MEDICAL PRACTICE

Clinical Problems

Progressive Neurological Deficits in Primary Polycythaemia

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Summary

Patients with primary polycythaemia may present clinical features which lead to an erroneous diagnosis of intracerebral neoplasm. Three such cases are described in detail in this report.

Introduction

Since the first descriptions of primary polycythaemia (polycythaemia rubra vera) appeared at the end of the nineteenth century it has been widely recognized that a diversity of neurological symptoms and signs are frequently associated with the condition. Reference is made in several series to such signs leading to an initial diagnosis of cerebral tumour, since "objective manifestations were of a progressive nature so that it was difficult to distinguish them from those of brain tumour,"[1] or "because of progressive signs and papilloedema a diagnosis of brain tumour was made."[2] Indeed craniotomy had been performed on occasions before the correct diagnosis was reached. Detailed descriptions are, however, infrequent, and for this reason we here report on three patients shown to have primary polycythaemia in whom the association of headache with a focal neurological syndrome gave an initial diagnosis of cerebral tumour.

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Case 1

A 56-year-old woman presented in 1959 with a three-month history of sensory change and weakness in the left limbs and headache. The symptoms had begun with pins and needles in the left hand. A few nights later she had awakened not knowing where her left arm was, and found to her surprise that she was lying on it. She was aware of the position of the arm only when looking at it, and it developed an "alien" quality. One month later the left hand became weak, and after a further two weeks she noticed a numb, tingling sensation in the left foot. Throughout the three-month period she had a throbbing headache in the right frontal region, which increased when stooping or bending.

There were no other neurological symptoms, her general health was good, and she had had no previous illness.

On examination she was found to be an alert, co-operative patient with plethora and central cyanosis. The cardiovascular and respiratory systems were normal, except that the blood pressure was 140/95 mm Hg. Mild splenomegaly was present.

In the nervous system there was no abnormality of the skull, neck, or cranial nerves; in particular, the optic fundi were normal. In the motor system tone was normal but there was weakness of all movements of the left hand and severe weakness of pyramidal type in the left leg. Surprisingly, the deep tendon reflexes were depressed on the left but the plantar response was extensor. Sensory testing showed gross loss of two-point discrimination and of joint position sense in the left hand with astereognosis and pseudoathetotic movement of the outstretched left arm. No inattention was detected.

Laboratory investigations were: Hb 20 g/100 ml; R.B.C. 9,240,000/mm^3; P.C.V. 74% M.C.V. 89 μm^3; W.B.C. 10,600/mm^3 (normal differential and no primitive cells); platelets 430,000/mm^3. Bone marrow examination showed erythroid hyperplasia without hyperplasia of the megakaryocytes or myeloid series. The arterial oxygen saturation was 90%. *X*-ray examination of the skull and chest and an intravenous pyelogram showed nothing abnormal. A plain abdominal film confirmed splenomegaly. Blood W.R. negative. E.E.G. showed brief episodes of 4-C/S waves mixed with sharp components in the right frontotemporal region. Air encephalography and C.S.F. examination showed no abnormality.

While an initial possibility was the presence of a right parietal lobe tumour, the normal air encephalogram together with a confirmed diagnosis of primary polycythaemia suggested that the neurological deficit was a manifestation of the latter condition. The patient was treated with venesection and radioactive phosphorus. One year later she was symptom-free and a blood count was within normal limits. Postal follow-up continued for 10 years, and in 1969 she confirmed that she was completely well and had not seen her doctor for any reason for two years.

Case 2

In 1963 a 39-year-old woman presented with a six-week history of weakness and sensory disturbance in the left limbs. This had first become apparent as paraesthesiae in the left hand, arm, and side of the neck while playing golf, the initial episode lasting three weeks. Ten days later similar disturbances recurred as repeated short episodes lasting up to five minutes, involving the left arm, left side of the face, and left shoulder, although these were not necessarily affected at the same time. Just before admission she experienced fleeting episodes of weakness in the left hand, on one occasion the hand becoming completely paralysed for a short time. The day before admission paralysis again occurred in the left hand and persisted, and on the day of admission the left leg was dragging. The only other symptom was severe occipital and frontal headaches for the previous year associated with menstruation.

The past history was complicated. The patient was born in Egypt of mixed parentage and moved to Paris at the age of 20. During pregnancy albuminuria developed and persisted for some years. At the age of 23 she lapsed into coma; this was attributed to uraemia but recovery was complete. When 28 years old she was investigated in Paris for hepatosplenomegaly. A diagnosis of reticulosis was made and she was treated with drugs and transfusions. Several relapses associated with abdominal swelling followed, requiring hospital treatment in both Paris and Egypt. Full details were not available. In addition there had been episodes of chest pain and one of pruritus involving all four limbs. Neurological examination at the time (1961) was said to have been normal. In 1962 she sustained multiple limb injuries in a car accident, and although she was unconscious for a few minutes there was no skull fracture.

When examined by one of us in 1963 she was found to be an intelligent, co-operative woman without obvious plethora or cyanosis. No abnormality was found in the cardiovascular or respiratory system. The blood pressure was 150/80 mm Hg. The liver was just palpable and the spleen moderately enlarged. In the nervous system the skull and neck were normal, the carotid pulsations being equal, and no neck bruit was heard. The only abnormality in the cranial nerves was pinkness of the optic discs with venous distension. In the motor system there was spasticity of the left arm with increased deep tendon reflexes, but both plantar responses were flexor. Power was reduced in the left arm, particularly in the hand, and mild weakness of pyramidal type was present in the left leg. No sensory loss was found.

Investigations were: Hb 17·7 g/100 ml; R.B.C. 6,500,000/mm^3; P.C.V. 63%; M.C.V. 97 μm^3; M.C.H.C. 28%; W.B.C. 12,400/mm^3 (neutrophils 82%, lymphocytes 9%, monocytes 5%, eosinophils 4%); platelets 430,000/mm^3. Red cell mass 2·5 l. (53 ml/kg); plasma volume 2·4 l. (51 ml/kg). Bone marrow examination showed erythroid hyperphlasia with increased megakoryocytes. Leucocyte alkaline phosphatase score 286 (normal 14-100); arterial oxygen saturation 95%; serum iron 102 μg/100 ml. Liver function tests normal. *X*-ray examination of the chest and skull and air intravenous pyelogram showed no abnormality.

An E.E.G. showed episodic slow wave activity in the right parietotemporal region, with lesser independent changes over the left temporal region. The C.S.F. was of normal composition, the pressure being 80 mm.

A diagnosis of primary polycythaemia was made. Improvement of the patient's neurological condition began before treatment was started, and after four weeks (at discharge) only minimal clumsiness of the left hand persisted. At that time the haemoglobin level was 14·8 g/100 ml (P.C.V. 49·5%) and the whte cell count 6,200/mm^3. The treatment used was venesection followed by anticoagulation and radioactive phosphorus.

One year later anticoagulants were withdrawn because of menorrhagia. After a further year intermittent frequent paraesthesiae recurred in the left limbs, with clumsiness and weakness of the hand. On readmission the haemoglobin was 16·0 g/100 ml with a normal white cell and platelet count. The leucocyte alkaline phosphatase score was 156. Treatment by venesection, anticoagulation, and radioactive phosphorus was again given. Recovery ensued and the patient had no further neurological symptoms. Her haemoglobin level was controlled by repeated venesections.

Case 3

This man was seen here in 1970 when he was aged 47. As he was severely dysphasic the details of his history were obtained from his wife.

Twelve years previously he began to have attacks in which there was a sensation of feeling far away coupled with discomfort in the stomach. He appeared physically normal and the E.E.G. showed only minor bilateral changes. A diagnosis of temporal lobe epilepsy was made and anticonvulsant therapy started. The last episode had occurred five years before the present illness.

In May 1970, while driving, the patient experienced a five-minute episode of double vision. Soon afterwards he developed difficulty in reading—he appeared to miss out words and his comprehension was impaired. He could write accurately but only very slowly. It was then noticed that he had difficulty finding the correct word. Soon the right leg began "to become exhausted and drag" and his right arm to become numb and tired. He used the right arm incorrectly. He would hold a knife and fork the wrong way round or put toothpaste on the wrong side of the brush. There was difficulty dressing but no difficulty in finding his way around the house. Headaches were inconspicuous. His difficulties had increased steadily in the six weeks before admission.

Examination showed a plethoric man with central cyanosis, a regular pulse, and normal blood pressure (115/70 mm Hg). The peripheral pulses were present. No arterial bruits were heard. The heart was of normal size and no murmurs were audible. Both the liver and spleen were enlarged two fingerbreadths and were of firm, smooth consistency.

On examination of the nervous system he was found to be alert and co-operated within the limit of his disability. He had a severe expressive and receptive dysphasia with dyslexia and dysgraphia. He was unable to copy simple gestures or to demonstrate the use of everyday objects. For example, when given a comb he held it the wrong way round and made vague stroking movements around his eyebrows. He could not copy simple shapes. He was aware of his difficulties, commenting "It's not proper, I realize that" or "It's not very rewarding."

The only cranial nerve abnormality was in the optic fundi, where the discs were pink and the veins distended but venous pulsation was preserved. No limb weakness or reflex change was present but the right plantar response was equivocal. Sensory testing could not be adequately performed.

Investigations were: Hb 19·9 g/100 ml; R.B.C. 6,900,000/mm^3; M.C.V. 84μm^3; W.B.C. 11,300/mm^3 (polymorphs 75%); platelets 385,000/mm^3. Red cell mass 2·63 l. (predicted normal 1·71 l.); blood volume 5·15 l. (predicted normal 4·48 l.); urea and electrolytes normal; uric acid 7·3 mg/100 ml; serum iron 105μg/100 ml. *X*-ray examination of the skull and chest and an intravenous pyelogram showed nothing abnormal.

An E.E.G. showed bilateral slow wave abnormalities with almost continuous low and medium voltage activity in the left anterior quadrant. A brain scan using ^{99}Tc showed an area of increased uptake high in the left parietal region which appeared relatively superficial on the posteroanterior scan.

Left carotid angiography (Dr. B. Kendall) showed a severe irregularity of the posterior wall of the internal carotid artery over a length of about 2·5 cm below the skull base associated with slight narrowing due to atheroma. There were peripheral occlusions of the angular and posterior temporal branches of the middle cerebral artery without collateral circulation from the filled vessels. There was mild dilatation of the lateral ventricle. No radiological evidence of a space-occupying lesion was seen.

The history of temporal lobe epilepsy succeeded after some years by the development of a progressive neurological deficit raised the possibility of an underlying cerebral neoplasm but physical examination suggested polycythaemia as a cause of the complex neurological disorder. Haematological investigations confirmed the presence of primary polycythaemia. The patient was treated by venesection and anticoagulation, the haemoglobin level and packed cell volume being reduced to normal over one week. Within the next few days, however, his condition deteriorated sharply, the dysphasia became very severe, thus making com-

munication impossible, and a moderately severe right hemiparesis developed. A repeat angiogram performed elsewhere two months later showed complete occlusion of the left internal carotid artery. Treatment with radioactive phosphorus was also given but he did not show any subsequent improvement.

Discussion

The diagnosis of primary polycythaemia was based on the presence of splenomegaly and a raised white cell count and the absence of a cause for secondary polycythaemia in all three cases. In two cases the red cell mass was also estimated. The importance of this estimation in establishing the presence of true polycythaemia has been emphasized.[3] Although not performed in Case 1, the level of the haemoglobin and the presence of splenomegaly make a "pseudopolycythaemia" unlikely.

Difficulties in the interpretation of signs or symptoms in primary polycythaemia which may erroneously suggest the presence of an intracerebral neoplasm may arise in several ways. Headache is very commonly reported in polycythaemia, but more important are the changes in the optic fundi which can be mistaken for papilloedema. Indeed, severe swelling of the optic discs has been reported.[4] The situation is further complicated by reports of raised cerebrospinal fluid pressure at lumbar puncture.[5]

Drew and Grant[4] reported that the association of polycythaemia rubra vera with intracranial neoplasia is an event of the greatest rarity,[4] but cerebral tumours may develop independently in patients with polycythaemia,[6] or other space-occupying lesions such as subdural haematomata may occur.[4] Indeed the disturbance of blood coagulation in polycythaemia (either occurring spontaneously or anticoagulant-induced) may predispose to such a complication.

The most widely-recognized association, however, is that of polycythaemia with cerebellar haemangioblastomas, although the haematological data presented in some reports are scanty, a situation noted by Ward.[7] The three cases reported here differ somewhat in that in association with headaches over a period of weeks the patients developed an increasing neurological deficit which could be attributed to a progressive hemisphere lesion. This mode of presentation lacks the recognized hallmark of vascular disease of the nervous system—namely, an abrupt onset often with episodic succession. Similar reports are infrequent. Transient cerebral ischaemic attacks, the "stroke-in-evolution," and acute cerebrovascular lesions are well documented; slowly evolving lesions are much less common, though they have been recorded, particularly in the earlier literature. Christian, in 1917,[8] reported on a man (Case 4) with a long history of headaches who experienced left-sided symptoms for six years before dying from a left hemiparesis which evolved over 10 days. The necropsy findings were of "cerebral artery thrombosis with areas of cortical degeneration." Hutchinson and Miller[9] described the case of a 45-year-old man with primary polycythaemia who developed progressive loss of vision leading to blindness (with normal fundi), "great mental change" with incomprehension, and, later, somnolence and coma. Seven years before the terminal illness he had had a fit. Bilateral occipital lobe infarction was found at necropsy.

In addition to the problem of diagnosis there is that of the management of such cases. There is little doubt that life expectancy is reduced in primary polycythaemia.[10] Cerebrovascular accidents due either to haemorrhage or thrombosis are a well-recognized complication and cause of death, but it is difficult to establish the prognosis of this group of patients. Among the 96 patients reported on by Campbell *et al.*[3] 49 deaths occurred, 9% of which were due to cerebral haemorrhage or infarction. In other series, reported by Videbaeck[11] before the advent of ^{32}P treatment, 25 out of 125 patients suffered a cerebrovascular episode and 19 died. Of the present three patients two did well, suggesting that the prognosis for recovery from a progressive vascular lesion can be good.

It is difficult to define a logical approach to the management of such patients before treatment with ^{32}P can become effective. Improvement did, in fact, follow venesection alone in the first patient. On the other hand, spontaneous recovery occurred in another patient (Case 2). It should be remembered, however, that venesection may on occasions apparently be responsible for a deterioration in the neurological condition, for Silverstein *et al.*[2] reported the worsening of a hemiparesis in one patient and the development of "cerebral accidents" in two others within 24 hours of phlebotomy.

In view of the incidence of cerebral haemorrhage, to which reference has been made above, anticoagulation must always carry a considerable risk in primary polycythaemia. Furthermore, apparently adequate anticoagulation does not necessarily prevent further thrombosis, at least of the arterial circulation, as evidenced in Case 3.

In spite of the hazards of therapy, however, it is suggested that the potential reversibility of severe neurological deficit warrants wider recognition of the progressive syndrome described. Furthermore, our experience suggests that clinical examination, particularly the finding of splenomegaly, will lead to the correct diagnosis.

Requests for reprints should be sent to Dr. N. F. Lawton.

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