



Unraveling complex relationships among dysphoric disorder, localization-related epilepsy, and mood disorders



Tetsufumi Suda *, Yasutaka Tatsuzawa, Taichi Mogi, Aihide Yoshino

Department of Psychiatry, National Defense Medical College, 3-2 Namiki, Tokorozawa, Saitama 359-8513, Japan

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ABSTRACT

Background: Dysphoric disorder (DD), characterized by intermittent pleomorphic symptoms, has been believed to be specific to epilepsy. However, our previous study revealed that DD in patients with localization-related epilepsy was associated with a lifetime diagnosis of mood disorders. The present study was conducted to estimate the prevalence of DD in patients with mood disorders, but not epilepsy, and to identify the clinical similarities and differences of DD in patients with either epilepsy or mood disorders.

Methods: Subjects consisted of 104 patients with localization-related epilepsy (group E) and 101 patients with DSM-IV mood disorders, but not with epilepsy (group M). After a diagnostic investigation for DD and the euthymic state, defined as the absence of any mood episodes during the last 12 months, we compared the clinical characteristics of DD in patients from groups E and M.

Results: Dysphoric disorder was apparently more common in group M (56.4%) than in group E (21.2%). However, 86.0% of patients in group M showed a temporal overlap between DD and the noneuthymic state, while 68.2% of patients in group E did not show this overlap. Moreover, the noneuthymic state was significantly associated with symptoms of DD, indicating that the diagnosis of DD was more likely to be overestimated when the subjects were in a noneuthymic state. The prevalence of DD, temporally independent of the noneuthymic state (pure DD), was estimated at 13.4% and 7.0% in groups E and M, respectively, and pure DD was 1.91 times more common in patients with epilepsy than in those with mood disorders. Diagnosis of pure DD was significantly associated with increased suicidality in group E, but not group M.

Conclusion: The present results suggest that DD is more familiar to epilepsy than mood disorders, although DD is not specific to epilepsy. Moreover, suicidality is specifically associated with DD in patients with epilepsy.

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1. Introduction

Dysphoria is a negative emotional state with multiple meanings and no clear standardized definition or classification. The term dysphoria is etymologically derived from Greek, and it denotes a hardly bearable distress that pertains to various objects, matters, and issues. In modern general psychiatry, the definition of dysphoria ranges from being synonymous with mild depression to being a complex emotion characterized by irritability, hostility, paranoid tendencies, and depression. In fact, dysphoria has no particular place in categorical diagnostic systems such as the Diagnostic and Statistical Manual of Mental Disorders (DSM).

In the psychopathology of epilepsy, however, a specific form of dysphoria has been known as a distinct clinical entity, namely dysphoric disorder (DD). Episodes of DD are characterized by intermittent pleomorphic symptoms (IPs), consisting of irritability, depression, pain, anxiety, insomnia, and euphoria. They occur, without external triggers and without clouding of consciousness, every few days to every few

months and last from a few hours up to two days [1]. The concept of DD originated from Kraepelin's description of "periodic dysphoria", which was first proposed in the early 1920s [2]. Kraepelin described patients with periodic dysphoria intermittently and suddenly exhibited pleomorphic symptoms, including affective symptoms with prominent irritability, although they possessed the positive personality traits of being quiet, modest, devoted, amicable, helpful, industrious, thrifty, honest, and deeply religious. Kraepelin also indicated that patients with periodic dysphoria showed a higher risk of committing suicide.

Diagnostic criteria and tools for identifying IPs were first developed in the late 1990s. In 1995, Blumer et al. [3] redefined periodic dysphoria as 'interictal dysphoric disorder' (IDD), adding anergia and fear to the original six IPs. Concurrently, Blumer et al. [1] developed the Seizure Questionnaire, a self-report questionnaire used to assess for the eight IPs. Mula et al. [4] later developed the Interictal Dysphoric Disorder Inventory (IDDI), a 38-item self-report questionnaire for evaluating the frequency, severity, global impairment, and time course of the disorder associated with seizures during the last 12 months. Using the IDDI, they suggested diagnostic criteria for IDD; of the 8 key symptoms occurring during interictal periods, the occurrence of three or more symptoms of at least moderate severity and distress are required for the diagnosis [4].

* Corresponding author.

E-mail address: t_suda@ndmc.ac.jp (T. Suda).

Dysphoric disorder also adds to the psychosocial burden of epilepsy. Recently, we reported that DD was associated with increased suicide risk and decreased quality of life in patients with localization-related epilepsy [5]. Moreover, lifetime diagnosis of mood disorders was significantly more prevalent in patients with epilepsy with DD (68%) compared with those without DD (20%).

Several important questions about DD remain unanswered: First, although the diagnosis of DD is associated with mood disorders in patients with epilepsy, prevalence of DD in patients with mood disorders, but not with epilepsy, has not been estimated. This is related to a further question concerning the specificity of DD to localization-related epilepsy. Second, if DD is prevalent in patients with mood disorders, the frequency with which DD temporally overlaps with mood episodes such as major depressive episodes needs to be elucidated. Since some symptoms of DD are also pivotal symptoms of major depressive episodes, if mood episodes are strongly associated with symptoms and severity of DD, DD temporally overlapped with mood episodes might merely reflect symptoms of mood episodes. Third, the impact of DD on psychosocial burden, such as increased risk of suicide and decreased quality of life, in patients with mood disorders as well as patients with epilepsy, if any, will need to be assessed. The present study was conducted to explore the abovementioned questions with respect to DD.

2. Material and methods

2.1. Subjects

A total of 205 Japanese adult outpatients were consecutively recruited from our clinic, 104 with localization-related epilepsy (group E), and 101 with mood disorders but not epilepsy (group M). The inclusion criteria were as follows: (1) diagnosis of localization-related epilepsy and mood disorders according to the International League Against Epilepsy (ILAE) criteria [6] and DSM Fourth edition (DSM-IV) [7] using the Mini-International Neuropsychiatric Interview (MINI) [8], respectively; (2) at least 18 years of age; (3) a Mini-Mental State Examination (MMSE) [9] score of greater than 20; (4) absence of dementia, pregnancy at the time of testing, or severe intellectual disabilities. Written informed consent was obtained from all patients. This study was approved by the ethics committee of the National Defense Medical College.

2.2. Interview and assessment

The following data were collected from all patients: gender, age at assessment, educational level, family history (FH) of epilepsy and psychiatric disorders, and medication history. Epilepsy-related information was also collected from patients with epilepsy, including their previous history of febrile seizures, age at epilepsy onset, seizure types, and seizure frequency during the last 3 months. Characterization of the types of epilepsy and seizure was based on clinical seizure semiology, electroencephalography, and magnetic resonance imaging (MRI) data. Remission of epilepsy was defined as the absence of all types of seizures for the last 12 months. Information pertaining to mood episodes was collected from patients with mood disorders. This included their age at the onset of their first mood episode, as well as the types and frequency of mood episodes during the last 12 months.

A comprehensive psychiatric investigation was conducted using the following four tools: the MINI, the IDDI, the 17-item Hamilton Depression Rating (HAM-D-17) scale [10], and the World Health Organization Quality of Life-BREF (WHOQOL-BREF) scale [11]. The Japanese versions of these tools have been validated previously [5,12,13].

Diagnosis of DD during the last 12 months was made according to Mula's criteria, and it required at least three of the eight key symptoms (depression, anergia, pain, insomnia, fear, anxiety, irritability, and euphoria), in moderate to severe form, and causing moderate to severe distress. According to Blumer's concept of IDD, the duration of DD was

divided into two categories: the typical duration (within 3 days) and the prolonged duration (longer than 3 days). Then, patients in groups E and M were classified into DD positive (DD (+)) and negative (DD (−)) groups, respectively. To explore whether episodes of DD temporally overlapped with DSM-IV mood episodes, DD was classified into two categories according to whether DD occurred during euthymic or noneuthymic states. Euthymia was defined as the absence of any mood episodes for a period of the last 12 months.

The HAM-D-17 scale was used to assess the severity of depressive symptoms at the time of the study. The WHOQOL-BREF scale was used to assess health-related quality of life (QOL). The WHOQOL-BREF scale consists of 26 items rated on a 5-point Likert scale, and the overall score is calculated as the mean of the 26-item scores. The MINI suicidality module (MINI-SM) was used to assess the suicide risk in the patients at the time of the study [8]. The MINI-SM consists of six items with varied weighting: recent suicidal thoughts (1 point), self-harm ideation (2 points), suicidal ideation (6 points), suicide planning (10 points), suicide attempts (10 points), and previous suicide attempts (4 points). A total score greater than 0, indicates suicidality, and the suicide risk is classified as low (1–5), moderate (6–9), or high (≥ 10) based on the score. We used the total score as a continuous variable in order to more precisely assess the severity of suicidality.

2.3. Statistical analyses

First, in order to compare the demographic and clinical factors in groups E and M, univariate analyses (t-test or χ^2 test) were performed. Second, in order to assess the effects of DD conditions (DD (+) and DD (−)) and subject groups (E and M) on demographic and clinical variables, two-way analysis of variance and multiple logistic regression analysis were performed. The statistical significance level was set at the 5% level ($p < 0.05$) for all statistical tests. Statistical analyses were calculated using the JMP software (version 11.2.0; SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Comparison of demographic and clinical characteristics between groups E and M

Group E consisted of 62 (59.6%) patients with temporal lobe epilepsy (TLE), 26 (25.0%) with frontal lobe epilepsy (FLE), and 16 (15.4%) with other types of localization-related epilepsy. Fifty-seven (54.8%) patients attained remission of seizures. Group M consisted of 60 patients with major depressive disorder and 41 with bipolar I/II disorder.

Table 1 shows the comparisons of demographic and clinical characteristics between groups E and M. Group E patients were significantly younger, less educated, took more antiepileptic drugs (AEDs), and had lower MMSE scores, lower HAM-D-17 scores, lower MINI-SM scores, and lower percentage of FH of psychiatric disorders than patients in group M. There was no significant difference between groups with regard to gender and FH of epilepsy.

3.2. Prevalence of DD in groups E and M and the association of DD with the noneuthymic state

Dysphoric disorder was apparently more common in group M (56.4%) than in group E (21.2%). As for the prevalence of DD in the subgroups, there were no significant differences between the types of epilepsy (TLE vs. FLE vs. others; $\chi^2 = 1.16$, $p = 0.56$) in group E, or between the types of mood disorder (major depressive disorder vs. bipolar I/II disorder; $\chi^2 = 2.49$, $p = 0.11$) in group M. With respect to the temporal overlap of DD and the noneuthymic states, 86.0% of patients in group M showed a temporal overlap between DD and the noneuthymic state, while 68.2% of patients in group E did not show this overlap. Since some symptoms of DD are also pivotal symptoms of a major depressive

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