Clinical Case Report

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Schizoaffective disorder comorbid with type 2 diabetes mellitus accompanied by frontotemporal atrophy and impaired cognition

A CARE compliant case report

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Abstract

Rationale: Brain atrophy coupled with impaired cognition may be a sign of dementia. However, growing evidence indicates that schizoaffective disorder (SAD) and type 2 diabetes mellitus (T2DM) play roles in the processes of frontotemporal atrophy and cognitive decline. Few cases of frontotemporal atrophy and impaired cognition have been reported in young adult patients with SAD and T2DM.

Patient concerns: A 34-year-old man was admitted for his 19th rehospitalization due to auditory verbal hallucinations (AVHs), delusions of persecution, mania, and fluctuating blood sugar levels. After admission, a brain computed tomography (CT) scan revealed that the patient's frontotemporal atrophy, which was first found in 2014, had gradually degenerated over time. The Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) revealed cognitive impairments. Based on the clinical assessment, his cognition and social function impairments were determined to mainly result from SAD and T2DM because the clinical characteristics and course of the disease did not coincide with the features of progressive aggravation of dementia.

Diagnoses: Diagnoses include the following: SAD-mania and T2DM.

Interventions: Paliperidone and sodium valproate coupled with quetiapine add-on treatment were prescribed for the patient.

Outcomes: The therapeutic strategy had a limited effect on the patient.

Lessons: Early onset of SAD and T2DM, as well as irregular treatment, resulting in brain atrophy coupled with cognitive impairments, may be the main causes of the patient's treatment resistance and poor outcome. The risks and benefits of treatment strategies should be individually assessed. Further neuroimaging, pertinent biomarkers, and genetic tests along with long-term follow-up are needed for precise evaluation of the patient's condition.

Abbreviations: AVHs = auditory verbal hallucinations, CT = computed tomography, ECG = electrocardiograph, FD = frontotemporal dementia, GMV = gray matter volume, ICD-10 = 10th edition of the International Classification of Diseases, MECT = modified electroconvulsive therapy, MMSE = Mini-Mental State Examination, MoCA = Montreal Cognitive Assessment, SAD = schizoaffective disorder, T2DM = type 2 diabetes mellitus.

Keywords: brain atrophy, impaired cognition, schizoaffective disorder, type 2 diabetes mellitus

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YB and MY equally contributed to this article.

Not applicable (because all procedures described were carried out as part of standard care).

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1. Introduction

In general, brain atrophy coupled with cognitive decline may be associated with physiological degradation or dementia in elderly populations. Furthermore, disproportionate atrophy, for instance, in some parts of the temporal lobes and the medial parietal cortex, is a known biomarker of neuronal degeneration.[1,2] In particular, frontal or anterior temporal atrophy and medial temporal atrophy have been reported to be associated with specific types of dementia such as behavioral variants of frontotemporal dementia[3] and dementia with Lewy bodies,[4] respectively. In addition, the presence of cognitive decline is also an obvious feature of dementia.[5,6]

However, brain atrophy coupled with impaired cognition is not a unique feature of dementia. Studies have reported that schizoaffective disorder (SAD) is associated with brain volume loss[7] and cognitive impairment.[8] In addition, type 2 diabetes mellitus (T2DM) has also been reported to be associated with brain atrophy[9] and age-related declines in cognitive function.[9,10] SAD- and/or T2DM-related brain atrophy coupled with impaired cognition is not often observed in clinical practice, and few cases with this clinical condition have been reported.

In this case report, we present a patient with diagnoses of SAD and T2DM with frontotemporal atrophy and impaired cognition. The identification of SAD- and T2DM-induced or dementia-induced brain atrophy and cognitive impairments was important for this patient. This case could improve psychiatrists' understanding of the effects of these clinically complicated conditions on the responses and prognoses of similar patients.

2. Case presentation

The patient was a 34-year-old male. He was apparently normal before the age of 18 years, without any mental disorders or physical diseases. However, in 2002, he was diagnosed with psychosis and T2DM. Insulin was required to stabilize his blood sugar levels; however, it was not used regularly. He had graduated from junior college at 18 years old despite suffering from a mental disorder. After graduation, he was able to obtain short-term jobs. He was married and had a healthy daughter. The patient and his family members did not discuss his relationship with his wife with the doctors. As of the current admission, he was living with his mother, who took care of him. He had been smoking for approximately 10 years or more, denying alcohol or other psychoactive substance abuse. He was the second child, with one older sister. His father and mother were both in good health. None of his family members had reported mental disorders.

In March 2002, the patient gradually developed delusions of persecution and reference, which made him believe, without evidence, that someone was following and commenting on him and that his classmates were plotting against him. Moreover, he exhibited an irritable mood, excitement, and even stayed up at night to sing. Subsequently, he was admitted to a hospital for the first time with a diagnosis of schizophreniform psychosis. Risperidone (3 mg/d) effectively reduced his psychotic symptoms. In August 2002, the patient was diagnosed with T2DM and received insulin to stabilize his blood sugar. Given the potential influence of blood sugar levels, we changed his medication from risperidone to perphenazine (8 mg/d). In 2005, perphenazine treatment was gradually discontinued, and the patient was able to enjoy a nearly normal life. Unfortunately, his symptoms, including delusions of persecution and unstable mood, gradually returned in 2006. During that hospitalization, we revised his diagnosis to schizophrenia and prescribed perphenazine (16 mg/d) and sodium valproate (500 mg/d). With the progression of his mental disorder, the patient gradually developed both psychotic and mood symptoms such as auditory hallucinations, delusions of persecution and grandiosity, irritability, elation, and increased energy, which met the criteria for SAD-mania based on the 10th edition of the International Classification of Diseases (ICD-10). His symptoms could be improved after each relapse with certain medications such as risperidone, perphenazine, lithium, valproate, and/or oxcarbazepine. However, he constantly failed to follow his doctor's prescriptions, which led to his as many as 19 rehospitalizations. On July 10, 2018, the patient was admitted to a hospital for the 19th time, as he again stopped taking his medications and relapsed. His mother stated that he could not resist shopping and gambling. The patient stated that he aimed to find specific methods to cure cancer. Moreover, he worried about his daughter, whom he feared might be harmed by "an unknown man." He was able to hear strange voices surrounding his ears but could not determine the origins of these voices, which irritated him.

Upon admission, his physical examination was normal; liver and kidney function, routine blood tests, and electrocardiograph (ECG) results were normal, as was his fasting glucose test due to insulin administration. According to his medical history and psychiatric interviews, diagnoses of SAD-mania and T2DM were made based on the ICD-10. When he was taking his medications irregularly in an outpatient setting, we represcribed paliperidone and sodium valproate at doses of 6 and 500 mg/d and gradually titrated the doses to 12 and 1500 mg/d, respectively. The patient has been taking the insulin aspart (18 μ, 17 μ, and 13 μ before each of three meals) and insulin glargine (16 μ before bed time) since 2017.

During admission, a computed tomography (CT) scan of the patient's head revealed visible frontotemporal atrophy that had existed since 2014 (Fig. 1). The patient's frontal and temporal lobe atrophy had degenerated over time, which suggested that the brain atrophy was possibly associated with his impaired cognition. Once the patient was in a cooperative state, the Mini-Mental State Examination (MMSE) was first used to screen orientation, repetition, digit span, immediate recall, long- and short-term memory, word list generation, attention and calculation, similarities, copying, and language.[5] He scored 27/30 on the MMSE, with points lost for calculation, copying a sentence, and following the order of a simple sentence, which implied potentially impaired cognition. Then, the Montreal Cognitive Assessment (MoCA) was employed for the further assessment of cognitive function due to its superior sensitivity and specificity over the MMSE for detecting patients with mild cognitive impairment with borderline scores on the MMSE.[6] He eventually scored 21/30 on the MoCA, with points lost for visuospatial abilities, attention, and delayed recall. Despite his impaired cognition, the patient was able to lead a routine life in the ward without any assistance.

On hospital day 15, the patient's excitement and delusions were still severe, although the auditory verbal hallucinations (AVHs) gradually stopped. Because paliperidone (12 mg/d) and valproate (1500 mg/d) were being taken by the patient, the chief psychiatrist fully reevaluated his mental and physical condition. Modified electroconvulsive therapy (MECT) was first considered, but the patient's mother refused because of fear of adverse events. Then, quetiapine add-on treatment was administered. During the

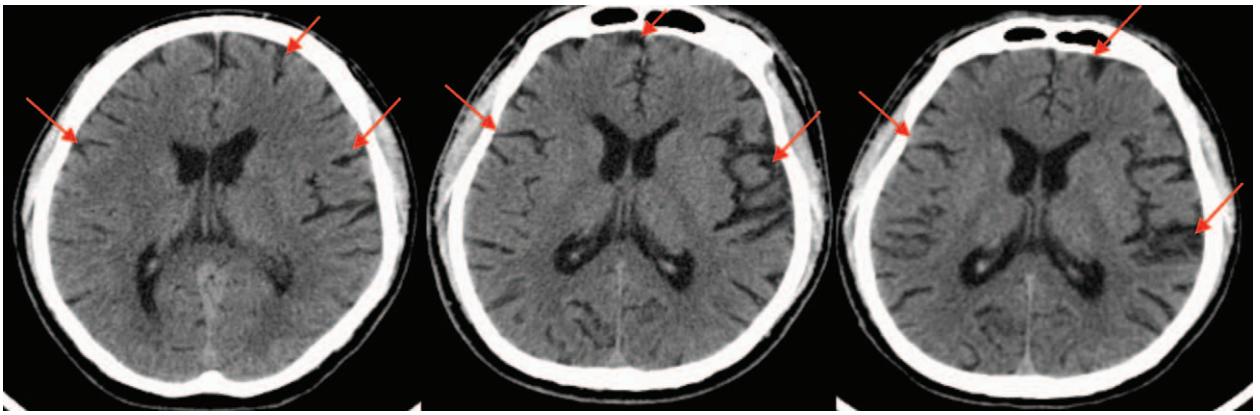

Figure 1. Brain CT (axial view) showed gradually increasing frontal and temporal lobe atrophy (red arrows) in 2014, 2017, and 2018, from left to right, respectively. The left-sided atrophy was more severe than the right-sided atrophy, and the temporal lobe atrophy was more severe than the frontal lobe atrophy. The images were obtained with a Philips Brilliance16-Row CT scanner.

process of titration, mild-to-moderate dizziness and somnolence were observed, but the patient's daily life was not affected. Finally, paliperidone (12 mg/d) and sodium valproate (1500 mg/d), as well as quetiapine (100 mg/d) add-on treatment, improved, but did not thoroughly eliminate his excitement and delusions. The patient's blood sugar level was stable. Considering his stable situation and that the residual symptoms that did not influence his daily life, the patient was discharged and underwent assessment 1 week later.

3. Discussion

Here, we present a case of SAD-mania and T2DM coupled with frontotemporal atrophy and impaired cognition. This was the patient's 19th rehospitalization since 2002. Due to his obvious psychotic and manic symptoms and medical history, diagnoses of SAD-mania and T2DM were made based on the ICD-10. After admission, the results of a routine brain CT scan showed frontotemporal atrophy, which had previously been recorded by neuroimaging and had been gradually worsening since 2014. Further cognitive testing with the MMSE and MoCA revealed his cognitive impairments. Full dosages of paliperidone and sodium valproate, as well as low-dose quetiapine add-on treatment, had limited effects on his condition.

Brain atrophy may be the cause of his psychotic symptoms. Neuroimaging studies have reported the relationship between psychotic symptoms and cortical thinning. Studies have implied that a reduction in the gray matter volume (GMV) of the left temporal lobe is associated with AVHs.[11,12] GMV reduction in the superior temporal gyrus is correlated with delusions.[13] In addition, GMV reduction is associated with not only psychotic symptoms but mood symptoms as well. Recently, a systematic review reported decreased cortical thickness in the left anterior cingulate/paracingulate and the left superior temporal gyrus, as well as several bilateral prefrontal regions in patients with mood symptoms.[14] The relationship between the patient's left frontotemporal atrophy and clinical symptoms is consistent with the aforementioned studies.

Although brain atrophy coupled with a decline in cognition confers predisposition to a condition similar to dementia,[1–6,15] patients do not always suffer from dementia. Studies have reported that SAD may contribute to this GMV reduction, predominantly in the frontotemporal regions.[16,17] In addition to SAD, T2DM is also associated with brain atrophy.[18,19] Cognitive impairments of patients with SAD have been reported,[20] especially in adolescents with SAD.[21,22] Diabetes-related cognitive deficits have also been reported; for instance, poor glycemic control is a risk factor for cognitive decline,[23] and T2DM might accelerate cognitive decline.[24] Although the cognitive level of this patient was assessed by different tools with differences in emphasis and sensitivity, they all demonstrated that SAD and T2DM contributed to his impaired cognition.

Based on these findings, it was essential to identify the causes of brain atrophy and cognitive impairments and make a differential diagnosis between SAD and dementia for this patient. After analyzing and assessing patient's past medical history and present condition, we reasoned that SAD and T2DM, instead of dementia, should be the diagnoses and were the causes of brain atrophy coupled with cognitive impairment. First, the patient was diagnosed with SAD and T2DM at an early stage of adulthood, suggesting that potentially pathophysiologic changes had already begun to occur during his childhood or adolescence, although his frontotemporal atrophy was revealed at the age of 30. These findings do not coincide with the dementia-related pathophysiological changes in the brain that are common in elderly individuals. In addition, gradual reductions in cognition and social function are obviously observed in patients with dementia. For this patient, cognitive impairments did not influence his daily life when he was stable. Furthermore, based on his medical history, his social function was only affected with fluctuation of psychotic and mood symptoms and blood glucose levels. However, despite this, we concluded that the patient only suffered from SAD and T2DM at present. Future cognitive tests, neuroimaging scans, and long-term follow-up are needed to understand his situation and outcome.

Paliperidone is well known as an atypical antipsychotic, and sodium valproate is widely used as a mood stabilizer for mental disorders. During admission, we primarily prescribed both medications for the patient's psychotic and mood symptoms based on previously effective treatment strategies. After noticing his brain atrophy, we initially intended to prescribe lithium instead, which has been proven to have a protective effect on the human brain.[25] However, due to the chronic kidney impairment caused by lithium, but not by valproate,[26] our chief psychiatrist

used sodium valproate as the treatment strategy. MECT has been widely used to treat schizophrenia spectrum disorders[27,28]; however, the patient's mother refused to allow this treatment because of fear of adverse events. Subsequently, quetiapine add-on treatment was administered, partly because he had never used this medication before, which might result in positive effect on his situation. Quetiapine was maintained at a low dose to avoid affecting his blood glucose metabolism.

4. Conclusion

Here, we describe a case of SAD comorbid with T2DM in a young adult. Frontotemporal atrophy and impaired cognition largely resulting from SAD and T2DM may be the main cause of his relapses, rehospitalizations, treatment resistance, and poor outcomes. In addition, brain atrophy in adults may reflect changes that have previously occurred during brain development. Moreover, fluctuations in the patient's blood sugar levels also played a critical role in the disease progression. Full-dosage paliperidone and valproate, as well as low-dose quetiapine add-on treatment, had limited effects on the patient's condition. The risks and benefits of the treatment strategies should be carefully considered. Further neuroimaging, pertinent biomarker analyses, and genetic tests should be seriously considered for a precise evaluation of the patient's conditions.

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Author contributions

YHB, MDY. and JL were involved in the management of the patient. ZQZ and HCY were the primary clinicians involved in the assessment, management, and follow-up of the patient. The article was written by YHB. The MMSE and MoCA were conducted by MDY. YHB, MDY, ZQZ, JL, and HCY provided final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors read and approved the final manuscript.

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References

[1] Jack CRJr, Albert MS, Knopman DS, et al. Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:257–62.
[2] McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:263–9.
[3] Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain 2011;134(Pt. 9):2456–77.
[4] McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB Consortium. Neurology 2017;89:88–100.
[5] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98.
[6] Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005;53:695–9.
[7] Lewine RR, Hudgins P, Brown F, et al. Differences in qualitative brain morphology findings in schizophrenia, major depression, bipolar disorder, and normal volunteers. Schizophr Res 1995;15:253–9.
[8] Miller LS, Swanson-Green T, Moses JAJr, et al. Comparison of cognitive performance in RDC-diagnosed schizoaffective and schizophrenic patients with the Luria-Nebraska Neuropsychological Battery. J Psychiatr Res 1996;30:277–82.
[9] Mogi N, Hattori A, Ushida C, et al. [Cognitive function and brain atrophy in elderly type 2 diabetic patients in comparison with non-diabetic elderly subjects]. Nihon Ronen Igakkai Zasshi 2001;38:388–92.
[10] Perlmuter LC, Hakami MK, Hodgson-Harrington C, et al. Decreased cognitive function in aging non-insulin-dependent diabetic patients. Am J Med 1984;77:1043–8.
[11] Allen P, Modinos G, Hubl D, et al. Neuroimaging auditory hallucinations in schizophrenia: from neuroanatomy to neurochemistry and beyond. Schizophr Bull 2012;38:695–703.
[12] Cui Y, Liu B, Song M, et al. Auditory verbal hallucinations are related to cortical thinning in the left middle temporal gyrus of patients with schizophrenia. Psychol Med 2018;48:115–22.
[13] Takahashi T, Wood SJ, Yung AR, et al. Progressive gray matter reduction of the superior temporal gyrus during transition to psychosis. Arch Gen Psychiatry 2009;66:366–76.
[14] Hanford LC, Nazarov A, Hall GB, et al. Cortical thickness in bipolar disorder: a systematic review. Bipolar Disord 2016;18:4–18.
[15] Shimizu S, Hirose D, Hatanaka H, et al. Role of neuroimaging as a biomarker for neurodegenerative diseases. Front Neurol 2018;9:265.
[16] Ivleva EI, Bidesi AS, Thomas BP, et al. Brain gray matter phenotypes across the psychosis dimension. Psychiatry Res 2012;204:13–24.
[17] Ivleva EI, Bidesi AS, Keshavan MS, et al. Gray matter volume as an intermediate phenotype for psychosis: Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP). Am J Psychiatry 2013;170:1285–96.
[18] Biessels GJ, Reijmer YD. Brain changes underlying cognitive dysfunction in diabetes: what can we learn from MRI? Diabetes 2014;63:2244–52.
[19] Wu G, Lin L, Zhang Q, et al. Brain gray matter changes in type 2 diabetes mellitus: a meta-analysis of whole-brain voxel-based morphometry study. J Diabetes Complications 2017;31:1698–703.
[20] Madre M, Canales-Rodriguez EJ, Ortiz-Gil J, et al. Neuropsychological and neuroimaging underpinnings of schizoaffective disorder: a systematic review. Acta Psychiatr Scand 2016;134:16–30.
[21] Roofeh D, Cottone J, Burdick KE, et al. Deficits in memory strategy use are related to verbal memory impairments in adolescents with schizophrenia-spectrum disorders. Schizophr Res 2006;85:201–12.
[22] Hooper SR, Giuliano AJ, Youngstrom EA, et al. Neurocognition in early-onset schizophrenia and schizoaffective disorders. J Am Acad Child Adolesc Psychiatry 2010;49:52–60.
[23] Tuligenga RH, Dugravot A, Tabak AG, et al. Midlife type 2 diabetes and poor glycaemic control as risk factors for cognitive decline in early old age: a post-hoc analysis of the Whitehall II cohort study. Lancet Diabetes Endocrinol 2014;2:228–35.
[24] Marseglia A, Fratiglioni L, Kalpouzos G, et al. Prediabetes and diabetes accelerate cognitive decline and predict microvascular lesions: a population-based cohort study. Alzheimers Dement 2019;15:25–33.
[25] Giakoumatos CI, Nanda P, Mathew IT, et al. Effects of lithium on cortical thickness and hippocampal subfield volumes in psychotic bipolar disorder. J Psychiatr Res 2015;61:180–7.
[26] Rej S, Herrmann N, Shulman K, et al. Lithium Use, but Not Valproate Use, Is Associated With a Higher Risk of Chronic Kidney Disease in Older Adults With Mental Illness. J Clin Psychiatry 2017;78:e980–5.
[27] Huang H, Jiang Y, Xia M, et al. Increased resting-state global functional connectivity density of default mode network in schizophrenia subjects treated with electroconvulsive therapy. Schizophr Res 2017;197:192–9.
[28] Bai Y, Yang X, Zeng Z, et al. A case report of schizoaffective disorder with ritualistic behaviors and catatonic stupor: successful treatment by risperidone and modified electroconvulsive therapy. BMC Psychiatry 2018;18:67.