Case Report / Olgu Sunumu
doi: 10.18678/dtfd.1447131

Duzce Med J, 2024;26(2):179-182
Düzce Tıp Fak Derg, 2024;26(2):179-182

Migraine Causality in Alpha-1 Antitrypsin Deficiency

Alfa-1 Antitripsin Eksikliğinde Migren Nedenselliği

Esra DEMİR ÜNAL
0000-0002-1752-9619

Neurology Clinic, Nevşehir State Hospital, Nevşehir, Türkiye

ABSTRACT

Alpha1-antitrypsin (A1AT) is an anti-inflammatory mediator with antiprotease activity associated with anti-inflammatory and immunomodulatory effects in various inflammatory conditions. A1AT deficiency (A1ATD) has been associated with various hyperinflammatory diseases, such as lung disease (emphysema and bronchiectasis), liver disease (chronic hepatitis, cirrhosis, and hepatoma), and skin diseases (panniculitis). Migraine with aura is one of the common migraine subtypes associated with neuroimmunologic activation and neuroinflammation which is associated with cortical spreading depression and glial hyperinflammation in etioradiopathogenesis, and the main mechanisms explained so far are hyperinflammation of pro-inflammatory mediators, sensitivity of trigeminal nerve fibers and pain-conjugated glial cells activation. In this case report, a causative perspective of migraine with aura and A1ATD was presented through etioradiopathogenetics mechanisms that show the central reflections of systemic hyperinflammatory processes, and the importance of peripheral hyperinflammatory conditions in migraine etiology was examined.
Keywords: Alpha-1 antitrypsin deficiency; cortical spreading depression; hepatocerebral pathways; migraine; neuroimmune activation; neuroinflammation.

ÖZ

Alfa1-antitripsin (A1AT), çeşitli inflamatuar durumlarda anti-inflamatuar ve immünomodülatör etkilerle ilişkili antiproteaz aktivitesine sahip bir anti-inflamatuar aracıdır. A1AT eksikliği (A1ATE), akciğer hastalığı (amfizem ve bronşektazi), karaciğer hastalığı (kronik hepatit, siroz ve hepatoma) ve cilt hastalıkları (pannikülit) gibi çeşitli hiperinflamatuar hastalıklarla ilişkilendirilmiştir. Auralı migren, etyopatogenezinde kortikal yayılan depresyon ve glial hiperinflamasyonla ilişkili nöroimmünolojik aktivasyon ve nöroinflamasyonla ilişkili olan yaygın migren alt tiplerinden biri olup şimdiye kadar açıklanan ana mekanizmalar, proinflamatuar mediatörlerin hiperinflamasyonu, trigeminal sinir liflerinin duyarlılığı ve ağrıyla konjuge glial hücrelerin aktivasyonudur. Bu vaka raporunda, sistemik hiperinflamatuar süreçlerin santral yansımalarını gösteren etioradiopatogenetik mekanizmalar üzerinden auralı migren ve A1ATE'nin nedensel bir perspektifi sunulmuş ve periferik hiperinflamatuar durumların migren etiyolojisindeki önemi incelenmiştir.
Anahtar kelimeler: Alfa-1 antitripsin eksikliği; kortikal yayılan depresyon; hepatoserebral yollar; migren; nöroimmün aktivasyon; nöroinflamasyon.

Corresponding Author
Sorumlu Yazar
Esra DEMİR ÜNAL
md.esrademir@gmail.com

Received / Geliş Tarihi : 06.03.2024
Accepted / Kabul Tarihi : 06.08.2024
Available Online / Çevrimiçi Yayın Tarihi : 20.08.2024

INTRODUCTION

Alpha-1 antitrypsin deficiency (A1ATD) is an autosomal recessive disease caused by a mutation in the SERPINA1 gene. A1AT is an anti-inflammatory mediator with antiprotease activity (1) associated with anti-inflammatory and immunomodulatory effects in various inflammatory conditions, such as rheumatoid arthritis, diabetes

Presented as a poster at the 57th National Neurology Congress (November 27-December 1, 2021; Antalya, Türkiye).

mellitus, cystic fibrosis, and asthma (2). A1ATD has been associated with various hyperinflammatory diseases, such as lung disease (emphysema and bronchiectasis), liver disease (chronic hepatitis, cirrhosis, and hepatoma), and skin diseases (panniculitis). Migraine with aura (MWA) is among the most common migraine type that the pathogenesis is associated with neuroimmunologic activation and neuroinflammation, which is thought to be associated with cortical spreading depression (CSD) and glial hyperinflammation (3). Current data obtained from animal models have shown that CSD occurs as a result of the release of proinflammatory mediators, activation of trigeminal nerve fibers and inflammation, as well as specific neuroinflammatory markers showing an increase in pain-conjugated glial activation on positron emission tomography (PET) (3). In this case report, a causative perspective of MWA in a patient diagnosed with A1ATD was presented through etioradiopathogenetics mechanisms that show the central reflections of systemic hyperinflammatory processes, and the importance of peripheral hyperinflammatory conditions in migraine etiology was examined.

CASE REPORT

A 35-year-old female patient was admitted with a headache and imbalance in gait that had been going on for six months. Her headache was a migratory character that could continue for over 24 hours and was localized in the right frontoparietal area with a throbbing quality. Her headache was accompanied by a feeling of conjugate photophobia and nausea induced by a movement that causes difficulties in daily life activity. There was a complaint of vision loss in both eyes, which started about 5-10 minutes before the headache, which she referred to as a serrated area in all directions. She did not describe a constrained view or diplopia in her neurological examination. In her medical history, she was diagnosed with A1ATD syndrome three months ago. Serum liver tests and abdominal ultrasonography (USG) were performed at the internal medicine clinic where the patient applied with the complaint of right upper quadrant pain. In serum examinations, elevation in liver function tests showed mild to severe steatosis in liver parenchyma and mild severe mesenteric panniculitis in the mesenteric root periphery, which was detected in USG (Figure 1. A). With the current findings, the patient was referred for biopsy for diagnostic evaluation of hepatocellular pathologies. The patient's liver biopsy showed mild-stage fibrosis (Figure 1. B). Dynamic liver magnetic resonance imaging (MRI) and triphasic upper/lower abdomen computed tomography (CT) showed no additional hepatobiliary pathology. There was no significant emphysematous appearance on the patient's thorax CT. In serum tests performed for hepatobiliary pathologies, a low A1AT level of 45 mg/dL (normal range, 93-224 mg/dL) was detected (turbidimetric method). Pulmonary function tests were normal. Liver function studies revealed elevated serum alanine aminotransferase (ALT) level of 245 U/L (average, 71-236 U/L), aspartate aminotransferase (AST) level of 155 U/L (average 68-148 U/L), and triglyceride level of 324 mg/dL (normally <150 mg/dL). Alkaline phosphatase and γ-glutamyl transferase were normal. With these results, the patient was diagnosed with A1ATD, and ursodiol was started during the follow-up period. Cranial MRI and MR angiography were performed regarding the patient's current complaints, and nonspecific ischemic gliotic areas in the bilateral frontal hemispheres were detected. There were no abnormalities regarding vasculitis in the serum parameters (i.e., erythrocyte sedimentation rate, serum protein immunofixation electrophoresis, complement C3, C4, etc.). The patient, who met almost all criteria for MWA and whose metabolic disorder continued at the time of admission, was followed up with non-steroidal anti-inflammatory drug (NSAID) therapy. During follow-up, there was no response to NSAID treatment as attack treatment, and the patient was switched to flunarizine (5 mg/per day) treatment. A significant improvement was observed when switching to flunarizine in prophylaxis.

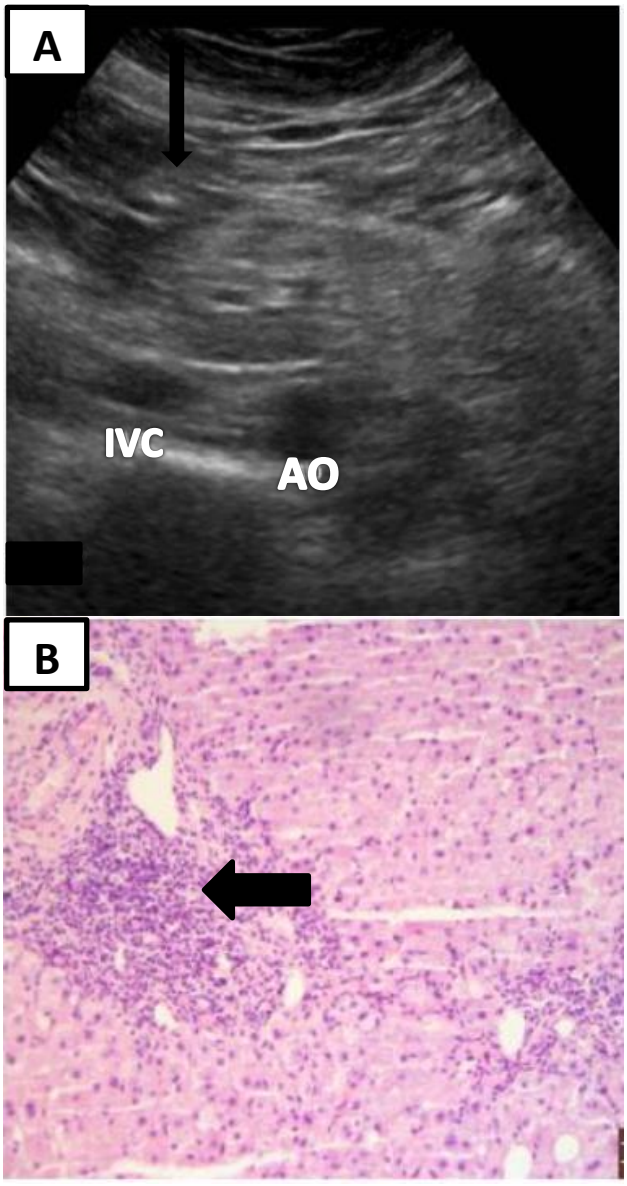

Figure 1. A) Abdomen ultrasonography showed mild to severe steatosis in liver parenchyma and mild severe mesenteric panniculitis in the mesenteric root periphery (black arrow), IVC: inferior vena cava, AO: aorta abdominalis, **B)** mild stage fibrosis was observed in the liver biopsy (black arrow)

DISCUSSION

A1AT is a glycoprotein produced mainly in the liver and acts primarily as a serine protease inhibitor to prevent the destruction of pulmonary structures by neutrophil elastase. It also has an immunomodulatory and anti-inflammatory effect as a positive acute phase reactant and its serum level increases in response to inflammatory stress in order to maintain the balance of proinflammatory processes (4). In studies on the relationship between A1ATD and inflammatory processes, A1ATD has been shown to be associated with proinflammatory mediators, including interleukin-1β (IL-1β) and complement activation. Also, increased levels of complement receptor-associated C3d and IL-1β have been shown in individuals with A1ATD with ZZ genotype (5,6). In a different study, NLRP3 expression by innate immune cells (mainly macrophages), which is conducted by the TLR-NF-κB pathway, results in an increase of the cellular contents of the pro-IL-1β and NLRP3 inflammasome in response to Alu RNA through TLR7 activation was reported in A1ATD (7).

MWA is a subtype of migraine that accounts for approximately 25% of all cases and is accompanied by visual (more than 90%), sensory, and motor auras before pain, of which association with various neuroinflammatory processes has been reported (3). The CSD model is among the mechanisms explained in the process of pain progression. This mechanism is a slow (2-5 mm/min) and spontaneous progressive depolarization of neurons and glia with low excitation thresholds in the cortical gray matter. This spreading process has been associated with hyperinflammation and has been reported to cause sensitization and activation of trigeminal afferents in the cranium (3). One of the most important studies examining the relationship between MWA and hyperinflammation so far was carried out by Hadjikhani et al. (8) that evaluated PET/MRI data of 18kDa translocator protein (an inflammatory marker) in the simultaneously acquired 11C-PBR28 PET on 11 MWA patients and mean tracer uptake (SUVR) in four regions of interest comprising the meninges plus the adjacent parameningeal tissues (PMT) were measured. Higher SUVR in PMT overlying occipital cortex was observed compared to control patients. The study detected increased signal (i.e., augmented 11C-PBR28 binding reflecting increased 18-kD translocator protein (TSPO) expression) in the meningeal and parameningeal areas in MWA patients, as evidence of persistent extra-axial inflammation evident in the occipital area. As a result of this study, it was concluded that the meningeal inflammatory process, which may develop due to various etiopathogenic inductors and progress with CSD, may contribute to hyperinflammation in the MWA pathophysiology (3).

In this case report, a patient diagnosed with de novo MWA after being diagnosed with A1ATD is discussed. The patient first applied with gastrointestinal complaints, and a significant increase in serum liver tests, as well as hepatic fibrosis on biopsy and panniculitis on abdominal USG, were detected. Following A1ATD diagnosis with existing hepatic pathology, MWA began without a previous migraine resume. In a study investigating potential connections between common genotypes of the SERPINA1 gene and cluster headache (CH), significant findings were revealed (9). The study found a significant difference in CH attack frequency in patients who are heterozygous or homozygous M allele carriers. This suggests a potential relationship between the presence of an S or Z allele and a higher attack frequency in CH, with potential implications for future research and clinical practice.

In a different study, 20 patients diagnosed with medication-overuse headaches, including migraine, and 18 healthy controls were included in the study. Proteomic analysis was performed using mono- (SDS-PAGE) and two-dimensional gel electrophoresis (2-DE) followed by liquid chromatography-tandem mass spectrometry (LC-MS/MS). This thorough analysis revealed disturbances in specific proteins in the serum of the patients, including A1AT, immunoglobulin heavy constant alpha 1, retinol-binding protein, and transthyretin, as a result of 2-DE combined with LC-MS/MS analysis (10). The causality of A1ATD and migraine is still doubtful and although no objective explanation has been made for the etiopathogenesis of this coexistence, there is a series of immunological and inflammatory evidence that both are triggered and aggravated by hyperinflammatory processes as pathophysiological inductors.

CONCLUSION

Various headache types have been described in several studies, especially in patients with hepatopulmonary diseases, and it is unclear in which mechanisms this causality occurs. The current studies suggest that various autoimmune inflammatory processes that cause differentiation in proteomic patterns may be critical players in the etiology of different headache types, particularly those associated with hyperinflammatory processes like migraine. There are also different opinions that the possible co-existence with proinflammatory mediators propagation from the peripheral hepatic system to the central nervous system and cause denovo migraine attacks by triggering the hyperinflammatory condition that can be detected in MWA patients' meningeal and parameningeal tissues. These findings open new avenues for future research, inspiring us to delve deeper into the etioradiopathogenetic changes during disease courses. New studies are needed in this field.

Informed Consent: Written informed consent was obtained from the patient for publication and accompanying images.

Conflict of Interest: The patient's data used in the figure was applied for a fee by units specialized in the relevant field in a private clinic, and it is stated that it was used with the patient's consent. There is no conflict of interest.

Financial Disclosure: None declared by the authors.

Acknowledgments: None declared by the authors.

Author Contributions: Idea/Concept: EDÜ; Design: EDÜ; Data Collection/Processing: EDÜ; Analysis/Interpretation: EDÜ; Literature Review: EDÜ; Drafting/Writing: EDÜ; Critical Review: EDÜ.

REFERENCES

1. Saryal S. Alfa-1 antitripsin eksikliği ve replasman tedavisi. Akciğer Bülteni. 2020;8(1):8-16. Turkish.
2. Cosio MG, Bazzan E, Rigobello C, Tinè M, Turato G, Baraldo S, et al. Alpha-1 antitrypsin deficiency: beyond the protease/antiprotease paradigm. Ann Am Thorac Soc. 2016;13(Suppl 4):S305-10.
3. Albrecht DS, Mainero C, Ichijo E, Ward N, Granziera C, Zürcher NR, et al. Imaging of neuroinflammation in migraine with aura: A [^{11}C]PBR28 PET/MRI study. Neurology. 2019;92(17):e2038-50.
4. Wanner A. Alpha-1 antitrypsin as a therapeutic agent for conditions not associated with alpha-1 antitrypsin deficiency. In: Wanner A, Sandhaus R, editors. Alpha-1 Antitrypsin. Humana Press, Cham; 2016. p.141-55.
5. O'Brien ME, Fee L, Browne N, Carroll TP, Meleady P, Henry M, et al. Activation of complement component 3 is associated with airways disease and pulmonary emphysema in alpha-1 antitrypsin deficiency. Thorax. 2020;75(4):321-30.
6. Kokturk N, Khodayari N, Lascano J, Riley EL, Brantly ML. Lung Inflammation in alpha-1-antitrypsin deficient individuals with normal lung function. Respir Res. 2023;24(1):40.
7. Lee J, Mohammad N, Lu Y, Kang K, Han K, Brantly M. Alu RNA induces NLRP3 expression through TLR7 activation in α-1-antitrypsin-deficient macrophages. JCI Insight. 2022;7(12):e158791.
8. Hadjikhani N, Albrecht DS, Mainero C, Ichijo E, Ward N, Granziera C, et al. Extra-axial inflammatory signal in parameninges in migraine with visual aura. Ann Neurol. 2020;87(6):939-49.
9. Summ O, Gregor N, Marziniak M, Gralow I, Husstedt IW, Evers S. Cluster headache and alpha 1-antitrypsin deficiency. Cephalalgia. 2010;30(1):113-7.
10. Pellesi L, Guerzoni S, Baraldi C, Cainazzo MM, Pini LA, Bellei E. Identification of candidate proteomic markers in the serum of medication overuse headache patients: An exploratory study. Cephalalgia. 2020;40(10):1070-8.