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Risk Factors for Disease Progression in Alzheimer's Disease

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1. Introduction

The most common form of dementia is Alzheimer's disease (AD) (Blennow et al., 2006). Due to worldwide demographic aging, its incidence and socioeconomic impact is going to be growing noticeably within the next fifty years (Sloane et al., 2002). Typically the disease progresses slowly with a mean decline of about 3 MMSE (Mini Mental Status Examination) pts/yr (Morris et al., 1993). On average, patients survive 8 years after the diagnosis has been established (Goldberg, 2007). But sometimes fast progressive AD forms with distinct clinical features are observed (Caselli et al., 1998; Josephs et al., 2009; Mann et al., 1989; Schmidt et al., 2010; van Everbroeck et al., 2004).

During the past few years AD has increasingly being understood as a disease that appears in rather heterogeneous variants (Blennow et al., 2006; Wilkosz et al., 2010; van der Vlies et al., 2009a; Iqbal et al., 2005; Querfurth & LaFerla, 2010). This accounts for its clinical profile, biomarker patterns or neuropathological features. Still, studies sufficiently interrelating symptomatology to neuropathology, pathophysiology and biopathochemistry are lacking. Factors, which might cause heterogeneity, appear to be diverse. For instance, different deterioration speeds may occur in different disease stages (Wilkosz et al., 2010; Brooks et al., 1993; Storandt et al., 2002). Also differences in the so-called cognitive reserve (Stern, 2006; Mortimer et al., 2005; Paradise et al., 2009) could account for phenotypical disparities. But furthermore, different biological causes or processes that converge on a common final pathophysiological pathway might evoke heterogeneity (Ritchie & Touchon, 1992). With ever growing evidence of AD heterogeneity, rapidly progressive AD forms (rpAD) might very well be one representative of such AD subentities.

In this book chapter, we review clinical evidence regarding AD heterogeneity in general and rapidly progressive AD (rpAD) in particular. Questions arising regard the epidemiological evidence for rpAD, its predictability, the biological / pathophysiological basis and the impact on therapeutic decision-making (subtype adapted therapy).

2. Excursus: evidence of AD heterogeneity

Different disease courses, regarding speed and slope, as well as different phenotypes might represent distinct subtypes of AD (Davidson et al., 2010; Geldmacher et al., 2000; Mangone, 2004). Several attempts have been made to characterize those subtypes, by definition of cognitive subgroup patterns, biomarker profiles in the CSF and recently using

neuroimaging (Wilkosz et al., 2010; Davidson et al., 2010; Boxer et al., 2003; Cummings, 2000).

Study	Mean survival	Age	n (patients with rpAD), gender	n, in parenthesis: n (subjects with prion disease)
Aksamit et al., 2001	n.a.	n.a.	13 (not all neuropathologically confirmed)	152 (31)
van Everbroeck et al., 2004	22mn	71	clinically diagnosed: 45 (19m, 26f); thereof 30 confirmed by post mortem	201 (52)
Collins et al., 2000	n.a.	n.a.	3	119 (14)
Gelpi et al., 2008	n.a.	n.a.	6	>900 (206)
Haïk et al., 2000	n.a.	n.a.	n.a.	465
Huang et al., 2003	n.a.	n.a.	1, m	46 (17)
Jansen et al., 2009	n.a.	n.a.	54	280 (146)
Jayaratnam et al., 2008	4.5mn	74	1, m	1
Josephs et al., 2009	3yrs	72	1, m	22 (8)
	1.2yrs	74	1, m	
Mahmoudi et al., 2010	21mn	74	1, m	1
Reinwald et al., 2004	40d	69	1, m	1
Schmidt et al., 2010	26.4mn	73	32 (15m,17f)	32
Tschampa et al., 2001	24mn	76	19 (4m, 15f)	56 (25)

Table 1. Neuropathologically confirmed rpAD cases imitating features of prion disease in different studies of rapid dementias. (Abbreviations: d=days, f=female, m=male, mn=months, n.a.=not available, yrs=years). Table modified from Schmidt et al., 2011.

2.1 Heterogeneity in AD neuropsychology and imaging

In a comprehensive overview Cummings presents the knowledge about different phenotypes of AD, which also correlate with marked differences in the focal metabolism or distinct types of focal atrophy (Cummings, 2000). Firstly, he mentions cognitive heterogeneity. Different AD phenotypes may reflect subtypes characterized by marked aphasia (Gorno-Tempini et al., 2008; Price et al., 1993), pronounced visuoconstructive disturbances (Furey-Kurkjian et al., 1996), the variant denominated as "posteriortcortical atrophy" (Benson et al, 1988; Tom et al., 1998) and a frontal variant (Foster et al., 1983). For all these speculative variants, different metabolism patterns have been demonstrated e.g. by means of FDG PET imaging (Foster et al., 1983; Grady et al., 1988; Haxby et al., 1988; Pietrini et al., 1996) - as a possible reflection of neurobiological heterogeneity. Boxer and colleagues for instance examined AD patients with similar cognitive profiles but marked differences in visuoconstructive abilities. More right than left cortical gray matter loss was seen in MRI imaging in the visuoconstructively impaired group (esp. right inferior temporal gyrus in contrast to the less spatially impaired group). Right inferotemporal atrophy might therefore be able to serve as an imaging surrogate marker for visuoconstructive disabilities. Another subtype might be AD with salient extrapyramidal signs. Those patients exhibit parkinsonoid

features, more severe cognitive decline (Clark et al., 1997) and an increased number of neurofibrillary tangles in neuropathology (Liu et al., 1997). Lewy body (LB) pathology is common (McKeith et al., 1996) in AD, but the group mentioned here was free from such LB features. Behavioral symptoms such as delusion, aggression, depression etc. seem as well to be heterogeneous and also show differences especially regarding metabolism (Cummings, 2000).

2.2 CSF biomarker evidence of heterogeneity

Iqbal and colleagues defined disease subtypes based on CSF marker profiles, age at onset, clinical profile and disease course (Iqbal et al., 2005). Van der Vlies et al. could also identify three AD subtypes using CSF marker profiles (based on Tau, phosphorylated Tau (pTau), and A β 1-42) - corrected for *ApoE* type, age, gender - showing distinct cognitive profiles on neuropsychologic testing (van der Vlies et al., 2009a, 2009b). Especially patients with very low A β 1-42 and high Tau and pTau performed worse on Visual association testing (VAT), Trail Making Tests (TMT) and Word Fluency (WF).

The differences in CSF marker profiles might imply the underlying pathophysiology to differ between subtypes. Although this is not proven to date, some findings support this hypothesis: Cerebrospinal fluid (CSF) contains a dynamic and complex mixture of proteins, which reflects physiological and pathological state of the CNS (Gawinecka & Zerr, 2010; Weller, 2001). In AD, levels of both major key players in the disease pathogenesis, namely Tau protein and A β , are altered in the CSF. These CSF changes are assumed to mirror the pathophysiological process in the brain, however, direct comparisons are lacking due to a long period between lumbar puncture and CSF tests on the one side and potential autopsy and neuropathological workup on the other side.

2.3 AD heterogeneity in neuropathology

Also from a pathology point of view evidence has been found to support hypotheses of Alzheimer heterogeneity. The basis of neuropathological classification are: Braak's staging, describing the distribution of neurofibrillary tangles (NFT), CERAD staging, describing the density of neuritic plaques and NIA-RIA criteria, being a synthesis of CERAD and Braak's criteria (Murayama & Saito, 2004). Regarding those criteria, neuropathological heterogeneity is observed. Ritchie et al. suggest three hypotheses to explain neuropathological heterogeneity in AD: 1) subtypes 2) disease stage effects 3) "compensation" (differences in cause / origin and progression of AD) (Ritchie & Touchon, 1992).

Especially heterogeneous cortical atrophy, of which right inferotemporal atrophy correlates with visuoconstructive impairment, can be found (Boxer et al., 2003). Recent papers reported heterogeneous A β deposition patterns in the end stages of the disease with variations throughout the neocortex, which cannot be completely explained by a regular build up of the pathologic protein during the course of the disease. This implies that other biological factors might be involved to build certain phenotypes (Cupidi et al., 2010). The morphology of A β deposits is influenced by the cyto- and fibroarchitectonics of the brain region in which they are found and by the amount of amyloid present (Wisniewski et al., 1989). Factors having an impact thereupon are not fully understood (Walker et al., 2008).

Studies, which focused on neurofibrillar tangles (NFT) in AD revealed significantly different NFT densities in various areas of the cerebral cortex without significant differences in the

duration of illness, suggesting a possible existence of subgroups. Two distinct subentities in AD with different densities of neurofibrillary tangles - but apparently without distinct clinical courses could be differentiated (Mizuno et al., 2003). Even in patients with presenilin (*PSEN*) mutations, the neuropathological distribution of different types of plaques, intensity of cerebrovascular amyloid and the number of NFT substantially differed among individuals, implying that missense mutations in *PSEN* genes can alter a range of key gamma-secretase activities to produce an array of subtly different biochemical, neuropathological and clinical manifestations (Maarouf et al., 2008).

Although the pathological and clinical heterogeneity of AD has been recognized and addressed to some extent in the literature, direct studies on clinico-pathological phenotypes are sparse. Some authors are arguing against the hypotheses of neuropathological heterogeneity. Armstrong et al. for instance examined eighty cases (Armstrong et al., 2000). They found that neuropathological differences were rather continuously distributed in contrast to the subtype hypotheses. Heterogeneity in plaque and tangle distribution correlated more with disease stage (stage hypothesis) rather than being explained by the presence of AD subentities. Nonetheless plaque load and distribution was significantly influenced by the presence of *Apoε* type 4 allele.

3. Definition and epidemiology of rapidly progressive AD

AD has been a clinical diagnosis since the McKhann Criteria were established in 1984 (McKhann et al., 1984). Neuroimaging and CSF parameters increasingly came into use especially in the first decade of the new millennium leading to newly proposed research criteria finally being accepted as a validated instrument to support the diagnostic concept (de Meyer et al., 2010; Dubois et al., 2010; Dubois et al., 2007; Gauthier et al., 2008).

Alois Alzheimer first described the hallmarks of AD with plaques and neurofibrillary tangles (NFT) more than a hundred years ago. In synopsis with the clinical presentation, neuropathological work-up allows a definite diagnosis. But it has become obvious that AD pathology can also exist without significant simultaneous cognitive impairment (Price et al., 2009). In cases when AD was diagnosed clinically and by post mortem work-up, heterogeneity has also been found to exist e.g. in terms of tangle distribution (Mizuno et al., 2003). Until today it remains subject to controversy how to relate clinical signs and symptoms to specific neuropathological lesion patterns or profiles.

Hypothetically clinically differing disease course could represent distinct subentities of AD in terms of heterogeneity. This accounts especially for speed of decline and distinct trajectories of that deterioration speed (Davidson et al., 2010; Mangone, 2004). Some attempts have been made to characterize these subentities by defining cognitive subgroup profiles, CSF biomarker patterns and neuroimaging characteristics (Wilkoosz et al., 2010; Davidson et al., 2010; Boxer et al., 2003; Cummings, 2000). (→ see section 2)

Disease progression rates have also been used to distinguish AD subtypes. But at the moment there is no consensus about the definition of the term “rapidly progressive AD”. Moreover the term «rapid» has been used rather arbitrarily. It has been doubtful whether “rapid” should be applied to characterize either the rate of cognitive deterioration - and if so, on which scales - or the disease duration time (survival time). In addition, the trajectories of decline have not been and even are currently not clearly known. They might differ among subentities, making a clear definition very difficult. The majority of AD researchers assume

a linear slope, but some investigators also suggest trilinear models of decline or even more trajectories (Wilkosz et al., 2010; Brooks et al., 1993).

A variety of definitions has been used in previous studies rather at will. The term “rapid” has been applied to describe a survival time below 4 years (Josephs et al., 2009), MMSE declines of >5 pts/yr (Doody et al., 2001), >3 pts/yr (Carcaillon et al., 2007), >4pts/0.5yrs (Dumont et al., 2005) or >2,56 pts/yr (Buccione et al, 2007) as well as CDR (Clinical Dementia Rating Scale) score progression from 1 to 2 or 3 within max. 3 yrs (Bhargava et al., 2006). Ito et al. observed an average MMSE loss of 5.5 pts/yr in mild to moderate AD in a metaanalysis (Ito et al., 2010). Encouraging a discussion and attempt to reach a consensus on the term "rapid cognitive decline", a threshold of 3 or more MMSE pt loss per six months has been proposed (Schmidt et al., 2011; Soto et al., 2008).

Owed to different definitions of "rapid", rpAD seems to constitute approximately 10-30% of the AD population. In a longitudinal study with more than 600 AD patients over a two years period, Cortes et al. discovered that almost one third of the patients declined faster than 3 MMSE pts. per year. A tenth deteriorated twice as fast as the whole groups average decline of approx. 4.5 pts per year on the MMSE scale (Cortes et al, 2008). Dumont and colleagues, in another prospective study, saw one quarter of the cohort decline faster than 4 MMSE points within half a year (Dumont et al., 2005). Recently Åsa Wallin and her research group were able to show that approximately 8% of their AD study population were characterized by a significantly higher mortality and a mean speed of cognitive deterioration of almost 5 MMSE pts/yr (Wallin et al., 2010). Table 2 gives overview of different studies describing rapid progression and its frequency.

study	definition of "rapid" [MMSE decline]	proportion of study population, (n (total))
Carcaillon et al., 2007	>3pt/yr	34% (254)
Ballard et al., 2001	>4pt/yr *	60% (101)
Cortes et al., 2008	>4.5/yr	11% (686)
Wallin et al., 2010	>5pt/yr**	8% (151)
Ballard et al., 2001	>7pt/yr *	32% (101)
Dumont et al., 2005	>8pt/yr	25% (312)
Soto et al., 2008a	multiple (>3pts/6months)	10%-54%
Soto et al., 2008b	>4pts/first 6 months	14% (565)

*(«Rapid» is not explicitly defined in this study. The numbers given are mere observations.)
** Special CSF biomarker cluster

Table 2. Frequency of rpAD in several clinical studies (longitudinal, cross-sectional, retrospective). «Rapid» has been defined by the authors in terms of MMSE decline (column 1) to specify a «rapid group» out of the AD continuum. (Abbreviations: MMSE=Minimental Status Examination, n=number, pts=points, yr=year). Table modified from Schmidt et al., 2011.

4. Factors associated with rapid progression

Much is known about clinical, pathobiochemical and hereditary factors altering the risk of developing Alzheimer’s disease, as well as how the risk to advance from Mild Cognitive Impairment (MCI) to manifest dementia is modulated by these. But there is a relative lack of

knowledge about which signs and symptoms, blood and CSF marker values as well as genetic factors actually predict the speed of deterioration in AD.

4.1 Clinical signs, symptoms and comorbidity as predictors of fast progression

Several factors such as genetic properties, environmental circumstances, cerebral atherosclerosis, cognitive reserve, medical and social support contribute to disease progression (Etienne et al., 1998).

sign / comorbidity	predictor of		
	slow progression	no influence or unclear	fast progression
apathy			Starkstein et al., 2006 (354)
apraxia (constructional)			Smith et al., 2001 (60)
atherosclerosis, atrial fibrillation,		Abellan et al., 2009 (686)	Laukka et al., 2010 (138)
hypercholesterinemia,			Mielke et al., 2007 (135)
hypertension, microvascular			Roselli et al., 2009 (162)
disease, myocardial infarction			Silvestrini et al., 2006 (53)
chronic systemic inflammation			Holmes et al., 2010 (300)
diabetes mellitus	Sanz et al., 2009 (608)		Roselli et al., 2009 (162)
psychotic symptoms			Mangone, 2004 (1000)
			Wilkosz et al., 2009 (201)
multitude of focal neurological signs			Josephs et al., 2009 (1)
			Schmidt et al., 2010 (32)
			Tschampa et al., 2001 (19)
			van Everbroeck et al., 2004 (45)
high educational level	Pavlik et al., 2009 (rate of decline) (478)	Pavlik et al., 2009 (survival) (478)	Roselli et al., 2009 (162)
low educational level			Mangone, 2004 (1000)
motor signs			Mangone, 2004 (1000)
			Portet et al., 2009 (388)
			Scarmeas et al., 2005 (533)
early fast decline			Soto et al., 2008b (565)
seizures			Volicer et al., 1995 (language function) (27)
severe cognitive impairment at disease onset		Hui et al., 2003 (mortality) (354)	Atchison et al., 2007 (150)
			Ito et al., 2010 (576)
			Marra et al., 2000 (45)
sex (male)			Roselli et al., 2009 (162)

Table 3. Clinical signs, symptoms and comorbidity as predictors of disease progression. Total number of subjects (AD) in the studies are given in parentheses. Table modified from Schmidt et al., 2011.

The role of comorbidity is subject to controversy. Diseases of the cardiovascular system and diabetes mellitus are commonly accepted as AD disease risk modulators. However, findings regarding their impact on disease progression are sometimes contradictory (Table 3) (Abellan van Kan et al., 2009; Mielke et al., 2007).

Fast deterioration also appears to be associated with the occurrence of certain signs and symptoms. Among those are especially early signs of the motor system. They are predictors of fast decline as well as poor outcome (Mangone, 2004; Portet et al., 2009; Scarmeas et al., 2005). Another potential indicator / predictor of a rapid disease course might be the presence of psychotic symptoms (Wilkosz et al. 2010). Table 3 provides an overview of the associations of comorbidity and symptoms with progression of AD.

Baseline cognitive status and preprogression rates in MMSE decline (estimated MMSE loss per time period from onset until diagnosis [pt/yr]) were used as predictive clinical markers as well. Another concept of predictive clinical markers has been demonstrated to be useful e.g. by Doody et al. in 2001. The baseline cognitive status as well as preprogression rates of MMSE decline were able to predict further speed of deterioration. Preprogression rates resemble the estimated MMSE loss per time period between the clinical onset to formal diagnosis (pts/yr).

It has been shown by Soto et al., that especially the early loss of 4 MMSE pts within half a year was predicting a poorer outcome (Soto et al., 2008b). Additionally, the baseline cognitive status is all the more capable of predicting the speed of decline regarding functional basic care abilities in AD (Atchison et al., 2007). The baseline level of cognition does not necessarily correlate with mortality, nonetheless, the cognitive decline rate features a considerable variability in some longitudinal studies (Hui et al., 2003). Recently a metaanalysis showed baseline ADAS-Cog values to be covariates of speed of decline (Ito et al., 2010). Santillan and coworkers proposed the use of a scale, consisting of the educational level, insight assessment, the presence of psychosis, the activities of daily living as well as MMSE. Measured at baseline this scale might be capable of estimating the risk of future deterioration (Santillan et al., 2003).

4.2 Imaging and prediction

An abundance of scientific work has been published regarding imaging in AD. The majority deals with either the early diagnosis of AD and differentiation MCI, AD and healthy subject, or makes statements about imaging and the risk of developing Alzheimer's disease, or it correlates atrophy rates to stages of AD. Literature about baseline imaging characteristics that actually predict the future speed of decline of AD patients (and not the risk of progression from MCI to AD) is scarce. Table 4 gives an overview.

4.3 Predictive biomarkers

4.3.1 CSF

CSF markers have become an important part of AD diagnostics. But also as predictors of fast decline, they might harbor a certain potential. For instance, rapid cognitive deterioration has been demonstrated to be indicated by high total Tau (Tau) protein or hyperphosphorylated Tau (pTau) as well as low A β 1-42 (411pg/ml or less) or a high Tau/A β 1-42 ratio (0.81 or higher) in the cerebrospinal fluid (CSF) respectively (Mungas et al., 2002). Therefore attempts have been made to suggest and validate Tau as well as its phosphorylated isoforms in particular as prognostic markers. Kester et al. discovered that especially elevated Tau

protein without proportionally elevated hyperphosphorylated Tau (pTau) might predict fast decline (Kester et al., 2009). Wallin and coworkers recently showed that subjects with very high levels of Tau (>1501 (±292) pg/ml) and pTau (>139 (±39) pg/ml) and at the same time low levels of Aβ1-42 (< 362 (± 66) pg/ml) deteriorate more rapidly and feature high mortality rates (Wallin et al., 2010).

study	slower progression or no influence	faster progression
Adak et al., 2004 (n=225, MRI)		higher ventricular volume
Kinkingnehun et al., 2008 (n=41, MRI, voxel based morphometry)		extensive cortical atrophy
Mungas et al., 2002 (n=120, MRI)		hippocampal atrophy, cortical atrophy
Ridha et al., 2008 (n=52, MRI)	hippocampal atrophy	
Sluimer et al., 2008 (n=65, MRI)	focal hippocampal shrinkage	generalized global atrophy and early onset and <i>Apoε4</i> negative
Swann et al., 1997 (n[AD]=24, MRI)	hippocampal atrophy	

Table 4. Imaging and the prediction of AD disease progression.

It has to be kept in mind that some studies the disease stage might be a confounder: Certain CSF marker levels or patterns could as well reflect the disease stage instead of being indicative or predictive for the deterioration rate. Data from serial, repeatedly performed lumbar punctures and CSF analyses are necessary to control this potential confounding factor. Only a small number of studies on this subject have been performed so far. The follow up intervals were short. Over a period of 24 months CSF Tau, pTau and Aβ1-42 appear to be quite constant (Sunderland et al., 1999; Blennow et al., 2007). This hypothesis has largely been undergirded by Buchave et al. However, they reported slightly increasing Tau values over two years (Buchhave et al., 2009). Contradicting these findings of constancy, Stomrud and colleagues demonstrated pTau to increase in a 4 years observation period. Furthermore this increment seemed to be associated with cognitive decline (Stomrud et al., 2010). Regarding Aβ1-42 levels, Huey and colleagues found these to slightly decrease while Tau staying stable observed over a period of 4 years (Huey et al., 2006).

4.3.2 Genetics

Efforts to investigate genetic predictors in AD have been significantly increased over the past years. A number of polymorphisms found seem to have predictive capability in regards of speed of decline. Nonetheless, several remain subject to discussion and controversy: Among those especially the *Apoε* gene. This polymorphism is a well established modulator of AD disease risk. But its significance as a predictor of progression is not yet as well examined. Some researchers claim, that the presence of the ε4 allele predicts fast

deterioration especially in mild AD (Cosentino et al., 2008). But in opposition, according to van der Vlies, early onset AD is especially rapid, if the subjects are negative for Apoε4 (van der Vlies et al., 2009b). A recent study of our research group came to the same result: the ε4 allele was exceptionally infrequent among rpAD cases (Schmidt et al., 2010). Clues mount up that lacking Apoε4 in AD is not only associated with a faster decline but also a more atypical course (van der Flier et al., 2011).

Nevertheless, the research group of Kester and colleagues found no predictive capability of Apoε whatsoever (Kester et al., 2009). An overview of different genetic markers associated with speed of decline is provided in Table 5.

gene/polymorphism	decline		
	slow	no influence	fast
<i>Apoε4</i>		Kester et al., 2009 (151)	Cosentino et al., 2008 (570)
<i>no Apoε4</i>			van der Vlies et al., 2009b (291) Schmidt et al., 2010 (32) van der Flier et al., 2011
<i>BuChE (K allele)</i>	Holmes et al., 2005 (339)		
<i>G51S PNP (AA genotype)</i>			Tumini et al., 2007 (321)
<i>HMGCR (A allele)</i>			Porcellini et al., 2007 (190+586, 97, 296)
<i>PSEN1 rs3025780 (TG genotype)</i>			Belbin et al., 2009 (714, 169)
<i>PSEN1 rs3025787 (CG genotype)</i>			Belbin et al., 2009 (714, 169)
<i>PSEN1 rs7152131 (CA genotype)</i>	Belbin et al., 2009 (714, 169)		
<i>ACT7 (GC + CC genotype)</i>			Belbin et al., 2008 (688+419)
<i>ACT-17 (AA genotype)</i>			Kamboh et al., 2006 (909)
<i>ACT promoter polymorphism (TT genotype) + Apoε4</i>			Licastro et al., 2005 (422)
<i>IL-1α -889 (*1/*1 genotype)</i>			Murphy et al., 2001 (114)
<i>IL-18 -137 (CC genotype)</i>			Bossu et al., 2007 (339)
<i>FAS -1377 (AG + GG genotype)</i>			Chiappelli et al., 2006 (137+144)
<i>RAGE G82S (GS + SS genotype)</i>			Li et al., 2010 (276+254)

Table 5. Genetic predictors of cognitive deterioration speed in AD Total number of subjects (AD) in the studies are given in parentheses.

5. Conclusion

Until recently, Alzheimer’s disease has been seen as a clinically rather homogeneous disease. But during the last decade several studies have differentiated early onset or late onset entities as well as fast declining forms. Classification and characterization of these disease subentities by means CSF biomarkers and search for indicative patterns as well as neuropsychological test batteries has been attempted. However, comprehensive approaches to characterize AD subtypes relating clinical characteristics to a neuropathological molecular level are lacking (Wilkosz et al., 2010; Doody et al., 2001). Latest pharmacological trials implicated that there may be different subtypes within Alzheimer’s disease exhibiting different susceptibilities to specific pharmacotherapies (Wallin et al., 2009). Hence, a superior characterization of the clinico-pathological heterogeneity and identification of predictive factors of disease progression should be able to improve our understanding of disease pathogenesis and allow better monitoring in therapeutic settings.

	rpAD	classical AD
survival	few years (2-3)	8-10 years
onset	still unclear, around the age of 73yrs in the study of Schmidt et al., 2010	around age 65yrs (below = early onset, above = late onset)
cognitive decline	>6 MMSE pts/yr → fast	approx. 3-6 MMSE pts/yr → slow
focal neurological signs	occurring in early stages, multiple (esp. extrapyramidal signs)	occurring in late stages
CSF biomarkers	very high Tau, very high pTau, very low A beta 1-42, proteins	high Tau, high pTau, low A beta 1-42, proteins 14-3-3
ApoE4	controversial: its influence on decline see Table 4, sometimes seen negative in very rapid cases (Mann et al., 1989)	established as a risk factor

Table 6. Classic AD and rpAD in comparison. Table modified from Schmidt et al., 2011.

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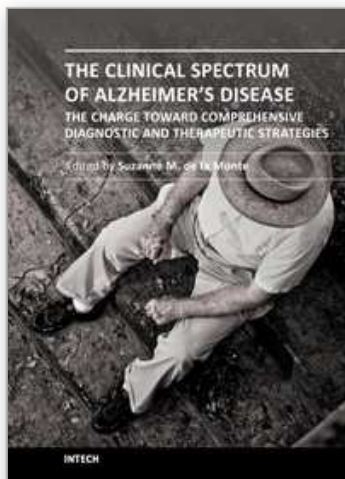
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The Clinical Spectrum of Alzheimer's Disease -The Charge Toward Comprehensive Diagnostic and Therapeutic Strategies

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The Clinical Spectrum of Alzheimer's Disease: The Charge Toward Comprehensive Diagnostic and Therapeutic Strategies is highly informative and current. Acknowledged experts in the field critically review both standard and under-appreciated clinical, behavioral, epidemiological, genetic, and neuroimaging attributes of Alzheimer's disease. The collection covers diverse topics of interest to clinicians and researchers alike. Experienced professionals and newcomers to the field will benefit from the read. The strengths and weaknesses of current clinical, non-invasive, neuro-imaging, and biomarker diagnostic approaches are explained. The perspectives give fresh insights into the process of neurodegeneration. Readers will be enlightened by the evidence that the neural circuits damaged by neurodegeneration are much broader than conventionally taught, suggesting that Alzheimer's could be detected at earlier stages of disease by utilizing multi-pronged diagnostic approaches. This book inspires renewed hope that more effective treatments could be developed based upon the expanding list of potential therapeutic targets.

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