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Brief Communication

Hypermobility in patients with functional seizures: Toward a pathobiological understanding of complex conditions

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ABSTRACT

Background: Functional seizures (FS), otherwise known as psychogenic nonepileptic seizures (PNES), are a common symptom presenting to neurology and epilepsy clinics. There is a pressing need for further research to understand the neurobiology of FS to develop mechanistically targeted treatments. Joint hypermobility is an expression of variation in connective tissue structure along a spectrum, and it has received increasing attention in functional neurological disorders, but there is lack of evidence of its relevance in FS.

Methods: In the present study, forty-two patients with FS and a non-clinical comparison group of 34 age/sex-matched controls were recruited. Joint hypermobility of all participants was quantified using the Beighton scale.

Results: In our sample, 24 (57%) patients with FS, and 7 (21%) of the comparison group met criteria for joint hypermobility ($p = 0.002$). Our statistical model revealed that patients with FS showed a significant degree of hypermobility compared to the comparison group (odds ratio = 11.1; Confidence interval: 2.1–78.0, $p = 0.008$), even after controlling age, sex, anxiety, and depression.

Conclusion: We found a significant association between FS and joint hypermobility, which was independent of anxiety and depression.

1. Introduction

Functional seizures (FS), otherwise known as psychogenic nonepileptic seizures (PNES), are a common symptom presenting to neurology and epilepsy clinics. They are paroxysmal episodes of altered awareness, resembling epileptic seizures or syncope. However, they are not explained by these or other medical disorders, and are not associated with epileptiform brain discharges. Prevalence estimates range between 2 and 50/100,000 and in the UK the annual incidence is estimated at 4·9/100,000 [1]. Approximately 20% of patients referred to tertiary epilepsy services with seizures have FS, and recent status epilepticus trials show that 8% of patients treated for status actually have FS [2,3]. Functional seizures are also associated with elevated morbidity and mortality rates, and engender significant health economic costs. One of the current treatments for FS is cognitive behavioral treatment (CBT), based on a fear avoidance model. However, this treatment is not widely available, and a recent multicenter trial in patients with FS compared CBT to standardized medical care demonstrated no difference in the primary outcome measure of seizure frequency, though there was some improvement in secondary outcomes [4]. There is therefore a pressing need for further research to understand the neurobiology of FS to develop mechanistically targeted treatments. However, to date, most research has focused on the putative psychological causes and comorbidities of FS such as anxiety, depression, and somatoform disorders, thereby engraining Cartesian dualistic approaches to patients with this condition. Nevertheless, FS lie at the diagnostic interface of neurology and psychiatry, and research should therefore encompass a holistic, cognitive neuroscientific approach to these embodied symptoms. Indeed,

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this approach is reflected in recent, expert led reviews of the potential mechanisms underlying FS [5]. However, one factor that has been neglected in these reviews is joint hypermobility, which has been shown to be associated with several neuropsychiatric disorders [6,7].

Joint hypermobility is an expression of variation in connective tissue structure along a spectrum that, at its extreme, includes disorders such as Ehlers–Danlos syndrome and Marfan syndrome. The connective tissue anomalies characteristic of joint hypermobility (e.g., collagen) causes both articular symptoms (including laxity and pain) and also extra-articular symptoms, such as fatigue, anxiety, gastrointestinal disorders, orthostatic intolerance, and pelvic and bladder dysfunction [2]. In western countries, the estimated prevalence of hypermobility is 10–20% with higher rates in younger and female populations [6]. In patients with functional neurological disorder, only fixed dystonia has previously been robustly associated with higher rates of hypermobility compared to the general population [8]. A recent service evaluation of a functional neurological disorder (FND) clinic reported that 21% of patients, including seven with FS had associated hypermobility [9]. However, this study was based on clinical data recorded in the medical history of patients suggestive of *potential* joint hypermobility or a prior history of two or more recurrent joint dislocations, and not direct clinical assessments. We have previously also demonstrated that patients with FS, compared to healthy controls, manifest interoceptive abnormalities that predict symptom severity, even after controlling for comorbid anxiety and depression [10]. Joint hypermobility itself is associated with interoceptive differences [7], and may therefore be implicated in the etiology of FS. We therefore investigated the degree of hypermobility, using direct clinical assessments, in patients with FS, compared to an age- and sex-matched control group. The research governance sponsoring committee of Fulham, London Health Research Authority approved the study protocol (IRAS 231863, REC 18/LO/0328). The study was conducted in accordance with the ethical guidelines set forth by the Declaration of Helsinki.

2. Methods

Forty-two consecutive patients with FS (age: 32.8 ± 11.7, female = 40) and a non-clinical comparison group of 34 age/sex-matched controls (age: 33.4 ± 12.2, female = 31) were recruited sequentially in a tertiary neuroscience center. The diagnosis of FS was made according to International League Against Epilepsy diagnostic criteria by at least two clinicians experienced in the diagnosis of epilepsy, and were documented ($n = 22$), clinically established ($n = 11$), or probable ($n = 9$) cases. Participants in the non-clinical comparison group were recruited by way of advertisements placed at St George's University/Hospital. All participants gave informed consent for the study. Joint hypermobility of all participants was quantified using the Beighton scale (BS) [11]. This scale ranges from 0 to 9, and consists of the following assessments: Hyperextension of the fifth finger (right/left), apposition of the thumb against the forearm (right/left), hyperextension of the elbows (right/left), hyperextension of the knees (right/left), increased forward flexion of the trunk. The widely used cutoff of $\geq$4 was used in the present study. In addition, anxiety and depression were assessed using the State-Trait Anxiety Inventory (STAI)-Trait, and the Beck Depression Inventory (BDI). A generalized linear model was applied in data analyses, whereby the presence of hypermobility was a dependent variable and age, sex, group, depression, and anxiety score were independent variables. Here, given the STAI-Trait and the BDI score deviated from normal distribution, the scores were compared between groups using non-parametric tests and were also categorized into presence of anxiety and depression or not based on the manuals of STAI and BDI in our model.

3. Results

In our sample, 24 (57%) patients with FS, and 7 (21%) of the comparison group met criteria for joint hypermobility ($p = 0.002$). Patients with FS reported lower levels of education (mean ± standard deviation: 15.2 ± 4.4, 17.9 ± 3.3, $p = 0.005$), higher body mass index (27.5 ± 7.4, 22.6 ± 4.7, $p = 0.005$), and greater levels of anxiety (median [interquartile range]: 43 [20.5], 28.5 [8], $p < 0.001$) and depression (19 [18], 2.5 [5.75], $p < 0.001$) than the comparison group. Here, 20 (48%) patients with FS, and 2 (6%) of the comparison group showed anxiety based on STAI-Trait, and 32 (76%) patients with FS (mild:7, borderline:5, moderate:8, severe:7, and extreme:5), and 1 (3%) of the comparison group (mild:1) showed depression based on BDI.

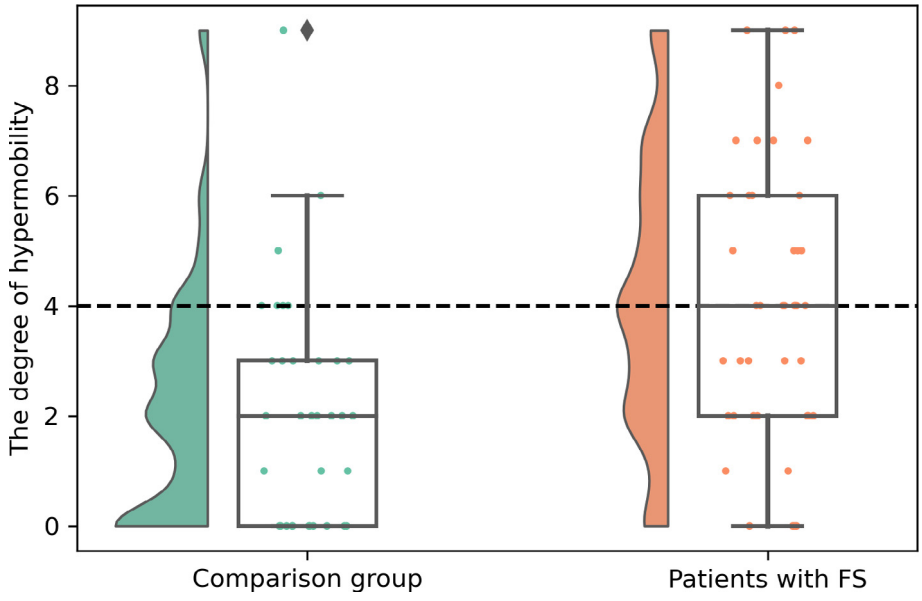

Fig. 1. Patients with functional seizures showed significant degree of joint hypermobility ($p < 0.001$) compared to the comparison group even after controlling age, sex, anxiety, and depression.

Our generalized linear model revealed that hypermobility defined with the Beighton scale was significantly more frequently observed in patients with FS compared to the comparison group (odds ratio = 11.1; Confidence interval: 2.1–78.0, $p = 0.008$), even after controlling age, sex, education, BMI, anxiety, and depression ($p = 0.245$, 0.609, 0.332, 0.236, 0.607 and 0.417, respectively). That is, hypermobility was significantly associated with FS and the association was independent of their anxiety, depression, and other potential confounding factors (Fig. 1).

4. Discussion

Notwithstanding the selective nature of our study population based in a tertiary center, our results suggest that joint hypermobility is more frequently observed in patients with FS compared to a non-clinical comparison group. Because our study participants contained significantly more women, the prevalence was higher in the comparison group compared to general population, and the prevalence among patients with FS was much higher still. Our results remained significant even after controlling for anxiety and depression, consistent with the view that joint hypermobility itself is an independent likelihood factor for FS, highlighting the need for novel diagnostic and therapeutic avenues. We propose that differences in autonomic control, interoception, and brain structure, associated with joint hypermobility [6,7,12,13], may predispose patients to FS. However, further research is required to replicate these results in a community-based sample, and further understand the treatment-relevant mechanisms that may underlie this relationship. In doing so, it may be possible to develop novel screening strategies and targeted therapies for these patients.

There are several limitations to this study. Firstly, our examination was not blinded to whether examinee came from the FS or comparison group. Although we were well aware of the risk of bias based on unblinded examination, and performed a very careful assessment to mitigate the risk, this risk cannot be completely avoided. Secondly, other potential confounding factors, such as occupation and chronic illnesses, were not analyzed because of lack of information.

In conclusion, we found a significant association between FS and joint hypermobility, which was independent of anxiety and depression. Further research is required to investigate the factors mediating the relationship between joint hypermobility and FS.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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