Changes of diffuse neurofibrillary tangles with calcification (DNTC) in a woman without evidence of dementia

Kosaka has proposed the term "diffuse neurofibrillary tangles with calcification" (DNTC) for a form of presenile dementia characterised by cortical dementia, neurofibrillary tangles, and neuritoplasm threads, but lacking plaques in the cerebral cortex, and coexisting with Fahr's type calcification and temporal or temporoparietal atrophy with neuronal loss and astrocytosis. 

We have recently encountered a similar pathological change, however, in a woman with no history of dementia. As a result, five other cases of idiopathic intracerebral calcification were reviewed, specifically to determine whether neurofibrillary tangles were present.

The recent case involved a 64 year old woman whose sudden death was attributed to ischaemic heart disease. Her brain, which weighed 1300 g, had calcified masses up to 2 cm in the cerebellum, with further patches of calcification in the cerebral hemispheres. Moderate generalised cerebral atrophy particularly affected the temporal lobes, and the ventricles seemed mildly dilated.

Histological examination showed calciospheres and larger concretions, predominantly in the dentate nucleus, central cerebellar white matter, cerebellar cortical granular layer, and basal ganglia, often related to capillaries. In addition, there was continuous calcification in the media and adventitia of many small arteries and veins in these areas (fig 1). The brain stem was not affected. Spongiosis and gliosis accompanied pronounced neuronal loss in the atrophic temporal cortex, these features being most obvious within the superficial laminae. Many neurofibrillary tangles (fig 2), which were tau positive, were present, but there were virtually no plaques. Tangles, without plaques, were also noted in the hippocampus and parahippocampal cortex. Otherwise neurons seemed unaffected, even in areas of dense calcification.

Subsequent enquiry confirmed that there was no history of neurological impairment or relevant past illness. Specifically, there had been no evidence of dementia or movement disorder. This was corroborated by her apparent state of well being—she had lived alone and was well nourished and of neat appearance. Review of archive material from the past 14 years yielded five further cases of Fahr's type calcification, two in males (aged 45 and 34 years) and three in females (aged 60, 30, and 6 years). All showed appreciable calcification of Fahr's type, but no evidence of neurofibrillary tangle formation. One patient had had psychosis and depression, but none had shown evidence of dementia during life.

Extensive calcification of the cerebellum and cerebrum has been recorded in patients with hypoparathyroidism and also as a result of high lead exposure, but a review of the medical literature failed to find an association between the calcification and tangle formation or dementia in such cases. One paper did refer to unexplained intracranial calcification in patients also with dementia, and an association with hypothyroidism was proposed. Extensive neuropathological examination of these cases was not, however, performed.

Diffuse neurofibrillary tangles with calcification (DNTC) seems to be a rare entity, largely confined to Japan, with only 16 cases recorded in the medical literature. The macroscopic and microscopic features in our 64 year old patient very closely match the findings described in patients with the postulated denting illness DNTC, except that the brain was rather heavier than in recorded cases. The patient did not manifest dementia during life, however: nor was there any suggestion of the movement disorders that may accompany DNTC.

Therefore, it is proposed that the term diffuse neurofibrillary tangles with calcification (DNTC) encompasses a specific constellation of neuropathological changes, but is not necessarily associated with dementia.
Fifty consecutive patients aged 6 to 88 (mean 31) years (35 male, 15 female) with isolated minor head injury were investigated. The examination included clinical neurological investigation and classification according to the Glasgow coma scale (GCS). Brain CT was performed within 12 hours in all cases. The following criteria were required: (a) head injury with loss of consciousness, (b) a clinical condition equivalent to a GCS score of 14–15 at examination, (c) absence of focal neurological deficits, and (d) no signs of intracranial lesion on CT. As a control group, 18 patients aged 2–67 (mean 33) years (14 male, four female) with severe head injury were included in the study. All had a GCS score ≤ 5 at admission, and the first CT showed intracerebral contusions.

Two blood samples were collected for analysis of protein S-100, the first as early as possible after the trauma (at admission), and the second 12 hours after injury. The S-100 protein serum concentrations were analysed with a commercially available two site immunoradiometric assay kit (San-tec Medical AB, Bromma, Sweden). Samples were analyzed in duplicate and those with more than 10% coefficient of variation were rejected. A value of 0.5 μg/l or more was considered pathological.

Forty two patients with minor head injury were followed up at nine months after head injury, including a personal interview. The patients were asked about 12 of the most frequent complaints described after head injury with concussion: headache, impaired memory, fatigue, dizziness, irritability, impaired concentration, insomnia, tinnitus, hearing defect, depression, anxiety, and double vision.

The first sample for measurement of protein S-100 was drawn between 0.5 and 9.0 (mean 3.2) hours after the trauma. In 37 patients a second sample was drawn 12 hours after injury. Ten patients had increased concentrations (mean 1.1, range 0.5–2.5 μg/l) in the first sample. Of the 37 second samples, four showed concentrations ≥ 0.5 μg/l. All showed a decrease compared with the first measurement (figure). Nine of 42 patients followed up showed increased serum concentrations of protein S-100 at the 12-month examination. The overall incidence of symptoms after concussion was 18 of 42 patients (43%). Six of the nine patients (67%) with an increase in protein S-100 reported symptoms after concussion. Persistent symptoms at follow up were reported by two of the nine patients with an increase in protein S-100 (22%), and nine of the 33 patients (27%) without an increase (table). In both groups, the most often reported symptoms were fatigue, headache, impaired concentration, dizziness, and impaired memory. The mean number of symptoms reported per patient was 1.4 in patients with an increase in protein S-100 and 1.2 in patients without an increase. All 18 patients with severe head injury showed serum concentrations of protein S-100 ≥ 0.5 (mean 7.0, range 0.5–15.7 μg/l) in samples drawn within 12 hours after the head trauma.

In the present report, the total incidence of symptoms after concussion was in accordance with previous studies. Increased serum concentrations of protein S-100 were detected in 10 of the 50 samples drawn within the first hours after minor head injury, and in four out of 37 assessed 12 hours after injury. The patient with the highest protein S-100 value (2-4 μl/l one hour after trauma) reported headache and fatigue lasting four weeks. Sixty seven per cent of the patients with S-100 increase reported complaints after the injury, whereas such symptoms appeared in only 36% of the patients without an increase in protein S-100. No difference was found for persistence of symptoms at follow up.

Persson et al reported three patients with severe head injury and persisting coma; two showed increased concentrations of protein S-100 in CSF. In our study, a protein S-100 serum concentration ≥ 0.5 μg/l was detected in all 18 patients with severe head injury with contusions verified by CT, indicating cellular leakage of the protein with disruption of the blood brain barrier. Furthermore, increased serum concentrations of protein S-100 were found in cases with normal CT, suggesting a protein leakage through the blood brain barrier due to cell injury, also in patients with minor head injury. Creatine kinase BB and neuron specific enolase have been found in patients with minor head injury. These biochemical markers are, however, present in tissues other than brain. As patients with head injuries often show thoracic, abdominal, and skeletal trauma, enzyme changes in multitrauma cases may be less specific for brain damage. Protein S-100 is known to be unique to the nervous system. After glial tissue damage followed by disruption of the blood brain barrier, it is reasonable to foresee the release of this organ specific marker in serum.

Brain CT is not very sensitive in evaluation of diffuse brain damage in patients with minor head injury, and MRI provides more information concerning primary brain damage. The greater availability of CT, however, implies that CT will remain the standard initial radiological investigation for head injury. Hence, a biochemical serum marker would be of particular value in clinical practice, to show the presence and eventual extent of diffuse brain damage. Even a slight increase of the protein S-100 concentration in serum could be interpreted as a sign of cell damage and reduced integrity of the blood brain barrier. This may improve our present poor understanding of the pathophysiology of brain damage in those patients who sustain symptoms after concussion despite normal radiological findings.

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