RESISTANT PSYCHOSIS IN A PATIENT WITH COEXISTING BETA-THALASSEMIA AND LATENT TOXOPLASMOsis

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Abstract
We present the case of a 44 year-old caucasian male (V.B) with a known psychiatric history of paranoid schizophrenia, admitted to “Prof. Dr. Al. Obregia” Clinical Hospital of Psychiatry during the months of May-July 2015 (67 days of hospitalization) for: compound and complex auditory and visual hallucinations, paranoid delusions, hallucinatory behavior, psychotic anxiety and sleep disturbances, symptoms which had intensified in the several months preceding admission despite following adequate antipsychotic treatment. We present the difficulties we encountered in treating his resistant psychosis, the process of diagnosing his co-morbidities (beta-thalassemia and latent Toxoplasma gondii infection), a differential diagnosis of the intense positive symptoms the patient presented and the implications of toxoplasmosis in the evolution and treatment of a paranoid schizophrenic patient.

Conclusion.
The scope of this paper was to show the importance of performing a differential diagnosis and a thorough work-up however certain we are of the patient’s initial presentation. We also wanted to emphasize the need for studies that present more effective treatments of resistant psychosis with fewer adverse reactions. The etiology of schizophrenia presents a tremendous challenge for both researchers and physicians, the latent toxoplasmosis infection observed in high prevalence among schizophrenic patients representing only a small part of what remains to be discovered. Ultimately we must draw attention to the importance of a multidisciplinary approach to every case encountered.

Key words: resistant schizophrenia, Toxoplasma gondii, Cooley's anemia, complex hallucinations

BACKGROUND
Treatment resistant schizophrenia represents a challenge for any psychiatrist, especially if the patient presents other co-morbidities like Cooley’s anemia and latent toxoplasmosis infection and a long course of evolution as is the case presented in this article. The issue of performing a well-documented differential diagnosis remains equally important to a chronic patient with a long psychiatric history and an apparently solid diagnosis of paranoid schizophrenia as it is in the case of an acute de novo psychotic episode. Research over the past years has shown a high prevalence of Toxoplasmosis infection in patients with neuropsychiatric symptoms and disorders, most prominently in paranoid schizophrenia and mood disorders, with influences on the course, severity, treatment approach and response. [17,18,19,20,21]

We present the case of a 44 year-old caucasian male (V.B) with a known psychiatric history of paranoid schizophrenia, admitted to “Prof. Dr. Al. Obregia” Clinical Hospital of Psychiatry during the months of May-July 2015 (67 days of hospitalization) for: compound and complex auditory and visual hallucinations, paranoid delusions, hallucinatory behavior, psychotic anxiety and sleep disturbances, symptoms which had intensified in the several months preceding admission despite following treatment with clozapine 300mg/day and flupenthixol decanoate depot 20mg/21days.

PAST PSYCHIATRIC HISTORY
The patient was first diagnosed with schizophrenia in 1991 at 21 years old, shortly after finishing national service. While in his military service, the patient recalls presenting social withdrawal, flattened affect and a decrease in volition, symptoms that caught the attention of the unit’s physician. Positive symptoms (auditory and visual hallucinations and delusions) were already present at his first psychiatric admission. In the following years after receiving the diagnosis, he had other 3 admissions in the psychiatric ward, in 1996, ’98 and ’99, after which his evolution was monitored in a non-hospital setting. Over the years, the patient underwent treatment with a wide range of antipsychotics (thioproperazine, olanzapine, risperidone etc.) but responded only partially, both positive and negative symptoms remaining present. In January 2015, while being treated with clozapine 500 mg/day, levomepromazine and alprazolam, he experienced a loss of consciousness accompanied by tonic-clonic seizures and post-critical confusion and was admitted to the local neurology emergency unit. His evolution was favorable under treatment with antiepileptic agents and a decrease in clozapine dosage. He was discharged with the diagnosis of G.40: localization-related (focal) (partial) idiopathic epilepsy and epileptic syndromes with seizures of localized onset, not intractable. Following this episode the patient’s positive symptoms worsened, the hallucinations becoming more prominent accompanied by hallucinatory behavior which eventually led to the admission to our ward.

The patient was never married, has no children,
was never employed and keeps a very close relationship with his sister who is also his caregiver. The patient doesn't use nicotine or alcohol and has no relevant family psychiatric history. From his family medical history we know that his father dyed from metastatic lung cancer. He denies having any allergies, is myopic and his medical history involved two right humeral fractures and one right scapular fracture, treated surgically in 2014 which the patient recounts occurred “when I was practicing boxing and when I jumped off a table...I was training" and an uninvestigated chronic anemia which was treated with iron supplements.

PSYCHIATRIC EXAMINATION performed on 19.05.2015: The patient appears to be his stated age, his overall appearance is slightly disheveled although dressed appropriately, wearing a suit and eye glasses, with adequate hygiene and grooming. He exhibits slight distress and anxiousness, seems uneasy but is cooperative. Motor activity appears to be in normal limits although he displays generalized jitteriness and restlessness. His speech lacks in spontaneity, is slow and halting, quiet, anxious and presents a slight stutter. There aren't significant abnormalities in his thought process, his answers are appropriate, most of the times to the point, at times circumstantial. The patient is very polite, almost manneristically so. The patient's thought content is pathological, marked by persecutory and grandiose delusions “These people I see are out to get me, they're in combat with me, they won't let me live." “I have been chosen by them, I'm the only one they can communicate with.” Perceptual disturbances are the prominent symptoms in this patient. He describes ego-dystonic compound hallucinations, both auditory: voices of people, “many of them, men and women", which commentate his actions, talk to him and are most of the times imperceptive; and visual hallucinations which are well-formed, complex, include numerous people, animals and objects “there are thousands of them, men and women, a whole world” “They are constantly looking at me”. He also describes scenic hallucinations “I see the other world, of those who are gone, I see where they are, what they're doing, I see people right in this room, they're looking at us.” He perceives the audiovisual hallucinations as being constant during the day while also interacting with “the other world" and the people in it in his dreams. The patient relates that the hallucinations had always “been there”, he admits to perceiving them during the past years, but that only in the last few months the voices had become imperative “My father is dead, he had glaucoma. They urge me to take out my eye, my left eye and give it to him to eat. In the last couple of months I have started to do what they're asking, I'm trying to find a way to take it out, I don't want to do it, but they're making me.” He describes his mood as being anxious “I'm frightened about what the voices are saying and making me do.” The quality of his affect is congruent with his mood and thought content, he exhibits moderate anxiety and a restricted range of emotions, both facial expression and voice lack spontaneity. In contrast to the patient's cognitive abilities (a score of 28 on MMSE with abstract reasoning within normal ranges and a well-developed vocabulary) he has a low level of functioning, an inability to hold a job or even day-to-day chores “I can't concentrate enough, I hear them and I see them, I would love to read novels, but I can't, they take over my mind.” The patient's judgment is fair, he understands the consequences of his actions and is able to distinguish right from wrong, but fails to follow his judgment and seems to be struggling with what the voices command him to do: “I know it will hurt, I know I shouldn't do anything to hurt myself but I can't help but try to do what they're asking in order for them to stop… They won't stop unless I do what they say and take out my eye”. The patient is able to test reality, but questions his own insight and admits that “I know I'm ill and that's why I see and hear the things I do, but they are so real that I can't but help to believe they're real and try to act on what they're telling me.”

PHYSICAL EXAMINATION revealed diaphoresis, pallor and tachycardia (110 bpm regular) while the neurological examination was unremarkable apart from a generalized tremor.

LABORATORY AND IMAGING TESTS
We reviewed the laboratory findings taken during his admission at the neurology unit in January which revealed a microcytic/hypochromic anemia (RBC 5.82 million cells/ml, HGB 11.5 g/dl, HCT 37.4%, MCV 64.3fl, MCH 19.8pg) with low serum iron (53ug/dl) - which the patient told had been treated with iron supplements and leukocytosis (WBC 13.5 k/µl)68.9ug/dl. In the follow-up CBC and iron studies the RBC indices were even lower (HGB 9.9g/dl, HCT 30.9%, MCV 60.2fl, MCH 19.3pg) with a serum iron level of 116ug/dl. A hemoglobin electrophoresis test was done which confirmed the diagnosis of beta-thalassemia minor (Hb A 5.7%, Hb A 93.6%, Hb F 0.7%). At the time of admission to our ward the patient's WBC was 10.05 k/µl which we attributed to the long-term treatment with clozapine.[12] CK, within normal range (42 U). Native CT was normal apart from a modest bi-frontal cortical atrophy. EEG was unremarkable.

COURSE AND TREATMENT
The patient was admitted on 19th May. During the first two days of admission we continued the patient's treatment with clozapine 300mg/day to which we added levomepromazine 50mg/day. The patient's hallucinations were present, even heightened in their commanding effect “They tell me that my father's glaucoma extended to his other eye, now I have to take out both of my eyes. Last night, I couldn't sleep, they wouldn't let me, I tried to find a gap, a breach so that I could take my eye out” The patient also accused nightmares with similar content to that of his hallucinations. At the recommendation of the hospital's GP the patient also started treatment with folic acid and vitamins for the recently diagnosed beta-thalassemia. Over the next days, haloperidol (15-20mg/day) and trihexyphenidyl (4mg/day) - the patient presented geniospams- were added to his treatment regimen with no effect on the patient's perceptual disturbances. During the evening of 29th May, the emergency psychiatric unit was called because the patient was intensely psychotic, anxious, asking the medical staff to “please, tie me up, they're telling me to take out my eye, I'm afraid I'll hurt myself or someone else, they're talking me”. At the patient's repetitive requests he was physically restrained for a total duration of an hour and administered 10mg diazepam, 200mg Leponex and 25mg levomepromazine. From the 2nd of June his treatment was changed to Leponex 300mg/day, amisulpride (500mg/day) and diazepam...
20mg/day. After two weeks the dosage of amisulpride was increased, first to 800mg/day and later to 1000mg/day which was continued for almost two weeks. The patient's complaints continued and so did his psychotic anxiety as the hallucinations persisted. There were only a few days in which he reported the voices were less imperative “They don’t seem to tell me to take out my eye so much”, but for the whole duration of his hospitalization the positive symptoms were resistant to treatment. With the signed consent of the patient and his caregiver, on the 25th and 29th of June he underwent two ECT sessions and on the 1st of July was subjected to the third. Not only did the ECT have no result on the patient's symptoms but the last ECT session resulted in the patient suffering a left scapular fracture for which he received orthopedic treatment and pain relief medication. We had to stop the ECT treatment. The patient continued having the same type of compound audio-visual hallucinations which he described vividly: “I can see their world and our world at the same time, I can also travel to their world, walk among them, infiltrate their group. I can see them now, they're standing where they always stand, thousands of them standing side by side on a spiral, a descending tower in the form of a spiral, they are watching us now. There are men, women, children, even animals.” The patient's positive symptoms also consisted of delusions of grandeur and disorganized thought content: “I was a tree in Belarus in another life, a saint planted me there. I'm still holding onto the branches lest I'll fall. I fear I'll break my bones if I do.” “The voices are talking about religion, I can see God with my mind's eye, he is talking to the mortals.” “They tell me I'm not my mother's son, that she was fertilized and I'm the son of another woman, whom I've met in 2002 among the people I see from the other dimension.” On the 16th of July the medical team decided to perform an indirect ELISA Toxoplasma gondii antibody detection test which showed a high level of IgG Toxoplasma antibodies (955.627 UI/ml). Over the rest of the hospitalization the patient received clozapine 150mg/day, aripiprazole 30mg/day and sodium valproate 1000mg/day with the positive symptoms remaining stable and not so imperative “I can see and hear them like I've always had but they've stopped telling me to take out my eye, they're talking among themselves about religion, they say I've hidden from them and they want revenge”. We continued the treatment for the rest of his hospitalization, the patient continued to present the same perceptual disturbances but they gradually became less commanding. He was discharged stable with the following treatment: Leponex 150mg/day, Abilify 30mg/day, Orfifil 1000mg/day and follic acid with the recommendation of a parasitological exam. So far the patient has followed the same prescribed treatment, didn’t follow-up with the parasitological evaluation and continued exhibiting the same chronic psychotic features but managing to “keep the voices under control.”

**DISCUSSION:** There are many notable features about this case. Firstly we are dealing with a case of chronic unremitting psychosis which remained resistant to treatment with clozapine augmented by other antipsychotic agents. One of our approaches after the combination of haloperidol with clozapine proved to be ineffective was to augment the patient's clozapine treatment with amisulpride, an antipsychotic found to be effective in patients with resistant psychosis.(5,6) The association brought no significant benefit to our patient. A second approach was ECT-augmented clozapine therapy. A 2016 meta-analysis concluded that ECT-augmented clozapine treatment may be both effective and a safe alternative to treatment of resistant psychosis. The same study suggests that a higher than usual number of ECT treatments may be necessary.(1) Regrettably, we were unable to perform more than three, due to the scapular fracture the patient suffered during his last ECT treatment. We attributed this event to the patient's beta-thalassemia co-morbidity in which extra-medullary hematopoiesis, bone fragility and consequent fractures are common findings (2, 3, 4) Moreover, an interesting aspect both Cooley's anemia and schizophrenia seem to be genetically linked with abnormalities found on chromosome 11.(6) Yet another attempt was adding aripiprazole and sodium valproate to the existing clozapine treatment taking into account studies which suggest an improvement in efficacy.(7,8,9,10) This choice of treatment combined with the addition of sodium valproate to clozapine proved to be somewhat successful in relieving the patient's psychotic anxiety and delusions, although faintly, of his intensity of his positive symptoms. The second prominent feature of the case is the differential diagnosis of the patient's chronic psychosis. What we found remarkable was the high discrepancy between the patient's cognitive level of functioning and the strength and vividness of his perceptual disturbances which, together with the resistant character of the exhibited pathology, at times made us question the diagnosis. We considered other known causes (13) of complex hallucinations as temporal epilepsy and Lhermitte's peduncular hallucinosis. The diagnosis of epilepsy was dismissed, the patient having a normal EEG and no past history of epileptic seizures apart from the above mentioned episode, occurred in January, considered to be a side-effect of the chronic clozapine treatment which is reported to increase the risk of seizures up to 6%, with certain studies suggesting seizure prophylaxis in patients undergoing treatment with clozapine following the first seizure occurrence.(14,15) The diagnosis of peduncular hallucinosis was discarded given the patient's long psychiatric history and his recount of what seemed to be the prodromal phase of his schizophrenia. Lastly, our team was very intrigued at finding a clear confirmation of a latent Toxoplasma gondii infection. Latent infection with this parasite has, in recent years, been repeatedly incriminated in the development of certain neuropsychiatric symptoms such as anxiety, agitation, mood fluctuations, paranoid psychosis and even specific disorders such as schizophrenia and depression.(17,18,19,20,21) Toxoplasmosis has a high prevalence among schizophrenic patients, demonstrated by over 40 studies, which also revealed a higher intensity of positive symptoms in the infected patients.(17) Our patient's powerful and detailed hallucinations were what drew our attention and made us investigate a possible Toxoplasma gondii infection. A study (18) which included a description of changes in the personality of infected human subjects highlighted traits which our patient exhibited: his excessive politeness, low confidence, manierisms and lack of aggressiveness and impulsivity. Another study emphasizes the impact that toxoplasmosis co-morbidity has on the course of illness and response to treatment. (21) As seen in our patient's case the study
results show a 15x higher probability of a continuous course of disease and a negative impact on treatment.\(^{21}\) Another confirmation of the importance the infection has on the evolution of schizophrenia is that a successful treatment approach to both co-existing morbidities was a good response to treatment with valproic acid, which once added to our patient's clozapine treatment was the only measure that improved his evolution and allowed for a discharge.

**CONCLUSIONS**

The scope of this article was to show the importance of performing a differential diagnosis and a thorough work-up however certain we are of the patient's initial presentation. We also wanted to emphasize the need for studies that present more effective treatments with less adverse reactions of resistant psychosis. The etiology of schizophrenia presents a tremendous challenge for both researchers and physicians, the latent toxoplasmosis infection observed in high prevalence among schizophrenic patients representing only a small part of what remains to be discovered. Ultimately we must draw attention to the importance of a multidisciplinary approach to every case encountered.

**References**


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