A case of adult-onset metachromatic leukodystrophy beginning with behavioral symptoms

Davranışsal belirtilerle başlayan yetişkin tip metakromatik distrofi olgusu

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SUMMARY

Metachromatic leukodystrophy is a rare inherited disorder of the nervous system with great clinical variability characterized by loss of both cognitive and motor functions upon extensive white matter damage by the accumulation of sulfatides. Although metachromatic leukodystrophy usually affects children, many cases of adult leukodystrophy have been reported in the literature in the last few years. Adult-onset leukodystrophy typically presents with a progressive syndrome that includes various combinations of cognitive impairment, spasticity, apraxia, ataxia, and upper motor neuron manifestations. In this article, we decided to present this case to draw attention to the fact that the adult form of metachromatic leukodystrophy, which presents with psychotic symptoms and behavioural problems, should be considered in the differential diagnosis of psychotic pictures. In a 48-year-old male patient who did not have any psychiatric or neurological problems before, symptoms such as meaningless shouting, running away from home, restlessness, and audio-visual hallucinations were added to the clinical picture that started with confusion and disorganized behaviour in a short time. MRI, plasma aryl sulfatase A level (ARSA) and gene analysis were performed for differential diagnosis in the patient. It is known that the patient has a sibling who died before the age of one, and two nephews diagnosed with an autism spectrum disorder. Heterozygous c.1283C>A (p P428Q) mutation was detected in the patient, which was not previously reported in the literature or mutation databases. The chromosomal region-22q13.33- in which the ARSA gene with this mutation is located is also a candidate region for autism. In this respect, it was thought that this mutation might be related to disorganized behavioural problems.

Keywords: adult metachromatic leukodystrophy, psychosis, neurologic symptoms, ARSA gene, mutation

ÖZET

Metakromatik lökodistrofi, sülfatidlerin birikmesiyle yaygın beyaz cevher hasarı oluşması üzerine hem bilişsel hem de motor fonksiyonların kaybı ile karakterize, büyük klinik değişkenliğe sahip, sinir sisteminin nadir görülen kalıtsal bir bozukluğudur. Metakromatik lökodistrofi genellikle çocukları etkilemekle birlikte son birkaç yılda literatürde birçok yetişkin lökodistrofi vakası bildirilmiştir. Yetişkin başlangıçlı genetik lökodistrofiler tipik olarak bilişsel bozulma, spastisite, apraksi, ataksi ve üst motor nöron belirtilerinin çeşitli kombinasyonlarını içeren ilerleyici bir sendromla kendini gösterir. Bu yazıda psikotik belirtiler ve davranış sorunları ile seyreden erişkin formu metakromatik lökodistrofinin psikotik tabloların ayırıcı tanısında düşünülmesi gerektiğine dikkat çekmek için bu olguyu sunmaya karar verdik. Daha önce herhangi bir psikiyatrik veya nörolojik sorunu olmayan erkek hastada, 48 yaşında konfüzyon ve dezorganize davranışlarla başlayan klinik tabloya kısa sürede anlamsız bağırmalar, evden kaçma, yerinde duramama gibi semptomlar ve görsel işitsel halüsinasyonlar eklendi. Hastada ayırıcı tanı için MR, plazma aril sülfataz A düzeyi (ARSA) ve gen analizi yapıldı. Hastanın bir yaşından önce ölen bir kardeşi ve otizm spektrum bozukluğu tanısı alan iki yeğeninin olduğu biliniyor. Hastada daha önce literatürde veya mutasyon veritabanlarında bildirilmeyen heterozigot c.1283C>A (p P428Q) mutasyonu saptandı. Bu mutasyona sahip ARSA geninin bulunduğu kromozomal bölge-22q13.33- aynı zamanda otizm için aday bir bölgedir. Bu açıdan bu mutasyonun dezorganize davranışsal problemlerle ilişkili olabileceği düşünülmüştür.

Anahtar Kelimeler: erişkin metakromatik lökodistrofi, psikoz, nörolojik belirtiler, ARSA geni, mutasyon

(Turkish J Clinical Psychiatry 2023;26:69-75)

DOI:10.5505/kpd.2023.43402

The arrival date of article: 22.06.2022 , Acceptance date publication: 26.07.2022

INTRODUCTION

Metachromatic leukodystrophy (MLD) is a lysosomal autosomal recessive sphingolipid storage disorder caused by the deficiency of the arylsulfatase A (ARSA) enzyme (1). The ARSA gene is located on chromosome 22q13.33. It is the first enzyme in the pathway that degrades sulfatides (3-O-sulfogalactosylceramides), an essential component of ARSA myelin (2). Decreased ARSA activity causes sulfatide accumulation in the central nervous system (CNS), peripheral nervous system (PSS) and other internal organs (1). MLD is named from the presence of metachromatic granules in the affected cells, which are formed as a result of the accumulation of sulfatide and sphingolipids in myelin (3). Neurological and behavioural symptoms result from progressive myelin degeneration and loss of axons in the CNS and PSS (1).

The incidence of metachromatic leukodystrophy is approximately 1 in 100,000 live births in the European population (4). In general, MDL is divided into three different clinical forms: the late infantile form, the juvenile form, and the adult form. European studies show that approximately 40-50% of patients have the late infantile form, approximately 30-40% have the juvenile form, and approximately 18-20% have the adult form (4). In the adult form, the first symptoms often suggest a psychiatric illness, particularly schizophrenia, as psychotic symptoms and behavioural abnormalities often begin before or accompany the decline of intellectual capacities (4). In adults, the first symptoms may develop even after the age of 60 (5).

Since adult form MLD starts with psychotic and mental symptoms, a case report was decided to draw attention to the fact that it should be considered in the differential diagnosis. In addition, we aimed to bring the c.1283C>A mutation, which was detected in the heterozygous condition in our patient as a new mutation that has not been reported in the literature or mutation databases before, to the literature. We obtained informed consent from the relatives of the patients to publish the case in medical journals.

CASE HISTORY

A 49-year-old male patient presented with complaints of running away from home, shouting for no reason, and restlessness. His complaints started one year ago as confusing the way home, trying to go to work outside of work hours, talking to himself, pointing somewhere and saying "they are coming". The patient, who had a COVID-19 infection 10 months ago, was hospitalized for this reason. After he was discharged, he left the quality control job at the textile company due to complaints of aggression toward his surroundings, hiding food and belongings, meaningless shouting, and leaving the job before the end of the working hours. Donepezil 10 mg, olanzapine 10 mg, and acetylsalicylic acid treatment were started for the patient who was admitted to psychiatry at that time. The patient's complaints continued to increase and intensify. Risperidone 4 mg and escitalopram 10 mg were added to the treatment because of not being able to take care of himself, constant abusive speech, and the desire to move frequently.

Since the patient's complaints did not regress, he was admitted to the neurology service 2 months ago. During this period, urinary stool incontinence also started, the current medications of the patient were discontinued, and clozapine 12.5 mg was started and gradually increased to 75 mg. Clozapine was increased to 100 mg as the patient's disorganized behaviours, audio-visual hallucinations and running away from home continued during the follow-up. Olanzapine 10 mg and quetiapine XR 150 mg were added. During the sixth month of follow-up, the patient's visual auditory hallucinations continued, and there was a partial decrease in his mobility.

Because the patient's symptoms, which are not typical for psychosis, changed rapidly and the drugs used caused intolerable side effects, drug changes were frequently made to reach the appropriate treatment. A typical image for metachromatic dystrophy was obtained on MRI was taken to investigate organic aetiology in the patient who showed progressive deterioration with atypical symptoms and did not respond to different treatment agents. Thus, a definitive diagnosis was made approximate-

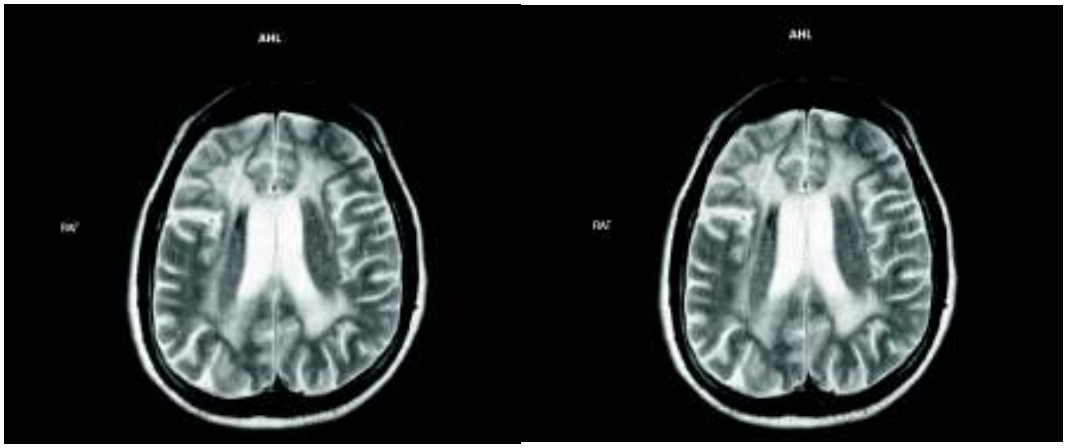

Fig.1. T2 FLAIR hyperintense diffuse lesions in the frontal subcortical deep white matter, periventricular white matter, and corpus callosum on MRI

ly one year after the onset of psychotic, disorganized behaviours in the patient.

His history of birth and childhood development was normal. There was no problem described in the school success of the patient who was a primary school graduate. He had no known history of chronic disease, except that he had been operated on for cystic kidney disease 22 years ago. He had completed his military service fully and on time. There was no history of trauma. There was no parental consanguinity in the family history. The patient had 6 living siblings. It was learned that one of his siblings died around the age of 1, and the cause of death was unknown. The patient's two nephews are diagnosed with autism.

In his neurological examination, he had significant spasticity and ataxia. In his mental state examination, he was conscious and had difficulty cooperating, and his orientation to place and time was lost. The amount of speech decreased; his speech was dysarthric. His affect was limited. There were audio-visual hallucinations. Neuropsychological tests, and nerve conduction studies such as VEP, and BAEP could not be performed because the patient could not cooperate.

Hemograms, biochemistry and sedimentation, thyroid function tests, and vitamin B12 and folic acid levels were within normal limits. HIV, syphilis, hepatitis B/C and tuberculosis tests performed to exclude treatable and acquired causes of white matter disease were negative.

CSF examination was normal. EEG was within normal limits.

In the evaluation of the supratentorial series in the MRI taken 1.5 months ago, confluent T2 FLAIR hyperintense diffuse lesions were observed in the periventricular white matter in the frontal subcortical deep white matter, which diffuses and thins the corpus callosum. More prominent enlargement of the hemispheric sulcus and fissures in the front and dilatation in the third and lateral ventricles were observed (Fig. 1).

A detailed investigation was initiated after the MRI result directed us to metachromatic leukodystrophy. The aryl sulfatase A level in the blood was found to be low (12 nmol/mg/17 hours; normal: 45-260 nmol/mg/17 hours). The change in p. Ser45Arg detected in the gene analysis to confirm the diagnosis is a variant that has been previously described and has been reported to be associated with metachromatic leukodystrophy in the Human Gene Mutation Database (HGMD). According to the American College of Medical Genetics (ACGM) criteria, it was evaluated as a “change of uncertain clinical significance”. In addition, the detected p. P428Q change has not been detected in any other disease before in the literature and was evaluated as “highly pathogenic” according to ACMG criteria.

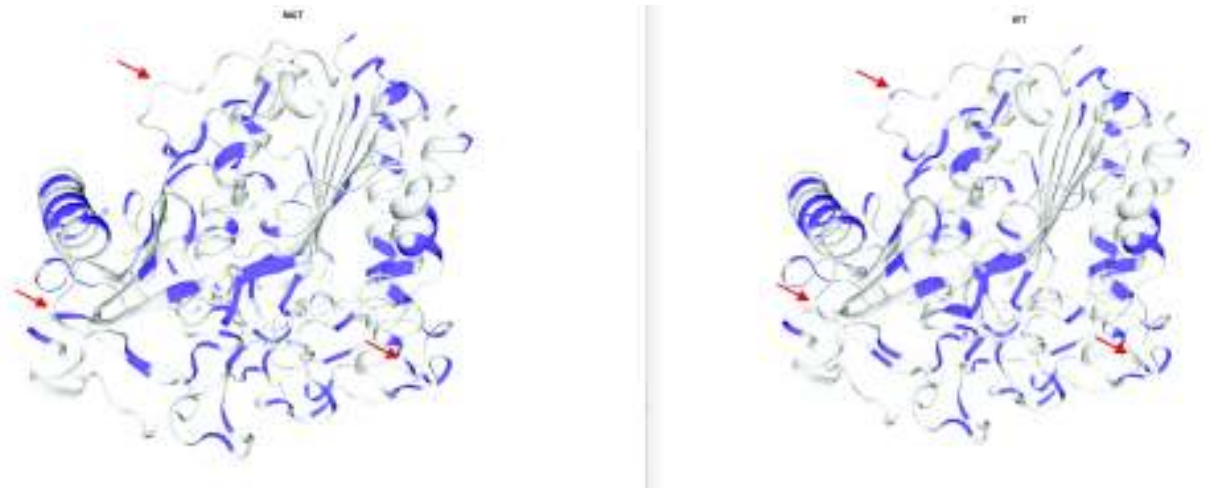

Figure 2. The molecular structure of the wild -type and mutant proteins according to their polarity (Mut on the left and wt-on the right). (http://swissmodel.expasy.org)

DNA Analysis

Genomic DNA was isolated from peripheral blood samples by using Next-generation sequencing. Whole-genome sequence analysis was performed by next-generation sequencing with an Illumina MiSeq instrument. Since the parents of the subject are not alive, the analysis could not be performed on them. However, from the family history, it is known that a sibling who died before the age of one and the two nephews of the subject have autism spectrum disorder. Comparisons of wild-type and mutant protein structures of ARSA were obtained with computational tools such as the Swiss Model (http://swissmodel.expasy.org).

Sequence analysis revealed the presence of 135C>A (p S45R) (p Ser45Arg)/c.1283C>A (p P428Q) (p. Pro428Gln) compound heterozygosity and the presence of the pseudo deficiency allele 1055A>G (p. N352S) in the heterozygous state. The changes in the protein structure are shown in Fig. 2.

The whole gene sequence analysis of the ARSA gene showed three sequence changes, 135C>A/1283C>A and pseudo deficiency mutation 1055A>G. Two of the mutations were previ-

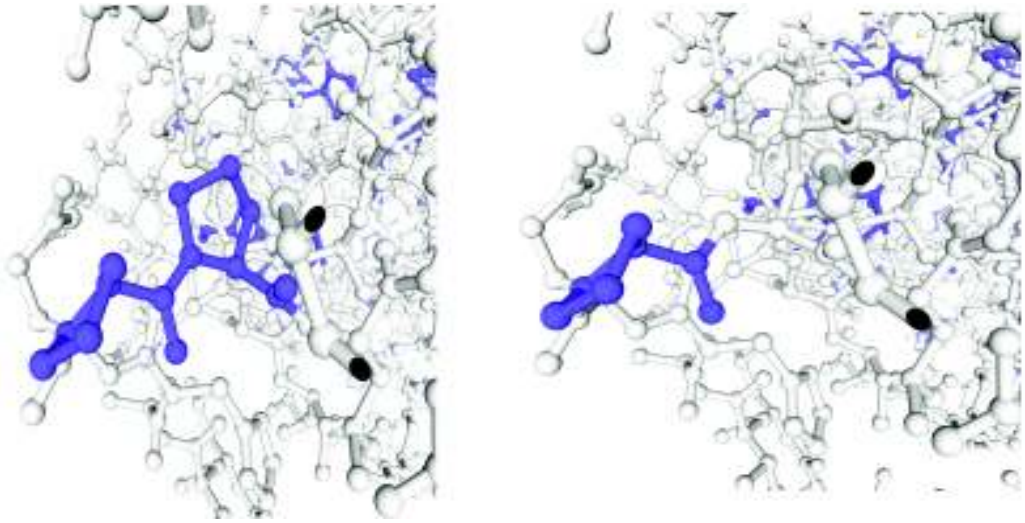

Fig. 3. Close caption of the newly found mutation P428Q. The left panel shows the wild type, and the right panel shows the mutant amino acid in the structure (http://swissmodel.expasy.org).

ously reported mutations, and one mutation was found in our subject and not reported in previous studies. Even though the pseudo deficiency allele 1055A>G, which causes the loss of an N glycosylation site, is found in patients and causes a great reduction in enzyme activity, patients show a clinically healthy phenotype. Therefore, the presence of the N352S mutation in the heterozygous state may not contribute to the disease phenotype of our patient (6).

On the other hand, the presence of 135C>A (p S45R)/c.1283C>A (p P428Q) compound heterozygosity is strongly suspected to cause the symptoms of the patient. The previously known S45R conversion was reported to be Disease-causing in different cases (7), and the c.1283C>A (p P428Q) mutation that was found at the heterozygous state in our patient is a new mutation that was not reported in the literature or mutation databases before. The newly identified C-to-A mutation causes a Pro-Gln conversion, and the localization of that amino acid in the protein's structure is in a region that is conserved among arylsulfatases PPLL (Pro-Pro-Leu-Leu) (8). It also resides in a region close to amino acid 424Glu, which participates in the regulation of dimer-octamer equilibrium by either protonation or deprotonation (9). Because of its position, this newly found mutation could be most likely pathogenic and may affect the activity of the enzyme. The structural changes at the molecular level as a result of the mutation are shown in Fig. 3.

DISCUSSION

Metachromatic leukodystrophy is an autosomal recessive disease caused by mutations in the ARSA gene located on chromosome 22q13.33 (5). More than 100 mutations causing MLD have been identified (4). In patients inheriting two mutant ARSA genes, sulfatides accumulate in microglia, oligodendrocytes and Schwann cells and cause extensive demyelination in the CNS and PSS.

Adult-onset leukodystrophies and genetic leukoencephalopathies include a diverse group of white matter neurodegenerative disorders with a broad age of onset and phenotypic spectrum. Patients typically present with the progressive syndrome that includes various combinations of cognitive impairment, spasticity, apraxia, ataxia, and upper motor neuron manifestations. Two distinct clinical presentations have been observed in adult MLD: patients with progressive motor or sensory deficits and patients with mental impairment. These two conditions may be caused by different specific mutations. It manifests itself with progressive gait disturbance mainly caused by spastic paraparesis or cerebellar ataxia in those with P426 L mutations from P426 L and I179S, the two most common mutations in late-onset MLD. It has been found that mental disturbance is insignificant at the beginning of the disease but becomes more pronounced as the disease develops. In contrast, the I179S mutation is manifested by schizophrenia-like behavioural abnormalities, social dysfunction, and mental regression; motor deficits are much less common (1).

We detected a heterozygous c.1283C>A (p P428Q) mutation in our patient, which has not been reported in the literature or mutation databases before. This new mutation is most likely pathogenic and may affect the activity of the enzyme. Analysis of the newly found P428Q mutation could not be performed because the patient's close relatives were not alive. However, it should be noted here that the nephews of the subject have autism spectrum disorder. The chromosomal region-22q13.33- in which the ARSA gene with this mutation is located is also a candidate region for autism. Individuals with 22q13.3 deletion syndrome, known as Phelan-McDermid syndrome (PMS), have autism-like behaviours. In a literature review covering 56 cases of PMS who showed signs of behavioural and neurological decompensation during adolescence or adulthood, one patient was found to have juvenile-onset metachromatic leukodystrophy, a severe demyelinating disorder caused by mutations in the ARSA gene at 22q13.33 (10). In this respect, it was thought that this mutation might be related to behavioural problems.

The definitive diagnosis of MLD requires a comprehensive evaluation based on a wide array of diagnostic procedures, including biochemical and molecular tests and neuroradiological (grey matter volume loss, white matter abnormalities) and neurophysiological evaluations (11). The most accu-

rate method in the diagnosis of hereditary genetic diseases is the detection of mutations by sequencing. However, since not all disease-associated mutations are currently identified, diagnosis can be made using MRI and determination of ARSA activity or sulfatide levels. Magnetic resonance imaging provides early detection of white matter damage. In the juvenile form, the central and periventricular white matter is primarily affected. As the disease progresses, subcortical structures of the white matter may also be affected. MRI findings consist of symmetric T2 hyperintensity in the frontal or periventricular white matter (12). Patients with adult-onset metachromatic leukodystrophy usually have frontal dominance. Loss of white matter volume causes brain atrophy in the late stages of the disease (13). The magnetic resonance imaging findings of our case were also in the form of frontal subcortical hyperintense with no contrast diffuse lesions in the white matter.

The adult form of MLD is characterized by nonspecific psychopathological symptoms. These include emotional lability, apathy, personality changes, schizophrenic disorder and dementia. The clinical course of the late-onset variant is slower (14). Psychiatric findings may be misdiagnosed as they may appear several years before neurological findings. Of the 129 MLD cases reported in the literature that started between the ages of 10 and 30, 53% had psychotic symptoms. Typical psychotic symptoms; auditory hallucinations, complex delusions, fragmentation of thought, inappropriate affect, bizarre behaviour and catatonic posture. Therefore, these initial statements may mimic schizophrenia (15). The later addition of motor signs, peripheral neuropathy and progressive loss of previously acquired abilities to the psychotic picture may help differentiate it from schizophrenia. In our case, the first complaints started with audiovisual hallucinations and bizarre behaviours.

Currently, there is no curative treatment method for metachromatic leukodystrophy. The positive results reported from different animal studies on hematopoietic stem cell transplantation (HSCT), gene therapy and enzyme replacement therapy have led to clinical trials investigating the efficacy of these approaches (16). Although HSCT is beneficial in some lysosomal storage diseases, the desired results could not be achieved in metachromatic leukodystrophy. Gene therapy is likely to be trialled in a limited number of patients in the near future (17).

In conclusion, we diagnosed our case with metachromatic leukodystrophy by examination, low blood arylsulfatase A level, imaging and gene analysis methods. Within the framework of this case, we wanted to emphasize that MLD, which is one of the metabolic diseases, can present with adult-onset psychotic symptoms by conducting a literature review regarding the diagnosis, clinical manifestations and treatment options of MLD.

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