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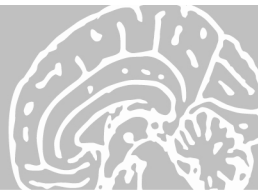

박 성 파
경북대학교 의학전문대학원 신경과학교실

Psychiatric problems and specific evaluation in epilepsy

Sung-Pa Park, MD, PhD
Department of Neurology, School of Medicine, Kyungpook National University, Daegu, Korea

People with epilepsy (PWE) have a higher risk of developing psychiatric problems than people without epilepsy. Approximately one quarter of PWE has been known to be suffered from depression. The frequency of psychiatric comorbidities was closely related to poor seizure control. Depression, anxiety, and psychosis 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 (AEDs), poor surgical outcome, and eventually, poor quality of life. Furthermore, depression and anxiety were closely associated with perceived stigma, obsessive-compulsive symptom, aggression, and perceived stress. Therefore, clinicians who take care of PWE in a busy clinical setting should search their psychiatric comorbidities by brief screening tools and treat them instantly to minimize their negative impacts.

Key Words: Epilepsy, Psychiatric problem, Depression, Anxiety, Suicide

Introduction

The comorbid psychiatric disorders in people with epilepsy (PWE) have been neglected for a long time. Psychiatric comorbidities 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%.[1] Its prevalence is almost same with the prevalence of drug-refractory epilepsy (25%) in a long-term observational study for 1,098 patients with newly diagnosed epilepsy in the UK.[2] However, despite major advances in the understanding and management of drug-refractory epilepsy, issues related to psychiatric problems in PWE remain underrecognized. Therefore, the purpose of this article is to clarify the relationship between epilepsy and psychiatric problems and to suggest practical strategies for their identification by clinicians.

Sung-Pa Park, MD, PhD
Department of Neurology, School of Medicine, Kyungpook National University, 680 Gukchaebosang-ro, Jung-gu, Daegu 700-842, Korea
TEL: +82-53-420-5769 FAX: +82-53-422-4265
E-mail: sppark@mail.knu.ac.kr

Epidemiology of psychiatric comorbidities

Among a couple of community-based studies, a representative study from Canada demonstrated a 17.4% lifetime prevalence of major depressive disorders (MDD) in PWE versus 10.7% in the general population.[3] 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%, which were 3.2 times,

4.8 times, and 3.6 times higher than those of people without epilepsy (PWoE).[4] 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 major depressive disorder (MDD), current generalized anxiety disorder (GAD), and suicidality were 21.9%, 18.6%, and 30.4% among 684 PWE who visited epilepsy clinics.[5] The frequencies of MDD, GAD, and suicidality were 4.7 times, 6.3 times, and 4.6 times higher than those of 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 frequent than in healthy controls.[6] Psychosis in PWE was the third most common psychiatric comorbidy, followed by depression and anxiety. In a meta-analysis of 4 case-control studies, its prevalence was 5.6% and 7.8 times higher than healthy controls.[7]

The relationship between psychiatric problems 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 with PET study. Reduced 5-HT1A binding in mesial temporal structures ipsilateral to the seizure focus was demonstrated in people with temporal lobe epilepsy (TLE).[8] Moreover, an inverse correlation between increased severity of depression symptoms and 5-HT1A receptor binding at the hippocampus ipsilateral to the seizure focus was found.[9] 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-HT1A in the anterior and posterior cingulated and raphe was manifested in patients with panic disorder, compared with controls.[10] 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 the 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).[11] This study clarified a bidirectional relationship between epilepsy and psychiatric comorbidities.

The impact of psychiatric problems

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 20-year period to investigate predictors of pharmacoresistance.[12] 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, $p = 0.04$).[13]

Psychiatric comorbidities 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.[14] In a MEPSY study, major risk factors for suicidality were MDD, GAD, and adverse effects of antiepileptic drugs (AEDs).5 Odds ratio of suicidality increased 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. Validation study of the Liverpool Adverse Event Profile (LAEP) as Korean

language found that depressive and anxiety symptoms were strongly correlated with LAEP total score.[15] An hospital survey of Korea also demonstrated that major predictors for LAEP total score were depression and anxiety.[16] However, some components such as tegmentum/mucosa/weight were 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).[17]

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 ones.[18] 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 affect on 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.[19] 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.4 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 a MEPSY study, the strongest predictor for QOL was adverse effects of AEDs rather than depression or anxiety.[20] However, adverse effects were affected by depression, anxiety, and seizure control in path analyses.

Other impacts of psychiatric problems

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 nondepressed or nonanxious ones.4 In a case control study of Korean PWE, 20% of them revealed obsessive-compulsive symptoms (OCS).[21] One of predictors to determine OCS was depression. Another case control study of Korean PWE represented that the severity of aggression in PWE was higher than that of PWoE.[22] Anxiety had a direct effect on aggression, but depression only had an indirect effect on aggression through perceived stigma.

In multiple surveys, 21-82% of PWE regarded perceived stress as an important precipitant for seizure.[23-25] In addition, PWE are easily stressful due to experiencing unpredictable seizure, driving or employment restriction, stigma, social discrimination, and AEDs side effects.[26] 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. 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.[27] 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 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 seizure control. Because perceived stress is a major precipitant for seizure, 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.

Table . The Korean version of Neurological Disorders Depression Inventory for Epilepsy

금일을 포함한 지난 2주간의 상황을 가장 잘 표현한 번호에 동그라미하세요 (Please circle the number that best describes them over the past 2 weeks including the day of the assessment)	항상 그렇다 (Always or often)	때때로 그렇다 (Sometimes)	가끔 그렇다 (Rarely)	아니다 (Never)
삶의 모든 것이 고달프다 (Everything is a struggle).	4	3	2	1
내가 한 것이 아무 것도 맞는게 없다 (Nothing I do is right).	4	3	2	1
죄책감에 시달린다 (Feel guilty).	4	3	2	1
죽는 게 낫다고 생각한다 (I'd be better off dead).	4	3	2	1
쉽게 좌절감을 느낀다 (Frustrated).	4	3	2	1
도대체 기쁜 일이 없다 (Difficulty finding pleasure).	4	3	2	1

Screening of psychiatric problems

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.[28] 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.[5] If so,why do clinicians ignore or underrecognize psychiatric comorbidites in PWE? There may be some reasons. First, they are so busy in outpatient clinic, and have no time to ask something. Second, they are like to focus on the disease itself, but not likely to concern to other issuses arising from patients. Third, they may be afraid of how to diagnose and treat them. Because of these reasons, it is justified that rapid screening tools for detecting psychiatric comorbidities, 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[29] and the Mini-International Neuropsychiatric Interview (MINI),[30] these take a long time to complete. For shortening conduction time, 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.[31] It takes less than 3 minutes to complete and a score of 〉15 is suggestive of a MDD. I validated the NDDI-E as Korean language and named the Korean version of the NDDI-E (K-NDDI-E).[32] The K-NDDI-E is presented in Table. A cutoff score suggestive of MDD was 11, which was much lower than that of the original version. To screen anxiety disorders, the Patient's Health Questionnaire-Generalized Anxiety Disorder-7 (GAD-7), which is a seven-item self-rating scale developed to screen for GAD, can be used.[33] 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 as Korean language.[34] A cutoff score suggestive supporting 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 Korean version of the Liverpool Adverse Event Profile (K-LAEP). The K-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.[35] For the detection of bipolar disorder, the MDQ may perhaps provide the most convenient and useful option, despite the lack of validation within an epilepsy population.[36] 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 accompany psychiatric problems

than people without epilepsy. Since psychiatric comorbidites have a negative impact on daily living in PWE, clinicians should routinely screen psychiatric symptoms and treat them appropriately. The application of K-NDDI-E and the GAD-7 might be an appropriate option for detecting psychiatric comorbidities instantly. I reviewed and summarized all of these issues as a review article in Journal of Clinical Neurology.[37]

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