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Paraneoplastic limbic encephalitis: clinico-pathological correlations

A M O Bakheit, P G E Kennedy, P O Behan

Abstract

Three new cases of limbic encephalitis in association with malignancy are reported. The literature on this condition is reviewed and the clinical, laboratory and histopathological features of cases proven at necropsy are correlated. The possible pathogenic mechanism of this disorder is discussed.

In 1960 Brierley *et al*[1] described three cases of subacute encephalitis with a clinical course of three, seven and 14 months in patients with oat cell carcinoma of the bronchus. At necropsy the main pathological changes were found in limbic structures, especially the hippocampal gyrus, Ammon's horn and amygdala. These changes consisted of subtotal neuronal loss, neuronophagia, astrocytic gliosis, microglial proliferation and perivascular cuffing. In contrast to herpes simplex encephalitis there were no intranuclear inclusion bodies and tissue necrosis was absent. Subsequently Corsellis *et al*[2] reported another three patients and reviewed similar cases in the literature. These authors were the first to recognise this complication as a non-metastatic manifestation of malignant tumours. To date 16 cases verified at necropsy with changes predominantly or only in limbic structures, have been reported in the English medical literature.[1-13] Most cases were associated with bronchogenic oat cell carcinoma, but other malignancies have also been implicated. We extend the observations of Brierley and others on this rare condition by describing three new cases.

Case reports

Case 1

A 64 year old right handed man had been well until seven to eight months before his admission to hospital in 1974. He presented with a history of progressive loss of recent memory and intermittent mental confusion. Although he could not give a detailed account of his illness, he had good insight into the fact that his memory was defective and he attributed this to "hardening of the arteries". There were no other symptoms.

The patient's past medical and family histories were non-contributory. He did not smoke and drank alcohol occasionally.

General physical examination revealed no abnormalities. His blood pressure was 140/70. On neurological examination he was mentally alert and cooperative but seemed somewhat euphoric. His speech was normal. Bedside assessment showed severe impairment of recent memory. For example, he was unable to recall a short sentence after three minutes. Memory for remote events, however, was preserved and there was no confabulation. His cranial nerves were intact, in particular there was no nystagmus or ophthalmoplegia. There was mild spasticity in the lower limbs but muscle power and coordination were normal in all limbs. Tendon reflexes were symmetrical and abdominal reflexes were present. Both plantar responses were extensor and there were no sensory or cerebellar signs.

On formal psychometric tests the patient's score on the Mill Hill vocabulary test was at the 90th percentile, indicating a verbal IQ of about 120, while on the Raven Matrices test he scored just below the 75th percentile. The latter score corresponds to a non-verbal IQ in the range of 105–110. On the Wechsler Memory Scale, however, his Memory Quotient was found to be 76. The overall picture therefore was that of unimpaired intellect with severe memory deficit.

His haemoglobin was 15·5 gm/dl. A full blood count, urea and electrolytes, liver and thyroid function tests and serum B12 were normal. Serological tests for syphilis in the blood and CSF were negative.

A chest radiograph demonstrated a mass in the right hilar region. Bronchoscopy was normal and a bronchial biopsy was not taken. However, cytological examination of bronchial secretions showed an inflammatory exudate with frequent macrophages but no malignant cells.

EEG revealed localised bursts of theta activity in the left fronto-temporal region but was otherwise normal. A brain scintiscan was normal and lumbar air encephalogram showed moderately severe symmetrical dilatation of the lateral ventricles and widening of the interhemispheric fissures. Cerebrospinal fluid (CSF) contained 40% protein of which 30% was gamma globulin. There were 21 lymphocytes per cu mm and no malignant cells. Lange colloidal gold curve was 0000000000.

The patient died from bronchopneumonia three months later. Necropsy examination revealed an oat cell carcinoma of the upper lobe of the right lung in addition to changes of bilateral bronchopneumonia. There were also a few small plaques of atheroma in the cerebral arteries but no stenosis or occlusion. On naked eye inspection of brain sections there was uniformly dark discolouration and

Glasgow University Department of Neurology, Institute of Neurological Sciences, Southern General Hospital, Glasgow, United Kingdom
A M O Bakheit
P G E Kennedy
P O Behan

Correspondence to:
Dr Bakheit, Glasgow University Department of Neurology, Institute of Neurological Sciences, Southern General Hospital, Glasgow G51 4TF, United Kingdom

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slight granularity throughout the hippocampi and amygdaloid nucleus. The size of Ammon's horns was not reduced. On microscopic examination there was subtotal loss of neurons in Ammon's horns and the entorhinal regions. In addition many large astrocytes and numerous hypertrophied microglial cells were present in these structures. There were also some foci of neuronophagia. The rest of the brain was normal except for a small incidental vascular malformation in the pons. A celloidin study confirmed these findings. No evidence of metastasis in CNS or elsewhere was found.

Case 2

A 55 year old man presented with acute mental confusion, agitation and aggressive behaviour. One week before his admission he had two tonic-clonic epileptic seizures. There were no other complaints.

He had been moderately depressed for two years before the onset of his present illness but he did not seek medical advice. He had also suffered from chronic bronchitis for many years. There was no family history of neurological or psychiatric illness. He did not smoke and drank moderate amounts of alcohol. His regular medication was salbutamol and betamethasone inhalers.

On physical examination he looked generally well. There were no abnormal physical findings in the cardiovascular, respiratory or gastro-intestinal systems. Blood pressure was 115/65. His mood was depressed and he was disorientated in time, place and person. His attention span was short and his recent memory was impaired. There were no focal neurological signs and, in particular, his speech and parietal lobe functions were normal.

Routine blood tests were normal. ESR was 10 mm/hr. A chest radiograph demonstrated changes of chronic obstructive airways disease and in addition, there was a poorly defined streaky linear shadow in the left upper zone. On bronchoscopy there were inflammatory changes in the right lower lobe apical segment but no other changes were present. Biopsy showed chronic inflammatory changes and some squamous metaplasia of mucosal epithelium but there was no evidence of malignancy. An EEG revealed a generalised slowing of all rhythms particularly over the left hemisphere and there was also sharp wave activity over the right temporal area. An isotope brain scan was normal. CSF contained one lymphocyte and 0·21 g/l of protein. CSF glucose was normal.

The patient's mental state progressively deteriorated until he died six weeks later from a chest infection.

Necropsy examination revealed a small cell carcinoma of the bronchus and bilateral bronchopneumonia. There were no intra- or extra-thoracic metastases. Macroscopic examination of brain sections showed rather small Ammon's horns with brown granularity, but there were no obvious other abnormalities. On celloidin brain sections there were some abnormalities which were restricted to the hippocampal formations and the amygdaloid nuclei. These consisted of neuronal loss, especially in Ammon's horns, intensive reactive changes in astrocytes and microglia and focal aggregates and perivascular cuffing by lymphocytes. The brainstem, spinal cord and cerebellum were normal.

Case 3

This was a 68 year old woman with a two to three months history of weight loss, frequent falls and progressive mental confusion. Her illness had started about two years before the onset of the present symptoms with a feeling of being generally unwell. She also had "odd turns" which consisted of episodes of lightheadedness and a feeling as if her head "was spinning round". These occurred about once every three months and lasted five minutes on each occasion. There was no loss of consciousness except on one occasion but no further details about this episode were available.

Seven years earlier she was diagnosed as having essential hypertension and was started on a thiazide diuretic which was later discontinued. There was no other past medical history of note. She was a heavy cigarette smoker for many years and she did not drink alcohol. There was no family history of neuropsychiatric illness and she was not on any regular medication.

On admission she was thin and looked generally ill. She had advanced finger clubbing. Her pulse was 80 beats/minute and regular. Blood pressure was 120/60 mm Hg lying and 100/60 standing. There were no other abnormal physical signs on general physical examination. The abnormal neurological findings were confined to severe impairment of recent memory, moderately severe limb ataxia and vertical nystagmus. Her speech was normal. She could name objects correctly, read, write and perform simple arithmetic. However, she could not remember her date of birth or her home address and she was unaware of current events. She was also unable to recall information given to her a few minutes before and was disorientated in time and place.

Her full blood count, urea and electrolytes, and liver and thyroid function tests were normal. ESR was 40 mm in the first hour. A chest radiograph demonstrated slight cardiomegaly and some loss of pulmonary translucency in both lower zones. Two days following admission the patient suddenly became hypotensive and died before the investigations were completed.

Necropsy examination revealed advanced ischaemic heart disease and a moderately differentiated adenocarcinoma of the bronchus which had metastasised to both kidneys. No abnormalities were noted on macroscopic examination of the brain and there were no cerebral metastases. Microscopy of the hippocampi, however, showed subtotal loss of pyramidal cells of Ammon's horns associated with an astrocytosis and microglial hyperplasia, clusters of microglia and evidence of neuronophagia together with slight to moderate

Table 1 Clinical and pathological features of PLE

Reference	Clinical features	Age/sex	Pathological changes				Course (months)
			LS	C	BS	SC	
1 (3 cases)	Lethargy, depression, agitation, confusion, poor recent memory and hand tremor. Temporary lobe seizures three months later.	53 M	+++	−	−	−	14
	Depression, agitation, ataxic gait and hallucinations.	58 M	+++	+	+	−	3
	Tiredness, depression, paraesthesia in hands. Poor recent memory and personality change three months later.	56 M	+++	−	+	NA	7
2 (2 cases)	Weight loss, three tonic-clonic seizures, ESR 45 mm/hr. Confusion and poor memory a month later.	60 M	+++	−	+	−	24
	Depression, confusion and poor recent memory.	80 F	+++	−	−	−	Several years.
3	Grand mal seizures, personality change, confusion, nystagmus, ataxia and dysarthria.	51 M	+++	+	++	NA	12
4	Depression, confusion, poor recent memory.	61 F	+++	−	−	+	3
5	Anorexia, weight loss, depression, insomnia, loss of libido, Rt. hemiparesis and upper quadrantanopia.	56 F	+++	−	−	−	3
6	Poor recent memory, hallucinations, sleepiness, ataxic gait, nominal dysphasia and weight loss.	61 M	+++	−	++	−	15
7	Seizures—one year. Confusion, poor recent memory, abnormal gait and hypersomnia—six months.	52 F	+++	−	++	−	12
8	Intermittent recent memory loss, confusion, paranoia, panic attacks, weight loss, proximal muscle weakness.	61 F	+++	−	−	++	24
9	Confusion, agitation, poor memory, reversed sleep pattern, nystagmus and positive snout reflex.	76 M	+++	−	++	−	4
10	Ataxic gait, diplopia—acute onset.	35 M	+++	++	++	++	60
11	Confusion, depression, tonic-clonic seizures, tremor, sweating, tachycardia, poor recent memory, confabulations.	41 M	+++	−	−	−	1
12	Depression, progressive dementia, focal and generalised seizures.	61 F	+++	−	−	−	8
13	Memory loss, tonic-clonic seizures.	26 M	+++	NA	NA	NA	NA

Abbreviations: LS = limbic system; C = cerebellum; BS = brain stem; SC = spinal cord; NA = not available; + = mild, ++ = moderately severe; +++ = severe changes.

cuffing of many vessels (both meningeal and parenchymatous) by lymphocytes. Similar, but less extensive, changes were present in the brain stem. The cerebellum was normal.

Discussion

Predilection for limbic structures is the most characteristic feature of herpes simplex encephalitis. This site is also preferentially affected in Wernicke's encephalopathy, a subgroup of patients with systemic lupus erythematosus and in some cases of systemic malignancy. In the latter, however, other parts of the neuraxis are usually involved. Only four cases of "pure" paraneoplastic limbic encephalitis (PLE) have been reported in the literature since 1960. Two of our three reported cases also belong to this category.

As would be expected the distribution of pathological changes in both our and other reported cases almost always correlated with the clinical presentation (table 1). Mental confusion, impairment of recent memory with normal cognitive function, hallucinations, depression, personality change and sleep disturbances were consistent findings, occurring in various combinations in more than 90% of all patients. This agrees with the findings of Gascon and Gilles who established the correlation between bilateral destruction of limbic neurons, behavioural changes and recent memory deficits.[14] However, the patient reported by Kawaguchi *et al* [10] did not appear to have any symptoms referable to the limbic system. This patient presented with ataxia and double vision and apparently did not have any memory impairment until his death five years later. On the other hand, clinical features characteristic of limbic encephalitis have been reported in a patient with bronchogenic oat cell carcinoma but neuropathological examination did not show any abnormalities in CNS.[15] Surprisingly, temporal lobe seizures occurred in only one of the 19 patients. Patients with PLE generally had few signs. Interestingly, brain stem signs did not always correlate with the necropsy findings. In one case there were

Table 2 Summary of the laboratory findings of PLE

Reference	Protein*	CSF cells	Glucose*	EEG	CT scan
1 (3 cases)	N	N	N	Sharp waves fronto-temp region	—
	90	24L	—	—	—
	90	37L	—	—	—
2	N	N	N	Bilateral slow waves	—
4	71	N	—	—	—
5	95	N	—	"Diffusely abnormal"—not specified	—
6	88	N	100	Generalised slow waves	—
7	N**	13L	N	Diffuse theta activity	N
8	N	N	N	N	N
9	54	7L	N	Theta activity	N
10	N	29L	70	N	N
11	1050	N	N	—	—
12	N**	31	N	"Epileptic pattern"—not specified	—
13	—	—		—	Lt temporal lobe lesion

Abbreviations: *mg/100 ml; **oligoclonal bands present; N = normal; — = not available; L = lymphocytes.

moderately severe pathological changes in the brain stem[7] but the patient had no symptoms or signs attributable to involvement of this structure. By contrast, the patient reported by Glaser and Pincus[5] had a right-sided hemiparesis and upper quadrantanopia in the absence of pathological changes outside limbic structures. One of our patients with "pure" PLE had mild spastic paraparesis but he also had a coincidental brain stem arterio-venous malformation. On the whole, however, patients with brain stem, cerebellar or spinal cord involvement frequently exhibited signs of involvement of these structures.

The CSF was examined in 15 cases and was found to be normal in only three. The main CSF findings were lymphocytic pleocytosis and moderately raised protein (table 2). Oligoclonal bands were detected in two patients. Brain CT scanning was generally unhelpful in diagnosis. MRI was done in two cases[8 9] and it was normal. The EEG is often normal and when changes occur they consist of non-specific generalised theta activity. This contrasts with the characteristic EEG features of herpes simplex encephalitis which may consist of slow or periodic high voltage complexes localised to the temporal lobes.[16]

The mean course of the disease varied with the type of underlying malignancy and ranged from a few weeks to five years. Symptoms of temporal lobe dysfunction predated the diagnosis of malignant disease in five patients and were the presenting symptoms in all but two of the remaining cases.

Most reported cases of PLE were due to bronchogenic oat cell carcinoma. Other associated tumours were: poorly differentiated transitional carcinoma of the bladder,[7] mediastinal teratoma,[10] malignant thymoma[11] and testicular carcinoma.[13] In two patients a primary neoplasm was not found at necropsy but there was metastatic spread of oat cell tumour in the paraortic (6) and mediastinal (2) lymph nodes.

Although remission of various neurological paraneoplastic syndromes are known to follow treatment of the underlying tumour, the effect of treatment of the primary tumour on PLE is disappointing. Only one reported case of histologically-proven limbic encephalitis associated with testicular carcinoma responded to orchidectomy and chemotherapy.[13] Interestingly, the patient's mental symptoms relapsed with recurrence of the tumour and resolved again with further treatment. Markham and Abeloff[17] and later Brennan and Craddock[18] reported a similar response in two cases of oat cell carcinoma of the bronchus. In neither case, however, was a histopathological diagnosis of limbic encephalitis made.

The pathogenesis of limbic encephalitis complicating malignancy is not clear. Corsellis *et al*[2] speculated that a slow viral infection might be responsible. Both the subacute course and the distinctive histopathological features of this condition without tissue necrosis suggest a non-viral aetiology. Furthermore, the characteristic intranuclear inclusion bodies of viral infections are absent and no viral particles have yet been demonstrated. An exception is the case of Dayan and colleagues[19] who found intranuclear inclusion bodies and isolated herpes simplex from the temporal lobe of a patient successfully treated for a moderately well-differentiated adenocarcinoma of the uterus 18 months previously. It is likely that this patient had a coincidental herpes simplex encephalitis since there was no evidence of tumour recurrence at necropsy.

Immune damage of limbic neurons is a more plausible explanation of PLE for the following reasons. First, oligoclonal bands in CSF have been reported in PLE (table 2). Secondly, an antibody with strong binding to limbic structures has been demonstrated in the serum of a patient with oat cell carcinoma of the bronchus.[20] In fact, oat cell carcinoma of the bronchus is the commonest malignancy causing limbic encephalitis. This lends further support to the immune hypothesis of PLE since small cell lung tumours express antigens which cross-react with specific neurons.[21] Thirdly, the predilection for limbic structures could be explained by the intimate involvement of these structures in immune regulation. Fourthly, the reported improvement of PLE with successful treatment of the underlying malignancy is probably due to reduction of tumour burden and hence antibody production. Anti-neuronal antibodies have also been described in malignant disease complicated by sensory neuropathy,[22] cerebellar[23] and retinal degeneration.[24] Although the significance of these circulating antibodies is not yet clear, their presence in diverse paraneoplastic neurological disorders suggests a common immunopathogenic mechanism.

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