CASE REPORT

Psychiatry and Clinical Psychopharmacology 2024;34(4):356-360
DOI:10.5152/pcp.2024.24949

Very Early-Onset Schizophrenia with Accompanying Obsessive-Compulsive Symptoms: A Case Report of a Female with 16p13.11 Duplication

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ABSTRACT

Psychosis is a complicated neuropsychiatric disorder that involves disruptions in perception and thinking, often resulting in hallucinations and delusions. Diagnosing and treating psychosis can be challenging due to its overlap with conditions such as obsessive-compulsive disorder. Recent research has focused on identifying the genetic and biochemical markers of psychiatric disorders, which can aid in better diagnosis and treatment. Schizophrenia, a type of psychosis, has a strong genetic component, making family history crucial for diagnosis, especially in cases with early onset. Research on very early-onset schizophrenia is limited due to the variability in its definition. Copy number variations (CNV) in the 16p13.11 chromosomal region have been associated with various neurodevelopmental disorders, including intellectual disability, autism, epilepsy, attention deficit hyperactivity disorder, and schizophrenia. The link between 16p13.11 CNVs and these conditions underscores the multifaceted role of genetics in neurodevelopmental disorders. Since these disorders often share common neuronal circuits, genetic variations affecting one disorder can impact others. Patients with atypical manifestations of psychosis and additional conditions should have a comprehensive evaluation, including further psychiatric, neuroimaging, genetic, and other specialized diagnostic tests. Taking a multidisciplinary approach is crucial for identifying all contributing factors and developing an effective treatment plan. This case report discusses a twelve-year-old female with very early-onset schizophrenia, obsessive-compulsive symptoms, intellectual disability, and a 16p13.11 duplication. It emphasizes the need for further research and a comprehensive management approach for such complex and treatment-resistant cases, which can provide valuable insights into the underlying pathophysiology of psychotic disorders.

ARTICLE HISTORY

Received: August 12, 2024
Revision Requested: August 24, 2024
Last Revision Received: September 07, 2024
Accepted: September 19, 2024
Publication Date: November 28, 2024

INTRODUCTION

Schizophrenia is a multifaceted and intricate psychiatric condition marked by a variety of symptoms such as hallucinations, delusions, disorganized thought processes, and significant impairments in social and occupational function.[1] Within this broad spectrum of symptoms, obsessive-compulsive symptoms have gained recognition as a common and influential component in those with schizophrenia in recent years. These obsessive-compulsive symptoms, characterized by persistent, intrusive thoughts and repetitive behaviors, add complexity to the clinical presentation and introduce additional challenges for effective management and treatment since it sometimes becomes difficult to differentiate between obsessive-compulsive symptoms and psychotic symptoms.[2] Obsessive-compulsive disorder (OCD) is notably a comorbid disorder with schizophrenia, and some authors consider OCD and schizophrenia in a spectrum of disorders as schizo-obsessive disorder.[3,4]

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Cite this article as: Kızıltan K, Özbezen Kızıltan E, Yerlikaya Oral E, Akgün Doğan Ö, Ersoy M, Karaçetin G. Very early-onset schizophrenia with accompanying obsessive-compulsive symptoms: A case report of a female with 16p13.11 duplication. *Psychiatry Clin Psychopharmacol.* 2024;34(4):356-360.

Recent studies indicate possible genetic etiological factors contributing to the clinical manifestation of schizophrenia.[5-7] Copy number variations (CNVs) in 16p13.11 have been linked to intellectual disability, autism, schizophrenia, epilepsy, and attention-deficit hyperactivity disorder as well as adolescent or adult-onset psychosis in some cases.[8] The genetic background and neuropsychiatric profile of these cases might indicate several overlapping genes that may be relevant to some pathways. It is especially important to thoroughly screen the 16p13.11 region in cases with childhood-onset psychosis.[9] In this case, we present a twelve-year-old female diagnosed with very early-onset schizophrenia accompanied by obsessive-compulsive symptoms, with a 16p13.11 duplication detected in whole exome analysis (WES).

CASE PRESENTATION

A 12-year-old female presented to our outpatient clinic with a sudden onset of psychotic symptoms, including quickly walking with a forward lean, slowed speech, and increased suspiciousness. She had shown paranoid behaviors during a recent psychiatric evaluation 2 weeks ago, such as questioning the notes being taken and the closed door. Her functionality had declined, preventing her from attending school. Consequently, she was admitted to our child and adolescent psychiatry ward for further diagnostic evaluation and treatment planning.

Upon detailing her medical history, it was discovered that she had been previously diagnosed with mild intellectual disability. One year ago, she applied to a psychiatry outpatient clinic where she exhibited obsessions related to contamination, doubt, symmetry, and writing disturbances. At that time, she was suspected of having OCD and was prescribed fluoxetine. Following an upper respiratory tract infection and a positive anti-streptolysin O test, she was evaluated for pediatric acute-onset neuropsychiatric syndrome (PANS). However, both lumbar puncture and electroencephalogram (EEG) tests revealed no abnormalities, ruling out PANS. Additionally, tests for autoimmune encephalitis and paraneoplastic syndrome markers in her blood and cerebrospinal fluid were negative. Initially, she responded well to fluoxetine, but 7 months later, she developed tactile urges, commanding auditory hallucinations, and referential delusions, leading to a change in medication to olanzapine.

MAIN POINTS

- We represent a very early-onset schizophrenia case with 16p13.11 variations.
- 16p13.11 variations can contribute to multiple neurodevelopmental conditions.
- Patients exhibiting atypical manifestations require a comprehensive assessment.

Both parents are healthy and non-consanguineous. In terms of family history, it was noted that her paternal grandmother had multiple sclerosis and her paternal grandmother's sister had schizophrenia.

During her hospital stay, consultations were conducted with neurosurgery, neuroradiology, and neurology to assess her clinical status. Electroencephalogram was normal and, aside from a developmental venous anomaly, no significant abnormality was identified in the brain MRI. Further investigations for Wilson's disease and inborn errors of metabolism were recommended. However, additional testing, including blood and urine amino acids and plasma copper levels, was found to be normal.

Based on her physical examination and medical history, a clinical genetics consultation was planned. The physical examination revealed minor dysmorphic findings, including narrow forehead, narrow upslanted palpebral fissures, a tubular nose, retrognathia, fleshy and up-turned earlobes, folded ear helices, and thin, long fingers and toes. Solo whole-exome analysis identified a 1.4 Mb duplication in the 16p13.11 recurrent region (BP2-BP3) (including MYH11). Segregation analysis in the parents showed a 1.2 Mb duplication in the 16p13.11 recurrent region and a 154.3 Kb deletion in the 1q32.2 region in the mother. The father's analysis showed no pathological genetic findings. The family received genetic counseling.

Upon evaluation, the case was diagnosed with schizophrenia and intellectual disability according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5). The patient was being treated with olanzapine before applying to our clinic. Due to extrapyramidal side effects from olanzapine 10 mg/day, the patient was trialed on risperidone (up to 4 mg/day) for better symptom improvement, since the patient had no history of risperidone use previously. Additionally, quetiapine (up to 900 mg/day) was added for antipsychotic treatment augmentation. Nevertheless, the patient showed no symptom improvement. After the patient's clinical condition was non-responsive to 3 different antipsychotic treatments under sufficient dosage and therapeutic duration, clozapine was then started and titrated up to 100 mg/day, leading to symptom improvement. However, increasing the dose to 200 mg/day caused increased obsessive-compulsive symptoms. Hence, the dose was lowered to 150 mg/day. In order to augment clozapine treatment and improve obsessive-compulsive symptoms that occurred secondary to clozapine treatment, aripiprazole was added and titrated up to 15 mg/day, resulting in improvement of the obsessive-compulsive symptoms. Biperidene was started due to extrapyramidal adverse effects resulting from the antipsychotic agents. With the discharge treatment of clozapine 150 mg/day, aripiprazole 15 mg/day, and biperidene 6 mg/day, the case was discharged with partial recovery regarding her psychotic and obsessive-compulsive symptoms at the end of 119 days.

After discharge, fluoxetine 20 mg/day was prescribed for her increased obsessive-compulsive complaints, but it was stopped due to behavioral disinhibition, and fluvoxamine was started and titrated up to 200 mg/day, further improving symptoms. The current treatment is clozapine 150 mg/day, aripiprazole 25 mg/day, biperiden 6 mg/day, and fluvoxamine 200 mg/day, along with cognitive behavioral therapy. However, no significant improvement in functionality has been achieved despite symptom management.

Informed consent has been obtained from the case's parents.

DISCUSSION

Psychosis is a highly complex neuropsychiatric disorder that involves disruptions in perception and thinking, often leading to symptoms like hallucinations and delusions. Its complexity and symptoms overlap with conditions such as OCD, making diagnosis and treatment challenging.[10] Since psychosis is often long-lasting, it requires continuous management. Effective treatment strategies must address factors that influence the disorder's progression and potential indicators of its development. Recent studies focus on uncovering the genetic and biochemical markers of psychiatric disorders like psychosis, which have traditionally been difficult to define. Discovering these markers can improve diagnosis and treatment.[11]

Schizophrenia, a form of psychosis, has a strong genetic component, making family history a crucial aspect of diagnosis, especially in cases with early onset.[12] Early-onset schizophrenia, appearing before age 18, and very early-onset schizophrenia, appearing before age 13, are particularly rare and complex. Epidemiological studies about very early-onset schizophrenia are scarce since its definition may vary according to the authors. According to a 2011 report by the National Institute of Mental Health, the prevalence of very early-onset schizophrenia is approximately 1 in 40 000.[13]

Copy number variations in 16p13.11 have been linked to numerous neurodevelopmental disorders.[14-17] Early research identified a connection between copy number variations in 16p13.11 and intellectual disability as well as autism.[14] These initial findings highlighted the role of genetic variations in developing these conditions, which are characterized by impairments in cognitive functions and social communication, respectively. Subsequent studies expanded the scope of clinical findings associated with CNVs in 16p13.11 to epilepsy, attention deficit hyperactivity disorder, and schizophrenia.[15-18] The 16p11.3 duplication, in particular, has been identified in various features and neuropsychiatric disorders, highlighting its complex role in human cognition and behavior. (Table. 1)[19] Despite this association, the phenotypic outcomes of 16p11.3 duplications are highly variable, demonstrating both reduced penetrance and variable expressivity. In our case, the 16p11.3 duplication was inherited from a clinically healthy mother, further illustrating the reduced penetrance associated with this genetic alteration. The variability in clinical presentation among carriers of the same duplication suggests that additional genetic, environmental, or epigenetic factors may influence the phenotypic outcome. The inheritance of the duplication from a healthy parent raises important considerations for genetic counseling. Families with a history of 16p11.3 CNVs should be informed about the potential for variable expressivity and the possibility of unaffected carriers. This case underscores the importance of comprehensive genetic evaluations and individualized risk assessments in families with CNVs associated with neuropsychiatric disorders.

Neurodevelopmental disorders often share common pathways and neuronal circuits in the brain. This means that genetic variations affecting one disorder

Table 1. Features of 16p13.11 Microduplications

1) Intellectual disability
2) Developmental delay
3) Delay in language development
4) Social, emotional and anxiety disorders a) Autism spectrum disorders b) Attention deficit hyperactivity disorder c) Schizophrenia d) Obsessive-compulsive symptoms/disorder
5) Heart conditions a) Ventricular septal defect b) Atrial septal defect c) Pulmonary stenosis
6) Epilepsy
7) Skeletal anomalies a) Scoliosis b) Hyperflexible joints c) Anomalies of skull
8) Eyes and vision anomalies a) Hyperopia b) Astigmatism c) Nystagmus
9) Hearing problems
10) Hands and feet anomalies a) Polydactyly b) Pes planus c) Arachnodactyly d) Clinodactyly
11) Anomalies of the brain, kidneys, urinary and genital systems a) Inguinal hernia b) Myelination delay c) Small corpus callosum d) Cerabral cyst e) Laryngomalacia f) Renal fusion g) Cleft palate/lip

can also impact others. For example, disruptions in the development or function of certain brain regions can lead to symptoms characteristic of multiple conditions. Therefore, it is not surprising that CNVs in 16p13.11 are linked to a range of neurodevelopmental disorders. The overlapping genetic basis of these disorders suggests that variations in the 16p13.11 region can contribute to multiple neurodevelopmental conditions. This highlights the importance of considering a broad range of potential impacts when studying genetic variations and their role in brain development and function. Understanding these overlaps can improve our ability to diagnose and treat these conditions by targeting the underlying genetic factors.

Given the heterogeneous nature of psychosis, atypical presentations are not uncommon. Patients exhibiting atypical manifestations and comorbidities require thorough examination and a comprehensive medical history assessment. Further diagnostic tests, including additional psychiatric evaluations, neuroimaging studies, genetic testing, or other specialized procedures, should be considered. The objective is to identify all contributing factors in order to customize a more effective treatment plan. A multidisciplinary approach is vital to ensure holistic and efficient management of the patient's health.

In conclusion, our case is a rare example in our child and adolescent psychiatry clinical practice with an atypical presentation as a female very early-onset schizophrenia case with accompanying obsessive-compulsive symptoms, intellectual disability, and neurological findings, treatment resistance, and genetic variations that were discovered later in the follow-up. We believe our case emphasizes the importance of further evaluation and the difficulties in the follow-up of very early-onset schizophrenia cases. Such atypical cases constitute valuable examples for a better understanding of the pathophysiology of the disease and the development of new treatment approaches and can make significant contributions to the literature.

Informed Consent: Informed consent has been obtained from the case's parents.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – K.K., E.Ö.K., E.Y.O., Ö.A.D., M.E., G.K.; DesignK.K., E.Ö.K., E.Y.O., Ö.A.D., M.E., G.K.; Supervision – K.K., E.Ö.K., E.Y.O., Ö.A.D., M.E., G.K.; Resources – K.K., Ö.A.D.; Materials – K.K.; Data Collection and/or Processing – K.K., E.Ö.K., Ö.A.D.; Analysis and/or Interpretation – K.K., E.Ö.K., E.Y.O., Ö.A.D., M.E., G.K.; Literature Search – K.K., E.Ö.K.; Writing – K.K., E.Ö.K., E.Y.O., Ö.A.D., G.K.; Critical Review – K.K., E.Y.O., Ö.A.D., M.E., G.K.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

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