Adrenoleucodystrophy: neurophysiological aspects

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SUMMARY Neurophysiological investigations (EEG, ERG, VEP) were carried out in 14 boys with adrenoleucodystrophy, and in two siblings with adrenocortical deficiency, but without neurological symptoms. Irregular large amplitude (200-800 microvolts) slow activity was found in the EEG of all adrenoleucodystrophy patients, usually more prominent over the posterior regions of the brain. No short duration spikes or complex wave forms were seen in any of the EEGs, even in those patients who had had seizures. Clinical deterioration was not always accompanied by an increase in EEG abnormalities. The ERG was of usual amplitude and wave form, while the VEP (flash) was altered in four cases. The two clinically unaffected siblings had normal ERG/VEP, and only a modest excess of slow waves in the EEG. The neurophysiological findings in adrenoleucodystrophy are not seen in other diseases with similar clinical symptoms in the same age group.

In 1923 Siemerling and Creutzfeldt¹ first described the concurrence of a sudanophilic leucodystrophy (indistinguishable from Schilder's disease) with adrenal insufficiency. Since then, some 60 cases have been reported. Two forms of adrenoleucodystrophy have been described: a more common juvenile type (all in males), and a more rare adult form. The juvenile type usually begins between 5 and 9 years of age with intellectual impairment, behavioural changes and a gradual disturbance of gait.^{2,3} Sometimes symptoms of adrenal insufficiency (such as hyperpigmentation of the skin) may precede the onset of neurological symptoms by several years, while in other cases there are no clinical symptoms of adrenal insufficiency throughout life. The disease is sex-linked, with recessive inheritance pattern. Progression of symptoms is fairly rapid and death usually occurs within 1 to 5 years.⁴ The adult form of the disease is more rare and only few cases have so far been reported with either autopsy or brain biopsy findings.^{3,5,6}

Macroscopic examination shows no alteration of brain surface but large areas of demyelination may be seen on section. The white matter is typically affected bilaterally, and the process usually begins in the parieto-occipital lobes, sparing the U fibres.

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There is severe loss of myelin in the affected areas, and demyelination may also be seen in the brain stem. Secondary degeneration of the corticospinal tracts in the pyramids and in the spinal cord occurs.⁴ The adrenal glands show various degrees of atrophy and the presence of ballooned cortical cells is a specific histopathological feature.⁵ Clinical and pathological aspects of the disease have been extensively reported, but neurophysiological investigations have been mentioned only as a minor detail, with the exception of a recent paper by Mamoli *et al*⁷ where the neurophysiological findings were reported in an affected family.

In the present study, neurophysiological investigations including the electroencephalogram (EEG), electroretinogram (ERG) and visual evoked potentials (VEP) are described in 14 young boys with proven adrenoleucodystrophy. In addition, two siblings with adrenocortical deficiency, but without neurological signs have also been studied.

Materials and methods

Fourteen boys aged from 5½ to 12 years admitted to the Hospital for Sick Children from 1970 to 1980 were diagnosed as suffering from adrenoleucodystrophy from clinical symptoms, biochemical data, neuroradiological and necropsy findings (four post-mortem examinations were carried out). A total of 34 EEG's were taken either in the department or at the patient's bedside. Eight patients had only one EEG, while the other six had two to five records. The two

Accepted 16 March 1981

siblings with only adrenocortical deficiency had three EEG's each. ERG/VEP studies were carried out in 12 of the patients and in the two siblings with a total of 22 records (single tests in seven patients). A standard technique was used to record the EEG using silver/silver chloride electrodes attached to the scalp with collodion, according to measurements from bony landmarks.⁸ The EEG's were taken with either Offner type T or Grass 8-10 channel EEG apparatus, using a time constant of 0.3, 0.4 or 1 second, HF response linear to 70 Hz and a paper speed of 60, 30 or 15 mm/s. ERG and VEP studies were carried out with techniques already described.^{9,10}

Results

CLINICAL SYMPTOMS

Symptoms began at ages between 5½ and 9 years (fig 1) in all but one child in whom the first symptoms appeared as early as age 3 years with intermittent weakness of the left leg and intermittent hoarseness of voice. Behavioural changes (hyperactivity, aggressiveness, disobedience, emotional lability) and intellectual deterioration were the most common and earliest features. Failing vision occurred in nine out of the 14 patients, but only in four of them as a presenting symptom. In the remaining patients, visual deterioration became obvious between 2 weeks and 2½ years after the onset of other symptoms. Skin hyperpigmentation was noted in only three cases, being already present when the first symptoms of the disease became obvious. Seizures occurred in five out of the 14 patients (mostly generalised convulsions, although

absences occurred in one patient) either as a presenting symptom or later in the course of the disease.

EEG FINDINGS

The timing of neurophysiological investigations in relation to the clinical events is given in fig 1. The first EEG's were taken between 2 months and over 4 years after the appearance of the first symptoms. The main overall abnormality consisted of an excess of irregular large amplitude (200 to 800 microvolts) slow activity, most marked posteriorly in the temporo-parieto-occipital areas (fig 2). This activity was independent of eye closure or eye opening. At the time of the first EEG no alpha rhythm was seen on eye closure in 11 out of the 14 cases. In case 1, with acute onset, the alpha rhythm was initially not present, but appeared in the second EEG taken 2 years later and persisted in subsequent records for several years. In all cases rhythmic activity in the rolandic regions was usually recognisable though not always well formed.

Whenever possible overbreathing was carried out and usually it elicited an increase in the amount and amplitude of the slow components, again maximal posteriorly. Sleep was achieved in two cases and sleep spindles appeared to be of normal configuration and frequency over both frontocentral regions. K complexes were symmetrically evoked by auditory stimuli. Infrequent ill-defined sharp elements with variable distribution were only seen in one case. No definite short duration spikes or complex waveforms were seen in any of the EEG's even in the five patients with seizures. Some asymmetry in the amount and amplitude of the slow components was seen in three cases, tending to fluctuate during the evolution

Fig 1 Timing of neurophysiological investigations (EEG, ERG, VEP) in relation to clinical events in 14 cases of adrenoleucodystrophy.

Fig 2 (Case 10) EEG's taken 5 months (above) and 6 months (below) after onset of illness. There is excess of irregular large amplitude slow activity maximal in the posterior regions of the brain.

of the disease (fig 3). However, no asymmetry was detected in the CT scan (carried out in two of them).

In the six patients with serial EEG's over a period of years (fig. 1), great variability in the evolution of the abnormalities was noticed. The EEG features did not usually worsen following clinical deterioration, and at times improvement was seen. In one patient (case 6), who had been admitted to hospital acutely ill (with a 24-hour history of headache, fever, vomiting, failing vision, confusion and disorientation), the EEG was carried out at the bedside. It showed a marked excess of irregular large amplitude slow components over a wide area of the two hemispheres, without clear localising signs or definite paroxysmal features (fig 4). Such EEG findings are usually seen in a diffuse encephalitic or encephalopathic process. During the next 24 hours, the child became more lucid and cooperative, and a second EEG the following morning showed an improvement over the anterior half of the brain, while the abnormality remained very marked posteriorly, where large amplitude slow activity persisted. Some rhythmic components were then recognisable in the

Fig 3 (Case 2) EEG's taken 19 months after onset of symptoms. Above: Irregular large amplitude slow activity with patchy distribution, more marked posteriorly. Bottom left: One day later diminution of slow activity. Bottom right: One week later marked asymmetry between the activities of the two hemispheres.

rolandic regions, but no alpha rhythm could be detected.

In the family of cases 2 and 3 there were three other male siblings. The older brother had died at age 6 years with the diagnosis of Addison's disease. The other two siblings did not have any signs of leucodystrophy, but adrenocorticotrophic hormone stimulation test had shown adrenocortical deficiency in both of them. The six EEG's taken between 4½ and 14 years showed a moderate excess of irregular intermediate slow activity with preservation of alpha rhythm and mu rhythm. There were no focal signs or paroxysmal features.

ERG/VEP FINDINGS

The ERG was present and of usual amplitude and waveform in all cases studied. The VEP was present with well-defined early components in eight out of the 12 cases investigated (including the two siblings). In two patients (cases 6, 10) the VEP deteriorated over a short period of time (1 and 3 months respectively). In another patient (case 12) (fig 5) only a low amplitude VEP was seen with none of the usual earlier components, while in case 4 no VEP was recognisable.

Fig 4 (Case 6) Top left: the first EEG, taken when this child was acutely ill, showed a marked excess of irregular large amplitude slow activity over a wide area of the brain. Top right: the second EEG, taken the following morning, showed some improvement over the anterior half of the brain. Bottom left: six days later the child had clinically improved and the EEG showed diminution in the amount of irregular slow waves and increase in rhythmic components. Bottom right: following clinical deterioration the EEG showed an increase in slow components particularly posteriorly with disappearance of rhythmic activities.

Discussion

Behavioural changes, intellectual deterioration, failing vision, with onset between 5 and 9 years of age

may occur in a variety of disorders such as sub-acute sclerosing panencephalitis, Spielmeyer-Vogt disease (juvenile type of neuronal ceroid-lipofuscinosis) as well as in adrenoleucodystrophy. In this context, combined EEG/ERG/VEP studies have proved to be of invaluable help in the differential diagnosis. The large amplitude slow components over the posterior regions of the brain with preservation of normal rhythmic activities in the paracentral areas, were the most common EEG features in our group of patients with adrenoleucodystrophy. Such EEG features are quite different from the runs of $1\frac{1}{2}$ to $2\frac{1}{2}$ per second wave and spike complexes seen in a group of patients with Spielmeyer-Vogt disease¹¹ as well as the periodic complexes characteristic of SSPE.¹² The ERG, while normal in our cases of adrenoleucodystrophy, is not recordable at an early stage in Spielmeyer-Vogt disease.¹³ The flash VEP is gradually reduced in amplitude and disappears in Spielmeyer-Vogt disease,¹³ while it has been normal in eight out of our 12 cases with adrenoleucodystrophy. (Three of our patients were tested over a number of years.) The poor or absent flash VEP noted in four of our cases could be due to loss of function of visual pathways or visual cortex or both. The only studies on visual evoked responses in adrenoleucodystrophy are those of Mamoli *et al*,⁷ who, however, used pattern stimuli; therefore their results are not strictly comparable with ours.

Intellectual deterioration followed by unsteadiness of gait, starting at about 5 to 10 years of age, may also be found in juvenile metachromatic leucodystrophy. However, the EEG abnormalities in metachromatic leucodystrophy, with a mixture of slow and fast components and early disappearance of normal rhythmic activities,¹⁴ are quite different from

Fig 5 ERG (recorded from a surface electrode on the bridge of the nose) and flash VEP (recorded from the mid-occipital region) in 2 patients. A normal ERG was seen in both. The VEP was normal in Case 14 (left) but of low amplitude with none of the usual early components in Case 12 (right). Stimulus at arrow. Both eyes stimulated simultaneously.

those seen in our adrenoleucodystrophy patients. The VEP instead may be poorly formed in metachromatic leucodystrophy (early components in particular) and may even be absent in some patients.¹⁵ Large amplitude EEG slow activity, most marked over the posterior regions of the brain, may also be seen in young patients with posterior fossa space-occupying lesions.^{16 17} However, in the specific clinical context the two pathological processes may be distinguished.

In reported cases of adrenoleucodystrophy, with EEG studies, posterior slow activity has been described.^{2 5 7 18-20} "Frontal slowing"³; "diffuse brain dysfunction"^{2 3 5 18 21} and paroxysms or spikes^{2 7} have, however, also been reported. In our study, we never found EEG slow activity prominent in the frontal regions either at an early or late phase of the disease. No short duration spikes or complex wave forms were seen in any of our patients, even in those with seizures. The severity of EEG abnormalities throughout the course of the disease was usually fluctuating often independently from the clinical course. It is important in acutely ill patients to repeat the EEG at intervals of a day or two (fig 4, case 6) to avoid misinterpretations. In contrast with other authors⁷ no marked diminution in the amplitude of EEG activity was ever observed in the later stages of the disease, even in those patients in whom the EEG was taken 3 months (case 8), 2 months (case 9) or 1 month (case 3) prior to death.

In the two neurologically unaffected brothers we studied, the mild EEG abnormalities may just be related to the endocrine disorder affecting these patients (Addison's disease),²² rather than predicting a leucodystrophy.⁷

In conclusion, EEG/ERG/VEP findings in adrenoleucodystrophy are sufficiently characteristic to exclude with confidence other disease processes occurring in the same age group with similar clinical neurological features.

We are indebted to our clinical colleagues, particularly to Dr John Wilson and Dr EM Brett for referring the patients and to Dr Magda Erdohazi (neuropathologist).

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