Cumhuriyet Medical Journal, 44(2): 228-232, 2022
DOI: http://dx.doi.org/10.7197/cmj.1088934

Cumhuriyet Medical Journal

| cmj.cumhuriyet.edu.tr | Founded: 2004 Available online, ISSN:1305-0028 Publisher: Sivas Cumhuriyet Üniversitesi

A Late Juvenile Onset Type Metachromatic Leukodystrophy Case Presenting With Continuous Pseudobulbar Crying

Aslı Bolayır[a*]

Malatya Turgut Özal University,Faculty of Medicine, Neurology Department, Malatya, Turkey

**Corresponding author*

Case Report

History

Received: 21/03/2022
Accepted: 30/06/2022

ABSTRACT

Introduction: Metachromatic leukodystrophy(MLD) is a rare inherited lysosomal disorder caused by autosomal recessive mutations in Arylsulfatase A(ASA) gene which encodes ASA enzyme. The disease is divided into late-infantile, juvenile and adult onset types according to the onset age.

Case: A 20 year-old female patient presented with continuous crying which started two days ago. She had generalized seizures for ten years, required two anti-epileptic drugs to control. Neurological examination revealed generalized spasticity with exaggerated deep tendon reflexes and extensor plantar responses. Her electroencephalogram showed paroxysmal cortical slowing without epileptic activities. Systemic examination and blood biochemistry was unremarkable. Brain magnetic resonance imaging (MRI) yielded abnormal findings, suggesting the diagnosis of MLD. ASA activity in the peripheral blood leukocytes was found to be decreased in a referral laboratory. Genetic examination revealed that the patient had a compound heterozygous mutation of I179S in the PSAP gene. The patient was discharged with partial improvement under quetiapine treatment.

Discussion and Conclusion: MLD is a progressive rare inherited disease caused by a deficiency in the enzyme activity of ASA. Inevitable neurological sequelae develop as the disease progresses. Generalized cortical atrophy and symmetrical extensive hyperintense signal changes in periventricular white matter on MRI, decreased activity of ASA and mutation in the PSAP gene confirm the diagnosis. In conclusion, we report a case with continous pseudobulbar crying, which can be the result of changes on MRI due to MLD.

Keywords: Metachromatic leukodystrophy, arylsulfatase A, pseudobulbar crying

Aralıksız Psödobulber Ağlama Atakları İle Başvuran Geç Juvenil Başlangıçlı Bir Metakromatik Lökodistrofi Olgusu

ÖZ

Giriş: Metakromatik lökodistrofi (MLD), Arilsülfataz A(ASA) enzimini kodlayan ASA geninde meydana gelen otozomal resesif mutasyon sonucu ortaya çıkan nadir ve kalıtımsal lizozomal bir hastalıktır. Hastalık, başlangıç yaşına göre geç infantil, juvenil ve yetişkin tip olmak üzere 3 gruba ayrılır.

Olgu: 20 yaşında kadın hasta iki gün önce başlayan ve aralıksız devam eden ağlama nedeniyle başvurdu. Hastanın ikili antiepileptik ilaç kullanımı gerektiren on yıllık jeneralize nöbet öyküsü de mevcuttu. Nörolojik muayenede yaygın spastiste, artmış derin tendon refleksleri ve ekstansör taban derisi yanıtları saptandı. Elektroensefalografide epileptik aktivite olmaksızın paroksismal kortikal yavaşlama izlendi. Sistemik muayenede ve laboratuvar tetkiklerinde belirgin özellik yoktu. Beyin manyetik rezonans görüntülemede (MRG), MLD tanısını destekleyen anormal bulgular tespit edildi. Referans bir laboratuvarda periferal kan lökositlerindeki ASA aktivitesi düşük saptandı. Yapılan genetik inceleme PSAP geninde heterozigot bileşik I179S mutasyonu olduğunu ortaya koydu. Hasta ketiapin tedavisi altında kısmi iyileşme taburcu edildi.

Tartışma ve Sonuç: MLD, ASA enzim aktivitesindeki defisitin neden olduğu progresif seyirli nadir kalıtımsal bir hastalıktır. Hastalık ilerledikçe kaçınılmaz olarak çeşitli nörolojik sekeller gelişir. MRG'de jeneralize kortikal atrofi ile periventriküler beyaz cevherde simetrik yaygın hiperintens sinyal değişiklikleri, ASA aktivitesinde azalma ve PSAP genindeki mutasyon tanıyı doğrular. Sonuç olarak biz, MRG'deki MLD'ye ait değişikliklerin neden olmuş olabileceği aralıksız devam eden psödobulber ağlama ile prezente olan bir MLD olgusu sunuyoruz.

Anahtar sözcükler: Metakromatik lökodistrofi, arilsülfataz A, psödobulber ağlama

Süreç

Geliş: 21/03/2022
Kabul: 30/06/2022

[a] *asliarslanturk@gmail.com* https://orcid.org/ 0000-0001-6566-3751

How to Cite: Bolayır A (2022) A Late Juvenile Onset Type Metachromatic Leukodystrophy Case Presenting With Continuous Pseudobulbar Crying, Cumhuriyet Medical Journal, June 2022, 44 (2): 228-232

Introduction

Metachromatic leukodystrophy (MLD) is a rare inherited lysosomal sphingolipid storage disorder, caused by a deficiency of Arylsulfatase A(ASA) enzyme, encoded by the aryl sulfatase A gene. It is inherited in an autosomal recessive way. Decreased activity of ASA causes demyelination by accumulation of sulfatides in the central and peripheral nervous system. A late-infantile, a juvenile form and an adult onset form are usually distinguished based on the age of onset. Unfortunately, none of them are curable. All forms have various neurological manifestations that can even result in death if left untreated. Here we report a late juvenile onset type MLD case presenting with continuous pseudobulbar crying.

Case Presentation

A 20 -year-old female patient was admitted to our emergency department because of continuous crying episode started two days ago. She did not have a medical history of parental consanguinity, perinatal asphyxia, neonatal seizures, or jaundice. Additionally, her maternal history did not include TORCH infection(toxoplasmosis, rubella, cytomegalovirus and herpes simplex) during pregnancy. She had two healthy little sister. Her medical history revealed that, until the first half of the age of nine, the developmental age in motor, language, and social quadrants were appropriate. In the second half of the ninth year, she suffered from a severe respiratory illness. After that, her developmental stages began to decline. Progressive deterioration in school performance, difficulty walking, sitting, and speaking appeared over a period of approximately 1 to 2 years. Then, depending on the spread of the disease, the patient became bed ridden and fully dependent for her daily activities She also had generalized seizures for 10 years requiring two anti-epileptic drugs (Sodium valproate 1000 mg/day, lamotrigine 25 mg/day) to control.

The patient underwent detailed systemic and neurological examinations. On admission, the patient had no eye-to-eye contact with medical staff or her relatives. Verbal communication was limited with a few words. Generalized serious spasticity and exaggerated deep tendon reflexes were detected in her motor system examination. Laboratory investigations including complete blood count, blood sugar, creatine phosphokinase, electrolytes, liver function tests, renal function tests, blood lactate level, arterial blood gas analysis, and urine analysis yielded normal results except for vitamin D deficiency and anemia due to iron deficiency. Because analyses of blood amino acids and urinary organic acids were unremarkable at the age of nine, they were not repeated again.

As the patient were continuously crying and the communication with her was almost impossible, we tried to exclude causes which could cause pain. Abdominal computed tomography (CT) images and X-rays of the bones were normal. She complained about sore throat, her pharynx was edematous and hyperemic, however, because of the absence of bacterial reproduction in the throat culture, we thought that the reason was continuous crying.

The electroencephalography (EEG), performed twice, showed paroxysmal cortical slowing, most pronounced in the left hemisphere, without epileptic activity.

The brain computed tomography (CT) revealed marked grey matter atrophy and hypodense signals in the corpus callosum and the bilateral periventricular and the deep cerebral white matter. Brain magnetic resonance imaging (MRI) showed symmetrical hyperintense signal changes in the periventricular white matter and the corpus callosum, atrophy of the brain stem, and the cerebellar hemispheres and increased thickness of diploe. The subcortical ‘‘u’’ fibers were spared. Radiating stripes with bands of normal signal intensity within the abnormal white matter, called tigroid-pattern, which is characteristic for MLD, was present(Figure 1). Magnetic resonance spectroscopy (MRS) showed low N-acetylaspartate (NAA) and a minimal increased choline level but there was no elevated myo-inositol peak. (Figure 2). These findings were compatible with the diagnosis of MLD. ASA activity in the patient’s peripheral blood leukocytes, measured in a referral laboratory was found to be decreased, supporting the diagnosis of MLD. Additionally genetic examination of this patient revealed that the patient had a compound heterozygous mutation of I179S in the *PSAP* gene.

A consultation with Psychiatry department was made and haloperidol and quetiapine were given to the patient in order to restrain her continuous crying. The patient was discharged with partial improvement under the treatment of quetiapine 75 mg/day. Also, physiotheraphy and continuation of antiepileptic drugs were recommened.

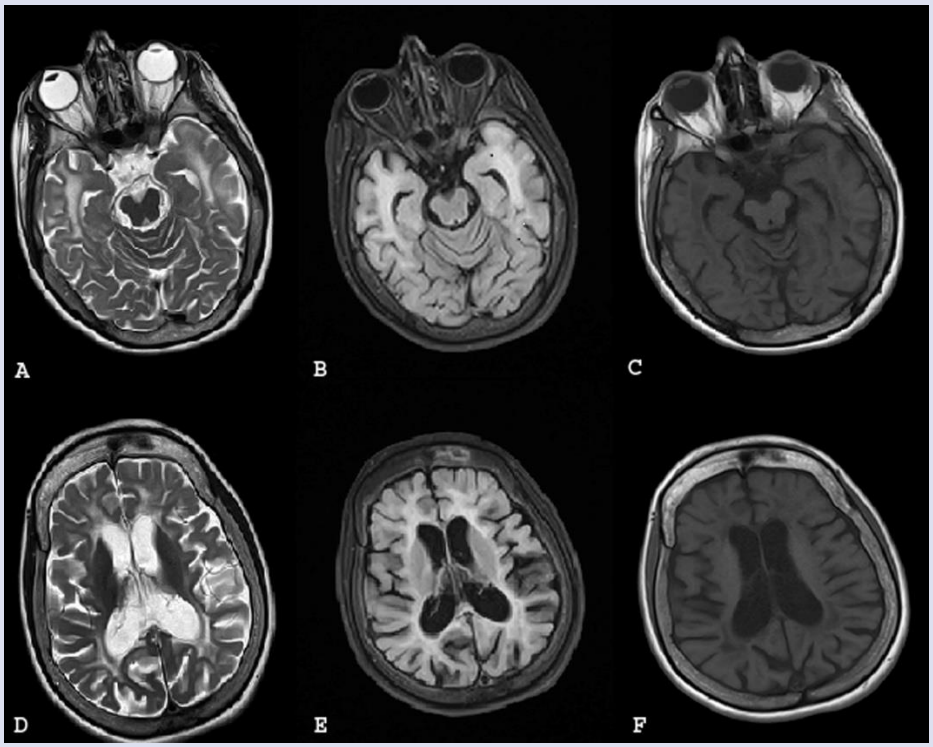

Figure 1. Symmetrical hyperintense signal changes in the periventricular white matter and corpus callosum, atrophy of the brain stem and the cerebellar hemispheres and increased thickness of diploe are seen on MRI. The tigroid-pattern, radiating stripes with bands of normal signal intensity within the abnormal white matter was evident.

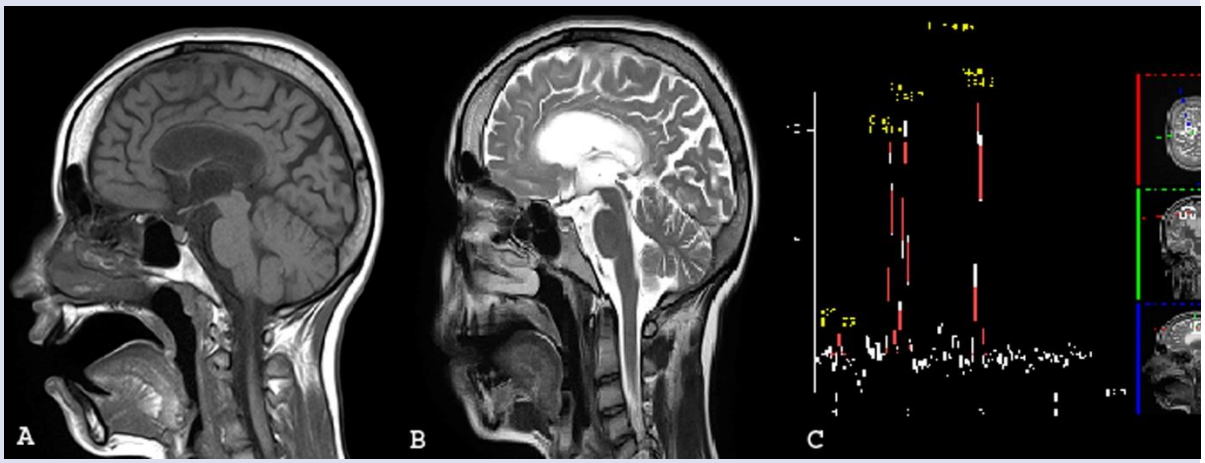

Figure 2. Magnetic resonance spectroscopy revealed a low NAA and a minimal increased choline level without elevated myo-inositol peak.

Discussion

MLD is a rare autosomal recessive inherited disease, caused by a deficiency in the enzyme activity of ASA. ASA is required for the hydrolysis of sulfated glycosphingolipids, also known as sulfatides, and its deficiency results in excessive accumulation of sulfatide in myelin in the nervous system, the bile ducts of the liver and the distal tubules of the kidney. The accumulation in the nervous system causes initially focal, later diffuse demyelination, which leads to motor and cognitive dysfunction[1].

Clinically, the differences in the residual enzyme activity of ASA cause a great variation in the onset age and the severity of the clinical course of the disease. Based on the age of disease onset, MLD can be divided into three forms: late infantile (0.5-2 years), juvenile (2-16 years), and adult (≥16 years forms) [2]. Late infantile

MLD is the most common form, which accounts for 50–60 % of all cases [3]. Its incidence is estimated to range from 1 in 40,000 to 1 in 170,000 newborns [4]. While early age at presentation results in a rapidly deteriorating phenotype with predominant motor impairment at diagnosis, in the juvenile form, symptoms often begin with deterioration of school performance or behavior abnormalities. Patients with the juvenile type often have one allele, so that low amounts of residual enzyme activity can occur [5]. Ataxia and mild pyramidal symptoms causing walking problems are the common first findings. Deep tendon reflexes may be reduced due to peripheral nerve damage [5]. Initially, the progression of the disease is slower than the infantile-onset form. However, when neurological signs become more pronounced, the decline is rapid and patients eventually lose all ability [6]. Spasticity becomes evident and many patients have epileptic seizures, whose incidence increases with disease duration and tend to be recurrent. While generalized seizures occur more frequently in infantile type, partial seizures are detected more common in juvenile type [7]. In our case, generalized seizures were also present since 10 years of age. The characteristic findings of the adult form are thought to be cognitive and behavioral retardation. Considering the age of disease onset and clinical findings of our case, it was found that she was compatible with the juvenile form. The end stage of the disease can last several years, duration is variable [8]. As the disease progresses, inevitable neurological sequelae develops, such as decorticate postures, impaired feeding and swallowing due to pseudobulbar palsy, seizures, and severe psychomotor retardation [1]. Regression of milestones and spasticity, the most characteristic manifestation of MLD, were also present in our case. Symmetrical extensive hyperintense signal changes in the periventricular white matter and generalized atrophy may have triggered pseudobulbar continuous crying in our case.

There are some characteristic radiological features of MLD in brain MRI, that is a significant method in diagnosing of the disease. Demyelination in MLD begins in the corpus callosum and then includes the periventricular white matter and eventually it leads to bilaterally symmetrical abnormal T2 signal hyperintensity. In the adult form, the disease usually starts in the rostrum and the frontal white matter, whereas in the infantile form, the onset is in the splenium of the corpus callosum and the parietooccipital white matter. The subcortical fibers (U fibers) are usually spared, as in our patient [9]. When the disease severity increases, the projection fibers, cerebellar white matter, basal ganglia and the thalami are also involved. T2-weighted images show decreased signal intensity, presumably as an outcome of metal or some other breakdown products aggregation in the brain [10]. Supratentorial atrophy can also be seen. The "tigroid pattern" is characteristic for MLD and consists of radiating stripes with bands of normal signal intensity within abnormal white matter[9]. It has been also demonstrated by histopathological studies, that these stripes are associated with perivascular preservation of myelin [10]. Brain MRI findings of our case were suggestive of the diagnosis of MLD.

Proton magnetic resonance spectroscopy(MRS) allows to obtain more detailed information from the chemical and anatomical information provided by MRI [11]. MLD patients have low N-acetylasparate levels (NAA) indicating diffuse neuronal loss and increased myo-inositol levels contributing to reactive gliosis in MRS [11,12]. MRS of our case revealed a low NAA level, compatible with MLD, but the myo-inositol level was not elevated.

Measurement of ASA enzyme activity, molecular genetic testing of ASA[7,8,13], detection of urinary sulfatides and estimation of metachromatic lipid deposits in nervous system tissue[13] are some of the methods used for the diagnosis of MLD. ASA gene sequence analysis can be used for prenatal diagnosis. ASA enzyme activity was found to be decreased in our case's peripheral blood leukocytes.

P426L and I179S are the two most frequent mutations in late-onset MLD, showing marked phenotypic heterogeneity in contrast to infantile MLD. Several studies have revealed that patients with P426L homozygote have progressive gait disturbance, especially due to spastic paraparesis or cerebellar ataxia. In addition, in these patients, while the mental disorder is mild at the onset of the disease; becomes evident as the disease progresses. In contrast, patients with the I179S compound heterozygous mutation often present with schizophrenia-like behavioral abnormalities, social dysfunction, and mental deterioration, while motor deficits are subtle[12]. Although the I179S compound heterozygous mutation was detected in our patient, motor deficit and gait disturbance were prominent from the onset of the disease.

No definite treatment for MLD exists. Bone marrow transplantation, stem cell transplantation, and genetic engineering are being tried to stop or slow the progression of neurological deterioration [14,15]. Application of recombinant human ASA, which has not reached the stage of universal recommendation and adaptation, is still a theory. So therapeutic options are limited to palliative and supportive treatments.

Conclusion

A 20-year-old female patient born of unconsanguineous marriage presented with continuous pseudobulbar crying, generalized seizures, developmental delay and spasticity. Her medical history, typical MRI findings and low ASA activity suggest late juvenile variant of MLD.

References

1. Patil SA, Maegawa GH. Developing therapeutic approaches for metachromatic leukodystrophy. Drug Des Devel Ther 2013;7: 729–745.
2. Kliegman RM, Stanton BF, St Geme JW, Schor NF, Behrman RE. Neurodegenerative disorders of childhood. In: Kwon JM, editor. Nelson Textbook of Pediatrics. 19th ed. Philadelphia: WB Saunders; 2011:2072.
3. Luzi P, Rafi MA, Rao HZ, Wenger DA. Sixteen novel mutations in the arylsulfatase A gene causing metachromatic leukodystrophy. Gene 2013;530:323–328.
4. Wang RY, Bodamer OA, Watson MS, Wilcox WR. Lysosomal storage diseases: diagnostic confirmation and management of presymptomatic individuals. Genet Med 2011;13: 457–484.
5. Gieselmann V, Krageloh-Mann I. Metachromatic leukodystrophy e an update. Neuropediatrics 2010;41(1):1-6.
6. Kehrer C, Groeschel S, Kustermann-Kuhn B, et al. Language and cognition in children with metachromatic leukodystrophy: onset and natural course in a nationwide cohort. Orphanet J Rare Dis 2014;9(1):18.
7. Groeschel S, Dali C, Clas P, et al. Cerebral gray and white matter changes and clinical course in metachromatic leukodystrophy. Neurology 2012;79: 1662- 1670.
8. Michael V Johnson Neurodegenerative disorders of childhood. In: Behrman RE, Kliegman RM, Jenson HB, eds. Nelson Textbook of Pediatrics. 18th ed. Philadelphia, PA: W.B. Saunders Company; 2008: 592- 598.
9. Martin A, Sevin C, Lazarus C, et al. Toward a better understanding of brain lesions during metachromatic leukodystrophy evolution. Am J Neuroradiol 2012;33(9):1731-1739.
10. Eichler F, Grodd W, Grant E, et al. Metachromatic leukodystrophy: a scoring system for brain MR imaging observations. Am J Neuroradiol 2009;30(10):1893-1897.
11. Assadi M, Wang DJ, Velazquez-Rodriquez Y, et al. Multi-voxel 1H MRS in metachromatic leukodystrophy. J Cent Nerv Syst Dis 2013;5:25-30.
12. Rauschka H, Colsch B, Baumann N, et al. Late onset metachromatic leukodystrophy genotype strongly influences phenotype. Neurology 2006;67:859–863
13. Gomez-Ospina N. Arylsulfatase A deficiency. GeneReviews 2020
PMID: 20301309
14. Kidd D, Nelson J, Jones F, et al. Long term stabilization after bone marrow transplantation in juvenile metachromatic leukodystrophy treated by bone marrow transplantation. Bone Marrow Transplant 1996: 1003-1008.
15. Pierson TM, Bonnemann CG, Finkel RS, Bunin N, Tennekoon GI. Umbilical cord blood transplantation for juvenile metachromatic leukodystrophy. Ann Neurol 2008;64: 583- 587.