

Depression and anxiety in people with epilepsy: Why should we identify?

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SUMMARY

Introduction. People with epilepsy (PWE) have a higher risk of developing depression and anxiety than people without epilepsy. However, understanding and management of that issue remain under-recognized.

Aim. To emphasize: a) the relationship between depression, anxiety, and epilepsy, and b) to suggest practical strategies for their identification by clinicians.

Methods. The current literatures was reviewed investigating the impact of depression and anxiety in PWE and those examining the validity of simple screening tools for the detection of depression and anxiety.

Review. Approximately one quarter of PWE have been known to be suffered from depression. The frequency of depression and anxiety was closely related to poor seizure control. Depression and anxiety have been reported to have a bidirectional relationship with epilepsy. The higher degree of depression and anxiety was more likely to elicit the suicidal ideation and attempt, adverse events and poor compliance of antiepileptic drugs, poor surgical outcome, and eventually, poor quality of life. Furthermore, depression and anxiety were closely associated with perceived stigma, obsessive-compulsive symptom, aggression, fatigue, and perceived stress.

Conclusions. Clinicians who take care of PWE in a busy clinical setting should identify their psychiatric problems by brief screening tools and treat them instantly to minimize their negative impacts.

Key words: epilepsy • depression • anxiety • impact • screening

INTRODUCTION

The comorbid psychiatric disorders in people with epilepsy (PWE) have been neglected for a long time. Psychiatric co-morbidities have not been a focus in the field of epilepsy research and management, although many recent epidemiological studies have found a high prevalence of depression and anxiety in PWE. For example, in a meta-analysis of 9 population-based studies, the prevalence of active depression in PWE was 24% (Fiest et al., 2013). Its prevalence is almost the same with the prevalence of drug-refractory epilepsy (25%) in a long-term observational study of 1,098 patients with new-

ly diagnosed epilepsy in the UK (Brodie et al., 2012). However, despite major advances in the understanding and management of drug-refractory epilepsy, issues related to depression and anxiety in PWE remain under-recognized.

AIM

The aims of the study are a) to emphasize the relationship between depression, anxiety, and epilepsy, and b) to suggest practical strategies for their identification by clinicians – using simple tests.

METHODS

Recent articles investigating the epidemiology and the impact of depression and anxiety in PWE and examining the validity of screening tools for the detection of depression and anxiety were included.

REVIEW AND DISCUSSION

Psychiatric aspects

Epidemiology of depression and anxiety

Among a couple of community-based studies examining the epidemiology, a representative Canadian study demonstrated a 17.4% lifetime prevalence of major depressive disorders (MDD) in PWE versus 10.7% in the general population (Tellez-Zenteno et al., 2007). Furthermore, it also manifested a 2.4 times higher prevalence of lifetime anxiety disorders and 2.2 times higher prevalence of suicidal thoughts in PWE versus the general population. In a hospital-based study in Korea, the frequencies of depressive symptoms, anxiety symptoms, and suicidal ideation in PWE were 27.8%, 15.3%, and 18.8%, respectively, which were 3.2 times, 4.8 times, and 3.6 times higher than those of people without epilepsy (PWoE) (Kwon and Park, 2013). These frequencies were increased by poor seizure control. The frequency of depressive symptoms was 6.2 times, the frequency of anxiety symptom was 9.7 times, and the frequency of suicidal ideation was 6.4 times higher in uncontrolled epilepsy than PWoE. In a Korean, Multicenter trial of Epilepsy and PSYchiatric diseases (MEPSY study), the frequencies of current MDD, current generalized anxiety disorder (GAD), and suicidality were 21.9%, 18.6%, and 30.4%, respectively, among 684 PWE who visited epilepsy clinics (Seo et al., 2015a). The frequencies of MDD, GAD, and suicidality were 4.7, 6.3, and 4.6 times higher than those of in PWoE. Bipolar symptoms were found to be common in PWE. In a survey of bipolar symptoms using the Mood Disorder Questionnaire (MDQ), 12.2% of PWE had bipolar symptoms which occurred six times more frequently than in healthy controls (Ettinger et al., 2005).

Relationship between depression, anxiety, and epilepsy

An abnormal secretion of serotonin (5-HT) in the central nervous system explains the common pathogenic mechanisms shared by depression, anxiety, and epilepsy. The role of 5-HT in human epilepsy has been identified by PET study. Reduced 5-HT_{1A} binding in mesial temporal structures, ipsilateral to the seizure focus,

was demonstrated in people with temporal lobe epilepsy (TLE) (Toczek et al., 2003). Moreover, an inverse correlation between increased severity of depression symptoms and 5-HT_{1A} receptor binding at the hippocampus ipsilateral to the seizure focus was observed (Hasler et al., 2007). Serotonin's anxiolytic effects may be related to an inhibition of noradrenergic activation through raphe nuclei projections to the locus ceruleus. For example, a lower binding of 5-HT_{1A} in the anterior and posterior cingulate and raphe was manifested in patients with panic disorder, compared with controls (Neumeister et al., 2004). Shared mechanism between depression and anxiety explains why selective serotonin-reuptake inhibitors (SSRIs) are effective in controlling depressive and anxiety symptoms together.

Recently, a matched longitudinal cohort study in a UK database demonstrated that the incidence rate ratio (IRR) of depression, anxiety, and psychosis was significantly increased for all years before epilepsy diagnosis (IRR, 1.5–15.7) and after diagnosis (IRR, 2.2–10.9) (Hesdorffer et al., 2012). This study clarified a bidirectional relationship between epilepsy and psychiatric problems.

Impact of depression and anxiety on epilepsy

Psychiatric comorbidities, especially depression, at the initial diagnosis of epilepsy can be a risk factor for pharmacoresistant epilepsy. A retrospective study from the UK analyzed data from 780 patients with newly diagnosed epilepsy who had been followed over a 20-year period to investigate predictors of pharmacoresistance (Hitiris et al., 2007). Depression preceding the onset of the seizure disorder was associated with a greater-than-twofold higher risk of developing pharmacoresistant epilepsy. A lifetime history of psychiatric disorders also appears to be related to poor postsurgical outcomes. A UK study that reviewed the medical records of 280 patients who underwent TLE surgery, found that patients with a preoperative psychiatric diagnosis were significantly less likely to remain seizure free (OR = 0.53, 95% CI = 0.28–0.98, $p = 0.04$) (Cleary et al., 2012).

Depression and anxiety are main predictors for suicidality. In a hospital-based study in Korea, the major predictors of suicidal ideation in PWE were found to be depression and other psychiatric symptoms rather than seizure-related variables (Lim et al., 2010). In the MEPSY study, major risk factors for suicidality were MDD, GAD, and adverse effects of antiepileptic drugs (AEDs) (Seo et al., 2015a). Odds ratio of suicidality in-

creased up to 45.5 compared with no risk factors when three risk factors were conjoined.

Comorbid psychiatric diseases are more likely to elicit subjective feelings of adverse effects of AEDs. A validation study of the Liverpool Adverse Event Profile (LAEP) translated into Korean, found that depressive and anxiety symptoms were strongly correlated with the LAEP total score (Park et al., 2012). A hospital survey in Korea also demonstrated that major predictors for the LAEP total score were depression and anxiety (Kim et al., 2015). However, a subclass associated with tegmentum/mucosa/weight by factor analyses was only affected by anxiety or duration of AED intake. Depression can be a risk factor for objective finding associated with AED side effects. In an observational study for 74 patients with newly diagnosed epilepsy receiving lamotrigine (LTG) monotherapy in Korea, depression was a sole predictor of LTG-induced rash (OR = 9.154, 95% CI 2.077–40.344, $p = 0.003$) (Park, 2013).

Depression is an important risk factor for nonadherence to AEDs. In a mail survey of the US, medication possession ratio (MPR) was significantly lower in depressed patients than nondepressed patients (Ettinger et al., 2014). Depression exerted a direct effect on adherence, and adherence had a direct effect on seizure severity. After all, depression, adherence, and seizure severity had a direct effect on quality of life (QOL).

The ultimate goal of epilepsy management is to improve QOL. Several recent studies have shown that depression and anxiety effect QOL. Among seizure-related, medical, AED-related, and psychiatric factors in a Korean hospital-based study, the strongest predictors of QOL were depression and anxiety, followed by seizure control (Park et al., 2010). Indeed, the QOL was significantly better in patients with drug-refractory epilepsy without comorbid depression and anxiety symptoms than in patients with 1 year of seizure freedom but with such symptoms. Patients with coexisting depression and anxiety were more likely to have a poor QOL than were those with only one of these conditions (Kwon and Park, 2013). Thus, clinicians should always consider the coexistence of depression and anxiety in each PWE and screen for both types of symptom simultaneously so as to prevent impairments in QOL. In the MEPSY study, the strongest predictor for QOL was adverse effects of AEDs rather than depression or anxiety (Lee et al., 2014). However, adverse effects were affected by depression, anxiety, and seizure control.

Other impacts of depression and anxiety on epilepsy

Perceived stigma is closely associated with psychiatric comorbidities. In a Korean survey for PWE, the frequency of perceived stigma was approximately 4 times higher in depressed or anxious patients than non-depressed or non-anxious patients (Kwon and Park, 2013). In a case control study of Korean PWE, 20% revealed obsessive-compulsive symptoms (OCS) (Seo et al., 2014). One of predictors to determine OCS was depression. Another case control study of Korean PWE reported that the severity of aggression in PWE was higher than that of PWoE (Seo et al., 2015b). Anxiety had a direct effect on aggression, but depression only had an indirect effect on aggression through perceived stigma.

Fatigue has been known to impair QOL in PWE. In a Korean survey for PWE, the level of fatigue was higher in PWE, especially in those with uncontrolled epilepsy, compared to controls (Kwon and Park, 2016). In that study, sleep-related impairment and depression were major determinants for fatigue, but epilepsy-related or AEDs-related factors were not.

Perceived stress is regarded as an important precipitant for seizure. In multiple surveys, 21–82% of PWE regarded perceived stress as an important precipitant of seizure (Balamurugan et al., 2013; Novakova et al., 2013; Ferlisi and Shorvon, 2014). In addition, PWE are easily stressful due to experiencing unpredictable seizure, driving or employment restriction, stigma, social discrimination, and AED side effects (Layne Moore et al., 2009). Although PWE are closely related to stress, it has not been well known whether the degree of perceived stress is higher in PWE than PWoE and which factors are important to increase perceived stress. Recently, I investigated perceived stress in PWE and identified its predictors (Park, 2015). Subjects who consecutively visited my epilepsy clinic were included. They were adults aged 18–70 years, had a current diagnosis of epilepsy taking one or more AEDs for at least 1 year. I used the Perceived Stress Scale (PSS) by Cohen and Williamson to measure perceived stress (Cohen, 1988). I found that the degree of perceived stress in PWE was not different from that of PWoE. However, the degree of stress was significantly higher in patients with uncontrolled epilepsy than in PWoE. Depression and anxiety were main predictors for perceived stress in PWE. In path analyses, depression exerted a direct effect on perceived stress. Anxiety and sleep-related impairment exerted a direct effect on perceived stress, and also exerted an indirect effect on perceived stress via

poor seizure control. Because perceived stress is a major precipitant of seizures, I concluded that a rapid detection and an appropriate management of psychiatric and sleep problems in PWE might be lessen stress and subsequently, prevent further seizures.

Screening of depression and anxiety

In a study of people with chronic epilepsy, 43% with a current MDD, 68% with a minor depressive disorder, and 38% with a history of a lifetime episode of MDD were unrecognized and untreated (Wiegartz et al., 1999). The MEPSY study reported that almost two third of patients who were diagnosed as MDD, GAD, or suicidality at the study enrollment did not have any psychiatric intervention before diagnosis (Seo et al., 2015a). If so, why do clinicians ignore or under-recognize psychiatric co-morbidities in PWE? There may be some reasons. Firstly, clinicians are so busy in outpatient clinic that they have no time to enquire about psychiatric co-morbidities. Secondly, they prefer to focus on the disease itself, and not likely to be concerned with other issues that patients may have. Thirdly, they may be afraid of how to diagnose and treat such co-morbidities. Because of these reasons, it is justified that rapid screening tools for detecting psychiatric co-morbidities, especially depression and anxiety, should be applied in a busy clinical setting.

Although comorbid depression and anxiety in PWE can be measured in structured psychiatric interviews, such as those employing the Structured Clinical Interview for DSM-IV axis I Disorders (Jones et al., 2005) and the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998), these take a long time to complete. In order to reduce such completion

times, the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) was developed in the USA as a validated screening tool for MDD in PWE that consists of a brief, 6-item questionnaire (Table 1) (Gilliam et al., 2006). It takes less than 3 minutes to complete and a score of >15 is suggestive of a MDD. We validated the NDDI-E translated into Korean and named the Korean version of the NDDI-E (K-NDDI-E) (Ko et al., 2012). A cutoff score suggestive of MDD was 11, which was much lower than that of the original version. The NDDI-E is now available in a number of languages and many clinicians are becoming increasingly familiar with this instrument in their clinical practice.

To screen anxiety disorders, the Generalized Anxiety Disorder-7 (GAD-7), which is a seven-item self-rating scale developed to screen for GAD, can be used (Table 2) (Spitzer et al., 2006). It takes less than 3 minutes to complete and a score of >9 is suggestive of GAD. Recently, the MEPSY study validated the GAD-7 that was translated into the Korean language (Seo et al., 2014). A cutoff score suggestive of a the diagnosis of GAD was 6, which was also much lower than that of the original version.

Depression and anxiety induced by AEDs can be measured by the LAEP (Baker et al., 1994). The LAEP is an appropriate instrument to measure common adverse effects of AEDs in the preceding 4 weeks. It consists of a 19-item questionnaire, and each item is evaluated on a 4-point Likert scale. Total scores range from 19 to 76, with higher scores being indicative of a greater burden of adverse effects. The item 3 (restlessness), item 5 (nervousness), and item 17 (depression) of the LAEP are useful for detecting depression and anxiety as AED-induced adverse effects.

Table 1. Neurological Disorders Depression Inventory for Epilepsy (NDDI-E)*

	Always or often	Sometimes	Rarely	Never
Everything is a struggle	4	3	2	1
Nothing I do is right	4	3	2	1
Feel guilty	4	3	2	1
I'd be better off dead	4	3	2	1
Frustrated	4	3	2	1
Difficulty finding pleasure	4	3	2	1

For the statements in the table, patients are asked to circle the number that best describes them over the past 2 weeks including the day of the assessment.

* Adopted from Gilliam et al., 2006

Table 2. Generalized Anxiety Disorder-7 (GAD-7) *

Over the last 2 weeks, how often have you been bothered by the following problems? (Use “√” to indicate your answer)	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3

* Adopted from Spitzer et al., 2006

For the detection of bipolar disorder, the Mood Disorder Questionnaire may perhaps provide the most convenient and useful option, despite the lack of validation within an epilepsy population (Hirschfeld, 2002). However, clinicians should acknowledge that these instruments are screening tools only and should not replace psychiatric referral and assessment.

CONCLUSIONS

PWE are more likely to have concurrent psychiatric problems than PWOE. Since psychiatric co-morbidities have a negative impact on daily living in PWE, clinicians should routinely screen psychiatric symptoms and treat them appropriately. The application of the NDDI-E and the GAD-7 might be an appropriate option for detecting psychiatric co-morbidities instantly.

CONFLICT OF INTEREST DISCLOSURE

The author has no conflict of interests to declare.

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