Neurochemical and Histopathologic Alterations Characteristic of Pick's Disease in a Non-demented Individual

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Abstract. In the course of investigating a large number of non-demented subjects, a 68 year old female dying of coronary artery disease was found to have Pick bodies in her grossly normal brain. Although only mild subcortical gliosis and no neuron loss were observed, Pick bodies were found throughout the brain and occasional balloon cells were noted. Pick bodies and numerous neurons were also ALZ-50 and Tau-1 immunoreactive. Retrospective studies indicated a lack of overt intellectual decline or depression in this individual. Frontal, temporal and occipital poles, amygdala, hypothalamus and nucleus basalis of Meynert (nbM) were analyzed for ChAT, AChE and MAO-A and -B enzymatic activities and for the binding of 5HT and imipramine. Cholinergic decreases were found only in subcortical structures. Serotonin binding decreases were widespread, excluding the nbM. Altered MAO-B activity was regionally variable, and no differences in MAO-A activity or imipramine binding were observed. Few differences in neurochemical alterations were observed in the current non-demented subject with abundant Pick bodies compared to previous studies of demented Pick's patients. This case strongly suggests that chemical dysfunction and neuropathological features of Pick's disease occur in advance of overt clinical manifestations of the disorder.

Key Words: Cholinergic neurochemistry; Cytoskeletal neuropathology; Monoamine Oxidase; Pick's disease; Retrospective cognitive studies; Serotoninergic neurochemistry.

INTRODUCTION

Pick's disease (PD), a neurodegenerative dementing disorder of unknown etiology, is often familial (1). The progression from onset of symptoms to death in PD is often more rapid than in Alzheimer's disease (AD) (2). Differences in symptoms can sometimes distinguish PD from AD clinically (3).

Well-circumscribed frontal and temporal cerebral atrophy often occurs in PD, although neuropathology characteristic of PD can occur in a grossly normal brain (4). The clinical diagnosis of PD is confirmed by the morphologic presence of Pick bodies or balloon cells or both in cerebrum (4), though as many as 60% of Pick's patients may lack both of these morphologic changes (5). Neuropathologic features diagnostic of PD and those of other dementing disorders, particularly AD, can occur simultaneously (6).

Neurochemical alterations of PD brain, particularly cholinergic markers, are less widespread than those reported in similar regions of AD brain (7-9). Other differences in chemical dysfunction occurring on a regional basis in the brain seem to distinguish PD from AD (8, 9).

During the course of studying a large series of non-demented individuals for a separate report (10), an individual with neuropathologic features diagnostic of PD was investigated. We report the neurochemical changes occurring in different brain regions which consistently exhibited Pick bodies from this non-demented individual.

MATERIALS AND METHODS

Subjects

Data from the brains of three age-, sex-, and postmortem interval-matched individuals were collected and compared to previously reported changes observed in larger populations of individuals (8, 11). The individual we report died as a result of critical coronary artery disease (cCAD) (10). Accordingly, observed neurochemical indices from this individual were compared to two non-demented individuals, one dying of cCAD and one without heart disease (nonHD).

Cognitive Studies

The lack of overt dementia is routinely established by retrospective investigation in all individuals lacking clinical history (10). The retrospective examination determining the cognitive status of the Case individual was more rigorous.

We interviewed three adjacent neighbors, who each knew the decedent well and had contact several times weekly, without the aid of a standardized instrument. These initial inquiries indicated the decedent was not demented. In fact, she provided the sole care for two bedridden demented family members (mother and son) while independently maintaining normal orderly operation of the household.

One of us (FWD) extensively interviewed two of the above individuals who had known the decedent 12 years and 5 months, respectively, while administering standardized questionnaires to determine the Case individual's cognitive and behavioral status prior to death. These interviews consisted of two measures of dementia and one measure of depression.

Modified Dementia Rating Scale (mDRS): The first measure of dementia was a modified version of the Dementia Rating...
Scale (DRS) (12). Following Kay (13), we included the everyday activities and habits sections of the DRS but eliminated the personality, interests, and drive section. The mDRS yields a score from 0 (best) to 17 (worst functioning). One study reported a mean mDRS score of 4.5 in a group of mildly demented subjects (14), while another investigator suggested a cutoff score of 4 (13). For these studies we considered an mDRS score of 4 or greater to reflect possible dementia.

Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): The IQCODE is a 26-item questionnaire in which the informant is asked to rate the degree of change over a 10 year period in a person’s memory and intelligence (15). Scores on this instrument correlate highly with the Mini-Mental State Examination (MMSE) (16) and are less affected by pre-morbid abilities than is the MMSE (17). The IQCODE has a high internal reliability and discriminates well between demented and general population samples (15, 18). For each of the 26 items the informant was asked to rate change on a scale of 1 (much better) to 5 (much worse). According to Jorm et al (15), an average score of 1 represents improved cognition, 3 represents no change and 5 represents considerable cognitive deterioration. We considered an IQCODE score of 4 or greater an indicator of possible dementia. Utilizing a cutoff score of 4 to define likely dementia, IQCODE scores correctly classified 92.7% of ADRDA subjects as demented and 88.1% of an over age 70 general population sample as normal (15).

Cornell Scale for Depression in Dementia: The Cornell scale is a 19-item depression rating instrument. Informants rate the severity of 19 symptoms of depression they have observed in the subject during the week prior to the interview. In our case, the observation period was described as 1 month prior to the subject’s death. While not intended to be used as a diagnostic instrument, the Cornell scale provides a quantitative index of depression severity. Total scores range from 0 to 38. Alexopoulos et al (19) reported scores of 1.4 in normal controls, 12.3 for subjects with minor depressive disorders, and 24.8 for those suffering major depressive disorders. Since we have no firm basis for assigning a cutoff score, the Cornell score is simply reported to give an idea of the degree of depression observed in the Case individual.

Histopathology

Tissue samples, as per routine in non-demented individuals, were taken only from frontal pole (FP), temporal pole (TP),
occipital pole (OP), hippocampal formation (H-PHG), and amygdala with adjacent pyriform cortex. These tissue samples were portions of those routinely retained as part of the coroner-authorized autopsy protocol. Samples were immersion fixed in 10% buffered formalin, embedded in paraffin, sectioned at 8 μm, and stained by the Bielschowsky method and with glial fibrillary acidic protein (GFAP), cresyl violet and hematoxylin and eosin (H&E).

Additional samples of FP and H-PHG were also immersion fixed in 4% buffered paraformaldehyde for immunohistochemical investigation. Fifty micron vibratome sections were immunostained utilizing standard ALZ-50 (20) or, after alkaline phosphatase pretreatment, Tau-1 methods (J. Geddes, unpublished observation).

**Neurochemistry**

Cortical samples were obtained from the FP, TP, and OP. Hypothalamus, nucleus basalis of Meynert (nBM) and amygdala were dissected according to previously reported methods (21–23). A series of chemical analyses were performed on each tissue sample from each subject, including: serotonin (5-HT) binding (24), imipramine binding (25), and acetylcholinesterase activity (AChE) (26). The kinetics of choline acetyltransferase (ChAT) (27), monoamine oxidase-A (MAO-A) (28), and monoamine oxidase-B (MAO-B) (29) were also assayed. Enzyme and binding activities were based on protein content in each tissue homogenate (30).

**RESULTS**

The brain of the Case individual, although somewhat small (1020 g), was grossly unremarkable and therefore not photographed. There was no lobar atrophy or significant sulcal widening. Inspection of coronal sections of fresh brain revealed no infarctions, no significant ventricular enlargement, and no apparent white matter loss or narrowing of the cortical ribbon. As a result, limited portions of this individual’s brain were retained at autopsy and subsequently studied.

The mDRS, IQCODE and Cornell depression studies strongly support cognitive normality and the lack of significant depression in the Case individual. Both informants indicated an mDRS score of 3.0 for the individual. The informant knowing the decedent a sufficient period of time indicated an IQCODE score of 3.65 for the individual. Both informants indicated a Cornell score of 5 for the individual.

Although neuron loss (cresyl violet) and gliosis (GFAP; subcortical only) were absent or mild, respectively (not shown), high densities of Pick bodies stained by the Bielschowsky method were found in every region of the Case individual’s brain investigated (Fig. 1a). Pick bodies were regionally distributed; TP and FP were more affected than OP. These Pick bodies were immunoreactive with ALZ-50 and Tau-1 in the FP and H-PHG; occasional Tau-1 and ALZ-50 immunoreactive neurons without Pick bodies were observed (Fig. 1c, d). Ballooned neurons were found in parahippocampal gyrus and pyriform cortex only.

![Fig. 2. Pockets of diffuse-form argyrophilic plaques stained by the Bielschowsky method were found only in the parahippocampal gyrus and pyriform cortex of the Case individual. Bar = 50 μm.](http://jnen.oxfordjournals.org/)

(Fig. 1b). Diffuse-form senile plaques stained by the Bielschowsky method were also found only in the parahippocampal gyrus and the pyriform cortex (Fig. 2). The non-HD control case was devoid of Pick bodies, balloon cells or argyrophilic plaques. Consistent with previous reports, the cCAD control had considerable numbers of argyrophilic plaques (10).

The maximum velocity (Vmax) of ChAT activity was unchanged in FP, TP and OP of the Case individual, but was decreased in nBM, amygdala and hypothalamus. These observations are similar to findings in demented Pick’s patients compared to controls (Table 1).

The activity of AChE was decreased considerably in nBM and amygdala of the Case individual. This was consistent with findings in demented Pick’s patients (Table 2).

The Vmax of MAO-A was unchanged in any region of

<table>
<thead>
<tr>
<th>Region</th>
<th>Case subject</th>
<th>Pick’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal pole</td>
<td>−13.4</td>
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<td>Temporal pole</td>
<td>−16.2</td>
<td>−35.3</td>
</tr>
<tr>
<td>Occipital pole</td>
<td>−24.3</td>
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<td>Nucleus basalis</td>
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<td>Hypothalamus</td>
<td>−64.3</td>
<td>−74.2*</td>
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<tr>
<td>Amygdala</td>
<td>−49.2</td>
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Percent difference in the Vmax of ChAT in regions of brain from a non-demented individual with Pick bodies compared to controls investigated simultaneously, and the percent difference in previously reported single point data for demented Pick’s disease patients and their respective controls (8).

ND = not determined.

*p < 0.05 compared to respective controls.
TABLE 2

Acetylcholinesterase Activity

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</thead>
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<td>−2.6</td>
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<td>Occipital pole</td>
<td>+2.1</td>
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<td>Nucleus basalis</td>
<td>−42.0</td>
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<td>Hypothalamus</td>
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<tr>
<td>Amygdala</td>
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<td>ND</td>
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</tbody>
</table>

Percent difference in AChE activity in regions of brain from a non-demented individual with Pick bodies compared to controls investigated simultaneously, and the percent difference from previously reported data for demented Pick's disease patients and their respective controls (8).

ND = not determined.

*p < 0.05 compared to respective controls.

TABLE 4

Maximum Velocity of Monoamine Oxidase-B Activity

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<th>Pick's disease</th>
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<td>+22.7</td>
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<td>Temporal pole</td>
<td>−5.9</td>
<td>+33.3*</td>
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<tr>
<td>Occipital pole</td>
<td>+53.9</td>
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</tr>
<tr>
<td>Nucleus basalis</td>
<td>+13.1</td>
<td>−40.0*</td>
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<td>Hypothalamus</td>
<td>+25.0</td>
<td>+52.4*</td>
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<tr>
<td>Amygdala</td>
<td>−67.5</td>
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Percent difference in the Vmax of MAO-B activity in regions of brain from a non-demented individual with Pick bodies compared to controls investigated simultaneously, and the percent difference in previously reported single point data from demented Pick's disease patients and their respective controls (11).

ND = not determined.

*p < 0.05 compared to respective controls.

this individual's brain. In demented Pick's patients only nbM showed a decrease in MAO-A activity (Table 3).

The Vmax of MAO-B in this individual was increased in OP, unchanged in FP, TP, hypothalamus and nbM, and decreased in amygdala. Compared to demented Pick's patients, among the regions of brain previously reported, the only difference is a lack of MAO-B activity decrease in nbM and an increase in hypothalamus (Table 4).

Serotonin binding in the brain of the reported individual was decreased in the TP, OP and hypothalamus, and unchanged in the nbM and FP. This pattern is similar to the findings in demented Pick's patients (Table 5).

Imipramine binding was unchanged in the brain of this or any of the previously reported demented Pick's patients (not shown).

DISCUSSION

An extensive retrospective investigation confirmed the patient did not exhibit cognitive impairment antemortem. Historical data suggest she may exhibit a familial form of Pick's disease; the patient's natural mother and son are also demented. Future neuropathological investigation of these living relatives may provide this confirmation.

Given the relative rarity of Pick's disease, discovery of a non-demented subject with the neuropathologic changes of Pick's disease was truly fortuitous. Descriptions of the clinical, pathological and neurochemical changes in Alzheimer-type dementia and in groups of humans with preserved mental status showing neocortical plaques or other aging changes (31–34) give precedent for similar findings in other dementing disorders. To the authors' knowledge, this case is unique; no central nervous system histologic or neurochemical examination of an individual demonstrating the histopathologic hallmarks of Pick's disease prior to the onset of overt dementing symptoms has been described. Regional neurochemical differences in this patient's brain showed chemical disturbances similar in almost every respect to the pattern of change observed in demented Pick's patients, both compared to their respective control populations.

TABLE 3

Maximum Velocity of Monoamine Oxidase-A Activity

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<th>Region</th>
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<th>Pick's disease</th>
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<td>Temporal pole</td>
<td>+4.4</td>
<td>−22.2</td>
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<tr>
<td>Occipital pole</td>
<td>+4.3</td>
<td>ND</td>
</tr>
<tr>
<td>Nucleus basalis</td>
<td>+4.6</td>
<td>−32.3*</td>
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<tr>
<td>Hypothalamus</td>
<td>+6.0</td>
<td>+17.8</td>
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<tr>
<td>Amygdala</td>
<td>+10.6</td>
<td>ND</td>
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</table>

Percent difference in the Vmax of MAO-A activity in regions of brain from a non-demented individual with Pick bodies compared to controls investigated simultaneously, and the percent difference in previously reported single point data from demented Pick's disease patients and their respective controls (11).

ND = not determined.

*p < 0.05 compared to respective controls.

TABLE 5

Serotonin Binding

<table>
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<tr>
<th>Region</th>
<th>Case subject</th>
<th>Pick's disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal pole</td>
<td>−20.0</td>
<td>−42.8*</td>
</tr>
<tr>
<td>Temporal pole</td>
<td>−57.1</td>
<td>−38.5*</td>
</tr>
<tr>
<td>Occipital pole</td>
<td>−63.6</td>
<td>ND</td>
</tr>
<tr>
<td>Nucleus basalis</td>
<td>+14.1</td>
<td>−7.9</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>−42.0</td>
<td>−54.2*</td>
</tr>
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Percent difference in serotonin binding in regions of brain from a non-demented individual with Pick bodies compared to controls investigated simultaneously, and the percent difference in previously reported data from demented Pick's disease patients and their respective controls (8).

ND = not determined.

*p < 0.05 compared to respective controls.
We suggest that our patient died of cCAD prior to manifesting recognizable cognitive dysfunction. The identification of diffuse morphology plaque formation in this case which lacked other changes of pathologic aging we attribute to the presence of cCAD (10, 34). In addition to the presence of Pick bodies and balloon cells, the present individual displayed ALZ-50 and Tau-1 immunoreactive neurons in a number of cortical areas. ALZ-50 immunodecorated neurons have been reported to precede Pick body formation (35). The high prevalence of Pick bodies in the relative absence of neuron loss and gliosis in this individual may suggest cytoskeletal alterations precede severe neuronal degeneration in Pick's disease.

Reports of the identification of normal and pathological aging in prospectively studied non-demented elderly humans have centered on Alzheimer-type alterations (cerebral amyloid deposition, ubiquitin immunoreactive neurites, senile plaques, and neurofibrillary tangles) (36). The difficulty of this type of study is self-evident; however, it could add to our understanding of these and other degenerative diseases if a common scientific thread could be identified. On the basis of the presented case, we speculate that both chemical and histologic pathologies occur in advance of behavioral and cognitive disturbances in Pick's disease.

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