



## Case Report



## Psychiatric Onset Alexander Disease: An Important Challenge in Neuropsychiatric Diagnosis: A Case Report

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**Citation** Arshiany, H., Ezzatian, B., Artounian, V., Alizadeh, F., Mohammadian, F. Psychiatric Onset Alexander Disease: An Important Challenge in Neuropsychiatric Diagnosis: A Case Report. *Basic and Clinical Neuroscience*, 13(2), 269-274. <http://dx.doi.org/10.32598/bcn.2021.1551.1>

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**Article info:****Received:** 05 Dec 2020**First Revision:** 28 Dec 2021**Accepted:** 02 Jan 2021**Available Online:** 01 Mar 2022**Keywords:**

Alexander disease, Late-inset, GFAP mutation, Psychiatric symptoms, Leukodystrophy

**ABSTRACT**

**Introduction:** Alexander disease is a heterogeneous group of diseases with various manifestations based on the age of disease onset. This rare leukodystrophy syndrome with mutations in the GFAP gene could present with developmental delay and seizure in the infantile form to ataxia and bulbar palsy in adulthood. However, psychiatric symptoms are not well-defined and are usually evaluated after disease diagnosis, not before disease investigations.

**Case Report :** Our patient is a 52-year-old Iranian woman with a history of depression since 17 years ago, a suicidal attempt two years ago, and ingestion of a large amount of opium with the intention of suicide 2 months ago. She was presented with disorientation and probably a delirious state in the last interview. Eventually, in comprehensive investigations, white matter hyperintensity in MRI and leukodystrophy was diagnosed to determine the cause of these changes, we did a gene study, found whole exon deletion of the GFAP gene, and made a diagnosis of late-onset Alexander disease.

**Conclusion:** Neurological-onset manifestation of Alexander disease, specifically late-onset form, is the most common clinical picture of disease and was seen in about 90% of patients, but psychiatric symptoms are not well-known, and psychiatric-onset disease was not described yet. Various gene mutations were described in late-onset Alexander disease; however, the large whole exon deletion which was revealed in our patient is a novel mutation and significantly needs to be explored. Here authors describe a late-onset Alexander disease with psychiatric-onset symptoms and novel large exon deletion in the GFAP gene.

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## Highlights

- Alexander disease is a rare heterogeneous disorder that could have various symptoms of the central nervous system involvement.
- The whole-exons deletion of the GFAP gene in an adult patient with features of Alexander disease is the first Gene mutation that was revealed in this case.
- Psychiatric onset Alexander disease is the one differential diagnosis in the patients with atypical psychiatric symptoms combined with soft neurological signs.
- Neurologic consultation and appropriate imaging and laboratory procedures could help early diagnosis and potential treatment.

## Plain Language Summary

Patients with atypical psychiatric symptoms are usually visited more times in the year without any significant benefit. They receive numerous medications and encounter significant complications due to mentioned polypharmacy. However, genetic, metabolic, or neurological causes could be considered in some treatment-resistant cases. We described the rare genetic disorder (Late-Onset Alexander disease) in the Iranian woman with atypical and treatment-resistant depression with suicidal attempts. We proposed holistic assessment in the patients with psychiatric symptoms which have atypical course or response to treatment or are accompanied by neurological and cognitive symptoms.

### 1. Introduction

**A**lexander disease is a leukodystrophy caused by dominant missense or indel mutations in the gene encoding the glial fibrillary acidic protein. This rare disease is generally a fatal disorder of the central nervous system, defined initially by the distinctive neuropathology consisting of abundant Rosenthal fibers within the cytoplasm and astrocytes (Balibi et al., 2010; Knuutinen et al., 2018; Park, Park, Kim, & Kwon, 2020).

The symptoms of Alexander disease vary depending on the age (infantile, juvenile, and adult), and within different forms, different symptoms and severity can be seen:

- **Infantile form:** The infantile subtype is the most common form manifesting with seizures, developmental delay, pyramidal tract signs, and progressive macrocephaly
- **Juvenile form:** The Juvenile type has a slower course with bulbar signs, ataxia, seizures, normocephaly, or megalcephaly
- **Adult form:** When the age of onset is late, bulbar symptoms and cerebellar dysfunctions develop gradually, requiring discrimination from adult-onset neurode-

generative disorders (Casasnovas et al., 2019; Gowda, Srinivasan, Jetha, K., & Bhat, 2019)

In this study, we present the late-onset Alexander disease with a psychiatric-onset feature which is rarely the initial manifestation of disease, and the new long heterozygote deletion in the GFAP gene.

### 2. Case Presentation

Our case is a 52-year-old Iranian housewife admitted to the Emergency Department of Roozbeh Psychiatric Hospital two years ago after a suicide attempt.

Her depression started at the age of 35, precipitated by several consecutive losses, including the death of her father and father-in-law, whom she loved dearly. At the time, she presented with a depressed mood, diminished interest in pleasurable activities, loss of volition and initiative, feelings of guilt and worthlessness, significant psychomotor retardation, and a lack of energy. She was diagnosed with major depressive disorder, and antidepressant medication was initiated. After an unsuccessful trial with selective serotonin reuptake inhibitors, venlafaxine (225 mg/d) was prescribed, which resulted in partial response, and the patient maintained symptom-free for 10 years. Unfortunately, at 45, she was diagnosed

with severe hypertension, so her doctor decided to discontinue venlafaxine gradually.

Her depressive symptoms re-emerged with venlafaxine discontinuance and never fully remitted with other prescribed antidepressants, like sertraline, citalopram, nortriptyline, or combination therapy with bupropion. She also experienced adverse effects such as tremor, headache, and nausea, which negatively affected her drug compliance.

At the age of 47, her only daughter died of a lower respiratory tract infection unexpectedly. This tragic event flared up her symptoms and resulted in 3 years of persistent major depression. Finally, three years later, the deterioration of her husband's cirrhosis pushed her to the brink of suicide.

She was admitted to the emergency department after her first suicide attempt at 50. She had ingested 30 tablets of clonazepam and 20 tablets of chlorpromazine. She was stabilized and put under suicide protection and later referred to Roozbeh Psychiatric Hospital for further evaluations. Her psychomotor activity was severely retarded, and her responses were slow and delayed. Physical and neurological examination was normal.

Regarding her poorly controlled hypertension and her previous good response to venlafaxine, a cardiology consult was requested, and a trial with duloxetine was started. Her symptoms began to improve at 60 mg/d. She was discharged after 12 days of hospitalization with controlled blood pressure, significant improvement in psychomotor retardation, and resolution of suicidal thoughts.

During follow-up visits, her depression went into complete remission, and her only complaints were memory difficulties and slow talking. One year later, her brother died, which again caused a relapse in her symptoms. She did not attend her follow-up visits for the next six months, and when she did, she reported that 2 months ago, she had ingested a large amount of opium with the intention of suicide. The opium ingestion had caused respiratory depression and necessitated intubation and ICU admission. The doctors had substituted her medications with chlorpromazine, clonazepam, and sertraline at discharge. Her son also reported that for the last month, she had been experiencing episodes of disorientation regarding time and place. During these episodes, the patient's behavior was odd. For instance, she would put her dentures in a flask and drink from it or try to pour fruit juice into her meal. She could not recall either incident. During the interview, she was partially disoriented to time but had an intact orientation to place and person.

She appeared confused and dazed. Her facial expression was blunt, and her psychomotor activity was retarded. Regarding her delirious state, we immediately asked for blood and urine workup, which all came back normal. Although the disorientation had substantially reduced, a brain MRI was requested to examine the probable underlying cause of the delirious state, and she was referred to the neurology department for further workup.

Her 60-year-old brother, mentioned above, had a history of cerebrovascular accident (CVA), dysarthria, paralysis, and urinary incontinence, resulting from the CVA. He died due to an infected bed ulcer. The patient also has a deceased daughter with an early marriage and divorce, two unsuccessful suicide attempts, and periods of depression, suggesting an underlying mood disorder.

### Neurological assessment

The patient was referred to Neurology Clinic with forgetfulness, object displacing, and inappropriate dressing from 2 months ago. Symptoms were much more serious and led to severe functional disability in the patient. By the time, she had experienced several fallings as well. Additionally, dizziness and fatigability were seen in the patient. Likewise, the patient suffered from disorientation regarding time and place.

In cognitive assessment, the patient underwent some examinations such as Montreal cognitive assessment (MOCA), which scored 27/30 (defect was in delay recall with a score of 4/5, clock-drawing test (CDT) with 2/3, and repetition with 0/1). Another memory test, known as the auditory verbal learning test (AVLT), was carried out, ending in 44/47.

In neurological examination, bilateral hyperreflexia was detected in the mentioned case, spasticity was observed in some muscles, and with respect to plantar reflex, bilaterally mute was reported. Positive Hoffman's sign was seen as well, which indicated that there might be some abnormalities in the pyramidal tract. Other examinations showed no abnormalities.

### Paraclinical assessment

The patient underwent comprehensive neurological and laboratory assessments, including brain imaging with contrast, vasculitis and coagulative tests, and infectious causes assessment to rule out other treatable causes of leukoencephalopathy.

We assessed the arylsulfatase enzyme to evaluate the possibility of metachromatic leukodystrophy, manifested with multi-system involvement, including pyramidal, bulbar, and cerebellar systems, and psychiatric manifestation similar to our patient's. The patient's EEG illustrated mild abnormality due to transient sharp activity.

MRI imaging has a material role in diagnosing this type of Alexander disease, i.e., adult-onset Alexander disease (AOAD). In this patient, AOAD involved the anterior part of frontal lobes, which is represented in different abnormal intensities MRI imaging acquisition with regard to white matter. It is characterized by the low intensity in T1-weighted; likewise, mild atrophy in the medulla oblongata is illustrated. However, it has a high intensity in T2-weighted images. Likewise, the relatively abnormal intensity at the periventricular area in the axial fluid-attenuated inversion recovery (FLAIR) image is conspicuous, implying white matter abnormalities. With respect to the T1-weighted contrast image, no abnormality is detected. Also, the anterior rim of the periventricular area has a low signal in the T2-weighted image. No enhancement was seen in the periventricular region.

### 2.3. Gene study

Next-generation sequencing was done for all genes that cause leukodystrophy. This individual has a large heterozygous deletion (exons 1-9) in the GFAP gene, so the case suffered from Alexander disease.

It seems that tolerance of the large genomic deletion (1-9 exons) in our patient is related to haploinsufficiency resistance. Haploinsufficiency is a condition that arises when the normal phenotype requires the protein product of both alleles, and a reduction of 50% of gene function results in an abnormal phenotype (Deutschbauer et al., 2005).

To the best of our knowledge, our patient is the first described case of whole-exons deletion of GFAP gene in a patient with features of Alexander disease.

## 3. Discussion

In Alexander disease, a combination of typical clinical symptoms and characteristics of neuroimaging could suggest the diagnosis, and to establish a definite diagnosis, genetic testing could be helpful and recommended.

Alexander disease was initially diagnosed in an infant with the symptom of macrocephaly and neurological deterioration, but over time, it was determined that the disease has three known varieties, and the adult-onset

type has the most heterogeneous presentation. The most known clinical sign of late-onset Alexander disease could be classified into three separate systems: bulbar, pyramidal, and cerebellar. However, other non-specific manifestations involving the oculomotor tract, autonomic system, seizure, sleep problems, and apnea are also seen in this heterogenic disease.

Pareyson et al. reported 11 cases of adult-onset Alexander disease with a comprehensive approach to diagnosis and treatment. In this review, bulbar and pyramidal dysfunction are the most common symptoms; however, bulbar signs are infrequent at disease onset (Pareyson et al., 2008).

In P. Balbi et al. review, the clinical spectrum of 112 cases of Alexander disease was analyzed. In this review, pseudobulbar signs were present in 80% of cases. Ataxia, oculomotor abnormality, pyramidal signs, and autonomic disturbance are other common signs (Balibi et al., 2010).

In general, neurologic-onset manifestations were seen in 90% of these cases. However, in our patient, no neurological symptoms were seen at the onset of the disease. Psychiatric symptoms are rarely considered an initial presentation of type 2 Alexander disease. However, in our patient, her initial manifestation was probably psychiatric.

Depression was reported in a handful of cases. Behavioral changes, unusual eating habits, and abnormal sleep rhythms were observed in a few juvenile patients (Franzoni et al., 2006; Kyllerman, Rosengren, Wiklund, & Holmberg, 2005; Sreedharan, Shaw, Jarosz, & Samuel, 2007). This case was initially diagnosed as a bipolar disorder but was genetically confirmed as Alexander disease after cognitive deterioration, apathy, neglect of personal care, memory loss, and bulbar and cerebellar symptoms, which emerged later in the course of the disease (Melchionda et al., 2013). Also, a family study of three siblings with suspected AOAD (confirmed only with MRI) described behavioral and affective changes, such as withdrawal, apathy, flat affect, prominent mood and personality disturbances, and predominant frontal executive dysfunction (impairment of set-shifting and mental flexibility, perseveration, flat affect, and anosognosia) in the affected patients (Lichtenstein et al., 2017).

Likewise, our case first presented with depression and was only diagnosed as AOAD after an additional work-up for cognitive deterioration and behavioral changes.

Whether psychiatric symptoms preceding AOAD is a simple co-occurrence of two etiologically separate events or is a specific presentation of the disease cannot be ar-

gued with certainty based on our current knowledge. Although, limited documentation of co-occurrence of psychiatric symptoms suggests that the actual co-occurrence could be much higher. This finding highlights the importance of considering AOAD in patients with abnormal psychiatric presentations or unusual course of illness, especially in the presence of neurological symptoms.

Zaver, and Douthit (2019) described a 25-year-old woman with a history of clumsiness, seizure, and dysarthria who was first diagnosed with anxiety and depression by a psychiatrist. However, after her brain MRI exam, diffuse hyperintensity in the ependymal region and periventricular tissue was detected, and ultimately genetic test for Alexander disease revealed missense variation in the GFAP gene (Zaver, & Douthit, 2019).

In neuroimaging and especially brain MRI, leukoencephalopathy, and brain stem involvement, significantly medullary atrophy is seen. However, there are diverse imaging findings between different types of Alexander disease.

In infantile form, five characteristic imaging presentations are seen. However, in late-onset Alexander disease, periventricular hyperintensities and brain stem, cerebellar, and spinal cord atrophy are predominantly seen, in contrast to frontal white matter involvement, which is not a common finding (Graff-Radford, Schwartz, K., Gavrilova, Lachance, & Kumar, 2014).

Although in our patient, neuroimaging findings, including mild atrophy in the medulla oblongata and periventricular hyperintensity in T2-weighted images, were in accordance with AOAD, frontal white matter involvement was absent, which is seen predominantly in the infantile form.

Toxic or hypoxic encephalopathy is the differential diagnosis with hereditary and genetic causes when approaching patients with leukoencephalopathy. Nevertheless, we should notice that these conditions create symmetric hyperintensities, which are not frontally predominant, and also, medulla atrophy is not characteristic of hypoxic encephalopathy (seen in our patient).

In addition, our patient had been admitted only one day in the ICU with close monitoring of O<sub>2</sub> saturation, and in this condition, severe hypoxic encephalopathy probably is not an expected finding.

We should mention that after hospital discharge, our patient had a normal cognitive function and could do her daily activities. However, after a few months, she be-

came delirious with cognitive impairment. This history is not correlated with the outcome of hypoxic encephalopathy, which is usually known as static encephalopathy and is not a progressive course.

A definitive diagnosis was made by GFAP gene sequencing. Many pathogenic mutations have been reported in Alexander disease; most are point mutation and indels (Quinlan, Brenner, Goldman, & Messing, 2007).

Alexander disease is considered a gain-of-function disorder because the GFAP mutations produce consequences that differ dramatically from those caused by the absence of GFAP (like our case study). Although the main cause of severe and lethal Alexander disease is the accumulation of toxic defective proteins in astrocytes as a consequence of point mutation in the GFAP gene, in this case, with deletion of 1-9 exons, GFAP protein is produced from intact allele with less than 50% performance. This phenomenon is called haploinsufficiency. Also, previous studies demonstrated the deletion of some exons like exon 5 (Green et al., 2018).

After discovering a pathogenic mutation, it is preferred to assess mutations in other family members who could be asymptomatic or minimally affected.

In the treatment approach, palliative and conservative therapies are at the forefront of treatment. In our patient, modafinil was prescribed to improve daytime sleepiness and fatigue, and duloxetine was continued to refine mood problems which both were effective.

Despite all this and due to the heterogeneity of this disease in clinical manifestations and brain imaging findings, many cases are not diagnosed, or a lot of them are visited by specialists in various fields, including Neurologists, Psychiatrists, Otorhinolaryngologists, and others with misdiagnosis for a long time.

Therefore, we suggest that in cases with psychiatric diagnoses, when the symptoms are atypical, or new unexplained symptoms appear, neurologic consultation should be done, and appropriate imaging and laboratory procedures should be performed. Eventually, if the diagnosis is not definitive, genetic consultation and testing are recommended.

This approach allows the patient to be correctly diagnosed, avoiding costly diagnostic procedures and inappropriate treatments with probable side effects, and ultimately reduces the emotional stress and burden of illness on the individual, the family, and the community.



## Ethical Considerations

### Compliance with ethical guidelines

All ethical principles are considered in this article. The participant were informed of the purpose of the research and its implementation stages. He assured about the confidentiality of their information and was free to leave the study.

### Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

### Authors' contributions

Evaluated the patient and her history: Fatemeh Mohammadian, Hedieh Arshiany, and Valentin Artounian; reviewed the literature and wrote the manuscript: Hedieh Arshiany, Behzad Ezzatian and Fatemeh Alizadeh.

### Conflict of interest

The authors declared no competing interest.

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