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Original Article / Orijinal Araştırma

Incidences of Terminal Zones of Myelination: An Evaluation of Patients aged 3–30 Years

Terminal Myelinasyon Zonlarının Görülme Sıklığı: 3-30 Yaş Arası Değerlendirme

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Abstract

Aim: Studies on terminal zones of myelination (TZM) generally focus on the infant to early childhood periods. Information concerning the incidence and localization in adulthood is rare and controversial. Our aim is to determine the localization and frequency TZM in patients aged 3–30 years using magnetic resonance imaging (MRI).

Material and Method: Images of 560 patients aged 3-30 years, whose cranial MRIs were reported as normal, were re-evaluated by two radiologists using a double-blind, retrospective method. Five different white matter (WM) regions (parietal peritrigonal WM; frontal, temporal, parietal, and insular subcortical WM) were reviewed for TZM. Turbo spin echo T2- and T1-weighted imaging and T2 fluid-attenuated inversion recovery sequences were used. The binary logistic regression analysis was used for the relationship of TZM with age and sex. The inter-observer agreement was evaluated by the kappa statistic.

Results: The incidences of TZM in all age groups were 28.7% in the insula, 14.6% in the temporal lobes, and 5.2% in the peritrigonal region. TZM were localized most commonly in the insula, followed by the temporal poles. The presence of peritrigonal TZM after five years of age was very rare (2.6%). Inter-observer agreement was significant for all regions (Kappa value < 0.05).

Conclusion: We detected TZM most often in the insular subcortical WM. It should be noted that insular and temporal TZM can be observed quite frequently, even in third decade.

Keywords: Insula, subcortical white matter, myelination, MRI

Öz

Amaç: Terminal miyelinasyon zonları (TMZ) ile ilgili çalışmalar genellikle infant-erken çocukluk dönemlerini kapsayacak şekilde yapılmıştır. Erişkinlikte insidans ve lokalizasyonu ile ilgili bilgiler nadirdir ve tartışmalıdır. Amacımız, manyetik rezonans görüntüleme (MRG) ile 3-30 yaş arası hastalarda TMZ lokalizasyonunu ve sıklığını belirlemektir.

Gereç ve Yöntem: Kranial MRG'leri normal olarak raporlanan, yaşları 3-30 arasında değişen 560 hastanın görüntüleri, iki radyolog tarafından çift kör, retrospektif yöntemle tekrar değerlendirildi. TMZ için beş farklı beyaz cevher (BC) bölgesi (parietal peritrigonal BC; frontal, temporal, parietal ve insular subkortikal BC) tekrar gözden geçirildi. T2 ve T1 ağırlıklı turbo spin eko ve T2-FLAIR (fluid-attenuated inversion recovery) sekansları kullanıldı. TMZ'nin yaş ve cinsiyet ile ilişkisi ikili lojistik regresyon analizi, gözlemciler arası uyum ise kappa istatistiği ile değerlendirildi

Bulgular: Tüm yaş gruplarında TMZ insidansı insulada %28.7, temporal loblarda %14.6 ve peritrigonal bölgede %5.2 idi. TMZ, en sık insulada lokalizeydi, bunu temporal poller izliyordu. Beş yaşından sonra peritrigonal TMZ varlığı çok nadirdi (%2.6). Gözlemciler arası uyum tüm bölgeler için anlamlıydı (Kappa değeri < 0.05).

Sonuç: TMZ'yi, en sık insular subkortikal BC'de saptadık. Insular ve temporal TMZ'lerin, üçüncü dekatta bile oldukça sıklıkla izlenebileceği unutulmamalıdır.

Anahtar Kelimeler: İnsula, subkortikal beyaz cevher, miyelinasyon, MRG

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INTRODUCTION

Magnetic resonance imaging (MRI) is the most commonly used non-invasive imaging method for evaluation of white matter myelination (WM). Persistent T2 hyperintensity on MRI images after 2 years of age is considered to be terminal zones of myelination (TZM). TZMs can easily be mistaken for pathology by the inexperienced. Therefore, it is important to distinguish it from WM lesions. Studies on TZM, which represent the late phase of myelination, generally focus on the infant to early childhood periods. Although TZM can be found in people up to the age of 40 years,[1] information concerning the incidence and localization in adulthood is rare and controversial. We aimed to determine the localization and frequency of TZM in patients aged 3–30 years using MRI.

MATERIAL AND METHOD

Study population

Between September 2019 and February 2020, 560 patients aged 3–30 years (median age 16 years) with completely normal cranial MRI scans were included in the study. MRI examinations that had not an optimal quality (due to motion artifacts etc.) were not included in the study. The cranial MRI scans were evaluated retrospectively. Therefore, we did not obtain consent from the subjects. None of the patients examined were premature or had perinatal hypoxic-ischemic encephalopathy, a systemic or neurological disease affecting the WM, a history of drug use, or any other chronic diseases. The ethics committee's approval was received (Approval Date: 29.04.2021; Approval Number: 386)

MRI Protocol

MRI was performed using a 1.5 Tesla (T) system (Aera, Siemens, Erlangen, Germany) with a 20-channel head coil. Intravenous sedation (ketamine 1 mg/kg) was performed when necessary (especially in children under 7 years of age) to prevent motion artifacts. Intravenous contrast material was not used for any of the patients. TZM evaluation was conducted using transverse and coronal plane turbo spin echo T2-weighted imaging (T2WI), transverse plane turbo spin echo T1-weighted imaging (T1WI), and T2 fluid-attenuated inversion recovery (T2-FLAIR) sequences (**Table 1**).

Image analysis

Image evaluations were conducted by two radiologists with at least 8 years of experience, one of whom was a pediatric radiologist. Five different WM regions (parietal peritrigonal WM; frontal, temporal, parietal, and insular subcortical WM) were evaluated in the MRI scans for TZM. The TZM inclusion criteria were the presence of T2WI hyperintensity with T1WI and T2-FLAIR isointensity according to the WM, and T2WI hyperintensity had to be present in at least two sections in both coronal–axial planes.

Statistical Analysis

Analyses were performed using IBM SPSS Statistics 22. The relationship of TZM with age and sex was evaluated by binary logistic regression analysis, and inter-observer agreement was evaluated using the kappa statistic.

RESULTS

A total of 560 patients (242 males, 318 females) aged 3–30 years (median age 16 years) were included in this study. The number of patients in each age group ranged from 14 to 44 (**Figure 1**).

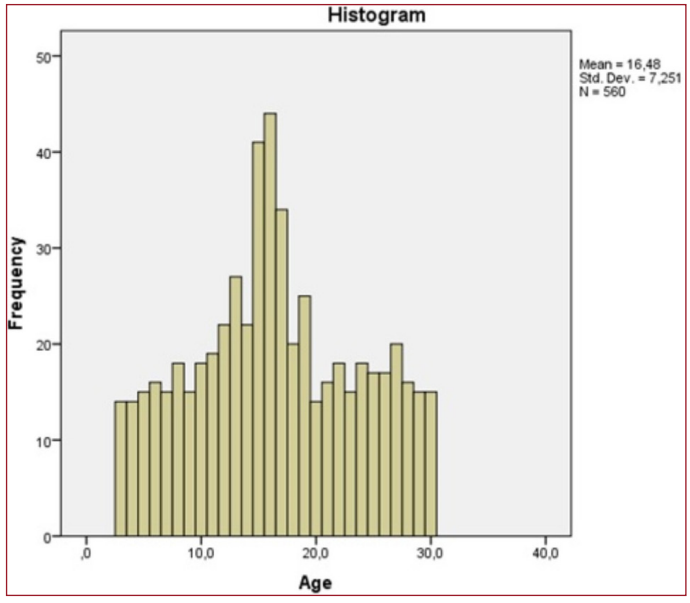

Figure 1. Histogram showing the number of patients according to age

The insula was the most common area of TZM localization in each age group (**Figure 2**). The incidences of TZM in all age groups were 28.7% in the insula (**Figure 3**), 14.6% in the temporal lobes (**Figure 4**), and 5.2% in the peritrigonal region. The presence of peritrigonal TZM after 5 years of age was very rare (in 56.6% of those aged 3–5 years, 1.4% of those aged 6–10 years, 1.2% in second decade, 0% in third decade). TZM were not detected in the frontal or parietal lobe. The incidences of TZM in the insula and temporal lobes were 13.8% and 9.8%, respectively, among in third decade.

Table 1: Magnetic resonance imaging sequence parameters.

	TR	TE	FOV	Matrix	Voxel	NEX	Interslice Gap
T2WI	3000–4000 msn	80–90 msn	175×200	280×320	0.62×0.62	3	0%
T1WI	550–600 msn	8–15 msn	175×200	280×320	0.62×0.62	2	0%
T2-FLAIR	7000–9000 msn (TI 2200 msn)	90–100 msn	175×200	280×320	0.62×0.62	3	0%

Note: TR: time repetition; TE: time echo; TI; time inversion; FOV: field of view; NEX: number of excitations; T2WI: T2-weighted images; T1WI: T1-weighted images; T2-FLAIR: T2 fluid-attenuated inversion recovery sequences.

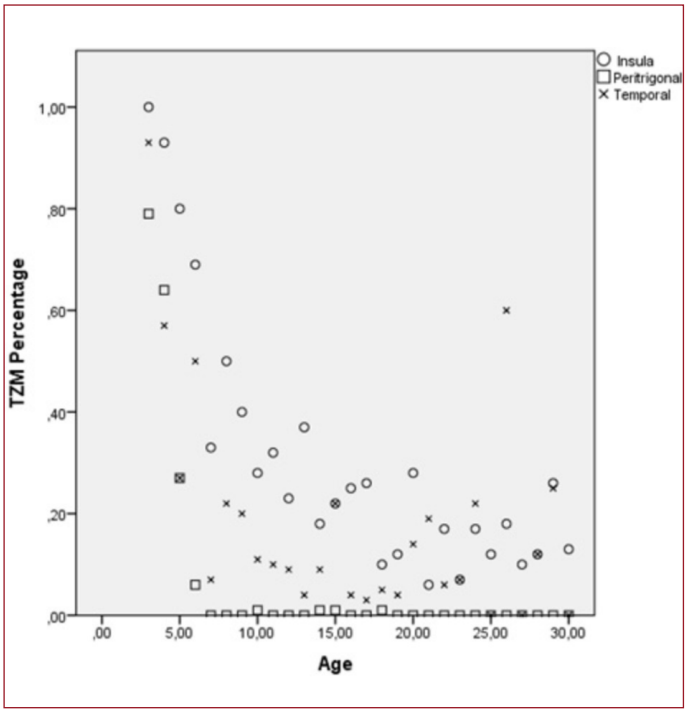

Figure 2. The distribution of insular, temporal, and peritrigonal TZM by age. TZM: terminal zones of myelination.

Based on binary logistic regression analysis, a significant correlation was found between age and TZM ($P < 0.0001$). There was no significant correlation with sex ($P > 0.1$). Cohen's kappa statistic was significant for inter-rater agreement (Kappa value < 0.05).

DISCUSSION

Myelination is a dynamic process. It begins in the cranial nerves during the 5th month of fetal life and continues throughout life.[2-4] Myelination progresses inferior to superior and posterior to anterior and centrifugal. MRI is a safe and non-invasive imaging method used to follow the process of myelination.[5,6] Myelination that similar to adults on MRI scans appears from age 1 year onwards on T1WI and from 2 years onwards on T2WI.[7,8] Persistent T2 hyperintensity on MR images after 2 years of age is considered to be TZM. However, complete myelination of the terminal zones may not be complete until fourth decade.[1] T2WIs are the most frequently used sequences to evaluate TZM.[9]

Most previous studies on TZM focused on the infant and early childhood periods. In those studies, TZM were detected in the parietal peritrigonal WM[10,11] or frontotemporoparietal subcortical WM.[12] Our findings concord with those of

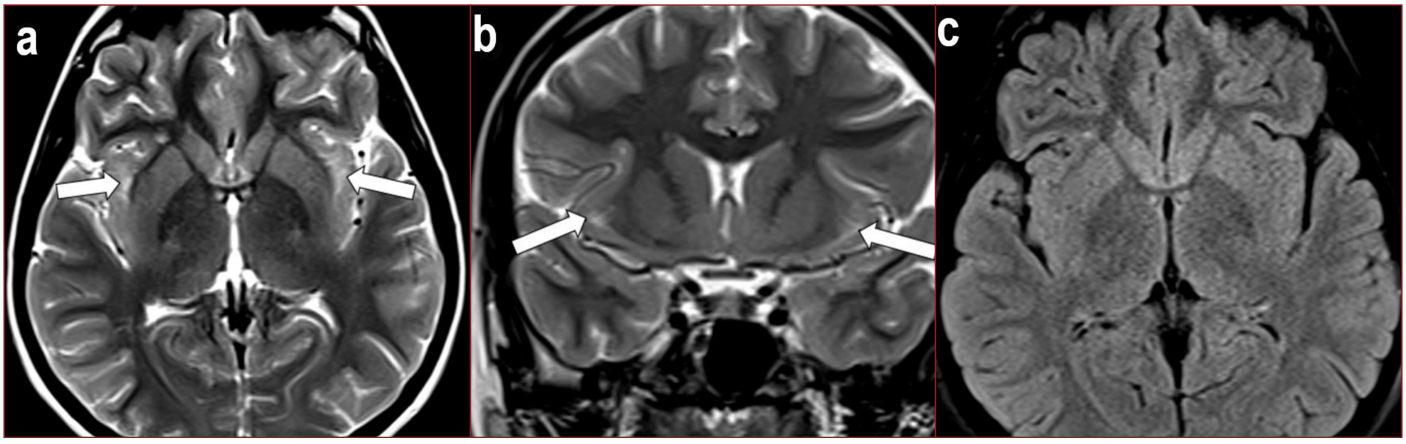

Figure 3. 16-years-old girl complains of dizziness. Hyperintense TZM (arrows) is present in bilateral insular subcortical WM in transverse (a) and coronal T2WI (b). Transvers T2-FLAIR (c) show isointensity according to white matter in same section. (TZM: Terminal zones of myelination, WM: White matter)

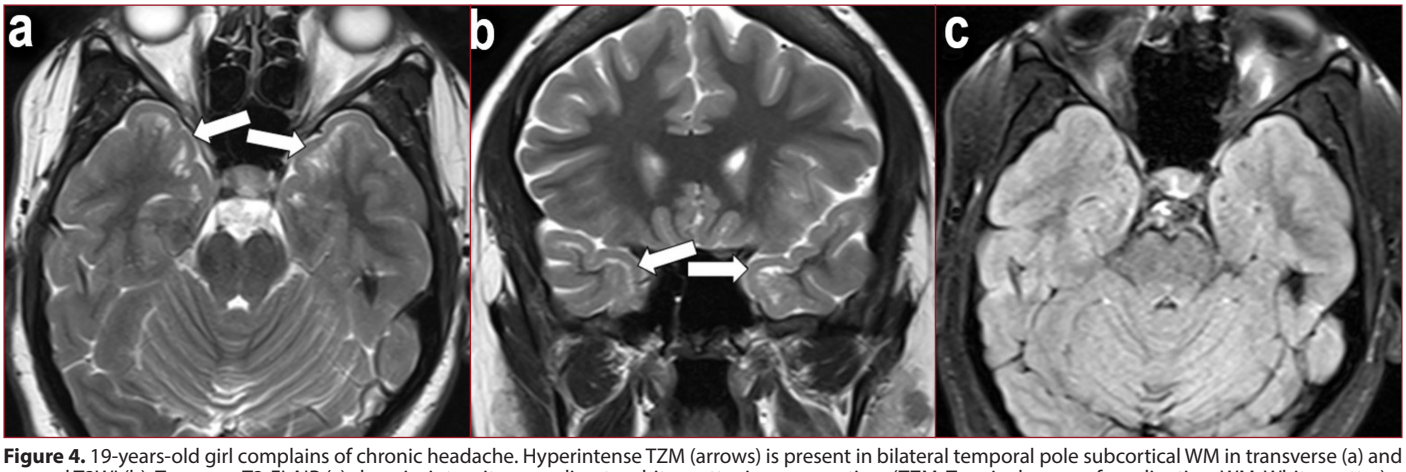

Figure 4. 19-years-old girl complains of chronic headache. Hyperintense TZM (arrows) is present in bilateral temporal pole subcortical WM in transverse (a) and coronal T2WI (b). Transvers T2-FLAIR (c) show isointensity according to white matter in same section. (TZM: Terminal zones of myelination, WM: White matter)

Parazzini et al.[12] in that TZM often occur in the subcortical WM; however, we found that the most common location was the insula, followed by the temporal poles. TZM in the peritrigonal WM were very rare after the age of 5–6 years.

Several autopsy studies showed that myelination of the frontal, parietal, and temporal subcortical association fibers was completed during early adulthood, and this may indicate completion of the higher intellectual functions.[13-15] Unlike these studies, our results showed that TZM occurred even during late adulthood (> 25 years old) and were most commonly localized in the insular subcortical association fibers.

Dennis et al.[16] stated that connection of the insula with other lobes continues until early adulthood. He suggested that this relationship decreased with age in the frontal and parietal lobes and increased in the temporal lobes. This may explain the later completion of myelination in the temporal and insular subcortical WM in our study.

We had some limitations. Our study was retrospective and all examinations in our study were obtained with 1.5 T MRI which has lower signal-to-noise ratio according to high-field MRIs. Studies with high-field MRIs (3T and above) will further reduce the contradictions on this subject.

CONCLUSION

Our results showed that, unlike other studies, TZM were most common in the insular subcortical WM. It should be remembered that insular and temporal subcortical TZM can occur at a significant rate, even in third decade. It should not be confused with pathological WM lesions.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kayseri City Hospital Clinical Researches Ethics Committee (Date: 29.04.2021, Decision No: 386).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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