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Functional seizures are not less important than epilepsy

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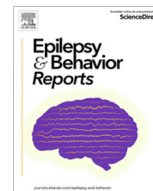
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Functional seizures are not less important than epilepsy

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ABSTRACT

Functional seizures (FS) are frequently encountered in neurology clinics, often affect young adults, and have significant negative impacts on many aspects of a person's life. In the current narrative review, we searched the literature regarding some of the consequences of FS (i.e., psychiatric comorbidities, social consequences, costs that are associated with the condition, cognitive impairment in patients with FS, the quality of life of the people with FS, and the increased risk of mortality that is associated with FS). Evidence shows that FS have significant negative consequences, comparable in their magnitude to those affecting patients with epilepsy. The clinical and scientific communities should take steps to address these consequences through clinical care and research that prioritizes, facilitates, and expedites evidence-based diagnosis and treatment for FS.

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1. Introduction

Functional seizures (FS), also known as psychogenic nonepileptic seizures (PNES) or dissociative seizures (DS), are characterized by paroxysmal events that semiologically may look like

epileptic seizures, but are not due to an underlying epileptic activity. Hence, the electroencephalogram does not show ictal epileptiform discharges. FS are instead thought to be caused by a complex set of interrelated psychological, social, and biological factors, and are often associated with psychological stressors [1,2]. This condition is frequently encountered in neurology clinics [3], often affects young adults and has significant effects on many aspects of a person's life [4].

In the current narrative review, we searched the literature regarding some of the consequences of FS, including psychiatric comorbidities, social consequences, financial costs associated with the condition, quality of life of the patients, and the increased risk of mortality that is associated with FS. We aimed to highlight and underscore the significance of FS in a concise and evidence-based manner.

2. Psychiatric comorbidities

People with FS are at higher risk for psychiatric comorbidities compared to the general population; this is comparable with that in the people with epilepsy [5–7]. Co-existing psychiatric disorders have a complex and intricate relationship with FS. They may represent a predisposing risk factor, a precipitant, an underlying cause, or a consequence of this chronic and disabling disorder [5–7]. While there are many similarities between patients with FS and those with functional movement disorders [8], people with FS have greater levels of depressive and anxiety symptoms, more frequent history of sexual abuse, greater levels of alexithymia, higher levels of dissociative symptoms, and distressing traumatic events occurring at an earlier age compared to those in people with functional movement disorders [9].

Depression is the most common psychiatric disorder among people with FS, with an average prevalence of 31% and cumulative lifetime rates ranging from 36% to 80% [6,10]. Depression occurs more often among people with FS than in the general population [11] or among people with epilepsy [10,12]. Remarkably, people with FS may not show the spectrum of symptoms that are typically associated with clinical depression. In a systematic review conducted by Walsh and colleagues [10], five studies used the Personality Assessment Index and showed that people with FS reported more physical difficulties than people with epilepsy. Therefore, people with FS may more frequently experience and report physical symptoms of depression and somatic expressions of distress rather than the cognitive or emotional aspects of depression; this may lead clinicians to overlook depression in this patient population [10,13]. Furthermore, depression may explain more variation in quality-of-life inventories among people with FS than seizure-related factors [14,15]. Depression may also predict the level of dysfunction experienced by these patients [12,14–18].

The prevalence of anxiety disorder among people with FS differs significantly in various studies (from 9% to 71%), because of the different methodologies and also the complexity of the clinical presentations of anxiety disorders (e.g., panic attacks, generalized anxiety disorder) [7]. In a systematic review and meta-analysis, the reported rate of panic attacks in FS ranged from 17% to 83%, with physical symptoms more commonly reported, and affective symptoms less so. 'Dizziness or light-headedness' was more frequent than 'fear of dying' in people with FS (68% vs. 23%) [19]. Of note, panic may play a role in FS characteristics as a response to heightened arousal in the absence of raised anxiety levels [20]. The increased autonomic arousal in FS [21] and the use of hyperventilation – a cardinal feature of panic attacks – to provoke FS support this hypothesis [22].

People with FS report higher rates of early life traumatic experiences than people with drug-resistant epilepsy [23]. Since

trauma plays an important etiological role in many cases of FS, it is not surprising that the prevalence of post-traumatic stress disorder (PTSD) among people with FS is high, ranging from 38% to 64% [24,25]. People with FS who had experienced traumatic events especially in their childhood tend to present more dissociative experiences, more psychiatric comorbidities (i.e., depression and anxiety), and a lower quality of life than those without a history of traumatic experiences [26–28].

People with FS may also suffer from comorbid personality disorders (e.g., borderline personality disorder) [11] and increased rates of suicide [29]. Neurologists must be aware of these patients' characteristics to provide support after the diagnosis of FS is made, preventing the devastating and at times fatal outcomes that may be associated with this condition (e.g., injuries, social problems, suicide, etc.). Beyond the direct consequences of FS, psychiatric comorbidities may impair the patients' functioning. Therefore, the added consequences of these comorbidities must be promptly recognized and treated as a priority to improve the quality of life of the people with FS.

3. Social consequences

Across nations and cultures, people who suffer from FS, continue to report detrimental effects on social aspects of their lives [4,30]. Studies have shown that across different nations and continents, people with FS have low rates of employment (approximately 1 in 3) and high rates of dependence on state-provided disability payments (where they are available to them) compared with the general populations [31–33]. The partners of people with FS may also experience higher rates of underemployment and social transfer payments than matched controls [4]. In addition, only a minority (about one-fifth) of adults with FS reported driving a motor vehicle in their routine daily lives [34] and driving restriction is a commonly endorsed barrier to socializing and accessing healthcare by these patients [35]. Furthermore, learning problems and educational difficulties are common among people with FS [36–38]. The associations between FS and education have been interpreted in two ways: 1) educational problems and learning disabilities may interact with other risk factors (e.g., adverse childhood experiences) to increase the risk for development of FS, and 2) reduced educational achievement may result from the onset of FS [39]. Finally, people with FS may experience problems in their marriage quality and marital outcomes [39,40].

Social aspects of life are important determinants of health and quality of life (QOL). Therefore, since FS have debilitating effects on patients' lives, they are frequently associated with a decreased QOL in these patients [39], even worse than that in people with epilepsy [14,41,42]. In addition, the caregivers' QOL scores in people with FS are comparable to those of caregivers for people with epilepsy [43]. Also, the employment rates, educational levels, driving rates, and marital status of people with FS are comparable with those in people with epilepsy (or may even be worse in people with FS) [14,39,40,43,44]. In brief, the detrimental social effects and burden of FS on individual patients, their caregivers, and the society at large, are comparable to those in people with epilepsy. We should emphasize that some of these detrimental social effects of FS may be inevitable in the light of the regulations or the greater societal good that needs to be placed over the good and well-being of an individual (e.g., driving restrictions). These issues should be addressed in future studies.

4. Impaired cognition

Mood and objective cognitive function are both important contributors to subjective cognitive function [45]. While people with

FS may complaint from impaired cognition (more than that by healthy controls), their cognitive impairment is usually not as bad as that in patients with epilepsy [46–48]. Nonetheless, cognitive impairment in patients with FS have potentially important clinical implications [49]. Cognitive impairment may lower the ability of patients to process and adjust to their emotional states appropriately [50]. In one study, people with FS showed improved cognition at one year of follow-up, particularly in language and executive functions. This implies the potential benefits of an early and accurate diagnosis, which may range from improved cognition to better management [48]. Cognitive function should be evaluated in all patients with FS and cognitive impairment should be considered in planning the neuropsychological rehabilitation of these patients [49].

5. Costs

Before the correct diagnosis has been established, people with FS usually receive treatment with antiseizure medications (ASMs) resulting in higher health care utilization and costs [51]. Multiple visits to the emergency departments, hospital admissions, outpatient visits, and extensive, repetitive, and often unnecessary diagnostic investigations (EEG, neuroimaging, and laboratory blood tests) can further increase the direct costs related to FS. In one study, the health care utilization and costs prior to and after the diagnosis of FS were calculated. The cost associated with FS during 12 months before the diagnosis was $\$4567 \pm \4329 USD per person; this cost was $\$2783 \pm \3404 USD during 12 months after the diagnosis (a reduction of nearly $\$1800$ per person) [51]. A small but rapidly growing body of studies have evaluated the economic impacts on health resource utilization and costs that are associated with FS [51–55]. These studies generally utilized retrospective designs with different study periods and evaluating various outcomes. The comparability of the results across these studies is hampered by the differences in itemization and calculation of the costs, healthcare systems, and temporal variability of the costs [55]. Despite these limitations, resource utilization cost studies have shown that FS represent a considerable source of healthcare costs [51–55]. The higher resource utilization is mainly related to a longer duration of FS due to misdiagnosis or delayed diagnosis. All studies in this field have consistently shown that ensuring confirmation of FS by video-EEG monitoring significantly reduces the costs associated with erroneous or delayed diagnosis of the condition [54–56].

Remarkably, most studies have focused on the direct costs that are associated with FS (i.e., healthcare resource utilizations, including hospitalization, outpatient visits, diagnostic investigations, physiotherapy, and use of medications). Only one study investigated the (indirect) social costs, related to welfare benefits and reduced work productivity with consequent loss of market income [4]. People with FS and their partners received welfare benefits (including subsistence allowances, disability pensions, social security and assistance) more frequently than controls. Furthermore, people with FS had lower levels of employment and lower earned income up to three years before the diagnosis [4].

Overall, there is consistent evidence from the literature indicating that FS are associated with a considerable direct and indirect economic burden on the health care systems, comparable to that associated with drug-resistant epilepsy [55]. Establishing an early diagnosis strategy is effective in minimizing undue healthcare resource utilization, and health and social costs. Although one preliminary study showed that intensive short-term dynamic psychotherapy can be cost-effective [57], further studies to evaluate the impact on healthcare costs of specific treatments for FS are required.

6. Quality of life

Functional seizures often have debilitating effects on patients' lives. A systematic review of health-related quality of life (QOL) in adults with FS concluded that the majority of studies on this issue were cross-sectional and of weak to moderate quality (14 articles were included for the review in 2015) [58]. However, there is consensus that many patients with FS have impaired QOL (comparable to those with epilepsy) [59,60]. In a recent study, the investigators observed more psychiatric comorbidities with poorer QOL in people with FS compared with those in patients with drug-resistant epilepsy [61]; this corroborates another recent study in which the authors observed that people with FS scored significantly higher in anxiety and depression scales and had lower levels of QOL compared with patients with epilepsy [42]. Other similar studies have provided the same evidence (of a poorer QOL in people with FS compared with that in patients with epilepsy) [62]. Depression (the strongest correlate), dissociation, somatic symptoms, impaired cognition, and family dysfunction are often negatively associated with health-related QOL in people with FS [41,58,63].

In clinical practice, outcome of FS is usually discussed in terms of seizure reduction; however, the relevance of FS reduction to QOL improvement is questionable [41,58]. Psychological and interpersonal factors are more importantly related with the QOL and these issues should be considered in the management process of people with FS [58]. The current existing evidence strongly suggests that mental health care may improve the QOL of people with FS [64].

7. Mortality

FS are known to be highly disabling [58]. There is now an emerging body of evidence suggesting that people with FS also have increased rates of mortality compared to healthy controls; this rate is comparable to mortality rates among people with epilepsy [4,65,66].

Historically, clinicians have documented numerous individual cases of iatrogenic mortality resulting from efforts to treat prolonged episodes of FS in emergency departments or hospitals [67–69]. In 2012, Duncan et al. systematically examined mortality rates among people with FS for the first time, comparing “premature” mortality (death prior to the age of 75) among 260 people diagnosed with FS in Scotland, to the rate of premature mortality in the general Scottish population [65]. They found a significantly elevated rate of premature mortality of 0.58% annually, compared to 0.41% annually in the general population [65]. Jennum et al. identified a cohort of all 1057 people receiving a first diagnosis of FS from 2011–2016 in the Danish National Patient Registry and compared them to 2113 controls matched by age, gender, and geography [4]. They conducted a Cox proportional hazard ratio estimate and found a mortality hazard ratio of 3.21 (95% confidence interval 1.92–5.34) for people with FS [4]. In 2020 Night-scales et al. conducted a study of 674 Australian patients diagnosed with FS through video-EEG monitoring, 3064 patients diagnosed with epilepsy alone, and 175 patients diagnosed with both conditions [66]. They calculated standardized mortality ratios for each cohort by comparing mortality rates to age-, sex-, and year-specific mortality rates for the general Australian population. Overall, mortality was 2.5 times greater in the FS group than in the general population (95% confidence interval 2.0–3.3), which was not significantly different from the elevated mortality seen in the epilepsy group (standardized mortality ratio 3.3) or in the comorbid FS + epilepsy group (standardized mortality ratio 3.7). Mortality rates were especially elevated in young adults (aged 18–29) with FS, with mortality 8.6 times greater than in the young

adult general population [57]. Patients with a history of substance use disorder also had a 2.5-fold increased risk of death compared to those without. Additional psychiatric comorbidities other than substance use disorders did not further elevate the risk of mortality among people with FS [66].

The elevated mortality rate seen in Nightscales' Australian cohort [66] closely matched the elevated rate seen in Jennum's Dutch cohort [4], and Nightscales et al. expanded their analysis by reviewing causes of mortality listed by the Australian Institute of Health and Welfare. The leading causes of death among their people with FS included "epilepsy" (24%), malignancy (18%), cardiovascular disease (16%), accidental poisoning (9%), respiratory disease (7%), and suicide (7%). The fact that "epilepsy" was identified as a leading cause of death among people with FS does raise the possibility of undiagnosed comorbid epilepsy among some of the patients diagnosed with FS, although no evidence of comorbid epilepsy was found on re-review of the records of those patients who died of "epilepsy." Other possible explanations of these deaths might include epileptic seizures provoked by drugs or alcohol, or iatrogenic death caused by efforts to control prolonged episodes of functional seizures. Even excluding all deaths attributed to "epilepsy," the patients diagnosed with FS still experienced mortality more than twice that of the general population [66].

In summary, multiple studies conducted across different nations and continents have consistently demonstrated elevated mortality rates among people with FS, comparable to the elevated rates of mortality among those with epilepsy. Risk of mortality may be particularly increased relative to the general population among younger individuals, and among those with a history of substance use disorder. Common causes of death include medical illnesses such as malignancy, cardiovascular and respiratory illness, as well as self-injurious behaviors such as suicide. The growing evidence of increased mortality among people with FS should motivate neurologists and psychiatrists to prioritize evidence-based diagnosis and treatment for FS.

8. Conclusion

Functional seizures incur significant negative consequences upon patients, including psychiatric comorbidities, social consequences, financial costs, impaired QOL, and increased risk of mortality. These negative impacts are comparable in their magnitude to those affecting people with epilepsy. The clinical and scientific communities should take steps to address these negative consequences through clinical care and research that prioritizes, facilitates, and expedites evidence-based diagnosis and treatment for FS. It is also important for the scientific community to investigate the timing of these consequences and associations and their temporal relationships with the onset of FS and the diagnosis of FS in future studies.

Contributions

All authors: Study design, data collection, manuscript preparation.

Disclosures

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Data availability

Not applicable.

Ethical statement

Not applicable.

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