Chapter

The Role of Personal and Immune Variables in the Development of Co-Morbid Affective and Related Psychopathological Syndromes in Partial Epilepsies in Relation to Handedness

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Abstract

The current study was performed in order to find the influence of premorbid personality traits and immune variables on psychopathological constructs including affective and related syndromes in patients with epilepsy separately for right-handers and left-handers. Ninety two patients with epilepsy have been included into the study. There were 85 right-handers and 7 left-handers. Assessment of psychopathological status of patients has been performed by using of Symptom Check List –90 (SCL-90) and the Hamilton rating scales for Depression and Anxiety. The Munich Personality test (MPT) was used for the assessment of personality trait. The amounts of different lymphocytes clusters were calculated. The multiple stepwise regression analysis was used to find the relationships between personality, immunity variables and affective and related psychopathological syndromes separately for right-handers and left-handers.In the right-handers significant relationships between the Neuroticism level (MPT) and value of HAM-D, Depression construct (SCL-90), Anxiety (SCL-90), Obsessions (SCL-90) and Phobia construct (SCL-90) have been obtained. In the left-handers stochastically significant correlations between Regulatory Index (CD4/CD8) with Depression construct (SCL-90) and Obsession construct (SCL-90) were revealed. Premorbid personality traits determine the affective, anxiety, obsessive and phobia syndromes strictly in right-handed patients with epilepsy, while immunity variables (CD4/CD) quite the contrary predispose to affective and obsessive syndromes strictly in left-handed patients.

Keywords: epilepsy, cerebral lateralization, handedness, immunity variables, personality constructs, depression, anxiety, obsessions, phobia

1. Introduction

Psychiatric co-morbidity in form affective and anxiety disorders are commonest among patients with epilepsy. The frequency of these disorders achieves 40–80% and 11–16% respectively [1, 2]. Principally, that these disorders cause additional issues in life of patients with epilepsy and make worse the social and clinical prognosis.

Several probable mechanisms explaining the development of concomitant psychopathological disorders in patients with epilepsy have been proposed during the last several decades. Thus, some authors regard the temporal lobe epilepsy especially with the left hemisphere focus and concomitant function reduction of frontal lobes (hypofrontality) and focal seizures with impaired awareness (FSIA) as the main risk factors for the development of co-morbid psychopathology and especially depression [3–11].

Nevertheless, such pure neurobiological approach may hardly be regarded as perfect since it can't explain the specific nature of different psychopathological disorders in epilepsy and shouldn't be regarded as universal one. In other words, why in some cases depression and anxiety, while in other cases psychosis or obsessive–compulsive disorder can origin is not properly understood.

In one our previous article we have shown that origin of depression or anxiety in temporal lobe epilepsy depends not only on focus localization but focus lateralization too. Thus, depression development has been observed mostly in patients with the right focus, while the anxiety in case of left focus [12].

In another study the interaction between depression and anxiety in dependence on focus lateralization in temporal lobe epilepsy has been studied [13]. Obtained results have shown that depression and anxiety had stronger and more close correlation in patients with the right focus compared with the left-sided focus. It implies the more solid and less differentiated syndrome in case of right-sided focus activity and more differentiated and looser association between depression and anxiety in case of left-focus activity [13].

Suggestion can be made, that some other pathogenetic mechanisms may take part in the origin of psychopathology in epilepsy, and premorbid personality constructs and immune mechanisms may be responsible for such role, since the psychoneuroimmunological interrelationship at present is regarded as principal factor in the pathogenesis of depressions, anxiety and psychoses. Nevertheless, the exact specific mechanisms which could explain the involvement of immunity in the pathogenesis of psychopathology are absent [14–17].

The certain role of immunity mechanisms in the pathogenesis of partial forms of epilepsy has been confirmed in our previous studies [18, 19]. Thus, the combination of immunity variables with focus lateralization, gender and handedness had influence on the frequency of focal sensory seizures (FSS) in epilepsy. Principally, that most high frequencies of FSS were observed in patients with low CD4/CD8 ratio with left temporal focus, female gender and left-handedness. Quite the contrary, the maximal frequency of FSS was observed in the patients with left frontal focus and high B-lymphocyte level. The left-handed patients with low CD8 and high CD4/CD8 ratio were characterized by more severe seizures. Similarly, severe seizures were also observed in left-handers with frontal left focus and high T-lymphocyte level. The stochastically significant correlation between CD4 cell level and length of remission has been also observed [18].

In the other article [19] the interaction between alexithymia score and immunity variables has been studied. The obtained results have shown that between alexithymia score and regulatory index CD4/CD8 the positive correlation exists. It implies that patients with epilepsy and alexithymic traits are characterized by higher immunity tension compared with non-alexithymic patients.

Obviously, the role of immunity variables in the genesis of co-morbid psychopathological symptoms and syndromes has not been properly studied yet. It concerns also the role of premorbid personality in relation to motor asymmetry in patients with epilepsy.

Here must be stressed, that motor asymmetry itself isn't important for the development of psychopathology and immunity functions but underlying cerebral structure and functions that determine the handedness can influence on psychopathological structure and immunity mechanisms in epilepsy.

In this context the data obtained by Knecht et al. [20], should be mentioned. In order to illustrate the relationship between the handedness and language dominance the authors have shown that the incidence of right hemisphere language dominance increases linearly with degree of left-handedness from 4% in strong right-handers to 27% in strong left-handers [20].

Obviously, the structural and functional cerebral organization in the right- and the left-handers is different, and by that may differently determine their psychopathology [21–23].

On the other hand, according to the model proposed by Geschwind and Behan, [21] and Geschwind and Galaburda [22, 23] between handedness and immune mechanisms the close relationships exist. The authors stressed the fact that frequency of auto-immune disorders in the left-handers is higher than in the right-handers. Taking into account these data the suggestion can be made that anomalous cerebral organization (lateralization) correlates with higher immunity tension that, in turn, can determine the specific psychopathology distinct from psychopathological symptoms of right-hander persons.

The role of cerebral lateralization in the development of some psychopathological syndromes and intelligence deficiency in patients with epilepsy has been revealed earlier in our previous works, although the state of immunity mechanisms in this context has not been studied properly yet [24, 25].

2. Objective

The current pilot study has been designed and performed in order to find the possible influence of cellular immune and premorbid personality constructs on co-morbid affective, obsessive and anxiety psychopathology in relation to handedness in patients with partial forms of epilepsy.

3. Material and methods

For the current study ninety and two patients with epilepsy have been selected and included into research design. There were 38 men and 54 women. Among them were 40 patients with diagnosis of symptomatic epilepsy and 52 - with diagnosis of cryptogenic epilepsy. The temporal-lobe epilepsy was diagnosed in 36 patients, the frontal-lobe epilepsy – in 16 patients and temporal-frontal epilepsy – in 40 patients.

The mean age of patients was 32,13 + −9,78 and varied from 18,0 to 74,0 years. The duration of epilepsy was 15,16 + −9,69 with range from 0 to 35 years. Neither age of patients, nor duration of epilepsy revealed stochastically significant discrepancies between left-hander and right-hander groups of patients (27,57 + −5,22 vs. 32,52 + −10,00; p = 0,06) and (16,86 + −8,76 vs. 15,00 + −9,81; p = 0,61) respectively.

All patients were scanned through MRT. No any visible pathology (hippocampal sclerosis or limbic pathologies) could be found in the left-hander and right-hander groups.

The visual EEG-method was used in order to detect the focus laterality, while data on ictal semiotics have not been taken into account. The left-sided foci were detected in 32 patients, the right-sided foci – in 30 patients, and bilateral foci – in 30 patients.

The new operational classification of seizure types by the International League Against Epilepsy has been used in the current study [26].

The assessment of seizures severity in accordance with National Hospital Seizure Severity Scale (NHS3) has been performed [27]. Principally, that statistically significant discrepancy between left-handers and right-handers for NHS3 score has not been observed (16,71 + −12,78 vs. 13,15 + −8,67; p = 0,495).

All patients were receiving antiepileptic drugs (AED) before and after inclusion into the study and any change of AED has not been designed and permitted. The antiepileptic drugs included mostly valproates, carbamazepine and lamotrigine in recommended standard doses. The left-hander and right-hander patients received the similar therapy.

Assessment of psychopathological status of patients has been performed by using of Symptom Check List −90 (SCL-90). This questionnaire represents a self-rated scale that has 9 psychiatric symptom groups, consisting of 90 items with a range of five degrees severity (0,1,2,3,4). The evaluated psychiatric constructs include somatization, obsessive–compulsive symptoms, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideations, and psychoticism [28, 29]. This scale is widely used in psychiatry and its validity has been proved in many studies, including our trials [24, 30].

Along with SCL-90 for the assessment of affective and anxiety constructs the Hamilton rating scale for Depression [31] and Hamilton rating scale for Anxiety [32] have been used.

For assessment of the premorbid personality features the Munich Personality Test (MPT) has been used [33]. The MPT represents a self-rating questionnaire and includes 51 questions depicting the different personality traits. The patients have filled in all rating scales themselves, and after that the obtained raw data have been transformed into six constructs in line with specific structure of scales. These constructs include Extraversion, Neuroticism, Rigidity, Frustration Tolerance, Tendencies to Isolation and Esoteric Tendency. The last two constructs form Schizoidia scale [33]. The other two control scales of MPT (Orientation towards Social Norms and Motivation) were not included in the final analysis [33].

The choice of MPT was dictated by fact that this test was widely used in different psychiatric disorders and has proved its efficacy [33].

Along with MPT the Toronto Alexithymia Scale (TAS-26) [34] was explored for assessment of alexithymia. This scale consists of 26 items, and each item can be scored in points from 1 to 5. The global alexithymia score in TAS-26 may be expressed from 26 to 130 points. All patients whose global TAS-26 score exceeds 74 points were regarded as alexithymic persons.

For the assessment of handedness Annett's scale was used [35]. Persons, with global score on that scale lower than – 5 points were regarded as left-handers, while persons with global score exceeded +5 points - as right-handers. Among all studied patients 85 persons were considered as right-handers (Mean + − Std. Dev.: + 21,9 + −2,7) in Annett's score and 7 persons as left-handers (Mean + − Std. Dev: −9,9 + −12,9).

The so-called pathological left-handedness has not been observed in our studied group. All patients were scanned through MRT and any visible pathology (hippocampal sclerosis or limbic pathologies) has not been observed in the left-hander group.

The blood samples were taken in every patient after he or she had been admitted to hospital. The analyses have been performed on cytofluorimeter FC 500 (Beckman Coulter).

The amounts of different lymphocytes clusters were calculated. Among them the number of T-lymphocytes (CD3+), T-helpers (CD3 + CD4+), T-cytotoxic (CD3 + CD8+), T-NK (CD3 + CD16 + CD56+), B-lymphocytes (CD3 + CD19+), Natural Killers (CD3-CD16 + CD + 56) and regulatory index (CD4/CD8 ratio) were analyzed.

4. Statistical analysis

The multiple regression analysis has been used in order to find any possible relationships between neurobiological and immunity variables on the one hand and SCL-90 constructs on the other hand separately within left-handers group and right-handers group [36, 37].

That method is usually used in order to find a probable dependence of one variable on several independent variables [36, 37].

Comparison of means of neurobiological, Immunological and psychopathological variables between right-handers and left-handers has also been done using Student's test.

5. Results

The main obtained results are shown in **Tables 1**-**3**. In **Table 1** the comparison of means of immunological and personality variables between right-handers and

Variable	Left-handers	Right-handers	Significance
Extraversion (MPT)	15,57 + −4,54	14,59 + −4,59	n.s.
Neuroticism (MPT)	15,43 + −4,08	13,41 + −5,89	n.s.
Frustration Tolerance (MPT)	8,00 + −4,12	9,37 + −4,20	n.s.
Rigidity (MPT)	13,29 + −5,02	13,04 + −4,80	n.s.
Isolation Tendency (MPT)	4,14 + −1,57	5,71 + −2,80	n.s.
Tendencies (MPT)	1,71 + −1,25	3,71 + −2,87	n.s.
Schizoidia (MPT)	5,86 + −1,35	9,39 + −4,74	n.s.
Alexithymia (TAS-26)	**58,43 + -9,27**	**67,94 + -9,26**	**p = 0,013**
T-lymphocytes	77,63 + −5,19	73,97 + −6,60	n.s.
T-helpers CD3 + CD4	46,59 + −8,94	46,59 + −6,71	n.s.
T-cytotoxic (CD3 + CD8+)	28,87 + −7,51	25,62 + −6,22	n.s.
T-NK (CD3 + CD16 + CD56+)	9,29 + −5,91	6,01 + −4,16	n.s.
B-lymphocytes (CD3 + CD19+)	10,24 + −3,02	12,62 + −4,97	n.s.
Natural Killers (CD3-CD16 + CD + 56)	9,81 + −3,20	11,69 + −5,69	n.s.
Regulatory index (CD4/CD8) ratio	1,79 + −0,79	1,97 + −0,65	n.s.

Note: statistically significant discrepancies are marked in boldface.

Table 1.
Comparison of mean values of Munich Personality Test constructs, and immune variables in groups of left-handers and right-handers.

Variable	Left-handed patients (N = 7)	Right-handed patients (N = 59)	Significance
HAM-D	3,86 + −3,08	8,08 + −7,65	N.S.
HAM-A	4,29 + −3,45	8,0 + −7,26	N.S.
Depression (SCL-90)	6,14 + −5,55	9,47 + −8,68	N.S.
Anxiety (SCL-90)	5,00 + −2,65	5,59 + −6,01	N.S.
Obsession (SCL-90)	6,14 + −4,45	8,34 + −6,47	N.S.
Phobia (SCL-90)	1,43 + −2,07	3,45 + −3,98	N.S.

Table 2.
Comparison of psychopathological variables in patients with left-handedness and right-handedness.

Group	*B* Neuroticism	*B* Frustration tolerance	*B* Alexithymia	*B* CD4/CD8 ratio	R2
HAM-A RH	—	**0,298**	—	—	**0,089**
HAM-A LH	—	—	—	—	—
HAM-D RH	**0,326**	—	—	—	**0,106**
HAM-D LH	—	—	—	—	—
Depression (SCL-90) RH	**0,751**	—	—	—	**0,250**
Depression (SCL-90) LH	—	—	—	**0,834**	**0,695**
Anxiety (SCL-90) RH	**0,401**	**–0,334**	**0,257**	—	**0,292**
Anxiety (SCL-90) LH	—	—	—	—	—
Obsession (SCL-90) RH	**0,432**	—	—	—	**0,186**
Obsession (SCL-90) LH	—	—	—	**0,780**	**0,608**
Phobia (SCL-90) RH	**0.317**	—	—	—	**0,101**
Phobia (SCL-90) LH	—	—	—	—	—

All statistically significant regression coefficients are marked in boldface.

Table 3.
Multiple forward stepwise regression analysis (values of beta coefficients) for different psychopathological constructs as dependent variable in right-handers and left-handers.

left-handers has been done. As can be seen the left-handers were characterized by less alexithymia score compared with right-handers (58,43 + −9,27 vs. 67,94 + −9,26, p = 0,013) The other personality constructs didn't show any differences.

Data on comparison of psychopathological data (SCL-90 constructs) and HAM-D and HAM-A are included in **Table 2**. Once again neither one difference has been obtained.

Table 3 include the results of multiple regression analysis between premorbid personality constructs, immunity variables and HAM-D, HAM-A and SCL-90 constructs separately for group of the right-handers and the left-handers.

As can be seen in the group of right-handers stochastically significant correlations exist between Neuroticism level (MPT) and expression of HAM-D

(b = 0,326), Depression SCL-90 (b = −0,751), Anxiety SCL-90 (b = 0,401), Obsession SCL-90 (b = 0,432) and Phobia SCL-90 (b = 0,317). It implies that the high level of Neuroticism predisposes to high expression of all mentioned psychopathological syndromes, although the role of this relationship should not be exaggerated due the small size of correlation and the final level of explained total variance (R2) was within 0.101–0,357 range.

In addition, in the right-hander group the level of Anxiety (SCL-90) was dependent on Frustration tolerance (b = −0,334), Alexithymia score (b = 0,257), and the final value of explained variance here achieved 0,292. In other words, the high Alexithymia level predisposes to Anxiety, while the high level of Frustration tolerance reduces the risk of Anxiety development.

Quite the contrary, in the group of left-handers have been revealed much more statistically significant correlations of high values despite the small size of left-handers group.

Thus, the regulatory index (CD4/CD8 ratio) correlates positively with Obsessions SCL-90 (b = 0.780) and Depression SCL-90 (b = 0,834). The final value of explained variance here achieved 0,695 for Depression and 0,608 for Obsession SCL-90. It implies that high immunity tension relates to high expression of mentioned variables and determines the affective psychopathological syndrome with co-morbid obsessions in left-handers with epilepsy.

6. Discussion

The current study is characterized by the unequal size of compared groups and too small left-handers group, that may be regarded as shortcoming and may be criticized. Here must be stressed that frequency of left-handedness in a general population usually reaches near 8–11% [38–41] and our findings are in full accordance with these data.

In one of our previous work has been shown that left-handers with epilepsy are characterized by much more frequencies of focal seizures (FS) and focal sensory seizures (FSS). In other words, the cerebral organization of left-handed patients with epilepsy predisposes to development of more frequent FS and FSS. Nevertheless, no any statistically significant correlations between mentioned seizure types and SCL-90 constructs have been revealed. It implies, that these seizure types *per se* don't determine the psychopathology constructs and affective and anxiety syndromes particularly. The exact mechanisms of such phenomenon remain unknown [42].

On the other hand, focal seizures with impaired awareness (FSIA) and focal to bilateral tonic–clonic seizures (FBTCS) had no significant discrepancies between right-handers and left-handers, but both significantly correlated with SCL-90 constructs. In implies that only these seizures can determine the psychopathology in left-handed patients. Although the FSIA and FBTCS frequencies have no significant discrepancies between left-handers and right-handers [42].

The obtained results in the current study have shown that only Alexithymia construct has discrepancy between right- and left-handers (67,94 + −9,26 versus 58,43 + −9,27, p = 0,013). The other personality constructs didn't show any discrepancy between right-handers and left-handers with epilepsy. It implies that right-handed patients are able to recognize respectively their affective incapability unlike left-handers.

Principally, that despite the small number of studied left-handers the statistically significant correlation between immunity variables and psychopathological constructs of SCL-90, have been observed.

Moreover, the values of observed correlations in the left-handers group reached 0,780 for Obsessions and 0,834 for Depression and explained respectively 0,608 and 0,695 of total variance. This implies the strong and practically functional connections between mentioned above variables.

The principal results of current study have shown that right-handers and left-handers with epilepsy have discrepancies in terms of interaction between premorbid personality traits and affective and related psychopathological variables on one hand, and between immunity variables and psychopathological constructs, on the other hand.

Thus, in right-handers the psychopathological syndromes are practically independent from immunity variables, while in the left-handers the strong positive correlations between immunity variables and psychopathological constructs exist.

In other words, the studied immune variables determine the psychopathological structure of co-morbid disorder strictly in left-handers.

Here must be stressed, that immunity variables were quite comparable in groups of left- and right-handers. It means that immunity tension as a whole doesn't depend on the handedness. In this context our data contradict the hypothesis of Geschwind, Behan [21], Geschwind, Galaburda [22, 23] about higher risk of immune pathology, including auto-immune disorders in patients with left-handedness. Nevertheless, not all studies could confirm this hypothesis [43–45].

Thus, In the study by McKeever and Riche [43] the Laterality quotients from the Edinburgh Handedness Inventory were unrelated to immune disorders in both sexes. Based on received data the authors conclude, that the Geschwind-Behan-Galaburda model about linkage between left-handedness and immune pathology couldn't be confirmed [43–45].

Nevertheless, the strong linkage between immunity and psychopathology seems to be the prerogative of left-handedness, but not of right-handedness in epilepsy.

Thus, in left-handers the high regulatory index CD4/CD8 score resulted in the more severe syndromes of Obsession and Depression. In other words, in such cases the more severe conglomerate of affective, and obsessive syndromes can appear in comparison with right-handers.

7. Conclusion

The principal conclusion from the current study concerns the fact, that prediction of co-morbid psychopathological syndromes in patients with epilepsy is quite possible based upon immunity data strictly in patients with left-handedness, but not in right-handedness.

Quite the contrary, in the right-handed patients with epilepsy the prediction of comorbid affective disorders is possible based on the premorbid personality traits, but not on the immunological variables. It implies that stronger interaction between immunity and psychopathological mechanisms seems to be the prerogative of left-handed patients.

The exact mechanism of such discrepancies between right-handers and left-handers with epilepsy are not known and should be elucidated in the future studies.

Conflict of interest

The authors have no conflict of interest to declare.

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