Title: Psychiatric Onset Alexander Disease: An Important Challenge in Neuropsychiatric Diagnosis

Running Title: Psychiatric onset Alexander Disease

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Abstract

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

**Case report:** Our patient is a fifty-two-year-old Iranian woman with history of depression from about 17 years ago, suicidal attempt two years ago and ingestion a large amount of opium with the intention of suicide 2 months ago who was presented with disorientation and probably delirious state in the last interview. Eventually in comprehensive investigations, white matter hyperintensity and leukodystrophy was diagnosed and ultimately to determine the cause of these changes with gene study, whole Exon deletion of GFAP Gene and Late Onset Alexander disease was determined.

**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.

On the other hand, various Gene Mutation were described in Late Onset Alexander Disease, however large whole Exon deletion which was revealed in our patient is a novel mutation and significantly need to be declared. Here authors describe a late onset Alexander disease with psychiatric onset symptoms and novel large Exon deletion in GFAP Gene.

**Keyword:** Alexander disease, Late-onset, GFAP mutation, Psychiatric symptoms, Leukodystrophy
**Introduction**

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

The symptoms of Alexander disease are various depending on the age (infantile, juvenile, and adult). Even within in different forms, different symptoms and severity may be witnessed:

- **Infantile form** - The infantile subtype is the most common form manifesting with seizures, developmental delay, pyramidal tract signs, and progressive macrocephaly.
- **Juvenile form** - Juvenile type has a slower course with bulbar signs, ataxia, seizures, normocephaly or megalencephaly.
- **Adult form** - When age of onset is high, bulbar symptoms and cerebellar dysfunctions develop gradually, requiring discrimination from adult onset neurodegenerative disorders (Casasnovas et al., 2019; Gowda, Srinivasan, Jetha, & Bhat, 2019)

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

**Case Presentation**

Our case is a fifty-two-year-old Iranian housewife, who was admitted to the emergency department of Roozbeh psychiatric hospital, two years ago, after a suicide attempt.

Her depression started at the age of thirty-five, precipitated by several consecutive losses, including the death of her father and father in law, which she loved dearly. At the time, she
presented with 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 SSRIs, Venlafaxine 225mg/d was prescribed, which resulted in partial response and the patient maintained symptom-free for ten years. Unfortunately, at the age of 45, she was diagnosed with severe hypertension, so her doctor decided to gradually discontinue venlafaxine.

Her depressive symptoms re-emerged with venlafaxine discontinuance, and never fully remitted with other prescribed antidepressants, including 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 lower respiratory tract infection, unexpectedly. This tragic event flared up her symptoms, and resulted in a three-year period 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 the age of 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 on 60mg/d. She was discharged after 12 days of hospitalization, with a controlled blood pressure, significant improvement in psychomotor retardation and resolution of suicidal thoughts.
During follow-up visits, her depression went in full remission and her only complaints were memory difficulties and slow talking. A 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 behaved odd. For instance, “she would put her dentures in a flask and drank from it” or “would try to pour fruit juice in 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 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 sixty-year-old brother mentioned above, had a history of CVA, and 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 referred to Neurology clinic with forgetfulness, object displacing and inappropriate dressing from 2 months ago. Symptoms were much serious that lead into severe functional disability in patient. By the time she had experienced several fallings as well. Additionally,
dizziness and fatigability were seen in patient. Likewise, patient suffered from disorientation regarding time and place.

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

In Neurological examination, bilateral hyperreflexia was detected in 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 Pyramidal tract. Other examinations showed no abnormalities.

**Para clinical assessment**

The patient undergoes comprehensive neurological and laboratory assessments including Brain imaging with contrast, vasculitis and coagulative tests, infectious causes assessment to rule out other treatable cause of Leukoencephalopathy.

We assess Arylsulfatase enzyme to evaluate probability of Metachromatic Leukodystrophy which is manifested with multi system involvement including pyramidal, bulbar and cerebellar systems and psychiatric manifestation as similar as our patient. Laboratory reports are given in table 1.

The patient’s EEG illustrated mild abnormality due to transient sharp activity.

MRI imaging has material role in diagnosis of this type of alexander disease, adult-onset (AOAD). In this patient, AOAD involved anterior part of frontal lobes by which is represented in different abnormal intensities MRI Imaging acquisition with regards to white matter. It is characterized by low intensity in T1-weighted; likewise, mild atrophy in medulla oblongata is
illustrated however, it has high intensity in T2-weighted images. Likewise, relatively abnormal intensity at periventricular area in axial FLAIR image is conspicuous which implies white matter abnormalities. With respect to T1-wighted with contrast image, no abnormality is detected. Also, anterior rim of periventricular area has low signal in T2-wighted image. No enhancement was seen in periventricular region.

**Gene Study**

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

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

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

**Discussion**

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

Alexander disease was initially diagnosed in infant with symptom of macrocephaly and neurological deterioration, but with going time, it was determined that the disease has three known varieties and adult –onset type has the most heterogeneous presentation. The most
known and majority clinical sign of late onset Alexander disease could classify in to three separate systems including: Bulbar, Pyramidal and Cerebellar system.

However, other non-specific manifestation with involvement of oculomotor tract, autonomic system, seizure, sleep problem and apnea are also not uncommon in this heterogenic disease.

Pareyson and et al reported 11 cases with adult-onset Alexander disease with comprehensive approach in 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, clinical spectrum of 112 cases of alexander disease were analyzed. In this review, pseudobulbar signs were present in 80% of cases. Ataxia, oculomotor abnormality, pyramidal sign and autonomic disturbance are other common signs. (Balbi et al., 2010)

In general, neurologic – onset manifestations were seen in 90% of these cases, in contrast to our patient whom no neurological symptoms were seen in the onset of disease.

Psychiatric symptoms rarely considered as an initial presentation of type 2- Alexander disease, in contrast to our patient, her initiative manifestation probably is 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 initially diagnosed as bipolar disorder, was genetically confirmed as alexander disease after cognitive deterioration, apathy, neglect of personal care, memory loss, and bulbar and cerebellar symptoms, 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 (Adult onset alexander disease) after supplementary workup for cognitive deterioration and behavioral changes.

Whether psychiatric symptoms proceeding AOAD, is a simple co-occurrence of two etiologically separate events, or is a specific presentation of the disease cannot be argued with certainty based on our current knowledge. Although, limited documentation of co-occurring psychiatric symptoms, suggests that the actual co-occurrence could be much higher. This 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 et al in 2019 describe a 25 year-old woman with history of clumsiness, seizure and dysarthria who firstly diagnosed with anxiety and depression by psychiatrist but afterthought in brain MRI, diffuse hyper intensity in ependymal region and periventricular tissue was detected and ultimately genetic test for Alexander disease revealed missense variation in GFAP gene in this patient. (Zaver & Douthit, 2019)

In Neuroimaging and specially, Brain MRI, leukoencephalopathy and brain stem involvement, significantly medullary atrophy is seen. Though, there are diversity in imaging findings between different types of Alexander disease.

In infantile form, five characteristic imaging presentation is seen, However, in late-onset Alexander disease, periventricular hyper intensities and brain stem, cerebellar and spinal cord atrophy predominantly has been seen, in contrast to frontal white matter involvement which is not common findings. (Graff-Radford, Schwartz, Gavrilova, Lachance, & Kumar, 2014)
Although in our patient, Neuroimaging findings including mild atrophy in medulla oblongata in addition to periventricular hyperintensity in T2-weighted images are in accordance with LOAD, on the other hand, frontal white matter involvement is the contrary issue which was seen predominantly in infantile form.

However, the toxic or hypoxic encephalopathy are the differential diagnosis with hereditary and genetic causes, when we approach to the patients with leukoencephalopathy but we should notice to the point that these causes create symmetric hyperintensities which not frontally predominant and also medulla atrophy is not characteristic for hypoxic encephalopathy. (which were seen in our patient)

In addition, our patient had been admitted only one day in ICU ward with close monitoring of O2 saturation and in this condition, severe hypoxic encephalopathy probably is not an expected finding.

Likewise, we should mention our patient after hospital discharge, had normal cognitive function and she was able to do daily activity but after a few months, she became delirious and cognitive impairment was detected. This history is not correlated with outcome of hypoxic encephalopathy which usually known as a static encephalopathy not a progressive course.

Definitive diagnosis was made by GFAP gene sequencing. Many pathogenic mutations have been reported in AxD, Majority of them is point mutation and indels. (Quinlan, Brenner, Goldman, & Messing, 2007; Yasuda et al., 2019)

Alexander disease is considered a gain-of function disorder in the sense that the GFAP mutations produce consequences that differ dramatically from those caused by the absence of GFAP (like that case in this study). Although the main cause of sever and lethal AxD is accumulation of toxic defective proteins in astrocytes as a consequence of point mutation in GFAP gene; but, 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-
besides, previous studies demonstrated that deletion of some exons like exon 5. (Green, 2018)

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

In the treatment approach, palliative and conservative cares are on 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.

In spite of 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 several
specialists in various fields including Neurologists, Psychiatrist, Otorhinolaryngologist and
others with a misdiagnosis for a long time.

Therefore, we suggest that in cases with psychiatric diagnosis when their symptoms are
atypical, or new unexplained symptoms are added, 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 should be recommended.

This approach allows the patient to be correctly diagnosed, avoiding many costly diagnostic
procedures and inappropriate treatments without any efficiency and with probable side effects
and ultimately reduce the emotional stress and burden of illness on the individual, the family
and the community.

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Conflicts of Interest and Source of Funding

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Uncategorized References


Figure legends

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- Table 1- Laboratory findings
- Fig.2(a-d): Brain MRI with FLAIR, T2-weighted and DWI sequences