COGNITIVE FUNCTIONS OF EPILEPTIC PATIENTS ON MONOTHERAPY WITH PHENOBARBITONE AND HEALTHY CONTROLS

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SUMMARY — Quantitative measurements have indicated that heredity, cerebral damage, psycho-social aspects, ictal and inter-ictal phenomena and antiepileptic drugs may interfere in the cognitive dysfunction of epileptic patients. In the present study objective methods included immediate and late recall and recognition of pictures, Stroop test and auditory selection. Twenty patients with symptomatic localized epilepsy aged 17-52 years (27±10, mean ±sd) were compared to age and socially matched healthy controls. Patients were on therapeutic serum concentrations (25±12 m/mi) of phenobarbitone and had active epilepsy with 1.94 generalized tonic-clonic, 0.85 simple partial and 6.28 complex partial seizures monthly (means). Patients performed worse than controls in all 6 tests ($p<0.05$ to $p<0.001$), indicating a generalized cognitive deficit related to seizures and/or barbiturate therapy. We suggest further studies should be carried out in populations with uniform monotherapeutic regimens and epileptic syndromes in order to isolate factors related to the cognitive dysfunction of epileptic patients.

Função cognitiva de pacientes epilépticos em monoterapia com fenobarbital e contrôles.

RESUMO — Estudos quantitativos anteriores têm demonstrado que hereditariedade, dano cerebral, aspectos psico-sociais, fenômenos ictais e interictais e drogas antiepilépticas interferem na disfunção cognitiva de pacientes epilépticos. Neste estudo os métodos objetivos incluiram memória e reconhecimento imediatos e tardio nas figuras, teste de Stroop e seleção auditiva. Vinte pacientes com epilepsia localizada sintomática entre 17 e 52 anos de idade (27±10, média ±d.p.) foram comparados a grupo controlado para idade e classe social. Os pacientes tinham concentrações terapêuticas (25±12 mg/ml) de fenobarbital e epilepsia ativa com 1,94 crises generalizadas tônico-clônicas, 0,85 parciais simples e 6,28 parciais complexas por mês (médias). Pacientes tiveram performances piores que controles em todos testes ($P<0.05$ a 0.001), indicando disfunção cognitiva generalizada relacionada com crises epilépticas e/ou tratamento com barbitúricos. Sugerimos que outros estudos com populações uniformes em regimes monoterapêuticos e síndromes epilépticas uniformes sejam realizados, para isolar fatores relacionados à disfunção cognitiva de pacientes epilépticos.

Reports from the 19th and early 20th century of mental deterioration in epileptic patients 23 **may be considered non-specific as the groups studied were of patients in mental institutions, not included in the mainstream of society, treated with various therapeutic regimens for epilepsy of long duration. Since Lennox^ studied cognitive dysfunction or deterioration many studies have indicated its high frequency** Heredity, **cjrebrai damage, psycho-social aspects, ictal and inter-ictal phenomena as well as antiepileptic drugs interfere in various aspects of cognitive**

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dysfunction 2,6,12,13,25,28,36,39. The relative effects of these factors have not been determined to date 30-34,39. The effect of EEG discharges has been elegantly demonstrated i.

Many present-day concepts of deleterious or advantageous effects of antiepileptic drugs are in fact based on little scientific evidence 36,39. in developing countries this type of investigation has not been carried out 3,7. The present study was designed to establish a technique for measurement of cognitive function in epileptic and healthy subjects to determine the various contributing factors, specifically seizures and phenobarbitone. Further studies, preliminarily published, have been carried out with the objective of evaluating the role of other drugs and of seizures[4]^.

METHODS AND SUBJECTS

PSYCHOMETRIC TESTS — A battery of quantitative measurements of cognitive functions developed specifically for investigation of epileptic patients and healthy subjects exposed to antiepileptic drugs 28 was adapted so that it became less dependent on verbal performance and could be carried out routinely and repeatedly on outpatients of a general hospital. The adapted battery lasts 25 minutes. It consists of 6 different tests and employs 3 cards, a portable tape player and a cassette tape, an automatic slide projector and 3 sets of 40 color slides showing landscapes, people, objects and animals.

In the immediate recall test subjects are shown 20 slides and the score is the number of slides they recall one minute later. In the immediate recognition test the same 20 slides are placed randomly among 20 other slides and the score is the number of slides the subjects identify correctly as belonging or not to those shown previously. In the Stroop test patients are shown a card in which the words red, blue and green are written in two columns of 20 words each, in black ink on a white background. In the second card 40 rectangles are displayed in 2 columns of 20, colored in red, blue and green. In the third, the words red, blue and green, are written in 2 columns of 20 words each, in conflicting colors. The latter card has 2 different sequences of words on its front and on its back, the former used for adaptation and the latter for testings. The subject reads aloud the words of card 1 then gives names to the colors of card 2, as rapidly as possible. Finally he/she has to name the color with which the words of card 3 are written, as fast as possible. The difference in time taken for reading cards 3 and 2 is the final score. In the auditory selection test a recording of 100 letters of the alphabet mixed randomly with 8 digits (1 to 8) is read out to the subjects at a frequency of 1 every 1.5 seconds. The subject must raise his/her hand and repeat in loud voice the numbers he/she hears. The score is given by the number of digits correctly identified. In the late recall test the same procedure for immediate recall is repeated, followed by the late recognition test, the procedure of which is the same as for immediate recognition.

SUBJECTS — All experimental subjects agreed to participate in the study after being fully informed about the trial procedure and consequences, according to the requirements of the Declaration of Helsinki.

The control group consisted of healthy men and women, free of neurological or psychiatric disorders and of any drugs, belonging to the hospital staff or to the families of patients. The group of patients consisted of epileptic subjects with localization-related symptomatic epilepsies or undetermined epilepsies with generalized tonic-clonic seizures, refractory to phenobarbitone therapy. They were obtained from a group referred to a specialized epilepsy clinic for drug changes in order to obtain better seizure control. A specific inclusion criteria for controls and patients was that they participated normally in community activities, were fully literate and capable of understading the cognitive function tests in an easy manner. Data obtained prospectively on patients included a detailed neurological, medical and seizure history, family and personal previous history, complete physical and neurological examination, questioning of side-effects and mental symptoms apparently associated with epilepsy or its treatment, and a routine EEG including sleep and waking records. The psychologists in charge of administrating the battery of tests were unaware of the patient's seizure or drug history. Patients were referred to the test at the same time that other groups of patients on monotherapy with other antiepileptic drugs were being tested in the same manner 4.

Blood samples for subsequent determination of phenobarbitone serum concentrations were collected at the time of psychometric testing. They were frozen at minus 20°C and analysed by gas liquid chromatography. Statistical analysis of the results was carried out using Student's t-test for unpaired observations and simple linear regression analysis.

RESULTS

The demographic and educational characteristics of the groups of 35 controls and 20 patients is shown in Table 1. Etiology of epilepsy was known in 3 cases of neurocysticercosis and was possibly related to febrile seizures in 2 other cases. Eighteen of the patients had symptomatic epilepsies with localization and the other 2 had indetermined epilepsies with isolated generalized tonic-clonic seizures. The frequency of the various seizure types is shown in Table 2.

	Subjects		Age (years)			Education		
	n	females	range	mean	sd	prim	sec	sup
Controls	35	20	17-52	27	10	4	23	8
PHB	20	10	17-57	28	10	12	8	0

Table 1 — Number (n), number of females, age (sd = stantard deviation) and educational level of groups of patients with epilepsy refractory to monotherapy with phenobarbitone (PHB) and matched controles. Educational level is described as primary (prim), secondary (sec) or University Degree (sup).

Seizure	mean	sd	n
GTC	1.94	2.94	15
SP	0.85	2.71	4
CP	6.28	12.7	10

Table 2 — Mean and standard deviation (sd) of the frequency of generalized tonic clonic (GTC), simple partial (SP), complex partial (CP) seizures, and number (n) of patients with each seizure type, in a group of 20 subjects on monotherapy with phenobarbitone.

At least one routine 8-channel EEG carried out in the 10/20 system for at least 30 minutes of useful recording- time, with hyperventilation, spontaneous or chloral hydrate--induced sleep and photic stimulation was (available. Isolated spike foci were found in 5 patients, spike foci with localized slowing in 3, localized slowing only in 4 cases, a generalized abnormality in one, and a secondarily generalized abnormality with spike foci and/or localized slowing in 4 cases. Two patients had normal records. Of 16 patients with focal features in their EEG, the abnormality was located in the temporal lobes in 12 cases. Computerized tomography (EMI 1010 Scanner) was carried out in 12 patients and was normal in 6. Localized cerebral edema was found in one case and 5 patients had intraparenchymal cerebral calcifications. CSF examination was normal in 4 cases.

The dose of phenobarbitone at the time of testing varied between 100 and 400 mg/day (160±85 mg/day, mean±standard deviation — m±sd). Serum concentrations measured by gas liquid chromatography varied between 8.4 and 57.3 ^g/ml (24.6±11.6, m±sd). All 20 patients reported side-effects in the form of mental or other symptoms they thought were related to phenobarbitone therapy including somnolence (19 patients), decreased libido (3), slowness of thought and behaviour (2), forgetfulness (1) depression (1), irritability (21), gengival hypertrophy (1) and learning difficulty (1).

Controls performed better than epileptic subjects in all 6 tests. In the immediate recall test results were respectively 14±3 (m±sd, range 8-20) and 10±4 (m±sd, range 1-15) ($p<0.001$). In late recall results were respectively 16±3 (m±sd, range 9-20) and 12±4 (m±sd, range 6-19) ($p<0.01$). In immediate recognition performances were respectively 39±2 (m±sd, range 36-40) and 36±4 (m±sd, range 22-40) ($p<0.01$). In late recognition performances were respectively 39±3 (m±sd, range 34-40) and 34±7 (m±sd, range 15-40) (p<^0.01). In Stroop test the results were respectively 10±6 sec (m±sd, range 1-27) and 23±19 (m±sd, range 6-75) ($p<0.01$). Finally in auditory selection the performances were respectively 8±0.2 (m±sd, range, 7-8) and 7±1 (m±sd, range 3-8) (p.<0.05).

Linear regression analysis of the absolute values of phenobarbitone serum concentrations and performance in the group of epileptic patients showed correlation coefficients of 0.29 and 0.20 (immediate and late recall); 0.22 and 0.35 (immediate and late recognition); 0.01 (Stroop test) and -0.19 (auditory selection) ($p>0.05$).

COMMENTS

Hutt et al.[1]^ in a study of 4 healthy subjects found a high correlation between higty concentration of phenobarbitone and deficits in perceptualmotor tests involving sustained attention. Binnie et al.[1] demonstrated short-lived impairment of verbal and spatial memory tasks in patients with epilepsy, related them to laterality of focus, but not to drug status or seizure history. The majority of studies published to date were carried out in groups of patients with various epileptic syndromes, often unspecified, on various antiepileptic drugs 21. Trimbel and Reynolds 37, **McLeod et al.20 and Camfield et al.[8] reported deficits in performance in relation to phenobarbitone. McLeod et al.[2]** did not specify syndrome or changes in seizure frequency between the two test occasions. Nonetheless, they maintained that measurements indicated a specific deficit of speed of access to information in the short term memory compartment, due to phenobarbitone.**

The relationship between epilepsy, drugs and cerebral function may be considered from varying aspects. While one reviewer concluded that carbamazepine impaired certain aspects and sodium valproate was devoid of clear effects on cognition 31, **another concluded the opposite** 35. **in the extensive work of Thompson and Trimble** 30-34^ **of Thompson et al.[2]^ and of Cull and Trimble n, subjects have been healthy volunteers or longterm residents of a residential centre for patients with epilepsy and (usually) other handicaps. The data of Binnie et al.[1] suggest that the latter may be substantially impaired by subclinical epileptiform activity in the EEG during long-term test sessions. The mainstream of epileptic patients were not included. The studies in normal volunteers were short-term, and the serum concentrations achieved were very low in the «therapeutic ranges»[24]. Work carried out in very similar experimental circumstances in healthy subjects exposed to higher but still therapeutic drug concentrations of carbamazepine, phenytoin and valproate showed impairment of measurements of oculomotor function thought to correlate closely with alertness, concentration and motor coordination** 6. **Measurements of oculotomor function, as smooth pursuit eye movements, involve associative areas of the cerebral hemispheres, brainstem and cerebellum, and could be considered measurements of cognition. Smooth pursuit is impaired by a variety of drugs that impair most tests of cognitive function including barbiturates, benzodiazepines and alcohol** 5,6.

Most research related to epilepsy and cognitive function did not use clear classifications of seizure types or syndromes (for reviews see references 7 and 21). In view of the vast differences that are now clear between syndromes as juvenile myoclonic epilepsy and localization-related epilepsies with complex partial seizures[22], the value of these studies has decreased since the publication of the ILAE classification of epileptic syndromes and epilepsies 9. **In one study** 26.27 **₀f patients with clearly defined seizure types and/or syndromes, on clinically used therapeutic serum concentrations of carbamazepine, phenytoin, primidone and phenobarbitone, conclusions were made difficult by methodological problems such as that of complex partial seizures which were significantly more frequent in the phenobarbitone than in the carbamazepine group. A basic point has been forward by Smith «perhaps more importantly, this study emphasizes the need to control for age, education and IQ when assessing individual neuropsychological test results». As stated before !<>, «the relationship between seizure type and intellectual ability is unclear», and «with respect to seizure frequency... the number of studies is small and further evaluation of the effect of seizure frequency is needed». From the point of view of clinical neurology or pharmacology[22] it may be doubtful to draw conclusions from disparate groups of patients who have complex polytherapeutic drug regimens decreased or increased** 32,34^ **from healthy volunteers tested within the first two weeks of expousure to drugs that have not reached a plateau of serum concentrations** 29,33, **₀r from statistically non-significant trends** 36.

The results of the present study indicate a generalized cognitive dysfuntion in patients with uncontrolled symptomatic epilepsies with localization or indetermined epilepsies, under treatment with therapeutic doses and serum concentrations of phenobarbitone. The control group was matched for age, sex and social class, but not so well for educational level. IQs were not measured. Furthermore, patients and

controls led similar patterns of life. None were or had been residents of institutions, and all led constructive lives in the community, albeit impaired by their disability.

The cognitive dysfunction determined in the present study may be related to the frequency of complex partial or generalized tonic-clonic seizures at the time of testing, to the cumulative effect of chronic epilepsy or to drug treatment with phenobarbitone. It is not difficult to envisage clinical studies which may address the role of present or past seizure patterns, of neurological, psychological or social factors related to chronic epileptic seizures, or of various drug regimens. Studies in this line, have been preliminarily published[4»!6. it is only by looking at patients with well defined neurological status 22, epileptic syndromes and seizure frequencies, on monotherapeutic regimens, that conclusions such as those put forward by present investigators may be reached objectively in the future. A further improvement in future studies should be better matching for educational level.

The lack of relationship between serum phenobarbitone and cognitive dysfuction in this study is indicative of the multifactorial origin of the cognitive deficit in the study population. The data of Binnie et al.[1 may be taken to put forward the hypothesis that the cognitive improvement shown in the studies of drug changes such as those reviewed by Trimble 35^ and Trimble and Thompson 38 reflect changes in seizure status at least as much as in serum drug concentrations.

The presently used battery of tests may be improved. Patients but specially healthy subjects achieved some excellent performances suggesting that they should be made more difficult. As almost all batteries used in studies of epileptic patients, that used here has not been validated anatomically in experimental animals or in human subjects. The evidence that the battery is measuring different aspects of cognitive function is circumstancial 28.

The present study and others 3,6,26,27,36 provide evidence that epilepsy per se, probably the frequency of present and past complex partial and tonic-clonic seizures, have a definite effect on cognitive function. Benzodiazepines given acutely and phenobarbitone acutely or chronically have definite effects. There is evidence that carbamazepine, valproic acid and phenytoin have less effects which have not been shown to be definitely different from each other in quality or severity.

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