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## Post-Mortem effects on vasopressin producing neurons in the Wistar rat

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## THE HYPOTHALAMIC LATERAL TUBERAL NUCLEUS IN HUNTINGTON'S DISEASE AND ALZHEIMER'S DISEASE

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### ABSTRACT

The hypothalamic lateral tuberal nucleus was studied in the brains of 5 patients with Huntington's disease (HD) and 6 patients with Alzheimer's disease (AD), as well as in 11 age matched controls. In the HD cases severe neuronal depletion occurred, accompanied by an increase of the glial density. The actual number of astrocytes, however, was comparable to that of controls, while the number of oligodendrocytes was decreased. In AD no neuronal loss occurred. Large numbers of neurons expressed Alz-50 immunoreactivity, although silver-staining tangles were rarely observed. Some A4/ $\beta$ -protein deposits were present.

### INTRODUCTION

In the rat the tuberal lateral hypothalamic area plays a role in feeding, movement, aggression, sexual behaviour, and autonomic regulation. As these functions may be altered in dementia in man, the pathological anatomy of the tuberal lateral hypothalamic area in man was studied. In primates the normal anatomy of this area is markedly different from that of subprimate species. While in the rat the whole area is more or less occupied by the medial forebrain bundle, with neurons diffusely interspersed between its fibers (Bleier et al., 1979), in man and higher primates at least three structures can be discerned: dorsally the medial forebrain bundle, ventrally, in a well demarcated mass, the lateral tuberal nucleus (NTL), and, surrounding this nucleus, the magnocellular tuberomamillary nucleus (Feremutsch, 1955; Diepen, 1962). As the NTL is the structure most easily to delineate, we started our quantitative investigations on this nucleus. Vogt and Vogt (1951) and Wahren (1952) had described neuronal loss in the NTL of Huntington's disease (HD) patients. Changes have not been described in AD, although recently Braak and Braak (1989) reported pathologic changes in the NTL of patients with an adult onset type of dementia, characterized by intraneuronal argyrophilic grains and silver-staining coiled bodies, containing straight filaments.



## MATERIALS AND METHODS

The brains of 5 HD and 6 AD patients, and 11 age matched controls were investigated. The brains were obtained from the Huntington's disease collection of the Department of Neurology, Leiden (HD brains and controls), and the Brain Bank of the Netherlands Institute for Brain Research, Amsterdam (AD brains and controls). All brains were formalin fixated and subsequently embedded in paraffin. The hypothalamus was removed and serially sectioned at 15  $\mu$  for HD brains and their controls or 6  $\mu$  for AD brains and their controls.

Every twentieth section of the HD hypothalamus and every fiftieth of the AD hypothalamus (controls conforming) was stained by cresyl violet/luxol fast blue (Klüver-Barrera; K-B), and these sections were used for counting and for reference. Selected sections were stained by several conventional techniques. Immunohistochemistry was performed by peroxidase-antiperoxidase staining with DAB or AEC as the final chromophores. The following commercially available monoclonal antibodies (mAb's) were used: anti-GFAP (Sanbio/Monosan, The Netherlands; dilution 1:10); Alz-50 (Abbott, United States; dilution 1:10). In addition Dr. Frangione, New York, kindly provided us with SP 28, a mAb against a synthetic polypeptide containing the N-terminal 28 amino acids of the A4/ $\beta$  protein of the AD-plaques (van Duinen et al., 1987). Sections from AD hypothalamus were pretreated by 20 min. incubation in 85% formic acid, before being incubated with this mAb (dilution 1:300).

Estimating the number of neurons in the NTL was performed by combining a systematic sampling method with associated point counting. In the consecutive K-B stained sections the NTL was delineated in ink. Then the area was systematically covered by moving a rectangular eye-piece grid in a locking tessellation pattern over the area (magnification x320). In every fifth position of the grid the nucleolated neurons within the confines of the grid were counted. Thus for the HD brains and their controls the sampling periodicity was 1:100, for the AD brains and associated controls 1:250. Glial cells were counted in a similar way, but only in HD brains and their controls.

## RESULTS

In controls the total number of neurons in the NTL was estimated to be about 60,000.

In HD patients (n=5; mean age 53.4 yrs.; range 27 to 74) this number was severely reduced: in 4 patients to less than 10,000, in 1 patient to about 24,000. The remaining neurons showed degenerative features. Gliosis was prominent, as expressed by an increased number of GFAP-positive astrocytes, many of them



showing morphologic changes. The total number of glial cells was reduced to about 80% of control. This reduction, however, was exclusively caused by depletion of oligodendrocytes. The number of astrocytes was not different from control values, and may even have been slightly higher (Kremer et al., in press).

The NTL of AD patients ( $n=5$ ; mean age 55.6 yrs.; range 45 to 64) the number of ganglion cells did not differ significantly from controls. Gliosis was absent. In these patients plaques were found within the confines of the NTL; they were visualised by SP 28 and by Methenamine Silver, but not by Congo Red, Thioflavin-S, Alz-50 or GFAP. A central core was absent. Very rarely a classical plaque was encountered. The plaque density was low. Plaques were not found in controls. Tangled neurons were rarely observed in silver impregnation stains (Palmgren, Holmes), but large quantities of neurons expressed Alz-50 immunoreactivity, as did many neurites in the neuropil of the NTL.

## DISCUSSION

The NTL is affected both in HD and in AD, but in a different way. In HD large amounts of its constituent neurons have died. As in the basal ganglia of HD patients, this neuronal loss is accompanied by gliosis, i.e. an increase in the density of the glial cells. Our results show that this increased density is not accompanied by an increase in the total number of glial cells. The number of oligodendrocytes is actually reduced. The astrocytes sustain themselves and respond to the neuronal loss, as is indicated by an increased expression of GFAP.

In AD the neurons do not disappear, but they do show AD-related cytoskeletal changes. These changes probably reflect an early phase of the disease in which mature argentophilic tangles are not found yet. Neuronal death does not occur. The plaques that are encountered should be classified as amorphous plaques (Rozemuller et al., 1989). They may reflect an early stage in plaque formation. Thus the disease process which characterizes AD is also expressed in the NTL, but later, or less severe, compared to the hippocampus and the neocortex.

The clinical relevance of the changes in these two forms of dementia is obscure. The function of the NTL is unknown, as are its neurotransmitters and/or neuromodulators, or its connections with other parts of the brain.