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The Time Onset of Post Stroke Dementia

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1. Introduction

In a population of 1 million inhabitants, 2400 patients will have a stroke every year, of whom fewer than 50% will be independent 1 year later (Hankey & Warlow, 1999). Many independent survivors have residual physical or cognitive deficits, or behavioural changes which can affect family life and have professional consequences (Leys et al. 2002). Post Stroke Dementia (PSD), that includes any dementia after stroke, irrespective of its cause, is therefore a clinical syndrome – and not a disease – and it appears to be one of the main causes of dependency in stroke survivors.

An huge increase in prevalence and burden of PSD is likely to happen (Mackowiak-Cordolani et al. 2005) because of the decline in mortality after stroke (Rothwell et al. 2004) and ageing of populations.

Therefore, stroke has been found to be a strong predictor of dementia. This association is present both for clinically apparent strokes as well as for subclinical strokes. More than 25% of patients develop dementia after their first or recurrent stroke. The prevalence is slightly lower when patients with pre stroke cognitive impairment are excluded. On the other hand, the diagnosis of vascular dementia (VaD) remains a controversial issue in many aspects and concepts. These nosologic problems are caused both by the methods, insufficient to ascertain the diagnosis, as well as by the weak consistency of the clinical concept of VaD itself. VaD is defined as a combination of clinical and neuropathological manifestations characterized by dementia in association with variegated brain lesions of vascular or circulatory origin (Ferrer, 2010); PSD obviously includes all cases of VaD but also these cases where stroke adds to an already clinically evident neurodegenerative cognitive impairment. One of the most intriguing issues on VaD, and in particular on PSD, is related to the time of development of cognitive decline.

In clinical practice, the 3-month time threshold is usually chosen to enable resolution of a possible acute post-stroke delirium, and to obtain a more reliable cognitive assessment with a complete regression of acute neuropsychological stroke-related deficits. As a matter of fact, it has been found that most cognitive impairments after stroke, in particular visual memory and visuospatial construction, resolve beyond the subacute time period. Moreover, as the time after stroke increases, so does the likelihood that an individual might have other cerebrovascular injuries that could further contribute to impair cognition.

The time course of PSD is strictly related to its pathophysiology: it may be 1) the direct consequence of a vascular lesion; 2) due to the additive effect of recurrent strokes and white matter lesions; 3) the result of pre-existing neuropathological Alzheimer's Disease (AD) or similar neurodegenerative dementias, such as Lewy Body Dementia (LBD) or Fronto-Temporal Dementia (FTD). Concerning these neurodegenerative conditions, it is not clear if the effect of stroke on dementia is due to a direct increase in neuropathological changes associated with AD-LBD-FTD, or to the synergic effect of AD-LBD-FTD pathology and vascular pathology.

Another relevant issue is the possibility to predict which patient will develop PSD. In this regard, recent data indicate an overlap between AD-LBD-FTD and PSD, which seems to share risk factors and neuropathology. In most population samples these disorders appear together, and the consensus is growing that a degenerative component has a more important role in determining PSD onset shortly after stroke than previously recognized. Therefore, anamnestic data have a fundamental role in this prognostic approach.

In this chapter, the authors try to clarify the "mystery" of the time onset of PSD. They will start with an overview concerning the new pathogenetic determinants of PSD. Later, they will attempt to offer a systematic analysis of the amount of data concerning PSD itself. PSD and its onset time really are a dilemma; aim of this chapter is to suggest a new potential approach to make clarity in this puzzled question.

2. Timing of Vascular Dementia (VaD) and Post Stroke Dementia (PSD)

One of the most intriguing issues on VaD, and in particular on PSD, is the time course of the development of cognitive decline. In other words, what is the "correct" timing to define "demented" a stroke patient? Tatemichi 21 years ago was the first to put VaD in a temporal context, by observing that 3 months after stroke about one fourth of the patients developed PSD (Tatemichi et al., 1990). Several subsequent studies confirmed this finding, so the time relationship between stroke and cognitive decline was included in the diagnostic criteria for VaD.

Nevertheless, this time interval has been variously faced by different diagnostic criteria. In the ADDTC criteria the diagnosis of ischemic vascular dementia is "probable" when in addition to dementia there is "evidence of two or more ischemic strokes by history, neurologic signs, and/or a single stroke with a clearly documented temporal relationship to the onset of dementia" (Chui et al., 1992).

In the NINDS–AIREN criteria the relationship between stroke and dementia is "within 3 months after a recognized stroke"; however, this time relationship is not mandatory. In fact, a diagnosis of VaD is also probable when a patient presents "abrupt deterioration of cognitive functions after stroke or fluctuating, stepwise progression of cognitive deficits" (Roman et al., 1993). In the ICD-10 criteria for VaD, subdivided into ethiologic subtypes, VaD with acute onset is a dementia developing rapidly (i.e. usually within 1 but no longer than 3 months) after a succession of strokes, or (rarely) after a single large infarction. The diagnosis of VaD due to multi-infarcts is even more vague, being the onset of dementia "more gradual (i.e. within 3–6 months) and following a number of minor ischemic episodes" (WHO, 1989).

In clinical practice, the 3-month time threshold is usually chosen to enable resolution of a possible acute post-stroke delirium and to obtain a more reliable cognitive assessment with a complete regression of acute neuropsychological stroke-related deficits. On the other hand, about 50% of acute stroke patients may show some improvement in global cognition up to 1 year after stroke (Ballard et al., 2003). Long-term improvement in generalized cognitive function seems to occur more frequently in patients who have experienced left hemisphere infarctions or very severe hemispheric stroke syndromes.

On the contrary, diabetes mellitus seems to compromise the ability to achieve long-term improvement in cognitive function after stroke, both ischemic and hemorrhagic, suggesting that management of this important vascular risk factor should be performed with care and consistency (Desmond et al., 1996; Tham et al., 2002). Recent data show evidence for an overlap between Alzheimer's disease (AD) and PSD, which appear to share risk factors and neuropathology (Snowdon et al., 1997; O'Brien et al., 2003). Whether the relationship between AD and PSD in determining cognitive decline is "additive" or due to a "cause–effect" mechanism remains to be determined. In most population samples, these two disorders appear together, and the consensus is growing that a degenerative component has a more important role in determining the PSD onset shortly after stroke than previously recognized (Roman & Royall, 2004; Rockwood et al., 1999). Substantial data indicate that comorbid ischemic cerebrovascular disease may contribute to convert patients with "preclinical AD" to a clinical form, thus unmasking, and anticipating, a previous pathological process (de la Torre, 2002).

What is said for AD probably is true for the other degenerative dementias as well, therefore in this Chapter we will use the definition of AD-LBD-FTD to indicate the main group of these neurodegenerative processes. Clinicians rarely diagnose AD until pathology has reached the cortical regions related to executive functions (Royall, 2002). If executive impairment caused by sub-cortical vascular disease is superimposed on AD pathology, then clinical AD is likely to be diagnosed earlier (Roman & Royall, 2004).

In this view, the occurrence of a new vascular lesion might unbalance a previous equilibrium thus revealing a "clinical" dementia syndrome. Therefore, anamnestic data have a fundamental role in the prognostic approach. Clinically, previous cognitive status and post-stroke delirium show an important correlation with the future development of PSD (Rothwell et al., 2005; Henon et al., 1999). Anatomical location of the lesion and its volume are also important (Gold et al., 2005). All the other risk factors for VaD and for stroke show a correlation, but this is probably due to the chance of new vascular events, including the silent strokes (Vermeer et al., 2003). Whether PSD represents the same clinical and pathological entity from the early phase up to the following years remains to be determined.

2.1 Post Stroke Dementia: A misleading definition

The comprehension of the pathophysiological phenomena influencing the time onset of cognitive decline after stroke is very complex, and involves researchers in different fields, such as pathologists, neuroradiologists, molecular biologists and physicians.

The term PSD includes all kinds of dementia developing after stroke, independently of the intrinsic features of the stroke itself. This term is probably become outdated, because its concept was conceived when researchers supposed that just the occurrence of stroke could

be responsible of the cognitive impairment and, subsequently, of dementia. Now, data show that this is a quite uncommon eventuality

In fact, in the largest number of cases, the occurrence of stroke seems to be only the clinical sign of an underlying vessels' disease. Nevertheless, it has been suggested that this vessels' disease could have a key role in the pathogenesis of vascular and neurodegenerative dementias.

Perhaps, VaD and sporadic AD-LBD-FTD could have a common origin, like a vascular disorder that affects the vessel wall (particularly the two inner layers), and that may have a wide range of clinical presentations. This heterogeneity is probably related to genetic differences between individuals; in fact, the genotypic variety allows the existence of different phenotypes. Because of those aforementioned concepts, epidemiological studies are not designed with uniform criteria (Pendlebury, 2009), since it is difficult to create a consensus concerning which kind of demented stroke patient deserves to be enrolled. In addition, many factors can influence the prevalence and incidence of PSD such as: the mean age of the study population, the exclusion or not of patients with aphasia or severe physical disability, the mortality rates, the delay between stroke onset and the cognitive assessment, the criteria used for the diagnosis of dementia, the presence of a previous cognitive impairment or dementia (Pendlebury, 2009).

Currently, we can safely affirm that: 1) the occurrence of stroke doubles the risk of PSD; 2) the attributable risk is the highest within the first year after stroke, then declines, while the relative risk of dementia remains stable around 2; 3) the risk of delayed dementia, including Alzheimer's disease (AD) and the other neurodegenerative dementias (LBD, FTD), also remains doubled 10 years and more after stroke. Researchers tried to fill this knowledge gap through the identification of the cause-effect relationship between specific pathological conditions and PSD. In particular, considerable efforts have been made in the attempt of understanding the role of specific cardiovascular risk factors determining PSD itself. In the Authors' opinion, the basic issues of this intense research activity are five, at least. They are: 1) What are the pathophysiological mechanisms of PSD?; 2) What are the risk factors more related to the development of PSD? 3) And which of them are more related to time onset of PSD? 4) Is it possible to create homogeneous groups of patients in order to perform a risk stratification of PSD? 5) Would it be possible to create a risk stratification also with regard to the time onset of PSD?

Obviously, it seems almost superfluous to say that no one has been able to give a satisfying answer to these fundamental questions. Until now, at least. However, it is precisely from these facts, apparently in conflict with each other, that we can draw the starting point not only to give a unified view of PSD, but also to explain the dilemma related to its onset time.

2.1.1 Role of risk factors

Currently, the state of affairs is quite garbled and there are no definitive data on this topic. However, scientific evidence allowed to set aside the idea that PSD is just the result of the occurrence of stroke. In fact, if the acute cerebrovascular event was the only responsible for the development of cognitive impairment, we would not be able to explain why not all stroke patients develop PSD.

In addition, we would not even have any plausible elucidation for the different time of onset of dementia in some patients than in others. Reported risk factors for pre- and post-stroke dementia are not always consistent between studies, probably owing to small sample sizes. To overcome this problem, available data was combined in a meta-analysis to attempt to determine the most significant factors involved in the development of PSD (Pendlebury et al., 2009).

All but one study addressed to the risk factors associated with pre-stroke dementia include patients with first ever and with recurrent stroke, so many of the patients will have had a past history of stroke. Patients with pre-stroke dementia are significantly older (weighted mean difference = 9.1, 8.4–9.8 years $p < 0.0001$) than those without pre-stroke dementia. Rates are also significantly higher in women and in those with little education, and in patients with medial temporal lobe atrophy, family history of dementia, previous stroke or TIA, leukoaraiosis, multiple infarcts, diabetes, atrial fibrillation, hypertension, and global cerebral atrophy (Pendlebury et al., 2009). Post-stroke dementia, like pre-stroke dementia, is associated with older age (weighted mean difference = 5.1, 4.6–5.7, years $p < 0.0001$) and low educational attainment, and also prior cognitive decline and premorbid disability (Pendelbury et al., 2009).

Associated vascular risk factors include diabetes and atrial fibrillation but not hypertension, ischemic heart disease, cholesterol, prior TIA or smoking. However, the majority of factors associated with post-stroke dementia are related to the stroke itself, and include hemorrhagic stroke, left hemisphere stroke, dysphasia, stroke severity, infarct volume, and the presence of multiple strokes separated in space and time (previous stroke, multiple infarcts, and recurrent stroke). Certain complications of stroke including incontinence, early seizures, acute confusion, hypoxic ischemic episodes and hypotension are also strongly associated with post-stroke dementia.

Being Caucasian is protective in comparison to black or Hispanic. It is unlikely that all the factors listed in are independent predictors of post-stroke dementia. Non-stroke-related risk factors that tend to remain significantly predictive of post-stroke dementia in multivariate analyses are age, low educational attainment, diabetes, atrial fibrillation, and leukoaraiosis (Pendlebury et al., 2009).

Therefore, although these risk factors are statistically independent, they could still be confounded by stroke-related factors. For example, atrial fibrillation and diabetes are associated with symptomatic stroke, asymptomatic stroke on imaging, recurrent stroke, multiple stroke lesions, and severity of stroke; and leukoaraiosis is associated with stroke severity and stroke recurrence. The factors associated with pre-stroke dementia are broadly similar to those for post-stroke dementia, perhaps unsurprisingly, since all but one study on the predictors of pre-stroke dementia include patients with recurrent as well as first-ever stroke. In pre-neuroimaging era, Fazio and Loeb frequently affirmed that in the past history of demented patients, the occurrence of TIAs was more frequent that in the general population. Medial temporal lobe atrophy, female sex and family history of dementia are much stronger predictors of pre- than post-stroke dementia, suggesting a more important role for primary degenerative pathology in pre-stroke dementia. Interestingly, hypertension, ischemic heart disease and prior TIA were associated with pre- but not post-stroke dementia. The fact that hypertension was not associated with post-stroke dementia may also be explained by the fact that hypertension is very common in both patients with and

without post-stroke dementia. Atrial fibrillation is associated with both pre- and post-stroke dementia, presumably since its prevalence increases with age, and it is linked to multiple and recurrent strokes and increased stroke severity. There is also some evidence that atrial fibrillation is associated with cognitive impairment and hippocampal atrophy in the absence of symptomatic stroke or even silent infarction (Ott, 1997; Knecht, 2008). Diabetes is a known risk factor for dementia and mild cognitive impairment and is associated with both pre- and post-stroke dementia. In addition to age-related physiological decline, diabetes disturbs microvascular functions through mechanisms including activation of protein kinase C, excess production of reactive oxygen species and cellular activation of the receptor for advanced glycation endproducts (RAGE). Further, animal studies show that diabetes exacerbates post-stroke brain damage (Zhang et al., 2009) and there is evidence that diabetes is associated with reduced recovery of cognitive function after stroke (Nys et al., 2005).

As a matter of fact, it is difficult to give an accurate image of the role that every risk factor could have in the pathogenesis of PSD. This syndrome seems to be a real complex phenomenon, and each of them could probably determine PSD with a power that is different for every patient.

In conclusion, stroke could be the acute event that reveals an underlying cognitive impairment. Probably, it would be essential to read between the lines, understanding the limits of research and the restricted margins of our classifications criteria. In the future, scientific evidences will maybe force us to give a new interpretation of these elements, that could be viewed like various components of the same pathological process.

Four major determinants deserve to be mentioned, in order to better clarify what it has been said. They are: 1) demographic and medical characteristics of the patient with PSD and their influence on stroke outcome, 2) neuroimaging characteristics, 3) stroke characteristics, 4) pre-existing pathological alterations. (Pendelbury et al., 2009).

These elements are crucial for the understanding of the most accredited theories about the ethiology of PSD, but especially to recognize the state of knowledge on its onset time.

2.1.2 Demographic and medical characteristics of the patient with PSD and their influence on stroke outcome

The most important demographic predictors of dementia after stroke, in sufficiently powered studies, are increasing age and low education level, but not gender, when the analysis is adjusted for age (Zhu et al., 2000).

The risk of dementia after stroke is higher in patients who were already dependent before stroke (Zhu et al., 2000). Pre-stroke cognitive decline without dementia, assessed by standardized questionnaires, is obviously associated with a higher risk of dementia after stroke (Zhu et al., 2000; Snowdon et al., 1997).

Diabetes mellitus, atrial fibrillation and myocardial infarction were also independent risk factors for dementia after stroke in several studies. (Zhu et al., 2000). Arterial hypertension, a risk factor for VaD and AD, has not been clearly identified as a risk factor for PSD. Epileptic seizures (Esiri et al., 1999), sepsis, cardiac arrhythmias and congestive heart failure are independently associated with an increased risk of dementia after stroke (Zhu et al., 2000).

However, the statistical relationship found between these disorders and dementia does not mean a causal relationship: it is also possible that dementia increases the risk of such events (Zhu et al., 2000). The influence of hyperlipidemia, hyperhomocysteinemia, alcohol consumption and cigarette smoking on dementia after stroke remains unproven (Zhu et al., 2000). The results concerning cigarette smoking should be interpreted with caution, because smoking influences mortality and stroke recurrence. ApoE4 genotype is associated with an increased risk of dementia after stroke (de la Torre, 2002).

The most common causes of PSD are VaD, AD-BLD-FTD and mixed dementia (Leys et .al., 2005). AD-BLD-FTD, mixed AD-BLD-FTD and VaD account for 19-61% of patients with PSD. Vascular lesions have a prominent role in the development of PSD in the following circumstances: patients with stroke who are too young to have AD-BLD-FTD, and who have dementia just after stroke; when cognitive functions were normal before stroke, impaired immediately after, and did not worsen or improve over time; when a specific vascular condition known to cause stroke and dementia is proven by a specific marker; and when the lesion is located in a strategic area (Alexander & Freedman, 1984; Benson & Cummings, 1982; Bhatia & Marsden, 1994; Ott & Saver, 1993).

Even when vascular lesions, Alzheimer's pathology and white matter changes do not lead to dementia by themselves, their cumulative effect can reach the threshold of lesions required to produce dementia (Pasquier & Leys, 1997); as well as when stroke, white matter changes, or both, occur in a patient with asymptomatic Alzheimer's pathology, the period of preclinical AD might be shortened (Pasquier & Leys, 1997). This hypothesis is supported by the results of several studies. In the Optima and in the Nun studies, among patients who met neuropathological criteria for AD, those with brain infarcts had poorer cognitive functions and a higher prevalence of dementia (Nagy et al., 1997; Snowdon et al., 1997). In the dementia substudy of the Systolic Hypertension in Europe Trial (SYST-EUR), nitrendipine decreased the incidence rate of stroke and AD (Forette et al., 1998), suggesting that stroke prevention reduces the risk of new-onset AD; previous cognitive decline and no dementia, likely to be degenerative in origin in most patients (Henon et al., 1995), is a risk factor for PSD (Henon et al., 2001). Most patients with previous cognitive decline and no dementia who developed PSD have a clinical presentation of AD, but it occurs months after a stroke.

The concept of mixed dementia might be useful for those patients because it emphasizes that these patients should be treated for AD but should also receive an appropriate therapy to prevent stroke. Treatment of these patients as thought they have AD, even if the time-course suggests AD, may make practitioners ignore the vascular component that is treatable, especially if the stroke occurs years before.

Moreover, both population-based studies (Aevarsson et al., 1995; Baldereschi et al., 1999; Woo et al., 1992; Tatemichi et al., 1994) and hospital based (Roth, 1955) studies have shown that patients with PSD have higher mortality rates than patients without dementia, independent of age and comorbidities (Aevarsson et al., 1995). The long term mortality rate is two to six times higher in patients with PSD, after adjustement for demographic factors, associated cardiac diseases, stroke severity and stroke recurrence (Desmond et al., 2002; Henon et al., 2003; Tatemichi et al., 1994). In patients with pre-existing dementia, mortality rates are two to five times higher (Barba et al., 2002; Henon et al., 2003). The increased

mortality among patients with PSD might be the result of several factors; 1) patients with dementia of any cause have high mortality (Helmer et al., 2001); 2) Stroke mortality may be high in patients with dementia (Helmer et al., 2001); 3) Dementia is associated with more severe vascular diseases and a higher risk of complications (Tatemichi et al., 1994); 4) Dementia may worsen co-occuring disorders; patients with dementia may receive less aggressive stroke prevention (Rockwood et al., 1997; Gurwitz et al., 1997), and less appropriate treatment of associate disorders (Krumholz et al., 1996) although causes of death can be similar in patients with and without PSD and management was similar for both groups in the Lille Study (Barba et al., 2002; Henon et al., 2003); 5) Patients with PSD may be less compliant to treatments necessary for stroke prevention (i.e. antithrombotic agents and treatment of vascular risk factors), which could lead to less effective prevention of new vascular events and a higher mortality rate. Furthermore, the New York study (Moroney et al., 1997) has demonstrated that dementia diagnosed 3 months after stroke was associated with a three times greater increased risk of stroke recurrence (relative risk: 2.71; 95% CI 1.36 – 5.42).

Dementia might be a marker for a more severe vascular disease leading to an increased risk of recurrence, but also an indicator of a less intensive stroke prevention and lack of compliance that can contribute to the increased risk of recurrence (Moroney et al., 1997). White matter changes could also be a confounding factor because they are associated with an increased risk of stroke recurrence (Henon et al., 2001).

In addition, the few data on the influence of PSD on functional outcome suggest that patients with PSD are more impaired and more dependent in daily living activities than patients with stroke who do not develop PSD (Tatemichi et al., 1990; Tatemichi et al., 1992; Barba et al., 2000; Lin et al., 2003; Prencipe et al., 1997).

In conclusions, many efforts have been made to define which kind of patient is at increased risk of PSD, but there are no definitive data. For the majority of the patients, the occurrence of stroke is only the clinical expression of a just advanced pathological process, which affect the brain and will lead to the loss of cognitive functions.

In this context, time of onset of PSD is strictly related to the pre-stroke conditions of the patient's brain. Actually, all the evidences confirm that dementia will occur more rapidly in individuals with the worst cognitive and clinical status. The strict connection between cardiovascular risk factors and PSD and the overlapping between VaD, particularly PSD, and AD-BLD-FTD, corroborate the hypothesis about the existence of a common pathogenetic mechanism (a vessel's wall disease), responsible not only for the pathogenesis of the classical "cardiovascular" risk factors, but also for a chronic brain hypoperfusion, which could cause/increase/accelerate the neurodegeneration of specific genetically predisposed neuronal populations and represent the starting point for VaD.

Obviously, the matter is quite complex, and there are no definitive data. This happens for many reasons, mainly related to the differences in inclusion criteria for subjects enrolled in clinical trials. We must also remember that all involved variables, particularly cardiovascular risk factors, have a wide range of clinical presentations between individuals, with a degree of complexity that is difficult to describe with a statistical program. So, it is very difficult to define the correct role that each of them could have in causing the occurrence of PSD and its onset time.

Later, the authors will attempt to clarify these concepts, starting from the assumption that every risk factor should not be considered independently from the others, but that each of them can be considered the epiphenomenon of the abovementioned underlying vascular disease. This perspective is of considerable relevance, because it allows a unique view of the heterogeneous landscape described in this chapter.

2.1.3 Neuroimaging charateristics

To our best knowledge, there is no study with functional neuroimaging techniques such a SPECT, PET, functional MRI, or spectroscopy, addressed to identify predictors of PSD in large series of consecutive patients with stroke. Functional neuroimaging studies have provided a useful conceptual framework for the understanding of VaD, but were not addressed to PSD. Plain neuroimaging has shown the frequent occurrence of silent infarcts, that is cerebral infarcts seen on CT or MRI scans that have never been associated with a corresponding neurological deficit. One study found no relation between silent infarcts and PSD (Bornstein et al. 1996), but the assessment of the pre-existing cognitive status was not standardized, and the study was underpowered. Other studies clearly identified silent infarcts as independent predictors of PSD (Tatemichi et al., 1990; Desmond et al., 2000; Henon et al., 2001; Pohjasvaara et al., 2000).

The influence of silent infarcts is more important when the delay between stroke and cognitive assessment is longer. In the Lille study, silent infarcts were associated with PSD in the third year but not in the second (Corea et al., 2001), and in the Maastricht study silent infarcts were independently related to dementia after 1 year, but not after 1 month or 6 months (Rasquin et al., 2004).

Global cerebral atrophy is associated with a higher risk of PSD (Linden et al., 2004; Desmond et al., 2000; Tang et al., 2004; Altieri et al., 2004; Ivan et al., 2004; Tatemichi et al., 1993).

Medial temporal lobe atrophy (MTLA) is most common in patients with stroke who have preexisting dementia (Henon H et al., 1998), but it can also be present in patients with stroke and no dementia. In the Lille study the cumulative proportion of 3-year survivors free of dementia was significantly lower in patients with MLTA (57.6% vs 80.8%) (Cordoliani-Mackowak et al., 2003).

MLTA clearly differentiates patients with dementia from those who do not have dementia after a first-ever ischaemic stroke, even after exclusion of patients who have pre-stroke cognitive impairment (Pohjasvaara et al., 2000; Ballard et al., 2003). Patients with stroke with MLTA might have a pre-clinical AD, which is clinically revealed by stroke (Pasquier & Leys, 1997). However, MLTA is not specific to AD, as it has also been observed in VaD (Jobst et al., 1998; Fein et al., 2000). In elderly patients with stroke and no dementia (with moderate to severe MLTA) after adjusting for age, volume of infarcts and cortical atrophy, do notably worse in tests of learning, story recall, visual reproduction, block design, and mental speed (Jokinen et al., 2004), suggesting that, in elderly patients who have stroke but no dementia, MLTA is associated with poor memory and visuo-spatial functions, whereas verbal and executive functions are preserved (Jokinen at al., 2004).

Presence and severity of white matter changes are independent predictors of PSD (Tang et al., 2004). However, there are major potential confounding factors: cerebral atrophy, which is more frequent in patients with white matter changes; lacunar infarcts, which share a common pathogenesis with white matter changes than those with stroke alone (Tatemichi et al., 1990; Pasquier & Leys, 1997). In a study to determine the neuroimaging correlates of cognitive ability in patients with lacunar infarcts, left frontal lobe atrophy and presence of thalamic infarct were independent predictors of worse cognitive performances (Mok et al., 2005).

Finally, silent infarcts, global cerebral atrophy, medial temporal lobe atrophy and white matter changes are predictors of PSD. There might be a lot of reasons to explain the inconsistency of data listed before: in particular the heterogeneity and the confusion of the selection criteria; the study samples not uniform. The simple occurrence of stroke cannot represent a crystal clear inclusion criteria. Every stroke is different than others, because there are many discrepancies in the basal conditions of the patient, in the etiology, in the pathogenesis and in the further mechanisms and evolution of stroke itself.

Moreover, following the "vessels disease" theory, stroke and atherosclerosis are not the disease, but only an epiphenomenon of a more complex matter. In addition, PSD occur more rapidly in those patients with a larger number of brain injuries, independently from their nature (vascular or neurodegenerative). Obviously, the aforementioned vessels' wall disease is not demonstrable with current neuroimaging techniques, because our detection tools allow only the identification of the consequences that this pathology produces on patients' brain, like strokes, silent and micro-infarcts, small vessels disease (cortical and sub-cortical), and cerebral atrophy. In the last years, TC-PET and SPECT have achieved a key role in the early diagnosis of Mild Cognitive Impairment (MCI) and AD-LBD-FTD. TC-PET and SPECT are perfusion techniques, at first. So, a chronic hypoperfusion in the early stages of AD-LBD-FTD has been demonstrated (Liu et al, 2011; de La Torre, 2010; Pakrasi & O'Brien, 2005). Consequently, you can not only suggest a possible role of chronic hypoperfusion in determining AD-LBD-FTD, but also suppose that new technologies could allow innovative and surprising findings concerning this fascinating issue, in the next future.

2.1.4 Stroke characteristics

Most studies found that a more severe clinical deficit at the onset of stroke is associated with a higher risk of PSD (Tatemichi et al., 1990; Desmond et al., 2000; Henon et al., 2001; Pohjasvaara et al., 1997). Studies that did not find this association (Kolmen et al., 1996; Altieri et al., 2004; Desmond et al., 2002), are characterized by high mortality rates in patients with severe deficits that may have created recruitment bias (because of a short delay between stroke onset and recruitment).

The risk of PSD and its severity are not influenced by the type of stroke (ischemic or hemorrhagic) (Linden et al., 2004; Pohjasvaara et al., 1998; Barba et al., 2000; Henon et al., 2001; Madureira et al., 2001; Rasquin et al., 2004). However, differences in survival rates between stroke subtypes are making the results difficult to interpret.

In the Framingham study large artery infarcts, lacunar infarcts and infarcts of unknown origin were associated with a higher risk of PSD than cardioembolic infarcts (Ivan et al., 2004). In other studies, the risk of PSD was lower in patients with small vessel occlusion

than in patients with large arterial stroke (Tatemichi et al., 1990; Desmond et al., 2000; Mok et al., 2004; Rasquin et al., 2004). Accordingly, a study evaluating stroke volumes showed a relationship between higher stroke volume and the risk of dementia (Sachdev & Brodaty, 1999).

However, all these results are influenced by the higher mortality rate in stroke subtypes associated with more severe deficits, in patients who are the most likely to develop PSD when they survive. Supratentorial lesions, left hemispheric lesions, anterior and posterior cerebral artery territory infarcts, multiple infarcts and so-called "strategic infarcts", i.e. cerebral infarcts that may lead to dementia on their own in the absence of any other lesion, have been found to be associated with an increased risk of dementia after stroke in at least two independent studies (Leys et al., 2005). However, strategic locations (left angular gyrus, inferomesial temporal and mesiofrontal locations, thalami, left capsular genu, caudate nuclei) were described more than 20 years ago, in single case reports, or in small series, usually without MRI, and without follow-up (Leys et al., 2005). Other vascular brain lesions interfering with the neuropsychological deficit cannot be excluded in the absence of MRI (Leys et al., 2005), and coexisting AD-LBD-FTD cannot be excluded in absence of follow-up (Leys et al., 2005). Therefore, the concept of strategic stroke should be revisited with large prospective studies, with MRI scans to exclude associate lesions, and a follow-up long enough to exclude associated AD-BLD-FTD (Leys et al., 2005). In conclusion, stroke itself is rarely the only responsible of PSD. The clinical experience and scientific data show that the occurrence of a "strategic" or "large" brain infarct is an unfrequent event. Only in these cases, in fact, the stroke could cause deterioration of patients' cognitive functions and subsequent PSD. As the authors said in the previous paragraphs of this chapter, stroke should be considered as the clinical expression of an underlying vascular disease, that could cause dementia through the synergistic and addictive effect of a large number of clinically unrevealed brain injuries. Stroke itself would be only able to anticipate the timing of dementia. However, stroke would not be the disease, but only one of its clinical signs. These concepts are supported by several data; in fact, apart from the previous cited strategic locations, PSD most likely occurs in patients with a "more severe clinical deficit at onset". The term "More severe clinical deficit" means the presence of a large number of previous brain injuries (vascular or neurodegenerative), together with a worse clinical condition, caused by a poorer detection and control of classical cardiovascular risk factors (hypercholesterolemia, diabetes, hypertension, heart failure and so on). In both of cases, the clinical landscape is dominated by the vascular disease, which is the responsible not only for the accumulation of these chronic damages, but also of the occurrence of stroke. Therefore, stroke is simply an epiphenomenon, that contributes to anticipate or to reveal an earlier cognitive impairment, causing PSD, which merely is another consequence of this complex pathological process. As matter of fact, it is not easy to predict which kind of stroke patient will develop dementia before from the others. Certainly, the onset of PSD will be more rapid in those patients with the worst degree of clinical and cerebral involvement.

2.1.5 Pre-existing brain lesions in stroke patients

Silent infarcts, i.e. cerebral infarcts seen on CT or MRI scans that have never been associated with a relevant neurological deficit, are associated with an increased risk of dementia after stroke (Leys et al., 2005).

Their influence seems to increase according to the duration of the follow-up: in the Lille study, silent infarcts were associated with dementia after stroke at year 3 but (Henon et al., 2001) not at year 2, and in the Maastricht study silent infarcts were independently related to dementia after 12 months, but not after 1 or 6 months (Rasquin et al., 2004).

Stroke patients with associated previous silent infarcts seem to have a steeper decline in cognitive function than those without, but this decline might be confined to those with additional silent infarcts after base-line. Global cerebral atrophy is associated with a higher risk of dementia after stroke (Leys et al., 2005). MTLA is more frequent in stroke patients who have pre-existing dementia but it may also be present in non-demented stroke patients. MTLA clearly differentiates demented from non-demented patients after a first-ever ischemic stroke, even after exclusion of patients who had pre-stroke cognitive impairment (Leys et al., 2005).

Stroke patients with MTLA may have pre-clinical AD-BLD-FTD that is clinically revealed by stroke (Leys et al., 2005; Pasquier & Leys, 1997; Firbank et al., 2007). However, MTLA is not specific for AD-BLD-FTD, as it has also been observed in VaD (Leys et al., 2005). The presence and severity of leukoaraiosis are independent predictors of dementia after stroke (Leys et al., 2005), but there are many potential confounders, such as cerebral atrophy, more frequent in patients with leukoaraiosis, lacunar infarcts, which share a common pathogenesis with leukoaraiosis, and stroke recurrence, which is more frequent in stroke patients with leukoaraiosis (Leys et al., 2005). Microbleeds are frequent in stroke patients and especially those with intracerebral arteriolopathies (Cordonnier et al., 2007) and in patients with VaD, and to a lower degree AD (Cordonnier et al., 2006).

However, the question of their influence on the risk of post stroke dementia has never been systematically addressed. All these data confirm that the presence of previous brain injuries (vascular or neurodegenerative) is related to a higher risk to develop PSD, and their severity related to a more rapidly onset time. However, this "severity" may be not the NIHSS score or similar, but from one side the underlying "vessel disease" and from the other side the presence of subclinical neurodegenerative processes, or both, that is the overlap between AD and VaD, that is another intriguing issue influencing the time of onset of PSD. Vascular and degenerative dementias might be closer than previously thought, being dementia a spectrum which has only at the two extremities a "pure" degenerative type or a"pure" vascular one, while the majority of cases are definitely the results of different combinations of the two, always present. VaD and AD may thus be considered supplementary over the cognitive decline landscape. In conclusion, the debate about the vascular and neurodegenerative components of non-genetic AD is ongoing (Ivan et al., 2004).

To solve the diagnostic dilemma "is "Alzheimer's dementia" Alzheimer's disease, vascular dementia, or both?" (Roman et al., 1993), the first much needed step is a revision of the current diagnostic criteria for vascular dementia, in which the description of mixed forms of dementia appear to be inadequate.

2.1.6 The onset of Post Stroke Dementia according to time

Individuals with PSD are patients in whom stroke is only the epiphenomenon of an underlying long-acting vascular disease. Accordingly, stroke patients younger than 45 years show very few instances of PSD. This long-acting vascular disorder, affecting in particular

the two inner layers of the vessel wall, may clinically occur with a wide range of clinical presentations.

Nevertheless, the mechanism that determine these different patterns of disease are not yet completely understood. This heterogeneity in clinical expression is probably related to genetic differences between individuals. As a matter of fact, in patients suffering from stroke, PSD would be determined by an underlying chronic cerebrovascular disease.

As a consequence, the time of onset of PSD would originate from the degree of severity of the abovementioned vascular disorder. In patients who have advanced chronic cerebrovascular disease, stroke would trigger the cognitive impairment and the time of onset of PSD will be extremely fast. On the other hand, in stroke patients with mild degree of "underlying" cerebrovascular disease, the risk of PSD will gradually increase over time, or be accelerated by the occurrence of subsequent single or multiple cerebrovascular events. In conclusion, with regard to vascular dementia and its various forms, it seems appropriate to say that the time of onset of PSD is closely linked to the severity of the impairment of the cerebral circulation. It has been shown that patients with global cerebral atrophy and MTLA may have pre-clinical AD clinically revealed by stroke (Leys et al., 2005).

There are several other significant predictors of PSD that are not related directly to the stroke itself, including increasing age, female sex, low education, race (increased in blacks, Hispanics and south-east Asians, and lower in Caucasians and Chinese), and leukoaraiosis. Most of these factors are also associated with AD-LBD-FTD. This, along with the fact that pre-stroke cognitive decline increases the risk of PSD, suggests an interaction between pre-existing degenerative pathology and stroke.

Neuropathological studies confirm that patients with AD pathology and cerebrovascular disease have a greater severity of cognitive impairment than those with similar severity of either pathology. Indeed, such "mixed" pathology is more common than either pure vascular or degenerative pathology. Vascular mechanisms may be important in the development of AD-BLD-FTD pathology: vascular risk factors are risk factors for AD-BLD-FTD also and cerebral hypoperfusion and microcirculatory changes may be a precursor of the neuropathological and clinical changes. In fact, it has been argued that there might be a pathogenic role of vascular disease in the basic phenomena of neuronal degeneration. The synthesis of these assumptions is called "Vascular Hypothesis of Alzheimer's disease" (de La Torre, 2011). According to this theory, AD would be primarily a vascular disease. Thus, "classical" cardiovascular risk factors would also be risk factors for AD, and neuronal degeneration would only be the result of an "energy crisis" of genetically predisposed neuronal populations. Several studies suggest that cerebral hypoperfusion is one of the earliest pathological signs in the development of cognitive failure (de la Torre, 2000). This phenomenon is more evident in the elderly, having already a dwindling cerebrovascular reserve due to advancing age. Other vascular risk factors may contribute to further decline in cerebral blood flow, resulting in unrelenting brain hypoperfusion. Brain hypoperfusion, in turn, can reach a critical threshold giving rise to a neuronal energy crisis via reduced ATP synthesis (Lassen et al., 1991). The ensuing metabolic energy crisis initially carves up ischemic-sensitive neurons in the hippocampus and posterior parietal cortex setting up cognitive meltdown and progressive neurodegenerative and later atrophic changes in the brain. Neuronal energy compromise accelerates oxidative stress, excess production of

reactive oxygen species, aberrant protein synthesis, ionic membrane pump dysfunction, signal transduction impairment, neurotransmitter failure, abnormal processing of amyloid precursor protein resulting in beta-amyloid deposition and axonal microtubule disruption from tau hyperphosphorylation (de La Torre, 2002). Lenzi and Altieri investigated factors that might contribute to the development of delayed PSD and to the definition of its clinical presentation. 191 patients who were dementia-free 6 months after stroke were enrolled (Altieri et al., 2004). Dementia was diagnosed according to the ICD-10 criteria (Altieri et al., 2004), while ethiologic diagnoses followed the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Associations (NINCDS–ADRA) for AD (McKhann et al., 1984), and the NINDS–AIREN group for VaD (Altieri et al., 2004). About 21% of patients developed delayed PSD during the 4-year follow up. This finding confirmed data reported in previous studies showing that dementia is a frequent consequence of stroke and that the risk of dementia development, though higher in the very short period after stroke, remains important in the long term (Desmond et al., 1996 ; Desmond et al., 2000 ; Barba et al., 2004 ; Henon et al., 1997). Further, Lenzi and Altieri (Lenzi & Altieri, 2007) excluded patients with pre-stroke dementia, known to markedly increase the incidence of PSD (Barba et al., 2004; Henon et al., 1997).

The clinical differentiation of delayed PSD yielded some intriguing results. Although the incidence of new cases of dementia was constant throughout the 4-year follow up, the cognitive pattern shifted from a predominant AD-BLD-FTD with cerebrovascular disease type in the first 2 years, and to a typical VaD type later on.

In this view, the time interval between stroke and dementia onset might be crucial as a means of differentiating between its ethiopathological subtypes: PSD which develops up to 15–20 months after stroke onset might present the clinical characteristics of the so-called "mixed dementia" arising from the unmasking effect of the vascular lesion on a previous degenerative process; subsequently, PSD may be due to the anatomical disruption of cortical relays and connections with other cortical or deeper structures, or to the cumulative effect of the new lesion which disrupts a previous functioning equilibrium (Tatemichi et al., 1990; Mungas et al., 2001 ; Mungas et al., 2002 ; Fein et al., 2000).

Let us remember that functional studies have shown that vascular patients may compensate for cognitive impairments by increasing both the number and the regional perfusion of activated areas. This last mechanism seems to be less effective and may, consequently, become inadequate after a new vascular event (Di Piero et al., 2001).

Both these mechanisms need a background of unimpaired neuronal network, and cannot be fully operative in presence of initial neurodegenerative processes. At present, is unclear if the interaction between stroke and degenerative pathology develop the unmasking previous degenerative changes, or whether there is a synergistic effect of stroke, perhaps through widespread synaptic or perfusional changes, that accelerates existing degenerative processes.

We can intuitively conclude that the presence of an underlying AD-BLD-FTD can dramatically influence the time onset of PSD. Therefore, individuals with AD-BLD-FTD will develop PSD much faster than those without AD-BLD-FTD. This event will occur both if the AD-BLD-FTD neuropathological changes are already evident, or when stroke represents the triggering event of an undiagnosed pathological condition.

3. Conclusion

Until recently, the term vascular disease was considered synonymous of atherosclerosis. Nowadays, scientific evidences show that atherosclerosis and its acute and chronic consequences could be only one of the possible manifestations of a more complex vascular disorder.

Probably, genetic differences allow the existence of a wide range of clinical expressions, in the context of a similar pathological process. First of all, we can recognize some individuals with a predominant "classical" vascular disorder; in these patients, the classical cardiovascular risk factors such as hypercholesterolemia, diabetes, hypertension and so on could lead to the genesis and development of the atherosclerotic plaque, which is the major target for the current strategies of prevention and treatment of the aterosclerothic disease.

In fact, in the largest part of cases, the aim of the modern medicine is to decrease the prevalence and the incidence of the acute and chronic cardio-cerebro-vascular consequences of this pathological process. The cognitive impairment of these patients manifests as VaD. We can also recognize another group of patients without the aforementioned "classical" vascular disorder.

These individuals are probably affected by a silent but persistent vascular disease, which could similarly lead to dramatic consequences. In these individuals, cardiovascular risk factors don't determine the development of atherosclerosis, but could cause a chronic brain hypoperfusion, responsible for the beginning and the progression of neuronal degeneration. The cognitive impairment of these patients manifests as AD-BLD-FTD. It could be speculated that vascular and degenerative dementias might be closer than previously thought, being dementia a spectrum which has only at the two extremities a "pure" degenerative type or a "pure" vascular one, while the majority of cases are definitely the results of different combinations of the two, always present.

VaD and AD may thus be considered supplementary over the cognitive decline landscape. However, their borders show an extensive and variable representation.

Nowadays, PSD is not considered as a specific entity requiring specific treatment. Patients with PSD are together patients with dementia and with stroke. Current guidelines for stroke prevention should be applied, but the specific issue of secondary prevention of stroke in patients with dementia (either pre-existing or new-onset dementia) is not addressed in any guidelines.

It has been proposed that lowering of blood pressure could, in theory, reduce the incidence of cognitive decline because of reduction in stroke recurrence rates and indirect effects on the anticipation of the clinical onset of AD-BLD-FTD (Pasquier & Leys, 1997): accordingly several controlled trials showed a beneficial effect of lowering blood pressure on the risk of dementia (Tzourio et al., 2003; Forette et al., 1998).

A symptomatic approach to dementia syndrome is necessary, depending on the presumed cause (AD-BLD-FTD, VaD or mixed). There have been no trials specifically done in PSD. However, both AD-BLD-FTD and VaD share a cholinergic deficit, and both disorders show some improvement when treated with cholinesterase inhibitors. Patients with AD-BLD-FTD and with vascular risk factors receive greater symptomatic benefits than patients with pure AD after short term treatment with rivastigmine, an inhibitor of acetylcholinesterase and

butyrilcholinesterase. The additional apparent benefits on disease progression detected in patients with hypertension and AD might be linked to drug effects on cerebrovascular factors. These findings could have an important effect on the way cholinesterase inhibitors are prescribed.

In conclusion, the time of onset may be an important variable in the evaluation of patients with PSD. Currently, together with other conventional diagnostic techniques, it will provide us some useful details on the degree of cerebral impairment in the subject under examination. In addition, it is a very attractive starting point for research. For these reasons, the authors suggest to give more consideration at the time of onset in PSD evaluation criteria, in order to better stratify patients' risk and to improve the state of knowledge regarding this dramatic pathology

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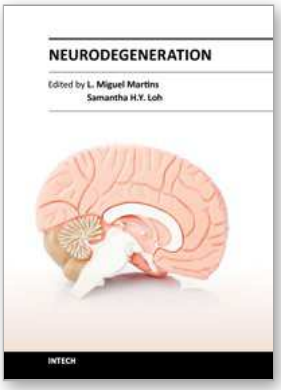

Neurodegeneration

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Currently, the human population is on a collision course for a social and economic burden. As a consequence of changing demographics and an increase in human individuals over the age of 60, age-related neurodegenerative disorders are likely to become more prevalent. It is therefore essential to increase our understanding of such neurodegenerative disorders in order to be more pro-active in managing these diseases processes. The focus of this book is to provide a snapshot of recent advancements in the understanding of basic biological processes that modulate the onset and progression of neurodegenerative processes. This is tackled at the molecular, cellular and whole organism level. We hope that some of the recent discoveries outlined in this book will help to better define the basic biological mechanisms behind neurodegenerative processes and, in the long term, help in the development of novel therapeutic approaches.

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