RESEARCH ARTICLE / ARAŞTIRMA MAKALESİ

DOI: 10.4274/atfm.galenos.2022.87004
Ankara Üniversitesi Tıp Fakültesi Mecmuası 2022;75(4):544-549

MEDICAL SCIENCES / DAHİLİ TIP BİLİMLERİ

Clinical Profile of Late-Infantile and Juvenile Metachromatic Leukodystrophy: A Retrospective Study

Geç İnfantil ve Jüvenil Metakromatik Lökodistrofinin Klinik Özellikleri: Retrospektif Bir Çalışma

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Abstract

Objectives: Metachromatic leukodystrophy (MLD) is a glycosphingolipid storage disease leading to demyelination and neurological impairment. Based on the age at onset, late-infantile, juvenile, and adult forms are defined. In this study, our aim was to define the clinical characteristics in late-infantile and juvenile forms.

Materials and Methods: Twelve children with either late-infantile or juvenile form of MLD were enrolled. Patient records were retrospectively analyzed to gather demographic, clinical, laboratory, and imaging data.

Results: Patients had a median age of 2 years (1.5-15) at the onset of symptom. Five (41.7%) patients had family history of MLD. Seven (58.3%) children were diagnosed as late-infantile form while 5 (41.7%) children were classified as juvenile form. In the late-infantile group, gait impairment (7/7, 100%) was the primary symptom, whereas behavioral/cognitive impairment (4/5, 80%) predominated the juvenile group. Eleven patients (91.7%) had cognitive impairment at the time of admission. Only one patient (8.3%) had epilepsy. While none of the patients in the juvenile group lost ambulation in follow-up, all late-infantile patients were non-ambulatory at their most recent visits.

Conclusion: Our findings, along with those of other studies, support the diverse clinical picture of these two types of MLD. It is essential to recognize the age-specific signs to make an early diagnosis of MLD. Our findings suggest that MLD should be thoroughly investigated in children with a neurodegenerative course. Moreover, siblings of MLD patients should also be carefully evaluated.

Key Words: Metachromatic Leukodystrophy, Late-Infantile, Juvenile, Children

Öz

Amaç: Metakromatik lökodistrofi (MLD), demiyelinizasyona ve nörolojik etkilenmeye yol açan bir glikosfingolipid depo hastalığıdır. Semptomların başlangıç yaşına göre geç infantil, jüvenil ve yetişkin formlara ayrılır. Bu çalışmada geç infantil ve juvenil formların klinik özelliklerini değerlendirmek amaçlanmıştır.

Gereç ve Yöntem: Geç infantil veya juvenil MLD tanısını almış on iki çocuk bu çalışmaya dahil edildi. Demografik, klinik, laboratuvar ve görüntüleme verileri geriye dönük olarak incelendi.

Bulgular: Hastaların semptom başlangıcında ortanca yaşı 2 (1,5-15) yıldı. Beş (%41,7) hastanın ailesinde MLD öyküsü vardı. Yedi (%58,3) çocuk geç infantil form, 5 (%41,7) çocuk ise juvenil form olarak sınıflandırıldı. Geç infantil grupta yürüme bozukluğu (7/7, %100) ana semptom iken, jüvenil grupta davranışsal/bilişsel bozukluk (4/5, %80) en yaygın semptomdu. Başvuru sırasında 11 hastada (%91,7) bilişsel etkilenme vardı. Bir hasta (%8,3) epilepsi tanısı aldı. Jüvenil gruptaki hastalar kontrollerde hala ambulatuvar iken, geç infantil gruptaki çocukların hiçbiri son kontrolde yürüyemiyordu.

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Received/Geliş Tarihi: 17.07.2022 **Accepted/Kabul Tarihi:** 01.11.2022

Sonuç: Literatürdeki diğer çalışmalara benzer şekilde çalışmamızın sonuçları geç infantil veya juvenil MLD formlarının birbirlerinden farklı bir klinik seyir izlediğini göstermiştir. Erken teşhis için yaşa özgü belirtileri tanımak önemlidir. Bulgularımız, nörodejeneratif seyirli hastalık gösteren çocuklarda MLD'nin kapsamlı bir şekilde araştırılması gerektiğini vurgulamaktadır. Ayrıca, MLD hastalarının kardeşleri de dikkatle değerlendirilmelidir.

Anahtar Kelimeler: Metakromatik Lökodistrofi, Geç İnfantil, Jüvenil, Çocuk

Introduction

Leukodystrophies are rare disorders that cause central nervous system impairment as well as peripheral nerve involvement in some cases. In the latest revision of white matter disorders, 30 disorders have been defined as primer leukodystrophies (1). Among this group, metachromatic leukodystrophy (MLD) is relatively common with varying range of prevalence (1/40,000-160,000) (2). MLD is an autosomal recessively inherited lysosomal storage disease. Mutations of the arylsulfatase A (*ARSA*) gene cause arylsulfatase A (ASA) deficiency, and much less frequently, mutations of *prosaposin (PSAP)* gene cause saposin B deficiency, both of which result in impaired enzymatic hydrolysis of sulfatide in MLD (3). Accumulated sulfatides lead to demyelination and neurodegeneration (3).

MLD is classified into late-infantile, juvenile, and adult types based on the age at disease onset. First manifestations appear around the age of two, between the ages of three and sixteen, and after the age of sixteen in late-infantile, juvenile, and adult types respectively (4). Clinical characteristics vary widely in different forms (5). The main hallmark of late-infantile type is rapid worsening in gross motor functions along with cognitive decline and gait disturbances (5,6). The juvenile type is characterized by deterioration in executive functions and linguistic skills, as well as new-onset attention problems and behavioral changes, accompanying ataxia and a relatively slow progressive gross-motor/fine-motor impairment (5,7). Cognitive and psychiatric impairments are the prominent features in adult-onset form which are less frequently followed by gait disturbances and polyneuropathy (2,8). Given high variability of first symptoms and disease course between subtypes and within subtypes, we aimed to present the clinical characteristics of MLD patients in this study.

Materials and Methods

Twelve patients with a late-infantile or juvenile form of MLD admitted to our hospital between May 2010-May 2017 were included in this study. Patient records were retrospectively reviewed to collect data on demographic, clinical, laboratory and imaging results. MLD was diagnosed based on ASA deficiency in all patients together with typical clinical and magnetic resonance imaging (MRI) features. Molecular analysis of *ARSA* gene was available in a limited number of patients. The time when the first neurologic, cognitive, or behavioral impairment occurred was defined as disease onset. For late-infantile form, the age of onset was defined as less than 30 months, and for juvenile form it was defined as 30 months to less than 16 years (5). The comprehensive biochemical and immunologic investigations of some of the patients were reported previously (9,10). This study was approved by the ethical committee of the Hacettepe University Faculty of Medicine (acceptance number: 17/511-21 and date: 13.06.2017).

Statistical Analysis

Statistical analysis of the data was performed with the SPSS 20 (Statistical Package for Social Sciences) program. Basic descriptive statistics were expressed with median, minimum, and maximum value.

Results

A total 12 patients (F/M: 4/8) were enrolled in this study (Table 1). The consanguinity rate among the study participants was 83.3%. Six (50%) patients had family history of MLD. Patients had a median age of 2.15 years (1.5-15) at disease onset. Patients were categorized based on age at onset as late-infantile in 7 (58.3%) and juvenile in 5 (41.7%). Gait impairment (7/7, 100%) was the main symptom in late-infantile group whereas behavioral/cognitive impairment (4/5, 80%) was the most common symptom in juvenile group. One patient in juvenile group (patient 9) was admitted as her older sibling had MLD. She had no evident complaint, though a slight difficulty in tandem walking and tremor were noted in our comprehensive neurological exam. Eleven children (91.7%) had cognitive impairment on admission. Only one case (patient 6) (8.3%) presented with seizures. Enzyme analysis showed low ASA levels (range: 1-9 µmol/g protein/h, normal: 50-990 µmol/g protein/h) and MRIs were compatible with MLD in all patients (Figure 1). Six patients (50%) had electroneuromyography study which showed demyelinating sensorimotor polyneuropathy. Five patients (41.7%) underwent molecular analysis. Allogenic hematopoietic stem-cell transplantation (HSCT) has been performed for two patients in juvenile group (patient 9 and 12).

Two patients in the late-infantile group had only an initial examination and did not attend any follow-up visits. Their medical reports revealed that they had died. For rest of the patients, last visits were performed at a median age of 8 years (2.5-18) and 5/10 (50%) patients were non-ambulatory in the last visit. They lost ambulation between 2-5 years of age. None

Table 1: Summary of clinical findings in individuals with MLD

Patient ID/ gender	Family history	Age of onset	First symptom(s)	Age at diagnosis	ASA activity	Disease causing mutation	Cognitive status at diagnosis	Age at loss of ambulation	Age at last visit	Clinical status at last visit
Late Infantile										
1/M	-	1.5	Frequent falls	3	4	ARSA: c.465 + 1G > A Homozygous	Mild impairment	2	3.5	No head control, sitting with or without support, and speech
2/M	+	1.5	Motor delay	2	7.7	NA	Moderate impairment	Never walked without support	NA	NA (exitus)
3/M	+	1.5	Unsteady gate	2	3	NA	Moderate impairment	2	2.5	Preserve head control and sitting with support, able to speak few words
4/M	+	1.5	Motor delay	2.5	4	NA	Mild impairment	Never walked without support	NA	NA (exitus)
5/M	-	1.5	Frequent falls	3	2	NA	Mild impairment	3	4.5	No head control, sits with support, unable to speak (exitus)
6/M	-	2	Frequent falls	7	4	ARSA: c.979G>A Homozygous	Moderate impairment	5	7.5	Preserve head control and sitting with support, unable to speak, frequent seizures (exitus)
7/M	-	2.3	Frequent falls	4	3	ARSA: c.893G>A Homozygous	Mild impairment	3	10.7	No head control, sitting with or without support, and speech
Juvenile										
8/M	+	3	Behavioral disturbances	8	2	NA	Moderate impairment	-	9	Cognitive problems, ataxia, tremor
9/F	+	3.5	No complaint (family history)	3.5	4	NA	Normal IQ	-	7.2	No cognitive decline, wide based gate, tremor
10/F	-	7	Frequent falls, decline in school performance	9.5	5.25	ARSA: c.868C>T Homozygous	Mild impairment	-	10	Cognitive problems, difficulty in walking on heels, tremor
11/F	+	7.9	Behavioral disturbances, unsteady gait	8	1	NA	Mild impairment	-	8.5	Cognitive problems, ataxia, tremor
12/F	-	15	Behavioral disturbances, decline in school performance	17	9	ARSA: c.473G>A Homozygous	Moderate impairment	-	18	Cognitive problems, ataxia, tremor

*All ages are reported by years, **M: Male, F: Female, ***NA: Not applicable, ****ASA: Arylsulfatase A (normal range: 50-990 µmol/g protein/h)

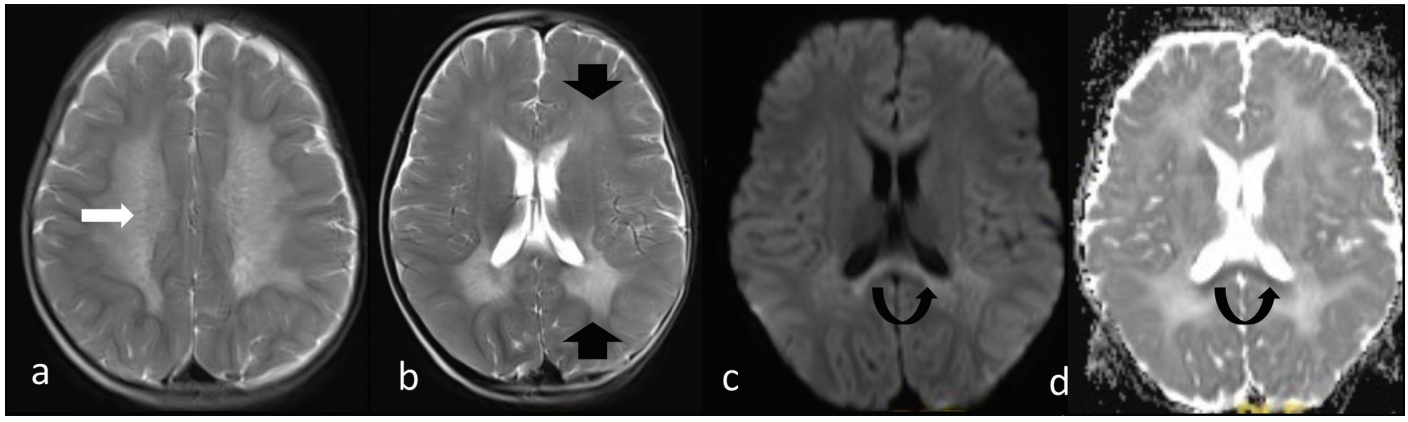

Figure 1: Axial MR images of patient 5; **a–b:** The typical pattern of distribution of white matter hyperintensity in T2 weighted images (black arrows), tigroid pattern formed from T2 hypointense stripes and dots in the background of diffuse hyperintensity (white arrow); **c–d:** restricted diffusion within the splenium of the corpus callosum (black arrows)

of the patients in the juvenile group lost ambulation. Two out of 10 (20%) died on follow-up (patient 5 and 6).

Discussion

Sulfatide accumulation impairs both the peripheral and central nervous systems in MLD. Increased sulfatides disrupt glial cells, cause myelin sheath instability, and possibly trigger inflammatory processes, all of which lead to progressive demyelination (2,11). Beside glial cells, neurons are also assumed to be affected (2,11). Damage in the peripheral and central nervous systems manifests motor and cognitive/behavioral problems in late-infantile and juvenile forms. In our study, the initial symptom of late-infantile group was gait disturbance. Other studies also showed patients with late-infantile form had prominent gross motor disfunction or regression at the time of diagnosis, following cognitive/language impairment, with a rapid decline (6,12).

Our patients did not have consecutive cognitive assessments, so we are unable to remark on cognitive decline; however, they demonstrated severe motor deterioration, and those who could walk lost ambulation between the ages of 2 and 5 years. Kehrer et al. (5) also noted the progressive impairment of gross motor functions and showed loss of any locomotion as well as loss of any head and trunk control before 40 months of age.

Juvenile MLD mainly manifests by impaired executive functioning and new onset psychiatric symptoms. Gross motor and fine motor dysfunctions are less frequently observed at initial presentation of juvenile MLD. Furthermore, motor deterioration is slower compared to late-infantile MLD (5,13). In our study, behavioral and cognitive problems were prominent symptoms in juvenile MLD patients with slight gross motor and fine motor impairment in some. On follow-up, all were able to walk without support.

Patients with MLD may have many comorbidities such as feeding difficulties, malnutrition, sleep and pain problems as well as seizures. These comorbidities might be overlooked in some patients if not queried (14). Adang et al. (15) pointed out the importance of multidisciplinary approach in the management and prevention of these comorbidities on their consensus statement. One patient suffered from seizures in our study. Epilepsy is frequent in MLD (13,16,17). In management of epilepsy, no specific anti-seizure drug is recommended. However, the use of anti-seizure medications which may cause direct bone marrow suppression should be avoided in children who are about to undergo or have recently had bone marrow transplantation (14).

Peripheral neuropathy may be prominent at initial presentation of MLD. Bindu et al. (16) showed broadcast hypomyelination accompanying aberrant myelin configuration and remodeling, moreover lamellar and prismatic tuff stone inclusions in both Schwann cell cytoplasm and endoneurium on light and electron microscopic examination, respectively, in sural nerve biopsies of late-infantile form of MLD. Beside polyneuropathy, neuropathic pain and neurogenic bladder dysfunction may develop in follow-up (18). In our cohort, no patient suffered from peripheral neuropathy symptoms such as neuropathic pain, bladder dysfunction which may not have been questioned during the severe course of the disease.

No curative therapy is available in MLD. Hematopoietic stem cell transplantation is a treatment option for presymptomatic or early symptomatic MLD. Studies in these subgroups have revealed less pronounced disease progression, with some patients experiencing disease stabilization after HSCT. Consequently, children should indeed be carefully accounted for HSCT (19,20). However, HSCT's therapeutic effectiveness for peripheral nervous system symptoms pales in comparison to that for central nervous system symptoms (2,18). Intrathecal

enzyme replacement, direct injection of adeno-associated virus-based vectors and hematopoietic stem cell-based gene therapies have been studied in MLD. Despite being considered promising novel procedures, none of them have been widely approved for clinical use (21-23). In our series, two children underwent HSCT. Patient 9 had no marked complaints; she was admitted to the hospital due to a positive family history of MLD. A detailed neurological assessment revealed mild deterioration in tandem gait and tremor. Patient 12 presented with behavioral changes and cognitive decline that had progressed over previous years. The patient 9 received allogenic bone marrow transplantation from her sibling. This treatment was not recommended for patient 12 in our center. However, the family insisted on the procedure. As a result, the transplant was performed from an unrelated donor in an outside institution. The follow-up period of both patients is limited, both patients are stable.

Study Limitations

This study has several limitations because of the retrospective nature, relatively small sample size and short follow-up time frame. One of the major limitations of this study was insufficient data regarding classification of motor functions. None of the patients had formal motor assessment tests on admission or follow-up. Evaluation of cognitive status was limited to IQ measurement or clinical judgment, lacking specific subtests. Most of the patents lacked genetic diagnosis. Despite the above-mentioned constraints, our study offers a remarkable data from a single center.

Conclusion

Late-infantile MLD is presented by gross motor function impairment on admission with rapidly progressive course, whereas the initial symptoms in the juvenile MLD patients are predominated by behavioral problems and cognitive impairment in the current study. Our results in accordance with previous reports show the diverse clinical picture of these two types of MLD. It is critical to recognize these age-specific symptoms to make an early diagnosis of MLD. The consanguinity rate was 83.3% in our study and five patients had a positive family history of MLD, yet only one patient was admitted in early symptomatic phase. These results demonstrate that MLD should be considered carefully in children with a neurodegenerative course in the populations with a high rate of consanguineous marriage. Furthermore, siblings of MLD patients should also be thoroughly assessed as HSCT may be a viable treatment option if MLD is identified early.

Acknowledgements: We thank our patients and their families for taking part in this study and the referring pediatricians, pediatric neurologists, and pediatric hematologists for their cooperation.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Ethics Committee of Hacettepe University Faculty of Medicine (approval number: 17/511-21).

Informed Consent: The study was a retrospective study.

Peer-reviewed: Internally peer-reviewed.

Authorship Contributions

Concept: C.G., D.A., K.K.O., M.T., Design: C.G., D.A., K.K.O., M.T., Data collection: C.G., D.A., Analysis or Interpretation: C.G., D.A., M.T Writing: C.G.

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Financial Disclosure: The author(s) received no financial support for the research, authorship, and/or publication of this article.

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