Differences in corpus callosum morphology between healthy adolescents and adolescents with migraine: a case control study

Abstract

Background/aim: This study objected to compare the measurements of corpus callosum substructures of adolescents with migraine and healthy adolescents.

Materials and methods: In a case-control design, adolescents aged 12-18 years with the diagnosis of migraine and healthy control group had brain magnetic resonance imaging examination. The CC dimensions including anteroposterior length, truncus, genu and splenium widths of the case and control groups were measured and compared.

Results: The sample consisted of 188 adolescents, 109 girls (58.0%) and 79 boys (42.0%). Of these 87 (46.3%) were in the migraine group and 101 (53.7%) were in the healthy control group. The mean genu and splenium width of the migraine group were significantly lower than the control group (p= 0.024 and p= 0.01 respectively).

Conclusion: The results of this study firstly demonstrated that CC splenium and genu widths were smaller in adolescents with migraine when compared to healthy adolescents. Our findings may contribute to enlighten migraine pathophysiology.

Key words: Migraine, corpus callosum, corpus callosum/diagnostic imaging, magnetic resonance imaging, child, adolescent

1. Introduction

Migraine is a neurological disorder; defined as paroxysmal headache attacks accompanied with autonomic nervous system dysfunction. Migraine is common among pediatric population, with an overall estimated prevalence of 8% [1]. Structural and functional magnetic resonance imaging (MRI) studies have contributed to the understanding of the pathophysiology of migraine and may guide new strategies for

treatment [2]. Structural changes of the white matter and grey matter resulting volumetric changes in nociception, visual and sensorimotor processing areas of brain were observed in adult patients with migraine [2-6]. Brain damage in adult migraine was found to be associated with longer migraine duration and attack frequency [7]. In pediatric age group studies on migraine have shown gray matter abnormalities in nociceptive and visual processing regions [8], and white matter abnormalities in deep and subcortical white matter as well as callosal commissure [8-11]. However the role of corpus callosum (CC) which is the largest white matter commissure connecting and coordinating the cerebral hemispheres in the pathophysiology of migraine have not been fully understood [12]. As it has attentive and inhibitory functions, CC structural abnormalities might be associated with an altered inhibitory pain control [13]. A study on adults reported reduced fractional anisotropy values of CC in migraine patients without aura compared with the control group which were negatively correlated with the duration of disease [14]. There is scarce knowledge on the structural alternations of CC in children and adolescents with migraine. In one study, children with migraine had abnormalities of diffusivity indexes observed in the CC when compared to healthy control group in Diffusion Tensor MRI which were not correlated with disease duration and attack frequency [15].

This study objected to compare the two-dimensional structural measurements of CC of adolescents with migraine to healthy adolescents. Secondarily we aimed to find out relationships of CC structural measurements with migraine duration and attack frequency. It was hypothesized that CC morphology was different between adolescents with migraine and healthy adolescents, and there was a negative relationship between CC morphologic measurements and migraine duration and attack frequency.

2. Materials and methods

2.1. Study design and participants

In a case-control design, adolescents aged 12-18 years who have been followed at Ankara Yıldırım Beyazıt University, Yenimahalle Training and Research Hospital Child Neurology Department with the diagnosis of migraine were recruited between December, 2019 and March, 2020 as the case group. The diagnosis of migraine is established by the International Classification of Headache Disorders, Third Edition (ICHD-3) diagnostic criteria [16].

The control group was composed of healthy adolescents who were admitted to Ankara Yıldırım Beyazıt University, Yenimahalle Training and Research Hospital Pediatrics Department with minor acute illnesses such as upper respiratory tract infections or for routine health monitoring. Children who had a history of perinatal problems, preterm birth, epilepsy, brain mass, vascular malformations, neurometabolic diseases, developmental delays, disabilities were not included in the control group. All adolescents and their parents provided written consent for the study.

The study was approved by the Ethics Committee of the Ankara Yıldırım Beyazıt University, Yenimahalle Training and Research Hospital.

2.2. Procedures

The adolescents in the migraine group and control group whose parents provided written consent for this study had brain MRI imaging for this study. Corpus callosum dimensions of the case and control groups were measured on sagittal T1-weighted spin echo images (TR 800 ms, TE 15 ms, 230 mm × 230 mm FOV, 5 mm slice thickness, 1 mm interslice gap) acquired with Siemens Magnetom Avanto 1.5 T MRI Unit. Two dimensional length between anterior most and posterior most points of CC was defined

as anterior-posterior (AP) length and divided into 3 parts by Witelson's method [17]: 1) Anterior third was defined as genu and the width between inner and outer anterior most points was recorded as genu width, 2) The mid-third of the CC was defined as truncus and width of the widest part of truncus was recorded as truncus width, 3) The posterior third was defined as splenium and width of the widest part of splenium was recorded as splenium width (Figure). A radiologist with 10 years experience (the first author) measured all parameters.

Information related to the migraine history of the child including the duration of migraine, number of attacks per month (as ≤ 1 per month, 2 or 3 attacks or ≥ 4 attacks) were elicited by a paediatric neurologist with 12 years experience (ANÇK).

2.3. Data analyses

Descriptive statistics were given as means and standard deviations (SD) if distributed normally; median, minimum and maximum values if not. Categorical variables were shown using numbers and percentages. A chi-square test was used to confirm the relationship of the categorical variables. Independent sample t test was used to compare CC measurements of case and control groups. Mann-Whitney U test was performed to confirm the difference between the two groups; Kruskal-Wallis test was used for more than two groups as non-parametric tests. Spearman Correlation test was used determine the relationship between the disease duration and CC measurements. One-Way ANOVA test was used to compare CC measurements of migraine with aura, migraine without aura and control groups when the variances are distributed homogenic in Levene test. When the results were significant post-hoc analysis and Bonferroni correction was used. If the variances were not distributed homogenic Welch-AVOVA test was used to compare 3 groups. For statistical significance $p < 0.5$ was used. All the

statistical analyses were conducted using the IBM SPSS for Windows Version 21.0 program (IBM Inc., Chicago, III., USA).

3. Results

The sample consisted of 188 adolescents, 109 girls (58.0%) and 79 boys (42.0%) aged between 12-18 years. Of these 87 (46.3%) were in the migraine group and 101 (53.7%) were in the healthy control group. The mean age of the sample was 15.07 ± 1.78. There were 48 (55.2%) girls and 39 (44.8%) boys in the migraine group, 61 (60.4%) girls and 40 (39.6%) boys in the control group. The groups were similar in terms of sex (p= 0.554). The mean ages of the migraine group and control group were 15.16 ± 1.78 and 15.00 ± 1.78 and was not significantly different (p= 0.537).

In the migraine group 12 (13.8%) patients had migraine with aura. The median duration of the migraine was 12 (minimum:1, maximum: 84) months. Twenty-two patients (25.3%) in the migraine group had migraine attacks ≤ 1 per month; 22 (25.3%) had 2 or 3 attacks per month, and 43 (49.4) had 4 or more attacks per month (Table 1).

The corpus callosum measurements of the migraine and healthy control groups are summarized in Table 2. The mean genu and splenium width of the migraine group were significantly lower than the control group (p= 0.024 and p= 0.01 respectively). To examine the effect of migraine attack frequency on the CC measurements, additional analysis was done in the migraine group. Adolescents who had 4 or more attacks per month were compared to those who had ≤ 1 per month and 2 or 3 attacks per month. There was no statistically significant difference between the three groups in terms of CC AP length (p= 0.978), CC genu (p= 0.397), splenium (p= 0.979), and truncus (p= 0.439) in the Kruskal-Wallis test. There were no statistically significant relationships in Spearman's correlation test between disease duration and CC AP length, genu width,

truncus width or splenium width (r= -0.112, p= 0.301; r= 0.008, p= 0.942; r= -0.137, p= 0.207 and r= -0.125, p= 0.249 respectively).

To compare the CC measurements (AP length, truncus width, genu width and splenium width) between the groups of migraine with aura, migraine without aura and control groups, a one-way ANOVA test was conducted. There was a significant difference between 3 groups on CC splenium width [F(2, 185) = 11.833, p = 0.001] but there was no significant difference between 3 groups in terms of AP length, genu width and truncus width [F(2, 185) = 0.047, p = 0.954, F (2,185)= 2.619, p= 0.076 and F(2,185)= 0.401, p= 0.670 respectively]. Post-hoc comparisons were done for CC splenium using Bonferroni corrections. The mean score for CC splenium width of migraine without aura group (M= 8.827, SD= 1.279) was significantly different than the control group (M= 9.766, SD= 1.293). However, migraine with aura condition (M= 9.083, SD= 1.1816) did not significantly differ from migraine without aura and control groups.

4. Discussion

This study compared the morphological measurements of CC substructures of adolescents with migraine and a healthy control group from Turkey. As the structural alternations of brain in migraine patients provided insight to the pathophysiology of the disease in the last decades, our study adds new information to the literature by reporting that the mean genu and splenium width of CC of the adolescents with migraine were significantly lower than the healthy control group.

Migraine is a well-known risk factor for structural changes in brain [6]. However, literature on structural alternations of CC in childhood migraine is scarce. The first important finding of our study is that both CC splenium width and genu width were lower significantly in migraine group compared to control group in adolescence. The

CC has important roles in interhemispheric transfer and integration of motor and sensory information and inhibitory functions [18]. It may be speculated that decrease in width of CC splenium and genu may be secondary to very early anatomical progression of migraine during adolescence. Migraine's effect may cause atrophy of CC splenium which radiates to an adjacent structure, CC genu. Two recent case control studies with microstructural imaging support our morphological findings. In the study of Coppola et al [19] patients with migraine showed altered diffusion tensor imaging metrics in the genu and splenium of the CC. Another study on patients with trigeminal neuralgia the functional anisotropy of the genu (p= 0.04) and body (p= 001) of CC were found to be significantly decreased compared to the control group [20].

Case reports have shown that CC splenium has been affected temporarily by migraine attacks especially with aura [21,22]. This has been related to cytotoxic edema during the migraine attack [21]. Our results imply that even adolescents with migraine without aura differ significantly from the healthy control group regarding CC splenium measurements. However, in our study, there was no difference of CC splenium width between groups of migraine patients with aura and without aura despite the fact that children with migraine without aura had longer duration of migraine compared patients with aura. It is important that this study included only 12 children who had migraine with aura, so there is need for studies with higher sample size including migraine with and without aura to examine the difference.

Other important finding of our study was that CC measurements did not differ according to attack frequency groups significantly. Also, there was no correlation of disease duration with CC measurements. As the median duration of migraine is 12 months in our sample, our results must be interpreted with caution. Studies with longer

duration of migraine or longitudinal follow-up studies may display the dynamics of CC structures in childhood migraine.

This study has important limitations. The generalizability of our sample is low, as the sample is from the capital of Turkey. Cause and effect relationships cannot be made as the study is not in a prospective design. The measurements were held manually. The radiologist was not blind to the diagnosis. There was no interobserver and intraobserver reliability assessments. In spite of these limitations this study has important strengths. Childhood age group is a valuable group to show the first alternations in brain morphology in migraine. Our sample size was relatively large when compared to other pediatric studies conducted with lower number of children [8,16]. The control group was free of many health conditions that may be associated with structural CC abnormalities. We firstly addressed a broad range of information on comparison of specific CC parts' morphological measurements of adolescents with migraine and healthy adolescents.

The results of this study firstly demonstrated that CC splenium and genu widths were smaller in adolescents with migraine when compared to healthy adolescents. Our findings may contribute to enlighten the role of CC in migraine pathophysiology.

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Table 1. The characteristics of the sample

Characteristics	Migraine without aura group (n= 75)	Migraine with aura group (n= 12)	Control group (n= 101)
Sex (n,%)			
Female	41 (54.7)	7 (58.3)	61 (60.4)
Male	34 (45.3)	5 (41.7)	40 (39.6)
Age (mean± SD)	15.0 ± 1.8	16.1 ± 1.7	15.0 ± 1.8
Migraine duration as months (median, min-max)	12 (2-84)	24 (1-60)	
Frequency of attacks			
≤ 1 attack per month (n,%)	16 (21.3)	6 (50)	
2-3 attacks per month (n,%)	19 (25.3)	3 (25)	
≥ 4 attacks per month (n,%)	40 (53.3)	3 (25)	

Table 2. The measurements of corpus callosum anteroposterior length, genu, truncus, splenium widths in the migraine and the control groups

Measurements of CC * (Mean± SD)	Migraine group (n= 87)	Control group (n= 101)	p value
AP † length	6.68 ± 0.44	6.70 ± 4.67	0.785
Genu width	7.52 ± 1.15	8.07 ± 2.05	0.024
Truncus width	5.90 ± 0.84	5.80 ± 0.77	0.405
Splenium width	8.86 ± 1.26	9.77 ± 1.29	0.001

*CC: Corpus callosum, †AP: Anteroposterior

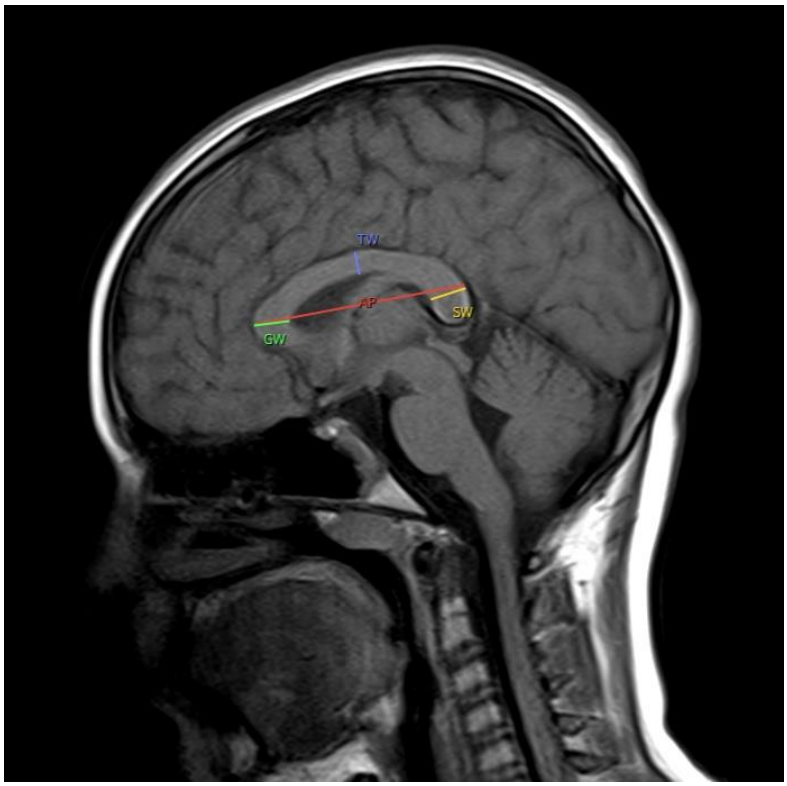

Figure. Midsagittal T1A magnetic resonance image demonstrating corpus callosum measurements of anteroposterior length (AP), genu width (GW), truncus width (TW) and splenium width (SW)