Original article

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What are the predictors of major depression in adult patients with epilepsy?

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ABSTRACT – Epilepsy is not only a chronic neurological disorder but also a condition associated with other comorbidities. The purpose of this study was to determine the prevalence of major depression in a cohort of adult patients with epilepsy (PWEs) living in north China, and investigate the predictors of major depression in PWEs. A total of 215 consecutive cases were enrolled and divided into two groups: PWEs with major depression and PWEs without major depression. Patients were assessed for demographic characteristics, epilepsy details, and social status. A total of 65 of 215 (30.23%) PWEs exhibited comorbid major depression. A binary logistic regression model revealed the strong predictor variables of major depression to be drug responsiveness (odds ratio [OR]=0.23; p=0<0.01; 95% CI [0.13-0.39]), presence of chronic medical illnesses (OR=0.19; p=0.015<0.05; 95% CI [0.05-0.72]), and employment status (OR=0.42; p=0.015<0.05; 95% CI [0.21-0.84]).

Key words: epilepsy, depression, predictor, China, drug responsiveness, chronic illness, social status

Epilepsy is a common chronic neurological disorder. The worldwide prevalence of epilepsy is estimated to range from 0.5 to 1.5% (Sander, 2003). Hesdorffer and colleagues estimated that 3.8% of people will develop epilepsy over the course of their lifetime, based on the Rochester project (Hesdorffer *et al*., 2011). China is a developing country with the largest population in the world. It is estimated that epilepsy affects 6.5 million people in China, with approximately 0.4 million new cases each year. During the last decade, a number of studies on the prevalence in China have been published, and the prevalence rates of epilepsy were found to be different according to the area surveyed, varying from 0.29‰ to 23.47‰ (Tibet, China) (Hao Tang *et al*., 1991; Zhao *et al*., 2010). A recent systematic review reported that the overall prevalence of epilepsy was 2.89‰ in mainland China (Gu *et al*., 2013).

Epilepsy is not only a chronic neurological disorder, but also a condition associated with other comorbidities (Duncan *et al*., 2006). Comorbidity is defined as the "*co-occurrence of two supposedly separate conditions at above-chance levels*" (Rutter, 1994). Common comorbidities among people with prevalent epilepsy include somatic,

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neurological, and mental health conditions (Jacoby *et al*., 1996; O'Donoghue *et al*., 1999; Beghi *et al*., 2002; Boylan *et al*., 2004; Gaitatzis *et al*., 2004a; Tellez-Zenteno *et al*., 2007; Ottman *et al*., 2011). Epilepsy is associated with early onset of psychiatric disorders, before or after a diagnosis of epilepsy, as well as suicide. These associations suggest common underlying pathophysiological mechanisms that both lower seizure threshold and increase risk for psychiatric disorders and suicide (Hesdorffer *et al*., 2012). Another similar study also supports this opinion (Adelöw *et al*., 2012). Increasing evidence reveals that epilepsy and depression may share common physiopathological, genetic, and environmental mechanisms (Gaitatzis *et al*., 2004b; Hermann *et al*., 2008).

The relationship between epilepsy and depression has been known since ancient times, but has been marked by an explosion of studies during the last two decades (Devinsky, 2003). More and more studies have confirmed that the relationship between epilepsy and depression is bidirectional. The prevalence of comorbid depression ranges from 12 to 80% in patients with epilepsy (PWEs) and a history of depression is associated with a 4- to 6-fold greater risk of developing epilepsy (Blumer *et al*., 1998; Kanner, 2003; Davies *et al*., 2003; Ettinger *et al*., 2004; Swinkels *et al*., 2005; Mohammadi *et al*., 2006).

Relative to other countries, China has the largest population of PWEs, however, data regarding depression in adult PWEs is limited. The purpose of this study was to determine the prevalence of major depression in a cohort of adult PWEs living in north China, using the criteria of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (American Psychiatric Association, 2000) for major depression, and determine predictors of major depression in adult PWEs.

Materials and methods

Patients

This research was approved by the Institutional Review Board of Beijing Friendship Hospital. Consecutive cases of PWEs from north China were identified by an epileptologist in the Neurological Department of Beijing Friendship Hospital. To be enrolled, patients had to fulfil the following criteria: diagnosis of epilepsy according to the International League Against Epilepsy (ILAE) criteria (Commission, 1981; Commission, 1989); age>18 years; availability of follow-up records detailing the duration of epilepsy (at least over two years); and good cooperation. Individuals with intellectual disability and progressive diseases were excluded.

Definition

Epilepsy was defined as repeated epileptic seizures which, in clinical practice, were considered as partial or generalised. The aetiology of epilepsy was classified as idiopathic, systemic, and cryptogenic, according to the proposal published by the ILAE in 1981 and 1989 (Commission, 1981; Commission, 1989).

Major depression was defined according to the criteria of DSM-IV-TR for major depression (American Psychiatric Association, 2000); a positive diagnosis for major depression was based on the presence of one of two core symptoms along with five of nine key symptoms over a minimum period of two weeks, accompanied by either impaired function or distress. The diagnosis of major depression was confirmed by a psychologist in our hospital.

The outcome of PWEs was divided into three types which included drug responsiveness, drug resistance, and undetermined, in the light of the consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies (Kwan *et al*., 2010).

Drug-responsive epilepsy was defined as epilepsy of patients who received an AED regimen with which they were seizure-free for a minimum period corresponding to three times the longest interval between seizures before intervention, or 12 months, whichever was longer.

Drug-resistant epilepsy was defined as epilepsy in which adequate trials demonstrated failure of two kinds of tolerated and appropriately chosen and used AED schedules (whether as monotherapy or in combination) to achieve sustained seizure freedom.

Undetermined outcome corresponded to insufficient information necessary to determine the outcome of an intervention, in terms of seizure control or occurrence of adverse effects, or both.

Abnormal EEG findings were defined as interictal and ictal epileptiform discharges, such as spikes, sharp waves, spike-wave complexes, slow spike-wave complexes, 3-Hz spike-wave complexes, polyspikes, and seizure pattern.

Abnormal neuroimaging findings were defined as a lesion associated with epilepsy, including developmental anomalies of cerebral structure, hippocampus sclerosis, focal cortical dysplasia, encephalitis, and cerebrovascular disease.

Chronic medical illnesses were defined as any chronic somatic illness that requires continuing treatment, including diabetes mellitus, hypertension, cardiac disease, hyperlipoidaemia, and respiratory disease.

Assessment procedures

All subjects were divided into two groups. One group corresponded to PWEs with major depression and

Table 1. Data taken from medical records.

Demographics	Gender Age
Epilepsy details	Age at seizure onset Duration of epilepsy Seizure type Aetiology of epilepsy Epileptic family history Previous status epilepticus EEG findings Neuroimaging findings Outcome of epilepsy Chronic medical illnesses
Social status	Education Marriage status Employment status

the other without major depression. Patients were assessed according to the aspects listed in *table 1*. Data were abstracted from medical records including details of demographics and epilepsy and social status.

Statistical analysis

Initially, the statistical significance of data analysis was tested with χ^2 test and Fisher's exact test. Statistical significance of differences between means was assessed with the non-parametric Mann-Whitney test. To explore which factor may predict major depression in PWEs, the stepwise logistic regression model was used.

A binary logistic regression model was used for variables. The statistical significance level was set at $p<0.05$.

Results

Data analysis revealed that 65 of 215 (30.23%) PWEs exhibited comorbid major depression. The PWEs with and without major depression were compared with regards to demographic, epilepsy and social factors. Detailed results are summarised in *table 2*.

Demographic data analysis

The groups of PWEs with or without major depression did not differ significantly with regards to gender ($\chi^2=2.91$; $p=0.088$). The average age of PWEs with major depression was older than those without major depression (t=2.34; $p=0.02<0.05$).

Epilepsy data analysis

The two groups did not differ significantly with regards to aetiology or EEG findings. Compared to the group of PWEs without major depression, the PWEs with major depression were diagnosed significantly more frequently with: partial seizures ($\chi^2=4.25$; $p=0.039<0.05$), previous status epilepticus ($\chi^2=11.81$; $p=0.001<0.01$), abnormal neuroimaging findings ($\chi^2=11.82$; $p=0.001<0.01$), and chronic medical illnesses ($\chi^2=8.91$; $p=0.003<0.01$). Moreover, PWEs without major depression presented with: older age at seizure onset (t=1.99; $p=0.048<0.05$), shorter duration of epilepsy (t=4.69; $p=0<0.05$), infrequent epilepsy family history ($\chi^2=3.84$; $p=0.05$), and more frequent drug-responsive epilepsy ($\chi^2=57.74$; $p=0<0.01$).

Social data analysis

The groups did not differ significantly with regards to education ($\chi^2=5.27$; $p=0.07$) and marriage status ($\chi^2=0.01$; $p=0.90$). Compared to the group of PWEs without major depression, significantly more PWEs with major depression were unemployed ($\chi^2=11.22$; $p=0.004<0.01$).

What are the predictors of major depression in PWEs

A binary logistic regression model was applied to assess the influence of different potential risk factors on PWEs with major depression independently. The following independent variables were analysed: age, seizure type, epileptic family history, previous status epilepticus, age at seizure onset, duration of epilepsy, neuroimaging findings, drug responsiveness, presence of chronic medical illnesses, and employment status.

According to the analysis, the strongest predictor variables of major depression were drug responsiveness (odds ratio [OR]=0.23; $p=0<0.01$; 95% CI [0.13-0.39]), followed by presence of chronic medical illnesses (OR=0.19; $p=0.015<0.05$; 95% CI [0.05-0.72]) and unemployment status (OR=0.42; $p=0.015<0.05$; 95% CI [0.21-0.84]).

Discussion

Epilepsy is defined, as proposed by the ILAE and the International Bureau for Epilepsy (IBE), as a disorder of the brain characterised by an enduring predisposition to generate epileptic seizures, and by the neurobiological, cognitive, psychological, and social consequences of this condition (Fisher *et al.*, 2005). The influence of epilepsy in PWEs is not only the epileptic seizure itself, but also the consequence of numerous factors.

Depression is widely recognised as a frequent psychiatric comorbidity in PWEs. Variable data between population-based studies and hospital-based studies exist in the literature regarding the overall incidence of depression in PWEs, due to variable inclusion

Table 2. Demographic, epilepsy and social factors in PWE with/without major depression.

	PWE with major depression (*n*=65)	PWE without major depression (*n*=150)	Statistical results
a. Demographics			
Gender (Male/Female)	34/31	97/53	χ^2=2.91, *p*=0.088
Mean age *(range)*	45.03 (20-75)	40.04 (20-79)	t=2.34, *p*=0.02
b. Epilepsy			
Age at seizure onset: mean *(range)*	18.77 (1-65)	23.31 (1-72)	t=1.99, *p*=0.048
Duration of epilepsy: mean *(range)*	26.20 (4-62)	16.81 (3-62)	t=4.69, *p*=0
Seizure type *(partial Sz/generalised Sz)*	52/13	99/51	χ^2=4.25, *p*=0.039
Aetiology of epilepsy *(idiopathic/symptomatic/ cryptogenic)*	14/35/16	50/64/36	χ^2=3.36, *p*=0.187
Epileptic family history *(yes/no)*	2/63	17/133	χ^2=3.84, *p*=0.05
Previous status epilepticus *(yes/no)*	5/60	0/150	χ^2=11.81, *p*=0.001
EEG findings *(abnormal/normal)*	57/8	129/21	χ^2=0.11, *p*=0.739
Neuroimaging findings *(abnormal/normal)*	26/39	27/123	χ^2=11.82, *p*=0.001
Outcome of epilepsy *(drug-responsive epilepsy/ drug-resistant epilepsy/ undetermined)*	6/14/1945	90/30/30	χ^2=57.74, *p*=0
Chronic medical illnesses	14 (21.5%)	11 (7.3%)	χ^2=8.91, *p*=0.003
c. Social status			
Education *(at primary school/high school/university)*	34/24/7	106/41/3	χ^2=5.27, *p*=0.07
Marriage status *(single and divorced/married)*	25/40	59/91	χ^2=0.01, *p*=0.9
Unemployed	31 (47.7%)	44 (29.3%)	χ^2=11.22, *p*=0.004

criteria, methods, and diagnostic approaches. However, depression affects, on average, one in every three patients with epilepsy (Kanner *et al*., 2012). Our study revealed that the prevalence of major depression in PWEs in north China is 30.23%, which is similar to previous reports in other countries.

Increasing evidence reveals that comorbid depressive disorder in PWEs may not only lead to an increased risk of suicide, poor responsiveness to AED therapy, greater adverse effects, poor compliance, and more medical costs, but also may reduce quality of life (QOL) of PWEs (Hermann *et al*., 2000; Kobau *et al*., 2006; Pena *et al*., 2009). Despite this high prevalence and its negative effect on QOL, depression is often under-diagnosed (Kanner, 2003; Gilliam *et al*., 2004) and under-treated (Boylan *et al*., 2004) in epilepsy clinics. Because of this, a growing number of epileptologists and psychologists have been attracted to this area, and articles have been increasingly published in the past decade.

Previous studies have found that comorbid depression and epilepsy are influenced by multifactorial variables including medical and social factors (Mensah *et al*., 2006). We collected the data on demographic, epilepsy, and social factors in order to determine which factor(s) are predictors of major depression in PWEs. The results reveal that drug responsiveness, presence of chronic medical illnesses, and employment

status were the predictor variables for major depression in PWEs. According to Mensah *et al*. (2006), drug-responsive epilepsy and chronic medical illnesses represent medical conditions and employment status a social condition. The heterogenicity of epilepsy is the first cause of major depression, and this is associated with many factors, such as aetiology, treatment, and prognosis. According to the consensus proposal proposed by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies, the outcome of PWEs can be divided into three types: drug-responsive epilepsy, drug-resistant epilepsy, and undetermined outcome due to insufficient information. The diagnosis of drug-responsive epilepsy or drug-resistant epilepsy is dependent on whether seizures recur after the patients are treated with AEDs (whether as monotherapy or in combination). This concept therefore combines both treatment and prognosis, which may have influenced major depression in PWEs in this study. This conclusion is supported by a number of studies. Although there were significant differences between PWEs with or without major depression, such as seizure type, epileptic family history, previous status epilepticus, age at seizure onset, duration of epilepsy, neuroimaging findings, *etc*, these were not significant predictors of major depression in PWEs. Based on this study, we therefore believe that drug responsiveness is a predictor of a lack of major depression in PWEs.

There are some studies which have examined the relationship between depression and chronic medical illnesses and the results show that depression was associated with an increased risk of chronic medical illnesses, such as cardiovascular disease, stroke, diabetes, and obesity (Penninx *et al*., 2013). Chronic medical illnesses are another medical condition of PWEs, which we have shown to be associated with an increased probability of major depression in PWEs.

Employment status is also one of the important factors of social function. PWEs find that it is difficult to join society because of their seizures, comorbidity (depression or anxiety) and psychosocial issues (stigma) that they face in the interictal period. These impairments may lead to disabilities in communication, social functions, personal care, mobility, skillful work, and engaging in employment, *etc*. (Grabowska-Grzyb *et al*., 2006; Kubota, 2011). A number of investigators were convinced that PWEs would experience more problems finding a job, compared to the general population (EUCARE, 2003). Our study indicated that the incidence of unemployed PWEs with major depression was higher than those without depression and this may be secondary to drug-resistant epilepsy. Thus, unemployed status can be a predictor of comorbid major depression in PWEs.

In this study, we have investigated predictor variables of major depression in PWEs, and this study provides a basis for future research that may be useful in clinical practice. Due to the limitation of the design of this study, an insufficient amount of information and data, relating to family history of psychiatric illness and depression prior to the onset of epilepsy, was collected. These two aspects may also be important factors and thus could also be predictors of major depression in PWEs, however, further research is required.

Conclusion

Our findings suggest that about one in three PWEs has major depression, and drug responsiveness, the presence of chronic medical illnesses, and employment status are predictor variables of major depression in PWEs. □

Disclosures.
None of the authors have any conflict of interest to disclose.

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