

# Menkes' disease: neurophysiological aspects

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**SUMMARY** The evolution of neurophysiological features including the electroencephalogram (EEG), electroretinogram (ERG), and visual evoked potentials (VEP) is reported in eight cases of Menkes' "kinky hair" disease. All EEGs were severely abnormal, with some characteristic features seen from 3–5 months of age, after the onset of clinical symptomatology. From the age of 5 months, the EEGs resembled hypsarrhythmic patterns. The ERG was not affected in any patient, but the VEP was either of low amplitude or completely absent in all but one of the six patients tested. All eight patients received copper injections without substantial effect on either the clinical course of the disease or the EEG features.

In 1962 Menkes *et al.* first described a rare sex-linked metabolic disease presenting in early infancy with failure to thrive, convulsions, and hypothermia. Because of the characteristic malformed hair found in the syndrome, Menkes called it "kinky hair disease." Later the term "steely hair disease" was used by Danks *et al.* who carried out metabolic studies (1972a, b, 1973a, b), and established that all these patients had a marked deficiency of serum copper and caeruloplasmin as well as a defect of copper transfer through the intestinal epithelium. The resulting lack of copper availability to the copper-dependent enzymes was thought to be the cause of all manifestations of this disease (Danks, 1975). However, parenteral administration of copper sufficient to increase serum copper levels does not appear to alter the clinical course of the disease (*Lancet*, 1975; Wheeler and Roberts, 1976).

Reports of neurophysiological studies in this disease have been very limited in spite of the fact that convulsions are a prominent early clinical feature. In the present study, the early and later features of the electroencephalogram (EEG) together with the electroretinogram (ERG) and visual evoked potentials (VEP) are reported in eight cases of proven Menkes' disease.

## Patients and methods

The eight boys had been admitted to the Hospital for Sick Children, Great Ormond Street, with Menkes' "kinky hair disease" diagnosed on very low levels of serum copper and caeruloplasmin, and on the abnormal hair with pili torti.

Twenty-four EEGs were taken using either Offner Type T or Grass 8/10 apparatus according to techniques previously described (Pampiglione, 1965). Clinical seizures were observed in the course of 10 EEGs (four cases) and sleep occurred during eight EEGs (six cases).

The ERG and VEP were recorded at the same time as the EEG in six patients (10 records) according to a technique already described (Harden and Pampiglione, 1970).

## Results

A summary of the clinical events as well as the timing of the neurophysiological investigations is given in Fig. 1. The onset of convulsions in case 8 was relatively late (age 6 months), and the diagnosis in this case was not made until the age of 2 years 4 months at which time the serum copper and caeruloplasmin levels were not as low as in the other cases, although the hair was typically malformed. The clinical aspects of cases 1, 2, and 3 have been published by Wheeler and Roberts (1976), and the unusual pathological findings of case 1 have been reported by Erdohazi *et al.*

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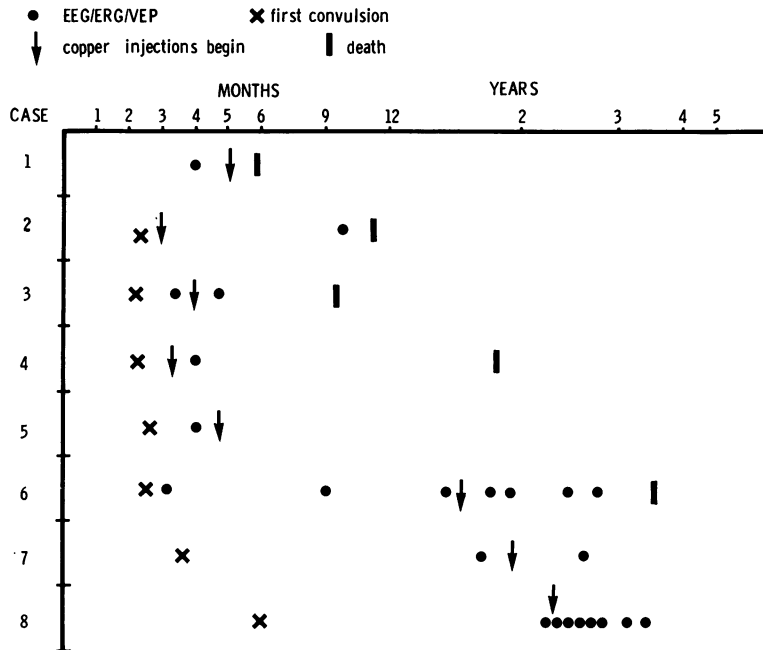


Fig. 1 Timing of neurophysiological investigations (EEG, ERG, and VEP) in relation to clinical symptomatology and treatment in eight cases of Menkes' disease.

(1976). All the patients had been admitted to other hospitals before being referred to the Hospital for Sick Children, but in only four cases was the diagnosis already known or suggested before referral to this hospital. All eight children received a course of copper (CuEDTA) injections during which time neurophysiological studies were repeated in four cases.

All patients except case 1 had seizures and were treated with anticonvulsants. At the beginning of the disease the seizures were usually focal and often prolonged (for over one hour) but later brief generalised tonic spasms were the most usual type of attack. Severe seizures with variable features continued to occur at irregular intervals despite anticonvulsant treatment.

All 24 EEGs showed a marked abnormality with an excess of slow activity, spikes, sharp waves, and sometimes complex waveforms. The discharges were not facilitated by photic stimulation. On occasions some of the abnormal features were lateralised or even focal although such localisation was not consistent. No rhythmic activity appropriate to the child's age was seen in either the occipital or Rolandic regions. No responses to photic stimulation were recognisable in the primary traces. In those patients who fell asleep there was little change in the EEG activity and no sleep spindles appeared. These general features were seen in the EEGs of all the patients

throughout the course of the disorder but some of the EEG abnormalities appeared in a rather characteristic way at different phases of the disease.

#### I Between 3 and 5 months of age

- Localised sharp waves of 100 to 600 microvolts occurred in runs for periods of 0.5–3 min. (Figs. 2 and 3). These episodes recurred in different regions at different times. Concomitant focal twitching was only infrequently observed.
- Diminished amplitude of activity limited to a fairly discrete area of one hemisphere was often seen (Fig. 2), at times slowly changing from one region to another but occurring independently of the discharges mentioned in (a) and unassociated with any obvious clinical change.

#### II After the age of 5 months

The discharges, instead of being localised, tended to become generalised although often multifocal and mixed with irregular slow activities reaching 300 to 1000 microvolts in a pattern resembling hypsarrhythmia (Fig. 4). The clinical seizures at this stage were usually in the form of one or more brief tonic spasms which were accompanied by a slow or sharp wave in the EEG and followed by a generalised decrease in the amplitude of the traces for 1–3 seconds. In two children tonic attacks lasting 5–10 seconds were also witnessed, and

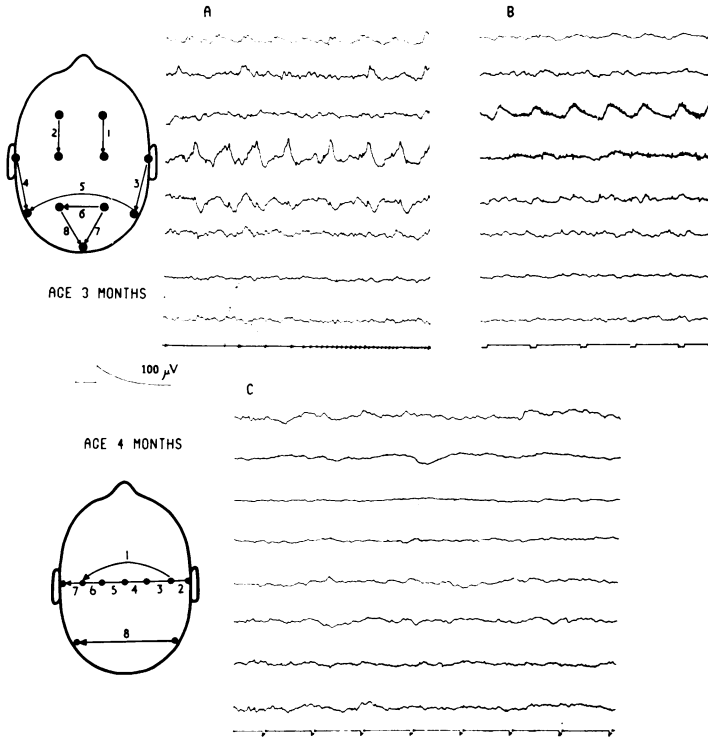


Fig. 2 Case 3. Note recurring discharges in A and B shifting in distribution (30 seconds interval between the two traces) and local areas of low amplitude activity especially in the right central region in C.

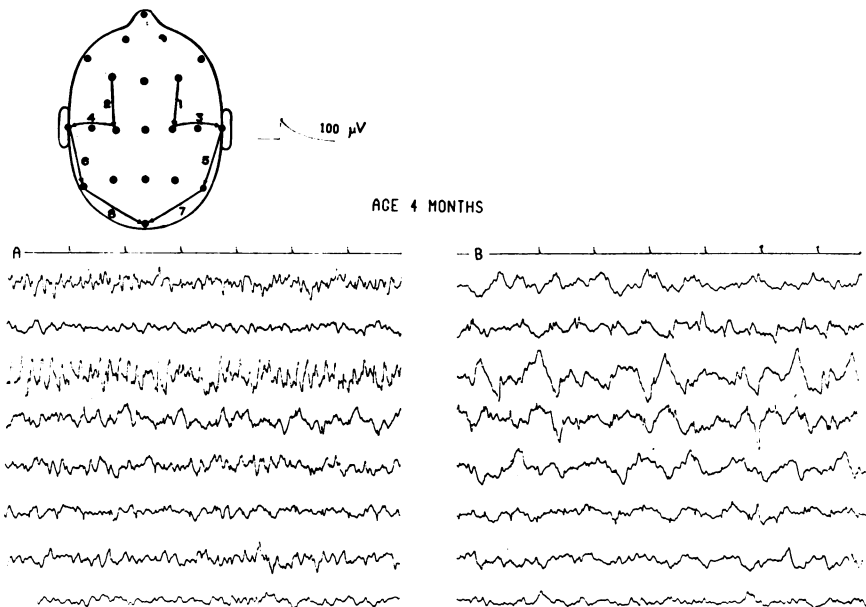


Fig. 3 Case 4. Note run of localised discharges in right central region in A which have disappeared in B (30 seconds later). Smaller amplitude discharges are recognisable over the left central region in B.

AGE 2 YRS 4 MONTHS

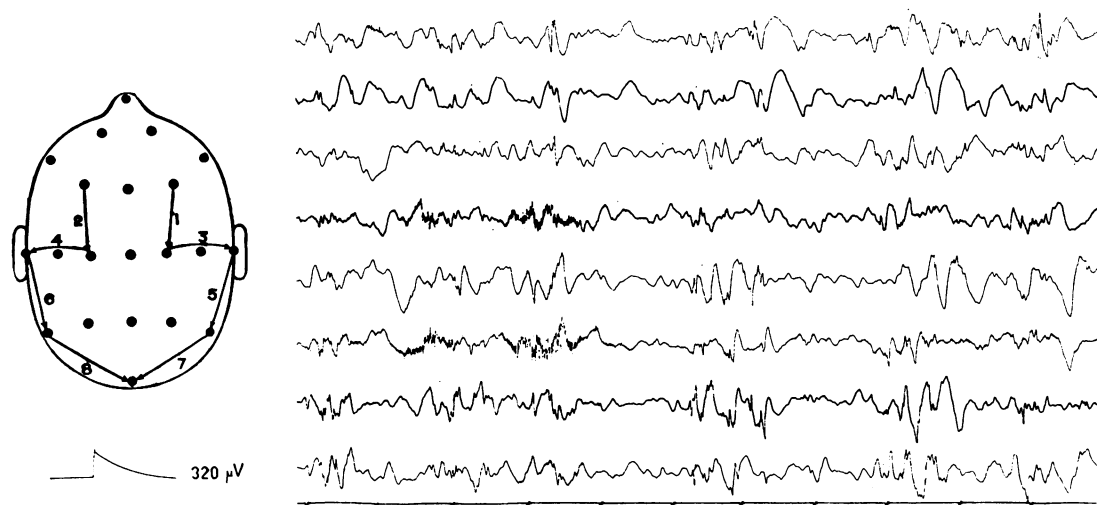


Fig. 4 Case 8. Marked generalised abnormality with large amplitude slow activity mixed with spikes and sharp waves. Note size of calibration signal.

generalised low amplitude activity at 10–20 c/s appeared during these somewhat longer seizures.

In the four patients followed up during the course of therapeutic copper injections, there was a slight and short-lived improvement in the EEG features of two children while no improvement at all was seen in the other two. In case 4 the copper injections began before the first EEG but the features I(a) and (b) described above were present. The severity of the EEG abnormality did not seem to be related to the serum level of either copper or caeruloplasmin.

The six patients who also had ERG/VEP investigations showed no abnormalities of the ERG which was of usual latency, amplitude, and waveform for the age of the child and conditions of stimulation. In the five patients tested between the ages of 3½ and 10 months the VEP was ill-defined and of low amplitude in four patients (Fig. 5), while in the remaining case the VEP was totally absent. Only one patient (case 8), repeatedly tested at the age of 2, 3, and 5 years, showed a normal VEP.

### Discussion

The EEG findings in the eight patients of the present series are in keeping with the few limited reports already published, such as the single case of Singh and Bresnan (1973) as well as Menkes *et al.* (1962) who described the EEG features as

“early multifocal abnormalities which later became diffuse.” In our patients the EEG abnormalities were already severe when convulsions began at the age of 2–5 months, and this may be important in view of the apparently normal post-natal period in these children. Unfortunately EEG data during the presymptomatic phase of the disease are scanty (Grover and Scrutton, 1975).

At least two mechanisms have been suggested to explain the neurological symptoms of the

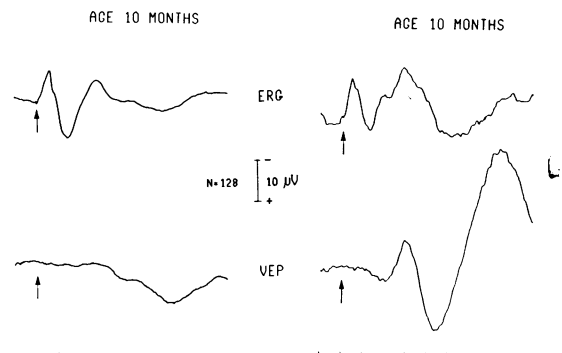


Fig. 5 ERG (non-corneal) and VEP (mid-occipital) in case 2 (left) compared with normal child of same age in (right). Binocular flash stimulation at arrow. Time marked in 25 ms intervals. Note similarity of amplitude and waveform of ERG in the two tracings but the VEP is very poorly defined in the patient with Menkes' disease.

disease: (1) impaired circulation due to the tortuosity of the blood vessels as observed by Wesenberg *et al.* (1969); (2) malfunction of the copper-dependent enzymes due to the low copper concentration in brain tissue (Walker-Smith *et al.*, 1973). It is, however, difficult to relate either of these processes with any certainty to the peculiar EEG features seen in the early phases of Menkes' disease. Because of the variability in the distribution of the peculiar EEG abnormalities, any large cortical ischaemic lesion is unlikely. On the other hand, the transitory and variably focal EEG changes seen in the first 3–5 months of life of these patients could well be due to a fluctuating disturbance in local blood supply, perhaps related to the tortuosity of the vessels. A shifting distribution of the EEG abnormalities, however, does not necessarily exclude a more generalised metabolic alteration, as, for example, hypocalcaemia in the newborn period gives rise to prolonged episodes of rhythmic discharges with varying focal distribution over one or other hemisphere (Pampiglione *et al.*, 1970; Pampiglione, 1973). However, in these hypocalcaemic babies the EEG between these runs of discharges may appear relatively normal unlike that of the patients with Menkes' disease.

Other genetically determined metabolic diseases with clinical manifestations occurring in the first year of life, including those described under such eponyms as Krabbe, Tay-Sachs, Santavuori, as well as phenylketonuria, have different abnormal features from those seen in the early stages of Menkes' disease (Clayton *et al.*, 1966; Kliemann *et al.*, 1969; Santavuori, 1973; Pampiglione *et al.*, 1974). Persistent localised EEG abnormalities may precede the full blown EEG picture of hypsarrhythmia either with pre-existing cerebral damage (Watanabe *et al.*, 1973) or in association with other structural lesions such as the tuberous sclerosis syndrome (Pampiglione and Moynahan, 1976), but again the EEG features contrast with the rapid fluctuations in distribution of abnormal activities as seen in the earlier phases of Menkes' disease.

Most of our ERG/VEP studies were carried out at a fairly early stage when it was difficult to assess clinically the visual awareness of these retarded babies. Contrary to our findings, some ERG abnormalities (usually affecting the "b" wave) have been mentioned in three single case reports of Menkes' disease, by Billings and Degnan (1971), Singh and Bresnan (1973) and Levy *et al.* (1974), but their documentation is not very clear. The ERGs of our patients have been recorded under photopic conditions, but it is unlikely that with such well-preserved ERGs any of our patients

would have any gross loss of function of the outer retinal receptor elements (rods, cones, and possibly bipolar cells). In one histopathological report of an eye from a patient with Menkes' syndrome, Seelenfreund *et al.* (1968) found a loss of retinal ganglion cells but this alone could not alter the ERG (Pampiglione *et al.*, 1974). An abnormal VEP was documented in five out of six patients examined by us, and this would suggest a gross loss of function of the visual pathways, visual cortex, or both which was already established soon after the onset of clinical symptomatology. The few other VEP studies in single cases (Billings and Degnan, 1971; French *et al.*, 1972; Singh and Bresnan, 1973; Levy *et al.*, 1974) have mostly reported an abnormally low amplitude response. It was somewhat surprising that case 8 in our series never showed any VEP abnormalities, but this child was less severely affected clinically and had longer survival than any of the other patients.

It has been postulated that copper injections should be started soon after birth, when clinical symptoms in Menkes' disease are not yet present (Wheeler and Roberts, 1976), although the caeruloplasmin level was found to be normal in the cord blood of a child who subsequently developed Menkes' disease (Lott *et al.*, 1975). From other evidence (Horn *et al.*, 1975), it seems that the distribution of copper may already be abnormal during early fetal life, and recently prenatal cerebral maldevelopment has been described (case 1 of our series) by Erdohazi *et al.* (1976), although this case was atypical clinically. In our series, copper injections did not have any obvious effect on either the clinical or the EEG evolution; this may well be due to irreversible damage occurring before the administration of copper supplement (Wheeler and Roberts, 1976). However, the continuing severity of the EEG abnormalities seems to be in keeping with an ongoing disease process rather than the sequelae of previous damage. It is interesting that raising the serum copper levels can correct the abnormal hair but has so little effect on the main clinical symptoms and EEG features.

It appears that neurophysiological studies carried out in children with Menkes' disease not only reflect the severe cerebral involvement from an early stage, but offer some help in the differential diagnostic problem of various disorders occurring in the first year of life. At present, treatment with copper injections does not seem to be effective but should other methods of treatment be attempted in the future, the EEG might be useful as a monitor of any possible beneficial effect on cerebral function.

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