Neurobiological and clinical predictors of remission and antiepileptic treatment efficacy in partial epilepsies

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SUMMARY

Introduction. The current knowledge of significance of some neurobiological and clinical variables in the prediction of remission length and seizures reduction in partial epilepsies remains sparse and even controversial.

Aim. The current study has been carried out in order to evaluate the possible relationship between epilepsy forms, gender, focus lateralization and handedness with therapeutic remission and seizures reduction during antiepileptic treatment in persons with partial forms of epilepsy.

Material and methods. One hundred and eight patients were studied. Handedness was evaluated using the Annett’s scale. Focus lateralization was detected by use of the EEG. Of the patients studied temporal lobe epilepsy (TLE) was diagnosed in 61 cases and frontal lobe epilepsy (FLE) in 47 cases. There were 44 men and 64 women, of which 83 were right-handed and 25 were left-handed. A left-sided focus was detected in 59 persons whilst a right-sided focus was noted in 49 persons. MANOVA was used for the analysis of interrelationship between four nominal fixed factors (epilepsy forms, gender, handedness, and focus laterality) and dependent variables of therapeutic remission and percentage seizures reduction.

Results. A favorable prognostic significance of FLE vs TLE was observed. In contrast gender, handedness, and focus laterality had no influence on the dependent variables when analyzed separately. However, when two, three and four independent variables were combined an influence on the dependent variables was observed; and some combinations may be used for prediction purposes of therapeutic remission and percentage in seizure reduction. The FLE in the men with the right-handedness and the left focus (FLE•M•Rh•LF) resulted in the maximal length of therapeutic remission and maximal seizures reduction, while the other combinations have resulted in less favorable treatment results. The TLE•M•Rh•RF and TLE•M•Lh•LF were the worst combinations for the remission length and TLE•Fe•Lh•LF for the seizures reduction.

Conclusions. The current study revealed the significance of combinations of some neurobiological and clinical variables in prediction of therapeutic remission and percent of seizures reduction irrespective of used antiepileptic drugs. These results may be used so as to aid patient selection before drug treatment in order to form the homogenous groups of persons.

Key words: temporal lobe epilepsy • frontal lobe epilepsy • gender • right-handedness • ambidexterity • left-handedness • focus laterality • therapeutic remission • seizures reduction
INTRODUCTION

The control over seizures or at least reduction in their frequency is considered to be one of the principal aims in the treatment of patients with epilepsy. Another and not less important aim in this context is the state of so-called sustained remission that, in turn, implies the lack of seizures during the long term. Nevertheless, there are data reporting that at least 25–40% patients with primary diagnosed epilepsy are resistant to antiepileptic drugs (Elwes et al., 1984; Hart et al., 1990; Hauser et al., 1990; Hauser et al., 1998; Semah et al., 1998; Kwan and Brodie, 2005; Schmidt and Löscher, 2005; Arzimanoglou and Ryvlin, 2005; Brodie, 2008). In such cases the mode of “probes and errors” prevails in the treatment strategy, and the choice of any new antiepileptic drug (AED) depends mainly on the previous experience of physicians and so-called elaborated standards of AEDs use.

The signs that could differentiate the patients in their drug response before the start of treatment are rather scarce and contradictory, although the general opinion exists that symptomatic partial forms of epilepsies, especially of traumatic origin and forms with cognitive deterioration (intelligence deficiency), early age at onset and concomitant psychotic disorders (i.e. depression), and status epilepticus, as a rule, are characterized by an unfavorable course and poor response to drug treatment (Elwes et al., 1984; Hart et al., 1990; Hauser et al., 1990; Sander, 1993). Most of these mentioned factors concern the so-called localized-related forms of epilepsy (Sander, 1993; Mattson et al., 1996; Semah et al., 1998; Semah and Ryvlin, 2005).

Temporal lobe epilepsy (TLE) seems to represent the most frequent diagnosis that occurs in 80–85% among all partial seizure forms. The data on prediction of drug efficacy in TLE are practically absent except that patients with a left-sided focus and with mesial temporal sclerosis represent the group with poor response to AED therapy, and neurosurgery seems rather to be the most effective treatment approach for such patients (Löscher, 2005, 2008; Schmidt and Löscher, 2005; Perucca, 2005).

Frontal lobe epilepsy (FLE) occurs less frequently but despite this is also characterized by indefinite prognosis and a trend to cluster of seizures and status epilepticus development.

Nonetheless, the data on gender differences and cerebral asymmetry (motor lateralization i.e. handedness) in terms of their predictive values in TLE and FLE patients have not been taken properly into account yet. It concerns as isolated significance of these variables as their interaction with focus lateralization, while all these data a priori could shed light on the pathogenesis of epilepsies and help in prediction of probable efficacy of AED treatment in specific patients with partial epilepsies.

The principal aim of the current study was to find possible neurobiological and clinical variables including data on epilepsy forms, gender, focus lateralization and handedness which potentially could be used as predictors of AED efficacy in patients with partial epilepsies. The analysis of specific AED efficacy and comparison of different drug responses have not been intentionally included in the current study since the primary focus has been on non-pharmacological predictors of treatment response. The comparison of different AEDs in terms of their influence on drug efficacy will be the subject of a future study.

MATERIAL AND METHODS

A cohort of 108 patients with epilepsy (44 men, 64 women) was studied and their principal characteristics are listed in Table 1. All patients had the diagnosis of partial cryptogenic epilepsy; only patients without any cerebral lesions on neuroimaging scans were included. The data on focus localization and laterality were obtained strictly by a visual EEG-method. Left-sided foci were detected in 59 patients and right-sided foci were detected in 49 patients. Patients with bilateral foci were excluded from the study. Similarly excluded were patients with frontal and temporal foci.

The diagnosis of epilepsy form was based on focus localization data (EEG, MR), as well as on clinical semiology of seizures. The diagnosis of TLE has been set in 61 cases, FLE – in 47 cases.

Two principle variables depicting the results of treatment with AEDs were used and included the length of therapeutic remission when on a specific AED (in months) and the percentage reduction in seizures during one year of treatment. The duration of therapeutic remission was obtained from patient diaries. The percentage reduction of all type seizures was calculated by dividing the seizures occurring after one year of treatment by the number of seizures per year before the treatment.

For the assessment of handedness the Annett’s scale was used (Annett, 1970). For those patients whose global score on that scale was lower than 5 points were re-
All data were statistically processed by the SPSS program (11th version) on a personal computer. Firstly the Student t-test was used for the assessment of differences in variables of remissions and percent of seizures reduction in males versus females, TLE versus FLE, right-handers versus left-handers and in left-sided focus versus right-sided focus patients (Table 2). Secondly, MANOVA was used for analysis of the interrelationship between nominal independent variables (fixed factors) and dependent quantitative variables. MANOVA represents a variant of multivariate analysis, which is widely used for the assessment of influence of certain nominal variables (fixed factors) upon variance of quantitative dependent variables. That analysis, estimating the variance, allows a single simultaneous comparison for three or more groups. The result becomes a type of screening test that indicated whether at least one group differed significantly from the others (Feinstein, 2002; Mathews and Farewell, 2007). In addition to the inter-

**Table 1. The principal clinical and neurobiological characteristics of studied patients**

| Duration of seizures | Frontal lobe form (FLE) | Temporal lobe form (TLE) |
|----------------------|-------------------------|-------------------------|
| 14.48±9.04 (yrs)     | Right-sided focus (RF)  | Right-sided focus (RF)  |
| Onset of seizures    | Left-sided focus (LF)   | Left-sided focus (LF)   |
| 14.85±10.08 (yrs)    | n=47                    | n=33                    |
| Mean age             | n=31                    | n=9                     |
| 30.26±8.96 (yrs)     | Left-sided focus (LF)   | Left-sided focus (LF)   |
| n=33                 | n=28                    |                         |
| Number of previous AED | 3.37±1.54               |                         |

| Males (M) | Right-handed (Rh) | Left-handed (Lh) |
|-----------|-------------------|------------------|
| n=44      | n=32              | n=12             |
| FLE-M-Rh-RF | n=3            | FLE-M-Lh-RF      | n=3              |
| FLE-M-Rh-LF | n=11           | FLE-M-Lh-LF      | n=1              |
| TLE-M-Rh-RF | n=9             | TLE-M-Lh-RF      | n=6              |
| TLE-M-Rh-LF | n=9             | TLE-M-Lh-LF      | n=2              |

| Females (Fe) | Right-handed (Rh) | Left-handed (Lh) |
|-------------|-------------------|------------------|
| n=64        | n=61              | n=13             |
| FLE-Fe-Rh-RF | n=9            | FLE-Fe-Lh-RF     | n=1              |
| FLE-Fe-Rh-LF | n=15           | FLE-Fe-Lh-LF     | n=4              |
| TLE-Fe-Rh-RF | n=14           | TLE-Fe-Lh-RF     | n=4              |
| TLE-Fe-Rh-LF | n=13           | TLE-Fe-Lh-LF     | n=4              |

EF – epilepsy form; FLE – frontal lobe epilepsy; TLE – temporal lobe epilepsy; G – gender; Fe – females; M – males; H – handedness; Lh – left-handers; Rh-right-handers; F – focus laterality; LF – left focus, RF – right focus.

Statistics

All data were statistically processed by the SPSS program (11th version) on a personal computer. Firstly the Student t-test was used for the assessment of differences in variables of remissions and percent of seizures reduction in males versus females, TLE versus FLE, right-handers versus left-handers and in left-sided focus versus right-sided focus patients (Table 2). Secondly, MANOVA was used for analysis of the interrelationship between nominal independent variables (fixed factors) and dependent quantitative variables. MANOVA represents a variant of multivariate analysis, which is widely used for the assessment of influence of certain nominal variables (fixed factors) upon variance of quantitative dependent variables. That analysis, estimating the variance, allows a single simultaneous comparison for three or more groups. The result becomes a type of screening test that indicated whether at least one group differed significantly from the others (Feinstein, 2002; Mathews and Farewell, 2007). In addition to the inter-

**RESULTS**

The main results are listed in Tables 2–7. The comparison of the length of therapeutic remission and percentage in seizures reduction in relation to epilepsy form, gender, handedness, and foci lateralization is presented in Table 2. As can be seen no significant discrepancies (except for epilepsy form) are observed in the compared groups, and TLE patients were characterized by...
shorter therapeutic remission in comparison with FLE patients. This implies that TLE in terms of therapeutic prognosis is less favorable than FLE. The other three independent items (gender, handedness and focus lateralization) had no effect on the dependent variables if they were compared separately. This suggests that used in isolation the said three independent variables are not good predictors of the dependent variables.

For the subsequent stage of the study MANOVA was used and the data are shown in Tables 3–7. Table 3 shows the data concerning the main influence of studied neurobiological variables on items of treatment outcome, and the maximal influence has been revealed for length of therapeutic remission. It can be seen that the interaction between two variables, i.e. epilepsy form and focus lateralization (EF • F), gender and handedness (G • H), and gender and focus lateralization (G • F) have the maximal influence on the length of therapeutic remission, and the most significant effect was observed when gender and focus were combined (η² = 0.084; p = 0.04). In addition, G • H has an influence on percentage in seizures reduction.

### Table 2. Comparison of mean values of remission and seizures reduction in studied clinical and neurobiological variables

| Variables | Remission therapeutic (months) | Reduction of seizures (%) |
|-----------|--------------------------------|---------------------------|
| Males     | 11.6 ± 15.5                    | 73.7 ± 36.1               |
| Females   | 8.11 ± 12.3                    | 70.0 ± 39.4               |
| Temporal lobe epilepsy (TLE) | **6.2 ± 11**                  | 65.2 ± 39.5               |
| Frontal lobe epilepsy (FLE)   | **13.2 ± 15.4 (p = 0.005)**    | 77.9 ± 35.6               |
| Left-Handedness                | 10.1 ± 16.5                    | 61.6 ± 44.3               |
| Right-Handedness               | 9.3 ± 12.9                     | 74.3 ± 35.9               |
| Left Focus                      | 9.2 ± 13.6                     | 66.4 ± 40.6               |
| Right Focus                     | 9.1 ± 13.2                     | 73.1 ± 36.8               |

Comparisons have been made between pairs of studied variables, i.e. between Males and Females, TLE and FLE, Left-handers and Right-handers, Left focus and Right focus patients. Statistically significant discrepancies in studied paired variables are marked in bold.

### Table 3. Results of MANOVA. The Influence of interaction of different factors on remission and reduction of seizures (Significance “p” and Strength of influence “η²”)

| Variables & their interaction | Remission therapeutic (months) | Reduction of seizures (%) |
|-------------------------------|--------------------------------|---------------------------|
| EF-G                          | p = 0.41                       | p = 0.605                 |
|                               | η² = 0.007                     | η² = 0.003                |
| EF-H                          | p = 0.974                      | p = 0.49                  |
|                               | η² = 0.000                     | η² = 0.005                |
| EF-F                          | p = 0.03                       | p = 0.96                  |
|                               | η² = 0.072                     | η² = 0.001                |
| G-H                           | p = 0.029                      | p = 0.050                 |
|                               | η² = 0.050                     | η² = 0.033                |
| G-F                           | p = 0.04                       | p = 0.105                 |
|                               | η² = 0.084                     | η² = 0.028                |
| H-F                           | p = 0.268                      | p = 0.55                  |
|                               | η² = 0.012                     | η² = 0.004                |
| EF-G • H                      | p = 0.013                      | p = 0.025                 |
|                               | η² = 0.065                     | η² = 0.048                |
| EF-G • F                      | p = 0.003                      | p = 0.026                 |
|                               | η² = 0.092                     | η² = 0.044                |
| G • H • F                     | p = 0.173                      | p = 0.21                  |
|                               | η² = 0.02                      | η² = 0.017                |
| EF • H • F                    | p = 0.671                      | p = 0.739                 |
|                               | η² = 0.002                     | η² = 0.001                |
| EF-G • H • F                  | p = 0.005                      | p = 0.712                 |
|                               | η² = 0.082                     | η² = 0.001                |

EF – epilepsy form; G – gender; H – handedness; F – focus laterality. Statistically significant values are marked in bold.
Table 4. Results of MANOVA. The mean values of remission duration and percent reduction in all seizures under influence of different combinations of two factors

| Variables & their interaction | Remission therapeutic (months) | Reduction of seizures (%) |
|------------------------------|-------------------------------|----------------------------|
| EF-F                         |                               |                            |
| FLE-RF                       | 15.3 ± 16 (n = 16)            | FLE-RF: 82.6 ± 35.1 (n = 16) |
| FLE-LF                       | 14.7 ± 16.5 (n = 31)          | FLE-LF: 71.9 ± 39.1 (n = 31) |
| TLE-RF                       | 6.7 ± 11.1 (n = 33)           | TLE-RF: 68.6 ± 37.2 (n = 33) |
| TLE-LF                       | 5.7 ± 10.4 (n = 28)           | TLE-LF: 61.3 ± 42.8 (n = 28) |
| FLE-RF > TLE-RF              | p = 0.033                    | FLE-RF > TLE-LF: p = 0.049  |
| FLE-LF > TLE-LF              | p = 0.018                    |                            |
| FLE-LF > TLE-RF              | p = 0.013                    |                            |
| G-H                          |                               |                            |
| Fe-Rh                        | 8.4 ± 10.4 (n = 51)           | Fe-Rh: 75.5 ± 36.6 (n = 51) |
| Fe-Lh                        | 10.6 ± 19.5 (n = 13)          | Fe-Lh: 47.8 ± 36.6 (n = 13) |
| M-Rh                         | 12.4 ± 16.5 (n = 32)          | M-Rh: 72.2 ± 36.8 (n = 32)  |
| M-Lh                         | 9.5 ± 12.9 (n = 12)           | M-Lh: 77.8 ± 35.5 (n = 12)  |
| M-Rh > Fe-Rh                 | p = 0.08                     |                            |
| G-F                          |                               |                            |
| Fe-RF                        | 10.2 ± 15 (n = 28)            | Fe-RF: 76 ± 36.2 (n = 28)   |
| Fe-LF                        | 6.9 ± 10.5 (n = 36)           | Fe-LF: 59.9 ± 43.0 (n = 36) |
| M-RF                         | 7.5 ± 10.9 (n = 21)           | M-RF: 69.4 ± 38 (n = 21)    |
| M-LF                         | 15.9 ± 18.2 (n = 23)          | M-LF: 77.8 ± 35.4 (n = 23)  |
| M-LF > M-RF                  | p = 0.037                    | M-LF > Fe-LF: p = 0.051     |
| M-LF > Fe-LF                 | p = 0.001                    | Fe-RF > Fe-LF: p = 0.058    |
| H-F                          |                               |                            |
| Rh-RF                        | 8.3 ± 10.9 (n = 35)           | Rh-RF: 73.7 ± 35.5 (n = 35) |
| Rh-LF                        | 11.4 ± 14.6 (n = 48)          | Rh-LF: 71.7 ± 38.2 (n = 48) |
| Lh-RF                        | 12.5 ± 18.2 (n = 14)          | Lh-RF: 71.8 ± 41 (n = 14)   |
| Lh-LF                        | 7.9 ± 15 (n = 11)             | Lh-LF: 46.1 ± 47.3 (n = 11) |
| No significant discrepancies for any comparisons | Rh-LF > Lh-LF: p = 0.03 | Rh-RF > Lh-LF: p = 0.022 |

EF – epilepsy form; FLE – frontal lobe epilepsy; TLE – temporal lobe epilepsy; G – gender; Fe – females; M – males; H – handedness; Lh – left-handers; Rh – right-handers; F – focus laterality; LF – left focus; RF – right focus.

Statistically significant discrepancies are marked in bold. Comparisons were made between different combinations of two factors.

Among the groups of three neurobiological variables the interaction between epilepsy form, gender and handedness (EF • G • H) and epilepsy form, gender and focus lateralization (EF • G • F) have significant effect on therapeutic remission ($\eta^2 = 0.065$; $p = 0.013$ and $\eta^2 = 0.092$; $p = 0.003$ respectively). Besides, these triplets have also an influence on seizures reduction. On the other hand, an interaction of four studied items (epilepsy form, gender, handedness and focus lateralization, EF • G • H • F) has influence only on the length of therapeutic remission ($\eta^2 = 0.082$; $p = 0.005$). Noteworthy, the combination of three or even four factors could not principally increase the influence on the variables of therapeutic response compared with combination of two factors. This implies that there is no need for further increasing number of independent factors for prognostic purpose in order to avoid the redundancy of information that, in turn, could not improve the prognostic precision.

Table 4–6 show the principal data on mean values of statistically significant discrepancy in outcome measures under the influence of different combinations of studied neurobiological variables. In these tables the significant discrepancies between the maximal and minimal values of treatment outcome (i.e. measures depict the patients with different prognosis, and the maximal values imply a favorable and minimal values an unfavorable outcome measures.

It must be stressed that comparisons within each group of variables were made, taking into account the different members of compared combinations. Thus, the analysis of percentage in seizures reduction (Table 3) revealed that mean seizures reduction in females with right-handedness was greater than in females with left-handedness (75.5 ± 36.6 vs 47.8 ± 47.6; $p = 0.013$), while in males no statistically significant discrepancies were detected in relation to handedness (72.2 ± 36.8 vs 77.8 ± 35.5; n.s.). Nonetheless, the comparison of males and females in the group of left-handers reveals a greater per cent in reduction of seizures in males compared with females (77.8 ± 35.5 vs 47.8 ± 47.6; $p = 0.048$). Besides, the right-handed men were characterized by
greater seizures reduction, than the left-handed women (72.2 ± 36.8 vs 47.8 ± 47.6; \( p = 0.036 \)). In other words, the handedness profile is more significant for seizures reduction in females, but not in males, and the right-handed females are characterized by more favorable results of treatment, than the left-handed females. On the other hand, in the males as a whole the handedness is not so significant for prediction of seizure reduction, although FLE in males was significantly more favorable than FLE in women (89.2 ± 19.4 vs 71.9 ± 40.7; \( p = 0.049 \)).

An analysis of influence of gender and focus laterality in combination revealed a trend to a greater reduction of seizures in males with a left focus than in females with a left focus (77.8 ± 35.4 vs 59.9 ± 43; \( p = 0.051 \)) and a trend to a greater seizures reduction in the right focus women compared with the left focus women (76 ± 36.2 vs 59.9 ± 43; \( p = 0.058 \)) (Table 3).

On the other hand, the combination of gender and focus lateralization also resulted in an influence on the length of therapeutic remission, and the maximal remission has been observed in males with left-sided focus compared with females with left-sided focus (15.9 ± 18.2 vs 6.9 ± 10.5; \( p = 0.001 \)), and males with the left-sided focus were characterized by longer therapeutic remission than males with the right-sided focus (15.9 ± 18.2 vs 7.5 ± 10.9; \( p = 0.037 \)). All these findings stress the favorable role of male gender combined with the left focus for outcome results compared with the combination of female gender with the left focus.

An analysis of handedness and focus lateralization revealed a discrepancy in seizures reduction in the group of patients with the left-sided focus, and a greater effect was observed in the right-handers than in the left-handers (71.7 ± 38.2 vs 46.1 ± 47.3; \( p = 0.03 \)). On the other hand, a comparison of dextral patients with the right focus and the left-handed patients with the left-sided focus revealed a greater percentage in seizures reduction in the former patients (73.7 ± 35.5 vs 46.1 ± 47.3; \( p = 0.022 \)). These data stress emphasize again the favorable role of right-handedness in seizures reduction (Table 4).

An analysis of factors which have an impact on the duration of therapeutic remission could reveal the dis-
Table 6. Results of MANOVA. The mean values of therapeutic remission duration and percent reduction in all seizures due combination of four clinical and neurobiological variables

| Variables & their interaction | Remission therapeutic (months) | Reduction of seizures (%) |
|-------------------------------|-------------------------------|---------------------------|
| FLE-M-Rh+LF | 24.1 ± 18.6 (n = 11) | FLE-M-Rh+LF | 88.7 ± 20.4 (n = 11) |
| TLE-M+Rh+LF | 8.4 ± 16.1 (n = 9) | TLE-M+Rh+LF | 61.9 ± 48.0 (n = 9) |
| FLE-M+Rh+RF | 17.7 ± 7.4 (n = 3) | FLE-M+Rh+RF | 100 ± 0 (n = 3) |
| TLE-M+Rh+RF | 1.7 ± 4.3 (n = 9) | TLE-M+Rh+RF | 53.4 ± 37.3 (n = 9) |
| FLE-Fe+Rh+LF | 8.0 ± 10.1 (n = 15) | FLE-Fe+Rh+LF | 63.6 ± 42.0 (n = 15) |
| TLE-Fe+Rh+LF | 5.0 ± 6.3 (n = 13) | TLE-Fe+Rh+LF | 73.3 ± 36.6 (n = 13) |
| FLE-Fe+Rh+RF | 13.0 ± 12.2 (n = 9) | FLE-Fe+Rh+RF | 74.6 ± 43.3 (n = 9) |
| TLE-Fe+Rh+RF | 7.4 ± 11.5 (n = 14) | TLE-Fe+Rh+RF | 80.5 ± 28.3 (n = 14) |
| FLE-M+Lh+LF | 24.0 ± 0 (n = 1) | FLE-M+Lh+LF | 100 ± 0 (n = 1) |
| TLE-M+Lh+LF | 0 ± 0 (n = 2) | TLE-M+Lh+LF | 78.5 ± 30.4 (n = 2) |
| FLE-M+Lh+RF | 4.3 ± 7.5 (n = 3) | FLE-M+Lh+RF | 83.3 ± 28.9 (n = 3) |
| TLE-M+Lh+RF | 12.8 ± 15.3 (n = 6) | TLE-M+Lh+RF | 71.0 ± 45.7 (n = 6) |
| FLE-Fe+Lh+LF | 11.3 ± 22.5 (n = 4) | FLE-Fe+Lh+LF | 50 ± 57.7 (n = 4) |
| TLE-Fe+Lh+LF | 4.5 ± 9.0 (n = 4) | TLE-Fe+Lh+LF | 12.5 ± 25 (n = 4) |
| FLE-Fe+Lh+RF | 60 ± 0 (n = 1) | FLE-Fe+Lh+RF | 100 ± 0 (n = 1) |
| TLE-Fe+Lh+RF | 6.3 ± 11.8 (n = 4) | TLE-Fe+Lh+RF | 57.3 ± 50.8 (n = 4) |

Significant Discrepancies

| Variables & their interaction | Remission therapeutic (months) | Reduction of seizures (%) |
|-------------------------------|-------------------------------|---------------------------|
| FLE-M-Rh+LF > FLE-Fe+Rh+LF | p = 0.009 | FLE-M-Rh+LF > FLE-Fe+Rh+LF | p = 0.04 |
| FLE-Fe+Rh+LF > FLE-M+Lh+LF | p = 0.001 | FLE-Fe+Rh+LF > TLE-M+Rh+LF | p = 0.03 |
| FLE-M+Lh+LF > FLE-M+Lh+RF | p = 0.046 | FLE-Fe+Rh+LF > TLE-M+Rh+RF | p = 0.004 |
| FLE-M+Lh+LF > FLE-M+Lh+RF | p = 0.02 | FLE-Fe+Rh+LF > TLE-M+Rh+LF | p = 0.03 |
| FLE-M+Rh+LF > FLE-M+Rh+RF | p = 0.031 | FLE-M+Rh+LF > TLE-M+Rh+LF | p = 0.0495 |
| FLE-M+Rh+LF > FLE-M+Rh+RF | p = 0.0004 | FLE-M+Rh+LF > TLE-M+Rh+LF | p = 0.045 |
| FLE-M+Rh+RF > FLE-M+Rh+RF | p = 0.028 | FLE-M+Rh+LF > TLE-M+Rh+LF | p = 0.05 |
| FLE-M+Rh+RF > FLE-M+Rh+RF | p = 0.0003 | FLE-M+Rh+LF > TLE-M+Rh+LF | p = 0.09 |
| FLE-M+Rh+LF > FLE-M+Lh+RF | p = 0.051 |
| FLE-Fe+Rh+RF > TLE-M+Rh+RF | p = 0.09 |

EF – epilepsy form; FLE – frontal lobe epilepsy; TLE – temporal lobe epilepsy; G – gender; Fe – females; M – males; H – handedness; Lh – left-handers; Rh-right-handers; F – focus laterality; LF – left focus; RF – right focus.

Statistically significant discrepancies are marked in bold. Comparisons were made between different combinations of four factors.

Distinct role of FLE compared with TLE. Noteworthy, that FLE patients compared with TLE patients were characterized by longer remission in the case of combination with the male gender and right-handedness, and irrespective of focus lateralization. In other words, the epilepsy form itself has the primary impact on the length of therapeutic remission, and the TLE as a whole is characterized by unfavorable prognosis in comparison with the FLE, while other factors, such as gender, handedness and focus lateralization, play only the supplementary role.

In the Table 5 the data on influence of three factors on outcome variables are presented. As can be seen the combination of male gender, FLE and right-handedness determined the favorable results of treatment as in the therapeutic remission, as in the percentage of seizures reduction in comparison with combination of male gender, TLE and right-handedness (respectively, 21.2 ± 17.2 vs 5.1 ± 11.9; p = 0.0017 and 89.7 ± 18.7 vs 57.7 ± 41.9; p = 0.01). Moreover, among the patients with FLE and right-handedness the mean value of therapeutic remission was longer in men than in women (21.2 ± 17.2 vs 9.4 ± 10.3; p = 0.006), but this rule could not be extrapolated on seizures reduction.

Noteworthy, the presence of FLE in the right-handed males may predict favorable results in the therapeutic remission duration, as in percentage of seizures reduction, while their mirror image combination i.e., the TLE in the left-handed women implies the worst results in therapeutic remission and seizures reduction.

On the other hand, the combination of the other three factors including epilepsy form, gender and focus laterality had also an effect on therapeutic remission and percentage of seizures reduction, and here the maximal favorable results were obtained for men with FLE and left-sided focus, while in women with FLE and left-sided focus, on contrary, unfavorable results were observed (24.1 ± 17.7 vs 8.7 ± 12.9; p = 0.009). Besides, the unfavorable results for the therapeutic remission were also obtained for TLE-Fe-RF and TLE-M-LF combinations (Tables 5 and 7). On the other hand the unfavorable results for seizures reduction were also ob-
1.7 ± 4.3; p = 0.0004). This implies again that TLE is not determined by right-handedness, while the unfavorable outcome for left-handedness is highly pronounced in the group characterized by longer length of therapeutic remission than the right-handed males (TLE·M·Lh·R·F > TLE·M·Lh·R·F; 12.8 ± 15.3 vs 1.7 ± 4.3; p = 0.028).

The contrary rule has been observed in the group of FLE males with the right focus: here the favorable outcome is determined by right-handedness, while the unfavorable by left-handedness (FLE·M·Rh·F > FLE·M·Lh·R·F; 17.7 ± 7.4 vs 4.3 ± 7.5; p = 0.046). Interestingly, that analogues comparison for women could reveal discrepancy between handedness strictly for FLE with the right-sided focus, but here unlike in the men group the left-handed women were characterized by longer length of therapeutic remission, than the right-handed women (60 ± 0 vs 13.0 ± 12.2; p = 0.0003), although these findings should not be overestimated because there was only one woman with left-handedness.

Table 7 summarizes all favorable and unfavorable combinations of studied independent variables in relation to prognosis. Practically all combinations are unambiguous in terms of prognosis, and each combination could predict strictly favorable or unfavorable treatment results.

**DISCUSSION**

As far as the authors are aware, the current study appears to be the first study in which an attempt has been made to link some neurobiological pretreatment varia-
bles with drug efficacy irrespective the used AEDs. The last circumstance may be considered as shortcoming of the study. Nevertheless, as has been mentioned above, we have not included, intentionally the questions of predictive value of the particular AED in the design of study and this problem has been remained beyond the scope of the current trial.

As observed (Table 3) the prediction of outcome rather does not depend on the number of used neurobiological factors, if there were not less than three factors. Indeed, the strength of factors influence on the final variable of therapeutic remission was rather weak and remained on the same level within the range of 0.044–0.092. Such findings should be explained appropriately, although this implies that there is no need to increase the amount of factors more than three in order to improve the prediction. Obviously, it is not possible to explain this rule entirely yet, but a suggestion can be made that between the studied independent variables (factors) connections exist and further increasing in their number could not result in obtaining more precise information. Nonetheless, an attempt to use the different amount of independent factors has been made. Interestingly, that use of maximal amount of four factors could result in prediction of therapeutic remission length and percent in seizures reduction.

The obtained findings have shown that selected four neurobiological variables (factors) may be used for prediction purposes of treatment response in patients with partial forms of epilepsy. Moreover, combination of some factors could predict a therapeutic remission, as well as a percentage in seizures reduction. It becomes evident, if one uses triplets of factors (Table 5), i.e. combinations of epilepsy form, gender and handedness, or epilepsy form, gender and focus laterality.

Obviously for the prediction purposes not less than three factors should be considered. Such predictors may be considered as universal ones and include FLE, male gender and left-sided foci. Moreover, the role of FLE becomes most evident in the right-handed males and in males with the left-sided focus, while in FLE males with a right-sided focus the trend to unfavorable results of treatment is observed (Table 5, 7). These findings seem to be rather unexpected and contradict general opinion about the unfavorable prognostic role of left-sided foci in patients with epilepsy (Semah et al., 1998; Löscher, 2005, 2008; Schmidt and Löscher, 2005; Semah and Ryvlin, 2005; Arzimanoglou and Ryvlin, 2008). Obviously, the mentioned opinion concerns mostly the concomitant psychopathological signs and intelligence deterioration in TLE, but not in FLE patients (Semah et al., 1998; Semah and Ryvlin, 2005; Löscher, 2005).

Noteworthy, in the combinations of factors the male and female gender determined quite the opposite results of treatment. Thus, such combinations as M·LF and FLE·M·LF determine the favorable results as for the therapeutic remission, as for seizures reduction. On the contrary, the Fe·LF and FLE·Fe·LF combinations signify the unfavorable results for both outcome variables. Similarly, in the FLE such combinations as FLE·M·Rh·LF; FLE·M·Rh·RF; FLE·M·LH·LF and FLE·Fe·Lh·RF were all favorable, while FLE·Fe·Rh·LF; FLE·Fe·Rh·RF and FLE·M·Lh·RF were unfavorable. The similar influence of gender was revealed in TLE and combinations TLE·Fe·Rh·LF and TLE·Fe·Rh·RF were regarded as favorable, while TLE·M·Rh·LF; TLE·M·Rh·RF; TLE·Fe·Lh·LF and TLE·Fe·Lh·RF as unfavorable in terms of prognosis (Table 7). Interestingly, that TLE was mostly unfavorable in male gender and, on contrary, more favorable in females. In other words, the role of epilepsy form (TLE versus FLE) should be taken into account only under condition of gender, and FLE seems to be mainly favorable in men, while TLE may be favorable in women. These findings stress the role of gender combined with epilepsy form, focus laterality and handedness in prediction of remission and percentage in seizures reduction in patients with partial epilepsy.

Principally, unlike the men the female gender has shown in some way a mirror–image relationship with outcome measures. Moreover, prognosis in women was worse than in men. It concerned particularly the therapeutic remission, and outcome results were much worse in the right-handed females and patients with the left-sided focus, than in men, whilst there existed a trend to longer therapeutic remission in females with FLE and the right-side focus (p = 0.07).

Findings on the unfavorable prognostic outcome in TLE are well known and rather trivial and in good agreement with numerous data by other authors (Semah et al., 1998; Semah and Ryvlin, 2005).

Based upon obtained data it can be concluded that for prognostic purposes before the start of treatment the interaction between gender, epilepsy form, handedness and focus laterally should be taken into account while the separate use of each of four studied factors as a rule could not help in the prediction of antiepileptic drug treatment. The only exclusion from this rule...
seems to be an epilepsy form, and TLE always determines the worse prognosis and therapeutic results than FLE, although the interaction between epilepsy forms and other neurobiological factors should also be taken into the final consideration.

According to obtained findings, in can be concluded that in any antiepileptic drug trials the some clinical and neurobiological factors should be taken into final account. The selection of patients into compared groups must be undertaken with equal representation of persons of each gender, epilepsy forms and even motor lateralization and focus laterality. Otherwise, the prevalence of male gender patients with FLE, right-handedness and the left focus epileptic activity could result in increased amount of positive results, that can be erroneously explained strictly as result of AED treatment itself, and, contrary, the prevalence of female gender patients with the right focus activity, sinistrality or even ambidexterity might lead to reduced final scores of drug treatment and by this to underestimation of drug efficacy per se.

The observation of a better therapeutic prognosis in men compared with women seems rather to be novel and unexpected. These findings should be replicated and explained in further studies. Here it should be emphasized, that female brain is thought to be less lateralized than that of the male brain. It concerns the speech function and handedness (Kulynych et al., 1994), and bilateral or even the right hemisphere speech representation in women has been observed more frequently than in men (Miller et al., 2005). In other words, among women the tendency to ambidexterity seems to be higher than in men. The lack of proper functional lateralization is thought to presume the insufficient maturation degree of the brain and this may be one of causes of insufficient response to treatment, although this statement must also be tested in a special trial.

To date the role of handedness in the treatment response has not been seriously investigated and needs to be addressed. Unfortunately, no universal concept of motor lateralization for prediction of neurological and psychiatric disorders development and outcome and for their treatment efficacy exists, except for the role of left-handedness in the development of autoimmune disease, migraine and developmental learning disability that has been proposed by Geschwind and Behan (1982) and Geschwind and Galaburda (1985a; 1985b).

In line with this hypothesis, the right hemisphere is thought to exert some influence upon the left hemisphere and this can lead to retardation of left hemisphere maturation that, in turn, can cause sinistrality (Geschwind and Behan, 1982; Geschwind and Galaburda, 1985a; 1985b).

From this point of view the brain of left-handers seems not to be regarded as a simple mirror image of brain of right-handers, but as a brain consisted rather of two right and not properly maturated hemispheres and the left-handedness seems to be a result of the left hemisphere lesions due the various environmental factors, and in particular, the hormonal effect of testosterone (Geschwind and Behan, 1982; Geschwind and Galaburda, 1985a; 1985b). In line with this theory, in the case of left hemisphere lesion, the right hemisphere can take its functions on itself and this could explain not only anomalous motor lateralization and localization of the speech centre in the right hemisphere, but probably other functions. Based upon these data, it can be suggested, that in left-handed patients with epilepsy (at some patients) the right hemisphere becomes dominant and responsible for the origin of pathological spike-wave activity, i.e. these patients have the right-sided focus activity.

The principal conclusion that can be made from the current findings is that dexterity represents the most optimal category of patients with partial epilepsy in terms of favorable prognosis overall and drug response in particular, although it concerns mostly the male gender patients with FLE and the left-sided focus of epileptic activity.

A speculative suggestion can be made, that for most antiepileptic drugs, despite discrepancies in their structure and mode of action, are mainly effective in the treatment of the epileptic patients with dexterity, i.e. in persons with normal cerebral lateralization, while their efficacy in patients with sinistrality or ambidexterity remains quite insufficient or questionable. Obviously, such a suggestion must be tested in special studies, although behind the so-called left-handedness or ambidexterity a great deal of various multifarious mechanisms of resistance may be hidden. Such putative mechanisms may be consequent to peculiarity in blood-brain barrier structure (The multidrug transporter hypothesis), as differences in drug targets etc., although neither of mentioned hypothesis has been entirely proven as in experiment, as in clinical conditions (Löscher, 2005; 2008). Clearly, further research on the interrelation between epilepsy and sinistrality and ambidexterity is required.
CONCLUSIONS
The current study revealed the significance of combinations of some neurobiological and clinical variables in prediction of therapeutic remission and percent of seizures reduction irrespective of used antiepileptic drugs. These results may be used to aid patient selection before drug treatment is began so as to achieve a homogenous groups of patients.

CONFLICT OF INTEREST DISCLOSURE
The authors did not declare any conflict of interest.

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