Painful extremities and neurological disorder in essential thrombocythaemia

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Summary: Six of 20 patients with essential thrombocythaemia had neurological features and 8 had peripheral vascular symptoms. Four had cerebrovascular ischaemia or stroke and 3 had gangrene. Pain in the extremities may be a striking symptom in this disorder.

Introduction
Essential thrombocythaemia (ET) is an uncommon myeloproliferative disorder occurring in all age groups but most frequently in middle age. It may be associated with haemorrhagic or thrombotic episodes with major sequelae or fatal outcome. It may, however, be symptomless and pursue a benign course (Hoagland & Silverstein 1978). The presenting symptoms may be neurological and of wide variety, and there may be unusual pains in the limbs; these are features we wish to emphasize. We were unfamiliar with them prior to experience of the first case, and have found that neurologists and physicians and vascular surgeons are often similarly unaware. We first examined the records and patients in our own hospitals. Dr Geoffrey Dean of the Medical Social Research Board then put us in touch with other hospital physicians who had had cases, and data on 20 patients are presented here.

Case report
A housewife, aged 43, was admitted to St Vincent's Hospital with a bizarre pattern of symptoms. There had been frontal headache for three weeks. For three days she had experienced burning, tingling pains in the tips of the fingers and toes on both sides. On the day before admission there had been transitory weakness of the right leg. There had been an episode of chest pain with extension to the arms. On the day of admission she became blind for a time and thereafter complained of blurred vision and inability to read. There was a past history of migraine. She looked pale and ill. She was agitated and moaning. Her gait was unsteady. She was noted to have difficulty in finding her mouth with a cup and to bite her fingers not realizing that she had finished eating her bread. She had great difficulty reading but no defect was found in her visual acuity or visual fields. She made a poor hand at drawing objects and could not put on her dressing gown, seeming unable to relate the left hand to the garment. No other abnormalities were found on neurological or general examination.

These findings were interpreted as indicating an ischaemic lesion in the basilar territory with persisting parieto-occipital dysfunction. The basic process was thought to be migrainous and an emotionally agitated state was invoked to explain her pains.

Over two weeks she improved and was able to go home. However, during admission and at home she was unsteady in walking and exhausted and depressed. Her life became dominated by pains in the hands and feet brought on by movement or usage and lasting a few hours. Sometimes she crawled to the lavatory on her hands and knees. Cold water on the hands produced instant pain. At times, the finger tips felt as if there were splinters under

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the nails and the feet as if on fire. Her fingers and the tips of the toes were said to become red and shiny and bear beads of sweat. The pains were helped by the use of a bed cage, keeping the feet elevated and holding the arms perpendicular. An isotope brain scan was normal. CT scan was not available. On admission a platelet count of 670 x 10⁹/l was recorded but its significance was not appreciated. White cell count was 5 x 10⁹/l with a normal differential. Serum K was 6.4 and 6.2 mEq/l. The diagnosis of ET was eventually reached at follow up when her spleen was found to be just palpable and platelet counts of 920 x 10⁹/l and 2000 x 10⁹/l were recorded. White cell count was 11.2 x 10⁹/l and 9.5 x 10⁹/l. Her symptoms remitted on aspirin and dipyridamole.

It was concluded that the platelet disorder had produced cerebrovascular and peripheral vascular vasospasm or microthrombosis or both. The elevation of serum K was attributed to rapid disintegration of platelets following drawing of blood.

Survey of 20 patients

The criteria for diagnosis of ET were a platelet count persistently exceeding 800 x 10⁹/l without evidence of polycythaemia or leukaemia or of general disease known to cause secondary thrombocytosis. Haemoglobin was required to be less than 18 g/dl, red blood count less than 6 x 10¹²/l, and packed cell volume less than 54%. The bone marrow might or might not show an excess of megakaryocytes. The spleen was palpable in 50% of cases. Presenting symptoms in the 20 patients are shown in Table 1. Their ages ranged from 18 to 83 years; there were 13 women and 7 men. Neurological diagnoses are shown in Table 2. It is possible that the association of migraine and epilepsy in one case each is fortuitous.

The following two case histories are illustrative of the neurological and general problems of these patients.

A housewife aged 57 presented in 1969 with subcutaneous bruising and was found to have ET. In 1971 she had episodes of weakness of the left leg and complained of burning in the soles of her feet. At times during 1972 the tips of her right index and middle fingers were sore, and red spots were noted on the medial planter surfaces. In 1973 the sole of her left foot was tender for a time. In 1975/76 she had typical episodes of vertebrobasilar ischaemia. In 1977 she had pain, cyanosis and tingling in the left hand.

A housewife aged 70 presented in 1972 with melaena, anaemia, confusion and congestive heart failure. She had ischaemia of two toes, one of them gangrenous. She was found to have ET and a gastric ulcer. In 1973 she had episodes indicating vertebrobasilar ischaemia and was given anticoagulants. In 1974 she required transfusion for anaemia. In 1976 she had deep vein thrombosis in the legs and was again given anticoagulants. Active treatment of her ET was begun.

Peripheral vascular features were present in 8 cases in this series. In 3 there was gangrene of the toes with normal pulses at the ankles and proximally. In one there was ischaemic skin change with pains in the toes, while distal pains with no abnormality on examination were present in 4 patients. This is a feature deserving emphasis.

**Table 1. Essential thrombocythaemia: presenting symptoms in 20 cases**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia</td>
<td>7</td>
</tr>
<tr>
<td>Bleeding or bruising</td>
<td>4</td>
</tr>
<tr>
<td>Gangrene</td>
<td>3</td>
</tr>
<tr>
<td>Deep venous thrombosis</td>
<td>2</td>
</tr>
<tr>
<td>Pains in extremities and stroke</td>
<td>1</td>
</tr>
<tr>
<td>Pains in extremities and migraine</td>
<td>1</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>1</td>
</tr>
</tbody>
</table>

**Table 2. Neurological diagnosis in 20 cases of essential thrombocythaemia**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bizarre cerebral ischaemia</td>
<td>1</td>
</tr>
<tr>
<td>Cerebral thrombosis</td>
<td>1</td>
</tr>
<tr>
<td>Transient vertebrobasilar ischaemia</td>
<td>2</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>1</td>
</tr>
<tr>
<td>Migraine</td>
<td>1</td>
</tr>
</tbody>
</table>
Discussion
ET is uncommon and unfamiliar to most members of the medical profession. Even when diagnosed, its association with various symptoms may not be recognized and symptomatic rather than specific treatment may be given.

The literature contains a number of surveys of neurological features (Levine & Swanson 1968, Korenman 1969, d'Eramo & Levi 1972, Preston et al. 1979, Davies-Jones et al. 1980). The conditions recorded include strokes at all ages including infancy, transient cerebral ischaemia, amaurosis fugax, confusional state, migraine, polyneuritis and radiculomyelopathy. In all these reports there is some mention of unusual and troublesome pains in extremities and peripheral vascular features. The most striking was the case of Spach et al. (1963) who described a girl of eight years who developed right-sided weakness, blindness, acrocyanosis and myocardial infarction. Over the next three weeks she had repeated episodes of pain in the finger tips and toes lasting ten minutes. During these, she would lie with her face in a pillow complaining of the severity of the pain. This is reminiscent of the presenting patient of this series. Korenman (1969) cites cases of pains in the extremities preceding cerebral manifestations.

Some authors concentrate on the peripheral aspects. Preston (1982) reported that many of his 15 patients were referred from vascular surgeons who are alerted to the possibility of the diagnosis by the frequent association of painful peripheral gangrene or pregangrene and bounding peripheral pulses. He stated that almost all patients respond promptly, often dramatically, to treatment.

The platelet count may vary from time to time and several estimations may be necessary to make a diagnosis. Levine & Swanson (1968) made the point that platelet activity may be increased while there is a normal count because of decreased survival time. Preston (1982) takes issue with the view that a platelet count of $1000 \times 10^9/l$ is necessary for the diagnosis of essential thrombocythaemia. One of his cases had a count below 600 and 6 were below 800. An increase in the white cell count might suggest the possibility of an excess of platelets. In doubtful cases a therapeutic trial of dipyridamole and aspirin may be justified.

We have excluded from this study patients with secondary thrombocytosis. Others who have studied thrombocytosis and neurological dysfunction have not made this distinction (Preston et al. 1979) and we have also seen patients with this association.

Dysfunction of platelets might produce symptoms by: (1) initiating thrombosis; (2) aggregating with fibrin in atherosclerotic vessels; (3) circulating aggregates producing obstruction; (4) release of vasoactive substances.

Spontaneous platelet aggregates have been found in symptomatic patients and relief supplied by platelet-suppressive drugs (Davies-Jones et al. 1980). The patients in our series come from many different centres and treatment was varied. Our impression is that where symptoms are present, dipyridamole and aspirin are of value, the former being probably the drug of choice. Anticoagulants are contraindicated.

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