Pituitary gland size in temporal lobe epilepsy

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SUMMARY

Reproductive functional disorders and endocrine disorders are common in epileptic patients, particularly in patients with temporal lobe epilepsy (TLE). Pituitary size has been measured in patient populations with several diseases, but not in those with TLE so far. We compared the pituitary gland height and the morphology of its superior margin between patients with TLE and age- and sex- matched controls on magnetic resonance imaging (MRI). We found a smaller pituitary gland in patients with TLE compared to controls without any change of the morphology of its superior margin. The pituitary gland seems to be a site to check on MRI when evaluating a patient with TLE. The implications of this finding related to etiopathogenesis and clinical practice have been discussed.

Key words: Pituitary gland – Magnetic resonance imaging – Height – Temporal lobe epilepsy

INTRODUCTION

Epilepsy has been known since ancient times. It has been proposed that the word either was originated from a Greek word meaning “to seize” (Blair, 2012) or from Latin meaning “to take possession of” (Bromfield et al., 2006). Epilepsy is a heterogeneous common disorder of the central nervous system with recurrent seizures and accompanying different kinds of symptoms (Blair, 2012). The overall prevalence of epilepsy is approximately 6 per 1000 (Bromfield et al., 2006). Following the development of epileptogenesis, a normal network changes into a hyperexcitable network (Bromfield et al., 2006). Epilepsy has two main categories: partial and generalized, depending on the site of origin for the developing seizures. Temporal lobe epilepsy (TLE) is the most common type of partial type epilepsy (Bromfield et al., 2006).

Reproductive functional disorders and endocrine disorders are common in epileptic patients, particularly in patients with TLE in both genders (Herzog, 1989; Morris AND Vanderkolk, 2005; Fawley et al., 2006).

It has been reported that 14-20% of women with TLE had amenorrhea and that more than 50% overall have some form of menstrual dysfunction, and more than half of the men who have TLE suffer from diminished potency or altered sexual interest (Herzog, 1989).

The most common reproductive disorders in women with TLE are as follows: premature ovarian failure, functional hyperprolactinemia, polycystic ovary syndrome, and hypogonadotropic hypogonadism (Fawley et al., 2006). Although different mechanisms have been proposed for the co-morbidity of reproductive disorders and

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Submitted: February 17, 2021. **Accepted:** June 30, 2021

TLE, the exact mechanisms are unknown. It is, however, a fact that reproductive function is common in this patient population.

Pituitary gland height (PGH) has been investigated in several diseases out of distinct medical disciplines such as eating disorders (Doraiswamy et al., 1990), thalassemia major (Isik et al., 2014), growth hormone deficiency (Alba et al., 2004; Dumrongpisutikul et al., 2018), Chiari II malformation (Patel et al., 2020), idiopathic intracranial hypertension (Batur Caglayan et al., 2019), multiple sclerosis (Saba et al., 2017), hypopituitarism (Uday et al., 2017) and primary hypothyroidism (Zhang et al., 2012) on Magnetic Resonance Imaging (MRI). PGH represents a good single measure for the assessment of the size of the gland (Lurie et al., 1990), and has been used to evaluate its function (Argyropoulou et al., 2005). Pituitary size, however, has not been measured in patients with TLE so far. We compared the PGH and the morphology of its superior margin between patients with TLE and age- and sex- matched control group, hypothesizing that this gland can be abnormal, probably smaller, compared to the control group given that neuroendocrine symptomatology is common in this group of patients.

MATERIALS AND METHODS

We used a TLE patient group of 42 subjects (19 females; mean age=30.69, SD=13.34) and age-and-sex- matched control group of 42 subjects (mean age=31.09, SD 12.06). The control subjects of the study did not have any neurological or psychiatric disorders, and were not under any drugs, chemical substances (i.e. oral contraceptives for female subjects, cortisone etc.) affecting the morphology of the brain. None was using alcohol. PGH was measured on 1.5 T MRI unit (Magnetom Vision Plus, Siemens, Erlangen, Germany) at the midsagittal plane using T1 weighted spin echo (SE) sequence. PGH was assessed as the maximum distance between the upper margin and base of adenohypophysis perpendicular to the base of sella turcica (Elster et al, 1991). Measurements were performed with the sensitivity of 0.01 cm. In addition to PGH, we also rated the morphology of the superior margin of the gland from 0 through 5. (Elster et al, 1991); 1- concave superior margin; 2-mild concavity of the superior margin (below 2 mm); 3-a plain superior margin; 4-mild convexity of the superior margin (below 2 mm); 5-convex superior margin (Figs. 1, 2). These measurements were made by a neuroradiologist (B.H) and an anatomist (K.Y.) and

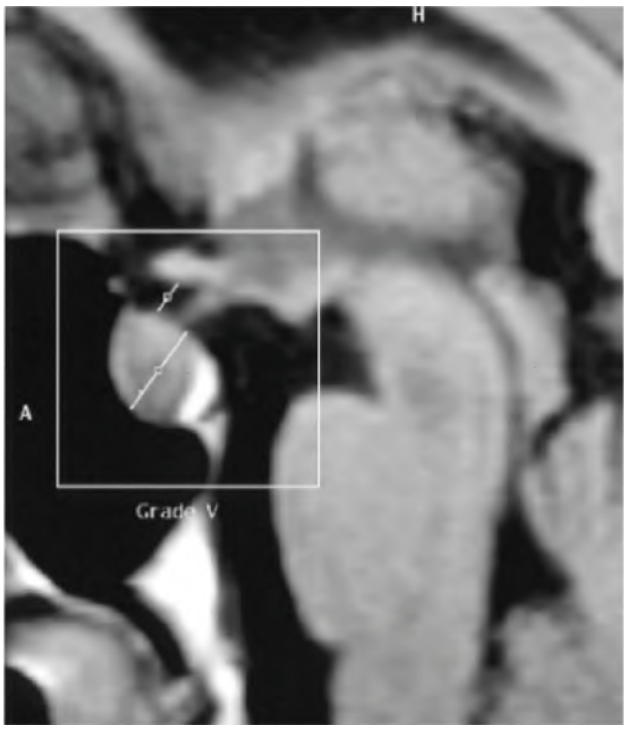

Fig. 1.- Pituitary gland - Grade V and measurement of PGH. The vertical line below in the figure refers to PGH measurement.

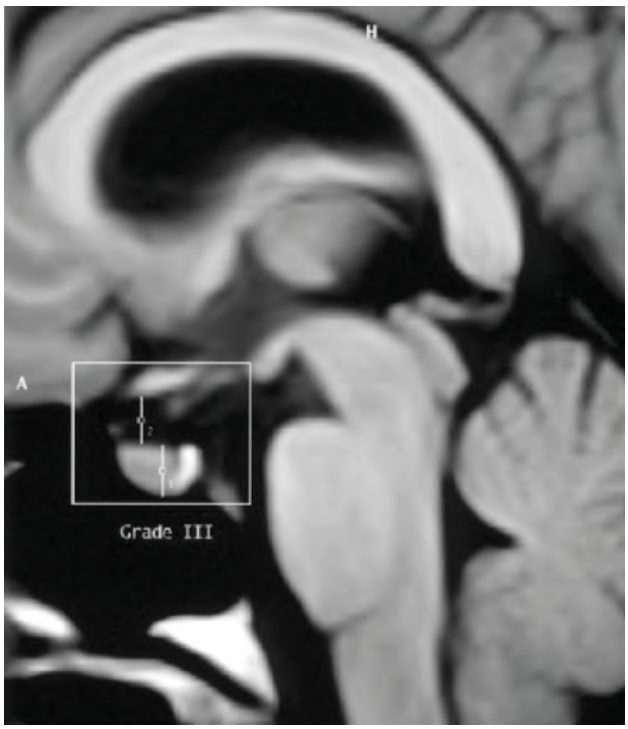

Fig. 2.- Pituitary gland - Grade III and measurement of PGH. The vertical line below in the figure refers to PGH measurement.

the consensus value was taken into consideration. For the statistical analysis Student's t- test, Pearson's correlation coefficient, Mann-Whitney test.

RESULTS

The mean duration of the illness was 14. 65 years (2-65 years), and the mean of the estimated number of the seizures per month was 5.44 seizures. The mean age of onset of epilepsy was 14.39 years (1- 62). There was no difference between male and female patients in terms of age at onset (mean=11.78, SD=14.08, for men and mean=17.5, SD=11.88 for women) and illness duration (mean=15.95, SD=12.40 for men, and mean=11.39, SD=7.2 for women) (ps=0.16). As a whole, TLE subjects had smaller PGH than their age-and-sex-matched controls (p=0.002) (Table 1). While male TLE subjects had a smaller pituitary gland than male control subjects (p<0.001), the size of pituitary glands of female TLE subjects did not differ from those of the female control subjects (p=0.41). There was no difference in PGH for the controls between two genders (p>0.05).

TLE and control groups had the similar means of ratings for the superior margin (p>0.05) (Table 1). When sexes were compared separately, both sexes in each group had the similar means of ratings for the superior margin (p>0.05). When patients with illness duration of more than 10 years (n=24) only were compared to controls, PGH was still smaller (p=0.001). When patients with illness duration equal to or less than 10 years (n=18) were compared to controls, the finding remained still significant (p=0.025).

There was no difference in the PGH between patients taking monotherapy (n=19) and polytherapy (n=23) (p>0.05).

DISCUSSION

In our preliminary study, we found a smaller pituitary gland in patients with TLE compared to age-and-sex-matched controls. The smaller PGH in epileptic patients was refined to male patients only, with no difference between female patients and female controls. Patients on monotherapy did not differ from patients on polytherapy for PGH measurements. We could not find a difference between patients and controls for ratings of the superior margin of the gland.

The association between epilepsy and reproductive disorders is unknown (Fawley et al., 2006). There are, however, several theories suggested so far, trying to explain the higher rate of endocrine disorders in patients with TLE. According to one of these theories, epileptic discharges in the limbic structures such as hippocampus might affect the pulsatile secretion of GnRH (gonadotropin releasing hormone) (Edwards et al., 2000). Hippocampus and cells related to reproductive function in the hypothalamus are highly connected. Therefore, the relation between epileptic discharges arising from hippocampus and hypothalamus seem to be mutual. Accordingly, reproductive disorders have been shown to effect the epileptic charges as well (Herzog, 1989).

The studies with animal models of epilepsy demonstrated hormonal fluctuations and change in the oestrus cycle following seizures (Amado and Cavalheiro, 1998).

Another theory that explained the relation between epilepsy and reproductive disorders was based on the effects of anti-epileptic drugs (particularly carbamezapine, barbiturates, and fenitoin) (Herzog,1989). Changes in testosterone (T)/luteinizing hormone (LH) ratio were reported in men with TLE compared to men with

Table 1. The comparison of the means of PGH (Pituitary gland height) and ratings of the superior margin in both groups.

Variable	TLE (n= 42)	Controls (n=42)	P value
PGH	0. 55 cm	0.66 cm	0.002
Rating of the superior margin	2.88	3.10	>0.05

extratemporal epilepsy as a result of antiepileptic drugs (Bauer et al., 2011). Serum estradiol and dehydroepiandrosterone sulfate (DHEAS) levels were found smaller in women with TLE when compared to those of the controls (Herzog et al., 2003). An inhibition on the pulsatile secretion of luteinizing hormone was considered as the effect of chronic epilepsy and the acute effects of seizures (Luef, 2010).

Antiepileptic drugs might cause imbalances in the endocrine system directly by affecting the serum levels of the hormones or indirectly affecting the neurotransmitter systems affecting the HPA axis such as GABA, glutamate. A common genetic background for TLE and endocrine disorders has also been suggested as a factor. According to this theory, TLE and associated reproductive endocrine disorders may represent the parallel effects of prenatal factors which are common to the development of both the brain and the reproductive system. A common neurotransmitter defect in both disorders has also been suggested to explain the higher rates of endocrine disorders seen in epileptic patients (Herzog, 1989).

Although our study design is cross-sectional, which can also be considered as a limitation, we found abnormal size of pituitary gland in TLE. As far as we know, this is the first study in the literature so far, in which pituitary gland size has been examined in this patient population.

In our structural MRI study, we were not able to find the reason(s) underlying this abnormality. Patients, however, receiving monotherapy and polytherapy at the time of the scan did not differ in PGH (data not shown). This might lead us to suggest that treatment with antiepileptic drugs contributed to a smaller pituitary gland. We, however, are aware that medication history of patients will be more critical at that point, rather than their current treatment, which we could not control in our cross-sectional study. A study in which pituitary gland size compared between those of patients with TLE who have been diagnosed recently and never treated before with those of age- and-gender-matched healthy controls would help answer the question of the effect of antiepileptic drugs on pituitary gland size in a better way.

We could not find a relation between illness duration and PGH. The pituitary gland might be smaller at the beginning of the disease process, or, alternatively, the reduction in the gland might occur in the first years of the disease following a plateau later. These suggestions are parallel to the theories of common genetic defect and effects of epileptic discharges, respectively.

We found smaller PGH in male epileptic patients only, but not in female patients. This might be due to a Type II error, as our female epileptic patient might not be representing the general population with common reproductive disorders. Alternatively, it might be the fact that the males be more vulnerable to the brain damage associated with epilepsy (Briellmann et al., 2000).

The most important limitation of the study is that we could not gather data on the profiles of the TLE patients on the existence of any reproductive disorder as they were undiagnosed for such a disorder. Although the reproductive disorders seem an important aspect of patients with TLE, it seems to be underdiagnosed and overlooked. New neuroimaging studies with TLE patients with and without reproductive disorders will better give us an idea about the pathogenesis of the comorbidity of these disorders, particularly considering the effects of treatment (untreated patients at the beginning of TLE vs. treated chronic patients).

As a conclusion, apart from changes in the volumes of hippocampus (Moghaddam et al., 2021; Riederer et al., 2020;Wu et al., 2020), amygdala (Sone et al., 2018; Na et al., 2020), thalamus (Wu et al., 2020), cerebellar vermis (Marcián et al., 2018), prefrontal cortex (Zhang et al., 2017), etc., change in the size of the pituitary gland should be added to the list of structures with morphometric changes seen in TLE patients as a result of epilepsy itself and treatment without any morphological changes of the superior margin of the gland. The pituiraty gland seems to be a site to check on MRI when evaluating a patient with TLE.

ACKNOWLEDGEMENTS

We are grateful to the MRI technicians at the Department of Radiology of Medical School of Uludag University for their time.

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