CASE REPORTS

MRI of the Brain, EEG Sleep Spindles and SPECT in the Early Diagnosis of Infantile Neuronal Ceroid Lipofuscinosis

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Prenatal diagnosis of infantile ceroid lipofuscinosis (INCL) recently has become possible. Diagnosis was first based on the electron-microscopic finding of inclusions in the chorionic villi (Rapola *et al.* 1990). Since the short arm of chromosome 1 was identified as the location of INCL (Järvelä *et al.* 1991), electron microscopy and DNA techniques have been combined for the diagnosis of INCL (Järvelä *et al.* in press).

The clinical diagnosis of INCL so far has been based on neurophysiological and ophthalmological findings (Santavuori *et al.* 1988). However, these may not appear until several months after the onset of the disease, at two years of age or later (Santavuori *et al.* 1990). The reliable prenatal diagnosis and late appearance of the previous diagnostic findings have encouraged the search for new diagnostic tools.

We present two girls with INCL who both had markedly abnormal brain MRIs at an early stage, in addition to other findings of diagnostic importance.

Case reports

CASE 1

This 27-month-old girl developed normally until the age of eight months. She could roll over at four months and crawl at nine months, but could not stand until 12 months and never learned to walk independently. By 12 months she was able to say a few words, but lost them quickly. Her head circumference was 42·8cm (second centile) at 10 months, compared with 35cm (50th centile) at birth and 42cm (50th centile) at the age of five months.

At 18 months she was definitely mentally retarded, but capable of limited contact with other people and able to play a little. She had no speech and her vision was impaired. She was hypotonic and ataxic, and had slight but frequent hyperkinesia in her upper arms (pronation-supination). Stretch reflexes in the legs were brisk. She was able to sit, crawl and stand up, but could not walk even with support. She was microcephalic (44·5cm). She was often irritable, cried a lot (day and night) and did not sleep well. Laboratory investigations and ophthalmological findings were normal, as were electroretinogram (ERG) and visual-evoked

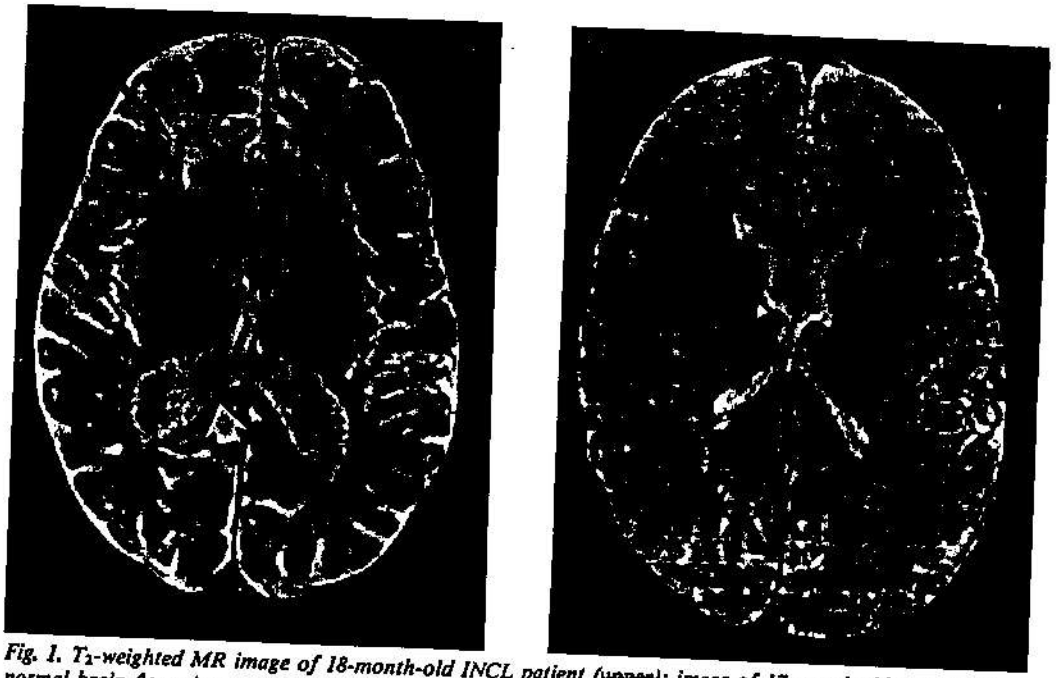

Fig. 1. T_2-weighted MR image of 18-month-old INCL patient (~~upper~~); image of 17-month-old child with normal brain (~~lower~~) presented for comparison. Lateral ventricles and sulci are dilated. Splenium of corpus callosum (white arrow) is thin. White matter is hyperintense in relation to cortical grey matter, while in normal brain peripheral white matter and cortical grey matter are isointense. Periventricular white matter (black arrow) has high signal intensity. Basal ganglia look hypointense and signal intensity in thalami is abnormally low.

potentials (VEP). EEG showed generalised background abnormality with occasional spikes. During sleep there were no sleep spindles.

Brain single-photon emission computed tomography (SPECT) was abnormal, showing slight hypoperfusion in the left temporal and both occipital regions. MRI (Fig.1) showed enlargement of the third and lateral ventricles, cerebral sulci and ambient cisterns. The corpus callosum was extremely thin and the heads of the caudate nuclei were a little smaller than usual. The cerebral white matter, especially in the periventricular regions, was abnormally hyperintense in relation to the cortical grey matter on T_2-weighted images. The basal ganglia appeared hypointense in relation to the white matter, having the same intensity as the cortical grey matter. The thalami had a strongly decreased signal intensity in relation to the basal ganglia. T_1-weighted images did not show any abnormal intensities.

Rectal biopsy verified the clinical suspicion of INCL, showing lipofuscin-like material with a homogeneous, finely granulated internal structure on electron microscopy.

Baclofen medication (25mg per day) significantly decreased the girl's irritability, but an evening dose of levomepromazine (5 to 10mg) was still needed for proper sleep. Physiotherapy was commenced. At the age of 20 months she still had some sleeping difficulties and was not eating well. She no longer picked up objects and had lost her playing ability completely, but she was able to walk a little with support. Stereotypies were less frequent and some extension tonus in the lower extremities was occasionally visible.

One month later her EEG was very flat, but ERG and VEP were normal. Median-somatosensory evoked potential (SEP) showed normal peripheral responses (N9, N13) and flat cortical responses. At the age of 25 months she was still able to sit up, but often toppled over. She was relatively calm, but still had some sleeping difficulties (mainly at home). Contact with other people was very poor. She showed no fixation to light and did not follow an object with her eyes. There was a suspicion of optic atrophy and probable narrowing of the retinal vessels, but other ophthalmological functions were still normal. Her EEG was still flat with occasional spikes; ERG and VEP were normal. Median-SEP showed normal peripheral and absent cortical responses. 2½ months later there was no significant change in her motor abilities, but non-corneal ERG was not recordable and flash-VEP was attenuated, with normal latency. EEG showed progressive attenuation.

Follow-up SPECT was markedly abnormal, with apparently normal perfusion only in the basal ganglia. The cerebellum and cerebral cortex were severely hypoperfused. ~~No side-to-side differences were found.~~

CASE 2

This 32-month-old girl is the eldest of two children of healthy parents. Pregnancy and delivery were uneventful. The girl's appetite has always been poor. Her first admission to hospital was for paronychia at 10 days of age.

Her neurological development was normal until the age of six months, when poor visual contact

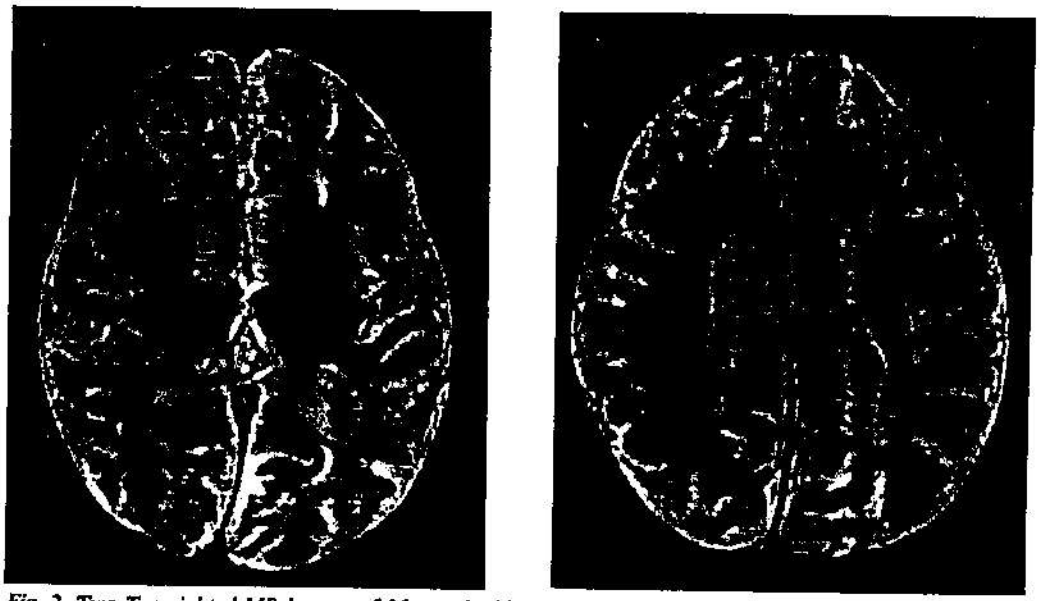

Fig. 2. Two T_2-weighted MR images of 26-month-old INCL patient, showing severe atrophic changes: ventricles and sulci large and splenium poorly visible; white matter has higher signal intensity than grey matter, which is reverse of normal relationship at this age; periventricular white matter is the most intense, and intensity loss of basal ganglia and thalami is remarkable.

was first suspected. She smiled at five weeks, rolled from prone to supine at three months, crawled at eight months, achieved sitting at 12 months and hare-like jumping at 13 months. She had some words by 12 months, which she lost soon afterwards. She hadn't learned to pull herself to stand, nor had she finger-thumb opposition.

When she was 10 months of age her mother suspected delayed motor development. Head circumference was 33cm (50th centile) at birth, 45cm (10th centile) at 13 months and 43·5cm (below second centile) at 23 months. At 16 months she could play a little, sit and crawl. She had no visual contact with other people, and demonstrated autistic-like behaviour. She was hypotonic, had slight truncal ataxia and had hyperkinesia in her upper arms. Stretch reflexes of the legs were brisk.

Laboratory investigations and ophthalmological findings were normal, as was the ERG, but the VEP was slightly depressed. The waking EEG was considered normal, despite having many artefacts. Brain CT showed slightly enlarged ventricles. The Sylvian fissures, interhemispheric space and some cerebral sulci, as well as the ambient cisterns, were abnormally large. At this point Rett syndrome was suspected.

At 19 months of age her condition deteriorated. She was definitely mentally retarded, microcephalic, and was not able to sit, crawl or take objects in her hands. She was hypotonic, had truncal ataxia and showed had choreo-athetotic movements of the extremities and the whole body. She was irritable and cried a lot, especially at night.

At the age of 23 months ophthalmological examination showed a brownish macula. ERG was unrecordable and VEP was remarkably flat. EEG was attenuated. Electron microscopical examination of a rectal biopsy specimen showed inclusions typical of INCL. The first myoclonic jerks were noticed by the age of two years.

At 26 months (when she was seen at our hospital) EEG showed progressive attenuation. MRI (Fig. 2) revealed severely enlarged ventricles and cerebral sulci, as well as moderately enlarged cerebellar sulci. The corpus callosum was extremely thin and the heads of the caudate nuclei were severely reduced in size. On T_2-weighted images, cerebral white matter was hyperintense and periventricular areas were more hyperintense than the periphery. Signal intensity was decreased in basal ganglia and the signal intensity loss was still more prominent in the thalami. T_1-weighted images showed normal intensity ratios. The girl was extremely irritable, with continuous athetotic movements. Baclofen medication was initiated, and she then became markedly less restless.

The last EEG, taken at the age of 31 months, was very flat and showed no spindles during sleep. Epileptic seizures started at that age.

Discussion

Raitta and Santavuori (1973) reported that the ERG of INCL patients is abolished early, even at a pre-clinical stage. In their series ERG was performed with contact-lens electrodes. In a more recent series (Santavuori *et al.* 1990), flash ERG (with non-corneal electrodes) was abnormal at a mean age of two (range 1·2 to 3·0) years and was abolished by 2·5 (range 1·7 to 3·4) years. The corresponding figures for

VEP were 1·9 and 2·5 years, respectively (Santavuori *et al.* 1990). Ophthalmological signs became obvious in the same series at a mean age of 25 months. The amplitude of the waking EEG became markedly attenuated at a mean age of two years (Santavuori 1973, Santavuori *et al.* 1990) and was flat by three years. This unique change, usually around the age of two years, is very sudden; if INCL is suspected it is important to repeat the EEG at one-month intervals. However, at that stage of the disease most children with INCL are irritable, so it is often difficult to obtain an artefact-free recording; therefore the sleep recording is also important for practical reasons.

Our case 1 showed no sleep spindles on EEG at first recording (or later). Unfortunately, no sleep recording was obtained for case 2 when she was investigated at our hospital at two years of age, but no sleep spindles were seen three months later. Santavuori *et al.* (1974) observed sleep spindles in only three of 33 INCL patients (aged 15, 18 and 20 months). Garofalo *et al.* (1988) reported that 10 of 12 sleep recordings of the Rett syndrome patients had abnormal background activity, with absent or rudimentary spindles during stage 3. They found normal activity in children younger than 2½ years of age. More attention should be paid to sleep spindles in other progressive disorders.

At an early stage INCL bears great clinical similarity to Rett syndrome, especially when the child has stereotypies of the hands. In early Rett syndrome cerebral CT and MRI are normal, and later show only non-specific atrophic changes (Hagberg and Witt-Engerström 1987, Xi-Ru and Dong-Hong 1988, Nihei and Naitoh 1990). The MRI findings (hypointense thalami and hyperintense white matter) of our two patients were thus strikingly different from the neurological findings in Rett syndrome.

The coincidence of thalamic abnormalities and missing sleep spindles in our patients is of interest, considering the suggested thalamic pacemakers of the sleep spindles (*e.g.* Niedermeyer and Lopes da Silva 1987).

SPECT of case 1 showed slight occipital hypoperfusion at the age of 19 months, which was in agreement with the clinical finding of impaired vision. Both then and six months later the patient's ERG and VEP were normal; thus SPECT might be more sensitive than neurophysiological methods for revealing visual impairment. The evolution of the SPECT findings of case 1 was extremely rapid; this reflects neuronal loss, which has been documented previously in neurophysiological (Santavuori 1973) and morphological (Haltia *et al.* 1973) studies.

We recommend MRI investigation and EEG waking and sleep recordings for every child with suspected progressive encephalopathy or INCL. It is important to bear in mind the slowing and attenuation of the background activity and sleep spindles. Repetition of the EEG at short intervals may be needed, as well as SEP and SPECT examinations. It is recommended that the clinical diagnosis is verified by electron microscopy.

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SUMMARY
Two patients with infantile neuronal ceroid lipofuscinosis are presented whose clinical diagnosis was based on the typical clinical picture, together with absent sleep spindles and MRI findings (hypointense thalami and hyperintense periventricular white matter) as early as 18 months in one girl. In addition to a flat cortical SEP, these abnormalities appeared earlier than the typical ERG and VEP findings used previously for clinical diagnosis of this condition. MRI of the other patient showed the same changes and EEG sleep spindles were absent by two years.

RÉSUMÉ
IRM du cerveau, fuseaux de sommeil á l'EEG et SPECT dans le diagnostic précoce de la lipofuscinose céroïde infnatile
L'article rapporte le cas de deux enfants présentant une lipofuscinose céroïde neuronale infantile. Le

diagnostic clinique fut établi sur une allure clinique typique, ainsi que sur l'absence de fuseaux de dommeil et les données IRM (thalamus hypo-denses et substance blanche périventriculaire hyperdense) dès l'âge de 18 mois pour une fille. En addition à un SEP cortical plat, ces anomalies apparurent plus tôt que les données classiques ERG et PEV utilisées antérieurement pour le diagnostic clinique de cette affection. L'IRM de l'autre patient révélait les mêmes modifications et les fuseaux de sommeil à l'EEG étaient absents à l'âge de deux ans.

ZUSAMMENFASSUNG

Kernspinntomographie des Gehirns, Schlafspindeln im EEG und SPECT zur Frühdiagnose der infantilen neuronal Ceroidlipofuszinose

Es werden zwei Patienten mit infantiler neuronaler Caroidlipofuszinose vorgestellt, bei denen sich die Diagnose auf das typische klinische Bild in Verbindung mit fehlenden Schlafspindeln und mit Befunden im Kernspinntomogramm (verminderte Intensität des Thalamus und vermehrte Intensität der periventrikulären weißen substanz) stützte, die bei einem Mädchen bereits im Alter von 18 Monaten nachweisbar waren. Zusammen mit einem flachen kortikalen SEP traten diese Anomalien früher auf als die typischen ERG und VEP Befunde, die man früher für die Diagnose diese Krankheitsbildes heranzog. Das Kernspinntomogramm des anderen Patienten zeigte dieselben Veränderungen und die Schlafspindeln fehlten im Alter von zwei Jahren.

RESUMEN

Imagen de Resonancia Magnética Cerebral, husos de sueño en el EEG y SPECT en el diagnóstico precoz de la ceroide lipofuscinosis neuronal infantil

Se presentan dos pacientes con ceroide lipofuscinosis neuronal infantil, cuyo diagnóstico clínico se basaba en las caracteristicas clínicas típicas, junto con ausencia de husos de sueño y hallazgos en la Resonancia Magnética (talamos hiporintensos e hiperintensidad de la substancia blanca periventricular) a la edad temprana de 18 meses en una niña. Además de unos Potenciales Corticales Sensoriales planos, estas anomalías aparecen antes que los tipicos hallazgos en el ERG y los Potenciales Evocados Visuales, utilizados previamente en el diagnóstico clínico de esta enfermedad. La Resonancia Magnética en el otro paciente mostró los mismos cambios y los husos de sueño *estaban ausentes a los dos años* de edad.

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