Treatment of interictal EEG discharges can improve behavior in children with behavioral problems and epilepsy

Ronit M Pressler MD, MRCPCH, Department of Clinical Neurophysiology, King's College Hospital, King's College London, London, UK

Richard O Robinson FRCPCH, Department of Paediatric Neurology, Guy's Hospital, King's College London, London, UK

Goigia A Wilson, Research Technician**,** Department of Clinical Neurophysiology, King's College Hospital, London, UK

Colin D Binnie MD, FRCP, Department of Clinical Neurophysiology, King's College Hospital, King's College London, London, UK

Address for correspondence

Dr. Ronit Pressler

Department of Clinical Neurophysiology

Kings College Hospital

Denmark Hill

London SE5 9RS

Tel (44) 20 7346 4342

Fax (44) 20 7346 3725

e-mail: ronit.pressler@kcl.ac.uk

Keywords: Anticonvulsants Child, Child Behavior Disorders, Electroencephalography, Lamotrigine,

Source of support: R. Pressler and G. Wilson were supported by the Fund for Epilepsy and by Glaxo Wellcome. Lamotrigine (Lamictal) and placebo tablets were provided by Glaxo Wellcome, Stevenage, UK (now GlaxoSmithKline).

Abstract

Objective: It is generally agreed that children should be treated for epilepsy only if they have clinical seizures. The aim of this study was to examine whether suppressing interictal discharges can affect behavior in children with epilepsy.

Study design: In a double blind, placebo-controlled, cross-over study, 61 children with well-controlled or mild epilepsy were randomly assigned to add-on therapy with either lamotrigine followed by placebo or placebo followed by lamotrigine. Ambulatory EEG recordings and behavioral scales were performed during baseline and at the end of placebo and drug phases. The primary hypothesis to be tested was that behavioral scales would improve specifically in patients with a reduction of EEG discharges during active drug treatment.

Results: Global rating of behavior significantly improved only in patients who showed a significant reduction in either frequency ($p<0.05$) or duration of discharges ($p<0.05$) during active treatment, but not in patients with without a significant change in discharge rate. This improvement was mainly seen in patients with partial epilepsy ($p<0.005$).

Conclusion: Our data suggest that suppressing interictal discharges can improve behavior in children with behavioral problems and epilepsy, particularly partial epilepsy. Focal discharges may be involved in the underlying mechanisms of behavioral problems in epilepsy.

List of abbreviations

AED: antiepileptic drug

Introduction

Children with epilepsy are at a higher risk of developing behavioral problems and psychiatric disorders than their healthy peers (1) or than children with other chronic disease (2). This is not only important for children with uncontrolled epilepsy and learning difficulties but also for that majority of children with epilepsy whose seizures respond well to antiepileptic drugs (AEDs) and who are educated in mainstream schools. Even those children have been found to have more learning and behavioral problems in school compared to matched controls and achieve less than expected for their age and IQ (3, 4).

Increased behavioral problems in children with epilepsy are a consequence of a number of interacting influences including underlying brain lesion, age of onset, AEDs, psychosocial issues**,** seizure type and frequency, and interictal EEG abnormalities (5, 6). Interictal discharges or subclinical epileptiform discharges occur in up to 80% of patients with ongoing epilepsy although they may not be seen in every EEG recording (7). The clinical relevance of these discharges is unclear; specifically it is uncertain whether they are truly subclinical or cause brief disruptions of cognitive function (as described by Aarts and colleagues as transitory cognitive impairment (8)) and behavior (6, 9). The only way to determine whether discharges cause cognitive and behavioral problems in children with epilepsy or are co-existent due to a common cause, is by finding whether cognition and behavior improve when EEG discharges are suppressed. It is generally agreed by neurologists and pediatricians that patients should be treated for epilepsy only if they have clinical seizures. Treating the EEG, so called 'EEG cosmetics', is generally condemned.

We aimed to test this view by performing a double-blind, placebo-controlled, cross-over trial to examine whether suppressing interictal discharges can improve behavior in children with epilepsy and by implication whether interictal discharges can cause psychosocial dysfunction. To avoid the confounding factor of changing seizure frequency on behavior we included only patients who were seizure free or who had infrequent seizures. It was essential to exclude an independent psychotropic

effect of the drug on behavior and thus we included both patients with and without interictal discharges. Consequently it was possible to compare behavioral changes in patients with and without a reduction of interictal EEG discharges.

Patients and Methods

Patients were recruited from pediatric outpatient clinics at three study sites: Guy's Hospital, King's College Hospital and The National Centre for Young People with Epilepsy (NCYPE), UK. Additional patients were referred to the study sites from hospitals in the South Thames Region. Patients aged 7 to 17 years were eligible if they had a confident diagnosis of epilepsy and were seizure free or were having occasional seizures but in whom the responsible clinician or parent/careers felt that further adjustments to AEDs was not warranted. The inclusion criteria for 'occasional seizures' took account of seizure severity and were defined as: no more than one generalized tonic-clonic seizure in the last six months or no more than one complex partial seizure or two simple partial seizures in the last month or no more than five absences occurring on any one day within the last three months. Other inclusion criteria were an IQ of ≥ 70 or mental age of at least 7 years. In keeping with the requirements of the local ethics committee some evidence of cognitive impairment or psychosocial dysfunction was required to provide ethical justification for participation. Specifically, parents were sufficiently concerned to about behavior/cognition to seek help. The protocol was approved by the ethics committee at all three study sites and written informed consent was obtained from all parents, all patients aged 16 years or over, and oral agreement from patients aged less than 16 years.

Patients were randomly assigned to receive lamotrigine (Lamictal, GlaxoWellcome, now GlaxoSmithKline, Stevenage, UK) followed by placebo or placebo followed by lamotrigine in addition to the current AED regime each for 13 weeks (figure 1). The dose of lamotrigine depended on age, weight and concomitant AEDs according to the recommendations current at the time the study was

conducted. For children on sodium valproate lamotrigine was tapered up to 2 mg/kg/day (12≤years of age) or 150 mg/day (>12 years of age). For children not on sodium valproate lamotrigine was tapered up to 10 mg/kg/day (12≤years of age) or 300 mg/day (>12 years of age). During a 4-week single blind phase all subjects received placebo to familiarize patients and parents with trial procedures and to provide a reference point if the subsequent phases showed an order effect.

At entry, physical and neurological examination, history, routine and ambulatory EEG, standard biochemical tests, AED concentrations and IQ tests (Wechsler Intelligence Scale for Children, WISC-III) were performed and behavioral scales completed by parents and teachers. Patients were assessed at the end of each treatment phase (weeks 17 and 31) when the following were performed: physical examination, lamotrigine blood levels, ambulatory EEG, neuropsychological tests, behavioral scales for parents and teachers and documentation of compliance, seizures and possible adverse events. Seizures were classified according to the criteria of the International League against Epilepsy.

Ambulatory monitoring was performed for a 12 to 24 hr period using the Oxford Medilog 8-channel cassette system or the digital Embla recording system. EEG recordings were analyzed visually and epileptiform discharges were defined as spikes, sharp waves, spike wave complexes or multiple spike discharges. A continuous run of epileptiform waveforms would be considered as one discharge, if not interrupted by normal activity of more than one second. Discharges were considered subclinical where ‘the available methods of clinical observation, applied under particular circumstances, failed to show any changes in the patient (8)’. Discharges were quantified in each patient during the eyes-open phase of a 12 to 24 hr period as frequency of discharges (number per hour) and discharge time (duration in seconds per hour). The minimum duration allocated to any single discharge was 1 sec.

We assessed behavior with the Conners’ Rating Scales for parents and teachers. The Conners’ Rating Scales are factor analytically derived scales for assessing problem behavior in children. The parents’ rating scale consists of a list of 93 questions and the teachers’ rating scale of 39 questions. Raw scores are translated into T-scores by sex and age. The T-scores have a mean of 50, a standard deviation of 10

and higher scores denote more serious behavior problems (10). The parents' rating scale has eight subscales designated as I) antisocial, II) anxious-shy, III) conduct disorder, IV) hyperactive-immature, V) learning problem, VI) obsessive-compulsive, VII) psychosomatic and VIII) restless-disorganized. The teachers' rating scale has six subscales labeled as I) anxious-passive, II) asocial, III) conduct problem, IV) daydream-attention, V) emotional-indulgence and VI) hyperactivity. Rating forms were completed by the same persons on all occasions.

The primary hypothesis tested was that behavioral scales would improve specifically in those patients who had a reduction of discharges during the active drug phase. Changes in global rating of behavior were analyzed by repeated measurement multivariate analysis of variance (MANOVA) between treatment groups (lamotrigine and placebo), with response to lamotrigine as covariant (with or without reduction of discharges). To identify the most relevant behavioral subscale the univariate test was used. A p-value of <0.05 was considered significant. All statistical tests were 2-tailed. Analysis was by intention to treat.

Results

Of the 64 patients screened, 61 were enrolled in the study and randomly assigned to receive first lamotrigine and then placebo or vice versa (figure 1). Thirteen children were withdrawn from the study, including two children who did not enter the double-blind treatment phase. Eight of these children had discharges. Patients in both groups had similar demographics and baseline characteristics (table 1). Two thirds of patents had interictal discharges at baseline (n=42) with a mean discharge rate of 9.7/hr (range 0-115.6/hr) and mean duration of 15.4 sec/hr (range 0-140 sec/hr). Patients with idiopathic partial epilepsy were more likely to have discharges (15/16) than patients with idiopathic generalized epilepsy (13/19) or with symptomatic partial epilepsy (14/26) ($\chi^2=7.36$; df=2; $p<0.05$). Most children (77%) were seizure free during the three months preceding baseline. Eight children had up to two

partial seizures per month, two between three and five absences per month and four had more than six absences per month, but no more than three absences on any one day. Children with seizures were more likely to have interictal discharges (12/14) than children without seizures (30/47), but this difference was not significant (χ^2=2.40; df=1; ns).

The seizure frequency did not change significantly during the study. Forty-seven patients were seizure free at baseline (47/61, 77%), 40 during the placebo phase (78%) and 38 during the lamotrigine phase (81%). In the three months preceding baseline the mean seizure frequency was 3.43 (SD 13.4) seizures per month, during placebo phase 3.24 (SD 10.4) seizures per month and during lamotrigine phase 3.28 (SD 14.9) seizures per month.

Twenty-one (44%) patients had a reduced frequency of discharges, whilst 16 (33%) patients either had no change or an increase in the frequency of discharges and 11 (23) patients had no discharges during either lamotrigine or placebo phase. Twenty-three (48%) patients had a reduced duration of discharges whilst 14 (29%) patients either had no change or an increase of discharge duration and 11 (23%) patients had no discharges in either lamotrigine or placebo phase. The effect of lamotrigine on discharges was similar across the types of epilepsies.

The mean behavioral scores at baseline as assessed by both parents and teachers for the whole group were all within the normal range (50 ± 1 SD). Considering scores of more than two SD above the mean as abnormal in individual patients, 13 (22%) had at least one abnormal score in the parental assessment and 20 patients (33%) had at least one abnormal score in the teachers' assessment.

There was no difference in global rating of behavior (combining parents' and teachers' scale) when comparing placebo and lamotrigine for the total group of patients (MANOVA: F=0.79; df=14; ns).

We found a significant improvement in global rating of behavior in the children who showed a reduction of discharges during the lamotrigine phase (MANOVA: frequency of discharges: F=2.17; df=14; $p<0.05$; duration of discharges: F=2.50; df=14; $p<0.05$). This improvement was seen across all parental subscales (range of mean difference for parental scale 0 to –3.9) and in 4 out of 6 subscales in

the teachers' scale (range of mean difference for teachers' scale +1.2 to –3.4). It was significant for the parental conduct disorder subscale ($p<0.05$) and parental psychosomatic subscale ($p<0.05$) (table 2). None of the teachers' subscales individually showed a significant difference in the univariate test. This effect depended largely on whether patents had a partial or generalized epilepsy (MANOVA: $F=3.53$; $df=14$; $p<0.005$). Patients with partial epilepsy were more likely to show an improvement of behavior when discharges were suppressed whereas a change of behavioral rating in patients with generalized epilepsy was independent of the effect on discharges. A similar difference was seen depending on which drug the patient was on (MANOVA: $F=2.78$; $df=28$; $p<0.001$). Patients with carbamazepine were more likely to have an improvement of behavior if discharges were suppressed than patients with sodium valproate or other drugs. However, patients with partial epilepsy showed a similar effect whether on carbamazepine or on other drugs. There was no order effect due to randomization (MANOVA: $F=1.01$; $df=14$; ns) nor presence of seizures (MANOVA: $F=0.26$; $df=14$; ns). A sub-analysis of children without seizures at baseline (n=35) showed the same trends in the behavioral scales and similar results in the general linear modeling: a significant change in the global rating of behavior during active treatment for patients with a reduction in frequency of discharges (MANOVA: frequency of discharges: $F=4.16$; $df=14$; $p<0.05$) or duration of discharges ($F=4.82$; $df=14$; $p<0.01$).

Adverse events were evaluated for 59 patients after exclusion of two patients who were withdrawn in the single blind baseline phase. Apparent treatment related adverse events were observed in 23 of 58 patients (40%) during the lamotrigine phase and in 19 of 52 patients (37%) in the placebo phase ($\chi^2=3.24$; $df=1$; ns). Adverse events led to withdrawal from the study in six patients: in five due to a rash and in one due to dizziness and nausea. The latter was later found to have a high phenytoin level of 31.7 µg/ml. All other adverse events were mild and transient and will be published in more detail elsewhere.

Discussion

In this study suppression of interictal discharges was associated with improved global rating of behavior in children with behavioral problems and epilepsy. This is the first study to present such evidence in patients with epilepsy under controlled conditions. The controlled study design with standardized behavioral questionnaires and an appropriate number of patients avoided methodological pitfalls as recently discussed (5).

Single observations and uncontrolled reports claim an improvement of cognitive functioning by suppressing discharges with AEDs in patients with epilepsy (8, 11). Our group has previously performed a preliminary study using sodium valproate or clobazam add-on to suppress discharges in ten children with uncontrolled epilepsy. A reduction of discharge rate was associated with improvement in global rating of psychosocial function in eight out of ten children (9). However, all but one patient showed an unexpected reduction in seizure frequency on active treatment making the result difficult to interpret. To remove this confounding factor in the present trial we included only patients who were either seizure free or were having few seizures. We found no significant differences between patients with and without seizures. In clinical practice, occasional seizures are not considered to represent any substantial seizure burden and these patients are often regarded as well controlled. Generalized spike-and-slow-wave discharges may be accompanied by subtle clinical changes (TCI) as demonstrated on close assessment including psychological monitoring (12). To exclude these children would involve ignoring a major group of subjects who might benefit from the treatment proposed. Even though all patients had a degree of behavioral and/or cognitive dysfunction reported by parents, this was not reflected by the baseline scores. Nevertheless, due to the design of the study the conclusions necessarily apply only to children with some concern about learning or behavior.

In clinical research, behavioral scales, such as the Conner Rating scale (4, 9) or the Achenbach Child Behavior Checklist (13), are often employed to compare t-score before and after intervention quantitatively rather than qualitatively defining what is a normal or abnormal score (4, 14, 15). This

may obtain a significant result which may or may not be clinically relevant, but this problem is inherent to all research using behavioral scales in children with mild problems. It is questionable which scale would have been the better choice.

Our findings are in contrast to a recent study in eight children with learning and behavioral problems whose behavior did not improve under active treatment with sodium valproate (16). However, only four patients had a reduction of discharges and more importantly no separate analysis was performed for patients with and without reduction of discharges.

It was mainly patients with partial epilepsy who benefited from discharges suppression. In our study lamotrigine had a similar effect on discharges in both partial and generalized epilepsy. Although a higher proportion of patients with idiopathic partial epilepsy had discharges, a lower proportion of patients with symptomatic partial epilepsy had discharges with a lower discharges frequency, making a relationship between baseline discharge frequency and magnitude of rating change unlikely.

Patients on carbamazepine were also more likely to show an improvement when discharges were suppressed compared to patients on other drugs. This was due to the choice of first line AEDs in partial and generalized epilepsy rather than due to an independent effect as carbamazepine is not associated with the improvement in partial epilepsy. It remains unclear whether the combination of lamotrigine and sodium valproate may cause more behavioral dysfunction than other combinations. It is well established that AED polytherapy itself is a risk for behavioral dysfunction in children with epilepsy (17). By adding another drug into the current regime of our patients it is possible that behavioral problems were accentuated in some. Nevertheless, we found a significant behavioral improvement in the lamotrigine group in the patients with a reduction of discharges.

Lamotrigine is one of the few AEDs, which suppresses discharges (18, 19, 20). It does not appear to adversely affect cognition in epileptic patients (19, 20). In a recent study low dose lamotrigine had a positive effect on reaction time measurements and on one out of six mood scales in healthy volunteers, however the number of volunteers tested was small (21). Furthermore, several uncontrolled studies

reported improved cognition and behavior (22, 23). This improvement was apparently unrelated to seizure control. We could not confirm an overall effect of lamotrigine but rather an indirect effect via suppression of interictal discharges. The changes on the behavioral scale seen in our patients cannot be attributed to drug effects alone as they are confined to those subjects who showed a reduction of epileptiform activity on lamotrigine, and were not seen in those who showed no reduction or had no discharges.

How are interictal discharges and psychosocial disturbances related? Interictal discharges and behavioral problems could both be caused by an underlying pathology, and thus be co-existing but independent phenomena. However, in our cross-over study the patients acted as their own controls and only those with a reduction in discharges showed an improvement of behavior. Interictal discharges may cause fragmented sleep, a well recognized cause of cognitive and behavioral problems (14, 24). In a recent study using lamotrigine no improvement of nocturnal discharges nor neuropsychological function could be found (25). Finally, interictal discharges may cause psychosocial disturbances by directly interacting with cognitive and behavioral function. Using EEG-linked cognitive tests, TCI has been found in 50% of patients investigated (12, 26). Generalized bursts lasting at least 3 seconds are most likely to produce demonstrable TCI, but they can also be found during briefer and focal discharges (8, 27). TCI may impair day-to-day psychosocial function (6, 9).

It is well established that children with focal EEG abnormalities and/or complex partial seizures are particularly vulnerable to psychiatric and behavioral disturbance (2, 6, 13, 15). Our results provide evidence for the first time that particularly focal discharges may play a role in the underlying mechanisms of behavioral problems. These results have far reaching implications for the treatment of children with epilepsy. Do we under-treat patients with epilepsy by aiming only to suppress clinically obvious seizures? If it can be shown that discharges are contributing to a patient's psychosocial difficulties, there arises the question of AED treatment of the subclinical EEG phenomena. Obviously this proposition may reasonably be disputed. However, the point at issue is not whether to treat the

EEG, but whether seizures, so subtle as to be recognizable only by EEG and behavioral monitoring, produce disability sufficient to justify treatment. This also questions the term ‘subclinical epileptiform or interictal discharge’: if discharges are causing cognitive changes like TCI and behavioral changes as seen in this study, they are strictly speaking neither subclinical nor interictal. A further dilemma is that discharges seen in the EEG may or may not cause TCI or behavioral problems depending in which area of the brain they occur. It has been shown that TCI is a specific dysfunction of the brain area where the discharges occur (8, 12, 27). Thus, discharges may cause a wider range of deficits than would be practical to test for in an individual patient. Semantic arguments apart, our study suggests that at least in children with epilepsy and additional behavioral disturbances, treatment of interictal discharges, if present, with appropriate AEDs should be considered. Further studies, with larger number of patients and long-term follow-up are needed to assess the benefit of suppressing discharges in patients with partial epilepsy.

Acknowledgements

We are very grateful for the support of the technical and medical staff at the Departments of Clinical Neurophysiology and Paediatrics at Guy’s Hospital, King’s College Hospital and NCYPE. We would like to thank Dr. Clough, Dr. Crouchman, Dr. McCormack, Prof. Ross, King’s College Hospital, Dr. Besag, NCYPE, Dr. El-Radhi, Queen Mary's Hospital, Dr. Evans, Lewisham Hospital, Dr. Hulse, Maidstone Hospital, Dr. Lin, Dr. Pohl, Dr. Robb, Guy’s Hospital, Dr. Robards, Pembury Hospital, Dr. de Silva, Farnborough Hospital and Dr. Stern, St. Thomas Hospital for patient referral.

Figure 1: **Trial profile**

Legend: A/E: adverse events, W/D withdrawn, P/V protocol violation, wks: weeks.

References

1. Rutter M, Graham P, Yule W. A neuropsychiatric study in childhood. Clin Dev Med 1970; 35/36:1-265.
2. Hoare P. The development of psychiatric disorder among schoolchildren with epilepsy. Dev Med Child Neurol 1984; 26:3-13.
3. Seidenberg M, Beck N, Geisser M, Giordani B, Sackellares JC, Berent S et al. Academic achievement of children with epilepsy. Epilepsia 1986; 27:753-9.
4. Aman MG, Werry JS, Turbott SH. Behavior of children with seizures. Comparison with norms and effect of seizure type. J Nerv Ment Dis 1992; 180:124-9.
5. Kwan P, Brodie MJ. Neuropsychological effects of epilepsy and antiepileptic drugs. Lancet 2001; 357:216-22.
6. Besag FMC. Childhood epilepsy in relation to mental handicap and behavioural disorders. J Child Psychol Psychiatry 2002; 43:103-31.
7. Ajmone Marsan C, Zivin LZ. Factors related to the occurrence of typical paroxysmal abnormalities in the EEG records of epileptic patients. Epilepsia 1970; 11:361-81.
8. Aarts JH, Binnie CD, Smit AM, Wilkins AJ. Selective cognitive impairment during focal and generalized epileptiform EEG activity. Brain 1984; 107:293-308.
9. Marston D, Besag F, Binnie CD, Fowler M. Effects of transitory cognitive impairment on psychosocial functioning of children with epilepsy: a therapeutic trial. Dev Med Child Neurol 1993; 35:574-81.
10. Conners CK. Conners' Rating Scales Manual. Instruments for use with children and adolescents. New York: Multi-Health Systems, Inc.; 1989.
11. Rugland AL. Neuropsychological assessment of cognitive functioning in children with epilepsy. Epilepsia 1990; 31 Suppl 4:S41-4.

12. Binnie CD. Cognitive impairment during epileptiform discharges: is it ever justifiable to treat the EEG? Lancet Neurol 2003; 2:725-30.

13. Weglage J, Demsky A, Pietsch M, Kurlemann G. Neuropsychological, intellectual, and behavioral findings in patients with centrotemporal spikes with and without seizures. Dev Med Child Neurol 1997; 39:646-51.

14. Stores G, Wiggs L, Campling G. Sleep disorders and their relationship to psychological disturbance in children with epilepsy. Child Care Health Dev 1998; 24:5-19.

15. Bagley C. Multiple influences on deviant behaviour in children with epilepsy. J Biosoc Sci 1973; 5:1-16.

16. Ronen GM, Richards JE, Cunningham C, Secord M, Rosenbloom D. Can sodium valproate improve learning in children with epileptiform bursts but without clinical seizures? Dev Med Child Neurol 2000; 42:751-5.

17. Bourgeois BF. Antiepileptic drugs, learning, and behavior in childhood epilepsy. Epilepsia 1998; 39:913-21.

18. Binnie CD, Van Emde BW, Kasteleijn-Nolste-Trenite DG, de Korte, R.A, Meijer, J.W., Meinardi, H. et al. Acute effects of lamotrigine (BW430C) in persons with epilepsy. *Epilepsia* 1986; **27:** 248-54.

19. Besag FM. Lamotrigine in the management of subtle seizures. Rev Contemporary Pharmacother 1994; 5:123-31.

20. Eriksson AS, Knutsson E, Nergardh A. The effect of lamotrigine on epileptiform discharges in young patients with drug-resistant epilepsy. Epilepsia 2001; 42:230-6.

21. Aldenkamp AP, Arends J, Bootsma HP, Diepman L, Hulsman J, Lambrechts D et al. Randomized double-blind parallel-group study comparing cognitive effects of a low-dose lamotrigine with valproate and placebo in healthy volunteers. Epilepsia 2002; 43:19-26.

22. Gibbs J, Appleton RE, Rosenbloom L, Yuen WC. Lamotrigine for intractable childhood epilepsy: a preliminary communication. Dev Med Child Neurol 1992; 34:369-71.

23. Buchanan N. The efficacy of lamotrigine on seizure control in 34 children, adolescents and young adults with intellectual and physical disability. Seizure 1995; 4:233-6.

24. Cortesi F, Giannotti F, Ottaviano S. Sleep problems and daytime behavior in childhood idiopathic epilepsy. Epilepsia 1999; 40:1557-65.

25. Placidi F, Marciani MG, Diomedi M, Scalise A, Pauri F, Giacomini P et al. Effects of lamotrigine on nocturnal sleep, daytime somnolence and cognitive functions in focal epilepsy. Acta Neurol Scand 2000; 102:81-6.

26. Binnie CD, Marston D. Cognitive correlates of interictal discharges. Epilepsia 1992; 33 Suppl 6:S11-S17.

27. Shewmon DA, Erwin RJ. The effects of focal interictal spikes on perception and reaction time. II. Neuroanatomic specificity. Electroencephalogr Clin Neurophysiol 1988; 69:338-52.