MIGRAINE COMA
MENINGITIC MIGRAINE WITH CEREBRAL OEDEMA ASSOCIATED WITH A NEW FORM OF AUTOSOMAL DOMINANT CEREBELLAR ATAXIA

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SUMMARY
A family with hemiplegic migraine has been documented for a period of over forty years. From this study and the literature we conclude that (1) migraine is a cause of recurrent coma which may be associated with life-threatening cerebral hemisphere oedema; (2) hyperpyrexia with CSF pleocytosis occurs in hemiplegic migraine, which may thus simulate viral meningoencephalitis; and (3) cerebral angiography is hazardous in hemiplegic migraine and may exacerbate coma and cerebral oedema.

In the family reported, cerebellar ataxia was present during recovery from attacks of hemiplegic migraine and affected patients ultimately suffered from persistent ataxia with radiological cerebellar atrophy. This syndrome thus constitutes a distinct form of late-onset autosomal dominant cerebellar ataxia and also of familial periodic ataxia. The status of 'cerebellar migraine' is reviewed.

INTRODUCTION
Migraine is not a common cause of coma. It is not among the standard causes of recurrent aseptic meningitis, nor within the usual differential diagnosis when hemiplegic stupor and a radiological ‘space-occupying lesion’ follow trivial head injury. If such a ‘neurosurgical’ illness recovers spontaneously, then the diagnosis of migraine may not be considered, unless the illness recurs.

The principal purpose of this paper is to document the extended history of a peripatetic family with one of the most consistently extreme forms of migraine reported in the literature. Two members of the family died, almost certainly of this illness, from ‘meningitis’ following trivial head injuries in 1915 and 1926. One other, under our care, survived respiratory arrest in 1979 only because of supported ventilation. We have also observed such features in severe migraine as CSF pleocytosis, fever, ominous clinical deterioration following cerebral angiography, and cerebral oedema, which have not always been regarded as characteristic of migraine. These features will be discussed in the light of current concepts of the pathogenesis of migraine.

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The cause of migraine is not known. The theory of vasoconstriction followed by vasodilatation has been challenged on several grounds. First, there is the question as to why cerebral infarction, as occasionally reported in migraine (Oppenheim, 1890; Murphy, 1955; Guest and Woolf, 1964; Hungerford et al., 1976; Cohen and Taylor, 1979; Dorfman et al., 1979), is actually very rare. Even in fatal migraine a causal infarction may not be found at autopsy (Neligan et al., 1977). Foster Kennedy (1931) when discussing ophthalmoplegic migraine, stated ‘...it is not easy to follow the dynamics by which the totality of migraine could be brought about by arterial spasm alone... By spasm of what artery can one explain the paralyses... often needing days, and occasionally weeks, in which to recover?’ Yet migrainous pareses do recover, and with a completeness and a regularity which contrasts with the residual disability which usually follows prolonged ischaemia of other origin. Secondly, Symonds (1952) found no evidence of vasoconstriction when carotid angiography was performed during hemiplegic migraine. Thirdly, recent investigators (Olesen et al., 1981; Lauritzen et al., 1983) have used intra-arterial radioisotope techniques to demonstrate that, during classical migraine, focal cerebral hyperaemia is followed by widespread oligaemia, a phenomenon likened to the spreading depression of Leão (1944). Therefore, because vascular mechanisms seemed unlikely to explain fully migrainous accompaniments, different authors (Holmes, 1926; Foster Kennedy, 1931; Kinnier Wilson, 1940; Osler, as discussed by Whitty, 1953; Ostfeld et al., 1955) have postulated that focal cerebral oedema, a reversible phenomenon, may explain the protracted, yet reversible, accompaniments of migraine, such as hemiplegia. Some support was lent to this hypothesis by Goltman (1936) by the direct demonstration, through a burr-hole previously inserted because of a suspected cerebral tumour, of oedematous brain swelling during migraine attacks. Furthermore, abnormalities of salt and water metabolism, with water retention and tissue swelling, may occur in migraine (Ostfeld et al., 1955), perhaps due to hypothalamic disturbance (Herberg, 1975). There have been two brief reports giving CT scan evidence of cerebral oedema in migraine (New and Scott, 1975; Harrison, 1981). We now report recurrent cerebral hemisphere oedema following the onset of hemiplegic migraine and its life-threatening manifestations.

In 1887 Gowers drew attention to the occurrence of fever in migraine and the necessity to distinguish this illness from meningitis—'recognition is important, otherwise you may make a diagnosis of fatal disease, and the patient may be well at your next visit'. More recently Bartleson et al. (1981) disputed such similarity and considered that the presence of CSF pleocytosis, unprovoked by 'invasive' neuroradiology, virtually excluded a diagnosis of migraine. In the migrainous family we report, hyperpyrexia and CSF pleocytosis have regularly accompanied recurrent migraine coma.

Affected members of this family (fig. 1) suffer from the additional feature of cerebellar ataxia precipitated by migraine attacks. Ultimately they develop the clinical features of autosomal dominant cerebellar ataxia, thus adding to the existing classifications of that syndrome (Harding, 1982). Cerebellar dysfunction in
migraine has been previously reported (Oppenheim, 1908; Chrást, 1954; Holub et al., 1965; Ohta et al., 1967; Golden and French, 1975; Swanson and Vick, 1978). Nevertheless the occurrence of cerebellar abnormality in true migraine has been questioned by Bruyn (1968), who reviewed the then existing literature on ‘cerebellar migraine’ and concluded, *inter alia*, that the Czech case of dominant, febrile ‘cerebellar migraine’ (Chrást, 1954) was ‘to all intents and purposes a case of meningoencephalitis’. Yet it has also been reported in the German literature (Holub et al., 1965) that the 11-year-old niece of Chrást’s patient died in 1956 from febrile hemiplegic/ataxic migraine with cerebral oedema. The striking clinical resemblance which the syndrome in this Czech/German family bears to that in the Australian/New Zealand/British family which we now report will be discussed.

A preliminary account of part of this work has been reported (Fitzsimons and Wolfenden, 1981).

![Family Pedigree](image-url)
CASE HISTORIES

Case 1. (III.13) (SH 334711)

This patient, our propositus, born October 28, 1956, has suffered from unilateral throbbing migrainous headaches, which until recently had recurred every four to eight weeks, since late childhood. There are usually no visual accompaniments, but he frequently experiences associated contralateral hemiparesis, spreading numbness and paraesthesiae. He is aware that these attacks have often been provoked by minor trauma or head injury.

He has had three admissions (1976, 1979, 1982) to hospital with coma. On March 25, 1976, when aged 19 years, he was admitted following the sudden complaint of blindness and then collapse. He was hyperthermic (40.1° C), hyperventilating and comatose, responding to no stimuli except pain. There was generalized hyperreflexia and both plantar responses were extensor. There was no papilloedema and no neck stiffness. His peripheral leucocyte count was 20000/mm$^3$, with neutrophilia. The CSF was normal on admission, but the following day it contained 51 leucocytes/mm$^3$ (70% polymorphs). No cause for infection was detected. Skull x-rays and an isotope brain scan were normal, and serological tests for syphilis were negative in blood and CSF. Respiration was briefly supported via endotracheal tube on March 26. Decerebrate rigidity and pinpoint pupils were recorded. Spontaneous recovery began four days after the onset of illness; angiography was not performed. During the ensuing two weeks, however, he suffered from severe hallucinations and there was some variation in his conscious state. Ataxia and dysmetria were also present. EEG on March 30 was generally of low voltage, but there were no focal features. There was more cerebral activity evident in the record of April 15, which revealed a 6–8 Hz alpha variant, together with paroxysms of moderately high voltage 1–4 Hz delta activity, without any definite lateralizing features. The CSF obtained on March 30 contained 14 polymorphs/mm$^3$ and 6 lymphocytes/mm$^3$. He was discharged on April 15, 1976 with left-sided cerebellar signs, and dysphonia due to paresis of his left vocal cord thought to have been caused by intubation. These signs were not present when he was reviewed on September 3, 1976, although his EEG was still markedly dysrhythmic with bilateral paroxysms of 2–4 and 5–7 Hz slow waves throughout the record.

His second major attack occurred when he was aged 22 years. On August 21, 1979 he experienced spreading left-sided paraesthesiae and there was some variation in his conscious state. Ataxia and dysmetria were also present. EEG on March 30 was generally of low voltage, but there were no focal features. There was more cerebral activity evident in the record of April 15, which revealed a 6–8 Hz alpha variant, together with paroxysms of moderately high voltage 1–4 Hz delta activity, without any definite lateralizing features. The CSF obtained on March 30 contained 14 polymorphs/mm$^3$ and 6 lymphocytes/mm$^3$. He was discharged on April 15, 1976 with left-sided cerebellar signs, and dysphonia due to paresis of his left vocal cord thought to have been caused by intubation. These signs were not present when he was reviewed on September 3, 1976, although his EEG was still markedly dysrhythmic with bilateral paroxysms of 2–4 and 5–7 Hz slow waves throughout the record.

Between August 22 and 28 he made a partial spontaneous recovery, with marked hour-to-hour fluctuations in his conscious state, headache, fever, tendon reflexes and plantar responses. Clonus was demonstrated. His EEG on August 27 no longer revealed high voltage paroxysms, although intermittent 0.5–2 Hz slow waves and general depression were still present on the right. An isotope brain scan on the same day showed greater perfusion of the right hemisphere than of the left and the static scintigraphs demonstrated a diffuse increase in isotope over the whole of the right hemisphere. Because of incomplete clinical resolution and some cerebral asymmetry in the original CT scan, vertebral and carotid angiography was performed via a femoral catheter on August 29. The carotid angiograms demonstrated lateral shift of the anterior cerebral vessels to the left of the midline and upward displacement of the right anterior cerebral artery. The findings were consistent with the presence of an avascular space-occupying lesion in the right frontal region. The vertebrobasilar system was normal.
During the hours following angiography the patient's condition deteriorated dramatically; his coma deepened, his fever rose to 41°C, there were variably dilated and sometimes unresponsive pupils, and his breathing became shallow. Both plantar responses were extensor. Respiratory arrest was followed by immediate intubation and artificial ventilation was maintained. Again, there was no neck stiffness and no papilloedema. The CSF pressure was 150 mm CSF and it contained 12 lymphocytes/mm³, but was otherwise normal. CT scan performed the following morning demonstrated oedema and swelling of the white matter throughout the right hemisphere (fig. 2). The right frontal horn was displaced posteriorly and the trigone anteriorly, and there was enlargement of the left temporal horn. These

Fig. 2A, B, C. CT scan with contrast (EMI Model 1010 scanner). Case 1, 30.8.79, nine days after admission with comatose migraine and one day after carotid angiography and respiratory arrest. There is generalized massive oedema affecting white matter of the right cerebral hemisphere. This has caused substantial effacement of the right lateral ventricle and lateral displacement of midline structures. Enlargement of the left temporal horn suggests early uncal herniation. (For purposes of consistency within this paper the left/right orientation of the original CT prints has been photographically inverted.)
findings suggested early uncal herniation. The oedema with midline shift was greater than had been present at the time of angiography and was now evidently the cause of the 'space-occupying lesion' indicated by the angiograms. His EEG had deteriorated markedly, and was characterized by diffuse 0.5–2 Hz slow waves, interspersed with periods of relative silence of 1–1.5 s duration, and general depression over the right hemisphere. Glycosuria (up to 19 mmol/l) and ketonuria were present on August 29, 1979, although his blood sugar level was normal.

A regimen of antipyretics and intravenous corticosteroids, mannitol, adenine arabinoside and phenytoin (300 mg/day) was commenced. He regained consciousness gradually over the next few days, was extubated on September 1, and his condition then rapidly improved. During recovery he suffered from episodes of migrainous headache (which responded to ergotamine), acute fear and hyperventilation, and was found to be ataxic, with bilateral dysmetria and dysdiadochokinesis. Phenytoin was discontinued on September 27, but cerebellar signs persisted for some months. A CT scan repeated on October 3, 1979 was normal, but cortical and spinal evoked responses (Dr J. C. Walsh, Royal Prince Alfred Hospital) performed that day were abnormal, with bilateral dispersion. Extensive investigations performed on admission, and again following angiography, revealed no specific evidence of infection. The following tests performed during this admission were negative or revealed no abnormality: multiple blood cultures, urine cultures, CSF culture and examination for micro-organisms including fungi and mycobacteria, repeated CSF and blood herpes simplex titres, titres of antibodies against leptospirosis and viruses including mumps and measles, urinary lead and porphyrin levels, blood lead, porphyrins and sugar, thyroid function tests, ingested drug and toxin screen (performed on admission), RA latex test, serum antinuclear factor and complement, convalescent blood T and B cell estimations, serum C1 esterase inhibitor, serum immunoglobulin quantitation, chest and skull x-rays, ECG, median motor and sensory nerve conduction studies, auditory and visual evoked responses (following recovery) and blood ammonia (during convalescence).

On October 11, 1979 he was discharged from hospital on pizotifen. Neither pizotifen nor a subsequent course of sodium valproate prevented attacks of spreading numbness in the left arm and leg, with right-sided headaches, during the ensuing months. These medications were therefore discontinued.

Because of the personal history of migraine and the family history revealed late during this admission, a diagnosis of atypical complicated migraine was made. Further investigations were therefore performed electively following discharge from hospital, including assays of 24 h urinary free adrenaline, noradrenaline, 5-HIAA, 5-HMMA, dopamine and serotonin. These measurements were normal (Dr M. Anthony, Prince Henry Hospital). In addition, serum amino acid analysis by paper chromatography was performed and indicated slight elevation of alanine content. The alanine concentrations measured in two subsequent random blood specimens were 0.73 and 0.6 mmol/l (normal < 0.5 mmol/l). The alanine levels in three other random blood samples were normal. In addition, serum alanine and pyruvate levels during a prolonged glucose tolerance test were normal, and no abnormal increase in alanine or pyruvate was detected after prolonged running exercise. Six consecutive 12 h urinary alanine estimations were normal. Because of the apparent intermittent elevation in blood alanine (a metabolic product of pyruvate), the possibility of a defect of the pyruvate dehydrogenase (PDH) complex was considered. Superficial skin biopsy was performed and cultured fibroblasts assayed for pyruvate dehydrogenase (native and Ca²⁺-activated), pyruvate carboxylase and phosphoenolpyruvate carboxykinase (Robinson et al., 1980). These values were normal. Deltoid muscle biopsy was performed because mitochondrial myopathy may present as an intermittent encephalopathy rather than as neuromuscular disease (Morgan-Hughes et al., 1982). Light microscopy, including histochemical staining for succinic dehydrogenase, and electron microscopy, were within broad normal limits; there were no ragged red fibres and no ultrastructural mitochondrial abnormalities.

The patient's third episode of coma commenced on March 22, 1982, when he was admitted to Sydney Hospital with a 4 h history of right-sided throbbing headache, vomiting, and numbness which had progressed from the left hand to the arm and leg over 20 min. He was drowsy and had a left hemiparesis. There was nystagmus on right lateral gaze, but no papilloedema. His temperature was
38.2°C, and the CSF contained 4 leucocytes/mm³ and 0.45 g/l protein. CT scan (fig. 3) showed a small dense right frontal lesion, consistent with minor haemorrhage, without demonstrable surrounding oedema or significant mass effect. His conscious state deteriorated overnight, so that he could not be roused except by pain. His temperature increased to 39°C, and there was ketonuria. His blood pressure was not elevated, nor had it been on any previous recording. Prothrombin time, PTTK and platelet count (249 × 10⁹/l) were normal. The following day episodes of stupor were interrupted by hallucinations of frightening lights and cries for help. His plantar responses varied, at times both being extensor, with left ankle clonus, and at other times flexor. Numbness of the left hand recurred and a left homonymous field defect was recorded. During the following two weeks the severity of his left-sided numbness and weakness fluctuated, exacerbations generally being associated with right-sided headache. His sleep rhythm was inverted. His resting serum pyruvate on April 7 was 107 μmol/l (normal ≤ 80 μmol/l), but two other measurements during convalescence were normal. EEG on March 25 revealed general suppression of all frequencies over the right hemisphere, with a 7 Hz alpha variant, 14 Hz sleep spindles and paroxysmal 2-3 Hz activity present on the left. Repeat CT scan on March 30 showed no alteration in the haematoma, but there was now substantial mass effect, not accounted for by the haematoma, with displacement of the right lateral ventricle approximately 1 cm to the left by hemisphere oedema. There was perisulcal contrast enhancement within the distribution of the right middle cerebral artery sparing that of the anterior and posterior cerebral arteries (fig. 3B,C). Cerebellar atrophy was evident (fig. 3E). Intravenous dexamethasone was commenced on April 5 after oedema had become apparent. Cerebellar signs, with dysarthria and ataxia, were present during his convalescence, and he was also dysphonic. He was discharged from hospital on propanolol therapy. Residual dysarthria, dysdiadochokinesis and heel-toe ataxia were still marked when he was reviewed in May 1982, but had partially resolved by October 1982.

The patient has not been treated with medications known to be toxic to the cerebellum, except for the phenytoin therapy for four weeks during 1979. There is no history of alcohol abuse, nor of ingestion of medications which may cause aseptic meningitis (von Reyn, 1983). A follow-up CT scan in October 1982 confirmed the presence of cerebellar atrophy, evident also in posterior fossa sagittal reconstructions, without significant cerebral atrophy. Curiously the small frontal area of high attenuation was still present (mean Hounsfield value of this lesion = 60; third ventricle CSF = 5; white matter adjacent to frontal horn = 7; occipital bone = 40). These values are consistent with the presence of calcification in the frontal lesion. Review of his 1979 angiograms revealed no evidence of arteriovenous malformation in this area.

When reviewed in September 1983 he had no significant nystagmus or dysarthria. There was minimal finger-nose ataxia, but marked truncal ataxia was evident when heel-toe walking or circle-walking was attempted. These cerebellar signs were not accompanied by ophthalmoplegia, optic atrophy, retinal pigment deposits or peripheral sensory abnormality. His intelligence is within normal limits, although considered to be less than that of his unaffected siblings, and to have deteriorated following his coma in 1976. Otherwise he remains in generally excellent health, punctuated at intervals by migrainous headaches associated with vomiting and a contralateral sensory disturbance. There has been subjective improvement in the frequency and severity of these headaches during his treatment with propanolol (current dose 40 mg thrice daily). His HLA haplotype is A1,3; Bw35; Bw40; Bw6; DRw3.

Case 2. (II.4)

The following history for the father of Case 1, born on November 27, 1918, was compiled from the case records of Tokanui Hospital, Taranaki Base (New Plymouth) Hospital, Palmerston North Hospital (New Zealand), Callan Park Hospital, Rozelle Hospital, Prince Henry Hospital (New South Wales, Australia) and The Royal Perth Hospital (Western Australia), and from recent personal observations by one of us.

The patient has suffered from episodic neurological disorder since late childhood. He classifies his attacks as being of two kinds, the 'slight' and the 'severe'. His slight attacks are typically migrainous, and in his youth occurred frequently, perhaps every five to six weeks. Characteristically, they
Fig. 3A–E. CT scans (GE Model 8800 scanner). Case 1. Admission of 22.3.82. A, noncontrast, and B–E, contrast-enhanced scans.

A, on admission 22.3.82. There is a small dense right frontal lesion consistent with haematoma. B, C, 30.3.82. There is now swelling of the right cerebral hemisphere causing partial effacement of the lateral ventricle and shift of midline structures. Perisulcal contrast enhancement within the territory supplied by the right middle cerebral artery is present. The haemorrhage is evident in these cuts (arrows). D, E, 13.4.82. There is midline cerebellar atrophy, with enlargement of the superior cerebellar sulci (e). Ventricular asymmetry is still present (d).
commenced with his being, for about an hour, 'on top of the world, full of energy and high spirits'. Such a mood inevitably presaged the onset of an attack, which would commence as a feeling of numbness and sometimes weakness in one hand, usually the right, progress to involve the ipsilateral arm and leg, and be associated with inability to speak. These focal symptoms would be followed by a severe and usually left-sided headache, when he would lie down to sleep and awaken refreshed several hours later.

The first of his more obviously severe attacks (apart from an undetailed 'minor stroke' when aged 15 years) occurred in 1942, at the age of 23. These severe attacks have been indistinguishable in their mode of onset from his lesser migraineous attacks, and have usually commenced with spreading numbness and contralateral headache. At this stage he may vomit, and slips into an unrousable febrile stupor or coma, requiring admission to hospital. Recovery has commenced some three to seven days later, is associated with fearful hallucinations such as to suggest psychiatric illness, and has generally been complete within two weeks, save for residual cerebellar ataxia, which has improved over the ensuing months.

Summaries from hospital records describe the following illustrative accounts. In 1932 when aged 13 years he was admitted to New Plymouth Hospital, New Zealand because of restlessness and confusion which followed a trivial head injury caused by a fall from a two-foot stool. These symptoms, and the associated generalized hyperreflexia, resolved spontaneously several days later. An inherited 'peculiar gait' was noted.

In 1942 he was admitted stuporose to New Plymouth Hospital following the onset of a right-sided headache associated with weakness and numbness of the left arm and leg and left facial numbness. Over the ensuing days there was bilateral but fluctuating hyperreflexia with, at times, bilateral extensor plantar responses. Recovery commenced three days after admission and improvement continued during the following week. His CSF on admission was normal, but three weeks after admission contained 16 lymphocytes/mm$^3$. His wife reported that, over the next four years, heavy manual work would precipitate attacks of unconsciousness, but his next recorded admission to hospital was not until 1946, when he was admitted following the onset of photophobia, aphasia and developing stupor. Bilateral hyperreflexia was present on admission, and by the following day a right-sided paresis, with bilateral extensor plantar responses, was evident. He had a fever of 101° F, and a tachycardia. His CSF was normal on admission but two days later it contained 13 lymphocytes/mm$^3$. He remained febrile for five days, during which time he was in a state 'varying from mild stupor to deep delirium'. On the basis of his mental state during recovery from the episode he was diagnosed as schizophrenic and was transferred for psychiatric institutional care.

In July 1947 he was admitted with right-sided paralysis and aphasia, lasting two weeks. One month later his physician recorded a normal neurological examination, except for hyperreflexia affecting all four limbs, and ataxia.

On November 29, 1948 he was admitted, while well, to Palmerston North Hospital for elective neurological investigation. Examination on admission revealed poor balance and a waddling gait, but no other abnormality. Air encephalography on December 1 was normal, as was the CSF. A left carotid angiogram performed on December 9 suggested a fine accessory circulation passing between the anterior and middle cerebral arteries in the left temporoparietal region. The possibility of a cerebral tumour was therefore considered. Later that day he was 'very drowsy' with a high fever (102°F) for which no infective cause was found. Repeat CSF examination was normal. Phenytoin therapy was commenced on the same day. A right hemiparesis, with a left extensor plantar response, was noted on December 10. An ataxic finger-nose test was recorded on December 13 and he was still 'confused'. His mental state improved over the following week, but incoordination of the left hand remained.

In 1954 he was admitted to hospital semicomatose, with right-sided spasticity and bilateral extensor plantar responses. CSF examination was normal. During recovery he remained restless and had delusions and hallucinations. Again, a diagnosis of catatonic schizophrenia was made, and he was treated by psychotherapy and ECT, during the course of which he improved.

In 1957 there was transient loss of vision, followed by difficulty speaking, weakness of the left arm
and stupor. There was a left extensor plantar response. The CSF contained 57 lymphocytes/mm$^3$ (84% polymorphs). He recovered in four days.

In 1958 he was admitted to hospital with stupor and right hemiparesis, fever (101–102° F) and a left extensor plantar response. CSF examination was normal. He recovered over ten days.

A similar episode occurred in 1959 when, following the onset of aphasia and severe headache, he was admitted with stupor, fever (101° F), a right hemiparesis and left extensor plantar response. The CSF contained 25 lymphocytes/mm$^3$ and 0.25 g/l protein. He made a rapid and apparently complete recovery within five days.

He attended for neurological consultation in 1959. It was then noted that, in addition to the above history, the clarity of his speech had deteriorated over recent years and that he had become more unsteady on his feet. Examination revealed scanning slurred speech, slight but definite cerebellar ataxia in all four limbs, more marked on the right, and an unsteady gait. There was no nystagmus and no other cranial nerve abnormality. There was bilateral hyperreflexia, especially on the left, with bilateral flexor plantar responses. He had an unsteady gait and a positive Romberg's test.

He migrated to Sydney, Australia, in 1960. In 1966 he was admitted to Callan Park (Psychiatric) Hospital, Sydney, with a two-day history of left-sided paralysis, drowsiness, dysarthria and confusion. He was febrile (38° C) with left-sided paralysis, bilateral extensor plantar responses and variable limb rigidity. EEG recorded two weeks after admission demonstrated bilateral low voltage theta activity, and 3–5 Hz delta waves present over the entire right hemisphere. As he recovered, a staggering cerebellar ataxia became evident, but during the time of his discharge, two weeks after admission, cerebellar signs were minimal.

In 1967 he was admitted to Prince of Wales Hospital, Sydney, because of collapse after ‘seeing spots’ in his visual field for 30 min. Cerebellar signs and a mild quadriparesis were recorded (Prof. J. Lance) and he was treated with cyproheptadine and ergotamine.

In 1970 he was again admitted to Callan Park Hospital with stupor and left hemiparesis. There was bilateral hyperreflexia, extensor plantar responses and, over the following week, fluctuating levels of consciousness. EEG on May 5, 1970 revealed a symmetrical 8 Hz alpha rhythm, which responded poorly to visual attention, and 1–2 Hz rhythms present continuously over the right hemisphere, suggesting an underlying structural abnormality. A right common carotid angiogram on May 13 demonstrated bowing of the anterior cerebral artery to the right of the midline, suggesting a space-occupying lesion in the left hemisphere, but there was no other abnormality of the intracranial circulation. Following this he became extremely restless and hallucinated for several days. An enlarged left pupil was recorded.

A left carotid angiogram was performed on May 25, 1970. This was normal. However, as was by now habitual following angiography, his clinical status deteriorated dramatically. He became aphasic and febrile, with fluctuating stupor, a right hemiparesis, bilateral extensor plantar responses and hallucinations. On May 27, EEG revealed an 8–9 Hz alpha rhythm, on the right only, and 1–2 Hz activity which was now most conspicuous on the left. He recovered clinically over two weeks, but had residual dysarthria, incoordination, ataxia and hyperreflexia.

In 1971 he was readmitted because of worsening cerebellar ataxia. Liver function tests and an isotope brain scan were normal. Air encephalogram revealed very marked cerebellar atrophy, and suggested some cerebral cortical atrophy. The CSF contained 6 mononuclear cells/mm$^3$ and 0.54 g/l protein. Skull x-rays were normal.

In 1974 he moved transcontinentally to Western Australia, where in 1977 he was admitted to Royal Perth Hospital, aphasic and with a right hemiparesis following an alleged grand mal seizure. There was marked dysarthria and truncal ataxia, and a CT scan demonstrated very gross atrophy of both cerebellar hemispheres and the cerebellar vermis. A more recent CT scan (January 13, 1983) demonstrated this cerebellar atrophy, as well as markedly asymmetrical cerebral atrophy, predominantly affecting the left cerebral hemisphere (fig. 4).

His attacks of migraine are now rare. Review in April 1983 revealed gross dysarthria, dysmetria, dysdiadochokinesis and ataxia, but only minimal horizontal nystagmus. He has pathological bilateral
hyperreflexia with equivocal plantar responses. His memory is poor, but there is no gross intellectual
deficit. There is no ophthalmoplegia, optic atrophy, retinal degeneration, clinical deafness or
peripheral sensory abnormality. There is no history of alcohol abuse, nor of ingestion of meningitis-
associated drugs, but he has been treated with phenytoin intermittently since 1948, apparently without
any evidence of acute toxicity. His HLA haplotype is A3; B18, Bw35; Bw6; Cw4 (A-11 not excluded).

Case 3 (III.12)

This patient, born on March 28, 1955, who works in a 'sheltered workshop', has apparently static
mild mental retardation and, because of 'clumsiness', he did not walk until the age of 2–3 years. His
mother's pregnancy and his neonatal health were normal.

Since childhood he has suffered from migrainous headaches, which are typically precipitated by
trivial head injury and preceded by tingling of the tongue, hemianopia, and numbness and weakness
which spread over the right arm and leg and last perhaps half an hour before the onset of headache. In
1967 a neurologist recorded that he had cerebellar signs with mild spasticity, thought to be of familial origin, and then vaguely described 'blackouts'.

More substantial evidence for posttraumatic migrainous hemiplegia is provided by The Royal Manchester Children's Hospital, England, where he was admitted in 1969, when aged 13 years, following a minor head injury sustained when he struck his head against a wall during a scuffle. Following this injury he complained of headache and became unconscious, and when initially examined by his practitioner was unresponsive to any stimuli except pain. There was no history of seizures. By the time of his hospital admission on January 2, 1969 he was restless, and he had a right hemiparesis with bilateral extensor plantar responses. He was not febrile. The following day he appeared mute. Bilateral carotid angiography performed on January 5 was normal and there was no untoward reaction. By January 6 he was becoming increasingly alert, and he was discharged on January 10 with minimal right-sided paresis, which subsequently recovered fully. In 1971, following his return to Australia, he again sought a neurological opinion because of recurrent 'turns'. One of these, associated with agitation, facial and hand numbness, and weakness, had followed a head injury caused by a fall while playing.

He was reviewed again in 1979 and 1982. In addition to his mental retardation, there were clear signs of cerebellar abnormality, including bilateral dysmetria, dysdiadochokinesis, and ataxia of heel-toe gait. There was generalized hyperreflexia with flexor plantar responses. His ocular fundi were normal, there was no ophthalmoplegia, and there were no sensory abnormalities. He is not alcoholic and has not taken medications which may cause meningitis or which are toxic to the cerebellum.

His EEG (performed while well in 1979) was dysrhythmic. The resting record showed 6-7 Hz alpha activity and prominent bursts of 4-6 Hz theta waves. Less frequent bursts of 3-4 Hz delta activity were also present in the resting record and these were accentuated on hyperventilation. A CT scan in 1982 revealed cerebellar atrophy, but no other abnormalities. In particular, there was no cerebral cortical atrophy. Assays of blood alanine, and of PDH, pyruvate carboxylase and phosphoenolpyruvate carboxykinase (Robinson et al., 1980) in cultured skin fibroblasts were normal. His HLA haplotype is A1, 11; B18, 40; Bw6; DRw3.

**Case 4 (III.10)**

This patient, born on September 14, 1946, a sister of the propositus, was recently noticed to be dysarthric. She had an ataxic heel-toe gait and a mild intention tremor. The remainder of the neurological examination was normal. She does not abuse alcohol and has not taken drugs which cause cerebellar disturbance. A CT scan in 1984 confirmed the presence of cerebellar atrophy (fig. 4). Her resting EEG revealed a normal symmetrical 10 Hz alpha rhythm, together with a focus of paroxysmal right posterior temporal slow wave (3-5 Hz) activity, which was exaggerated by hyperventilation, when 2 Hz activity was also present in the same area. There is no history of classical migraine nor of frequent headache. However, when she was aged about 25 years she collapsed following a trivial head injury on a bench, and then remained in bed for several days because of lethargy, severe headache and slurred speech.

**Case 5 (I.1)**

The grandfather of the propositus, born on February 18, 1875, migrated from Lincolnshire, England, to New Zealand, and apparently was affected by ataxia and migraine. The doctor who referred his son (Case 2) to hospital in 1932 commented 'The father of this boy has a peculiar gait and this boy seems to have inherited it'. The 1971 history of Case 2 records that 'his father used to use a stick to help him keep his balance'. The 1948 notes of Case 2 state that his father was 'mentally defective' and that 'he used to have some sort of attack—in one attack he certainly became unconscious. The attacks were infrequent and occurred many years ago'. Subject II.2 cannot recall any resemblance between his father's medical condition and that of his brother (Case 2), and attributed his father's limp to injury. This patient died at the age of 79 years.
Cases 6 and 7 (II.1 and II.5)

Subject II.2, an eminent businessman, writes concerning his sisters: 'Beatrice died of meningitis at the age of 4 years on 12.3.1915. Joan died of meningitis at the age of 5 years on 8.7.1926.' The 1932 New Plymouth Hospital records of Case 2 (II.4) report that two family members 'died following trivial head injuries and going into convulsions'. The New Zealand Registrar-General's Department has recorded that Case 6 died of 'cerebral haemorrhage' with 'heart failure', and that Case 7 died of 'sub-dural haemorrhage' with 'convulsions' and terminal 'heart failure'. Case 7 was apparently retarded. It is not known whether autopsies were performed.

DISCUSSION

These case histories illustrate several important aspects of severe migraine which have not always been recognized, namely its place in the differential diagnosis of recurrent coma, its presentation as febrile meningoencephalitis with accompanying fever, CSF pleocytosis and psychosis, and the occurrence of life-threatening cerebral oedema which may be intensified by angiography. In addition, cerebral CT scans in 4 cases confirmed the diagnosis of cerebellar degeneration.

Migraine Coma and Head Injury

Coma or profound stupor, often precipitated by trivial head injury, was the cardinal recurrent clinical feature of our patients. In the absence of an available history the prognosis of the earlier episodes of coma in Case 1 were considered poor, and yet recovery contradicted these predictions. Clearly migraine is an important, albeit rare, cause of coma, and one in which the immediate prognosis is usually excellent. It may simulate a neurosurgical emergency as in 'footballer's migraine' (Matthews, 1972), in which visual field abnormalities have followed trivial sporting injuries. Hemiparetic and confusional migraine may likewise be precipitated by minor trauma (Verret and Steele, 1971 (Case 8); Glista et al., 1975; Ehyai and Fenichel, 1978 (Case 3)). The 'neurosurgical' presentation of migraine is highlighted by the fact that carotid angiography demonstrated an avascular space-occupying mass caused by cerebral oedema during attacks of hemiplegic migraine in Cases 1 and 2. Similar angiographic findings led to exploratory neurosurgical operation in a previous case of hemiplegic migraine (Murphy, 1955). It is therefore important to consider the possible presence of migraine in those undiagnosed or clinically atypical cases of traumatic coma in which the initial CT scan is negative, because the later development of cerebral oedema in hemiplegic migraine may cause a life-threatening increase in intracranial pressure. Despite its uncertain pathogenesis, the potentially transient nature of such profound coma as that shown by Case 1 in 1976 and 1979 makes supportive measures, which may include artificial ventilation, amply justified. One question raised but not answered by this study is whether head trauma in patients who suffer from the more usual forms of classical or complicated migraine will precipitate a more severe, but reversible, clinical syndrome following head injury than will the same trauma in nonmigrainous subjects.
CSF Pleocytosis and Fever in Migraine

The present study has shown, unequivocally, that increased CSF cellularity may occur in hemiplegic migraine, and was, in our family, not a rare migrainous accompaniment. CSF pleocytosis (4–57 leucocytes/mm$^3$ with varying proportions of cell types) was documented on many occasions over periods of up to twenty-five years. Most of these elevated CSF leucocyte counts did not follow invasive neuroradiological investigation. The CSF composition in migraine has recently been the subject of controversy. Bartleson et al. (1981) and Casteels-van Daele et al. (1981) believed that CSF pleocytosis in migraine is sufficiently rare for its presence to raise doubts about the diagnosis. Bartleson et al. (1981) further argue that 3 of those 6 quoted cases of CSF pleocytosis reported by Whitty (1953) (2 cases), Symonds (1952), Kremenitzer and Golden (1974), Dooling and Sweeney (1974) and Schraeder and Burns (1980) could be explained by previous invasive neuroradiology. They themselves reported 7 patients in whom the acute onset of clustered migrainous headaches with hemiplegia and/or sensory disturbance was accompanied by moderate CSF pleocytosis. They considered that this pleocytosis constituted a major argument for a viral disease in these cases, and that these patients did not suffer from true hemiplegic migraine. The instances we report contradict this argument, unless it is held that autosomal dominant hemiplegic migraine predisposes to recurrent viral meningitis. Furthermore, in our family the usual interval between severe attacks has been about three years, so that such a prolonged catastrophe-free interval following meningitic coma does not argue against a migrainous aetiology (Bartleson et al., 1981). Indeed, a subject with familial hemiplegic migraine may never experience a second episode of hemiplegia (e.g., the isolated migrainous hemiplegia experienced by the mother of Case 1 reported by Verret and Steele, 1971). The differing reports on the CSF composition in hemiplegic migraine may in part relate to the timing of the CSF examination in relation to the acute illness. In general, in our patients, the CSF leucocyte counts were higher several days after the onset of migraine than at the time of admission to hospital. The substantial pleocytosis (185 polymorphs/mm$^3$) reported by Symonds (1952) was in CSF obtained during recovery from hemiplegia, at the time of hospital admission late in the course of an attack of migraine. Two days later the CSF contained 5 leucocytes/mm$^3$. The CSF pleocytosis (290 leucocytes/mm$^3$) reported by Neligan et al. (1977) was also recorded during initial recovery from hemiplegia in the course of a subsequently fatal attack of migraine. These findings suggest that the CSF leucocyte count may fluctuate, but generally increases during a migrainous hemiplegic episode and that CSF examination late in an episode may be diagnostically informative. They lend some support to the hypothesis of Wolff (1980, p. 105) that a sterile perivascular inflammatory reaction develops during migraine and may be important in its pathogenesis.

Fever was a characteristic feature of this family’s migraine and has been reported incidentally in previous accounts of migraine (see Peters, 1934; Chrást, 1954;
Holub et al., 1965; Neligan et al., 1977; Wolff, 1980, pp. 115–116 (Case P.C.); Gastaut et al., 1981 (Cases 1 and 2); Ferguson and Robinson, 1982). The documented fevers and CSF pleocytosis in migrainous coma now confirm the importance of hemiplegic or comatose migraine in the differential diagnosis of recurrent aseptic meningitis. Indeed our Case 1 was initially diagnosed (and, in 1979, treated) as viral meningoencephalitis, before details of the family history became available. Thus migraine must be distinguished from infective, neoplastic, immunological and drug-related iatrogenic (see von Reyn, 1983) causes of this syndrome, and from ‘Mollaret’s meningitis’.

Cerebral Oedema and Vascular Features in the Patients Reported

Radiological cerebral hemisphere oedema accompanied migraine attacks in this family and characteristically developed during the week following the onset of an attack. In 1979 and 1982 Case 1 sustained extensive hemisphere oedema which could not reasonably be explained by the minor frontal haemorrhage or by ischaemia not sufficiently severe to cause infarction. In Case 2, the ‘space-occupying lesion’ revealed by angiography (1970) was not evident on CT scan (1977, 1983); it now seems probable that this swelling was also focal cerebral oedema. These findings confirm recent brief reports (New and Scott, 1975; Harrison, 1981) that cerebral oedema occurs in hemiplegic migraine, and the direct observation of migrainous brain oedema reported by Goltman (1936; see above). It is noteworthy that the CT scan reported by Harrison (1981) was obtained during the second week of a migraine attack, in line with our own experience that radiological cerebral oedema develops late after the onset of hemiplegic migraine. There is at least one previous report (Murphy, 1955) of major arterial displacement evident on angiography in a patient who later recovered almost completely from a small deep infarction (confirmed at operation) caused by hemiplegic migraine; the angiographic and surgical findings support a diagnosis of cerebral oedema in that patient. Neligan et al. (1977) were perplexed because autopsy of a 41-year-old patient with hemiplegic migraine who died four months after respiratory arrest and prolonged hypoxia revealed no evidence of a severe ischaemic insult which could have explained her respiratory arrest. They therefore thought that massive hemisphere oedema may have resulted in secondary medullary failure. Our Case 1 confirms that massive cerebral hemisphere swelling may be a life-threatening phenomenon in hemiplegic migraine. There is therefore now substantial evidence that cerebral oedema occurs in hemiplegic migraine, even though it may be delayed in onset, and not evident on CT scan early during a migraine attack. This has important implications for the pathogenesis and treatment of migraine, especially hemiplegic or comatose migraine. Certainly it seems justified to use agents such as dexamethasone, and perhaps osmotic diuretics, to minimize cerebral oedema in some cases of hemiplegic migraine.

The surprisingly normal CSF pressure measurement recorded at the time of severe cerebral oedema in Case 1 may have been artefactual. However it is worth noting that Bruyn (1968) believed that normal manometric CSF findings in 2 cases
reported by Whitty (1953) eliminated the possibility that brain oedema was present during their attacks of hemiplegic migraine. Whitty (1953) himself thought that the normal CSF pressures in these cases and that of Symonds (1952) might be explained if increased brain water occurred at the expense of the volume and pressure of the CSF. It is now known (Reulen et al., 1977) that pressure gradients do exist between oedematous brain tissue and CSF.

The 1982 CT findings in Case 1 implicated ischaemia within the distribution of one middle cerebral artery, although on its own such limited ischaemia could not explain the patient’s coma or cerebral oedema. More widespread ischaemia, with involvement of both cerebral hemispheres and/or the vertebrobasilar system, may have been present. Indeed radioisotope studies indicate that there is widespread cerebral oligaemia, beyond the territory supplied by any one cerebral artery (Bousser et al., 1980; Olesen et al., 1981; Lauritzen et al., 1983), even when the presence of migrainous infarction (Bousser et al., 1980) suggests that vascular damage may be more restricted. However, metabolic abnormality (which might cause secondary oligaemia (Lauritzen and Olesen, 1984), cerebral oedema and/or hypothalamic disturbance, all of which are potentially reversible phenomena) may have been more important than ischaemia in the causation of prolonged coma. In general, if a cerebrovascular occlusion is sufficiently severe to cause coma, satisfactory recovery is rare (Levy et al., 1981). A schema of the complex vascular/neuronal interactions in migraine has been proposed by Lance (1982).

The constellation of symptoms in ‘vertebrobasilar migraine’ (Bickerstaff, 1961a, b) includes ataxia and unconsciousness, although in his initial descriptions Bickerstaff emphasized that if unconsciousness does occur in this migraine variant, it is brief (perhaps minutes). Since 1961, migraine which is associated with ataxia (Golden and French, 1975; Lapkin et al., 1977; Swanson and Vick, 1978; Hockaday, 1979) and/or prolonged impairment of consciousness or confusion (Gascón and Barlow, 1970; Lee and Lance, 1977), has been considered to be of ‘vertebrobasilar’ origin, as has any associated hemiparesis. The present study indicates that this is an oversimplification.

In 1982 Case 1 sustained a small frontal haemorrhage which may have been precipitated by migrainous ischaemia. However, it is difficult to be certain about the relationship, if any, of this haemorrhage to the general manifestations of migraine. Cerebral haemorrhage associated with migraine has been reported by Peters (1934), Dunning (1942) and, recently, by Dorfman et al. (1979), who described haemorrhage with infarction in a 16-year-old migraineur. Wolff et al. (1953) documented cutaneous temporal and preauricular haematoma or oedema considered to be spontaneous during migrainous headaches in 11 subjects and it was later suggested that similar intracranial events might occur in migraine (Wolff, 1980, p. 89). Functional platelet abnormalities, which occur during migraine and which result in fluctuating levels of plasma serotonin (Anthony et al., 1967), might play a role in such haemorrhages, and/or in vascular insufficiency during migraine.
The Hazards of Angiography in Migraine

Carotid angiography precipitated the onset or deterioration of hemiparesis or stupor and fever on 4 of the 5 occasions on which it was performed in members of this family; one such episode (Case 1, August 30, 1979) was nearly fatal and was associated with a demonstrable increase in cerebral oedema. Clinical deterioration following cerebral angiography has frequently been mentioned (Whitty, 1953 (Case 1 and Appendix Case); Chrast, 1954; Blau and Whitty, 1955; Murphy, 1955; Dukes and Vieth, 1964; Dooling and Sweeney, 1974; Ehyai and Fenichel, 1978 (Case 3); Bartleson et al., 1981 (Cases 5 and 6); Lauritzen et al., 1983), but seldom emphasized in case reports of severe migraine. In addition, Wolff (1980, p. 113), under the heading of 'ophthalmoplegic migraine', reported that events such as hemiplegia or aphasia, which sometimes lasted for days or weeks, had been precipitated by angiography in four New York patients of H. G. Wolff; angiography was therefore avoided following migraine attacks. It is thus apparent that this procedure carries an unusually high risk of serious complication in certain migrainous patients, although the reason for this effect is obscure. It is, however, well recognized that radiological contrast media may damage the blood-brain barrier (Rapoport et al., 1974; Waldron et al., 1974) and that experimental angiographic lesions to this barrier result in histological cerebral oedema (Sterrett et al., 1976). Injected contrast agents may, rarely, cause adverse CNS reactions with cerebral oedema following any angiographic procedure, especially when prolonged (Lalli, 1980; Studdard et al., 1981).

Mental Impairment and Psychosis in Hemiplegic Migraine

Several of our cases were mentally retarded, or considered to be intellectually slow when compared with their unaffected siblings, in accordance with previous reports that children with hemiparetic migraine may be intellectually impaired (Verret and Steele, 1971, 3 out of 8 cases; Hosking et al., 1978, 3 out of 6 cases). Such retardation could possibly be due to the cumulative effects of migrainous damage. However, retardation in our Case 3 was present in early childhood before the recognized onset of severe migraine, and there was no CT evidence of cerebral atrophy.

Pathological terror marked the recovery from attacks of migraine in Cases 1 and 2. Case 2 was treated with ECT for catatonic schizophrenia in 1954 and his migrainous hallucinations were sufficiently severe for him later to be admitted for psychiatric institutional care in Australia. There is no present evidence of schizophrenia in Cases 1, 2 or 3. Feely et al. (1982) reported members of a family with hemiplegic migraine whose recurrent psychoses were often independent of headache. This raises the question as to whether some previously reported patients with the poorly-characterized syndrome of febrile 'catatonic stupor' may have suffered from the same episodic cerebral disturbance as our patients. The characteristics of 'lethal catatonic stupor' and 'acute exhaustive psychoses' have been reviewed by Adland (1947). Typically there is an acute-onset 'endogenous panic reaction', which is associated with high fever, vasomotor lability, rigidity, peripheral leucocytosis,
CSF pleocytosis and progressive coma leading to death with oedema of the cerebral white matter (Malamud and Boyd, 1939; Laskowska et al., 1965). Malamud and Boyd (1939) attributed catatonic death to 'vasomotor lability commonly seen in schizophrenics'. Many later authors would more positively categorize 'catatonic stupor' as intrinsically schizophrenic, although organic causes of 'catatonia' have now been classified by Gelenberg (1976), and include lesions adjacent to the third ventricle (Cairns, 1952). It would not be justified to take this comparison too far between febrile migrainous stupor with hallucinations and cerebral oedema, on the one hand, and febrile catatonic stupor with hallucinations, vascular collapse and cerebral oedema, on the other. Yet the evidence suggests that in an acute presentation, the one disease may need to be included in the differential diagnosis of the other. Perhaps there are common pathophysiological mechanisms in such febrile 'catatonic' comas, possibly within the dopaminergic pathways of the hypothalamus.

Cerebellar Ataxia and Atrophy

Acute-on-chronic cerebellar ataxia is a characteristic of this family's disease, which thus falls within the definitions both of familial periodic ataxia (Hill and Sherman, 1968; Donat and Auger, 1979), in which residual ataxia may persist, and autosomal dominant cerebellar ataxia (Harding, 1982), the subclassification of late-onset being modified by the onset of ataxia in early childhood in Case 3. However, their illness does not fall easily into any of the four categories of late-onset autosomal dominant cerebellar ataxia proposed by Harding (1982). The clinical features of our family’s illness strikingly resemble those of the family reported by Chrast (1954) under the heading 'migraena cerebellaris'. He described a 22-year-old patient (S.V.) with hemiplegic migraine, whose ‘major attacks’ lasted for over a week and were characterized by high fever, neck stiffness, hemiparesis, hemianopia, hallucinations, obtundation or coma, and cerebellar signs. One episode of severe hemiplegic migraine was provoked by vertebral arteriography. This patient’s mother, uncle and grandfather also suffered from hemiplegic migraine. Holub et al. (1965) detailed this family in a subsequent paper, in which they reported the death of S.V.’s 11-year-old niece (the daughter of S.V.’s apparently unaffected sister) from hemiplegic migraine, with hyperpyrexia (40.1°C). This patient also had a history of ‘meningitic’ hemiplegic migraine with ataxia. Autopsy revealed severe cerebral oedema but no infarction. This family and our own cases clearly belong to the same category within any clinical subclassification of migraine. The fatal case of dominant hemiplegic migraine with ataxia reported by Neligan et al. in 1977 may be similarly classified. Hemiplegic migraine and ataxia has also been described by Ohta et al. (1967) and Golden and French (1975), but their cases differed from our Cases 1, 2 and 3 in that there was no prolonged unconsciousness during migraine attacks.

Five possible causes of cerebellar ataxia with migraine may be considered. (1) Cerebellar damage related to recurrent hyperthermia (Lefkowitz et al., 1983). This is improbable; the magnitude of the recorded fevers was not sufficiently high and, in Case 3, ataxia was evident before the onset of any recognized attacks of
febrile migraine. Case 4, in whom cerebellar atrophy is marked, has not suffered from migraine coma. (2) Cerebellar degeneration caused by phenytoin. In no case has there been collateral evidence for phenytoin toxicity, and nystagmus, an early sign of phenytoin toxicity, was notably minimal or absent in these patients. Phenytoin could not have accounted for the onset of cerebellar signs in 1976 and again in 1982 in Case 1, for ataxia in Cases 3, 4 and 5, nor for the ataxic gait in Case 2 before December, 1948 (he received phenytoin only later). A recent double-blind CT study (Ballenger et al., 1982) revealed no association between phenytoin therapy and cerebellar atrophy. (3) Cerebellar degeneration secondary to recurrent vascular insufficiency caused by vertebrobasilar migraine (Bickerstaff, 1961a, b). (4) Genetic linkage. Hemiplegic migraine and cerebellar dysfunction could be the product of closely linked dominant genes, an attack of the former exacerbating the latter. Some support for this possibility is given by the lack of any history of hemiparesis, coma or frequent headaches in Case 4, although she did sustain one illness suggestive of posttraumatic ‘cerebellar migraine’. Her clinical picture, however, may simply reflect the fact that intrafamilial variation in the severity of the different manifestations of any autosomal dominant illness is common. (5) Metabolic defects. The cerebellar pathology and migrainous vascular phenomena could represent independent consequences of an underlying metabolic defect with periodic manifestations. The significance, if any, of the occasional hyperalaninaemia in Case 1 is not known. There are two previous reports of hyperalaninaemia in children with intermittent syndromes somewhat similar to that reported here. Lonsdale et al. (1969) reported a 9-year-old child with intermittent febrile obtundation, ataxia and hyperalaninaemia. Blass et al. (1970, 1971) reported hyperalaninaemia and hyperpyruvicacidemia in an 8-year-old boy with pyruvate decarboxylase deficiency and an intermittent febrile cerebellar ataxia which was relieved by dexamethasone. The cerebellum is said to be vulnerable to deficiency of pyruvate dehydrogenase (PDH), a multienzyme complex subject to fine in vivo regulation (Reynolds and Blass, 1976). However, assays of enzymes which metabolize pyruvate were normal in cultured fibroblasts from our Cases 1 and 3. This does not entirely exclude primary or secondary PDH abnormality in the CNS, as CNS PDH levels may be low in the presence of normal fibroblast enzyme levels (DeVivo et al., 1979). Although no fundamental metabolic defect has yet been identified in these patients, this fifth hypothesis seems the most plausible explanation for the diverse manifestations of this syndrome.

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