

Short report

# Adult ceroid-lipofuscinosis: diagnostic value of biopsies and of neurophysiological investigations

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**SUMMARY** In a sibship of ten, three brothers presented with an adult form of ceroid-lipofuscinosis. The diagnosis was confirmed by necropsy of the first patient and was made by electron microscopy of eccrine sweat glands and of skeletal muscles in the two others. Somatosensory evoked potentials were characterised by biphasic, nearly monophasic, very high voltage complexes totally unlike those found in normal controls. Similar sensory evoked potentials were however recorded in other types of ceroid-lipofuscinosis. While electron microscopy of easily available tissues gives fairly specific results, sensory evoked potentials can bring supportive diagnostic evidence in adult ceroid-lipofuscinosis.

Electron microscopy of skin, conjunctival and skeletal muscle biopsies represents an adequate diagnostic method for the infantile, late infantile and juvenile ceroid-lipofuscinoses. Electroretinography, visual evoked potentials (VEPs) and electroencephalography (EEG) are also widely used<sup>1</sup> while somatosensory evoked potentials (SEPs)<sup>2</sup> rarely have been recorded in such conditions. Our present report deals with the diagnostic value of morphological and SEP data in adult ceroid-lipofuscinosis (Kufs type).

### Case reports

The family tree is presented in fig 1. Case II—3 died at age 33; full necropsy data reported elsewhere<sup>3</sup> confirmed the diagnosis of generalised ceroid-lipofuscinosis.

**Case II—4:** onset of the disease was at the age of 32 yr with rare epileptic seizures, slowly progressive dementia, mask-like facies, cog-wheel rigidity and cerebellar features; bedridden by age 38 yr. Normal fundi. Decrease of the b wave on scotopic electroretinogram, normal photopic ERG, normal VEP. Normal brain stem auditory evoked potentials (BAEP). EEG: bilateral theta rhythms and atypical spike waves. Normal motor and sensory conduction velocities. CT of the brain: diffuse cortical atrophy with enlargement of the lateral ventricles. A skeletal muscle biopsy at age 33 revealed subsarcolemmal membrane-bound osmiophilic inclusions with curvilinear and rectilinear profiles. A skin

biopsy at age 36 included eccrine sweat glands in which vacuoles with small amounts of curvilinear and rectilinear profiles (fig 3a). Semi-thin sections of a skin biopsy demonstrated a vacuolisation of the eccrine sweat glands; electron microscopy showed membrane-bound vacuoles containing curvilinear, rectilinear and fingerprint profiles as well as lipid droplets (fig 3b, c). SEPs were recorded (fig 2). Plexus, P13 and N19 components had normal latencies. The following part of the cortical response had as in case II—4 an abnormal nearly monophasic waveform with an amplitude was 5.8  $\mu$ V and never exceeded 10.5  $\mu$ V.

**Case II—7:** a 34-year-old unskilled worker suffered progressive mental deterioration for one year, with akinesia, mild rigidity and epilepsy. Normal fundi, ERG, VEP. Normal BAEP. EEG: dysrhythmic record with spikes; intermittent light stimulation elicited two short grand mal seizures of 25 s duration. Normal motor and sensory conduction velocities. CT of the brain: slight cortical atrophy. A muscle biopsy revealed large amounts of subsarcolemmal auto-fluorescent and acid phosphatase positive granules, characterised ultrastructurally by curvilinear and rectilinear profiles (fig 3a). Semi-thin sections of a skin biopsy

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Received 27 March 1982 and in revised form 1 July 1982.  
Accepted 10 July 1982

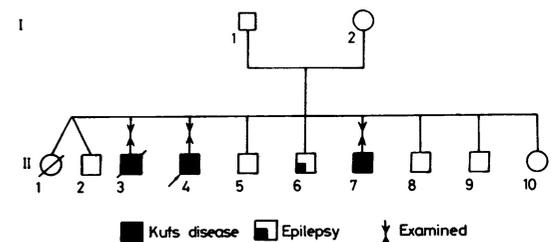


Fig 1 Family tree.

*Adult ceroid lipofuscinosis*

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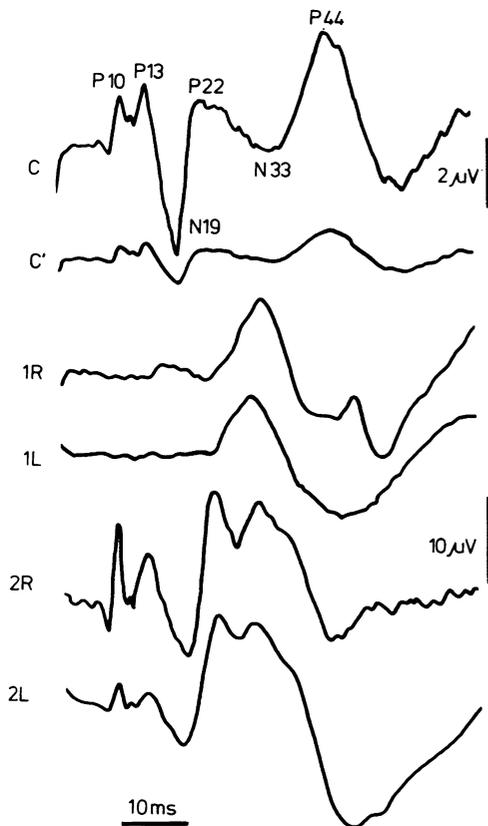
following part of the cortical response had as in case II—4 an abnormal nearly monophasic waveform with an amplitude varying from 16 to 23  $\mu$ V, thus clearly exceeding the control values.

**Discussion**

Adult ceroid-lipofuscinosis or Kufs' disease encompasses cases with autosomal recessive inheritance and one family with an autosomal dominant transmission.<sup>5,6</sup> Few ultrastructural data are available and no characteristic biochemical or enzyme features have been reported. There are no ocular symptoms but a ballooning of the retinal ganglion cells may be present.<sup>3,7</sup> We limit our discussion to the form starting in adult life which is characterised by low intelligence, progressive mental deterioration starting during the third or the fourth decade, rare epileptic seizures and myoclonic jerks, extrapyramidal rigidity and cerebellar tremor. Death occurs between 30 and 60 years.

It had been deemed impossible to diagnose adult ceroid-lipofuscinosis without necropsy or at least without a brain biopsy. There is no longer any good reason to perform a brain biopsy except in rare circumstances.<sup>6</sup> Eccrine sweat glands and skeletal muscle biopsies<sup>8</sup> offer a safe and easy way to establish the diagnosis, revealing in our cases specific inclusions with curvilinear and rectilinear profiles comparable to the ones found at necropsy in the first patient of the sibship.<sup>3</sup> It is therefore reasonable to start with skin and muscle biopsies when suspecting Kufs' disease. Only repeated failure to show significant inclusions in an otherwise fairly typical case would require rectal or appendix biopsies in order to obtain neurons.

Scarce literature data limited to late infantile and early juvenile types of ceroid-lipofuscinosis<sup>2,9</sup> as well as own unreported investigations in two patients with juvenile ceroid-lipofuscinosis and one with the early juvenile type have prompted us to check SEPs in our Kufs' patients. Combined with morphological investigations, SEPs could indeed represent a non-invasive and apparently promising procedure to help in detecting potential candidates, since in our cases, one of them being at an early clinical stage, abnormal cortical potentials of very high amplitude were reported. Our results suggest that amplitude enhancement of the cortical SEP might be common to all ceroid-lipofuscinosis types, except perhaps in the infantile form for which no results of this kind are known. The physiological mechanisms underlying this response remain undetermined; there are no adequate anatomico-physiological correlations as yet available despite fragmentary evidence on cellular pathology of ceroid-lipofuscinosis.<sup>10</sup> In Kufs' disease at least, it is probably not the same mechanism as the one responsible for the high amplitude VEPs obtained in late infantile ceroid-lipofuscinosis since



**Fig 2** Short term somatosensory evoked potentials in one control (C and C') and two Kufs patients.

C: control, expanded amplitude-scale; C': control, same amplitude scale as patients; 1: case II-4; 2: case II-7; R: right; L: left. P 10: plexus potential; P 13: cervical component; N 19, P 22, N 33, P 44: cortical components. In the Kufs' patients, the cortical response has been changed to a biphasic nearly monophasic high voltage complex. SEP were recorded on both sides after median nerve stimulation, an electrical 0.2 ms duration square-wave pulse of constant current being delivered through a bipolar surface electrode.<sup>4</sup> One scalp electrode was placed at C 3 or C 4 (10-20 international system) with reference to an Erb's point electrode at the site of the stimulus. The potentials were recorded over a 60 ms period, using a band pass of 16.0 to 1,600 Hz and a two channel averager with 512 addresses per channel. Usually 1,024 sweeps were averaged. Positivity at the scalp electrode was plotted as an upward deflection.

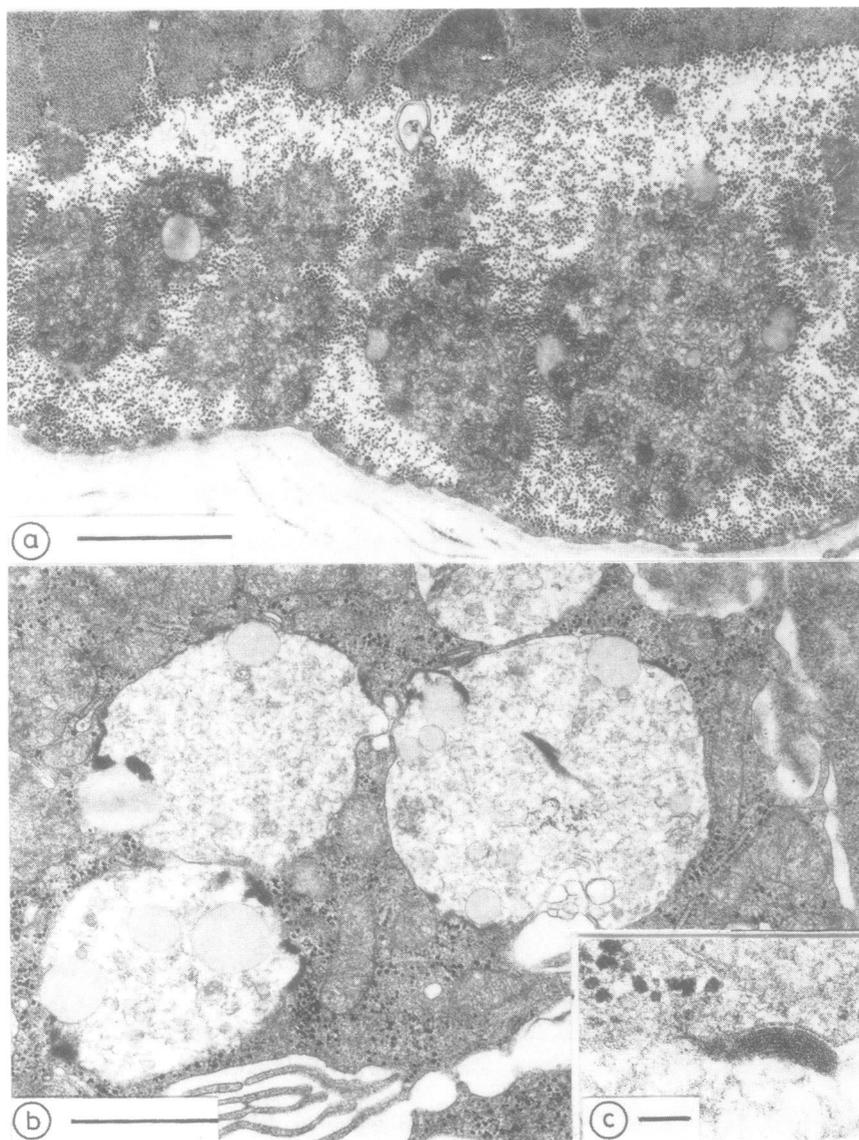


Fig 3 Electron-microscopy of case II-7. (a) Skeletal muscle biopsy: numerous membrane-bound inclusions containing curvilinear and rectilinear profiles. (b) Skin biopsy: in eccrine sweat glands, membrane-bound vacuoles are found with a few osmiophilic profiles, lipid droplets and granulo-filamentar material. (c) Inset: at a higher magnification, fingerprint profiles can be observed in such vacuoles (standard electron microscopic techniques, A-B: scale = 1  $\mu$ m; C: scale = 0.1  $\mu$ m).

VEPs in our Kufs' patients were not significantly altered.

This work has been supported by the FGWO (grant no. 3.0004.81), the Baron Charles Bracht Foundation and by a bestowal of Mrs Vincentelli. The skilful help of our technicians is gratefully acknowledged.

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