EEG prediction of brain metastases

A controlled study with neuropathological confirmation

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SYNOPSIS A retrospective study comparing the EEG findings of two groups of patients with primary systemic malignant disease (mainly bronchial carcinoma) was carried out. One group of 13 patients (20 EEGs) had proven supratentorial cerebral metastases at necropsy, some also subtentorial, and the other group of 10 patients (15 EEGs) had no cerebral involvement at necropsy. The latter group was studied to assess the possible confusing effects in the EEG of metabolic derangements and other factors which would interfere with accurate prediction of the presence of metastases. The EEGs were masked and assessed independently by two raters using a special proforma. They found that recordings from patients with cerebral metastases had persistent focal delta activity, intermittent focal or local delta activity, persistent or intermittent lateralized delta activity, monorhythmic frontal delta activity in the alert patient, as well as a higher frequency of post-central background rhythms. These factors predicted the presence of cerebral metastases (when they were 2 cm in diameter or larger) in 12 out of the 13 patients (four of these without localized neurological disorder), the EEGs being taken on average eight weeks before death. It is concluded that the EEG is valuable in the investigation of these patients.

Clinicians planning treatment for patients with proven primary malignant disease seek help from the electroencephalographer in the detection of possible cerebral metastases. The electroencephalographic (EEG) changes produced by such deposits are already well known (Van de Drift and Magnus, 1961; Fischer-Williams *et al.*, 1962), and the value of the EEG was also shown by Strang and Marsan (1961) in a combined EEG and neuropathological study. However, the assessment of recordings from patients with malignant disease can be difficult because of confusing factors. These patients may often have involvement of several organs, which leads, for example, to disturbance of electrolytes, raised blood urea, and biochemical changes associated with jaundice. In addition, profound alterations in the EEG may result from treatment with chemotherapeutic agents (Rudolf, *et al.*, 1973), hormones, and tranquillizers. All of these may

reduce the reliability of EEG assessment of patients suspected of having cerebral metastases.

The present study was carried out in order to overcome some of these difficulties and reassess the value of the EEG in patients with malignant disease. It was designed to use only cases proven at necropsy and 'blind' EEG rating procedure. Some of the preliminary findings have already been reported (Rowan *et al.*, 1971), but here we give a more detailed account and emphasize particularly the importance of monorhythmic frontal delta activity.

METHOD

PATIENTS All patients in the investigation were adults who fulfilled the following three criteria: firstly, referral to the EEG Department for assessment of suspected secondary deposits in the brain; secondly, pathological confirmation of malignant disease in the body apart from the brain; thirdly, neuropathological proof of the presence or absence of a cerebral metastatic lesion or lesions. The particular cases selected all had supratentorial deposits with or without cerebellar lesions. Patients who had

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systemic malignant disease but unrelated cerebral conditions, such as primary intracerebral neoplasms, meningiomas, or cerebral infarction, were excluded.

The patients for the study were selected using the EEG Department's computer file (Krauthammer *et al.*, 1966) from 1965 to the present time, and the ordinary department files to 1954. Difficulty was experienced in finding adequate numbers for the non-metastatic group, while there were many with confirmed brain metastases. Indeed, patients without cerebral metastases had obviously been 'selected out' at every stage. They were often not sent for EEG unless they had symptoms referable to the brain. Further, those not suspected of having cerebral disease sometimes had no neuropathological examination. Hence, this group may not be entirely typical of patients with systemic malignant disease without cerebral metastases. In spite of these problems, an attempt was made to keep the metastatic and non-metastatic groups similar in relation to number of patients, age, sex, and site of primary tumour as well as in the timing of EEGs in relation to death.

Twenty-three patients fulfilled all the criteria and composed the two groups as follows: 13 patients (20 EEGs) with proven cerebral metastases and 10 patients (15 EEGs) in the group without cerebral metastases.

The twenty-three patients in the metastatic group ranged in age from 37 to 66 years (average 53.5 years) and in the non-metastatic group from 43 to 78 years (average 65.2 years). The site of the primary tumour was the bronchus in eight of the 13 in the metastatic group and five of the 10 in the non-metastatic group. In the remainder, the primary tumours included three from breast, two each from kidney and stomach, and one each from cervix, oesophagus, and skin (malignant melanoma). The interval between the last EEG and death averaged in the metastatic group 37 days and in the non-metastatic group 40 days. Most patients had one EEG recorded within a month of

death but in both groups there were three patients in whom the EEG nearest to demise was taken as long as three months before. The average duration of illness—that is, the known length of time that the patient had had a primary tumour—was somewhat different in the two groups; it was three years for the metastatic group and for the non-metastatic one and a half years.

The metabolic states of the two groups were also somewhat different: patients in the group without cerebral metastases all had a raised sedimentation rate; five also had an elevated blood urea nitrogen and the majority were anaemic and some were cachectic.

In addition to the finding of suitable patients, the EEG computer file was also used in a search for all patients, whether with malignant disease or not, who were coded as having monorhythmic frontal delta EEG activity (MFD). This is one of the many features that are noted on a tick sheet completed at the time the EEG is reported. The computer print-out also gives the referral diagnosis, hence the relative frequency of MFD for the different diagnostic categories can readily be obtained. In all there were 301 patients coded as having MFD.

RATING PROCEDURE The EEGs, none of which had previously been seen by either of the two raters (A.J.R. and N. de M. R.) were selected and coded by D.F.S. In addition, they were masked so that the name and other information were not available except as specified below. Annotations made by previous reporting electroencephalographers were also obliterated. The order of the records was randomized and the raters were required not only to work independently but in opposite directions, one starting from EEG no. 1 and rating to record 35 and the other *vice versa*.

The two raters had quite different EEG training and experience, so preliminary sessions were held. For these a separate series of tracings showing a variety of focal disorders was used and on them the

TABLE 1
PRINCIPAL TYPES OF SLOW ACTIVITY IN EEGS OF METASTATIC AND NON-METASTATIC GROUPS

Group	Delta				Diffuse slow activity (theta or delta)	MFD
	Persistent focal	Intermittent focal or local	Persistent lateralized	Intermittent lateralized		
Metastatic (20 EEGs)	9	3	3	9	18	13
Non-metastatic (15 EEGs)	1	0	0	2	14	9

Significant differences, using a Chi square test, between the groups in column 1 ($P < 0.01$), columns 2 and 3 combined ($P < 0.001$) only.

raters established agreed operational criteria for the abnormalities seen. They recorded their assessments on a proforma especially devised for the project. This allowed information about important EEG parameters to be scored in a semiquantitative fashion. The only non-EEG information available to the raters was the age, handedness, drugs given, and level of arousal of the patient. Frequency and asymmetries of alpha rhythm were noted, as were similar aspects of beta activity. Attention was paid to slow components whether theta or delta activity, in particular whether diffuse, lateralized, local, or focal. In addition to this, their amplitude and persistence were noted. MFD was similarly but separately assessed. The occurrence of sharp waves and spikes and their location were also scored. Responses to hyperventilation and photic stimulation were noted but, as these activations were carried out inconsistently because the patients were often seriously ill, information on these was subsequently disregarded.

After the raters had finished their assessments, discrepancies were discussed and an agreed 'assessment' was obtained in each case. Only when this had been done were the patients' case notes examined and detailed information extracted from the pathological files. As a result cross-contamination of the EEG and other data was reduced to a minimum.

TABLE 2
MONORHYTHMIC FRONTAL DELTA ACTIVITY (MFD)
RELATED TO LEVEL OF AROUSAL

Group	With MFD		No MFD	
	Alert	Not alert	Alert	Not alert
Metastatic (20 EEGs)	11	2	4	3
Non-metastatic (15 EEGs)	0	9	5	1

Significant differences, using a Chi square test, between columns 1 and 2 ($P < 0.001$).

RESULTS

Focal delta activity which was persistent occurred in nine of the 20 EEGs in the metastatic and one of the 15 recordings from the non-metastatic group (Table 1). Intermittent focal or local and persistent lateralized delta activity appeared in six EEGs in the metastatic group and was not seen in the non-metastatic category. Intermittent lateralized delta activity was noted in nine of the tracings from the metastatic and in two from the

TABLE 3
EEG, NEUROLOGICAL, NEUROPATHOLOGICAL FINDINGS IN 13 PATIENTS WITH METASTATIC DEPOSITS

Case no.	EEGs (no.)	Timing before death (months)	Main EEG features		Localized neurological signs	Pathology (largest diameter) (cm)
			Type	Site		
1*	1	3	Persistent focal delta, MFD	R. frontal	Nil	Multiple, including cerebellar (5 × 2.5)
2	1	1	Local theta, MFD	R. frontotemporal	L. hemiparesis	Multiple (4)
3	2	30-10 d	1st diffuse theta 2nd local delta, MFD	L. temporal	R. homonymous hemianopia	Multiple (2.5)
4	2	4-1	1st nil definite 2nd nil definite		Nil	Multiple (1.5)
5	1	5	Persistent focal delta, MFD	R. temporal	L. hemiparesis	Multiple (5 × 5)
6	1	3 w	Local delta, MFD	R. temporal	R. facial weakness	Multiple (6)
7	1	3 w	Persistent focal delta, MFD	L. frontal	R. hemiparesis	Single (7)
8*	3	2½-1	1st diffuse delta 2nd persistent focal delta 3rd persistent focal delta, MFD	R. hemisphere R. frontotemporal R. frontotemporal	Nil	Single (2.5 × 3.5)
9*	2	30-10 d	1st nil definite 2nd local delta, MFD Localized theta, MFD	L. frontal	Nil	Multiple, including cerebellar (2.0) Multiple (3 × 2.5)
10	1	4½			L. facial weakness, R. hemiparesis	
11	3	1-½	1st diffuse delta, localized sharp waves 2nd persistent focal delta, MFD 3rd persistent focal delta, MFD	R. frontal R. frontal L. frontotemporal	L. sided Jacksonian fits	Single (2.5 × 1.5)
12	1	3 d	Persistent focal delta, MFD	L. frontal	R. hemiparesis	Single (6)
13*	1	4	Persistent focal delta, MFD	L. frontal	Nil	Multiple, including cerebellar (2.5)

* Patients with no focal neurological signs, but definite EEG changes (see text). d = days. w = weeks.

non-metastatic group. Diffuse slow activity, a combination of theta and delta activity in varying proportions, was seen more or less equally from the EEGs of both groups. There were two EEGs in the whole series from the metastatic group of patients showing intermittent focal or localized theta waves without any delta activity. However, in both instances there were diffuse mixed theta and delta components and MFD.

Monorhythmic frontal delta activity characterized 13 of the 20 EEGs from the metastatic group and nine of the 15 EEGs from the other category. However, when the state of awareness of patients was considered differences emerged between the groups (Table 2). Considering only recordings when the patient was reported to be alert, MFD occurred in 11 of the 20 EEGs in the metastatic group but was not seen at all in any of the 15 EEGs in the non-metastatic group of patients. The possible relationship of the occurrence of MFD to cerebellar metastases was next studied. Four EEGs from patients with cerebellar lesions had MFD and one did not; the tendency for this association did not reach statistical significance.

Other features which distinguished the EEGs of metastatic from non-metastatic groups of patients included the frequency of post-central background activity which was on average 7 Hz in the non-metastatic and 8 Hz in the other category. Asymmetries of this background activity were not seen in the non-metastatic group of EEGs but asymmetries of amplitude were apparent in eight EEGs and asymmetries in amount in seven EEGs of the metastatic category. Both amplitude and amount tended to be depressed on the side of the lesion, with the exception of those tumours which were exclusively in the frontal lobe. Asymmetries of beta activity did not appear to be helpful in separating the two categories of patient.

Sharp waves or spikes alone or in combination occurred in the EEGs of both groups, in five (three from one patient) of 20 in the metastatic and three (two from one patient) of the 15 in the non-metastatic category. There were no spike and wave complexes. Only one patient with a seizure disorder had sharp waves in the EEG. This patient had metastases.

The various EEG features which had been shown to characterize the tracings of patients in

the metastatic group were considered together in relation to the neurological and neuropathological findings as well as the timing of the individual EEGs before death of the patient (Table 3). Only one of these patients (no. 4), on whom the recordings were carried out one and four months before death, had entirely negative EEG findings. He had no localized neurological abnormality and at neuropathological examination there were multiple metastases, all of which were 1.5 cm or less in diameter. In all other patients metastases were at least 2.0 cm in diameter. A further four patients (nos 1, 8, 9, 13, marked with asterisks in Table 3) had no localized neurological disorder but all had definite EEG findings. Two patients (nos 1 and 13) with single recordings showed definite focal delta and MFD activity. A further patient (no. 8) had

TABLE 4
OCCURRENCE OF MONORHYTHMIC FRONTAL DELTA
ACTIVITY IN 301 PATIENTS

Disorder	(No.)	(%)
Intracranial tumours	82	29.5
Cerebrovascular disease	58	19.3
Epilepsy of unknown aetiology	40	13.3
Head injury	35	11.6
Endocrine and metabolic	24	8.0
Intracranial infarction	21	7.0
Psychiatric	16	5.3
Other neurological (including degeneration)	14	4.7
Malformations of cerebrospinal pathways	4	1.3
Total	301	100.0

three EEGs, two of which showed focal delta activity and MFD; the other one, more distant in time from the death of the patient, showed only diffuse delta activity. A fourth patient (no. 9) is of particular interest as the first recording taken 30 days before death was entirely negative. However, that recorded 20 days later showed localized delta and theta activity as well as MFD. Taking the group as a whole and considering the timing of the EEGs, it was noted that a definite abnormality could be observed eight weeks before death whether neurological signs were present or not.

As monorhythmic frontal delta activity was a phenomenon of particular importance in the

interpretation of the EEGs from patients with malignant disease, it was examined in a wider context, by use of the EEG department's computer file. MFD occurred in 30% of all patients who had intracranial tumours and of these a third were metastatic and two-thirds of primary type (Table 4). Other prominent causes of MFD were cerebrovascular disease, epilepsy, and head injury, but 8% of the EEGs which showed this phenomenon were from patients with metabolic, electrolyte, and endocrine disorder and who did not have intracranial pathology.

DISCUSSION

Patients with malignant disease are sent regularly to the EEG Department when there is some indication of cerebral dysfunction, even if the features are non-specific or ill defined—for example, headache or drowsiness—whether or not there are demonstrable neurological signs. If abnormal, the EEG can provide useful information for the clinician in deciding whether to proceed with removal of a primary tumour or to embark on a course of less radical treatment. Strang and Marsan (1961) in their EEG study of patients with cerebral metastases comment that confusing factors such as a raised blood urea or deranged liver function may either mask or simulate neurological signs and make EEG interpretation more difficult. We therefore set out to reassess the usefulness of the EEG in determining whether cerebral metastases were present or not in the face of these 'confusing factors'.

The use of 'blind' rating of EEG phenomena has been shown in a variety of clinical and research situations to be of great value in increasing the power of the EEG (Speirs *et al.*, 1972; Swash and Rowan, 1972). Bias in the assessment is eliminated and fine differences emerge which may be tested statistically. In the present study pathological confirmation is of greatest importance as contamination of the control group by other types of disease can be avoided. It proved difficult to obtain an appropriate control group that matched the study group but this approach uniquely characterizes our study and allows clear statements to be made on the findings in both groups. Using these techniques, we were able to show not only that

persistent or intermittent focal delta activity occurred in the EEGs from patients with metastatic disease, a fact well known to other authors (Van der Drift and Magnus, 1961; Fischer-Williams *et al.*, 1962), but also that persistent or intermittent lateralized delta waves were observed more or less exclusively in the EEGs from patients with secondary brain tumours. On the other hand, diffuse slow activity, both in the theta and delta ranges, was seen more or less equally in the metastatic and the non-metastatic groups. The post-central background activity also had some value in discriminating between EEGs of one group and the other. It was found that in the non-metastatic group the background activity was 1 Hz less than for the other category. Asymmetry of its amount and amplitude was also observed. There was a diminution in both amount and amplitude in a high proportion of those EEGs from patients with metastases and this was not observed in the other category of EEG.

A further refinement of the criteria for diagnosis of secondary deposits was shown by the detailed study of MFD. This phenomenon often regarded as a sign of a deep-seated lesion (Van der Drift, 1957) seemed initially to be equally prevalent in the EEGs from the two groups of patients. However, the phenomenon, if found in a patient who was alert, was a useful sign indicating the presence of brain secondaries. Taking this in a wider context it occurred in a variety of disorders as reported earlier by Cordeau (1959). However, in the present study, almost 10% of 301 patients showing MFD had no cerebral disease and were diagnosed as having metabolic, endocrine, or electrolyte disturbance alone. This fact probably accounts for the occurrence of the phenomenon in the patients without cerebral metastatic lesions since this group had severe systemic disorder with raised sedimentation rate and elevated blood urea nitrogen—features rarely seen in our group of patients with brain secondaries.

Using the various criteria already described, we were able to detect the presence of secondary deposits in 12 of the 13 patients in the series, a yield similar to that of Strang and Marsan (1961). Only one patient had a completely normal EEG and, in addition, there were no focal neurological signs. We did not specifically set out to test the

view of Strang and Marsan that size was a critical factor in the prediction of a secondary deposit on EEG grounds but we did note that one patient in whom multiple lesions were less than 1.5 cm in diameter had a normal EEG. Four others had no localizing neurological signs and yet had definite EEG findings, sometimes months before death. There was however one striking false positive. This patient showed an anterior temporal delta wave focus with associated sharp waves and spikes in the same location but there was no clinical evidence of seizures. She was known to have a peripheral neuropathy thought to be related to her systemic carcinoma. Neuropathological investigation of the brain, however, was completely negative. No definite explanation could likewise be found for the lateralized intermittent delta activity in two other patients in the non-metastatic group.

This study confirms the view that the EEG can be of great value in the investigation of patients suspected of having cerebral secondary deposits. In combination with the radioisotope brain scan (Burrows, 1972), it forms a useful screening procedure which is non-invasive and therefore not particularly irksome for patients who, because of their basic condition, may be in great distress.

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