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SPECIAL ISSUE

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Clinical features of Alzheimer's disease

Abstract The preclinical stage of Alzheimer's disease is inconspicuous and there are – almost by definition – no reliable and valid symptoms and signs which would allow a very early diagnosis before the manifestation of irreversible deficits. For a clinical diagnosis of dementia, cognitive impairment has to be severe enough to compromise the activities of daily living. In the mild dementia stage, difficulties with declarative memory are usually prominent; depressive symptoms are not infrequent, but the patient usually manages to live alone. Supervision is needed in the moderate dementia stage, when other cognitive domains are affected in a more obvious manner and non-cognitive disturbances of thought, perception, affect, and behavior put increasing stress on the caregivers. Complete dependence of the patients, who frequently develop neurological disturbances, is typical of the late stage of illness. The life expectancy of patients with a clinical diagnosis of Alzheimer's disease is significantly reduced, but to date there is hope that the period of relative well-being and not of suffering can be prolonged with modern symptomatic treatment interventions.

Key words Alzheimer's disease · Dementia · Clinical symptoms · ADL-activities of daily living

Introduction

Alzheimer's disease (AD) is the most frequent cause of dementia. It frequently takes a typical clinical course which reflects the underlying expanding neuropathology. The slow progression of the illness from a subclinical to a severe stage of dementia is outlined in our contribution. The average duration of survival of AD patients is 5 to 8 years after clinical diagnosis (Bracco et al. 1994; Kurz and Greschniok 1994; Walsh et al. 1990). The length of the pre-dementia phase cannot be established with today's clinical research tools. Theoretical considerations based on neuropathological and molecular biological findings suggest that this subclinical stage of illness may extend over several decades. The clinical stages are outlined in the present paper overlap, and patients gradually progress from the mildest to the most severe manifestations of illness.

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The pre-dementia stage

Meticulous neuropsychological investigation may reveal very mild cognitive impairment five years before the clinical diagnosis of a dementia syndrome can be established according to contemporary diagnostic standards (Linn et al. 1995). The pattern of the subdiagnostic difficulties includes mild impairment in acquiring new information. Other demanding cognitive tasks, including the ability to plan or to access the semantic memory store, can also be compromised causing similar cognitive problems. The differentiation between incipient AD and a reversible condition (e.g., dementia syndrome of depression) or benign, non-progressive memory impairment is unreliable. At the pre-dementia stage of AD, patients do not show a significant deterioration in Activities of Daily Living (ADL).

At this stage, individuals may take advantage of memory aids and of other supportive strategies to overcome or compensate their cognitive deficits. The performance of complex work tasks may be reduced. Patients tend to avoid difficult challenges and downplay or dissimulate their problems.

In addition, non-cognitive alterations of behavior, including social withdrawal and depressive dysphoria, may be present five years before a clinical diagnosis is made (Jost and Grossberg 1995).

Mild dementia stage

In most patients, a significant impairment of learning and memory is the outstanding clinical feature. In some indi-

viduals, however, aphasic or visuoconstructional deficits may prevail. Short-term memory, old declarative memory from the patient's earlier years, and implicit memory are affected to a much lesser degree than the declarative recent memory. Memory impairment usually interferes with various cognitive domains and normally plays a key role in the patient's difficulties with ADL. The patient's reduced ability to plan, judge, and organize may not only show in complex tasks, but also in more difficult household chores (managing bank account; preparing meals, etc.). Communication may begin to suffer from shrinking vocabulary, decreasing word fluency, and less precise expressive language, even though a patient may still appear eloquent, "fluent", and even verbose on casual inspection. An impairment of object naming and semantic difficulties with word generation can be demonstrated by means of neuropsychological tests (Chobor and Brown 1990; Locascio et al. 1995). Constructional apraxia can be revealed on drawing tasks (Moore and Wyke 1984). Spatial disorientation frequently causes major problems in driving, as patients are less capable of estimating distances and speed. Because they have an increased risk of accidents, patients with a diagnosis of AD should not be allowed to drive a vehicle (Trobe et al. 1996).

At the mild stage of AD, patients may still be able to live independently for most of the time. But due to significant cognitive difficulties in several domains, they will need support with a variety of organizational matters. If a patient wishes to remain at home, arrangements for a support system should be made at this stage before more intensive or permanent supervision is necessary.

Non-cognitive disturbances in AD are more frequent than previously thought (Haupt et al. 1992). Symptoms of depression may prevail in the early stage of illness (Burns et al. 1990). These emotional disturbances are typically mild and fluctuating, but also full-blown depressive episodes can occur. The person may partly present understandable emotional reactions to reduced cognitive and ADL skills or to reduced social contacts while his insight is, at least, partly retained. Patients with severe depressive disturbances show reduced cell counts in the locus coeruleus and other aminergic brain stem nuclei (Förstl et al. 1992; Zubenko et al. 1989). A reduced dorsofrontal blood flow can be shown in patients with severe apathy (Craig et al. 1996).

Subtle impairment of complex motor tasks may remain unnoticed on standard neurological examination (Kluger et al. 1997).

Moderate dementia stage

Due to the severe impairment of recent memory, patients may appear to "live in the past" (Beatty et al. 1988). Logical reasoning, planning, and organizing significantly deteriorate at this stage. Language difficulties become more obvious as word finding difficulties, paraphasia, and circumstanciality increase (Romero et al. 1995). Reading skills deteriorate and the comprehension of texts becomes incomplete (Cummings et al. 1986). Writing becomes increasingly insecure with a graving number of mistakes and omissions (Neils et al. 1989). Patients become distractible and gradually lose insight into their condition. Longer (ideomotor) sequences of action can no longer be organized, until, finally, the skills of using household appliances, dressing, and eating are lost. The patient's spatial disorientation increases (Haupt et al. 1991; Liu et al. 1990). Cortical visual agnosia is often present and can include the inability to recognize familiar faces (prosopagnosia). One third of AD patients at this stage develop illusionary misidentifications and other delusional symptoms which are triggered by their cognitive deficits, but also by the underlying disease process (Förstl et al. 1993; Reisberg et al. 1996). Up to 20% of the patients develop hallucinations, mostly of visual quality, which may be associated with a particularly severe cholinergic deficit (Lauter 1968; Perry et al. 1990). At this stage, anosognosia prevails, but residues of insight may contribute to "catastrophic reactions" following minor distress. Patients often lose emotional control and develop temper tantrums which may be accompanied by physical or verbal aggression. Aimless and restless activity like wandering, hoarding, etc., are common (Devanand et al. 1997). Patients in this moderate state of illness cannot survive in the community without close supervision. They are incapable of managing financial or legal matters. Household gas or electrical appliances are a constant source of danger to the patients, but also to their carers. Hospital or nursing home admission may be delayed or even avoided, if a closely knit support system is in place. During this phase, there is a maximum strain on partners and other carers due to the patient's non-cognitive behavioral problems and somatic symptoms (Jost et al. 1995; Steele et al. 1990). Restlessness, aggression, disorientation, and incontinence are the most frequent factors which precipitate the breakdown of family support (Haupt and Kurz 1993; Stern et al. 1997). Sphincter control is insufficient and can be aggravated by "pseudo-incontinence" as a consequence of spatial disorientation and clumsy handling of clothes. Many patients are at an increased risk of falls provoked by a hesitant, festinating gait, and a stooped posture (Förstl et al. 1992).

Severe dementia stage

Specific modular cognitive deficits cannot be teased apart at the late stage of illness, when almost all cognitive functions are severely impaired. Even early biographical memories can be lost. Language is reduced to simple phrases or even single words. Patients are increasingly unable to articulate the even simplest of needs. However, many patients can receive and return emotional signals long after the loss of language skills. This emotional receptiveness has to be remembered while the patient is completely dependent on comprehensive nursing care.

Patients often misunderstand and misinterpret nursing interventions, and this may lead to aggressive reactions. Subgroups of patients may develop stereotyped motor pro-

grams like yelling or wandering. Restlessness and aggression may also be an expression of pain or the consequence of a profoundly disturbed circadian rhythm. A large proportion of patients shows extreme apathy and exhaustion.

Patients need support while eating, and even the most basic motor functions (chewing and swallowing) may be impaired as an expression of extreme apraxia. Double incontinence is frequent (Franssen et al. 1993). Other motor disturbances (e.g., rigidity and primitive reflexes) may interfere with nursing support. Extrapyramidal motor symptoms are usually due to a comorbidity with Parkinson's disease. Snouting and grasping reactions are the most frequent primitive reflexes and are associated with frontal lobe atrophy (Förstl et al. 1992). Myoclonus and epileptic seizures can be observed in a smaller proportion of patients with severe AD, but are more frequent as compared with the general elderly population (Förstl et al. 1992; Romanelli et al. 1990). Many bedridden patients develop decubital ulcersatrious contractions and infections.

After the clinical diagnosis of AD, life expectancy is reduced by one third (Heymen et al. 1987). A long persistence of symptoms, the severity of illness, old age, male sex, and physical disease are major risk factors for mortality in AD (Bowen et al. 1996; Burns et al. 1991; Kurz and Greschniok 1994). Pneumonia followed by myocardial infarction and septicaemia are the most frequent causes of death in AD (Förstl and Hewer 1993).

References

Beatty WW, Salmon DP, Butters N, Heindel WC, Granholm EL (1988) Retrograde amnesia in patients with Alzheimer's disease or Huntington's disease. Neurobiol Aging 9:181–186

Bowen JD, Malter AD, Sheppard L, Kukull WA, McCormick WC, Teri L, Larson EB (1996) Predictors of mortality in patients diagnosed with probable Alzheimer's disease. Neurology 47: 433–439

Bracco L, Gallato R, Gricoletto F, Lippi A, Lepore V, Bino G, Lazzaro MP, Carelly F, Piccolo T, Pozzilli C, et al. (1994) Factors affecting course and survival in Alzheimer's disease. A 9-year longitudinal study. Arch Neurol 51:1213–1219

Burns A, Jacoby R, Levy R (1990) Psychiatric phenomena in Alzheimer's disease. III: Disorders of mood. Brit J Psychiatry 157: 81–86

Burns A, Lewis G, Jacoby R, Levy R (1991) Factors affecting survival in Alzheimer's disease. Psychol Med 21:363–370

Chobor KL, Brown JW (1990) Semantic deterioration in Alzheimer's: The patterns to expect. Geriatrics 45:68–75

Craig AH, Cummings JL, Fairbanks L, Itti L, Miller BL, Li J, Mena I (1996) Cerebral blood flow correlates of apathy in Alzheimer disease. Arch Neurol 53:1116–1120

Cummings JL, Houlhan JP, Hill MA (1986) The pattern of reading deterioration in dementia of the Alzheimer type: observations and implications. Brain Lang 29:315–323

Devanand DP, Jacobs DM, Tang MX, Del-Castillo-Castandeda C, Sano M, Marder K, Bell K, Bylsma FW, Brandt J, Albert M, et al. (1997) The course of psychopathology in mild to moderate Alzheimer's disease. Arch Gen Psychiatry 54:257–263

Förstl H, Besthorn C, Geiger-Kabisch C, et al. (1993) Psychotic features and the course of Alzheimer's disease: relationship to cognitive, electroencephalographic and computerized tomography findings. Acta Psychiatr Scand 87:395–399

Förstl H, Burns A, Levy R, Cairns N, Luthert P, Lantos P (1992) Neurological signs in Alzheimer's disease. Arch Neurol 49: 1038–1042

Förstl H, Hewer W (1993) Medical Morbidity in Alzheimer's Disease. In: Burns A (ed) Ageing and Dementia. Edward Arnold, London, Boston, Melbourne, Auckland

Franssen EH, Kluger A, Torossian CL, Reisberg B (1993) The neurologic syndrome of severe Alzheimer's disease. Relationship to functional decline. Arch Neurol 50:1029–1039

Haupt M, Kurz A (1993) Predictors of nursing home placement in patients with Alzheimer's disease. Int J Geriat Psychiatry 8: 741–746

Haupt M, Pollmann S, Kurz A (1991) Disoriented behavior in familiar surroundings is strongly associated with perceptual impairment in mild Alzheimer's disease. Dementia 2:259–261

Haupt M, Kurz A, Romero B, Pollmann S (1992) Psychopathologische Störungen bei beginnender Alzheimerscher Krankheit. Fortschr Neurol Psychiatr 60:3–7

Heymen A, Wilkinson WE, Hurwitz BJ, Helms MJ, Haynes CS, Utley CM, Gwyther LP (1987) Early-onset Alzheimer's disease: clinical predictors of institutionalization and death. Neurology 37:980–984

Jost BC, Grossberg GT (1995) The natural history of Alzheimer's disease: A brain bank study. J Am Geriatr Soc 43:1248–1255

Kluger A, Gianutsos JG, Golomb J, Ferris SH, George AE, Franssen E, Reisberg B (1997) Patterns of motor impairment in normal aging, mild cognitive decline, and early Alzheimer's disease. J Gerontol Psychol Sci 52B:28–39

Kurz A, Greschniok P (1994) Überlebenswahrscheinlichkeit bei Alzheimer-Krankheit. Versicherungsmedizin 270:59–62

Lauter H (1968) Zur Klinik und Psychopathologie der Alzheimerschen Krankheit. Psychiat Clin 1:85–108

Linn RT, Wolf PA, Bachman DL, Knoefel JE, Cobb JL, Belanger AJ, Kaplan EF, D'Agostino RB (1995) The 'preclinical phase' of probable Alzheimer's disease. A 13-year prospective study of the Framingham cohort. Arch Neurol 52:485–490

Liu L, Gauthier L, Gauthier S (1990) Spatial disorientation in persons with early senile dementia of the Alzheimer type. Am J Occup Ther 45:67–74

Locascio JH, Growdon JH, Corkin S (1995) Cognitive test performance in detecting, staging, and tracking Alzheimer's disease. Arch Neurol 52:1087–1099

Moore V, Wyke MA (1984) Drawing disability in patients with senile dementia. Psychol Med 14:97–105

Neils J, Boller F, Gerdeman B, Cole M (1989) Descriptive writing abilities in Alzheimer's disease. J Clin Exp Neuropsychol 11: 692–698

Perry EK, Kerwin J, Perry RH, Blessed G, Fairbairn AF (1990) Visual hallucinations and the cholinergic system in dementia. J Neurol Neurosurg Psychiat 53:88

Reisberg B, Auer SR, Bonteiro I, Boksay I, Sclan SG (1996) Behavioral disturbances of dementia: an overview of phenomenology and methodologic concerns. Int Psychogeriat 8: 169–180

Romanelli MF, Morris JC, Ashkin K, Coben LA (1990) Advanced Alzheimer's disease is a risk factor for late-onset seizures. Arch Neurol 47:847–850

Romero B, Pulvermüller F, Haupt M, Kurz A (1995) Pragmatische Sprachstörungen in frühen Stadien der Alzheimer Krankheit: Analyse der Art und Ausprägung. Z Neuropsychol 6:29–42

Steele C, Rovner B, Chase GA, Fostein M (1990) Psychiatric symptoms and nursing home placement of patients with Alzheimer's disease. Am J Psychiatry 147:1049–1051

Stern Y, Tang MX, Albert MS, Brandt J, Jacobs DM, Bell K, Marder K, Sano M, Devanand D, Albert SM, et al. (1997) Predicting time to nursing home care and death in individuals with Alzheimer disease. J Am Med Assoc 277:806–812

Trobe JD, Waller PF, Cook-Flannagan CA, Teshima SM, Bielianskas LA (1996) Crashes and violations among drivers with Alzheimer disease. Arch Neurol 54:411–416

Walsh JS, Welch HG, Larson EB (1990) Survival of outpatients with Alzheimer-type dementia. Ann Intern Med 113:429–434

Zubenko GS, Moossy J, Martinez AJ, Rao GR, Kopp U, Hanin I (1989) A brain regional analysis of morphologic and cholinergic abnormalities in Alzheimer's disease. Arch Neurol 46: 634–638