychiatry clinic of UMHAT Aleksandrovska. There is no objective data on a family history of psychiatric disorders. She finished school with special education needs due to mild intellectual disability. The patient's parents divorced, and she lives with her mother and grandmother. She spends most of the time at home playing on the phone. She has no close friends and no need for social communication.

She had her first seizure at the age of one and her last at the age of 12. She was diagnosed with TSC in 2005 (2 years old), when multiple subcortical lesions were observed in MRI predominantly on the right side, with additional localization in the temporal and occipital regions (Fig. 1, Fig. 2). A treatment with valproic acid 600 mg/daily and levetiracetam up to 2000 mg/daily has been initiated. In 2018 (at the age of 15), a 10 mm Subependymal giant cell astrocytoma (SEGA) and renal angiomyolipomas were detected in the MRI. Consequently, treatment with everolimus (an agent with metabolic and endocrine side effects) 5 mg/daily has been started.

Fig. 1. This image shows tubers in the temporal and occipital lobe and RML in the front left lobe

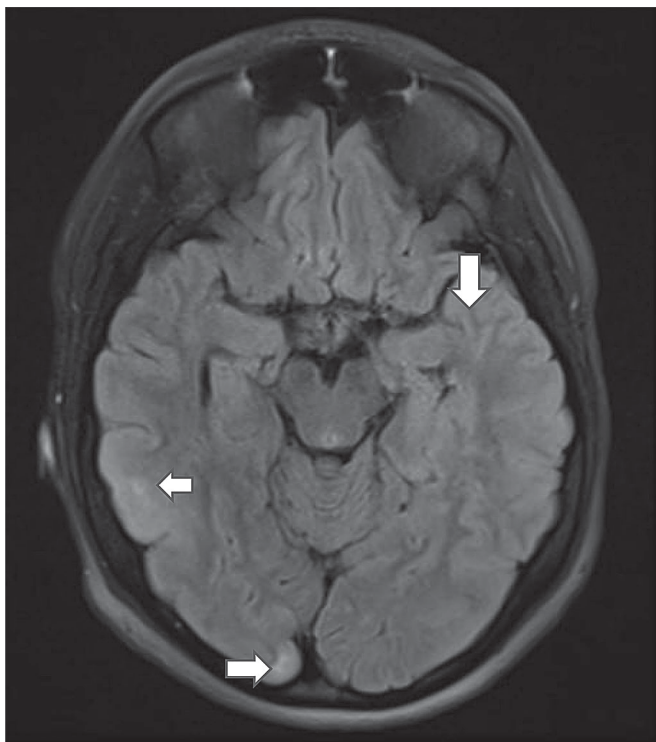
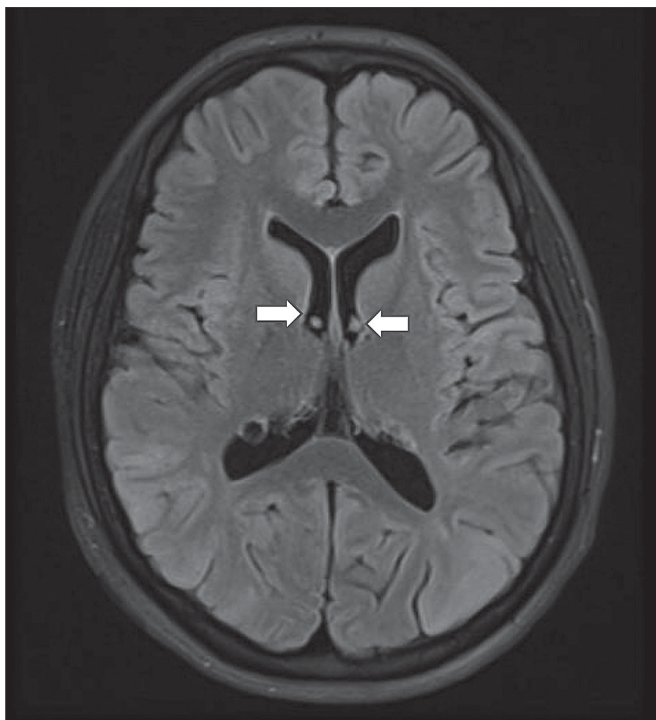


Fig. 2. In this image, calcified subependymal nodules on the walls of the lateral ventricles are shown. (also, multiple tubers in the frontal, parietal and occipital lobe are seen)



The first signs of a psychiatric disorder were reported at the age of 15 (in 2018). She had mood swings with suicidal thoughts and autoaggressive behavior (superficial cuts on the forearms). These symptoms were treated with quetiapine 50 mg/daily.

In 2021, due to auditory hallucinations and paranoid delusions, the patient was admitted to the hospital. She was discharged on therapy with risperidone – 3 mg/daily and quetiapine 300 mg/daily. Subsequently, the patient was in remission, but increased body weight and dyslipidemia were observed (no objective data of BMI), and the therapy was changed to aripiprazole 30 mg/daily (better metabolic profile) in March 2023. Following this change and partial treatment compliance, a second psychotic episode was registered. The patient came to the hospital in September 2023 due to an acute psychotic relapse.

She exhibited verbal and physical aggression towards her mother, stating that she has been poisoned, watched, and monitored and insisting that her mother is not her mother (Capgras' Syndrome). Because of the risky, psychotic-motivated behavior, she was admitted to the clinic for therapeutic clarification.

Regarding somatic status, all results were normal, except amenorrhea (everolimus-induced), BMI-26, and from ECG, QT/QTc was 439/603. The cardiologist recommended only observation.

In the beginning, the patient was hostile, suspicious, and uncooperative, with a dysphoric mood and paranoid delusions, along with selective mutism. We evaluated her condition with the Brief Psychiatric Rating Scale 24 (BPRS24) (9), and the score was 97 points. In the hospital, we initiated intramuscular treatment with haloperidol up to 15 mg/daily/i.m., zuclopenthixol acetate 50 mg/i.m. (twice), and diazepam 10 mg/i.m. (only the first day). The therapy for TSC was resumed (everolimus 10 mg/daily, levetiracetam 2000 mg/daily, and valproic acid 600 mg/daily). Throughout the treatment, the contact improved, but the patient was still paranoid, insisting that she was a man and needed to change her name and documents. We switched the treatment to oral zuclopenthixol up to 30 mg/daily and elevated the dose of valproic acid to 1000 mg/daily. Mild extrapyramidal symptoms were observed, and biperiden 2 mg/daily was added to the therapy.

At the discharge, the ECG QT/QTc was 366/463, and the BPRS24 score was 54 points. After a month, the BPRS24 score was reduced to 39 points, and two months later, the score was 37. The maintenance treatment was reduced to zuclopenthixol 10 mg/daily. The patient was in remission without extrapyramidal symptoms and started attending a daycare center for mental rehabilitation.

DISCUSSION

As far as we know, not many cases of psychosis in TSC were reported, and most of them are of the paranoid-hallucinatory type [5, 6, 7]. Due to the early onset of TSC and the consequent tubers in the brain, the psychosis is secondary (organic delusion disorder). The localization of the tubers in the brain probably causes the specific psychiatric presentation. Seven natural TAND clusters are found, and they correspond to TAND checklist items and tubers localization [10]. In our case, there are tubers and radial migration lines that correspond to almost all of the seven areas of the natural TAND clusters. Only the cluster eat/sleep is still not affected (Tabl. 1). Despite the organic genesis of the psychosis, the use of antipsychotics is indisputable. Because of the multiorgan impairment, the treatment is very challenging [11], not

only for acute but also for maintenance treatment. The first choice of treatment is an antipsychotic that is less seizurogenic and has fewer side effects, like risperidone, quetiapine, and olanzapine [6, 7, 8]. In our case, dyslipidemia and ECG changes were registered, which could be side effects of atypical antipsychotics. Therefore, we decided to use a typical antipsychotic agent, such as zuclopenthixol. We observed a good acute therapeutic response, which continued as an almost full remission during maintenance treatment with low-dose zuclopenthixol. To our knowledge, there is only one more case that reported a good response to zuclopenthixol but depot (long-lasting) form [8]. In our case, the patient has good therapeutic adherence and family support, and therefore, we decided not to apply depot medication.

Table 1. In this table, the natural TAND clusters are shown and the corresponding tubers and RML localization. In bold are the tubers and RML also seen in our case.

Natural TAND cluster (TAND checklist items)	Localization of tubers and radial lines of migration (RML)
Scholastic (reading, writing, spelling, mathematics)	Tubers in the parietal and temporal lobe
Neuropsychological (memory, disorientation, attention difficulties, neuropsychological attention deficits, visuospatial, dual-tasking, executive skills)	RML in the prefrontal cortex, predominantly in the left
Autism Spectrum Disorder-Like (inflexible, unusual language, repetitive behaviour, poor eye contact, peer difficulties, delayed language)	Tubers in the right temporal lobe , especially in the inner temporal cortex (fusiform face area)
Dysregulated behaviour (aggressive outbursts, temper tantrums, self-injury)	Without any tubers in the left temporal lobe , decreased globus pallidus
Overactive/Impulsive (overactive, impulsive, restless)	RML in the front left area
Mood/Anxiety (mood swings, anxiety, depressed mood, extreme shyness)	Tubers in the somatosensory cortex, RML in the parietal lobe
Eat/Sleep (eating difficulties, sleeping difficulties)	Tubers and RML in the cerebellum

CONCLUSION

Psychosis in tuberous sclerosis is very rare. Treatment of psychosis, in this case, is challenging because of the multiorgan presentation of the TSC and the side effects of the psychotropic medications. Zuclopenthixol appears to be an appropriate choice because of its good effect on

psychotic symptoms and minimal to no side effects. TSC is a lifelong illness, and its course and clinical presentation are dynamic because of the appearance of new tubers/hamartomas. Therefore, the observation of this type of case should be multidisciplinary, not only of neurologists and internal medicine doctors but also of psychiatrists.

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Please cite this article as: Natzkova J, Penchev M, Stoyanova V. Treatment with zuclopenthixol of a woman with psychosis and tuberous sclerosis: A case report. *J of IMAB*. 2024 Oct-Dec;30(4):5878-5881. [[Crossref](#) - <https://doi.org/10.5272/jimab.2024304.5878>]

Received: 29/07/2024; Published online: 29/11/2024



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