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Ultra-Resistant Schizophrenia Comorbid with Temporal Epilepsy: A Case Report

M.Chtibi[1*], H. Zarouf[1], I. Hanine[1], S. Belbachir[1], A. Ouanass[1]

[1]Faculty of Medicine and Pharmacy of Rabat Arrazi Psychiatric Hospital in Salé

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***Corresponding author:** M. Chtibi
Faculty of Medicine and Pharmacy of Rabat Arrazi Psychiatric Hospital in Salé

Abstract **Case Report**

Resistant schizophrenia is a significant public health issue due to high treatment costs and institutional dependence of patients. Despite the various definitions currently available to define resistant schizophrenia, along with existing clinical guidelines, their impact on daily clinical practice remains limited. While clozapine has been endorsed by national clinical guidelines, its utilization remains suboptimal, with delays in initiation and instances of ineffectiveness. Ultra-resistant schizophrenia is defined by clozapine's inefficacy even after a well-conducted treatment. The relationship between epilepsy and epilepsy-related psychoses is intricate. Individuals with epilepsy are more likely to develop psychotic disorders, while those suffering from primary psychotic disorders also have an increased risk of epilepsy. These findings suggest the presence of shared predisposing factors. We present the case of a patient with clozapine-resistant schizophrenia associated with temporal epilepsy.

Keywords: Ultra-Resistant Schizophrenia, Clozapine, Temporal Epilepsy.

INTRODUCTION

Schizophrenic illness continues to be a public health concern, with a prevalence of 1% in the general population. According to estimates from the World Health Organization (WHO), it ranks among the top ten most debilitating diseases. Life expectancy is reduced by an average of ten years compared to the general population [1, 2]. Resistant schizophrenia, also known as refractory schizophrenia or treatment-resistant schizophrenia, is a severe form of schizophrenia that doesn't adequately respond to conventional pharmacological treatments. The definition of treatment-resistant schizophrenia has evolved over time based on research advancements and diagnostic criteria used. Currently, there is no uniform or consensus definition of treatment-resistant schizophrenia. This pertains to both the duration of treatment beyond which refractory response can be identified and the number of antipsychotics attempted to alleviate the debilitating symptoms associated with this condition. Suzuki *et al.*, conducted a meta-analysis [3] of 33 studies to evaluate the criteria used for resistance. The criteria employed during these thirteen years of investigation by various researchers allowed them to define treatment-resistant schizophrenia as follows:

- The use of 3 antipsychotics at daily doses equivalent to 400-800 mg of chlorpromazine.
- The duration of treatment initiation varies between 4 and 6 weeks.
- A decrease of at least 20% in the PANSS (Positive and Negative Syndrome Scale).
- A score of 35 or lower on the BPRS scale or a score of 3 or lower on the CGI scale.

The authors noted that social functioning did not serve as a primary judgment criterion throughout these years of study. Additionally, the realm of cognitive impairments was not an integral part of the definitions of treatment-resistant schizophrenia [3].

In 2017, according to a study conducted by Howes and colleagues [4], treatment-resistant schizophrenia is defined by the following criteria:

- Moderate symptom intensity for 12 weeks.
- At least moderate functional impairment.
- At least two prior treatments with different antipsychotics for a minimum of 6 weeks, with a daily dosage equivalent to 600 mg of chlorpromazine.
- Adherence to at least 80% of prescribed doses. Plasma levels of antipsychotics monitored at least once.

- If possible, at least one prospective antipsychotic trial to confirm treatment resistance.

Clozapine is currently the only medication approved for patients with treatment-resistant schizophrenia, and it is associated with a lower rate of hospital readmission compared to other antipsychotics [5]. However, a significant delay in initiation in routine clinical practice has been reported. The management of schizophrenia must consider several resistance factors, including early onset of the disease, family history of schizophrenia, poor treatment adherence, low insight, treatment side effects, and substance abuse. Furthermore, schizophrenia is often associated with neurodevelopmental and neurodegenerative concepts. The neurodevelopmental model of schizophrenia posits early anomalies (genetic, gestational, or perinatal) that largely remain latent until puberty or early adulthood. Various environmental factors would then contribute to promoting the clinical expression of this early vulnerability. Numerous studies have highlighted a high prevalence of mental disorders in individuals with epilepsy, and a correlation between schizophrenia and epilepsy has been observed. This correlation is partly attributed to a shared alteration of brain structures, such as the temporal lobe and the diencephalon, which are associated with limbic functions. Brain structures related to limbic functions, like the temporal lobe and diencephalon, are implicated in both schizophrenia and epilepsy. In the context of schizophrenia, well-documented neuropathological alterations such as cerebral ventricular dilation, predominant atrophy in the temporal region, and entorhinal cortex dysplasia have been observed. Findings from neuropathology, genetics, and brain imaging suggest that structural brain abnormalities and genetic anomalies are present in both individuals with schizophrenia and those with epilepsy. Ultra-resistant schizophrenias exhibit the criteria for treatment resistance in addition to a lack of adequate response to clozapine, despite at least two plasma levels showing concentrations ≥ 350 ng/ml. These plasma level measurements are not only useful for confirming treatment adherence in patients but also due to the established connection between clozapine response and its plasma levels [6].

Interest and Objective of our Study

Through the analysis of a case, the objective of this study is to:

- Describe the clinical and paraclinical features of ultra-resistant schizophrenias.
- Present the peculiarities of comorbidity between schizophrenia and temporal epilepsy.
- Highlight the clinical and therapeutic challenges posed by this comorbidity.

Clinical Case Presentation

Mr. B is a 27-year-old unmarried man, working as a carpenter. He was admitted to the psychiatric hospital due to aggressive behavior, showing episodes of agitation accompanied by object destruction. It has been reported that he assaulted his sister by punching her, resulting in a dental injury. The patient comes from a modest socio- economic background. His education has been limited, ending after the fifth year of primary school to work as a carpenter. The initial signs of his illness apparently date back to 2015. Gradually, he started isolating himself, withdrawing socially, and spending his days locked in his room. His behaviors became peculiar. Subsequently, he began experiencing episodes of agitation, accompanied by delusional ideas of persecution, claiming that he was being pursued, along with auditory hallucinations. After his family decided to seek advice from a psychiatric hospital, he was put on a treatment regimen of risperidone. This approach led to a significant clinical improvement, even though his condition did not fully revert to its pre-illness level. Throughout his post- treatment follow-up, he strictly adhered to his treatment, resulting in noticeable progress. These advancements enabled him to resume his carpentry profession. Over a span of three years, his condition remained stable thanks to the treatment. In 2018, following a gradual reduction of medication doses and the complete discontinuation of the prescribed treatment by his doctor, the patient reportedly began to experience insomnia, soliloquies, and unmotivated laughter. He became aggressive and suspicious of those around him. Faced with this deterioration in his condition, his family consulted several doctors, which led to multiple treatment attempts with various medications such as risperidone, amisulpride, olanzapine, and haloperidol. Despite appropriate doses and durations of treatment, along with good therapeutic adherence and regular follow-up appointments, the patient's condition showed no improvement. Upon admission, the patient displayed psychomotor calmness, and vital signs were stable. His thoughts were dominated by a vague, poorly systematized delusion centered around themes of persecution, bewitchment, and mystico-religious notions. This delusion appeared to be influenced by intuitive, interpretative, and hallucinatory mechanisms. The patient reported auditory hallucinations. He was admitted and treated with amisulpride, with plans to initiate clozapine therapy. An incidental discovery of arterial hypertension (HTN) was made in the patient. Consequently, he was placed on bisoprolol treatment for it. Prior to commencing clozapine therapy, a preliminary assessment was conducted, including a complete blood count (CBC), a cardiac evaluation, and an electroencephalogram (EEG). The results of these examinations did not reveal any significant abnormalities. The patient was treated with clozapine at a dose of 700 mg per day. However, no improvement was observed, and the episodes of agitation persisted despite this treatment. A combination of several antipsychotic medications was introduced, including risperidone, amisulpride, and haloperidol, but there was

no clinical improvement noted. Positive symptoms persisted, and there was an increase in episodes of agitation, particularly with the use of haloperidol. A repeat EEG revealed frontal abnormalities this time, and brain magnetic resonance imaging (MRI) showed bilateral frontotemporal cortical atrophy with a 33% decrease in overall gray matter. Currently, the patient is stabilized on a combination of medications including clozapine 700 mg/day, aripiprazole 30 mg/day, sodium valproate 2g/day, phenobarbital (Gardénal) 150 mg/day, clobazam (Urbanyl) 300 mg/day, and lamotrigine 200 mg/day.

DISCUSSION

Although clozapine is commonly considered the primary treatment for patients with treatment-resistant schizophrenia, one-third to two-thirds of them still experience persistent positive symptoms despite adequate duration and dosage of clozapine monotherapy [7]. For patients who do not respond optimally to clozapine, having "ultra-resistant schizophrenia" [8], the prescription of a second antipsychotic in conjunction with clozapine could become a therapeutic option. Combining clozapine with other antipsychotics seems to be a common practice, as shown by certain surveys. Our patient was put on several combinations with a lack of symptom improvement and, in some cases, even symptom exacerbation. The addition of adjunct medications to an antipsychotic to enhance therapeutic response is a strategy frequently employed in patients who are resistant or partially resistant to antipsychotics. Several molecules have been suggested as adjunctive treatment to antipsychotics in patients with treatment-resistant schizophrenia, aiming to enhance antipsychotic effectiveness. This includes mood stabilizers and antidepressants. Following the administration of multiple combination treatments, our patient showed no improvement in symptoms, and in some cases, experienced a deterioration in his condition. As a result, a reevaluation was decided upon, including repeating an electroencephalogram (EEG) and a brain MRI. These examinations revealed anomalies, specifically temporal lobe epilepsy on the EEG, and bilateral frontotemporal cortical atrophy with a decrease in cortical gray matter on the brain MRI. Psychiatric comorbidities are very common in epilepsy, affecting 20 to 30% of epilepsy patients (9). After depression and anxiety, psychosis is the third most frequent psychiatric comorbidity, with an estimated prevalence of 5.6% (10). The prevalence of psychosis in epilepsy is over 7 times higher than the frequency of primary schizophreniform disorders in the general population [11]. Epilepsy and epileptic psychoses have a complex and bidirectional relationship, as not only are epileptic patients more at risk of developing a psychotic disorder, but patients with primary psychotic disorders also have an increased risk of developing epilepsy, suggesting common susceptibility factors [12]. After initiating anti-epileptic treatment for our patient with temporal epilepsy, the episodes of agitation disappeared. Temporal epilepsy [13] is defined as an epileptic syndrome characterized by the occurrence of simple or complex partial seizures, which can subsequently generalize, associated with unilateral or bilateral temporal EEG abnormalities.

It is Customary to Distinguish two Main Types

- Amygdalo-hippocampal seizures, characterized by ascending epigastric discomfort, nausea, pronounced autonomic signs, fear or panic, and olfactory-gustatory hallucinations.
- Seizures originating from the external temporal cortex, simple partial seizures with auditory hallucinations or illusions, dream-like state, visual perceptual disturbances, or language disturbances.

It is important to note that the patient exhibited both auditory and visual hallucinations, as well as pronounced anxiety. These symptoms could be attributed either to schizophrenia or to temporal epilepsy. In the study by Klirova *et al.*, treatment-resistant hallucinations were associated with increased metabolic activity, as observed in FDG-PET scans, in brain regions associated with language [14]. Brain imaging of patients with treatment-resistant schizophrenia is a widely discussed topic in the literature. In our case, brain MRI findings were suggestive of bilateral frontotemporal cortical atrophy with a marked decrease of 33% in cortical gray matter. In the meta-analysis by Mouchlianitis *et al.*, out of ten morphological studies, four of them identified a global decrease in gray matter, and five identified localized decreases in more than 25 brain regions, including the left middle frontal gyrus, right precentral and right middle temporal gyri. Other studies have highlighted involvement of white matter. Furthermore, PET and SPECT studies have identified a variety of metabolic abnormalities such as decreased perfusion in frontal regions, as well as reduced regional cerebral blood flow (rCBF) in frontotemporal areas both at rest and during activity [15].

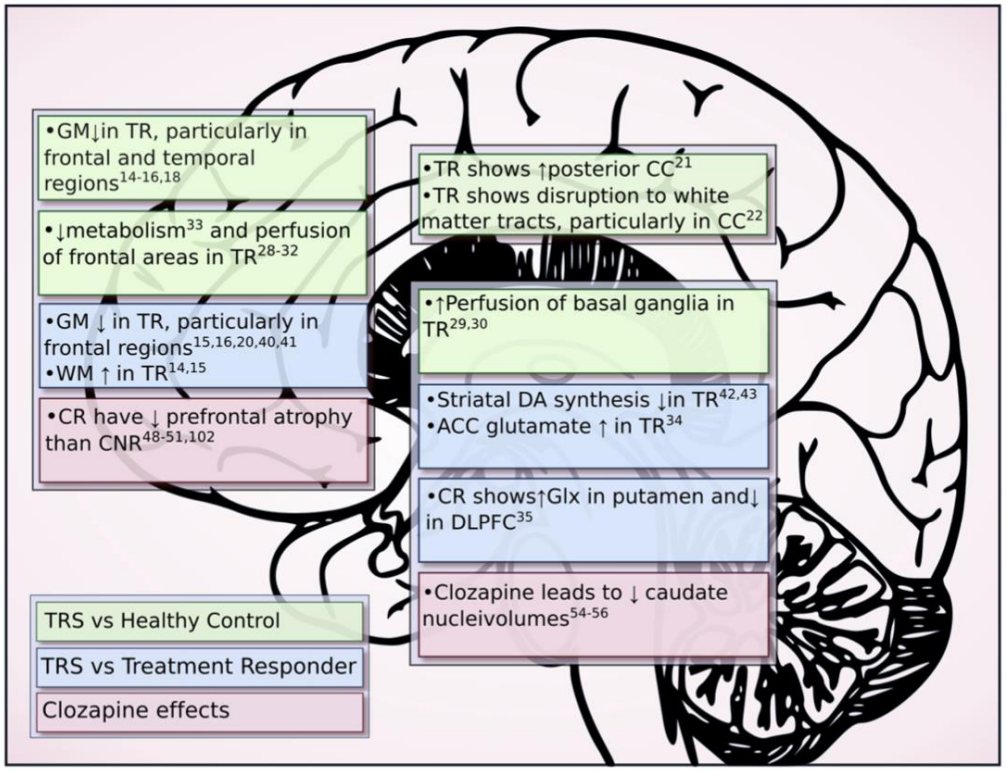

Figure 2. Summary of neuroimaging findings in treatment resistant schizophrenia
ACC – anterior cingulate cortex; CC – corpus callosum; CR – clozapine responder; CNR – clozapine non-responder; DLPFC – dorsolateral prefrontal cortex; Glx – glutamate +glutamine; GM – grey matter; TR – treatment resistant; WM – white matter

Furthermore, patients with temporal epilepsy manifesting with psychotic symptoms exhibit similar brain morphological abnormalities as those suffering from schizophrenia, such as decreased gray matter in the frontotemporal lobes, highlighting a potential common pathophysiology of psychotic symptoms between these two conditions [16].

CONCLUSION

The relationships between epilepsy and schizophrenia have been the subject of numerous discussions and controversies. Both are chronic and debilitating conditions frequently associated with impaired quality of life. Despite the clear differences between these two conditions, there are certain similarities in terms of symptomatology and the affected brain structures. Individuals with temporal epilepsy accompanied by psychotic symptoms exhibit brain alterations comparable to those observed in people with schizophrenia, such as a decrease in gray matter in the frontotemporal regions. This similarity suggests a potential shared pathophysiology for psychotic symptoms between these two conditions. However, there is still no definitive consensus on the nature of their relationship. Further research is needed to better understand the possible links between these two conditions and to guide therapeutic approaches.

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