Journal of Neurology, Neurosurgery, and Psychiatry, 1981, **44**, 62–67

Epileptic phenomena in bismuth toxic encephalopathy

A BUGE, V SUPINO-VITERBO, G RANCUREL, AND C PONTES

From the Department of Neurology, Salpêtrière Hospital, Paris, France

SUMMARY Seventy patients admitted to hospital with bismuth encephalopathy had repeated clinical and EEG examinations. All the patients exhibited myoclonic jerks, but no paroxysmal features ever appeared on EEG. Computed tomography showed cortical hyperdensities. Seizures were observed in 22 patients, but epileptic EEG patterns appeared only when the bismuth blood level was below 1500 μg/l. It is suggested that a high cortical intracellular bismuth concentration induces a "cortical inhibition" which causes suppression of physiological electrical brain activity, the absence of EEG paroxysmal phenomena during myoclonic jerks, and explains the rarity of epileptic seizures.

In a previous paper we described clinical and EEG features, characteristic of the encephalopathy produced by oral intake of bismuth salts.[1] Of 45 patients then examined, 14 had presented with convulsive seizures, personally observed in four cases. One patient had a seizure during EEG recording, which demonstrated its epileptic nature. Some authors state[2] that epileptic phenomena in bismuth encephalopathy are very frequent but others feel that they are extremely rare.[3]

In order to decide this issue we studied 70 patients admitted to "La Salpêtrière" hospital, with special regard to epileptic phenomena, correlating EEG observations with bismuth levels in blood, urine and CSF. Computed tomography was carried out in five cases, which permitted us to visualise intracerebral bismuth at different phases of evolution of the encephalopathy.

Material and method

Seventy patients with bismuth encephalopathy were admitted to "La Salpêtrière" hospital between 1973 and 1978 There were 14 male patients aged 38 to 70 years and 56 females aged 24 to 84 years. All had received orally five to 20 g daily of bismuth subnitrate over a period ranging from four weeks to 30 years for complaints related to the digestive tract. EEGs were recorded daily during the acute phase of the illness, every two days during the recovery phase, and monthly afterwards during the first year. The EEG was recorded with standard equipment at a time constant of 0·3 s. The paper speed was 15 mms^{-1}, the amplification varied between 3·5 and 7·5 $\mu v\ mm^{-1}$ pen deflection. Photic stimulation was always carried out, but overbreathing could be performed only by patients able to cooperate. Two night records were carried out in three patients. Bismuth blood levels sampled every day ranged from 150 to 2200 μg/l (normal less than 20 μg/l). Levels from 200 to 9600 μg/l were found in urine and from 10 to 100 μg/l in the CSF. Five patients had computed tomography (CT) once; three patients twice. Four serial CT scans were obtained in another patient.

Since interruption of bismuth administration was the only specific therapeutic measure available supportive non specific therapy was the main regimen. Anticonvulsant drugs were not given routinely, because it was felt that their effect upon respiration would be harmful. However 5 to 10 mg diazepam was given intravenously if seizures tended to be repetitive. All the patients recovered within three to 12 weeks after interruption of bismuth administration. However, in a few cases some disorder of behaviour or memory persisted for a longer period.

Results

Myoclonic bismuth encephalopathy was separated in two clinical phases: (1) a prodromal period lasting from one week to several months during

Address for reprint requests: Dr V Supino-Viterbo, Clinique Neurologique, Hopital de la Salpêtrière, 47 Boulevard de l'Hopital, 75651 Paris Cedex 13, France.

Accepted 10 July 1980

which cognitive and affective disorders were predominant. The patients were asthenic, somnolent, depressed, anxious, sometimes with visual hallucinations and even delusion of persecution (three cases). Jerky movements of varying severity were seen in this phase (15 patients), and disturbances of writing and speech occurred more rarely; (2) a second phase of encephalopathy of rapid onset appeared abruptly in 24 to 48 hours. Four symptoms were constant: confusion (reaching coma or dementia) dysarthria, disturbances of walking and standing and pseudo-tremor accompanied by myoclonic jerks. Myoclonic jerks were always present in this phase; sometimes they predominated in the upper limbs and distally, at other times they were diffuse and involved the facial and axial muscles. They were increased by voluntary movements and by stimuli (change of position, noise).

The EEG showed a particular pattern already described by us,[4] with monomorphic waves three to five Hz involving both temporo-rolandic and frontal areas, unaffected by eye opening. No alpha rhythm was seen on the occipital regions, but in most patients there was a diffuse beta rhythm of low voltage (fig 1). In our present study of 70 patients, 22 had convulsive seizures, all during the peak of the illness, never during the prodromic phase or the recovery period. Seizures were mostly generalised with loss of consciousness, and marked clonic movements. The differentiation between repetitive myoclonic jerks and epileptic seizures was sometimes difficult. In most cases photic stimulation induced or increased myoclonic jerks, but no paroxysmal phenomena appeared on the EEG.[3 4] However, in our present series of 70 patients, two had convulsive seizures induced by photic stimulation consisting of recruiting symmetric bilateral spikes on the EEG initially bioccipital then diffuse. The seizures consisted of turning of the head to the right, raising of the left arm, followed by generalised clonic movements. No lateralisation appeared on the EEG before, during or after the seizure. These patients, however, also had spontaneous seizures with the same clinical semiology. Bismuth blood level was 800 μg/l in the first of these patients 1200 μg/l in the second.

In the acute phase of the illness, epileptic seizures seemed to have different electrical features related to the bismuth blood concentration, which in some way represents cerebral metal concentration. In all our patients, when bismuth blood level was above 1600 μg/l, the EEG was of very low voltage and there were no paroxysmal phenomena. Only in very long recordings could we observe a few polymorphic and sharp theta bursts preceded and followed by flat EEG. These theta bursts and the clinical seizures occurred concomitantly in one patient (fig 2). With lower bismuth blood level (below 1500 μg/l), paroxysmal phenomena appearing on the EEG and accompanying generalised clonic epileptic seizures occurred (fig 3). During the acute phase two patients showed lateralised abnor-

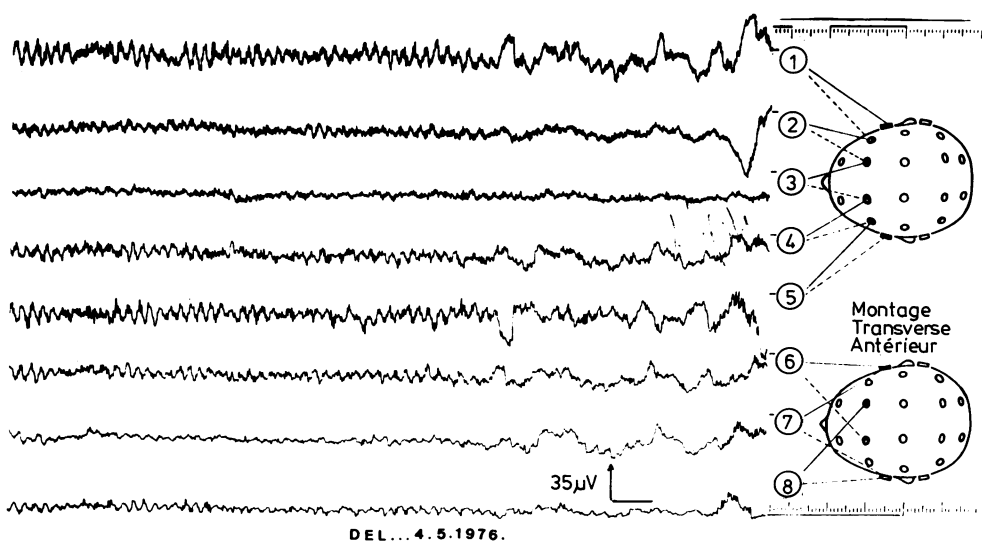

Fig 1 *Monomorphic 4–5 Hz diffuse activity characteristic of bismuth toxic encephalopathy in acute phase. Bismuth blood level 1600 μg/l. Calibration 35 μv, 1–5 s.*

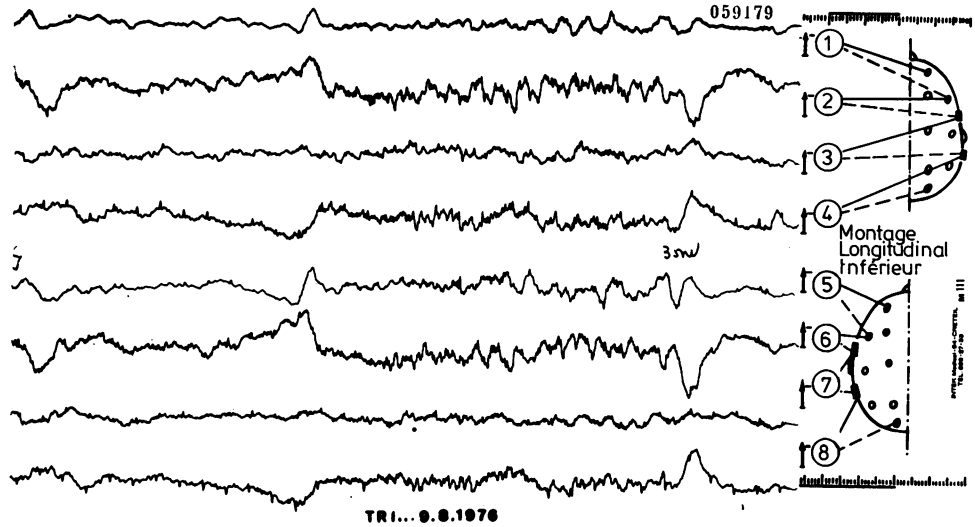

Fig 2 *Theta synchronous bursts preceded and followed by flat recording in a patient with concomitant epileptic seizures. Blood bismuth level 2200 µg/l. Calibration 35 µv, 1–5 s.*

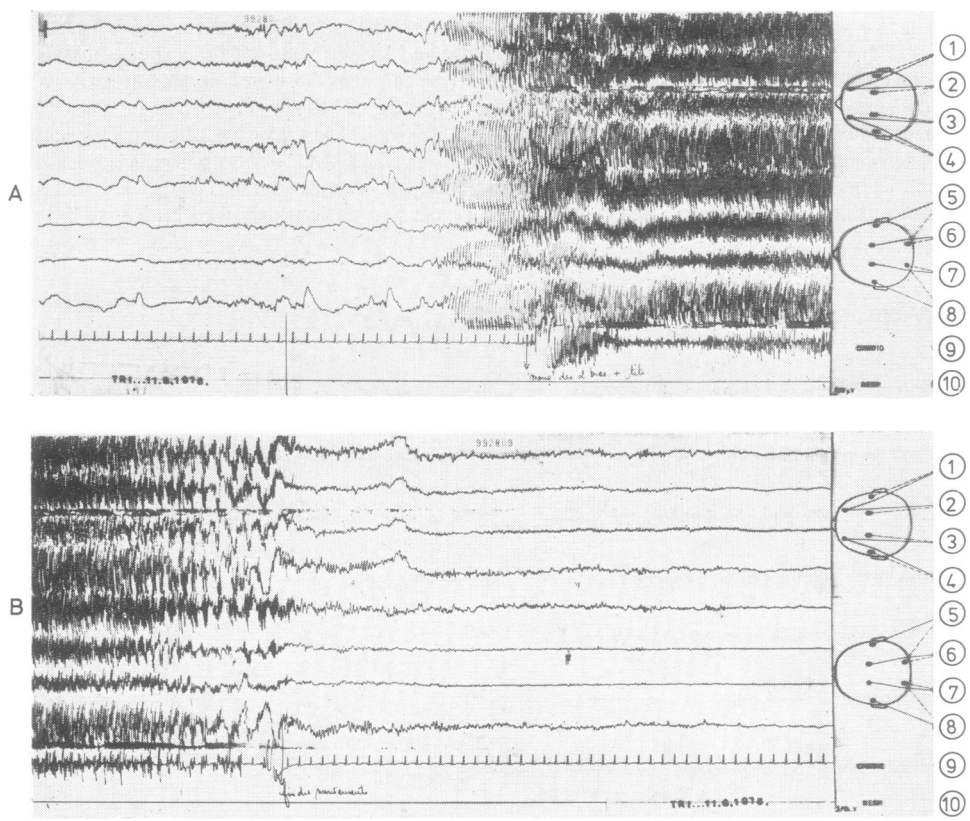

Fig 3 *Same patient as fig 2, two days later. Recording during tonic clonic seizure: A seizure start with recruiting diffuse spikes and tonic phase; B the tonic-clonic phase and end of seizure.*

malities or lateralisation of recruiting spikes during seizures. In one of these patients two CT scans were carried out; the first, two days after the interruption of bismuth intake, showed bilateral cortical areas of heterogenous hyperdensity in central grey nuclei and in the left temporo-insular regions; the second CT scan, 15 days later, showed a regression of these abnormalities, which nevertheless were still present in the same area.

We observed another phenomenon during recovery in three patients, namely the presence of slow theta-delta waves involving one side in the temporo-frontal region. A CT scan 20 days before in one of these patients, showed hyperdensity areas mainly in left temporal regions (fig 4). These EEG abnormalities appeared when the patient was recovering and the bismuth blood level was much lower (between 50 and 150 μg/l), and seemed to involve the regions where the bismuth concentration had been the highest.

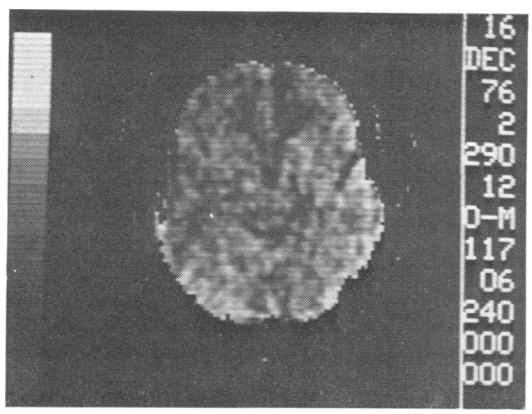

Fig 4 *45 yr old patient, 2 days after stopping bismuth intake. CT scan without injection of contrast, after bone substraction, showing heterogeneous diffuse areas of cortical hyperdensity, particularly in the left temporo-occipital regions and in temporo-insular region.*

Discussion

Bismuth toxic encephalopathies were first observed during an epidemic, which occurred simultaneously in Australia and France, between 1973 and 1977. The occurrence of 50 cases in Australia[5] and over 1000 cases in France[1 6 7] has not yet been explained. Bismuth levels in serum, urine and CSF have been often found to reach 2500 μg/l (atomic absorption method).[8] An accurate study of clinical and EEG data has shown a peculiar discordance between the frequency of clinical epileptic phenomena (myoclonic jerks and convulsive seizures) and the absence of paroxysmal events on the EEG. Our present study of 70 patients leads us to put forward the following comments: (1) myoclonic jerks are always present in the acute phase of the illness, but have no correlation with the EEG[3 4]; (2) seizures are less frequent than expected (22 in 70 patients), in spite of the high level of brain metal concentration in bismuth encephalopathy; (3) seizures appear when the encephelopathy is confirmed and never as a first symptom or during recovery.

Only five cases could be studied with CT scan during the acute phase of intoxication and again one or two years later during the sequelae or the recovery period. There are several anatomical reports of patients who died of acute bismuth encephalopathy; the most important study being that of Escourolle *et al.*[9] The bismuth levels measured with Castaing's micro catheter on these 12 brains were very high (reaching 25 mg/kg). Bismuth metal was mostly concentrated in cerebral cortex, particularly in frontal areas and in the temporo-parieto-occipital junction. Grey nuclei, thalamus and cerebellar cortex contained a similar level of bismuth. In the centrum semiovale and in white matter, much lower levels were found. CT examination in our five cases are in accord with these biochemical data (fig 4).

One patient who died of an accident, and whose bismuth blood level had already returned to normal, had a high concentration of intracerebral bismuth three months after recovery.[9] Even if bismuth blood level does not faithfully represent bismuth concentration in brain matter, it can be used to separate clinical, EEG and CT scan features in three phases: (1) *bismuth blood level above 2000 μg/l:* no paroxysmal phenomena appear in the EEG even during myoclonic jerks or convulsive seizures. The bismuth hyperdensities in the CT scan are very marked in these cases; (2) *bismuth below 1500 μg/l:* sharp abnormalities correlated with seizures appear on EEG. If they are lateralised or show a topographical predominance, CT scan suggests that these paroxysmal abnormalities first involve the cortico and subcortical areas where the hyperdensities (and therefore probably neuronal concentrations of metal) seem to be least, spreading then to the whole brain; (3) during the phase of recovery (*bismuth below 50 μg/l*), the epileptic phenomena disappear, but sometimes some slow abnormalities remain corresponding to the areas where the CT hyperdensity had been greatest.

Bismuth seems to facilitate slow and to inhibit paroxysmal phenomena in the EEG. The characteristic pattern of 4–5 Hz monomorphic, diffuse rhythm, already described by us in,[4] not influenced by stimulation and unchanged even during sleep,[10] could be interpreted as due to the presence of intra-cerebral bismuth. The bismuth in neurones and glia is probably the cause of the suppression of physiological distribution and reactivity of cerebral electrical activity. The striking absence of electrical paroxysmal events and the relative low frequency of epileptic seizures could be correlated to some property of the bismuth metal, which increases cerebral epileptic threshold, to cause a sort of "cortical inhibition".

Bismuth has a very high atomic number and relevant atomic weight. In contrast, aluminium, which has a low atomic number and low atomic weight, produces an encephalopathy characterised by very sharp EEG records and by convulsions.[11 12] Aluminium gel has been used locally to induce experimental epileptic foci in animals.

CT findings in bismuth encephalopathy, are characterised by hyperdensities, found in basal ganglia, cerebelum and in the cerebral cortex; they appear very clearly after bone substraction. They disappear slowly and are imperceptible by two to three months after the onset of the encephalopathy. These hyperdensities contrast with hypodensities of the white matter, which are observed in periventricular regions and in the centrum semiovale. The density of these abnormalities seems to depend on the very high atomic number (83) of bismuth metal. These CT hyperdensities are not increased by injection of contrast medium. Necropsy studies have shown a very uneven concentration of bismuth level in the brain, greatest in the regions rich in neurons. There is no necrosis, no haemorrhage, and no sign of gross alterations of blood-brain barrier. Finally no cerebral intraparenchymatous oedema was observed in the 5 cases.[13 14] The CT hyperdensities disappeared during recovery. Dilatation of ventricles and of cisternal spaces in all the patients disappeared one year after intoxication. On the other hand, in two patients out of five enlargement of cortical suci remained.

The CT aspects of bismuth encephalopathy appear completely different from those of other known encephalopathies. The cortical hyperdensities in the grey nuclei are found in no other intoxication by heavy metals. Lead encepholapathy shows oedema and necrosis and even micro haemorrhages, without CT hyperdensity.[15] Fahr's syndrome with calcifications of central grey nuclei and cerebellar dentate nuclei, is very different because of the selective topography and the higher density of calcium deposits compared to bismuth. All intracerebral calcifications are very easily distinguished from bismuth hyperdensities by their shape, their topography, and their limited extent. Bismuth hyperdensities are much more homogeneous, more continuous and diffuse, and always are bilateral. In Wilson's disease, there may be hyperdensities in the central grey nuclei, due to the accumulation of copper, but these remain of low intensity and are never found in the cortex. Hyperdensities due to angiomas and phacomatoses do not resemble those seen with bismuth encephalopathy.

References

1 Buge A, Rancurel G, Dechy H. Encéphalopathies bismuthiques. Données étiologiques et épidémiologiques. *Nouve Presse Méd* 1978; **7**:39, 3531–4.

2 Lhermitte F, Degos F, Signoret JL. Encéphalopathies réversibles par les sels insolubles de bismuth. *Nouve Presse Méd* 1975; **4**:419–20.

3 Gastaut JL, Tassinari CA, Terzano G, Picornel I. Etude polygraphique de l'encéphalopathie myoclonique bismuthique. *Rev Electroencephalogr Neurophysiol Clin* 1975; **3**:295–302.

4 Supino-Viterbo V, Sicard C, Risvegliato M, Rancurel G, Buge A. Toxic encephalopathy due to ingestion of bismuth salts: clinical and EEG studies of 45 patients. *J Neurol Neurosurg Psychiatry* 1977; **40**:748–52.

6 Burns R, Thomas D, Barron VJ. Reversible encephalopathy possibly associated with bismuth subgallate ingestion. *Br Med J* 1974; **1**:220–3.

6 Buge A, Rancurel G, Poisson M, Dechy H. Encéphalopathies myocloniques par les sels de bismuth. *Nouve Presse Méd* 1974; **3**:36, 2315–20.

7 Buge A, Rancurel G, Dechy H. Encéphalopathies myocloniques bismuthiques. Formes évolutives complications tardives, durables ou définitives. *Rev neurol* 1977; **133**:6–7, 401–5.

8 Bourdon R, Galliot M, Prouillet F. Dosage du cuivre, du plomb, du manganèse, du bismuth et de l'or dans les liquides biologiques par spectrométrie d'absorption atomique sans flamme. *Ann Biol Clin (Paris)* 1974; **32**:413–22.

9 Escourolle R, Hauw JJ, Bourdon R, Simon P, Jaudonm C, Gray F. Etude neuropathologique et toxicologique de 13 cas d'encéphalopathie bismuthique. *Rev neurol* 1977; **133**:153–63.

10 Billiard M, Besset A, Renaud B, Baldy-Moulinier M, Passouvant P. L'insomnie dans l'encéphalopathie bismuthique. *Rev Electroencephalogr Neurophysiol Clin* 1977; **7**:147–52.

11 Alfrey AC, Gary R, Legendre MS, Kachny WD. The dialysis encephalopathy syndrome. Possible

aluminium intoxication. *New Engl Med J* 1976; **294:**184–8.

12 Buge A, Poisson M, Masson S, Bleibel JM, Lafforgue B, Raymond P, Jaudon MC. Encéphalopathie prolongée et réversible chez un dyalisé chronique. Responsabilité probable des sels d' Aluminium. *Nouve Presse Méd* 1978; **7:**2053–9.

13 Gardeur D, Buge A, Rancurel G, Dechy H, Metzger J. Bismuth encephalopathy and cerebral computed tomography. *J Computer Ass Tomography* 1978; **2:**436–8.

14 Metzger J, Buge A, Rancurel G, Gardeur D. Aspects tomodensitométriques de trois observations d'encéphalopathies bismuthiques aigues. *Rev neurol* 1978; **134:**619–24.

15 Hungerford GD, Ross P, Robertford HJ. CT in lead encephalopathy. A case report. *Radiology* 1977; **123:**91–2.