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 been 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 "posteriorcortical 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 Aβ1-42) - 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 Aβ1-42 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 Aβ, 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 visuonstructive impairment, can be found (Boxer et al., 2003). Recent papers reported heterogeneous Aβ deposition patterns in the end stages of the disease with variations throughout the neocortex, which cannot be completely explained by a regular built 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 Aβ 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 presenelin (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 Apoe 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 (Wilksz 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 (Wilkozs 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 (Etiene et al., 1998).

| sign / comorbidity | slow progression | no influence or unclear | fast progression |
|--------------------|------------------|-------------------------|-----------------|
| apathy             |                  |                         | Starkstein et al., 2006 (354) |
| apraxia (constructional) |          |                         | Smith et al., 2001 (60) |
| atherosclerosis, atrial fibrillation, hypercholesterinemia, hypertension, microvascular disease, myocardial infarction | Abellan et al., 2009 (686) | Laukka et al., 2010 (138) |
| hypercholesterinemia, hypertension, microvascular disease, myocardial infarction |             |                         | Mielke et al., 2007 (135) |
| chronic systemic inflammation |                  |                         | Roselli et al., 2009 (162) |
| diabetes mellitus | Sanz et al., 2009 (608) |                         | Roselli et al., 2009 (162) |
| psychotic symptoms |                  |                         | Mangone, 2004 (1000) |
| multitude of focal neurological signs |                  |                         | Wilkosz et al., 2009 (201) |
| 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) |
| early fast decline |                  |                         | Portet et al., 2009 (388) |
| seizures           |                  |                         | Scarmeas et al., 2005 (533) |
| severe cognitive impairment at disease onset | Hui et al., 2003 (mortality) (354) |                         | Atchison et al., 2007 (150) |
| sex (male)         |                  |                         | Soto et al., 2008b (565) |
|                    |                  |                         | Volicer et al., 1995 (language function) (27) |
|                    |                  |                         | Ito et al., 2010 (576) |
|                    |                  |                         | Marra et al., 2000 (45) |
|                    |                  |                         | 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 Aβ1-42 (411pg/ml or less) or a high Tau/Aβ1-42 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 Apoε4 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 Apo4 (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 Apo4 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 |
|-------------------|---------|------|--------------|------|
| Apoε4             |         | Kester et al., 2009 (151) | Cosentino et al., 2008 (570) | van der Vlies et al., 2009b (291) |
|                   | no Apoε4|      |              |      |
| BuChE (K allele)  | Holmes et al., 2005 (339) | Tumini et al., 2007 (321) |
| G51S PNP          |         |      |              | Porcellini et al., 2007 (190+586, 97, 296) |
| (AA genotype)     |         |      |              | Belbin et al., 2009 (714, 169) |
| HMGCR (A allele)  |         |      |              | Belbin et al., 2009 (714, 169) |
| PSEN1 rs3025780   |         |      |              | Belbin et al., 2009 (714, 169) |
| (TG genotype)     |         |      |              | |
| PSEN1 rs3025787   |         |      |              | |
| (CG genotype)     |         |      |              | |
| PSEN1 rs7152131   | Belbin et al., 2009 (714, 169) | |
| (CA genotype)     |         |      |              | |
| ACT7              |         |      |              | |
| (GC + CC genotype)|         |      |              | |
| ACT-17 (AA genotype) |       |      |              | |
| ACT promoter      |         |      |              | |
| polymorphism      |         |      |              | |
| (TT genotype) + Apoε4 |      |      |              | |
| IL-1α -889        |         |      |              | |
| (*1/*1 genotype)  |         |      |              | |
| IL-18 -137 (CC genotype) |   |      |              | |
| FAS -1377         |         |      |              | |
| (AG + GG genotype)|         |      |              | |
| RAGE G82S         |         |      |              | |
| (GS + SS genotype)|         |      |              | |

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 | around age 65yrs (below = early onset, above = late onset) |
|                                | the study of Schmidt et al., 2010          |                                             |
| 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.

6. Acknowledgement

This book chapter is based on “Rapidly progressive Alzheimer’s Disease” (Schmidt et al. accepted for publication in Arch Neurol). The work was supported by the BMBF (Determinants for disease progression in AD, KNDD-2 (German Network for Degenerative Dementia) 2011-2013, grant 016/1010c

7. References

Abellan van Kan, G., Rolland, Y., Nourhashémi, F., Coley, N., Andrieu, S., & Vellas, B. (2009) Cardiovascular disease risk factors and progression of Alzheimer’s disease. *Dement Geriatr Cogn Disord.*, 27(3), 240-246
Adak, S., Illouz, K., Gorman, W., Tandon, R., Zimmerman, E.A., Guariglia, R., et al. (2004) Predicting the rate of cognitive decline in aging and early Alzheimer disease. *Neurology*, 63(1), 108-114

Aksamit, A.J., Preissner, C.M., & Homburger, H.A. (2001) Quantitation of 14-3-3 and neuron-specific enolase proteins in CSF in Creutzfeldt-Jakob disease. *Neurology*, 57(4), 728-730

Armstrong, R.A., Nochlin, D., & Bird, T.D. (2000) Neuropathological heterogeneity in Alzheimer’s disease: a study of 80 cases using principal components analysis. *Neuropathology*, 20(1), 31-37

Atchison, T.B., Massman, P.J., & Doody, R.S. (2007) Baseline cognitive function predicts rate of decline in basic-care abilities of individuals with dementia of the Alzheimer’s type. *Arch Clin Neuropsychol*, 22(1), 99-107

Ballard, C., O’Brien, J., Morris, C.M., Barber, R., Swann, A., Neill, D., et al. (2001) The progression of cognitive impairment in dementia with Lewy bodies, vascular dementia and Alzheimer’s disease. *Int J Geriatr Psychiatry*, 16(5), 499-503

Belbin, O., Beaumont, H., Warden, D., Smith, A.D., Kalischek, N., & Morgan, K. (2009) PSEN1 polymorphisms alter the rate of cognitive decline in sporadic Alzheimer’s disease patients. *Neurobiol Aging*, 30(12), 1992-1999

Belbin, O., Dunn, J.L., Chappell, S., Ritchie, A.E., Ling, Y., Morgan, L., et al. (2008) A SNP in the ACT gene associated with astrocytosis and rapid cognitive decline in AD. *Neurobiol Aging*, 29(8), 1167-1176

Benson, D.F., Davis, R.J., & Snyder, B.D. (1988) Posterior cortical atrophy. *Arc Neurol*, 45(7), 789-793

Bhargava, D., Weiner, M.F., Hynan, L.S., Diaz-Arrastia, R., & Lipton, A.M. (2006) Vascular disease and risk factors, rate of progression, and survival in Alzheimer’s disease. *J Geriatr Psychiatry Neurol*, 19(2), 78-82

Blennow, K., de Leon, M.J., & Zetterberg, H. (2006) Alzheimer’s disease. *Lancet*, 368(9533), 387-403

Blennow, K., Zetterberg, H., Minthon, L., Lannfelt, L., Strid, S., Annas, P., et al. (2007) Longitudinal stability of CSF biomarkers in Alzheimer’s disease. *Neurosci Lett*, 419(1), 18-22

Bossù, P., Ciaramella, A., Moro, M.L., Bellincampi, L., Bernardini, S., Federici, G., et al. (2007) Interleukin 18 gene polymorphisms predict risk and outcome of Alzheimer’s disease. *J Neurol Neurosurg Psychiatr*, 78(8), 807-811

Boxer, A.L., Kramer, J.H., Du, A.-T., Schuff, N., Weiner, M.W., Miller, B.L., et al. (2003) Focal right inferotemporal atrophy in AD with disproportionate visual constructive impairment. *Neurology*, 61(11), 1485-1491

Brooks, J.O., Kraemer, H.C., Tanke, E.D., & Yesavage, J.A. (1993) The methodology of studying decline in Alzheimer’s disease. *J Am Geriatr Soc*, 41(6), 623-628

Buccione, I., Perri, R., Carlesimo, G.A., Fadda, L., Serra, L., Scalmana, S., et al. (2007) Cognitive and behavioural predictors of progression rates in Alzheimer’s disease. *Eur J Neurol*, 14(4), 440-446

Buchhave, P., Blennow, K., Zetterberg, H., Stomrud, E., Londos, E., Andreassen, N., et al. (2009) Longitudinal study of CSF biomarkers in patients with Alzheimer’s disease. *PLoS ONE*, 4(7), e6294
Carcailon, L., Pérès, K., Pérè, J.-J., Helmer, C., Orgogozo, J.-M., & Dartigues, J.-F. (2007) Fast cognitive decline at the time of dementia diagnosis: a major prognostic factor for survival in the community. *Dement Geriatr Cogn Disord, 23*(6), 439-445

Caselli, R.J., Couce, M.E., Osborne, D., Deen, H.G., & Parisi, J.P. (1998) From slowly progressive amnestic syndrome to rapidly progressive Alzheimer disease. *Alzheimer Dis Assoc Disord, 12*(3), 251-253

Chiappelli, M., Nasi, M., Cossarizza, A., Porcellini, E., Tumini, E., Pinti, M., et al. (2006) Polymorphisms of fas gene: relationship with Alzheimer’s disease and cognitive decline. *Dement Geriatr Cogn Disord, 22*(4), 296-300

Clark, C.M., Ewbank, D., Lerner, A., Doody, R., Henderson, V.W., Panisset, M., et al. (1997) The relationship between extrapyramidal signs and cognitive performance in patients with Alzheimer’s disease enrolled in the CERAD Study. Consortium to Establish a Registry for Alzheimer’s Disease. *Neurology, 49*(1), 70-75

Cortes, F., Nourhashemi, F., Guérin, O., Cantet, C., Gillette-Guyonnet, S., Andrieu, S., et al. (2008) Prognosis of Alzheimer’s disease today: a two-year prospective study in 686 patients from the REAL-FR Study. *Alzheimers Dement, 4*(1), 22-29

Cupidi, C., Capobianco, R., Goffredo, D., Marcon, G., Ghezzi, B., Bugiani, O., et al. (2010) Neocortical variation of Abeta load in fully expressed, pure Alzheimer’s disease. *J Alzheimers Dis, 19*(1), 57-68

Cummings, J.L. (2000) Cognitive and behavioral heterogeneity in Alzheimer’s disease: seeking the neurobiological basis. *Neurobiol Aging, 21*(6), 845-861

De Meyer, G., Shapiro, F., Vanderstichele, H., Vanmechelen, E., Engelborghs, S., De Deyn, P.P., et al. (2010) Diagnosis-Independent Alzheimer Disease Biomarker Signature in Cognitively Normal Elderly People. *Arch Neurol, 67*(8), 949-956

Doody, R.S., Massman, P., & Dunn, J.K. (2001) A method for estimating progression rates in Alzheimer disease. *Arch Neurol, 58*(3), 449-454

Dubois, B., Feldman, H.H., Jacova, C., Cummings, J.L., Dekosky, S.T., Barberger-Gateau, P., et al. (2010) Revising the definition of Alzheimer’s disease: a new lexicon. *Lancet Neurol, 9*(11), 1118-1127

Dubois, B., Feldman, H.H., Jacova, C., Dekosky, S.T., Barberger-Gateau, P., Cummings, J., et al. (2007) Research criteria for the diagnosis of Alzheimer’s disease: revising the NINCDS-ADRDA criteria. *Lancet Neurol, 6*(8), 734-746

Dumont, C., Voisin, T., Nourhashemi, F., Andrieu, S., Koning, M., & Vellas, B. (2005) Predictive factors for rapid loss on the mini-mental state examination in Alzheimer’s disease. *J Nutr Health Aging, 9*(3), 163-167

Etiene, D., Kraft, J., Ganju, N., Gomez-Isla, T., Gemelli, B., Hyman, B.T., et al. (1998) Cerebrovascular Pathology Contributes to the Heterogeneity of Alzheimer’s Disease. *J Alzheimers Dis, 1*(2), 119-134
Foster, N., Chase, T.N., Fedio, P., Patronas, N.J., Brooks, R.A., & Di Chiro, G. (1983) Alzheimer's disease: focal cortical changes shown by positron emission tomography. *Neurology*, 33(8), 961-965

Furey-Kurkjian, M., Pietrini, P., Graff-Radford, N., Alexander, G., Freo, U., Szczepanik, J., et al. (1996) The visual variant of Alzheimer's disease: distinctive neuropsychological features. *Neuropsychology*, 10, 294-300

Gauthier, S., Dubois, B., Feldman, H., & Scheltens, P. (2008) Revised research diagnostic criteria for Alzheimer's disease. *Lancet Neurol*, 7(8), 668-670

Gawinecka, J., & Zerr, I. (2010) Cerebrospinal fluid biomarkers in human prion diseases. *Future Neurology*, 5(2), 301-316

Geldmacher, D., Santillan, C., & Fritsch T. (2000) Development of a scale to predict decline among mildly demented Alzheimer disease patients. *Neuropadiatrie*, 31(Suppl 1S), S93

Gelpi, E., Heinzl, H., Hoftberger, R., Unterberger, U., Strobel, T., Voigtlander, T., et al. (2008) Creutzfeldt-Jakob disease in Austria: an autopsy-controlled study. *Neuropadiatrie*, 30(4), 215-221

Goldberg, R.J. (2007) Alzheimer’s disease. *Compr Ther*, 33(2), 58-64

Gorno-Tempini, M.L., Brambati, S.M., Ginex, V., Ogar, J., Dronkers, N.F., Marcone, A., et al. (2008) The logopenic/phonological variant of primary progressive aphasia. *Neurology*, 71(16), 1227-1234

Grady, C.L., Haxby, J.V., Horwitz, B., Sundaram, M., Berg, G., Schapiro, M., et al. (1988) Longitudinal study of the early neuropsychological and cerebral metabolic changes in dementia of the Alzheimer type. *J Clin Exp Neuropsychol*, 10(5), 576-596

Haïk, S., Brandel, J.P., Sazdovitch, V., Delasnerie-Lauprêtre, N., Peoc’h, K., Laplanche, J.L., et al. (2000) Dementia with Lewy bodies in a neuropathologic series of suspected Creutzfeldt-Jakob disease. *Neurology*, 55(9), 1401-1404

Haxby, J.V., Grady, C.L., Koss, E., Horwitz, B., Schapiro, M., Friedland, R.P., et al. (1988) Heterogeneous anterior-posterior metabolic patterns in dementia of the Alzheimer type. *Neurology*, 38(12), 1853-1863

Heinemann, U., Krasnianski, A., Meissner, B., Varges, D., Kallenberg, K., Schulz-Schaeffer, W.J., et al. (2007) Creutzfeldt-Jakob disease in Germany: a prospective 12-year surveillance. *Brain*, 130(Pt 5), 1350-1359

Holmes, C., Ballard, C., Lehmann, D., David Smith, A., Beaumont, H., Day, I.N., et al. (2005) Rate of progression of cognitive decline in Alzheimer’s disease: effect of butyrylcholinesterase K gene variation. *J Neurol Neurosurg Psychiatr*, 76(5), 640-643

Holmes, C., Cunningham, C., Zotova, E., Woolford, J., Dean, C., Kerr, S., et al. (2009) Systemic inflammation and disease progression in Alzheimer disease. *Neurology*, 73(10), 768-774

Huang, N., Marie, S.K., Livramento, J.A., Chammas, R., & Nitrini, R. (2003) 14-3-3 protein in the CSF of patients with rapidly progressive dementia. *Neurology*, 61(3), 354-357

Huey, E.D., Mirza, N., Putnam, K.T., Soares, H., Csako, G., Levy, J.A., et al. (2006) Stability of CSF beta-amyloid(1-42) and tau levels by APOE genotype in Alzheimer patients. *Dement Geriatr Cogn Disord*, 22(1), 48-53

Hui, J.S., Wilson, R.S., Bennett, D.A., Bienias, J.L., Gilley, D.W., & Evans, D.A. (2003) Rate of cognitive decline and mortality in Alzheimer’s disease. *Neurology*, 61(10), 1356-1361
The Clinical Spectrum of Alzheimer’s Disease
– The Charge Toward Comprehensive Diagnostic and Therapeutic Strategies

Iqbal, K., Flory, M., Khatoon, S., Soininen, H., Pirttila, T., Lehtovirta, M., et al. (2005) Subgroups of Alzheimer’s disease based on cerebrospinal fluid molecular markers. *Ann Neurol*, 58(5), 748-757

Ito, K., Ahadieh, S., Corrigan, B., French, J., Fullerton, T., & Tensfeldt, T. (2010) Disease progression meta-analysis model in Alzheimer’s disease. *Alzheimers Dement*, 6(1), 39-53

Jansen, C., Schuur, M., Spliet, W.G.M., van Gool, W.A., van Duijn, C.M., & Rozemuller, A.J.M. (2009) [Eleven years of autopsy on account of Creutzfeldt-Jakob disease in the Netherlands]. *Ned Tijdschr Geneeskd*, 153, A172

Jayaratnam, S., Khoo, A.K.L., & Basic, D. (2008) Rapidly progressive Alzheimer’s disease and elevated 14-3-3 proteins in cerebrospinal fluid. *Age Ageing*, 37(4), 467-469

Johnson, J.K., Head, E., Kim, R., Starr, A., & Cotman, C.W. (1999) Clinical and pathological evidence for a frontal variant of Alzheimer disease. *Arch Neurol*, 56(10), 1233-1239

Josephs, K.A., Ahlskog, J.E., Parisi, J.E., Boeve, B.F., Crum, B.A., Giannini, C., et al. (2009) Rapidly progressive neurodegenerative dementias. *Arch Neurol*, 66(2), 201-207

Kamboh, M.I., Minster, R.L., Kenney, M., Ozturk, A., Desai, P.P., Kamerer, C.M., et al. (2006) Alpha-1-antichymotrypsin (ACT or SERPINA3) polymorphism may affect age-at-onset and disease duration of Alzheimer’s disease. *Neurop Mol Aging*, 27(10), 1435-1439

Kester, M.J., van der Vlies, A.E., Blankenstein, M.A., Pijnenburg, Y.A.L, van Elk, E.J., Scheltens, P., et al. (2009) CSF biomarkers predict rate of cognitive decline in Alzheimer disease. *Neurology*, 73(17), 1353-1358

Kinkingnéhun, S., Sarazin, M., Lehéricy, S., Guichart-Gomez, E., Hergueta, T., & Dubois, B. (2008) VBM anticipates the rate of progression of Alzheimer disease: a 3-year longitudinal study. *Neurology*, 70(23), 2201-2211

Laukka, E.J., Fratiglioni, L., & Bäckman, L. (2010) The Influence of Vascular Disease on Cognitive Performance in the Preclinical and Early Phases of Alzheimer’s Disease. *Dement Geriatr Cogn Disord*, 29(6), 498-503

Li, K., Dai, D., Zhao, B., Yao, L., Yao, S., Wang, B., et al. (2010) Association between the RAGE G82S polymorphism and Alzheimer’s disease. *J Neural Transm*, 117(1), 97-104

Licastro, F., Chiappelli, M., Grimaldi, L.M.E., Morgan, K., Kalsheker, N., Calabrese, E., et al. (2005) A new promoter polymorphism in the alpha-1-antichymotrypsin gene is a disease modifier of Alzheimer’s disease. *Neurop Mol Aging*, 26(4), 449-453

Liu, Y., Stern, Y., Chun, M.R., Jacobs, D.M., Yau, P., & Goldman, J.E. (1997) Pathological correlates of extrapyramidal signs in Alzheimer’s disease. *Ann Neurol*, 41(3), 368-374

Maarouf, C.L., Daugs, I.D., Spina, S., Vidal, R., Kokjohn, T.A., Patton, R.L., et al. (2008) Histopathological and molecular heterogeneity among individuals with dementia associated with Presenlin1 mutations. *Mol Neurodegener*, 3, 20

Mahmoudi, R., Manckoundia, P., Morrone, I., Lang, P.-O., Dramé, M., & Novella, J.-L. (2010) Atypical case of Alzheimer’s disease mimicking Creutzfeldt-Jakob disease: interest of cerebrospinal fluid biomarkers in the differential diagnosis. *J Am Geriatr Soc*, 58(9), 1821-1823
Mangone, C.A. (2004) [Clinical heterogeneity of Alzheimer’s disease. Different clinical profiles can predict the progression rate]. Rev Neurol, Apr 1;38(7), 675-681
Mann, U.M., Mohr, E., Chase, T.N. (1989) Rapidly progressive Alzheimer’s disease. Lancet, 2(8666), 799
McKeith, I.G., Galasko, D., Kosaka, K., Perry, E.K., Dickson, D.W., Hansen, L.A., et al. (1996) Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. Neurology, 47(5), 1113-1124
McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E.M. (1984) Clinical diagnosis of Alzheimer’s disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer’s Disease. Neurology, 34(7), 939-944
Mielke, M.M., Rosenberg, P.B., Tschanz, J., Cook, L., Corcoran, C., Hayden, K.M., et al. (2007) Vascular factors predict rate of progression in Alzheimer disease. Neurology, 69(19), 1850-1858
Mizuno, Y., Ikeda, K., Tsuchiya, K., Ishihara, R., & Shibayama, H. (2003) Two distinct subgroups of senile dementia of Alzheimer type: quantitative study of neurofibrillary tangles. Neuropathology, 23(4), 282-289
Morris, J.C., Edland, S., Clark, C., Galasko, D., Koss, E., Mohs, R., et al. (1993) The consortium to establish a registry for Alzheimer’s disease (CERAD). Part IV. Rates of cognitive change in the longitudinal assessment of probable Alzheimer’s disease. Neurology, 43(12), 2457-2465
Mortimer, J.A., Borenstein, A.R., Gosche, K.M., & Snowdon, D.A. (2005) Very early detection of Alzheimer neuropathology and the role of brain reserve in modifying its clinical expression. J Geriatr Psychiatry Neurol, 18(4), 218-223
Mungas, D., Reed, B.R., Jagust, W.J., DeCarli, C., Mack, W.J., Kramer, J.H., et al. (2002) Volumetric MRI predicts rate of cognitive decline related to AD and cerebrovascular disease. Neurology, 59(6), 867-873
Murayama, S., & Saito, Y. (2004) Neuropathological diagnostic criteria for Alzheimer’s disease. Neuropathology, 24(3), 254-260
Murphy, G.M., Claassen, J.D., DeVoss, J.J., Pascoe, N., Taylor, J., Tinklenberg, J.R., et al. (2001) Rate of cognitive decline in AD is accelerated by the interleukin-1 alpha -889 C allele. Neurology, 56(11), 1595-1597
Paradise, M., Cooper, C., & Livingston, G. (2009) Systematic review of the effect of education on survival in Alzheimer’s disease. Int Psychogeriatr, 21(1), 25-32
Pavlik, V.N., Doody, R.S., Massman, P.J., & Chan, W. (2006) Influence of premorbid IQ and education on progression of Alzheimer’s disease. Dement Geriatr Cogn Disord, 22(4), 367-377
Pietrini, P., Furey, M.L., Graff-Radford, N., Freo, U., Alexander, G.E., Grady, C.L., et al. (1996) Preferential metabolic involvement of visual cortical areas in a subtype of Alzheimer’s disease: clinical implications. Am J Psychiatry, 153(10), 1261-1268
Porcellini, E., Calabrese, E., Guerini, F., Govoni, M., Chiappelli, M., Tumini, E., et al. (2007) The hydroxy-methyl-glutaryl CoA reductase promoter polymorphism is associated with Alzheimer’s risk and cognitive deterioration. Neurosci Lett, 416(1), 66-70
Portet, F., Scarmeas, N., Cosentino, S., Helzner, E.P., & Stern, Y. (2009) Extrapyramidal signs before and after diagnosis of incident Alzheimer disease in a prospective population study. Arch Neurol, 66(9), 1120-1126

Price, B.H., Gurvit, H., Weintraub, S., Geula, C., Leimkuhler, E., & Mesulam, M. (1993) Neuropsychological patterns and language deficits in 20 consecutive cases of autopsy-confirmed Alzheimer’s disease. Arch Neurol, 50(9), 931-937

Price, J.L., McKeel, D.W., Buckles, V.D., Roe, C.M., Xiong, C., Grundman, M., et al. (2009) Neuropathology of nondemented aging: presumptive evidence for preclinical Alzheimer disease. Neurobiol Aging, 30(7), 1026-1036

Querfurth, H.W., & LaFerla, F.M. (2010) Alzheimer’s disease. N Engl J Med, 362(4), 329-344

Reinwald, S., Westner, I.M., & Niedermaier, N. (2004) Rapidly progressive Alzheimer’s disease mimicking Creutzfeldt-Jakob disease. J Neurol, 251(8), 1020-1022

Ridha, B.H., Anderson, V.M., Barnes, J., Boyes, R.G., Price, S.L., Rossor, M.N., et al. (2008) Volumetric MRI and cognitive measures in Alzheimer disease: comparison of markers of progression. J Neurol, 255(4), 567-574

Ritchie, K., & Touchon, J. (1992) Heterogeneity in senile dementia of the Alzheimer type: individual differences, progressive deterioration or clinical sub-types? J Clin Epidemiol, 45(12), 1391-1398

Roselli, F., Tartaglione, B., Federico, F., Lepore, V., Defazio, G., & Livrea, P. (2009) Rate of MMSE score change in Alzheimer’s disease: influence of education and vascular risk factors. Clin Neurol Neurosurg, 111(4), 327-330

Santillan, C.E., Fritsch, T., & Geldmacher, D.S. (2003) Development of a scale to predict decline in patients with mild Alzheimer’s disease. J Am Geriatr Soc, Jan;51(1), 91-95

Sanz, C., Andrieu, S., Sinclair, A., Hanaire, H., & Vellas, B. (2009) Diabetes is associated with a slower rate of cognitive decline in Alzheimer disease. Neurology, 73(17), 1359-1366

Scarmeas, N., Albert, M., Brandt, J., Blacker, D., Hadjigeorgiou, G., Papadimitriou, A., et al. (2005) Motor signs predict poor outcomes in Alzheimer disease. Neurology, 64(10), 1696-1703

Schmidt, C., Redyk, K., Meissner, B., Krack, L., von Ahsen, N., Roeber, S., et al. (2010) Clinical features of rapidly progressive Alzheimer’s disease. Dement Geriatr Cogn Disord, 29(4), 371-378

Schmidt, C., Wolff, M., Weitz, M., Bartlau, T., Korth, C., & Zerr I. (2011) On rapidly progressive Alzheimer’s disease. Arch Neurol. Accepted for publication.

Silvestrini, M., Pasqualetti, P., Baruffaldi, R., Bartolini, M., Handouk, Y., Matteis, M., et al. (2006) Cerebrovascular reactivity and cognitive decline in patients with Alzheimer disease. Stroke, 37(4), 1010-1015

Sloane, P.D., Zimmerman, S., Suchindran, C., Reed, P., Wang, L., Boustani, M., et al. (2002) The public health impact of Alzheimer’s disease, 2000-2050: potential implication of treatment advances. Annu Rev Public Health, 23, 213-231

Sluimer, J.D., Vrenken, H., Blankenstein, M.A., Fox, N.C., Scheltens, P., Barkhof, F., et al. (2008) Whole-brain atrophy rate in Alzheimer disease: identifying fast progressors. Neurology, 70(19 Pt 2), 1836-1841

Smith, M.Z., Esiri, M.M., Barneton, L., King, E., & Nagy, Z. (2001) Constructional apraxia in Alzheimer’s disease: association with occipital lobe pathology and accelerated cognitive decline. Dement Geriatr Cogn Disord, 12(4), 281-288
Soto, M.E., Andrieu, S., Arbus, C., Ceccaldi, M., Couratier, P., Dantoine, T., et al. (2008a) Rapid cognitive decline in Alzheimer’s disease. Consensus paper. J Nutr Health Aging, 12(10), 703-713

Soto, M.E., Andrieu, S., Cantet, C., Reynish, E., Ousset, P.-J., Arbus, C., et al. (2008b) Predictive value of rapid decline in mini mental state examination in clinical practice for prognosis in Alzheimer’s disease. Dement Geriatr Cogn Disord, 26(2), 109-116

Starkstein, S.E., Jorge, R., Mizrahi, R., & Robinson, R.G. (2006) A prospective longitudinal study of apathy in Alzheimer’s disease. J Neurol Neurosurg Psychiatry, 77(1), 8-11

Stern, Y. (2006) Cognitive reserve and Alzheimer disease. Alzheimer Dis Assoc Disord, 20(Suppl 2), S69-74

Stomrud, E., Hansson, O., Zetterberg, H., Blennow, K., Minthon, L., & Londos, E. (2010) Correlation of longitudinal cerebrospinal fluid biomarkers with cognitive decline in healthy older adults. Arch Neurol, 67(2), 217-223

Storanndt, M., Grant, E.A., Miller, J.P., & Morris, J.C. (2002) Rates of progression in mild cognitive impairment and early Alzheimer’s disease. Neurology, 59(7), 1034-1041.

Sunderland, T., Wolozin, B., Galasko, D., Levy, J., Dukoff, R., Bahro, M., et al. (1999) Longitudinal stability of CSF tau levels in Alzheimer patients. Biol Psychiatry, 46(6), 750-755

Swann, A., O’Brien, J., Ames, D., Schweitzer, I., Desmond, P., & Tress, B. (1997) Does hippocampal atrophy on MRI predict cognitive decline? A prospective follow-up study. Int J Geriatr Psychiatry, 12(12), 1182-1188

Tom, T., Cummings, J.L., & Pollak, J. (1998) Posterior cortical atrophy: Unique features. NNCS, 4(1), 15-20

Tschampa, H.J., Neumann, M., Zerr, I., Henkel, K., Schröter, A., Schulz-Schaeffer, W.J., et al. (2001) Patients with Alzheimer’s disease and dementia with Lewy bodies mistaken for Creutzfeldt-Jakob disease. J Neurol Neurosurg Psychiatry, 71(1), 33-39

Tumini, E., Porcellini, E., Chiappelli, M., Conti, C.M., Beraudi, A., Poli, A., et al. (2007) The G51S purine nucleoside phosphorylase polymorphism is associated with cognitive decline in Alzheimer’s disease patients. Hum Psychopharmacol, 22(2), 75-80

van der Flier, W.M., Pijnenburg, Y.A., Fox, N.C., & Scheltens P. (2011) Early-onset versus late-onset Alzheimer’s disease: the case of the missing APOE ε4 allele. Lancet Neuro, 10(3), 280-8

van der Vlies, A.E., Koedam, E.L.G.E., Pijnenburg, Y.A.L., Twisk, J.W.R., Scheltens, P., van der Flier, W.M. (2009a) Most rapid cognitive decline in APOE epsilon4 negative Alzheimer’s disease with early onset. Psychol Med, 39(11), 1907-1911

van der Vlies, A.E., Verwey, N.A., Bouwman, F.H., Blankenstein, M.A., Klein, M., Scheltens, P., et al. (2009b) CSF biomarkers in relationship to cognitive profiles in Alzheimer disease. Neurology, 72(12), 1056-1061

Van Everbroeck, B., Dobbeleir, I., De Waele, M., De Deeyn, P., Martin, J.-J., & Cras, P. (2004) Differential diagnosis of 201 possible Creutzfeldt-Jakob disease patients. J Neurol, 251(3), 298-304

Volicer, L., Smith, S., & Volicer, B.J. (1995) Effect of seizures on progression of dementia of the Alzheimer type. Dementia, 6(5), 258-263
Walker, L.C., Rosen, R.F., & Levine, H. (2008) Diversity of Aβeta deposits in the aged brain: a window on molecular heterogeneity? Rom J Morphol Embryol, 49(1), 5-11

Wallin, A.K., Blennow, K., Zetterberg, H., Londos, E., Minthon, L., & Hansson, O. (2010) CSF biomarkers predict a more malignant outcome in Alzheimer disease. Neurology, 74(19), 1531-1537

Wallin, A.K., Hansson, O., Blennow, K., Londos, E., & Minthon, L. (2009) Can CSF biomarkers or pre-treatment progression rate predict response to cholinesterase inhibitor treatment in Alzheimer’s disease? Int J Geriatr Psychiatry, 24(6), 638-647

Weller, R.O. (2001) How well does the CSF inform upon pathology in the brain in Creutzfeldt-Jakob and Alzheimer’s diseases? J Pathol, 194(1), 1-3

Wilkosz, P.A., Seltman, H.J., Devlin, B., Weamer, E.A., Lopez, O.L., DeKosky, S.T., et al. (2010) Trajectories of cognitive decline in Alzheimer’s disease. Int Psychogeriatr, 22(2), 281-290

Wisniewski, H.M., Bancher, C., Barcikowska, M., Wen, G.Y., & Currie, J. (1989) Spectrum of morphological appearance of amyloid deposits in Alzheimer’s disease. Acta Neuropathol, 78(4), 337-347
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.

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following:

Schmidt C, Wolff M, Shalash A and Zerr I (2011). Risk Factors for Disease Progression in Alzheimer's Disease, The Clinical Spectrum of Alzheimer's Disease -The Charge Toward Comprehensive Diagnostic and Therapeutic Strategies, Dr. Suzanne De La Monte (Ed.), ISBN: 978-953-307-993-6, InTech, Available from: http://www.intechopen.com/books/the-clinical-spectrum-of-alzheimer-s-disease-the-charge-toward-comprehensive-diagnostic-and-therapeutic-strategies/risk-factors-for-disease-progression-in-alzheimer-s-disease
