

## LETTERS TO THE EDITOR

### Neurofibrillary tangles in the brain of a 16 month old infant

Neurofibrillary tangles of paired helical filaments are well known histopathological hallmarks of Alzheimer's disease and other neurodegenerative disorders. At certain predilection sites, they also occur in the brains of many physically and mentally normal aged people and their prevalence augments sharply with increasing age. Recent studies have suggested that moderate numbers of tangles, often together with amyloid deposits, indicate a pathological form of brain aging that may remain clinically silent.<sup>1</sup> It is less widely known, however, that neurofibrillary tangles are also found in a number of rare CNS disorders of unrelated aetiologies, some of which occur in young people.<sup>2</sup>

We have recently examined a 16 month old boy whose mother had measles virus pneumonia during the last days of pregnancy. The child had dermatological manifestations of measles shortly after birth, recovered completely, and was neurologically unremarkable. After four months, he started with intractable seizures, mental retardation, and motor impairment. The EEG showed Radermecker complexes typical of subacute sclerosing panencephalitis. Increasing antimeasles virus IgG in serum and CSF confirmed the diagnosis. The boy died at the age of 16 months.<sup>3</sup>

The atrophic brain (weight 580 g) showed multiple cortical cysts and typical neuropathological hallmarks of subacute sclerosing panencephalitis. Measles virus

antigen was detected by immunohistochemistry in cortical and reactive white matter astrocytes, and endothelial cells but only very occasionally in neurons. Although silver stains failed to disclose clearcut neurofibrillary tangles, immunostaining with a monoclonal antibody recognising a paired helical filament specific phosphorylated epitope of microtubule associated protein tau, AT8,<sup>4</sup> showed clusters of immunoreactive neurons surrounded by numerous neuropil threads in the isocortex of both temporal lobes. The immunostained material within neurons appeared delicately fibrillar, sometimes granular (figure). The morphology of these structures corresponded to early stages of neurofibrillary tangles<sup>5,6</sup> and was not compatible with that of cells transiently expressing phosphorylated tau epitopes during development. Smaller numbers of these lesions were also reactive with an antiserum to bovine tau, but they remained negative with an antibody to high molecular weight neurofilament proteins and with a monoclonal antibody to paired helical filaments recognising ubiquitin. Colocalisation of measles virus antigen and paired helical filament tau within the same neuron was not seen. Electron microscopy showed the immunoreactive structures to be composed of 12-15 nm thick straight filaments (figure, inset).

To the best of our knowledge, this infant with rapidly progressing subacute sclerosing panencephalitis after a perinatally acquired measles infection with an extremely short incubation period is by far the youngest person in whom neurofibrillary change has been reported. This finding is important as it underscores the fact that aging is not a necessary prerequisite for the formation of paired helical filaments in neurons. It is in line with the notion that the formation of neurofibrillary tangles in various unrelated neurological disorders, including Alzheimer's disease, is a non-specific response of the neuronal network to different primary pathological processes that may occur at different ages. It argues against the widely accepted opinion that neurofibrillary

tangles are sequelae of the aging process of the brain.

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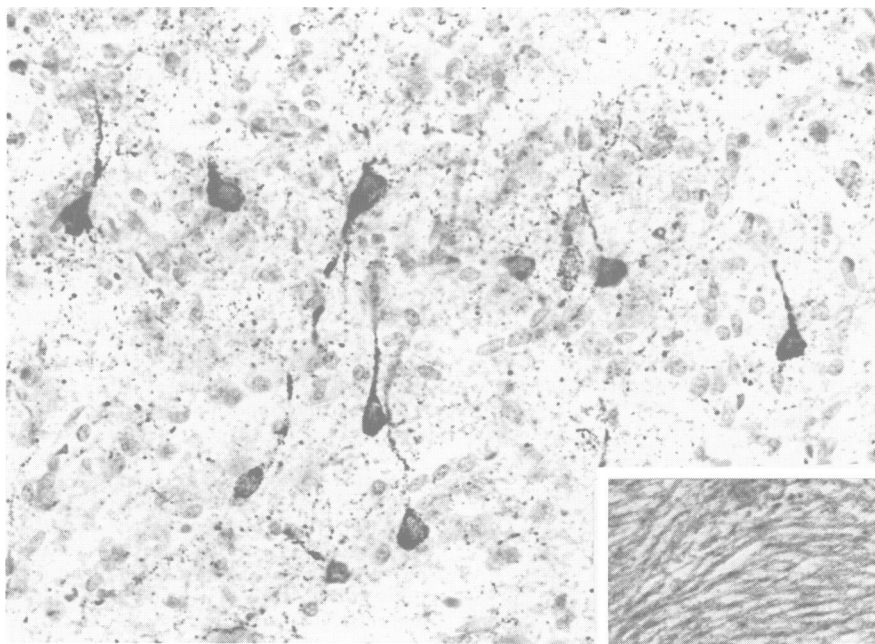
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### Dysarthria-clumsy hand syndrome due to infarction of the cerebral peduncle

In the original description of dysarthria-clumsy hand syndrome Fisher defined "clumsiness" as "awkwardness, slowness of fine manipulations, difficulty in writing, wavering ataxia on the finger to nose test not clearly cerebellar in type."<sup>1</sup> The syndrome is commonly related to a small infarction within the basis pontis,<sup>1</sup> but other locations such as the genu of the internal capsule, the corona radiata, and the cerebellum have been reported.<sup>2</sup>

Our patient had dysarthria-clumsy hand syndrome due to infarction of the mesencephalic cerebral peduncle. This localisation has not previously been reported.

A 67 year old man with a five year history of type II diabetes mellitus and arterial hypertension suddenly noticed slurred speech, heaviness of the right arm, and difficulty in writing. Seven hours after onset of the symptoms he showed intact cognitive functions but very dysarthric speech. Speech function was assessed with a phonetic test battery.<sup>3</sup> Speech tempo was measured as syllable rate/s in a sample of connected speech of about 10 s and of syllable repetition rates using a sound spectrograph (CSL: Kay Elemetrics). In our patient dysarthria was characterised by slurred speech, slowed articulatory movements and speech rate (syllable repetition rate 4.5 syllables/s; normal rate: > 6 syllables/s), and reduced modulation of pitch and intensity. His voice was breathy and slightly hoarse. He showed Horner's syndrome on the left—confirmed by cocaine testing—but no other cranial nerve involvement. Facial and intraoral sensations were normal to pinprick, touch, and proprioception. Different shapes (cube, ring,



AT8 immunoreactive neurons surrounded by numerous neuropil threads in the inferior temporal gyrus ( $\times 300$ ). Inset: ultrastructure of AT8 immunoreactive fibrillar inclusion. 12-15 nm straight filaments ( $\times 64\ 000$ ).

ball) were accurately identified. His tendon reflexes were slightly increased on the right and there was a Babinski's sign. His right upper limb showed a slight pronator drift, slowing of rapid alternating movements (pronation/supination), and fine finger tipping. Writing was impaired and hardly readable. The finger to nose test was slightly dysmetric on the right. There was no ataxia on the heel to knee test. Superficial and deep sensation were intact. His gait was slightly unsteady with a tendency to fall to the right.

At discharge after three weeks the dysarthria had almost resolved and he was not so clumsy. Writing was still difficult and tendon reflexes were more pronounced on the right side.

T1 and T2 weighted MRI on day 7 documented infarction of the central two thirds of the left ventral cerebral peduncle, extending as a small strip into the left tegmental region at the pontomesencephalic junction (figure). On day 7 HMPAO-SPECT showed symmetric and homogeneous tracer uptake in both cerebellar hemispheres (right:left ratio 0.97).

Transcranial magnetic stimulation (Magstim 200 S) was performed on days 4 and 20. Compound muscle action potentials were recorded using special surface electrodes from both halves of the tongue, both sides of the orbicularis oris muscle, and both abductor digiti minimi and tibial anterior muscles. A detailed description of the

method and data from normal subjects have been previously reported.<sup>4</sup> Central conduction time to the right arm was delayed, whereas latencies to the left arm and both lower limbs were normal. On day 4 responses of the tongue to left hemispheric stimulation were absent on the right and delayed on the left. Responses of the right orbicularis oris muscle were also absent. On day 20 the central conduction time to the right arm had improved up to an abnormal side difference (3.5 ms; upper limit 2.6 ms). Responses of the tongue and orbicularis oris muscle were restored. Median nerve somatosensory evoked potentials on day 4 were within the normal range.

Our patient had the characteristic features of dysarthria-clumsy hand syndrome described by Fisher.<sup>1</sup> As shown by MRI the lesion affected the central two thirds of the left ventral cerebral peduncle at the location of the pyramidal tract. Functional involvement of the left corticospinal and corticobulbar tracts was confirmed by clinical findings and transcranial magnetic stimulation. Central conduction times ameliorated with clinical improvement, suggesting that clinical signs and transcranial evoked potential abnormalities were due to the same acute lesion. As sensory function (normal intraoral superficial sensation and intraoral stereognosis) was unimpaired and somatosensory evoked potentials were within normal limits, an afferent disturbance could be ruled out. Additional impairment of the cerebellum was excluded by MRI. Crossed cerebellar diaschisis disclosed by SPECT has been reported with lesions affecting the upper half of the basis pontis and is attributed to cerebropontocerebellar tract involvement.<sup>5</sup> In our patient, however, HMPAO-SPECT showed symmetric tracer uptake in both cerebellar hemispheres, making such involvement highly unlikely. His clumsiness could be attributed to impairment of the corticospinal tract as shown clinically, electrophysiologically, and by imaging investigations. A disorder of the corticofacial and corticohypoglossal pathways mediating the articulatory movements of the orbicularis oris and tongue muscles therefore remains the only explanation for dysarthria.

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### Transient alien hand syndrome: is this a seizure or a transient ischaemic attack?

The alien hand syndrome is usually persistent but has been reported as a paroxysmal phenomenon attributable to epilepsy. In our patient the alien hand syndrome formed the main complaint in a transient ischaemic attack.

The patient was a 62 year old right handed Portuguese man with arterial hypertension, first detected in 1980, and Leriche syndrome. He was a heavy smoker (about 60 pack/years) and used to take moderate amounts of spirits and beer. On 18 July 1994, on awakening, he felt as if his wife was touching his right forearm. Astonished and worried, he saw his own left arm and hand making automaton-like gestures, of which he was fully aware but could not consciously inhibit. His left hand would repeatedly grope for and grasp his right hip, trunk, and arm, coming up and down and picking his clothes. Sometimes, the arm tended to abduct with some forward displacement. For short periods he could control the unwanted activity by holding the left arm by his side; however, the abnormal behaviour pattern recurred every time he released the arm.

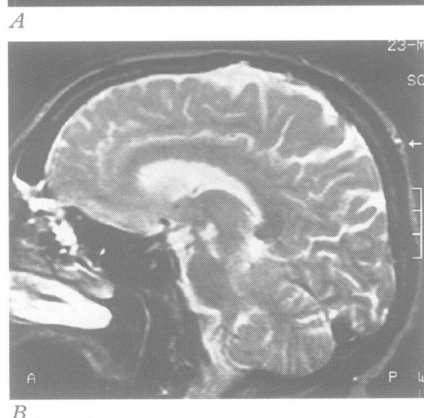
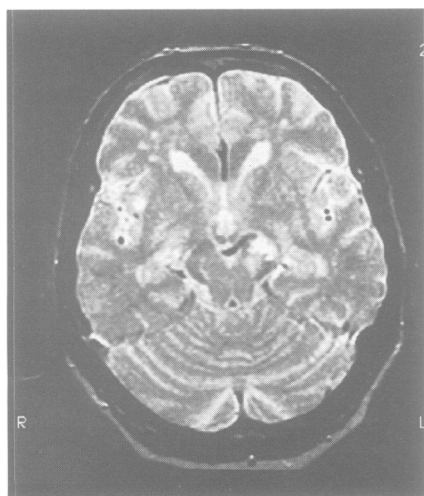
Trying to stand up, the patient noted that he could hardly move his left leg. It dangled on attempts to walk, although he could transfer some weight to it. Facial mimicry seemed to be preserved. At that time, the patient realised that his left side (including face and trunk) felt "heavy" and insensible to touch and pain.

After five to 10 minutes the automaton-like movements, especially those of the hand, decreased. Displacement of the left arm persisted to a lesser degree for a further 10 minutes. Volitional control of the arm and hand was then possible, without any residual weakness. There was parallel recovery of leg strength and face and trunk sensation. Arm and leg hypaesthesia gradually recovered in the next eight hours.

One hour after disease onset his blood pressure was 220/110 mm Hg. Brain CT showed focal hypodensities in the left internal capsule and right occipital cortex. He was discharged in the same evening, after blood pressure control and complete neurological recovery. He was advised to stop smoking and abstain from alcohol and was started on oral hypotensive medication and acetylsalicylic acid (200 mg/day).

Three weeks later full cognitive and neurological examination was normal. General examination showed reduced distal leg pulses with bilateral femoral bruits. Laboratory analyses disclosed dyslipidaemia and slight polycythaemia. Electrocardiograms and a transthoracic echocardiogram were normal. Two EEG studies (including one after sleep induction with diazepam) were normal or yielded non-specific results.

Duplex ultrasonography disclosed bilateral plaques on carotid bulbs. The right sided lesion was extensive with possible ulceration. Brain MRI confirmed old ischaemic lesions in the left internal capsule, right occipital lobe, and the left cerebellar hemisphere. Magnetic resonance angiography of the brain showed normal blood flow through both carotid and vertebral arteries and the basilar artery. Cervical MRA showed a focal signal void immediately beyond the origin of the right internal carotid artery, suggesting slight narrowing of its proximal segment.



(A) Axial section on MRI (TR 2080 ms, TE 90 ms) showing area of increased signal intensity at the central two thirds of the left cerebral peduncle, extending as a small strip into the left tegmental region at the pontomesencephalic junction. (B) Left parasagittal section.