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Conventional and Spectral EEG Analysis in Children Treated with Cytotoxic Agents*

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Abstract—*One hundred and six EEG investigations were carried out in 17 children with various types of neoplastic disease without cerebral involvement during one or more courses of treatment with cytotoxic agents EEGs were recorded before and 24 hr after administration of the drugs. The EEGs were evaluated visually and by spectral analysis. A transient slowing of the dominant frequency in the alpha band by about 1 Hz and a decrease in the relative power of alpha activity by 20–30% was observed in only 4 patients. These children did not show any clinical or biochemical signs of neurotoxicity. The children did not receive the same antineoplastic treatment. One patient received very high dose methotrexate, 2 patients received vincristine combined with other cytotoxic agents and the other patient received L-asparaginase. It is suggested that EEG changes in patients receiving intravenous cytotoxic treatment usually occur only where there is pre-existing impairment of the blood–cerebrospinal fluid barrier or blood–brain barrier. No clinical signs of epilepsy, new epileptiform waves in the EEG or long-term changes in the background activity of the EEG were observed in this pilot study.*

INTRODUCTION

IN RECENT years, considerable progress has been made in the treatment of neoplastic disease in childhood. Survival times have been extended and complete remissions are now more frequent. As a consequence of this trend, the long-term side effects and adverse effects of chemotherapy have an increasingly important bearing on the quality of life of these patients.

Among other side effects, the occasionally reported neurotoxicity of these drugs and drug combinations [1–7] should be given greater consideration in planning treatment regimens. Neurotoxicity may cause cerebral metabolic changes which can be identified by electroencephalography (EEG). The investigations which have been carried out so far have been for the most part retrospective and have shown that various antineoplastic agents, especially vincristine [8–10], methotrexate [11–13] and asparaginase [14–16], may cause generalized EEG changes as well as focal disturbances and paroxysms.

In the prospective pilot study reported here, the aim was to establish whether high doses of cytotoxic agents, as used in the treatment of childhood neoplasia, gave rise to EEG changes and, if so, what was the nature of these changes and how long did they last. The EEG recordings were analysed by conventional methods and by computerized spectral analysis. Computer-aided spectral analysis makes it possible to measure what proportion of the total EEG activity is accounted for by the various frequency bands and to plot it as a spectrum. In this way, the dominant and subdominant frequencies of the background activity of various regions of the brain may be precisely determined, allowing precise monitoring of any frequency variations [17].

MATERIALS AND METHODS

Patients

Electroencephalographic investigations were carried out in 17 patients with various types of neoplastic disease. The patients comprised 14 male and 3 female patients, aged from 8 to 16 yr (mean age 12.6 yr). The patients were studied during one or more courses of treatment with cytotoxic agents. Nine of the patients had previously received treatment with cytotoxic agents. The other 8 patients had not received any antineoplastic therapy before the present study. Neoplastic involvement of the brain or other disorders of the central nervous system were not present in any of the patients.

In all of the patients an EEG was recorded immediately before administration of the cytotoxic agent. A further EEG recording was made 24 hr after administration of the drug,

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except for one patient where, due to the treatment schedule, EEGs were recorded 12, 24 and 48 hr after administration of the drug. Altogether, 17 patients received 49 courses of cytotoxic treatment during the study. During the study 106 electroencephalograms were recorded. During each course of treatment all symptoms reported by the patient (headaches, dizziness, nausea) were recorded and general clinical and neurological examinations were carried out. In addition, the following biochemical tests were run: electrolytes (Na, K, Ca, Cl), glucose, uric acid and blood pH.

Table 1 gives a breakdown of the type of disease, treatment given and the number of EEG recordings made. The treatment schedules for cytotoxic treatment were as follows:

Course A. Vincristine: 0.05 mg/kg body weight (maximum single dose 2 mg) i.v.; methotrexate: 7.5 g/m^2 body surface by infusion over 6 hr; citrovorum factor: 15 mg i.v., 3 hr after infusion of methotrexate (see above), then 9 injections every 3 hr i.v., followed by 8 doses orally every 6 hr.

Course B. Methotrexate: 500 mg/m^2/24 hr, 1/3 dose i.v., 2/3 dose by i.v. drip infusion over 24 hr methotrexate intrathecal: 12 mg/m^2 (maximum single dose 15 mg) 2 hr after the start of the infusion.

Course C. L-Asparaginase: 600 units/m^2/day i.v. for 10 days.

Course D. Vincristine: 1.5 mg/m^2 (maximum single dose 2 mg) i.v. one day 1; adriamycin: 75 mg/m^2 i.v. *or* actinomycin D: 2 mg/m^2 i.v. on day 2.

Course E. Vincristine: 1.5 mg/m^2 (maximum single dose 2 mg) i.v. on day 1; cyclophosphamide: 500 mg/m^2 i.v. on day 2; 5-fluorouracil: 300 mg/m^2 i.v. on day 2.

Course F. Vincristine: 2 mg/m^2 (maximum single dose 2 mg) i.v. on day 1; actinomycin D (A-D): 2 mg/m^2 i.v. *or* adriamycin (ADR): 60 mg/m^2 i.v. on day 1; cyclophosphamide: 45 mg/kg body weight i.v. on day 2.

Course G. Cytosine arabinoside: 150 mg/m^2/day i.v. for 5 days.

Course H. Cyclophosphamide: 1200 mg/m^2 i.v.

Course I. Cytosine arabinoside: 100 mg/m^2/day i.v. for 7 days; VP 12-213: 100 mg/m^2/day i.v. for 5 days.

The EEGs were recorded on an 18-channel Van Gogh electroencephalograph, recording from bipolar leads and against a Goldman–Offner average reference lead. Twenty-one ball

Table 1. Breakdown of patients

Patient	Age in years	Diagnosis	Number of EEG recordings	Type and number of treatment courses
B.D. ♂	13	Ewing's sarcoma	14	A × 6
M.L. ♂	12	Ewing's sarcoma	10	D × 3 and E × 3
F.M. ♂	16	Ewing's sarcoma	7	F (ADR) × 1 and F (without ADR / without A-D) × 1
C.M. ♀	11	Ewing's sarcoma	4	D × 1 and E × 1
M.B. ♂	15	Ewing's sarcoma	7	F (A-D) × 2 and (ADR) × 2
S.P. ♂	13	ALL*	8	B × 3 and C × 1
J.O. ♀	9	ALL	2	B × 1
Ro.M. ♂	9	ALL	2	B × 1
R.G.L. ♂	11	ALL	2	B × 1
O.R. ♂	8	ALL	2	B × 1
G.B. ♂	13	ALL	6	B × 2
K.W. ♂	13	AML†	3	I × 2
G.U. ♂	15	Non-Hodgkin's lymphoma	8	F (ADR) × 2
Z.R. ♂	15	Non-Hodgkin's lymphoma	4	H × 1 and G × 1
R.M. ♂	11	Reticulum cell sarcoma of the lower jaw	4	G × 1 and (A-D) × 1
V.J. ♂	14	Malignant tumour of the chest wall	3	F (without ADR without A-D) × 1
L.S. ♀	11	Ovarian stroma cell carcinoma	20	F (A-D) × 5 and (ADR) × 5

*ALL = acute lymphatic leukaemia.
†AML = acute myeloid leukaemia.

electrodes were placed on the scalp according to the international ten–twenty system.

In order to make the recordings as far as possible under standardized conditions, and to avoid EEG changes due to drowsiness, the patient was required to fix his gaze on a light source for a period of one minute. Immediately after this, the patient was asked to close his eyes and the EEG was then recorded on analogue magnetic tape. The EEG recordings were evaluated visually by two experienced physicians, working independently, and were also subjected to automated analysis.

Automatic spectral analysis was carried out on a Bio 16 computer (AEG-Telefunken) using an EEG spectral analysis programme (ESAP) [17]. Ten 4-sec segments of an artefact-free trace from each derivation were subjected to computer analysis. The analysed data were accessed via an output tape and presented graphically and in tabular form. Data on the dominant frequency in the alpha band and on the relative power of the alpha, theta and delta activity in the parietal and occipital regions were analysed. In our spectral analysis programme the dominant frequency is that at which the electroencephalographic waves have maximum amplitude. This frequency is expressed in Hz. The relative power of the alpha activity is the area under the spectral curve contained within the alpha band (7.5–12.5 Hz) as a percentage of the area containing all the frequency bands of a trace. The relative power of the theta activity (3.5–7.5 Hz) and delta activity (0.5–3.5 Hz) are calculated in a similar fashion.

RESULTS

Effects of cytotoxic agents on background activity

Background activity before and 24 hr *after administration of cytotoxic agents.* Only in 4 out of 17 patients was a decrease in dominant frequency of about 1 Hz and a decrease in relative power of the alpha activity of about 20–30% observed in at least one course of treatment. This decrease was confirmed both by visual (Fig. 1) and by automated (Fig. 2) analysis. These EEG changes were no longer observed in recordings carried out 6–28 days later. These 4 patients were not homogeneous with respect to the underlying disease or with respect to the medication received.

The first patient was a 13-year-old boy (B.D.) with an osteogenic sarcoma of the left humerus. This patient showed well-defined slowing of the EEG on each of 6 occasions after receiving Course A (high-dose methotrexate and vincristine). Exceptionally, EEGs were recorded in this patient 12 hr as well as 48 hr after administration of methotrexate, and it may be assumed that in this case the EEG changes occurred within the first 12 hr and passed off within 3–5 days. Whereas these EEG changes were observed after high doses of methotrexate (doses of 7.5 g/m^2 body surface) in this case, no clear EEG changes were observed in 5 other patients who received 9 courses of treatment with moderately high doses of methotrexate (Course B).

In the second patient (L.S.), an 11-year-old girl with a stroma cell carcinoma of the left ovary, a total of 10 courses of treatment with cytotoxic agents (Course F) were administered

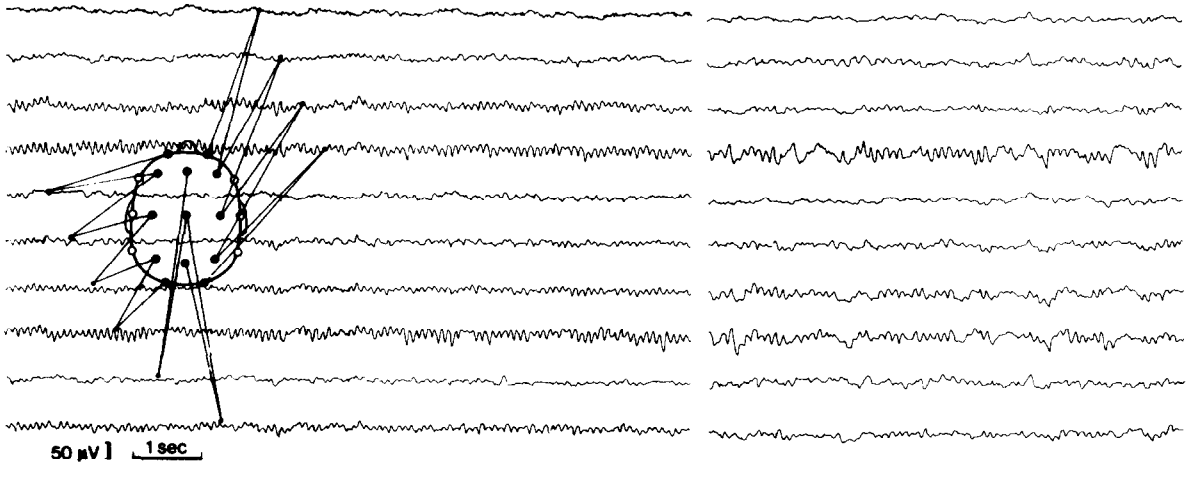

Fig. 1. *Conventional recording of* 1 *out of* 4 *patients in whom transient changes of electrical brain activity were observed after administration of cytotoxic agents (B.D., male,* 13 *years old). Left: regular* 10.5 Hz *alpha background activity before a course of cytotoxic treatment (Course A). Right:* 24 hr *after administration of cytotoxic agents the background activity is irregular, slowed to* 9 Hz *and interspersed with delta and theta waves, mainly on the right side.* (*Time constant* 0.3 sec.)

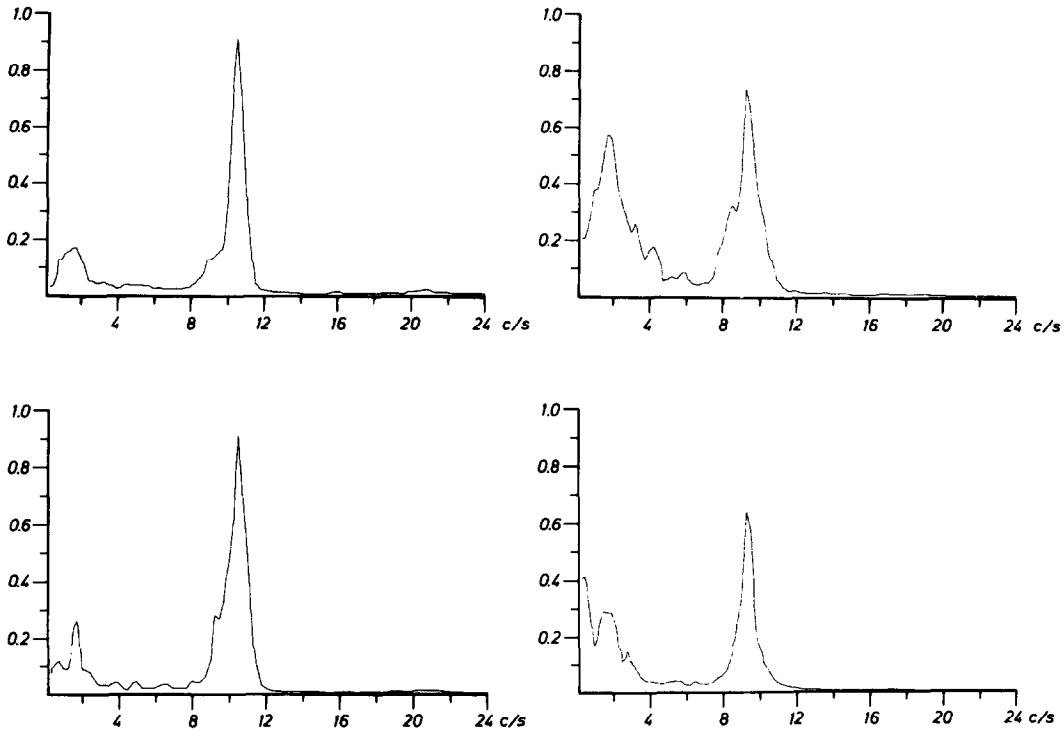

Fig. 2. Power spectrum normalized as function of frequency of a 40-sec segment (parieto-occipital bipolar leads) of the EEG recording shown in Fig. 1. Right hemisphere above, left hemisphere below. Before a course of treatment with cytotoxic agents (left) there is a high peak around 10.5 Hz. Twenty-four hours after administration of the cytotoxic agents (right) the spectrum has been shifted towards slower frequencies.

at regular intervals of one month. In 5 of these courses of treatment there was a decrease in the dominant frequency and in the relative power of the alpha activity 24 hr after administration of the drugs. One month later, immediately before the beginning of the next course of treatment, these slowings were no longer detectable.

We observed significant EEG changes after the administration of cytotoxic agents in another two patients. One of these patients (V.J., 14 years old), suffering from a malignant tumour (Ewing's sarcoma) of the right thoracic wall, showed a decrease in the dominant frequency and in the relative power of alpha activity 24 hr after intravenous injection of vincristine and cyclophosphamid. These changes were detectable both by spectral analysis and by visual evaluation.

Another 13-year-old patient (S.P.) was suffering from acute lymphatic leukaemia (ALL). In this patient 4 different courses of treatment were monitored electroencephalographically. In 3 of these courses of treatment methotrexate was administered alone (Course B) or in combination with vincristine. During these 3 courses of treatment the EEG did not show any changes as compared with the pretreatment record. During a further course of treatment (Course C) the patient received 600 units of L-asparaginase (Crasnitin®) per day for 7 successive days. Twenty-four hours later the EEG showed a significant decrease in dominant frequency and in relative alpha activity as compared with the EEG recorded before the beginning of this course of treatment.

Two of these four patients (L.S., V.J.) were given anti-emetics to control the severe nausea caused by the cytotoxic agents. In these cases it was not clear whether the EEG changes should be attributed to the cytotoxic agents or to the anti-emetics. In order to answer this question, an additional investigation was carried out in patient L.S. The patient received two anti-emetics (Largactil® and Torecan®) *without* cytotoxic agents and EEGs were recorded after 8 and 24 hr. There was no decrease in the dominant frequency in the alpha band or in the relative power of alpha activity as compared to an EEG recorded immediately before the anti-emetics were given. For administrative reasons it was not possible to carry out similar investigations in patient V.J., nor was it possible to carry out detailed EEG follow-up studies in these four patients.

Long-term studies of background activity. In 5 children who had received at least three courses of treatment with cytotoxic agents, the

dominant frequency in the alpha band and the relative power of alpha, theta and delta activity before the first and before the last courses of treatment were compared. In two cases (G.B., M.B.) the dominant frequency in the alpha band was increased by 0.25 and 0.30 Hz respectively within 4 and 6 months, while there was a slight increase in the relative power of alpha activity and decrease in theta and delta activity. In the other three cases no clear changes in the EEG were recorded within $1\frac{1}{2}$, 2 and 10 months. None of the long-term studies revealed any slowing of the EEG.

Paroxysmal EEG changes

In two patients (Z.R. and V.J.) sub-clinical EEG paroxysms with spike and wave complexes were recorded even before administration of the cytotoxic agents. One of these patients (Z.R.) was suffering from cerebral palsy, presumably due to birth trauma. This patient had not previously been treated with cytotoxic agents. The second patient (V.J.) had previously been treated with vincristine, actinomycin and cyclophosphamide several months before the beginning of the present study. In both cases, the paroxysms were not exacerbated by the cytotoxic therapy.

In another four patients (M.L., F.M., O.R. and R.G.L.), in whom there were no paroxysmal changes in the initial electroencephalogram, isolated bursts of slower or sharp waves without spikes were recorded 24 hr after administration of the cytotoxic agents. These were transient changes which were no longer in evidence one week later.

DISCUSSION

In 17 patients (14 male and 3 female), aged from 8 to 16 yr, treated with cytotoxic agents for neoplastic disease, conventional and spectral analytical EEG studies were carried out immediately before and 24 hr after administration of the cytotoxic agents. In the majority of cases more than one study was carried out since the patients received several courses of treatment. In 13 cases there were either no changes at all in the EEG background activity or the changes which occurred were not evaluable.

In 4 out of 17 (24%) patients we observed a decrease in dominant frequency of about 1 Hz and a decrease in relative power of the alpha activity of about 20–30% 24 hr after the administration of cytotoxic agents. These EEG changes were transient and were no longer in evidence in EEGs recorded 6–28 days later. The changes were not accompanied by clinical or biochemical signs of neurotoxicity. The 4 patients showing EEG changes did not receive the same treatment. One patient received very high dose methotrexate, 2 patients received vincristine in combination with other cytotoxic agents and the other patient received L-asparaginase. We suspect that in the great majority of cases the blood–cerebrospinal fluid barrier or the blood–brain barrier must be impaired before intravenous cytotoxic therapy can cause EEG changes.

There is no evidence that repeated treatment with cytotoxic agents can lead to long-term changes in EEG background activity. In 5 children who received at least 3 courses of treatment with cytotoxic agents within a period of $1\frac{1}{2}$–10 months, there was no decrease in the dominant frequency or in the relative power of the alpha activity.

No clinical signs of epilepsy were observed in any of the 17 cases investigated here during treatment with cytotoxic agents. Sub-clinical spike and wave complexes recorded in two patients before the start of treatment were not exacerbated during treatment. Isolated bursts of slow waves and/or sharp waves without spikes were recorded in only 4 cases 24 hr after administration of the cytotoxic agents. Thus there is no evidence that cytotoxic agents, in the dose range used here, have a convulsant effect, even in children, who are known to be more prone to epileptiform reactions than adults.

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