Different rates of progression have been observed among patients with Alzheimer disease. Risk factors that accelerate deterioration have been identified and some are being discussed, such as genetics, comorbidity, and the early appearance of Alzheimer disease motor signs. Progressive forms of Alzheimer disease have been reported with rapid cognitive decline and disease duration of only a few years. This short review aims to provide an overview of the current knowledge of rapidly progressive Alzheimer disease. Furthermore, we suggest that rapid, in this context, should be defined as a Mini-Mental State Examination score decrease of 6 points per year.

Alzheimer disease (AD) is the most common cause of dementia. It represents a major public health challenge of growing significance. The classic form of AD progresses slowly, with survival of approximately 8 years and mean cognitive decline of approximately 3 Mini-Mental State Examination (MMSE) points per year. In some cases, rapidly progressive AD (rpAD) has been observed, and its clinical profile recently has been described. Clinical heterogeneity has been demonstrated and categories have been established, such as early-onset or late-onset, familial, and rapidly declining forms.

Although classification attempts based on biomarker profiles have been proposed, comprehensive studies are lacking to relate the distinct clinical appearance of different AD subtypes to specific neuropathologic features and biomarker patterns. Patients with an AD phenotype show heterogeneity in clinical signs, biomarkers, cognitive profiles, and disease progression rates. The following variables have been suggested to explain this phenomenon: different progression speeds in various disease stages (ie, nonlinear decline), compensatory mechanisms (ie, cognitive reserve), and disease subtypes that represent different biologic causes converging on a common final pathway (ie, biologic and neuropathologic).

All of these factors probably contribute to the expression of specific disease phenotypes to some extent. In the clinical setting, it is important to recognize disease heterogeneity and to understand the biologic variables involved for advancing diagnostic procedures, improving estimation of progression, and adapting treatment strategies.

The experience of the German Prion Disease Surveillance Unit, which is located at the Department of Neurology at Georg-August-Universität Göttingen, Germany, spans almost 2 decades. More than 5000 cases of rapidly progressive dementia are reported each year. A multitude of differential diagnoses have to be considered, such as inflammatory, metabolic, vascular, and neurodegenerative conditions, as well as prion disease (approximately 120 patients per year are eventually diagnosed as having Creutzfeldt-Jakob disease). Alzheimer disease is a major differential diagnosis of prion disease in humans and has been identified as such in various Creutzfeldt-Jakob disease surveillance centers worldwide.

Among a cohort of patients referred for rapidly progressive dementia who are initially suspected to have...
prion disease, our group recently identified patients diagnosed as having AD by neuropathologic examination.

Results of the clinical, genetic, biomarker, and neuropathologic workup of patients demonstrating an especially rapidly progressive form of AD suggested that rpAD may constitute a distinct subtype. This hypothesis should be studied more carefully so it can be confirmed or rejected.

Herein, we review clinical evidence regarding the rpAD subentity. Basic questions include: Does epidemiological evidence exist for rpAD? Can rpAD be predicted? What is the biologic basis of rpAD? Could the identification of AD subtypes, including rpAD, lead to more precise future therapeutic concepts?

**DEFINITION AND EPIDEMIOLOGY OF rpAD**

Alzheimer disease is diagnosed based on clinical criteria, increasingly supported by neuroimaging and cerebrospinal fluid (CSF) biomarkers. Postmortem examination allows a definitive diagnosis. Although clinical appearance and neuropathologic hallmarks have defined AD since its early descriptions in the literature, AD pathologic conditions can exist without significant simultaneous cognitive impairment. Complicating matters, heterogeneity is observed in AD neuropathologic conditions (eg, tangle distribution). Relating neuropathologic lesion profiles to specific clinical signs and symptoms remains controversial. Disease courses that differed clinically in speed and slope were reported; various phenotypes were suggested to represent distinct subtypes of AD. Several attempts have been made to characterize these subtypes by defining cognitive subgroup patterns, CSF biomarker profiles, and neuroimaging characteristics. Disease progression rates also have been used to characterize AD subtypes. However, no consensus exists regarding the definition of rpAD. Moreover, the word rapid has been used ambiguously. It is unclear whether rapid should characterize the survival time or the rate of cognitive decline (and if so, using which scale). Furthermore, the trajectories of decline are unknown and may differ among subtypes of AD, impeding clear definitions. Most investigators assume a linear decline, but others suggest 3 or even 6 trajectories.

Various definitions for rapid have been used in previous studies. For example, the word has been used to describe survival shorter than 4 years and MMSE score decreases of more than 5 points per year, more than 3 points per year, more than 4 points per 6 months, or more than 2.56 points per year, as well as Clinical Dementia Rating Scale score progression from 1 to 2 or 3 within a maximum of 3 years. In a meta-analysis, Ito et al observed a mean MMSE score decrease of 5.5 points per year in patients with mild to moderate AD. An attempt to propose a consensus defined rapid cognitive decline as a decrease of 3 or more MMSE points per 6-month period.

Using different definitions of rapid, data indicate that approximately 10% to 30% of AD cases represent rpAD. Cortes et al performed a longitudinal study spanning 2 years among 686 patients with mild to moderate AD; 30% of patients had a decline that exceeded 3 MMSE points per year, and 11% of patients had a mean (SD) decline of −4.57 (0.23) MMSE points per year, which was twice as fast as the mean of the whole cohort. In another prospective study, 24.8% of a cohort with AD experienced rapid decline, defined as a 4-point decrease in MMSE score within 6 months. In a recent study by Wallin et al, approximately 8% of the study population with AD had a significantly higher mortality rate and mean cognitive decline of 4.9 MMSE points per year. Table 2 gives an overview of studies with different designs that show rpAD and its frequency.

### PREDICTORS OF RAPID PROGRESSION

Much is known about which clinical, biochemical, and genetic factors influence the risk of developing AD or modulate the risk of advancing from mild cognitive impairment to dementia. However, little is known about what clinical signs, CSF biomarkers, and genetic factors predict speed of progression in AD.

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**Table 1. Rapidly Progressive Alzheimer Disease (AD) Cases Mimicking Creutzfeldt-Jakob Disease in Studies of Rapid Dementias**

<table>
<thead>
<tr>
<th>Source</th>
<th>Survival Time, Mean Age, Mean y</th>
<th>No. of Patients With Rapidly Progressive AD</th>
<th>No. of Patients With Prion Disease/Total No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aksamit et al, 2001</td>
<td>NA NA</td>
<td>13 (Not all neuropathologically confirmed)</td>
<td>31/152</td>
</tr>
<tr>
<td>Everbroeck et al, 2004</td>
<td>22 mo 71</td>
<td>45 (19 M, 26 F) clinically diagnosed, 30 confirmed by postmortem examination</td>
<td>52/201</td>
</tr>
<tr>
<td>Collins et al, 2000</td>
<td>NA NA</td>
<td>3</td>
<td>14/119</td>
</tr>
<tr>
<td>Gelpi et al, 2008</td>
<td>NA NA</td>
<td>6</td>
<td>206/700</td>
</tr>
<tr>
<td>Hakl et al, 2000</td>
<td>NA NA</td>
<td>NA</td>
<td>348/465</td>
</tr>
<tr>
<td>Huang et al, 2003</td>
<td>NA NA</td>
<td>1 M</td>
<td>17/46</td>
</tr>
<tr>
<td>Jansen et al, 2009</td>
<td>NA NA</td>
<td>54</td>
<td>146/280</td>
</tr>
<tr>
<td>Jayaratnam et al, 2008</td>
<td>4.5 mo 74</td>
<td>1 M</td>
<td>1</td>
</tr>
<tr>
<td>Josephs et al, 2009</td>
<td>3 y 72</td>
<td>1 M</td>
<td>8/22</td>
</tr>
<tr>
<td>Mahmoudi et al, 2010</td>
<td>12 mo 74</td>
<td>1 M</td>
<td>8/22</td>
</tr>
<tr>
<td>Reinwald et al, 2004</td>
<td>40 d 69</td>
<td>1 M</td>
<td>1</td>
</tr>
<tr>
<td>Schmidt et al, 2010</td>
<td>26.4 mo 73</td>
<td>32 (15 M, 17 F)</td>
<td>0/32</td>
</tr>
<tr>
<td>Tschampa et al, 2001</td>
<td>24 mo 76</td>
<td>19 (4 M, 15 F)</td>
<td>25/56</td>
</tr>
</tbody>
</table>

**Abbreviations:** F, female; M, male; NA, not available.
COMORBIDITY AND CLINICAL SIGNS 
AND SYMPTOMS

Contributing to disease progression are many factors, including cognitive reserve, medical and social support, genetics (ie, apolipoprotein E genotype [APOE]), and environmental and cerebrovascular pathologic conditions. The role of comorbidity is controversial. Cardiovascular disease and diabetes mellitus commonly are known to modulate AD risk. Findings are contradictory regarding their influence on AD progression (Table 3). Certain clinical features seem to be associated with rapid deterioration. Early appearance of AD motor signs predicts rapid decline and poor outcome. High burden of psychotic symptoms may indicate a rapid disease course. Table 3 gives an overview of the association of comorbidity and symptoms with AD progression.

Baseline cognitive status and preprogression rates of MMSE score decline (ie, the estimated MMSE point decrease per year per period from onset until diagnosis) have been used as predictive clinical markers. Preprogression rates of MMSE score decline have been shown to correlate with speed of further deterioration, and early loss of at least 4 MMSE points within 6 months predicts poor outcome. Also, baseline cognitive status among patients with AD predicts speed of decline in functional basic-care abilities. Baseline level of cognition does not necessarily correlate with mortality rate; the rate of cognitive decline showed substantial variability in prospective investigations. A recent meta-analysis demonstrated that baseline Alzheimer’s Disease Assessment Scale–Cognitive values represent a covariate in speed of deterioration. Santillan et al proposed a scale based on educational level, insight assessment, the presence of psychosis, activities of daily living, and MMSE score. This baseline score may predict the risk of future decline.

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**Table 2. Frequency of Rapidly Progressive Alzheimer Disease (rpAD) in Longitudinal, Cross-sectional, and Retrospective Clinical Studies**

<table>
<thead>
<tr>
<th>Source</th>
<th>MMSE Score Point Decrease Defining rpAD</th>
<th>Patients With rpAD, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcaillon et al, 2007</td>
<td>&gt;3.0/y</td>
<td>83/254 (33.9)</td>
</tr>
<tr>
<td>Cortes et al, 2008</td>
<td>&gt;4.5/y</td>
<td>74/686 (10.8)</td>
</tr>
<tr>
<td>Ballard et al, 2001</td>
<td>&gt;4.0/y</td>
<td>61/101 (60.4)</td>
</tr>
<tr>
<td>Wain et al, 2010</td>
<td>&gt;4.9/y</td>
<td>12/151 (8.3)</td>
</tr>
<tr>
<td>Ballard et al, 2001</td>
<td>&gt;7.0/y</td>
<td>32/101 (31.7)</td>
</tr>
<tr>
<td>Dumont et al, 2005</td>
<td>40/6 mo</td>
<td>79/312 (24.8)</td>
</tr>
<tr>
<td>Soto et al, 2008</td>
<td>Multiple definitions, consensus proposal: &gt;3.0/y</td>
<td>(9.5-54.0)</td>
</tr>
<tr>
<td>Soto et al, 2008</td>
<td>&gt;4.0/y</td>
<td>77/565 (13.6)</td>
</tr>
</tbody>
</table>

Abbreviation: MMSE, Mini-Mental State Examination.

a Not explicitly defined. The values are observations.

b Special cluster of cerebrospinal fluid markers.

---

**Table 3. Comorbidity and Clinical Signs and Symptoms Predicting Rate of Cognitive Decline in Alzheimer Disease (AD)**

<table>
<thead>
<tr>
<th>Source</th>
<th>Comorbidity or Symptom</th>
<th>Speed of Influence on Rate of Cognitive Decline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starkstein et al, 2006 (n=354)</td>
<td>Apathy</td>
<td>Fast</td>
</tr>
<tr>
<td>Smith et al, 2004 (n=60)</td>
<td>Apraxia (constructional)</td>
<td>Fast</td>
</tr>
<tr>
<td>Laukka et al, 2010 (n=138); Mielke et al, 2007 (n=135); Roselli et al, 2009 (n=162); Silvestrini et al, 2006 (n=53)</td>
<td>Atherosclerosis, atrial fibrillation, hypercholesterolemia, hypertension, microvascular disease, myocardial infarction</td>
<td>Fast</td>
</tr>
<tr>
<td>Abellan van Kan et al, 2009 (n=686)</td>
<td>Atherosclerosis, atrial fibrillation, hypercholesterolemia, hypertension, microvascular disease, myocardial infarction</td>
<td>None or unclear</td>
</tr>
<tr>
<td>Holmes et al, 2009 (n=300)</td>
<td>Chronic systemic inflammation</td>
<td>Fast</td>
</tr>
<tr>
<td>Roselli et al, 2009 (n=162)</td>
<td>Diabetes mellitus</td>
<td>Fast</td>
</tr>
<tr>
<td>Sanz et al, 2009 (n=608)</td>
<td>Diabetes mellitus</td>
<td>Slow</td>
</tr>
<tr>
<td>Mangone, 2004 (n=1000); Wilkousz et al, 2010 (n=201)</td>
<td>Psychotic symptoms</td>
<td>Fast</td>
</tr>
<tr>
<td>Josephs et al, 2009 (n=1); Schmidt et al, 2010 (n=32); Tschampa et al, 2001 (n=19); Everbroeck et al, 2004 (n=45)</td>
<td>Many focal neurological signs</td>
<td>Fast</td>
</tr>
<tr>
<td>Roselli et al, 2009 (n=162); Pavlik et al, 2006 (n=478)</td>
<td>High educational level</td>
<td>Fast</td>
</tr>
<tr>
<td>Pavlik et al, 2006 (n=478)</td>
<td>High educational level</td>
<td>Slow</td>
</tr>
<tr>
<td>Mangone, 2004 (n=1000)</td>
<td>Low educational level</td>
<td>Slow</td>
</tr>
<tr>
<td>Mangone, 2004 (n=1000); Portet et al, 2009 (n=388); Scaroneas et al, 2005 (n=533)</td>
<td>Motor signs</td>
<td>Fast</td>
</tr>
<tr>
<td>Soto et al, 2008 (n=565)</td>
<td>Early fast decline</td>
<td>Fast</td>
</tr>
<tr>
<td>Volicer et al, 1995 (n=27)</td>
<td>Seizures</td>
<td>Fast (language function)</td>
</tr>
<tr>
<td>Atchison et al, 2007 (n=150); Ito et al, 2010 (n=576); Marra et al, 2000 (n=45)</td>
<td>Severe cognitive impairment at disease onset</td>
<td>Fast</td>
</tr>
<tr>
<td>Hui et al, 2003 (n=354)</td>
<td>Severe cognitive impairment at disease onset</td>
<td>No or unclear influence on mortality</td>
</tr>
<tr>
<td>Roselli et al, 2009 (n=162)</td>
<td>Male sex</td>
<td>Fast</td>
</tr>
</tbody>
</table>

a Total numbers of patients with AD are given in parentheses.
Cerebrospinal Fluid. Rapid cognitive decline has been associated with high total tau or phosphorylated tau (ptau) levels, low β-amyloid 1-42 (Aβ1-42) level (≤411 pg/mL), or a high ratio of total tau to Aβ1-42 (≥0.81). Therefore, total tau and its phosphorylated isoforms are possible prognostic markers. In particular, elevated total tau level without a proportionally elevated ptau level may predict rapid progression. Wallin et al recently demonstrated that patients with a combination of low Aβ1-42 level (<362.66 pg/mL), high total tau level (>152±292 pg/mL), and high ptau level (>139±39 pg/mL) have faster decline and higher mortality rates. For all absolute values cited herein, one should keep in mind that cutoff values and methods of determining biomarkers may vary among different laboratories. As a marker of rapid neuronal destruction, 1-3-3 protein is sometimes present in patients with rpAD.

Disease stage may be a confounding factor because altered CSF biomarker levels can be associated with stage instead of progression rate. As a control, data from longitudinal studies are needed among patients with successive lumbar punctures and CSF analyses. Few studies have been performed pertaining to this subject, with short follow-up periods. Cerebrospinal fluid total tau, ptau, and Aβ1-42 levels seem to be stable among patients with AD during 2 years of follow-up. However, Buchhave et al reported longitudinally increasing total tau levels in AD during a 2-year period. Stomrud et al showed that ptau levels increased during a 4-year period. Furthermore, Stomrud et al showed that ptau levels increased during a 4-year period and were associated with cognitive decline. During a 4-year period, Huey et al demonstrated that Aβ1-42 levels decreased slightly but total tau levels were stable.

Genetics. Research regarding genetic predictors has increased enormously. Various polymorphisms seem to predict the speed of deterioration. Some remain controversial, especially the APOE polymorphism. Although APOE is well characterized as a disease risk modulator, its importance as a predictor of progression is not well understood. Cosentino et al concluded that a rapid decline occurs in patients with mild AD if the APOE ε4 allele is present. Conversely, van der Vlies et al argued that early-onset AD is especially rapid if APOE is not present. In a recent study by 2 of us, the ε4 allele was rare among patients with rpAD. However, Kester et al found no predictive capability in the presence of APOE. An overview of other genetic biomarkers associated with the speed of deterioration is given in Table 4.

CONCLUSIONS

Historically, AD has been regarded as a homogeneous disease. Many recent studies have acknowledged early-onset, late-onset, or rapidly declining forms, and classification attempts at using CSF biomarkers and neuropsychological test batteries have been suggested. Nevertheless, comprehensive approaches to characterizing AD subtypes on a clinicopathologic-molecular level are lacking. Recent pharmacological trials indicated that different AD subtypes may exist, with different susceptibilities to specific pharmacotherapies. Therefore, better characterization of clinicopathologic heterogeneity and identification of predictors in disease prognosis should improve our understanding of the pathogenesis of AD, aid the development of clinical diagnostic tools, and allow reliable prediction of progression and assignment to differential therapeutic strategies.

We encourage discussion to more clearly define rpAD in terms of survival time, cognitive decline, and functional decrease. A uniform definition would facilitate AD research and render results more comparable overall. Classical AD and rpAD features are summarized in Table 5, but data are lacking. Based on our review of the literature pertaining to rpAD, we suggest that rapid, in this context, should be defined as an MMSE score decrease of 6 points per year, consistent with the proposal by Soto et al. Given the knowledge regarding nonlinear decline, it is important to relate the speed of deterioration to disease stage to avoid false conclusions of heterogeneity. The
Table 5. Comparison of Classic Alzheimer Disease (AD) and Rapidly Progressive AD

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rapidly Progressive AD</th>
<th>Classic AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td>Few (2-3 y)</td>
<td>8-10 y</td>
</tr>
<tr>
<td>Age at onset</td>
<td>Unclear, approximately age 73 y in the study by Schmidt et al(^a)</td>
<td>Approximately age 65 y (&lt;65 y is early onset, &gt;65 y is late onset)</td>
</tr>
<tr>
<td>Rate of cognitive decline</td>
<td>&gt;6 MMSE points per year (ie, fast)</td>
<td>Approximately 3-6 MMSE points per year (ie, slow)</td>
</tr>
<tr>
<td>Focal neurologic signs</td>
<td>Occurring in early stages, multiple (especially extrapyramidal signs)</td>
<td>Occurring in late stages</td>
</tr>
<tr>
<td>CSF biomarkers</td>
<td>Very high total tau and ptau levels, very low Aβ1-42 level, 14-3-3 protein sometimes present (exact values unclear)</td>
<td>High total tau and ptau levels, low Aβ1-42 level, 14-3-3 protein usually absent</td>
</tr>
<tr>
<td>APOE ε4 genotype</td>
<td>Controversial: see Table 4 for its influence on decline: sometimes absent in rapid cases(^b)</td>
<td>Established as a risk factor</td>
</tr>
</tbody>
</table>

Abbreviations: Aβ1-42, β-amyloid 1-42; CSF, cerebrospinal fluid; MMSE, Mini-Mental State Examination; ptau, phosphorylated tau.

use of the MMSE is limited because test results are dependent on language function. Results of the MMSE should not be relied on in the presence of aphasia, which is sometimes an initial symptom of AD. In this case, standardized assessment tools should be used. Otherwise, the advantages of the MMSE are that it is short, widely known, commonly administered, and easy to perform even in non-specialized practices.

Another approach to defining rpAD could be based on survival time or a compound index of survival time and MMSE score. Survival of 2 years or less in patients with rpAD is consistent with observations thus far and with approved criteria defining rapid dementia in prion disease diagnostics.\(^9\) Survival time or disease duration should be measured from the estimated time point when the first symptoms become apparent (as suggested by Doody et al\(^{15}\)) because different periods until formal diagnosis may falsify the calculated survival time.

These suggestions should be evaluated and validated in prospective longitudinal studies with larger study populations. By means of this review, we encourage discussion of rpAD as a distinct subtype.

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Author Contributions: Drs Schmidt and Zerr had full access to all the data in the study and take responsibility for the accuracy of the data and the accuracy of the data analysis. Study concept and design: Schmidt, Korth, and Zerr. Acquisition of data: Schmidt, Wolff, Weitz, and Zerr. Analysis and interpretation of data: Schmidt, Weitz, Bartlau, and Korth. Drafting of the manuscript: Schmidt, Weitz, Bartlau, and Zerr. Critical revision of the manuscript for important intellectual content: Schmidt, Wolff, Bartlau, Korth, and Zerr. Obtained funding: Zerr. Administrative, technical, and material support: Schmidt, Wolff, Weitz, and Zerr. Study supervision: Schmidt, Korth, and Zerr.

Financial Disclosure: None reported.

REFERENCES


Announcement

Richard Mayeux, MD, MSc, the Gertrude H. Sergievsky Professor of Neurology, Psychiatry, and Epidemiology at Columbia University, has been named chair of the Department of Neurology and neurologist-in-chief at Columbia University Medical Center. The appointment, which became effective March 1, 2011, was announced jointly by Lee Goldman, executive vice president for health and biomedical sciences and dean of the Faculty of Medicine at Columbia University, and Herbert Pardes, president and CEO of New York Presbyterian Hospital.

Timothy Pedley, MD, an internationally recognized authority on epilepsy and clinical neurophysiology and founder of Columbia’s Comprehensive Epilepsy Center, stepped down when he became president-elect of the American Academy of Neurology. In addition to his work at the academy, Pedley will continue to have administrative responsibilities in the department and play an increased role in the Epilepsy Center. Pedley is past president of the American Neurological Association, the American Epilepsy Society, and the American Clinical Neurophysiology Society. He is a fellow of the American Association for the Advancement of Science and a member of the Institute of Medicine.

Mayeux, director of the Gertrude H. Sergievsky Center for Neuroepidemiology and Genetics and codirector of the Taub Institute for Research on Alzheimer’s Disease and the Aging Brain, is an internationally recognized authority on Alzheimer disease and other dementias, and his work has resulted in more than 300 articles, chapters, and books dealing with various aspects of Alzheimer disease and other degenerative diseases of the aging brain. His many honors and awards include the 2007 Potamkin Award of the American Academy of Neurology, the Leadership and Excellence in Alzheimer’s Disease Award from the National Institute on Aging, the John Stearns Award for Lifetime Achievement in Medicine from the New York Academy of Medicine, and the Henry Wisniewski Lifetime Achievement Award in Alzheimer’s Disease Research from the Alzheimer’s Association. Mayeux has been elected to the Association of American Physicians, the American Epidemiological Society, and the Institute of Medicine of the National Academies.