Clinical and Etiological Studies on Dementia of Alzheimer Type and Multiinfarct Dementia

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av

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ABSTRACT

CLINICAL AND ETIOLOGICAL STUDIES ON DEMENTIA OF ALZHEIMER TYPE AND MULTIINFARCT DEMENTIA.

by

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1. Clinical studies. Clinical diagnosis of dementia has been made largely on the basis of clinical findings supported by appropriate radiological and laboratory investigations. A minority of patients have treatable or reversible underlying causes for their dementing syndrome. It is important to distinguish between the two main forms of dementia Alzheimer's disease, senile dementia of Alzheimer type (AD/SDAT) and MID so that advantage can be taken of any future progress in treatments.

In the clinical study significant differences between several diagnostic procedures were found between patients with AD/SDAT and MID. Blood pressure was significantly lower in the AD/SDAT group and focal neurological signs were seen in 70% of the MID patients but only in 6% of patients with AD/SDAT. Electrocardiogram was normal in all patients with AD/SDAT but pathological in 75% of the MID patients. Electroencephalogram showed generalized slow frequencies in 79% of the AD/SDAT patients and localized changes in 65% of the MID patients. Computerized tomography showed a significantly greater dilation of the ventricular system in MID patients compared to AD/SDAT patients and controls. Monoamine metabolites in the cerebrospinal fluid were lower in AD/SDAT patients and normal in MID patients. Psychopathological signs were found to be more variable and more pronounced in the AD/SDAT group compared with MID patients.

2. Etiological studies. Immunoglobulin and albumin were found changed in serum and CSF of both AD/SDAT and MID, indicating a more active immune response in MID and a less dense cerebrospinal fluid barrier in both MID and AD/SDAT. There appears to be a consumption of IgG in the central nervous system in patients with AD/SDAT.

Abnormal chromosomes appearing as acentric fragments, i.e. without visible centromeres, were found in 90% of patients with AD/SDAT, 30% of patients with MID, and not at all in the control group. Increased aneuploidy was also seen both in patients with MID and AD/SDAT.

Diabetes mellitus in old age and AD/SDAT do not seem to coexist. Furthermore, patients with AD/SDAT have changed carbohydrate metabolism with decreased fasting blood sugar concentrations, increased glucose tolerance and higher concentration of insulin during an oral glucose tolerance test.

Key words: dementia of Alzheimer type - multiinfarct dementia - clinical studies - diagnosis - blood cerebrospinal fluid barrier function - cytogenetic changes - blood glucose - insulin secretion
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Umeå University
Umeå 1983
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To
Rut
Charlotte, Henrik and Sofia
Original Papers

The present thesis is based on the following papers:

I  Bucht, G., Adolfsson, R. & Winblad, B.
DEMENTIA OF ALZHEIMER TYPE AND MULTIINFARCT DEMENTIA -
A CLINICAL DESCRIPTION AND DIAGNOSTIC PROBLEMS
Submitted to J. Am. Geriatr. Soc.

II  Bucht, G. & Adolfsson, R.
THE COMPREHENSIVE PSYCHOPATHOLOGICAL RATING SCALE (CPRS) IN
PATIENTS WITH DEMENTIA OF ALZHEIMER TYPE AND MULTIINFARCT
DEMENTIA
Submitted to Acta Psych. Scand.

III  Alafuzoff, I., Adolfsson, R., Bucht, G., & Winblad, B.
ALBUMIN AND IMMUNOGLOBULIN IN PLASMA AND CEREBROSPINAL FLUID,
AND BLOOD CEREBROSPINAL FLUID BARRIER FUNCTION IN PATIENTS
WITH DEMENTIA OF ALZHEIMER TYPE AND MULTIINFARCT DEMENTIA
J. Neurol. Sciences. Accepted for publication.

IV  Nordenson, I., Beckman, G., Adolfsson, R., Bucht, G. & Win-
blad B.
CYTOGENETIC CHANGES IN PATIENTS WITH SENILE DEMENTIA
Age and Ageing. Accepted for publication.

V  Bucht, G., Adolfsson, R., Lithner, F. & Winblad, B.
CHANGES OF BLOOD GLUCOSE AND INSULIN SECRETION IN PATIENTS
WITH DEMENTIA OF ALZHEIMER TYPE
Acta Med. Scand. Accepted for publication.

These papers will be referred to in the text with the roman numerals.
INTRODUCTION

The essential feature of dementia is a deterioration of mental functions caused by diffuse cerebral dysfunction. The causes of dementia are numerous, and comprehensive lists have been published by Slaby & Wyatt (1974) and Haase (1977).

To be considered demented the intellectual disabilities must be of a sufficient severity to interfere with social and occupational functioning. The deficit is multifaceted and involves memory, judgement, abstract thought, and a variety of high cortical functions, as well as changes in personality and behaviour. The state of consciousness must not be clouded (DSM-III, Am. Psychiat. Ass. 1980). Neuropathologists have recognized two main forms of organic dementias, Alzheimer's disease and senile dementia of Alzheimer type (AD/SDAT) and dementia due to cerebral softenings, probably secondary to cerebral arteriosclerosis (Alzheimer 1898, Fischer 1968, Tomlinson et al 1970, Jellinger 1976). Clinically, AD/SDAT is defined as a dementia with an insidious onset and an uniformly progressive deteriorating course (Wells 1977, Liston 1979a, 1979b). The essential clinical features of vascular dementia, "multiinfarct dementia", are a stepwise deterioration in intellectual functioning and a patchy distribution of mental deficits. Focal neurological signs and symptoms may also be present (Alzheimer 1898, Rothschild 1941, Roth 1955, Ehrentheil 1957, Slater & Roth 1959, Hachinski et al 1974). In some instances both MID and AD/SDAT may co-exist with clinical features of both diseases, so called "mixed". Neuropathological studies of brains from demented patients show that AD/SDAT i.e. brains with neurofibrillary tangles and senile plaques account for approximately 50% of all dementias and contribute to another 20%. Based on the amount of cerebral softening present, MID probably accounts for approximately 17% and contributes to another group of about the same size (Tomlinson 1980). Thus, AD/SDAT and MID, alone or together, accounts for between 80 and 85% of all cases of dementia. The co-existence of AD/SDAT and MID, "mixed", is well established and occurs in approximately 15% of the cases. Approximately 15% of the autopsy
cases have other specific causes of dementia or show no changes at all (Corsellis 1962, Tomlinson et al 1970, Jellinger 1976).

**Clinical aspects**

The clinical diagnosis of dementia and a judgement regarding the type of disorder causing the dementia have been made largely on the basis of clinical findings supported by appropriate radiological and laboratory investigations (Hutton 1980, Roth 1981). In recent years patients with apparent dementing illnesses have tended to receive a closer medical scrutiny. This is partly due to a number of reports in the medical literature suggesting that a significant minority of such patients have treatable or even reversible underlying causes for their dementing syndrome, such as depression, nutritional - metabolic - endocrine diseases, normal pressure hydrocephalus and space occupying lesions within the skull (Marsden & Harrison 1972, Freemont 1976, Smith et al 1976, Katzman 1977, Victoratos et al 1977, Hutton 1982, Portera-Sanchez et al 1982). It is also important to distinguish between different forms of dementia so that advantage can be taken of any future progress in treatments. Recent research has been able to establish some of the etiological features of AD/SDAT; the deficiencies of neurotransmitters in the brain and cerebrospinal fluid being the most striking findings (Gottfries et al 1965, Pope et al 1966, Gottfries et al 1969, Davies & Maloney 1976, Perry et al 1977, Adolfsson et al 1979, Mann et al 1981). MID-patients might improve if underlying factors such as hypertension, arteriosclerosis of cervical arteries, and cardiac diseases are treated correctly (Hachinski et al 1974, Bousser 1977, Hutton 1980, Birkett & Raskin 1982).

The diagnostic accuracy of the clinical diagnosis AD/SDAT varies between different studies. Affective disorders are the most common forms of psychiatric disabilities misdiagnosed as dementia (Roth 1955, Ron et al 1979). Todorov et al (1975) found in a retrospective study with histopathological verification of the diagnosis a significant coefficient of agreement between the clinical and
anatomical diagnosis but the different classes of dementia were only partially separable (50% overlap). Furthermore, there are clinical cases of apparent dementia where no distinctive pathological changes are found at biopsy or autopsy (Hughes et al 1973). In 1898 Alzheimer described the main diagnostic features of vascular dementia and its pathological anatomical correlate. Other authors have described the clinical differences between vascular dementia and AD/SDAT (Rothschild 1942, Roth 1955, Ehrentheil 1957, Slater & Roth 1969). Hachinski et al (1975) converted the symptoms of vascular dementia into an "ischemic score", which has been proven to be useful in differentiating MID from AD/SDAT in a post-mortem study (Rosen et al 1980). Several clinical studies have tried to differentiate MID and AD/SDAT by using a single or a few different investigative methods and most of them find group differences, but no single diagnostic tool has so far been proven to be able to separate MID and AD/SDAT in the single case (Rothschild 1942, Gordon & Sim 1967, Radue et al 1978, Roberts et al 1978, Harrison et al 1979, Hontela et al 1979, Striano et al 1981, Snowrenen et al 1982). Few prospective studies, however, have been performed using a wide range of different investigative methods in an attempt to differentiate between MID and AD/SDAT.

Etiological aspects
The typical histopathological alterations in AD/SDAT are the senile plaques and the neurofibrillary tangles (Alzheimer 1907). The senile plaques are composed of degenerative neuronal terminals, amyloid and reactive microglial cells, macrophages and astrocytes (Wisniewski & Terry 1973) and in the end stage an amyloid mass bordered by some glial cells (Terry & Wisniewski 1970). The neurofibrillary tangles consist of twisted tubules, usually in a pair, therefore referred to as paired helical filaments (Kidd 1963, Wisniewski et al 1976, Wisniewski & Soifer 1979). The paired helical filaments are assembled in bundles in the perykaria creating the neurofibrillary tangle. The paired helical filaments are composed of a protein, similar to the α-tubulin of normal neurotubuli. The presence of amyloid in the senile plaques and in the
vessel walls suggests that immunological factors may be involved in the development in AD/SDAT (Glenner 1978). Further, brain specific antibodies have been found to be increased in the serum of the aged and particularly in patients with AD/SDAT (Nandy 1978).

The development of histopathological changes in the brains of patients with Down's syndrome who have an extra chromosome 21, has led to a search for chromosomal abnormalities in AD/SDAT. Chromosomal aberrations have been reported (Nielsen et al 1968, Bergener & Jungklass 1970, Nordenson et al 1980), but others have not found these changes (Mark & Brun 1973, Brun et al 1978, Sulkava et al 1979). Ward et al (1979) reported aneuploidy in both sporadic and in familial cases of AD/SDAT, especially in the latter. There is also an increased risk of developing AD/SDAT among first order relatives of about 4 times than in the general population (Slater & Cowie 1971, Heston & Mastri 1977).

A possibility of a slow virus etiology for AD/SDAT, as in Jacob-Creutzfeldt's disease, has also been proposed. Suggestive of a viral etiology is the appearance of senile plaques and amyloid depositions similar to those in AD/SDAT in experimental scrapie virus infections (Wisniewski et al 1975). Transmission attempts have been made using material from cases with AD/SDAT on experimental animals. In familial cases of AD/SDAT this resulted in a spongiform encephalopathy but without senile plaques and neurofibrillary tangles (Gibbs & Gajdusek 1978).

Environmental agents have also been suspected to be of etiological importance, especially metals, such as aluminium. Experimentally, aluminium produces neurofibrillary tangles (Klatzo et al 1965, Crapper & Dalton 1973), although of a different type than those seen in AD/SDAT. Increased amounts of aluminium have also been found in the cortex from patients with Alzheimer's disease (Crapper et al 1976).
No satisfactory theory for the causation of AD/SDAT has so far been presented. Etiological alternatives, viral, immunological and toxic environmental agents, may very well interact with hereditary factors to produce the disease (Crapper & deBoni 1978).

Disturbances in neurotransmitter concentration and function have repeatedly been reported the last ten years. Catecholamine disturbances with reduced concentrations of dopamine and noradrenaline and increased monoamine oxidase activity have been found in different parts of the brains from demented patients (Gottfries et al 1965, Adolfsson et al 1979, 1980, Mann et al 1980). The cholinergic system has been shown to have a specific relation to memory and cognitive function (Drachman 1977). Davies and Maloney (1976) found that cholineacetyl transferase (ChAT) is reduced in AD/SDAT, while no change in postsynaptic receptors was observed (White et al 1977) and no reduction of ChAT was found in normal aging (Bowen et al 1979). The reduction of ChAT activity in AD/SDAT also correlates with the number of senile plaques and the degree of dementia (Perry et al 1978, Sims et al 1981).

The etiology of MID is thought to be the occurrence of multiple small or large cerebral infarcts (Fischer 1968, Worm-Petersen & Pakkenberg 1968, Hachinski et al 1974). Most authors are of the opinion that the occurrence of dementia due to cerebral infarction is well correlated with intra- and extracerebral arteriosclerosis (Worm-Petersen & Pakkenberg 1968, Bousser 1977, Birkett & Raskin 1982). Hypertension and heart disease are also believed to play an important part in the development of MID (Hachinski et al 1974). Cerebral softenings, however, are not infrequently present in subjects in whom no evidence of clinical dementia have been found (Tomlinson et al 1968, deReuck et al 1982). Tomlinson et al (1970) found that the ischemic destruction of cerebral tissue must be of a particular amount before evidence of dementia develops. They found that all patients with more than 100 ml of destroyed brain tissue were demented.
MATERIALS AND METHODS

Clinical studies (I, II)
Forty-one patients with mild to moderate dementia, all living at home, were subjected to a clinical examination. The patients were divided, on anamnesis and presentation on admission, into two groups, one with a presumed diagnosis of AD/SDAT and the other with MID using the diagnostic criteria stated in the DSM-III (Am. Psychiat. Ass. 1980). Two patients were excluded after the first examination due to concomitant diseases. The AD/SDAT group included 19 patients (9 men and 10 women; mean age 63 yrs, range 53-73 yrs; duration of illness 3.2±1.0 yrs). The MID group included 20 patients (11 men and 9 women; mean age 71 yrs, range 58-84 yrs; duration of illness 3.2±2.2 yrs). The selection of control persons was done through a letter to every person above 60 yrs of age in the community of Umeå requesting their participation in the study. After a telephone interview, 31 healthy elderly normals were selected (16 men and 15 women; mean age 67 yrs, range 60-72 yrs). The patients and the control persons were investigated while staying 2-7 days at the Department of Internal Medicine, University hospital, Umeå. A thorough clinical and psychiatric examination was performed including extensive laboratory tests (see I). Lumbal puncture was performed and monoamine metabolites were determined in the cerebrospinal fluid (CSF). Radiology included a chest X-ray and computed tomography of the brain (CT-scan). An electrocardiogram (ECG) and an electroencephalogram (EEG) were also performed. In study II, 18 of the patients with the diagnosis AD/SDAT and the 20 patients with the diagnosis MID were rated on the Comprehensive Psychopathological Rating Scale (CPRS) (Åsberg et al 1978). The CPRS consists of a range of items describing psychiatric symptoms (reported by the patients) and signs (observed items). A subscale consisting of items measuring common symptoms in patients with dementia was constructed.
Etiological studies (III, IV, V)

Albumin and immunoglobulin in plasma and cerebrospinal fluid (III)

Twenty patients with AD/SDAT (9 men and 11 women; mean age 65 yrs, range 53-79 yrs) and 23 patients with MID (12 men and 11 women; mean age 71 yrs, range 55-85 yrs) were investigated. All patients were mildly to moderately demented. Sixteen healthy persons (12 men and 4 women; mean age 69 yrs, range 62-74 yrs) without signs of dementia or immunological diseases served as controls. Blood and CSF sampling were performed under standardized conditions (see III).

The concentrations of the major classes of circulating immunoglobulins (IgA, IgM, IgG) and albumin were determined by rocket immunoelectrophoresis (Laurell 1972). Transudation of IgG through the blood-CSF barrier and local synthesis of IgG in the central nervous system were calculated as described by Tibbling et al (1977) and Schuller & Sagar (1981). Blood-CSF barrier function was graphically demonstrated by Reiber's evaluation graph for protein profile in the central nervous system (Reiber 1980).

Cytogenetic changes in patients with senile dementia (IV)

Nineteen patients with a diagnosis AD/SDAT (10 men and 9 women; mean age 64 yrs, range 52-84 yrs), 17 patients with the diagnosis MID (9 men and 8 women; mean age 71 yrs, range 58-83 yrs) and eleven institutionalized patients with Down's syndrome (3 men and 8 women; mean age 30 yrs, range 18-65 yrs) were included. As controls, 20 individuals (12 men and 8 women; mean age 66 yrs, range 49-85 yrs) were chosen randomly from an ongoing health screening program of the elderly. The patients with dementia were all mildly to moderately demented and all living at home at the time of the investigation. Blood sampling and the cytogenetical procedure were performed under standardized conditions (see IV). The slides were stained in Giemsa (10%), G-banded (Wang & Fedoroff 1972) and C-banded (Sumner 1972). Screening for chromosome breakage was performed on Giemsa-stained (non-banded slides).
Blood glucose and insulin secretion in patients with dementia (V)

A. Retrospective study of records of patients with dementia

The prevalence of diabetes mellitus in different types of dementia was studied in a retrospective study of all records of patients with a dementia diagnosis hospitalized at Umedalen's hospital, Umeå, between 1971 and 1980. 839 records were studied and classified as either AD/SDAT, MID or confusional states. The diagnostic criteria used were those stated in the DSM-III (Am. Psychiat. Ass. 1980). The diagnosis of overt diabetes mellitus was established on the grounds suggested by the National Diabetes Data Group (1979).

B. Metabolic study of the different patient groups

Five different groups of patients and controls were investigated with a fasting blood sugar and an oral glucose tolerance test (OGTT). Methods for blood glucose determination and calculation of the areas under the OGTT curves were performed as described by Lithner (1974). The first group consisted of 45 patients with the diagnosis AD/SDAT (22 men and 23 women; mean age 70 yrs, range 52-85 yrs), the second group consisted of 66 patients with the diagnosis cerebrovascular disease (CVD) without dementia (34 men and 32 women; mean age 70 yrs, range 43-87 yrs), the third group consisted of 15 patients with MID (5 men and 10 women; mean age 75 yrs, range 61-83 yrs), the fourth group consisted of 30 unselected nondiabetic hospitalized patients (15 men and 15 women; mean age 72 yrs, range 58-84 yrs) and the fifth group of 31 healthy elderly non-hospitalized persons (16 men and 15 women; mean age 68 yrs, range 61-73 yrs). The first four groups were all on the same diet and had approximately the same amount of activity and were all hospitalized at the Department of Internal Medicine, Umeå University during the investigation. The fifth group was not hospitalized, their diet habits were not controlled and they were also physically more active than the patients in the first four groups. The mean weight did not differ between the different patient groups.

Insulin levels during the OGTT were determined in 10 patients with
AD/SDAT (3 men and 7 women; mean age 71 yrs, range 61-80 yrs) and in 10 healthy elderly persons (5 men and 5 women; mean age 70 yrs, range 67-72 yrs). Insulin levels in serum were determined with a radioimmune assay method (Jalow & Berson 1969).

Malabsorption was also investigated through an A-vitamin load and a xylose-absorption test in patients with AD/SDAT.

RESULTS AND DISCUSSION

Clinical studies (I, II)
The differential diagnosis between AD/SDAT and MID is a common clinical problem (Birkett 1972, Hughes et al 1973, Todorov et al 1975 and Ron et al 1979). Several large retrospective but few prospective studies on the differential diagnosis and the outcome of treatment of dementia have been performed. The combined studies suggest a treatable cause for the dementing illness in approximately 15% of the patients (Marsden & Harrison 1972, Freemon 1976, Smith et al 1976, Katzman 1977, Victoratos et al 1977, Hutton 1982, and Portera-Sanchez et al 1982). In our study we selected mildly to moderately demented patients with either AD/SDAT or MID, based on the course of the illness and presentation on admission (Table 1).

Table 1  Background data on the three studied groups

<table>
<thead>
<tr>
<th></th>
<th>AD/SDAT</th>
<th>MID</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>19</td>
<td>20</td>
<td>31</td>
</tr>
<tr>
<td>Male/female</td>
<td>9/10</td>
<td>11/9</td>
<td>16/15</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>63.0±6.0***°</td>
<td>71.4±7.8</td>
<td>67±3.5*</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>159±11</td>
<td>167±12</td>
<td>168±8</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>67±12</td>
<td>72±10</td>
<td>71±11</td>
</tr>
<tr>
<td>Duration of illn./yrs</td>
<td>3.2±1.0</td>
<td>3.2±2.2</td>
<td></td>
</tr>
</tbody>
</table>

*** p <0.001, * p <0.05, MID compared with AD/SDAT and controls
° p <0.05, controls compared with AD/SDAT
The anamnestic data showed striking differences between the two investigated groups with dementia. Sixty-three % of the AD/SDAT patients were free of other diseases, while 65% of the MID patients had cardiovascular diseases. The occurrence of depression earlier in their lives was also more common among MID patients (30%) than in AD/SDAT patients (5%).

The physical examination of patients with dementia is important in establishing the cause of the dementia (Rothschild 1941, Roth 1955, Ehrentheil 1957, Wells 1977). Our investigation revealed significantly lower systolic blood pressure in the AD/SDAT patients compared with both MID and controls and the diastolic blood pressure was significantly lower in the AD/SDAT patients compared with the MID patients. This difference has also been established by other authors (Ladurner et al 1981, Portera-Sanchez et al 1982). For the differentiation of MID from AD/SDAT Hachinski et al (1975) constructed an "ischemic score", which, in a post-mortem study has been shown to be useful in distinguishing these two disorders (Rosen et al 1980). Our two groups of demented patients differed significantly in this respect, the AD/SDAT group having a significantly lower score than the MID group (Table 2).

Table 2  Physical data on the three studied groups

<table>
<thead>
<tr>
<th></th>
<th>AD/SDAT</th>
<th>MID</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>133±16***</td>
<td>158±15</td>
<td>152±21</td>
</tr>
<tr>
<td>Diastolic</td>
<td>77±19**</td>
<td>93±10</td>
<td>87±11</td>
</tr>
<tr>
<td>Focal neurological signs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N/total</td>
<td>1/19</td>
<td>14/20***</td>
<td>1/31</td>
</tr>
<tr>
<td>Ischemic score*</td>
<td>0.7±1.1</td>
<td>9.9±2.6</td>
<td></td>
</tr>
<tr>
<td>Heart (rel.vol. cm^3/m^2)</td>
<td>423±36</td>
<td>488±135</td>
<td>456±89</td>
</tr>
</tbody>
</table>

*  After Hachinski et al (1975)

*** p<0.001, AD/SDAT compared with MID and controls

** p<0.01, AD/SDAT compared with MID

*** p<0.001, MID compared with AD/SDAT and controls
That the neurological examination in most cases differentiates MID from AD/SDAT has consistently been reported (Harrison et al 1979, Ladurner et al 1981, Sluss et al 1982).

Routine laboratory examinations showed that all laboratory data were within the normal range in all investigated groups of patients. The primary aim of routine laboratory tests is to exclude potentially remediable causes to the dementia (Marsden & Harrison 1972, Freemon 1976, Wells 1977, Gershon & Herman 1982).

ECG with signs of coronary heart disease or cardiac hypertrophy was exclusively found among the demented patients with MID (Table 3). Other authors have also stated that the occurrence of coronary heart disease or previous myocardial infarction are indicative of MID (Rothschild 1942, Hontela & Schwartz 1979).

Table 3  ECG findings

<table>
<thead>
<tr>
<th></th>
<th>AD/SDAT</th>
<th>MID</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>Normal</td>
<td>19 (100)</td>
<td>5 (25)</td>
<td>22 (74)</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>0</td>
<td>3 (15)</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Cardiosclerosis/hypertrophy</td>
<td>0</td>
<td>12 (60)</td>
<td>4 (13)</td>
</tr>
</tbody>
</table>

An EEG, with localized slow wave activity and asymmetrical findings, is more common in MID patients, while patients with AD/SDAT show more homogenous generalized slow wave activities over both hemispheres (Gordon & Sim 1967, Roberts et al 1978, Striano et al 1981, Soininen et al 1982b). In our study generalized slow frequencies were found in 79% of AD/SDAT patients and localized slow frequencies and abnormalities in 65% of the MID patients (Table 4). There is, however, an overlap between the EEG findings in different
forms of dementia, which diminishes the diagnostic value in individual patients.

Table 4  EEG findings

<table>
<thead>
<tr>
<th></th>
<th>AD/SDAT</th>
<th>MID</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>Normal</td>
<td>2 (11)</td>
<td>4 (20)</td>
</tr>
<tr>
<td>Generalized slow frequencies</td>
<td>15 (79)</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Localized slow frequencies</td>
<td>1 (5)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Generalized and local slow frequencies</td>
<td>1 (5)</td>
<td>8 (40)</td>
</tr>
<tr>
<td>Local abnormalities</td>
<td>0</td>
<td>3 (15)</td>
</tr>
</tbody>
</table>

When visible infarcts or an irregular and dilated ventricular system is seen on the CT-scan this technique is of diagnostic value in identifying MID (Radue et al 1978, Roberts et al 1978). Our findings is that the MID patients have a significantly greater dilatation of the ventricular system than both controls and AD/SDAT. The cortical atrophy did not differ significantly between the three groups and does not seem to be of diagnostic help, at least, not in patients with mild to moderate dementia as in our study (Table 5).

Table 5  CT-scan of the brain

<table>
<thead>
<tr>
<th></th>
<th>AD/SDAT</th>
<th>MID</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (n)</td>
<td>17</td>
<td>20</td>
<td>28</td>
</tr>
<tr>
<td>Cortical atrophy (0-3)</td>
<td>1.2±0.9</td>
<td>0.9±0.8</td>
<td>0.7±0.7</td>
</tr>
<tr>
<td>Ventricular dilatation (0-3)</td>
<td>1.1±0.9</td>
<td>2.2±0.7***</td>
<td>0.4±0.6</td>
</tr>
<tr>
<td>Visible infarcts (n)</td>
<td>1</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

*** p< 0.001, MID compared with AD/SDAT and controls
Contrary to our findings, Soininen et al (1982) found a more pronounced asymmetrical ventricular dilatation in a group of AD/SDAT patients. Wells (1977) rightly stated that the CT-scan alone must not be relied upon when trying to differentiate between different causes of dementia.

A routine lumbar puncture and analysis of blood cells, proteins and glucose is of no value in differentiating MID from AD/SDAT, but is important in that it aids discovery of other causes of dementia. Monoamine metabolites in the CSF have been extensively investigated in AD/SDAT. Lower concentrations of homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA) have been found (Gottfries et al 1969, Mölsä 1980). In our investigation AD/SDAT patients had significantly lower concentrations of HVA than controls and a lower HVA than the MID patients. 5-HIAA was lower in AD/SDAT patients compared with MID and controls, although not significantly. MID patients did not differ from controls (Table 6). The overlap between the groups was however great, which limits this test as a diagnostic tool.

Table 6 CSF-monoaminemetabolites

<table>
<thead>
<tr>
<th></th>
<th>AD/SDAT</th>
<th>MID</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M±SD</td>
<td>M±SD</td>
<td>M±SD</td>
</tr>
<tr>
<td>HVA (nmol/1)</td>
<td>159±98*+</td>
<td>227±93</td>
<td>242±101</td>
</tr>
<tr>
<td>5-HIAA (nmol/1)</td>
<td>98±62</td>
<td>132±41</td>
<td>125±42</td>
</tr>
<tr>
<td>HMPG (nmol/1)</td>
<td>57±16</td>
<td>59±14</td>
<td>61±11</td>
</tr>
</tbody>
</table>

* p < 0.05, AD/SDAT compared with controls
+ p < 0.1, AD/SDAT compared with MID

Rating of the demented patients on the CPRS showed significant differences in the psychopathology between the two groups (AD/SDAT and MID). The AD/SDAT group has a more variable psycho-
pathology than the patients with MID. In table 7 the proportion of patients in each group (AD/SDAT and MID) with a score above 1 are listed. The psychopathological signs that differed most between the groups were "long-term memory", "specific speech defects", "disorientation", "perplexity" and "distractability". We could, however, not confirm that mood disorders and emotional lability symptoms, which most authors consider to be a frequent accompanying symptom in patients with MID, were specifically related to the MID group (Rothschild, 1941, Roth 1955, Ehrentheil 1957, Birkett 1972) (Table 7).

Table 7 Proportion (%) of patients with AD/SDAT and MID with a score above 1 on the CPRS* variables

<table>
<thead>
<tr>
<th>Observed items</th>
<th>AD/SDAT</th>
<th>MID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apparent sadness</td>
<td>11.1</td>
<td>0</td>
</tr>
<tr>
<td>Elated mood</td>
<td>16.7</td>
<td>5.0</td>
</tr>
<tr>
<td>Labile emotional response</td>
<td>22.2</td>
<td>10.0</td>
</tr>
<tr>
<td>Sleepiness</td>
<td>5.6</td>
<td>5.0</td>
</tr>
<tr>
<td>Distractability</td>
<td>27.8</td>
<td>0</td>
</tr>
<tr>
<td>Perplexity</td>
<td>50.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Disorientation</td>
<td>89.0</td>
<td>50.0</td>
</tr>
<tr>
<td>Specific speech defects</td>
<td>44.5</td>
<td>5.0</td>
</tr>
<tr>
<td>Perseveration</td>
<td>27.8</td>
<td>5.0</td>
</tr>
<tr>
<td>Overactivity</td>
<td>5.6</td>
<td>0</td>
</tr>
<tr>
<td>Slowness of movement</td>
<td>33.3</td>
<td>10.0</td>
</tr>
<tr>
<td>Agitation</td>
<td>5.6</td>
<td>0</td>
</tr>
<tr>
<td>Global rating of illness</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Recent memory</td>
<td>94.5</td>
<td>75.0</td>
</tr>
<tr>
<td>Long-term memory</td>
<td>89.0</td>
<td>25.0</td>
</tr>
</tbody>
</table>

* From Åsberg et al (1978)

Mood disorders are regarded as a specific complication of cerebrovascular diseases as such (Marshall et al 1977) and not necessarily
associated with dementia. In fact, dementia as a symptom after stroke is unusual (Tomlinson et al 1968, deReuck et al 1982). Furthermore, the evaluation of cognition after stroke is difficult, while patients wrongly could be classified as demented. Thus, one explanation for the discrepancy between earlier observations and the present study could be a predominance of stroke patients, without dementia in earlier studies. Psychopathological signs like "distractability", "perplexity", "disorientation" and "specific speech defects" determine the quality of the verbal contact with the patient. That these symptoms are less pronounced in MID patients could partly explain that they generally are considered to have at least a partial or good contact with their surroundings and a better preservation of their personality. Rothschild 1941, Ehrentheil 1957, Birkett 1972). Further, the significantly better "long-term memory" observed in MID patients compared with AD/SDAT patients probably contributes to the better relative preservation of personality observed in MID patients.

Most authors agree that the best way to separate AD/SDAT from MID is by the course of the illness, associated arteriosclerotic diseases and a neurological and neurophysiological investigation (Ehrentheil 1957, Hachinski et al 1974, Ladurner et al 1981, Reisberg & Ferris 1982). Gustafson and Nilsson (1982), however, used a dementia rating scale mainly based on the psychopathology of Alzheimer's and Pick's disease but their results still indicate that it is possible to distinguish MID from the primary degenerative dementias using this scale. Most other authors try to separate AD/SDAT from MID with psychometric tests. Significant differences are found between the two diseases and AD/SDAT patients performed significantly and consistently lower than MID patients, although the type of cognitive deficits is similar for the two disorders e.g. focal or diffuse (Perez et al 1975, Ladurner et al 1981).

In studies I and II we have chiefly used routine clinical methods in investigating the patients and controls. Most of these methods
show group differences between AD/SDAT, MID and controls. The investigations, however, show an overlap between the different forms of dementia and the controls and no one method can be used alone as a diagnostic tool. To differentiate between different kinds of dementias, and to find underlying treatable causes for a dementing illness, it is of vital importance to perform a thorough investigation of every patient with dementia symptoms.

Etiological studies (III, IV, V)

Albumin and immunoglobulin in plasma and cerebrospinal fluid (III)

Patients with MID had significantly higher concentrations of plasma IgG (p<0.001) and a slightly elevated IgA compared with AD/SDAT patients and the controls. CSF-Alb was significantly higher in the MID group compared with the controls (p<0.01) and slightly higher compared to AD/SDAT patients. AD/SDAT patients had significantly lower concentrations of CSF-IgG than the MID patients (p<0.05). The CSF/plasma IgG ratio was lower for the AD/SDAT group and the CSF plasma Alb ratio was higher for the MID group compared with the other two groups (Table 8).

Table 8 CSF/Plasma ratios for IgG and Alb x 10^3 and CSF IgG index (CSF/plasma IgG ratio):(CSF/Plasma Alb ratio)

<table>
<thead>
<tr>
<th>Group</th>
<th>Number</th>
<th>IgG ratio x 10^3</th>
<th>Alb ratio x 10^3</th>
<th>CSF IgG index</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD/SDAT</td>
<td>20</td>
<td>1.9 ± 1.7</td>
<td>9.8 ± 3.5^</td>
<td>0.20 ± 0.23*</td>
</tr>
<tr>
<td>MID</td>
<td>15</td>
<td>2.3 ± 1.8</td>
<td>14.2 ± 6.5^</td>
<td>0.18 ± 0.13°</td>
</tr>
<tr>
<td>Controls</td>
<td>16</td>
<td>2.9 ± 2.2</td>
<td>7.7 ± 3.4</td>
<td>0.34 ± 0.23</td>
</tr>
</tbody>
</table>

^ p< 0.05, AD/SDAT compared with MID patients
* p< 0.05, AD/SDAT compared with controls
°° p< 0.01, MID compared with controls
Figure 1. Evaluation graph for protein profile of cerebrospinal fluid according to Reiber (1980)
IgG ratio = CSF/plasma IgG x 10
Alb-ratio = CSF/plasma Alb x 10

a. Explanation to figure. 1. Normal range; 2. B-CSF-B dysfunction with proportionally increased IgG; 3. B-CSF-B dysfunction with disproportionally increased IgG; 4. B-CSF-B dysfunction with additional increased IgG locally produced in the CNS; 5. range for values with a locally in CNS synthetized IgG; 0. biologically irrelevant range.

b. Controls  c. MID  d. SDAT

- Males  - Females
Both patients with MID and AD/SDAT fell into an area which Reiber (1980) designates as "biologically irrelevant", while controls fell into the area for the normal range (Figure 1). Transudation of IgG through the blood cerebrospinal fluid barrier was higher in the MID group compared both with the controls (p<0.001) and the AD/SDAT patients (p<0.01). The AD/SDAT patients showed a significantly higher transudation when compared to controls (p<0.01). No signs of local synthesis were found in either type of dementia.

The high plasma IgG levels in the MID group indicate a more active immune response in this group. Whether this is due to specific brain reactive antibodies (Nandy 1978) or a secondary manifestation due to vascular damage in the body remains to be established (Beregi et al 1978). Elevated concentrations of CSF-Alb in the MID and AD/SDAT groups and an increased CSF/plasma Alb ratio in the MID group indicate either a less dense blood cerebrospinal fluid barrier function or a lower CSF turnover of albumin in the CNS. The high transudation values found in MID patients point towards a disturbed barrier function as being the underlying mechanism, which seems reasonable concerning the vascular background of this disease (Fischer 1968, Worm-Petersen & Pakkenberg 1968, Bousser 1977). The low CSF/plasma IgG ratio and CSF-IgG index in the AD/SDAT group along with a moderately higher transudation value compared with controls may indicate a consumption of IgG in the CNS. This binding could be explained by the findings of IgG in amyloid in senile plaques and vessel walls (Tomlinson et al 1970, Ishii & Haga 1976, Torack & Lynch 1981). Whether this binding is specific, e.g. involving brain reactive antibodies (Nandy 1978) or nonspecific, remains to be investigated. Both groups of demented patients fell into the area "biologically irrelevant" (Ganroth & Laurell 1974, Reiber 1980). It appears that this pattern is specific for demented patients and could be explained with an increased transudation of albumin and an antibody binding in the CNS.

**Cytogenetic changes in patients with senile dementia (IV)**

In accordance with other cytogenetic studies of senile dementia,
no deviations from normal banded karyotypes were found in the patients with AD/SDAT (Mark & Brun 1973, Brun et al 1978, White et al 1981). An increased frequency, however, of structurally abnormal chromosomes was observed in patients with AD/SDAT compared with both MID patients and controls (Table 9). All patients with AD/SDAT, except two, had at least one out of 100 cells carrying one or more abnormal chromosomes compared with 5 out 17 with MID and 2 out of 11 patients with Down's syndrome and none out of 21 controls. The abnormal chromosomes looked like acentric fragments, i.e. there were no visible centromeres (Figure 2).

Fig 2. Cell from a male SDAT-patient showing chromosomes without visible centromeres (arrows).
TABLE 9

CHROMOSOMAL BREAKAGE IN PATIENTS WITH DEMENTIA, DOWN'S SYNDROME AND CONTROLS

<table>
<thead>
<tr>
<th>CHROMOSOMAL ABBERATIONS (per 100 cells)</th>
<th>gaps</th>
<th>chromatid breaks</th>
<th>chromosome breaks</th>
<th>fragments</th>
<th>Total</th>
<th>No of cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dementia of Alzheimer type (SDAT) (n=19)</td>
<td>1.94</td>
<td>±2.12</td>
<td>±1.39</td>
<td>±0.55</td>
<td>±1.64</td>
<td>±3.19</td>
</tr>
<tr>
<td>Multiinfarct dementia (MID) (n=17)</td>
<td>1.99</td>
<td>±1.68</td>
<td>±0.77</td>
<td>±0.49</td>
<td>±1.77</td>
<td>±2.90</td>
</tr>
<tr>
<td>Down's syndrome (n=11)</td>
<td>2.18</td>
<td>±1.12</td>
<td>±1.21</td>
<td>±0.46</td>
<td>±0.40</td>
<td>±2.09</td>
</tr>
<tr>
<td>Controls (n=20)</td>
<td>2.38</td>
<td>±2.22</td>
<td>±0.93</td>
<td>±0.43</td>
<td>±0.00**</td>
<td>±2.72</td>
</tr>
</tbody>
</table>

* _p < 0.05, MID compared to SDAT

*** _p < 0.001, Down's syndrome and controls compared to SDAT
Informative metaphases indicated premature centromere division of whole chromosomes with a random chromosome involved. Similar chromosome abnormalities in cells from patients with senile dementia have been reported by other authors (Bergener & Jungklass 1970, Martin et al 1981) but others have been unable to confirm this observation (Nielsen et al 1968, Mark & Brun 1973, Brun et al 1978, White et al 1981).

The chromosomal anomaly was most frequent in patients with AD/SDAT but was also observed in some of the patients with multiinfarct dementia and in a low frequency in Down's syndrome, but were not seen in the controls. This might imply that this aberration is pathognomonic for some types of dementia although not for AD/SDAT.

The degree of aneuploidy was elevated in the patients with AD/SDAT (9.8% cells with aneuploidy) and MID (9.8% cells with aneuploidy) compared with controls (6.5% cells with aneuploidy), although cells with acentric fragments were excluded. Other authors have also reported increased aneuploidy in patients with AD/SDAT (Ward et al 1979, Nordenson et al 1980). No deviations, however, from normal diploid chromosome number could be found by other authors (Nielsen et al 1968, Mark & Brun 1973 and Martin et al 1981). This may be due to the relatively low number of patients studied or the relatively higher percentage of very old individuals included as controls in these studies.

The mechanism behind premature division of the centromeres is not known. An attractive hypothesis is that premature centromere division is connected with "hetero-chromatinization" of the affected chromosomes i.e. the inactive part of the chromosome being larger than normal. Increased amounts of "heterochromatin" have been found in neuronal and glial cells from patients with AD/SDAT (Crapper et al 1979, deBoni & Crapper-MacLachlan 1980). However, it remains to be shown that "heterochromatinization" is a general phenomenon in AD/SDAT and that it also occurs in other tissues. AD/SDAT has, however, been suggested to be a systemic disease with
changes also in other tissues (Adolfsson et al 1980, Carlsson et al 1980, Bucht et al 1983). Our findings of structural chromosomal changes in lymphocytes in patients with AD/SDAT strengthen this suggestion. The predominant neuronal lesion in AD/SDAT is the neurofibrillary tangles which consist of paired helical filaments. If AD/SDAT is a generalized disease the disorganized microtubules might be present in other tissues outside the central nervous system. Microtubules or other fibrillary elements are responsible during cell division for accurate chromatid separation and distribution of chromosomes to the daughter cells. Thus, the increased frequency of fragments and the neurofibrillary tangles in AD/SDAT might be associated phenomena, both related to impairment of neurofibrills and microtubules.

Blood glucose and insulin secretion in patients with dementia (V)
The retrospective study of records of patients with dementia shows that 457 had MID, 317 AD/SDAT and 65 confusional states. Sixty-three of these patients were also found to have overt diabetes mellitus. None of the patients with diabetes mellitus were found in the group of patients with AD/SDAT, 55 were found in the group of patients with MID and 5 in the group of patients with confusional states. These findings suggest that AD/SDAT and diabetes mellitus in old age may not co-exist.

Lower fasting blood sugar was found in patients with AD/SDAT compared with the other four groups and significantly lower compared with patients with CVD and hospitalized controls. The mean area under the OGTT-curve was smaller in the group of patients with AD/SDAT compared with all other groups and significantly smaller compared with the group of patients with CVD and the hospitalized controls (Table 10). The basal level of insulin before starting the OGTT was the same in a group consisting of patients with AD/SDAT and healthy elderly controls. During the OGTT patients with AD/SDAT had higher levels of insulin (Figure 3).
Fasting blood sugar and the area underneath the OGTT curves in patients with SDAT, CVD and MID and in control patients. The statistical comparison between SDAT and the other studied groups was performed with Scheffé's method of posterior contrast.

<table>
<thead>
<tr>
<th>Study group</th>
<th>n</th>
<th>Age (years) M±SD</th>
<th>Weight (kg) M±SD</th>
<th>Sex Male/female</th>
<th>Fasting blood sugar (mmol/l) M±SD</th>
<th>Oral glucose tolerance test (area) M±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Senile dementia of Alzheimer type (SDAT)</td>
<td>45</td>
<td>70.1±7.8</td>
<td>64±11</td>
<td>22/23</td>
<td>4.31±0.62</td>
<td>20.99±3.39</td>
</tr>
<tr>
<td>Cerebrovascular Disease (CVD)</td>
<td>66</td>
<td>70.4±9.8</td>
<td>64±13</td>
<td>34/32</td>
<td>5.08±0.88</td>
<td>26.71±6.75</td>
</tr>
<tr>
<td>Multiinfarct dementia (MID)</td>
<td>15</td>
<td>74.5±6.9</td>
<td>65±12</td>
<td>5/10</td>
<td>4.61±0.62</td>
<td>24.17±4.56</td>
</tr>
<tr>
<td>Hospitalized controls (C_hosp)</td>
<td>30</td>
<td>71.9±6.7</td>
<td>63±16</td>
<td>15/15</td>
<td>4.81±0.86</td>
<td>25.38±5.16</td>
</tr>
<tr>
<td>Normal elderly (C_eld)</td>
<td>31</td>
<td>67.6±3.5</td>
<td>71±11</td>
<td>16/15</td>
<td>4.53±0.54</td>
<td>21.39±3.06</td>
</tr>
<tr>
<td>SDAT &lt; CVD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p&lt;0.01</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>SDAT &lt; MID</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td>SDAT &lt; C_hosp</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p&lt;0.05</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>SDAT &lt; C_eld</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
</tbody>
</table>
Insulin levels in serum in arbitrary units during the OGTT in 10 patients with senile dementia of Alzheimer type (SDAT) and 10 age matched healthy elderly persons (C). The difference in insulin level is statistically significant at 90 minutes (p<0.05).

From this study it seems that the patients with AD/SDAT have a changed carbohydrate metabolism with decreased fasting blood glucose and an increased glucose tolerance, i.e. smaller areas under the OGTT curve. The difference in blood sugar concentration and the area underneath the OGTT curve are not significantly changed when AD/SDAT patients were compared with healthy elderly normal persons. An explanation for this might be that the healthy elderly persons were not hospitalized, were on a different diet and were physically more active than the other four groups, conditions which all contribute to an increased glucose tolerance. No signs of malabsorption could be found when patients with AD/SDAT were examined with different malabsorption tests.

We have no satisfactory explanation for the elevated insulin
levels in patients with AD/SDAT, but a decreased insulin sensitivity of the cells in patients with AD/SDAT, leading to a compensatory increase in insulin levels could explain this. Also, the neurotransmitters are of importance in the regulation of insulin and glucagon release, both by the sympathetic and parasympathetic nervous system (Woods & Porte 1974, Bereiter et al 1981, Steffens 1981). Cholinergic and catecholaminergic substances also play an important role in the modulation of insulin and glucagon release in the pancreas (Feldman & Lebowitz 1970, Woods & Porte 1974, Lindström & Sehlin 1983) and a deficit of those might explain the elevated insulin levels we found in patients with AD/SDAT.

On the other hand, different neurotransmitters are sensitive to hypoglycemia and hypoxia (Davis & Carlson 1973, Gibson & Blass 1976, Hedner 1977, Hedner & Lundborg 1977, Blass & Gibson 1978). If an error in the metabolism leading to hypoglycemia is the primary defect in patients with AD/SDAT, this could be the explanation for the impaired synthesis of acetylcholine.

It has recently been discovered that patients with AD/SDAT have low levels of somatostatin in their brains (Davis et al 1980, Rosser et al 1980). Somatostatin is a potent inhibitor of insulin secretion (Alberti et al 1973) and a deficiency of somatostatin in the pancreas in patients with AD/SDAT could explain our findings of high insulin levels.

If our findings of low blood sugar and high serum insulin concentrations in patients with AD/SDAT are a primary defect causing the transmitter deficiencies, or, perhaps, more likely are due to the known transmitter deficiencies in AD/SDAT remains to be established. Whatever the cause of the hypoglycemia is in AD/SDAT, the already low concentrations of brain neurotransmitters are further negatively influenced by the lack of an important source of energy or perhaps a lack of metabolites necessary for the production of neurotransmitters.
GENERAL SUMMARY AND CONCLUSIONS

I. Clinical studies

Significant differences between several diagnostic procedures were found in a prospective study comparing patients with Alzheimer's disease and senile dementia of Alzheimer type (AD/SDAT) and multiinfarct dementia (MID). The majority of the patients with AD/SDAT were free of other diseases, while the majority of MID patients had cardiovascular disease. Blood pressure was significantly lower in the AD/SDAT group and focal neurological signs were seen in 70% of the MID patients but only in 6% of patients with AD/SDAT. All AD/SDAT patients had a normal electrocardiogram (ECG) while 75% of the MID patients had a pathological ECG. Electroencephalogram (EEG) showed generalized slow frequencies in 79% of the AD/SDAT patients and localized slow frequencies or abnormalities were seen in 65% of the MID patients. Computerized tomography showed visible infarcts in only 25% of the MID patients, but this group had a significantly greater dilation of the ventricular system than patients with AD/SDAT. Monoamine metabolites in the cerebrospinal fluid were lower in the AD/SDAT group than in the MID and control groups. MID patients had normal concentrations. Rating of psychopathological signs showed that AD/SDAT patients have a more variable psychopathology than patients with MID. MID patients had less pronounced psychopathological signs, especially those which make a verbal and personal contact with the patient possible, possibly explaining the generally accepted opinion that patients with MID have a better preservation of their personalities.

On the basis of these findings, the following laboratory investigations are proposed in patients with dementia in order to detect underlying treatable diseases and differentiate between AD/SDAT and MID.
I Somatic status examination including a thorough neurological assessment.

II Mental status examination, including a rating of psychopathological signs.

III Laboratory investigations
   Complete blood count
   Electrolytes
   Liver function tests.
   Thyroid function tests
   Vitamin B₁₂ and folic acid
   Fasting blood sugar
   Urine analysis
   Electrocardiogram
   Electroencephalogram

These investigative methods will in most instances reveal the correct diagnosis. In some instances, when the diagnosis is unclear, this list should be completed with cerebrospinal fluid investigations, computerized tomography of the brain or other specific investigations.

In the future other more refined investigative methods might become available and enable a further increase in diagnostic accuracy. Some examples of these might be improved cytogenetic procedures, albumin and immunoglobulin determination in serum and CSF, based upon established differences between different dementia disorders.

II Etiological studies
1. Study of immunoglobulin and albumin in patients with AD/SDAT and MID indicates a more active immune response in MID patients and a less dense blood cerebrospinal fluid barrier in both patients with MID and AD/SDAT. A consumption of IgG in the central nervous system seems to be present in patients with AD/SDAT, possibly explaining the findings of IgG and amyloid in senile plaques and vessel walls. The differences in IgG and albumin in CSF
and serum in patients with MID and AD/SDAT could possibly also be of diagnostic value.

2. Abnormal chromosomes, appearing as acentric fragments, i.e. chromosomes without visible centromere, were found in 90% of patients with AD/SDAT, 30% of patients with MID, 20% of patients with Down's syndrome, but not at all in the control group. Informative metaphases indicated premature centromere division as the probable cause. Increased aneuploidy was seen both in patients with MID and AD/SDAT.

The appearance of acentric fragments in patients with dementia could be of diagnostic value in differentiating the dementias, and especially in differentiating organic dementia from other diseases with dementia symptoms.

3. Diabetes mellitus in old age and AD/SDAT do not seem to coexist. Furthermore, patients with AD/SDAT have a changed carbohydrate metabolism with decreased fasting blood sugar concentration, increased glucose tolerance and higher concentration of insulin during an oral glucose tolerance test. These findings could either be an effect of the known transmitter deficiencies in AD/SDAT or, on the other hand, be an explanation for the transmitter deficiencies, because hypoglycemia leads to a decrease in the production of most neurotransmitters.
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