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Case Report

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Successful Treatment of a Treatment Refractory Patient with Clozapine Retrial

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Abstract

This case study presents a paradigm for a clozapine retrial to treat and help a seriously ill treatment-resistant psychiatric patient, particularly in the context of rare genetic disorders. This patient's bizarre behavior included sustained and remarkable retropulsion, disrobing, unprovoked striking out at others, urinating and defecating in inappropriate places, mutism, and lying on the floor of the hallway for extended periods of time. Multiple diagnoses as well as varied and extensive genetic and psychopharmacological treatment resulted in an interrupted clozapine induction trial producing the only improvement. That incomplete trial had to be discontinued due to leukopenia. The case is particularly noteworthy for its comprehensive diagnostic workup, leading to the identification of a novel PDGFRB gene mutation associated with Primary Familial Brain Calcification (PFBC). The main finding for this case was a thorough and complete clozapine retrial that brought significant improvement. The principle conclusions of this case highlights the value of genetic testing, the importance of human connection and durable compassionate care, and a re-challenge of clozapine treatment.

Keywords: Psychosis • Treatment refractory • Clozapine • Retrial • Bizarre behavior • Schizophrenia • Genetic testing

Introduction

This case study presents a paradigm for a clozapine retrial to treat and help a seriously ill patient. A 50-year-old Caucasian male was admitted to an inpatient psychiatric unit of a local academic institution following assessment in the psychiatric emergency department. He was assessed when the police found him running naked in a field. He was screaming and agitated, telling police he was "Baby Jesus." During his admission to the outlying facility his agitation improved but his behavior became increasingly bizarre, interspersed with periods of normal behavior and speech. Approximately six weeks after admission he was transferred to a state psychiatric hospital with University affiliation for stabilization. Soon thereafter he developed catatonic features and his bush francis catatonia scale score was consistent with catatonia. He has had periods of mutism, with occasional phrases spoken clearly. He continued to exhibit bizarre behavior, including remarkable retropulsion, disrobing, unprovoked striking out at others, urinating and defecating in inappropriate places, and lying on the floor of the hallway for extended periods of time.

Case Presentation

This patient first unfortunately came to the attention of psychiatric services at age 32 when he was diagnosed with schizoaffective disorder associated with bizarre speech and behavior. At that time he had no physical health symptoms. There is no record of psychiatric symptoms prior to that time. In childhood he was considered slow, and attended special education classes in high school. Neuropyschological testing when he was 38 and then 39 years old revealed a full-scale IQ of 63 and 80, respectively. Both assessments revealed non-verbal learning disability with remarkable rote memory skills, strong verbal ability, and strong auditory attention. When he was 45 years old his Montreal Cognitive Assessment (MoCA) scale score was 15 (out of 30), with intact cognitive ability in naming, some impairment in abstraction, orientation, and attention and poor construction tasks congruent with global brain impairment [1]. Since the time of his admission to the outlying facility when he was 44 years old his physical health symptoms have evolved including blepharospasm, dystonia, rigidity, right upper extremity tremor, episodes of autonomic instability, significant dysphagia for liquids, halted speech, and unintentional weight loss despite his voracious appetite. He had lost 150 pounds in 2½ years, though his weight had stabilized. His medical diagnoses included Diabetes Mellitus Type II (DM Type II) (not abated despite extreme weight loss), constipation, hypertension, and anemia of chronic disease.

Little is known of the patient's family history. Both parents are deceased. The patient has two living sisters and three living brothers. One sister died in her 20s of a ruptured cerebral aneurysm. One brother died from myocardial infarction in his 50s. There is some family history of mental illness among immediate family members and, per report and observation, one brother exhibited similar bizarre behavior and a tremor of an upper extremity however was never psychiatrically hospitalized [2-6].

Results and Discussion

In a recent study of PDGFRB mutation carriers, 80% were found to have psychiatric symptoms, 40% had movement disorders, and 40% had cognitive impairment among symptomatic mutation carriers. The median age of clinical onset of symptoms was 31 years [4]. Psychiatric features include hallucinations, delusions, confusion, delirium, dementia, and catatonia. In addition depression, anxiety, panic attacks, aggression,

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irritability, personality changes and personality disorders are evident. Physical symptoms include Parkinsonism, seizures, headache, vertigo, paresis, stroke, syncope, ataxia, dysarthria, tremor, and orthostatic hypotension [6]. Among PFBC patients, brain calcifications are likely due to metastatic deposition, disruption of blood brain barrier, or a neuronal calcium metabolism disorder6. Brain PET-CT findings typically include reduced glucose uptake in the globuspallidus, putamen, frontal, temporal, and parietal cortices bilaterally, similar to those of this patient [7].

Clozapine is a reasonable choice to treat refractory catatonic or psychotic features of patients with PFBC. Anecdotal evidence from case reports reveals evidence of the efficacy of clozapine in such cases [8]. Medications alone do not provide a comprehensive treatment paradigm [8-10]. Throughout his treatment at a state psychiatric center, the human connection with caregivers was positive.

Despite his symptoms he had many people he could interface with and he had valuable human contact. Although the available treatments seemed to be insufficient to eradicate his symptoms, it was clear he knew his inpatient experience surrounded him with people who cared and had hope they would make a difference in his life [11-20].

Diagnosis

This patient has had multiple extended psychiatric hospitalizations at various facilities. He has been extensively investigated due to the combination of psychiatric and neurodegenerative symptoms he manifested [1,19]. This patient was treated at a state psychiatric hospital associated with a University. As such, he received much more than the typical and usual diagnostic workup commensurate and equal to his treatment refractory state [21-25].

The patient exhibited catatonia and had a number of diagnoses including bipolar disorder manic phase, learning disability, schizoaffective disorder bipolar type, history of alcohol use disorder, mild mental retardation, and attention deicit hyperactivity disorder [26-28]. He is noted to have extraordinary memorization abilities. Examples of his memory are that he will spontaneously recite the alphabet backward (correctly and rapidly), recites the 50 states of the US in reverse alphabetical order, and recites the US presidents in reverse chronological order. As he deteriorated, his symptoms and the results of the Computerized Tomography scan particularly were most consistent with a frontotemporal dementia [12,13,16,29].

Treatment

Psychopharmacological treatment has been varied and extensive. When each class or combination of classes (four antipsychotics including clozapine, Selective Serotonin Reuptake Inhibitors, benzodiazepines, mood stabilizers, antihypertensives, etc.) had been administered for sufficient periods without effect, they were slowly discontinued [2-4,11]. Electro Convulsive Therapy (ECT) trial was considered at a number of points. Permission from the court was sought and granted for ECT. With documented 36 ECT treatments this patient showed minimal improvement in his behavior. He continued to walk backwards although he was less aggressive with Activities of Daily Living help, although only with selected staff members.

The patient's brain Positron Emission Tomography-Computerized Tomography (PET-CT), Magnetic Resonance Imaging (MRI), and Computerized Tomography (CT) scans were very abnormal (Table 1).

Table 1. Tests and results.

Test	Negative results	Positive results
PET/CT	No neurodegenerative disorder, dementia unlikely	Traumatic brain injury
MRI	Inconclusive for iron deposition with neurological impacts of brain degeneration (due to pt's inserted metallic object). No mass	Has stable chronic periventricular white matter changes
CT	No intracranial mass No acute mental status changes No lymphoma No chest adenopathy	Positive for pseudomembranous colitis Positive for splenomegaly
Laboratory	No lead/heavy metal poisoning No infectious diseases No additional metabolic disease Normal thyroid normal vitamin e no hepatitis normal ceruloplasmin level (copper deposits), no Wilson's	Folic acid and vitamin B12 high diabetic C.Diff Jan2013 repeated UTI NMS x1 following 2 doses Haldol
Audiology	Normal hearing	-
Genetic testing	No prion disease (including no familial fatal insomnia) No lysosomal storage disease Niemann-Pick Type C, Gene 2 (responsible for 5% of cases) No Fragile X Syndrome	Niemann-pick disease type c, gene 1 (responsible for 95% of cases)
Sleep study	-	Abnormal with increased REM latency, mild apnea/hypopnea
Neuropsycholo gical testing	Low average IQ 80 Remarkable memory skill Strong verbal ability Strong auditory attention Montreal Cognitive Assessment (MoCA) scale score was 15 with intact	Some impairment in abstraction, orientation, and attention; and poor construction tasks. Congruent with global brain impairment.
EEG	Normal	-
ANA Screen	Screen positive (1:2560), however no autoimmune	-
Rheumatology	No findings	-
Speech language pathology	No recommendations	-
Prednisone for presumptive vasculitis	No response	-

MRV (Magnetic Resonance Venography)	No dural venous sinus thrombosis	--
M RA	No central nervous system vasculitis, stenosis, or aneurysm	-
(Magnetic Resonance		
CT for Pheo- chromocytoma	No renal artery stenosis No pelvic mass	-
Bush francis catatonia scale		Score 23 indicates catatonia
Dystonia	Levadopa	-
Examined for movement disorders	Huntington's - No autosomal dominant diseases in family therefore ruled out. Parkinson's disorder – no testing or clinical support for this diagnosis and may be side effects of antipsychotic medications.	-
Oncology consult	No hematologic malignancy No multiple myeloma No testicular cancer	Anemia from a chronic disease
Vital signs	-	Hypertensive Autonomic instability (BP fluctuations, temperature fluctuations)
Legal	-	Criminal mischief Public nudity
Psychotropics	Fluphenazine olanzapine Clozapine (discontinued due to significant decrease in WBC) divalproex seroquel buspirone lorazepam	Can be re-challenged on clozapine
ECT	Unable to find documentation of prior ECT treatment	Diagnostic ECT trial

However, he had no evidence of biochemical, metabolic, autoimmune, or infectious causes of his presentation and scan findings. His refractory psychiatric disorder prompted additional testing [20,27]. Serum testing for common genetic disorders was negative, as was testing for prion disease. He had multiple subspecialty consultations. The results of nearly three years of extensive investigations proved inconclusive; the diagnosis remained schizophrenia.

Early during his admission, the patient was prescribed a variety of antipsychotic regimens (including an interrupted clozapine induction) without improvement in his condition [2, 3]. Low- dose clozapine led to a significant drop in the patient's white blood cell count and was discontinued. A short course of high dose prednisone did not alter his symptoms. Levodopa did not improve the patient's tremor, but stimulated temporary aggression and was tapered off. The patient's catatonic symptoms did not respond to a trial of high dose midazolam. Approximately 24 months after admission the patient had increased compulsivity. For example, he relentlessly scratched his legs to the point of significant bleeding, was unresponsive to re-direction or medications such as diphenhydramine or chlorpromazine. He was prescribed naltrexone. The introduction of naltrexone evoked a temporary significant improvement in the patient's catatonic symptoms and compulsivity. After several weeks of mutism the patient began interacting appropriately with staff and family for continuous periods of minutes to hours. His inappropriate behaviors disappeared during these times. Despite an increased dose of naltrexone, the "waking" effect waned, and the patient again became persistently mute and bizarre.

This patient's case was presented at a University Grand Rounds and discussed in detail. Conclusions drawn were that there is importance in the diagnosis of schizophrenia and that the most contemporary diagnostic instrument is the clinical interview. Consultants also offered that the role of long term psychiatric institutions for the care of such patients cannot be underestimated.

After many other avenues of investigation, including consultation with a metabolic geneticist that led to completion of a DNA whole-exome sequencing, the patient did not have a different explanation for his symptoms. These tests were completed when this patient was 47 years old. Clozapine was reconsidered at this point as the initial trial was interrupted due to a drop in the WBC. This patient was clearly treatment resistant and another trial of clozapine was hoped to be potentially the only treatment that could affect his behavior and psychotic symptoms [30-32]. This trial of clozapine was in combination with lithium to contribute to mood stability and may provide protection for his WBC. Soon after the patient again experienced appropriate interaction with staff and family, accompanied by appropriate behavior. A dose-response effect occurred, with prolonged periods of appropriate interaction and behavior lasting days. The patient's white blood count remained within acceptable limits. The patient's compulsivity disappeared during periods of "waking". Discussions with the patient during "waking" revealed he had no recollection of bouts of mutism accompanied by bizarre behavior.

The results of the whole-exome testing revealed a heterozygous mutation in the *PDGFRB* gene with D1020N variant. Per the reporting geneticist, this mutation had not been previously reported as either pathogenic or benign. Mutations of the *PDGFRB* gene are associated with Primary Familial Brain Calcification (PFBC), a neurodegenerative disease typically characterized by calcium deposits in the brain, cognitive impairment, psychiatric symptoms, and involuntary movements [4, 5]. This patient likely has a novel genetic mutation associated with PFBC.

Conclusion

This case highlights the importance of timely treatment of psychiatric symptoms, even when the etiology of these symptoms is under investigation or considered part of a larger neurodegenerative process. At the same time, it is important to consider re-challenge or providing an adequate trial of clozapine duration and dose on occasions when patients remain refractory to all other treatment modalities.

Among patients with symptoms and signs consistent with neurodegenerative processes, the utility of genetic testing is worth

considering. Whole-exome analysis is an important option, especially when a variety of mechanisms of neurodegeneration are under diagnostic consideration.

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