Original Article

Functional (Psychogenic) Seizures are Associated with Thyroid Disorders

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Abstract

Objective: We investigated medical comorbidities in patients with functional seizures (FS) and those with epilepsy (idiopathic generalized epilepsies [IGEs] or temporal lobe epilepsy [TLE]). We hypothesized that the nature of medical comorbidities differs between these three groups. This might be helpful to postulate on the pathophysiology of FS. **Materials and Methods:** In a retrospective study, all adult patients with a diagnosis of IGE, TLE, or FS were recruited at the outpatient epilepsy clinic at Shiraz University of Medical Sciences, Iran, from 2008 until 2020. The three groups of patients were matched with regard to their age. Age, sex, and medical comorbidities were registered routinely for all patients at the time of the first visit. **Results:** Nine hundred and sixty-six patients were studied (254 patients with IGE, 467 persons with TLE, and 245 individuals with FS). The groups differed significantly with regard to having medical comorbidities. The most striking difference was comorbid thyroid disorders; this was more common among patients with FS. The diagnosis of FS was independently significantly associated with thyroid disorder comorbidity (odds ratio: 2.77, 95% confidence interval: 1.06–7.23; $P = 0.038$). **Conclusion:** Thyroid disorders are significantly associated with FS. We can make the following suggestions to advance the field: a. It is necessary to reproduce this observation in larger multicenter studies; b. We recommend to evaluate thyroid function in all patients with FS; c. It might be helpful to design clinical trials to investigate whether correction of any clinical or subclinical thyroid disorders changes the treatment outcome in patients with FS.

Keywords: Comorbidity, epilepsy, psychogenic, psychogenic nonepileptic seizures, seizure

Introduction

Functional seizures (FS) or psychogenic nonepileptic seizures (PNES) are paroxysmal and self-limited events that superficially look like epileptic seizures, without ictal epileptiform discharges in electroencephalography.[1] These seizures are relatively common occurrences in epilepsy centers.[1] FS are often associated with psychiatric comorbidities.[2] A few studies have also investigated medical (somatic) comorbidities in this patient population.[3-8] Psychiatric and somatic comorbidities are also common in people with epilepsy.[9] However, epilepsy is not a single entity; various brain disorders may cause epileptic seizures.

The exact nature of the relationship between nonneurological medical (somatic) illnesses and brain (neuropsychiatric) disorders, including epilepsy or FS, is not clear. However, hypothetically, they could have a complex relationship. Medical (somatic) illnesses may contribute to the risk of developing brain disorders through biological mechanisms. For example, some noncentral nervous system disorders may affect the brain through immune-mediated mechanisms.[10] Therefore, it could be helpful to investigate medical comorbidities in patients with brain disorders, particularly in those with an unknown or unclear etiology (e.g., FS). In case of discovery of any striking medical comorbidity, new horizons may be opened into the clarification of the underpinnings and pathophysiology of such disorders, at least in some patients. On the other hand, being diagnosed

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with a medical illness could be a stressor for many people. In individuals with high biological susceptibility to stress-related pathology, even mildly stressful experiences may precipitate FS.[8]

In the current study, we investigated the known medical (somatic) comorbidities in patients with FS and also those with epilepsy (idiopathic [genetic] generalized epilepsies [IGEs] or temporal lobe epilepsy [TLE]). We hypothesized that these patients commonly have significant medical comorbidities, but the nature of medical comorbidities differs between these three groups of patients. This might be helpful to postulate on the pathophysiology and underpinnings of FS.

Materials and Methods

Participants

This was a retrospective chart review study. All adult patients (18 to 49 years of age at diagnosis) with an electroclinical diagnosis of IGE, TLE, or FS were recruited at the outpatient epilepsy clinic at Shiraz University of Medical Sciences, Shiraz, Iran, from 2008 until 2020. In people with FS, interictal EEG was normal and they had a confirmed diagnosis of FS by capturing their typical events under the video-EEG monitoring. Patients with comorbid seizure types (e.g., FS and epilepsy) were excluded.

Data collection

The three groups of patients were matched with regard to their age (as a significant factor in having medical comorbidities). Age, sex, and known medical comorbidities (self-declared; i.e., somatic problems that patients were aware of their presence) were registered routinely for all patients at the time of the first visit. Presence of medical comorbidities was inquired as a part of our structured interview with the patients; however, the history was not consolidated with other tests to confirm the diagnosis and the assessment did not include the follow-up information (comorbidities were reported at the time of diagnosis).

Statistical analyses

Values were presented as mean ± standard deviation for continuous variables and as number (percent) of subjects for categorical variables. Pearson's Chi-square test, one-way analysis of variance, and binary logistic regression test were used for statistical analyses. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. P <0.05 was considered statistically significant.

Standard protocol approvals, registrations, and patient consents

The Shiraz University of Medical Sciences Institutional Review Board approved this study (IR.SUMS.REC.1398.757).

Data availability statement

The data are confidential and will not be shared as per the regulations of Shiraz University of Medical Sciences.

Results

Nine hundred and sixty-six patients were studied (254 patients with IGE, 467 persons with TLE, and 245 individuals with FS). The mean age (± standard deviation) of the patients was 29 (± 7) years (28 ± 6 years in IGE, 29 ± 7 years in TLE, and 29 ± 7 years in FS; P = 0.053). The sex ratio was significantly different between the groups (female to male ratio: [152:102] in IGE, [223:244] in TLE, and [158:87] in FS; P = 0.0001, degree of freedom = 2]).

Table 1 shows the medical comorbidities in these three groups of patients. In total, 191 patients (19.8%) reported having any medical comorbidities. After an initial screening of the data and for the statistical purposes, we categorized the medical comorbidities into five groups: 1. cardiovascular (n = 65 patients): any heart problems, hypertension, lipid disorders, diabetes mellitus; 2. gastrointestinal (n = 15 patients): any gastric, hepatic, or intestinal disorders; 3. thyroid (n = 31 patients): hypo- or hyperthyroidism; 4. immunological (n = 27 patients): rheumatological or asthma; and 5. other (n = 53 patients). In case of multiple comorbidities, we arbitrarily adopted the following strategy to include each patient in one category only: immunological diseases had priority over others (one patient had both asthma and hypertension); thyroid disorders had priority over others (five patients had both thyroid and cardiovascular problems).

The groups (IGE *vs.* TLE *vs.* FS) differed significantly with regard to having medical comorbidities [Table 1]; patients with FS more frequently reported having medical comorbidities than others. The most striking difference was comorbid thyroid disorders; this was more common among patients with FS.

Since the sex ratio was significantly different between the groups (more women with FS) and also because thyroid disorders are generally more common among women in Iran and other places in the world,[11,12] we included these two variables (i.e., diagnosis and sex, as covariates) in regression analysis model to clarify the role of each variable in association

Table 1: Medical comorbidities in three groups of patients

	IGE (n=254), n (%)	TLE (n=467), n (%)	FS (n=245), n (%)	P
Cardiovascular	24 (9.4)	29 (6.2)	12 (4.9)	0.105
Gastrointestinal	4 (1.6)	10 (2.1)	1 (0.4)	0.206
Thyroid	6 (2.4)	9 (1.9)	16 (6.5)	<0.00001
Immunological	8 (3.2)	11 (2.4)	8 (3.3)	0.722
Other	15 (5.9)	17 (3.6)	21 (8.6)	0.021
Total	57 (22.4)	76 (16.3)	58 (23.7)	0.029

Cardiovascular=Any heart problems, hypertension, lipid disorders, diabetes mellitus, Gastrointestinal=Any gastric, hepatic, or intestinal disorders, Thyroid=Hypo - or hyperthyroidism, Immunological=Rheumatological, asthma, Degree of freedom=2 for all comparisons. IGE=Idiopathic generalized epilepsies, TLE=Temporal lobe epilepsy, FS=Functional seizures

with thyroid disorders (the dependent variable). The results of the binary logistic regression analysis showed a significant model ($P = 0.0001$), able to predict 96.8% of the patients with thyroid disorders (as a comorbidity). Sex was significantly associated with thyroid disorder comorbidity (OR: 5.11, 95% CI: 1.76–14.83; $P = 0.003$). However, the diagnosis of FS was also independently significantly associated with thyroid disorder comorbidity (OR: 2.77, 95% CI: 1.06–7.23; $P = 0.038$).

It is noteworthy to mention that the three groups were different with regard to their current medications (e.g., ethosuximide is never prescribed for focal epilepsies and phenytoin is not an ideal drug in IGEs; patients with FS should not receive any anti-seizure medications [but, about 60% of them do]). However, we did not collect such data to be objective.

Discussion

"Functional seizures" is a worldwide common phenomenon.[1] While there is an increasing evidence of abnormal brain function and connectivity in patients with FS, the neurobiological underpinnings of this common neuropsychiatric condition remain largely unclear yet.[13,14] In the current study, we observed that thyroid disorders are significantly associated with FS (odds ratio of 2.77 compared with that in people with epilepsy). Whereas we cannot establish a cause-and-effect relationship between thyroid disorders and FS based on the current study, this is an important observation for the following reasons.

Thyroid hormones have been implicated in multiple processes related to brain formation and development in mammals (e.g., neuronal progenitor proliferation, neuronal migration, and functional maturation).[15] The main mechanism of thyroid hormone action is modulation of the gene expression in target cells through the binding of T3 to specific nuclear thyroid hormone receptors.[16] Thyroid hormone receptor mutations have been linked to a range of behavioral and cognitive dysfunctions, including changes in sensory, attention, emotion, and memory functions.[15] Furthermore, a recent study identified the expression of thyroid-stimulating hormone receptors and thyroglobulin in the limbic regions of the adult human brain.[17] Limbic regions are normally involved in cognitive processes and emotional responses and dysfunction of the limbic regions is implicated in FS.[14] The amygdala shows high levels of thyroid hormone receptors; it is likely to be an important target region for thyroid hormone action.[16] Interestingly, hypothyroidism that is the most common hormonal disease in adults (as we also observed in the current study) is frequently accompanied by emotional disorders.[16] Hypothyroidism-induced inability to properly extinguish fear memories and the strong recall of these memories could increase the risk of pathological responses to traumatic experiences and resistance to their treatment.[16] For example, in patients with posttraumatic stress disorder (PTSD), abnormal thyroid hormone levels have been reported.[16] Finally, alterations in functional connectivity of resting state brain networks (a common observation in patients with FS[14]) have been associated with subclinical hypothyroidism in one study.[18] Our observation that thyroid disorders are strongly associated with FS as comorbidities corroborates that above observations and discussions very well.

Conclusion

While our study has some limitations (e.g., the self-declared nature of the inquiry of medical comorbidities that may underestimate the true frequencies of these problems and also the retrospective design that may cause recall bias), we can conclude that thyroid disorders are significantly associated with FS. Based on this significant observation, we can make the following suggestions to advance the field:

a. It is necessary to reproduce this observation in larger multicenter studies
b. We recommend to evaluate thyroid function in all patients with FS
c. It might be helpful to design clinical trials to investigate whether correction of any clinical or subclinical thyroid disorders changes the treatment outcome in patients with FS.

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Conflicts of interest

There are no conflicts of interest.

References

1. Asadi-Pooya AA, Sperling MR. Epidemiology of psychogenic non-epileptic seizures. Epilepsy Behav 2015;46:60-5.
2. Walsh S, Levita L, Reuber M. Comorbid depression and associated factors in PNES versus epilepsy: Systematic review and meta-analysis. Seizure 2018;60:44-56.
3. Asadi-Pooya AA, Homayoun M. Medical comorbidities in patients with psychogenic non-epileptic seizures (functional seizures). Neurol Sci 2020;41:2143-6.
4. de Wet CJ, Mellers JD, Gardner WN, Toone BK. Pseudoseizures and asthma. J Neurol Neurosurg Psychiatry 2003;74:639-41.
5. Asadi-Pooya AA, Rabiei AH, Tinker J, Tracy J. Review of systems questionnaire helps differentiate psychogenic nonepileptic seizures from epilepsy. J Clin Neurosci 2016;34:105-7.
6. Robles L, Chiang S, Haneef Z. Review-of-systems questionnaire as a predictive tool for psychogenic nonepileptic seizures. Epilepsy Behav 2015;45:151-4.
7. Dixit R, Popescu A, Bagić A, Ghearing G, Hendrickson R. Medical comorbidities in patients with Psychogenic Nonepileptic Spells (PNES) referred for video-EEG monitoring. Epilepsy Behav 2013;28:137-40.
8. Popkirov S, Asadi-Pooya AA, Duncan R, Gigineishvili D, Hingray C, Miguel Kanner A, *et al.* The aetiology of psychogenic non-epileptic seizures: Risk factors and comorbidities. Epileptic Disord 2019;21:529-47.
9. Guekht A. Epilepsy, comorbidities and treatments. Curr Pharm Des 2017;23:5702-26.

10. Menon V, Subramanian K, Thamizh JS. Psychiatric presentations heralding Hashimoto's encephalopathy: A systematic review and analysis of cases reported in literature. J Neurosci Rural Pract 2017;8:261-7.
11. Wouters HJ, Slagter SN, Muller Kobold AC, van der Klauw MM, Wolffenbuttel BH. Epidemiology of thyroid disorders in the Lifelines Cohort Study (the Netherlands). PLoS One 2020;15:e0242795.
12. Aminorroaya A, Meamar R, Amini M, Feizi A, Tabatabae A, Faghih Imani E. Incidence of thyroid dysfunction in an Iranian adult population: The predictor role of thyroid autoantibodies: Results from a prospective population-based cohort study. Eur J Med Res 2017;22:21.
13. Allendorfer JB, Nenert R, Hernando KA, DeWolfe JL, Pati S, Thomas AE, *et al.* FMRI response to acute psychological stress differentiates patients with psychogenic non-epileptic seizures from healthy controls – A biochemical and neuroimaging biomarker study. Neuroimage Clin 2019;24:101967.
14. Asadi-Pooya AA. Neurobiological origin of psychogenic nonepileptic seizures: A review of imaging studies. Epilepsy Behav 2015;52:256-9.
15. Stepien BK, Huttner WB. Transport, metabolism, and function of thyroid hormones in the developing mammalian brain. Front Endocrinol (Lausanne) 2019;10:209.
16. Montero-Pedrazuela A, Fernández-Lamo I, Alieva M, Pereda-Pérez I, Venero C, Guadaño-Ferraz A. Adult-onset hypothyroidism enhances fear memory and upregulates mineralocorticoid and glucocorticoid receptors in the amygdala. PLoS One 2011;6:e26582.
17. Naicker M, Naidoo S. Expression of thyroid-stimulating hormone receptors and thyroglobulin in limbic regions in the adult human brain. Metab Brain Dis 2018;33:481-9.
18. Kumar M, Modi S, Rana P, Kumar P, Kanwar R, Sekhri T, *et al.* Alteration in intrinsic and extrinsic functional connectivity of resting state networks associated with subclinical hypothyroid. J Neuroendocrinol 2018;30: e12587. https://doi.org/10.1111/jne.12587.