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RESEARCH ARTICLE

Evaluation of relationship between digit ratio (2D: 4D) and epilepsy: Can 2D:4D be a clue for epileptogenesis?

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ABSTRACT

Objective: The aim of the study was to investigate the possible association between the 2D:4D ratio and epilepsy in male and female adults, and to compare the ratios of epilepsy patients and healthy control subjects.

Patients and Methods: A case-control study carried out at a neurology and biophyiscs department in Ankara Yıldırım Beyazıt University, Faculty of Medicine from May 2016 to January 2017. The 2D:4D ratios of both the left and right hands of 172 epilepsy patients and 202 matched healthy controls were recorded. All participants also completed the Edinburgh handedness inventory.

Results: A significant positive correlation between the 2D:4D ratio and epilepsy was found for both females and males; a lower ratio for the left hand was associated with a higher possibility of epilepsy. In addition, a lower ratio in a specific hand was associated with that hand being used to complete the handedness test.

Conclusions: The 2D:4D ratio serves as a predictor for increased risk of epilepsy. Thus, it could be used as a marker to differentiate patients with epilepsy from healthy controls.

Key words: Digit ratio, 2D:4D, Edinburg handedness test, epilepsy, hand

INTRODUCTION

Epilepsy encompasses a group of chronic neurological disorders characterized by a wide range of seizures originating from the brain [1]. Known risk factors for the development of epilepsy are divided into two major categories: genetic sources and acquired risk factors such as brain tumors, trauma, stroke; however, in some cases the cause remains unknown [2].

The definition of symmetry is a similarity between two opposite halves or sides in size, shape, and position. While the human body is considered to be symmetrical from an external perspective, it is not perfectly so. For example, the right kidney is usually located lower in the abdomen than the left kidney. While the spleen lies on the left side of the abdominal cavity, the liver and gallbladder are on the right side. Moreover, the left laryngeal nerve arises from the thorax, whereas the right laryngeal nerve arises from the vagus nerve, and the straight sinus continues as the left transverse venous sinus, while the superior sagittal venous sinus continues as the right transverse venous sinus [3]. Furthermore, there are slight but important differences between the right and left brain hemispheres.

The human brain is functionally and morphologically asymmetrical. This asymmetry is reflected in handedness [4] and various diseases [5-8] which have been studied extensively in recent years.

Previous studies have investigated the ratio of the length of the second and fourth digits (2D:4D ratio) [9] in relation to autism [8, 10], homosexuality [11], heart disease [5], health [12, 13], speech [14], and components of reproductive success [15] which are all associated with levels of sex hormones [16]. However, no study has investigated the association of this ratio with epilepsy.

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Previous studies have reported correlations between this ratio and prenatal sex steroids as well as sex hormones including testosterone and estrogen [16, 17]. For instance, the development of the second digit is affected by estrogen levels, while that of the fourth digit is affected by testosterone levels [18, 19]. Hence, the sex-specific levels of testosterone and estrogen during the prenatal period significantly affect the 2D:4D ratio [16, 18].

We investigated the association between the 2D:4D ratio in patients with epilepsy and compared it with healthy controls, and determined the relationship between these variables and handedness.

PATIENTS AND METHODS

Subjects

In total, 172 (83 males and 89 females, mean age 37.01 years) patients with epilepsy from the neurology clinic of Ankara Yıldırım Beyazıt University, Faculty of Medicine and 202 (94 males, 108 females, mean age 36.91 years) healthy controls were included in this study. The length of the second and fourth digits on each patient's hand was measured and the 2D:4D ratio was calculated. This study was approved by the Ethics Committee of XXX. Written consents were obtained from every patient and healthy subject included in the study. Healthy controls are consistent with patient group according to age and gender. No malignancy, systemic disease and neurological disease were detected in healthy individuals in the control group and none of them had history of chronic drug use.

The participants' digit lengths were accurately measured using a digital caliper. The second and fourth digits of both the right and left hands were measured, from the proximal crease to the tip of the digit, and the 2D:4D ratio for each hand was calculated. Each measurement was taken twice for all participants. Individuals with hand trauma, edema, swelling, or an abscess were excluded.

Measurement of the 2D:4D ratio.

The participants' handedness was determined using the Edinburgh handedness inventory adapted by Geschwind and Behan [20]. This survey, which was translated into Turkish, included questions concerning the hand used to perform functions such as writing, eating, brushing teeth, opening cans, and so forth. Handedness was calculated using the following formula: [(right – left)/(right + left) × 100]. Positive values indicated right-handedness and negative values indicated left-handedness.

All statistical analyses were performed using the student's t-test. A p-value < 0.05 was considered to indicate statistical significance. Statistical Package for the Social Sciences 22.0 for Windows (IBM Corp., Armonk, NY) was used for statistical analyses

RESULTS

The handedness inventory revealed that 4.8%, 6.4%, and 88.7% of epilepsy patients were left-handed, bimanual, and right-handed, respectively. Of the control group, 5.7% of subjects were left-handed, 6.8% were bimanual, and 87.5% were right-handed.

The mean 2D:4D ratio for epilepsy patients was 0.97 (min, 0.89; max, 1.073; standard deviation [SD], 0.039) for the right hand and 0.89 (min, 0.89; max, 1.04; SD, 0.034) for the left hand, while that of healthy controls was 0.969 (min, 0.88; max, 1.07; SD, 0.04) for the right hand and 0.983 (min, 0.88; max, 1.1; SD, 0.04) for the left hand.

The mean 2D:4D ratio of the right hand of female epilepsy patients was 0.976 ± 0.040; however, that of the right hand of female control subjects was 0.971 ± 0.044. The mean ratio of the left hand of female epilepsy patients was 0.981 ± 0.037 and 0.982 ± 0.044 in female controls subjects (Table 1). Thus, there was a significant correlation between the ratios of the right (p = 0.047) and left (p = 0.026) hands in each group (Table 1).

The mean 2D:4D ratio of the right hand was 0.977 ± 0.040 in male epilepsy patients and 0.968 ± 0.037 in male controls. That of the left hand was 0.978 ± 0.033 in male epilepsy patients and 0.984 ± 0.037 in male controls (Table 2). Thus, there was a significant correlation between the ratios of the right (p = 0.027) and left (p = 0.045) hands in both groups (Table 2).

Table 1. Comparison of the mean 2D:4D ratios, standard deviations, and standard error of the mean for the left and right hands of female epilepsy patients and female control subjects

Hand	Participants	F	Mean 2D:4D	SD	SEM	p*
RH	PE	89	0.976	0.040	0.007	**0.047**
RH	HC	108	0.971	0.044	0.006	
LH	PE	89	0.981	0.037	0.007	**0.026**
LH	HC	108	0.982	0.044	0.006	

RH, right hand; LF, left hand; F, female; PE, patients with epilepsy; HC, healthy controls; SD, standard deviation; SEM, standard error of the mean. *Student's t-test

Table 2. Comparison of the mean 2D:4D ratios, standard deviations, and standard error of the mean for the left and right hands of male epilepsy patients and male control subjects

Hand	Participants	M	Mean 2D:4D	SD	SEM	p*
RH	PE	83	0.977	0.040	0.006	**0.027**
RH	HC	94	0.968	0.037	0.005	
LH	PE	83	0.978	0.033	0.005	**0.045**
LH	HC	94	0.984	0.037	0.005	

RH, right hand; LF, left hand; F, female; PE, patients with epilepsy; HC, healthy controls; SD, standard deviation; SEM, standard error of the mean. *Student's t-test

DISCUSSION

The 2D:4D ratio, which is affected by levels sex hormones during development, may be a possible indicator for epilepsy. Epileptogenesis is the gradual process of the brain becoming epileptic [2]. Sex hormones such as testosterone and estrogen play an important role in the underlying etiology of epilepsy and affect seizure activity in animal models [21, 22] and in humans [23-25]. However, many factors concerning epilepsy remain unknown, including the morphological status of patients with epilepsy. Therefore, we investigated the 2D:4D ratio as a morphological marker for patients with epilepsy, because during the prenatal period, exposure to sex hormones may affect the 2D:4D ratio of the embryo which does not change after week 14 of gestation [9, 19, 26]. In this study, we did not investigate levels of sex hormones as they are influenced by medications in many patients, and would therefore not yield meaningful results. We found no differences in the 2D:4D ratio between epilepsy patients. However, comparing epilepsy patients to control subjects, the ratio of the right hand was significantly higher and that of the left hand was significantly lower in epilepsy patients in both males and females.

Our results are similar to a previous study that measured the digit lengths of 240 healthy students [13]. Next, we used our values to investigate the correlation between the 2D:4D ratio and epilepsy.

Many diseases are associated with the 2D:4D ratio; however, each has a specific correlation that may depend on sex and handedness. Manning *et al.* measured the 2D:4D ratios of children with autism (n = 72), their parents (n = 88), and their siblings (n = 34), in addition to healthy sex- and age-matched control participants [8]. They found that children with autism had a lower mean ratio for both hands compared to the normal population. A study that investigated 50 autism patients and 53 controls indicated that the ratios of both hands were higher in the autism group for both females and males [10]. In contrast to these studies, we found that in epilepsy patients, both males and females had lower ratios compared to healthy controls. This distinction may help differentiate the ratios of patients with epilepsy and autism.

Trivers *et al.* conducted a longitudinal study (1998–2002) that investigated changes in the 2D:4D ratio of 108 Jamaican children [12]. They found that the ratio was stable and no significant changes occurred over time. These results indicate that there was no need to measure our patients' 2D:4D ratios during childhood because it remains constant and is a valid measure in epilepsy patients of all ages.

Fink *et al.* investigated the association between coronary heart disease and the 2D:4D ratio, neck circumference, waist and hip circumference, and body mass index in 117 female and 127 male participants [27]. They showed that a low ratio in the left hand was a potential indicator for heart disease in males. While we found a similar result in our study, we also found that the right hands of males had higher ratios in both males and females. Therefore, the characteristics of the 2D:4D ratio may be different for various diseases.

The results of the handedness test showed that approximately 88% of patients with epilepsy and healthy controls in our study were right-handed. The mean 2D:4D ratio was lower in the right hand than the left hand for right-handed participants. While it was expected that the ratio would be higher in the right hand than the left hand for left-handed participants, we were unable to accurately measure it because only 5% of the participants were left-handed.

Consequently, a high 2D:4D ratio in the right hand and a low 2D:4D ratio in the left hand may serve as a possible indicator of epilepsy. Moreover, it may also indicate an underlying genetic etiology of epilepsy, due to prenatal testosterone levels. Our study is important because this is the first study in the literature that evaluate the relation of 2D:4D digit ratio and epilepsy. Further multi-center and longutidinal studies are strongly needed to address this fundamental topic.

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