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CASE REPORT Open Access

Psychotic symptoms in Fabry disease: a rare case report following discontinuation of enzyme replacement therapy

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Abstract

Introduction Fabry disease is a rare X-linked lysosomal storage disorder characterized by α-galactosidase A enzyme deficiency, leading to systemic accumulation of glycosphingolipids. Among psychiatric symptoms, depression is the most frequently reported, while psychotic symptoms are extremely rare, with fewer than ten cases documented in the literature.

Case presentation In the presented case, a 22-year-old female patient with a diagnosis of Fabry disease developed psychotic symptoms—including auditory hallucinations, persecutory and referential delusions, and disorganized behavior—approximately one week after discontinuing enzyme replacement therapy (ERT). A multidisciplinary evaluation revealed no acute pathology that could explain the psychotic presentation. ERT was reinstated, and olanzapine and fluoxetine were initiated to address her psychotic and obsessive symptoms, resulting in a partial clinical improvement and ongoing outpatient follow-up.

Discussion This case highlights a temporal relationship between ERT discontinuation and the emergence of psychotic symptoms, suggesting a possible link with metabolic imbalance. Unlike previously reported cases where such symptoms were attributed to cerebrovascular complications, the current case points toward potential neurochemical mechanisms.

Conclusion Clinicians should be aware that psychotic symptoms may emerge in Fabry disease, particularly in the context of treatment non-adherence. This case aims to enhance clinical awareness of rare neuropsychiatric manifestations in lysosomal storage disorders and underscores the essential role of a multidisciplinary approach in managing such complex presentations.

Keywords Fabry disease, Psychosis, Enzyme replacement therapy (ERT), Multidisciplinary approach, Case report

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Introduction

Fabry disease is a rare X-linked recessive lysosomal storage disorder and ranks as the second most common condition within this disease group [4]. Fabry disease, also known as Anderson-Fabry disease, was first described independently in 1898 by German dermatologist Johannes Fabry and British dermatologist William Anderson. It results from mutations in the *alpha-galactosidase A* (*GLA*) gene, leading to reduced or absent enzymatic activity. Consequently, glycosphingolipids—particularly globotriaosylceramide (Gb3)—accumulate within lysosomes. Over time, this accumulation causes progressive damage across multiple organ systems and presents with a highly variable clinical picture. Prominent somatic features of Fabry disease include cornea verticillata, angiokeratomas, hypertrophic cardiomyopathy, proteinuria, chronic kidney disease, and early-onset cerebrovascular events [9]. From a psychiatric perspective, depression is the most commonly reported comorbid condition among patients with Fabry disease [11]. Psychotic symptoms, however, have been reported in fewer than ten cases in the literature. In some instances, these rare symptoms appear secondary to cerebrovascular complications, while in others, they have been observed concurrently with Fabry disease without a clearly established causal relationship. To date, it remains unclear whether the emergence of psychotic symptoms in Fabry disease is due to neurological involvement or directly linked to the underlying pathophysiology of the disorder [11].

This case report presents the detailed clinical course of a young woman diagnosed with Fabry disease who developed psychotic symptoms following the discontinuation of enzyme replacement therapy (ERT). The report also discusses the implications of psychiatric manifestations in the diagnosis and treatment processes of rare metabolic disorders such as Fabry disease.

Case presentation

A 22-year-old unmarried woman presented to the psychiatry outpatient clinic for the first time. She was a university graduate, living with her family and was the youngest of eight siblings. Her presenting complaints included an acute onset of insomnia, auditory hallucinations in the form of voices asking questions and giving commands, delusional beliefs that she and her family were the targets of witchcraft, increased suspiciousness toward others, persecutory delusions such as falsely believing she was receiving threatening messages via the internet despite the absence of any such messages, and ideas of reference involving colors, for example interpreting the color red as a personal message concerning her honor. Following clinical evaluation of these symptoms, which had been continuing for a week, she was admitted to the inpatient psychiatry unit with a preliminary diagnosis of a psychotic episode. There was no history of substance use or recent initiation of new medications prior to the onset of symptoms, as confirmed by collateral information obtained from her family.

According to the history obtained from the patient and her family, she had been diagnosed with Fabry disease approximately four years prior. Around one year earlier, following stressful life events such as her university graduation and the end of a romantic relationship, she developed depressive symptoms within a few weeks, including low mood, loss of interest in previously pleasurable activities, decreased energy, and social withdrawal, which persisted for approximately one year and caused marked impairment in her social functioning. Without receiving any psychiatric treatment, her symptoms gradually diminished over time and eventually subsided to a level where a psychiatric diagnosis could no longer be established. During this period, she continued regular follow-up and treatment for her Fabry disease.

Approximately two weeks before her psychiatric admission, the patient discontinued her enzyme replacement therapy (ERT) for Fabry disease without informing her physician, due to gastrointestinal side effects and a perceived lack of treatment benefit. Corroborative history from her family confirmed that these concerns were genuinely experienced and not the result of psychotic or obsessive doubts. About one week after discontinuing ERT, she began to exhibit psychotic symptoms. In addition, disorganized behaviors were observed, such as burning or discarding useful household items, placing books in the washing machine, and storing clothes in the refrigerator. As her symptoms worsened, she experienced diffuse bodily pain and fluctuating consciousness, prompting an emergency department visit. Neurological and metabolic evaluations, including physical examination and laboratory tests, revealed no acute pathology. While the metabolic disease team attempted to reinitiate her treatment plan, effective communication with the patient was not possible, and she was therefore referred to psychiatry. Upon evaluation, the Department of Psychiatry diagnosed her with a first psychotic episode, leading to her admission to the inpatient psychiatry unit.

Her medical history revealed a diagnosis of Familial Mediterranean Fever (FMF), for which she began colchicine treatment at the age of 14. At age 17, genetic analysis identified a heterozygous *c.289G > C (p.A97P)* mutation, and her LysoGb3 level was measured at 2.4 ng/mL (normal < 1.3), leading to a diagnosis of Fabry disease. Intravenous ERT with agalsidase alfa was initiated at the age of 19. Systemic evaluations revealed bilateral cornea verticillata, optic disc edema in the left eye, sensory polyneuropathy on electromyography (EMG), and left ventricular diastolic dysfunction on echocardiography.

Due to gastrointestinal symptoms, endoscopy and colonoscopy were performed, with findings consistent with celiac disease. In addition to these, approximately one year prior her psychiatry consultation, she developed asymmetry of the right side of her face and weakness on the right side of her body; magnetic resonance imaging (MRI) revealed a lacunar infarct. Family history indicated parental consanguinity and a clustering of autoinflammatory diseases within the family, including FMF, ankylosing spondylitis, and psoriatic arthritis.

In consultation with the neurology department, acute neurological pathologies—including stroke, hemorrhage, metabolic encephalopathy, and seizure-related states—were ruled out by examination, laboratory investigations, and brain MRI, which revealed no new lesions beyond the previously known lacunar infarct. Autoimmune encephalitis was considered but deemed unlikely in the absence of clinical features. Based on the persistence of persecutory delusions, auditory hallucinations, and disorganized behavior lasting for more than one week and causing marked social and functional impairment, the clinical picture met DSM-5 diagnostic criteria for Schizophreniform Disorder. As no organic or substance-related cause was identified, antipsychotic treatment was indicated to manage acute psychotic symptoms. During inpatient follow-up, the metabolism unit was consulted, and ERT was reinitiated. Concurrently, olanzapine was started at a dose of 5 mg/day. A partial reduction in auditory hallucinations was observed after five days of olanzapine treatment; however, the cleaning-related behaviors, which had been present since the onset of illness, increased in severity, leading to adjustment of the treatment regimen to olanzapine 10 mg/day and fluoxetine 20 mg/day. With the updated treatment plan, a marked improvement in auditory hallucinations was achieved, although delusional beliefs did not fully resolve. Throughout her inpatient stay, the patient demonstrated compliance with psychiatric treatment, and a partial improvement in functioning was noted. However, full remission was not achieved. The patient's Positive and Negative Syndrome Scale (PANSS) score was 124 at admission, which decreased to 95 and then to 88 during follow-up.

On the 19th day of hospitalization, upon the request of the patient and her family, discharge was planned, and outpatient psychiatric follow-up was arranged. During outpatient visits, the patient continued on fluoxetine and olanzapine combination therapy without experiencing any medication-related side effects. The patient attended the first outpatient follow-up one week after discharge and was monitored regularly for 3 months.At the 3-month follow-up, the patient had a PANSS score of 70, reflecting an approximate 44% reduction from the baseline score of 124, and a Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score of 13, corresponding to a 35% reduction from the baseline score of 20. The patient also showed improved insight and adherence to treatment, indicating a state of partial remission. Psychotropic medication was maintained at olanzapine 10 mg/day and fluoxetine 20 mg/day, with follow-up continuing in a state of partial remission under regular psychiatric and multidisciplinary monitoring.

Discussion

Fabry disease is a lysosomal storage disorder that poses challenges to clinical management not only due to its systemic effects but also because of its rare neuropsychiatric complications. In the literature, depression is consistently reported as the most common psychiatric symptom among Fabry patients, whereas psychotic symptoms are described as extremely rare. For instance, in a retrospective study involving 33 patients, depression was identified in 18% of cases, while psychotic symptoms were reported in only one patient, and were interpreted as part of an acute confusional episode [6]. In contrast, a recent systematic review has shown that Fabry disease may be associated not only with depression but also with anxiety, attention deficits, agitation, and even psychotic symptoms. Moreover, these symptoms can persist even in patients receiving ERT, and their severity and presentation may vary depending on individual factors such as age, gender, and treatment adherence [11]. In most previously reported cases, psychotic symptoms were attributed to cerebrovascular complications. For instance, in the first reported case of psychosis associated with Fabry disease, paranoid ideation and auditory hallucinations emerged six years after diagnosis and were successfully managed with phenoxybenzamine [7]. In one case, they were considered coincidental without establishing a causal relationship with Fabry disease [5]. In another case, antipsychotic treatment led to symptom improvement; however, a definitive link between the psychotic symptoms and Fabry disease could not be established [12]. In a more recent report, psychotic symptoms in a patient receiving ERT were associated with thalamic lesions [3]. The presented case offers a distinct perspective when compared to existing literature. The emergence of psychotic symptoms shortly after the patient voluntarily discontinued her regular ERT regimen highlights that adherence to treatment is critical not only for managing the somatic aspects of Fabry disease but also to prevent neuropsychiatric manifestations, possibly mediated through interactions between ERT, neuroinflammation, and neurotransmitter systems. Although treatment discontinuation in some patients may theoretically be influenced by psychotic ideas of persecution or obsessive concerns about adverse effects, this was not the case in our patient. The decision to stop ERT was attributed to gastrointestinal side effects, which were also confirmed

by family members, indicating that discontinuation was based on somatic intolerance rather than psychiatric misinterpretation. Although the exact neurobiological mechanisms underlying psychotic symptoms in Fabry disease remain unclear, it has been suggested that lysosomal dysfunction may exert various effects on the central nervous system. Accumulation of globotriaosylceramide (Gb3) due to α-galactosidase A deficiency may contribute to microvascular injury, neuronal degeneration, and neuroinflammation within brain tissue [10]. Involvement of brain regions such as the thalamus, hippocampus, and frontal cortex may disrupt emotional regulation, perception, and cognitive functions, thereby facilitating the development of psychotic symptoms. Additionally, dysregulation of dopaminergic and glutamatergic pathways has been proposed in Fabry patients, both of which are known to be closely associated with psychotic symptomatology [2]. Discontinuation of ERT could, in theory, influence these pathways; however, the present data are insufficient to determine whether such changes contributed to symptom onset.

Moreover, while most cases reported in the literature associate psychotic symptoms with structural brain lesions or cerebrovascular causes, in the present case, although a lacunar infarct was identified on brain MRI performed approximately one year prior, these lesions were deemed temporally unrelated to the onset of psychotic symptoms. Following a multidisciplinary evaluation in consultation with the neurology department, no neurological pathology was identified that could account for the psychotic presentation, and no causal link was established between the brain lesion and the psychiatric symptoms. These observations are compatible with—but do not prove—that psychotic features may have developed as a result of neurochemical alterations related to enzyme deficiency, rather than secondary to structural damage.Additionally, the emergence of psychotic symptoms shortly after the discontinuation of ERT distinguishes this case from previously reported ones and underscores its clinical uniqueness.

It is well established that psychiatric symptoms can emerge not only in Fabry disease but also in other lysosomal storage disorders. A recent review emphasized the need for individualized treatment approaches in enzyme deficiency disorders, including Fabry disease, highlighting the complexity and variability of neuropsychiatric manifestations in these conditions [8].

Furthermore, the consensus guidelines published by the European Fabry Working Group emphasize that discontinuation of ERT should only occur when medically necessary, as interruptions may lead to serious clinical consequences, including worsening of somatic symptoms, accelerated disease progression, and increased risk of renal or cardiac complications [1]. In our case, the episode of fluctuating altered consciousness was not considered a direct consequence of ERT discontinuation, as neurological and metabolic evaluations revealed no acute pathology, and it was instead interpreted as part of the acute psychiatric presentation. This highlights the need to carefully consider the role of ERT adherence in preventing both somatic and neuropsychiatric complications in patients with Fabry disease.

Although the temporal association between ERT discontinuation and the onset of psychotic symptoms is striking, establishing a causal relationship requires future studies utilizing advanced biomarkers and neuroimaging techniques. The development of such neuropsychiatric manifestations may involve contributions from neuroinflammatory processes, genetic vulnerability, lysosomal dysfunction, or systemic stress. Therefore, longitudinal prospective studies are needed to better understand the relationship between ERT adherence and psychiatric outcomes in patients with Fabry disease.

In the presented case, challenges in maintaining treatment adherence and continuity contributed to difficulties in ongoing care, which ultimately resulted in the patient's discharge from the psychiatric unit upon request by both the patient and her family. Another limitation is the use of oral rather than long-acting injectable antipsychotics, which are generally preferred in patients with established diagnoses and persistent adherence problems. In this case, however, the diagnostic uncertainty at the time of presentation, the patient's young age, first psychotic episode, and lack of prior antipsychotic exposure supported the decision to initiate oral rather than injectable treatment. Additionally, although the patient underwent a general medical evaluation in the emergency department—including laboratory tests and physical examination—and consultations were obtained from relevant specialties such as metabolism and neurology, a psychiatric consultation was not requested at that stage. This oversight may have delayed the initiation of appropriate psychiatric care, representing another limitation.

Beyond the limitations specific to this case, several broader issues must be acknowledged. First, because this is a case report from a single patient, the findings cannot be generalized, and a causal relationship between the discontinuation of enzyme replacement therapy and the onset of psychotic symptoms cannot be definitively established. Second, advanced neuroimaging or biomarker analyses were not performed, limiting the ability to investigate potential neurobiological mechanisms. Third, psychosocial stressors and comorbid conditions (such as FMF and celiac disease) may have contributed to the psychiatric presentation, and these cannot be fully isolated. In particular, the patient had a comorbid diagnosis of Familial Mediterranean fever (FMF) and was on regular colchicine therapy. While this condition could

not be completely ruled out as a background factor, it was not considered to have played a direct role in the acute psychiatric presentation, since treatment adherence was maintained and no FMF-related exacerbations were reported.

On the other hand, once the psychiatric evaluation was performed, the decision to admit the patient to the inpatient unit enabled close monitoring, appropriate treatment planning, and a multidisciplinary approach, which can be considered a strength of this case.

Although rare, the potential for psychotic symptoms in Fabry disease should not be overlooked, and a multidisciplinary approach is essential throughout the diagnostic and follow-up processes. While patients may present to emergency services with somatic complaints, the possibility of underlying psychotic features must also be considered, and psychiatric consultation should be sought when indicated. This case supports the need for physiological monitoring alongside careful assessment for potential neuropsychiatric complications. Coordinated efforts among psychiatry, neurology, and metabolic specialists are crucial in managing this complex clinical spectrum.

Patient and family perspectives

Patient: "When I decided to stop the regular treatment I was receiving for Fabry disease because I felt it was not helping me, I didn't expect my body to react so quickly and intensely."
Family: "After learning that our daughter had discontinued the treatment she had been receiving for her long-standing Fabry disease, we became deeply concerned about the strange behaviors, unusual thoughts, heightened sensitivity, and fears that began to emerge. Seeing her symptoms improve after restarting treatment brought us great relief. However, witnessing this improvement has also caused us to feel uncertain about whether she truly needs to continue the treatment."

Conclusion

Rare metabolic disorders such as Fabry disease should be recognized as potential contributors to neuropsychiatric symptoms. This case is notable in illustrating a temporal association between recent discontinuation of enzyme replacement therapy and the onset of psychotic features in one patient; however, causality cannot be established from a single case. It supports the importance of monitoring not only somatic manifestations but also depressive and psychotic symptoms in these patients. A multidisciplinary approach—grounded in collaboration among psychiatry, neurology, and metabolic specialists—is essential for effective disease management. This case aims to raise awareness of the potential for psychosis in Fabry disease and to encourage clinicians to remain vigilant toward this rare but clinically significant presentation. Our observations suggest that interruption of ERT may precipitate or unmask psychotic features in susceptible Fabry patients; therefore, close psychiatric surveillance is warranted around treatment lapses.

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Written informed consent for the publication of this case report and any accompanying images was obtained from the patient and their family

Clinical trial registration
Not applicable. The present article does not involve a clinical trial.

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Not applicable. The present article does not involve a clinical trial.

Standards of reporting
This case report was written in compliance with the CARE guidelines.

Authors' contributions
N.G. conducted patient interviews, collected data, performed the literature review, and wrote the main manuscript. A.G. conducted patient interviews, collected data, performed the literature review, and contributed to manuscript writing. N.K. conducted patient interviews, collected data. All authors reviewed the manuscript.

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Consent for publication
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