Abstract

Establishing the diagnosis in patients with clinical signs and symptoms suggesting primary degenerative disease with marked frontal lobe involvement is difficult. Neuroimaging methods, in particular positron emission tomography (PET) with the tracer $^{18}$fluoro-2-deoxyglucose (FDG) and cerebrospinal fluid (CSF) examination of $\beta$-amyloid and tau-protein levels may give additional information. We report five patients with clinical and radiological features of degenerative dementia with predominantly frontal involvement and one patient with primary progressive aphasia. Diagnostic work-up included computed tomography (CT), magnetic resonance imaging (MRI), PET and tau-protein and $\beta$-amyloid level determination in CSF. While neuropsychological performance varied among patients, CT and MRI demonstrated persistently frontal lobe involvement. PET revealed corresponding changes with frontal hypometabolism, but in addition, four patients (among them two with no corresponding temporal changes in CT or MRI) showed a decreased glucose uptake in the temporal cortices. CSF samples from five patients revealed elevated $\beta$-amyloid 1–42 and tau levels in three and two patients, respectively. Reduced $\beta$-amyloid 1–40 was found in two patients. We conclude that occurrence of clinical symptoms of frontotemporal dementia is accompanied by frontal hypometabolism regardless of additional clinical findings. The value of determination of $\beta$-amyloid and tau protein levels remains to be determined.

Key words

Frontotemporal dementia · Magnetic resonance imaging · PET · Tau protein · $\beta$-amyloid

Introduction

Clinical signs of frontotemporal dementia (FTD) comprise disinhibition, loss of initiative, hyper-oral tendencies, utilization behavior, echolalia, perseveration and reduced speech output [2, 19, 20]. Assessment includes a thorough physical and neurological examination, neuropsychological testing and neuroimaging procedures such as computed tomography and magnetic resonance imaging especially to exclude other types of dementia such as vascular dementia or brain tumors.

Accurate clinical diagnosis is often difficult to establish. While definite diagnosis can be obtained only by analysis of neuropathological features, correct diagnosis is of increased importance with the advent of new drugs for the treatment of Alzheimer’s disease.

Recent studies indicate that functional neuroimaging methods such as positron emission tomography (PET) with $^{18}$fluoro-2-deoxyglucose (FDG) may facilitate the diagnosis of Alzheimer’s disease [7], but only sporadic reports exist about the diagnostic value of PET for diagnosis of FTD [8, 34].

Cerebrospinal fluid (CSF) examinations are necessary to exclude other medical conditions in particular inflammatory diseases of the central nervous system. CSF examinations can be extended to $\beta$-amyloid 1–42, $\beta$-amyloid 1–40 [10, 29] and tau-protein [9], which are
discussed to be biochemical markers for Alzheimer’s disease.

We report a series of 6 patients with clinical symptoms of FTD with special emphasis on clinical work up including PET and CSF levels of β-amyloid 1–42, β-amyloid 1–40, and tau-protein.

Patients and methods

Between 1992 and 1996, six patients admitted to the Section of Geriatric Psychiatry, University of Heidelberg were clinically diagnosed as FTD or primary progressive aphasia according to history, medical and psychopathological state and neuropsychological assessment after exclusion of a history of head trauma, birth injury, electroconvulsive therapy, or substance abuse. Symptoms of frontotemporal dementia were quantitatively assessed using the 9-point FTD scale [6]. According to latest consensus criteria [21] that have considered frontotemporal dementia and primary progressive aphasia as prototypic syndromes for frontotemporal lobar degeneration we have included both patients with clinical diagnosis of frontotemporal dementia and with primary progressive aphasia [16].

Clinical evaluation and assessment

All patients underwent thorough general and neurological examinations including computed tomography, MRI, and laboratory studies in order to exclude metabolic, toxic, and inflammatory causes of their dementia syndrome. None of the patients had evidence of cerebrovascular disease on CT and MRI scans.

Severity of cognitive impairment was assessed using the Mini Mental State Examination (MMSE) [3], the Global Deterioration Scale (GDS) [25], and the Brief Cognitive Rating Scale (BCRS) [24]. For further neuropsychological characterization, the following tests were applied: cognitive flexibility – Weitbrecht test (FWT) [22]; verbal fluency – controlled word association (FAS) [31]; attentional performance – Alterskonzentrationstest (AKT) [22]; declarative memory performance – Buschke selective reminding task (BSR) in the German version [12] and praxia – Apraxia test [12].

For interindividual comparison, test results were converted into z-values on the basis of the norm values established for healthy controls [13, 22, 31]. Z-values of less than –1 represent a test performance below those of 66% of an age-matched healthy control sample, while z-values of less then –2 refer to a performance worse than 98% of an age-matched healthy control sample.

Apparative tests

CT was obtained using standard 8 mm slices parallel to orbito-meatal line, MRI was obtained with routine T1-weighted sagittal and T2-weighted axial sequences. Both were rated qualitatively by the authors (J. P., M.E.) with respect to general and frontal atrophy on a 4-point scale (absent, mild, moderate, marked). Electroencephalography (EEG) was obtained using standard 16-channel recording using the 10–20 method for electrode placement, monopolar and bipolar leads (EEG) was obtained using standard 16-channel recording using the 10–20 method for electrode placement, monopolar and bipolar leads were used. Methods for CSF analysis (β-amyloid and tau-protein) are described elsewhere [9, 10, 29].

PET scans were obtained after intravenous injection of 160–380 mBq [18F]fluorodeoxyglucose at the Max Planck Institute in Cologne. Patients were examined in a resting state on an ECAT EXACT scanner, and local cerebral metabolic rates of glucose (CMRGlc, in µmol/100 g/min) in the whole brain were determined in 47 slices comprising the whole brain using the Sokoloff model with adjustment of K1 to measured activity and a lumped constant of 0.42 [33]. Slices were oriented along the AC-PC line.

The study was approved by the local ethical committee.

Patient characteristics and apparative findings

The clinical, neuropsychological, neuroimaging, and PET findings of the patients are listed below and summarized in Table 1 (clinical rating scales), Table 2 (neuropsychological testing), and Table 3 (CSF findings).

Patient 1

A 51 year old male, (who ran a transportation business) was admitted with a 10 month history of progressive cognitive decline, memory deficits, and paranoid delusions.

Neurological findings were normal except for grasping and a positive palmo-mental reflex. During the clinical course he developed signs of severe behavioral dis...