Alterations of muscarinic acetylcholine receptors in atypical Pick’s disease without Pick bodies

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SHORT REPORT

Pick’s disease is a rare form of neurodegenerative dementia, neuropathologically characterised by circumscribed frontotemporal lobe atrophy as well as by severe neuronal loss and gliosis in the atrophied regions. Nowadays, the use of the term “Pick’s disease” is restricted to cases showing lobar atrophy with Pick bodies and tauopathy, and Pick’s disease is included under the nomenclature of frontotemporal lobar degeneration (FTLD), a type of frontotemporal dementia characterised by neuronal loss and gliosis in the affected cerebral cortices and subcortical nuclei. In the pyramidal tract, the right cerebral peduncle was degenerated but the hypoglossal nucleus and the anterior horn of the spinal cord were preserved.

Neocortical cholinergic deficits have been extensively investigated in some forms of neurodegenerative dementia in relation to memory disturbance, especially in Alzheimer’s disease and dementia with Levy bodies. However, investigation into the cholinergic systems in fronto-temporal dementia has been inadequate, and have only been undertaken in the frontal lobe degeneration type of dementia and in the Pick type with Pick bodies. Systemic studies of muscarinic acetylcholine receptors (mAchR) in atypical Pick’s disease have never been done.

In this study, we estimated the total amounts of mAchR and the levels of the mAchR subtypes in atypical Pick’s disease.

METHODS

We examined brains from five cases of atypical Pick’s disease (mean (SD) age, 71.4 (6.4) years, range 64 to 81; mean postmortem delay to specimen retrieval 3.4 (1.4) hours (table 1). The clinical, neuropathological, and neurochemical features of these cases have been described in detail previously. In summary, all cases showed semantic dementia and had a clinical diagnosis of FTLD. There was no family history of this disorder in any case. Neuropathologically, all cases showed lobar atrophy of the frontal and temporal lobes with temporal lobe dominance. There was moderate to severe degeneration with neuronal loss and gliosis in the affected cerebral cortices and subcortical nuclei. In the pyramidal tract, the right cerebral peduncle was degenerated but the hypoglossal nucleus and the anterior horn of the spinal cord were preserved.

Immunohistochemical analyses in all cases showed ubiquitinopathy with ubiquitin accumulation in intraneuronal and dendritic inclusions in the atrophied cortex. Immunoblots of samples from the cases did not show detectable amounts of insoluble tau.

The dissected brain tissues were immediately frozen in liquid nitrogen, and then stored at −80°C until used.

For comparison, we studied 11 cases of Alzheimer’s disease (mean age 78.4 (8.7) years, range 63 to 86; mean postmortem delay 2.6 (1.9) hours), seven cases of dementia with Levy bodies (mean age 85.2 (6.9) years, range 78 to 93; mean postmortem delay 1.5 (1.4) hours), and seven cases of dementia with Lewy bodies (mean age 79.7 (7.1) years, range 68 to 96; mean postmortem delay 3.2 (1.6) hours).

Background: Atypical Pick’s disease without Pick bodies is a type of frontotemporal dementia characterised by semantic dementia and temporal dominant lobar atrophy with ubiquitinopathy. No neurochemical analyses have ever been reported in this condition.

Objective: To investigate muscarinic acetylcholine receptors [mAchR] and their subtypes (M1–M4) in atypical Pick’s disease.

Subjects: Five cases of atypical Pick’s disease were studied. They were compared with nine control cases, 11 cases of Alzheimer’s disease, and seven cases of dementia with Lewy bodies.

Methods: A [3H]quinuclidinyl benzilate (QNB) binding assay and an immunoprecipitation assay using subtype specific antisera were used.

Results: The total amount of mAchR in the temporal cortex was lower in atypical Pick’s disease than in controls or Alzheimer’s disease cases, but there were no significant differences between the three groups in the frontal cortex. In the temporal cortex, there was a smaller proportion of the M1 receptors in atypical Pick’s disease than in the controls or in the patients with Alzheimer’s disease and dementia with Lewy bodies. In contrast, the proportion of M2 receptor was higher in atypical Pick’s disease than in the other three groups.

Conclusions: Depletion of postsynaptic cholinoreceptive neurones in the temporal cortex is more severe in atypical Pick’s disease than in other neurodegenerative dementia disorders.
bodies (mean age 77.9 (6.9) years, range 68 to 86; mean postmortem delay 4.4 (1.5) hours), and nine controls with no notable neuropathological findings (mean age 84.9 (5.3) years, range 73 to 91; mean postmortem delay 5.7 (5.6) hours). All cases selected for comparative study, except for two of the cases in the control group, had been used previously in another study.15

The methods used have been described previously in detail.16 In brief, the amounts of total mAchR in all cases were estimated at the specific binding sites of [3H]QNB, and ranged from 800 to 2500 fmol/mg membrane protein. The proportions of specifically precipitated mAchR subtypes were estimated as the differences in the amounts of bound [3H]QNB precipitated with specific antisera and those precipitated with non-immune serum.

### RESULTS

The amounts of mAchR at the [3H]QNB binding sites in membrane preparations ranged from 0.8 to 2.3 pmol/mg protein (frontal cortex) and from 0.8 to 2.1 pmol/mg protein (temporal cortex). In the temporal cortex, values for the [3H]QNB binding sites in atypical Pick’s disease were significantly lower than in the control or Alzheimer’s disease groups, although no substantial differences were not found between atypical Pick’s disease and dementia with Lewy bodies. In contrast, the proportion of anti-M2 complex was higher in atypical Pick’s disease than in the other groups. Comparisons between the other three groups are omitted here, as they have been dealt with elsewhere.16

### DISCUSSION

There have been few systematic neurochemical studies on cholinergic alterations in cases of fronto-temporal dementia. Wood et al reported that the activity of choline acetyltransferase (ChAT) and the numbers of mAchR were unchanged in the cerebral cortex in three cases of Pick’s disease with Pick bodies.17 Both Hansen et al and Francis et al found that ChAT activity was similar to control values, and that the numbers of mAchR were decreased in the temporal cortex in all of seven cases of Pick’s disease with Pick bodies, although the decrease was less than in Alzheimer’s disease.21,22 Procter et al showed that the numbers of mAchR did not fall in 10 cases of Pick’s disease with Pick bodies or in six cases of fronto-temporal dementia of the frontal lobe degeneration type, but did fall in nine cases of Alzheimer’s disease in the frontal, temporal, and parietal cortices.23 In summary, previous studies on Pick’s disease with Pick bodies and the frontal lobe degeneration type of fronto-temporal dementia have shown that numbers of mAchR are either preserved or reduced to some extent, although ChAT activity—which indicates presynaptic cholinergic innervation—is preserved.

The incidence of atypical Pick’s disease is similar to that of Pick’s disease with Pick bodies in Japan.24 Our results show that the decrease in mAchR was more severe in the temporal cortex in atypical Pick’s disease than in controls or Alzheimer’s disease cases. However, no substantial differences were found in the total amounts of mAchR between atypical Pick’s disease and dementia with Lewy bodies. This may account for the finding that the neocortical cholinergic deficit is more extensive in dementia with Lewy bodies than in Alzheimer’s disease.25

In the frontal cortex, the proportion of M3 receptors was lower in atypical Pick’s disease than in Alzheimer’s disease. This result may reflect the relatively higher proportion of M2 receptors in atypical Pick’s disease, but this is not known for certain. In the temporal cortex, there was a decrease in the proportion of M1 receptors, the most abundant muscarinic acetylcholine receptor in the cerebral cortex,26 while the proportion of M2 receptors, which exist at presynapses of the...
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cholinergic system, increased. The lower level of M1 receptors in atypical Pick’s disease may reflect the greater severity of neuronal losses in the temporal cortex in this condition in comparison with Alzheimer’s disease or dementia with Lewy bodies, because all cases of atypical Pick’s disease showed severe neuronal loss with gliosis in the anterior portions of the temporal lobes. Moreover, the higher level of M2 in atypical Pick’s disease raises the possibility that the presynaptic M2 receptors are upregulated as a result of the loss of cholinoreceptive neurones in the temporal cortex, although it is not possible to determine the absolute proportion of M1 to M4 receptors by our immunoprecipitation method. These findings suggest that projecting cholinergic neurones are relatively preserved, in contrast to the loss of cholinoreceptive neurones in the temporal cortex, although ChAT was not estimated in this study. A previous neuropathological study showed that the nucleus basalis of Meynert, from which the cholinergic neurones project to the temporal cortex, was mildly degenerated in Pick’s disease, including atypical Pick’s disease, supporting our hypothesis.

Acetylcholine esterase inhibitors are used in the treatment of Alzheimer’s disease, and are also of potential use in dementia with Lewy bodies and vascular dementia. Unfortunately, our study suggests that these agents may be ineffective in treating cholinergic deficiency in patients suffering from atypical Pick’s disease, because the cholinoreceptive neurones appear to be more severely affected than the projecting presynaptic cholinergic neurones.

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