Prevalence of dementia in a population of ischemic stroke survivors- a pilot study

by

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Abstract

We conducted a pilot study to determine the prevalence of dementia and cognitive impairment 3 months after an incident ischemic stroke. All patients were obtained from a community-based stroke registry. We studied 10 cases in phase I (training period) and 26 cases in phase II. The following data were collected: subtypes of stroke, neurological examination, neuropsychological battery according to the Canadian Study on Health and Aging (CSHA) protocol, the CAMDEX questionaire on activity of daily living, and diagnosis according to CSHA. Three raters (2 neurologists and one neuropsychologist) evaluated all subjects. A behavioral neurologist who had not seen any of the patients also participated at the diagnostic classification. Raters were paired two by two in consensus teams.

We found poor agreement between individual raters at the domain level as well as at the diagnostic level (dementia; cognitive impairment but no dementia). Agreement was moderate at the level of consensus between teams of neurologist-neuropsychologist (Intraclass Correlation Coefficient = 0.64). In phase 2, one consensus team diagnosed 6 individuals as demented and the other 3. Most cases had impairment in one or more cognitive domains. Our study is limited by 1- poor operationalization and lack of validation of research criteria, 2- subjectivity of the neurologic examination, 3- difficulty in identifying borderline cases with mild dementia, 4- difficulty in studying stroke survivors with various handicaps such as mild-moderate aphasia.

We present a grant proposal for a larger study that takes into account the difficulties experienced in this pilot phase.

Keywords: Vascular dementia; reliability study.

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Chapter 1

Background

1.1 Epidemiology of vascular dementia

The epidemiology of vascular dementia is closely related to the evolving concepts of dementia. At the turn of the century the coining of the term "arteriosclerotic dementia" by Binswanger[1] suggested a pathophysiological explanation that persisted for many decades. In 1907 Alzheimer published his landmark paper on senile dementia. Since both pathologies seemed to be clearly demarcated not much work was done on the possible association of the two. Moreover, some physicians would still use both terms interchangeably. This undoubtedly complicated research in this area. For many years the main area of research was on degenerative dementia. It was only after work of Tomlinson et al[2] and Hachinski et al[3], who coined the term "multi-infarct dementia", that the pendulum swung back to research on vascular dementia. The Ischemic Score[3] was the first research tool that could be used in epidemiological studies allowing differentiation between Alzheimer'disease (AD) and vascular dementia (VaD).

Finnish studies appeared in the early 1980's on the prevalence of VaD[4]. Prevalence between 1 and 3% for subjects over 65 years was observed and represents a benchmark against which other studies should be compared. Interestingly, parallel studies carried out in Lundby, Sweden[5], at a much earlier time (1947-1952 and 1957-1972), using different research criteria, arrived at a similar proportion. The latter study was smaller in scope with very few observations in the older age group. Later studies were done after the

introduction of CT scannning. The use of computed tomography (CT) is no guarantee of higher accuracy since no guidelines existed in the early 1980's on the differentiation of the two conditions. Clinical scales allow recognition of pure entities (AD or VaD) but seems to be unable to tease out cases with mixed etiologies. Such overlap represents, according to many authors, up to 10-20% of dementia cases.

The epidemiology of vascular dementia presents many difficulties[6] such as lack of standardized definitions, uncertainty about pathophysiological mechanisms, variability across studies related to the use of different diagnostic tools, no validation of research criteria, the use of non-representative populations, hospital-based or pathological series, and lack of a clearcut relationship between clinical findings on the one hand and laboratory data such as CT , nuclear magnetic resonnance (NMR) and even pathology on the other. The latter point has been well described by Brust: "neither clinical nor pathologic evidence of stroke necessarily means that cerebrovascular disease has anything to do with a patient's dementia". The lack of a gold standard is certainly the major difficulty in this field. General practitioners also reflect this uncertainty by neglecting to put the diagnosis of vascular dementia on death certificates[7].

More recent studies have shown that the accuracy of a clinical diagnosis of vascular dementia (85% according to Erkinjuntti et al)[8] approaches a level that could be used in epidemiological studies. Currently it is not possible to differentiate VaD from mixed cases with certainty. It is customary to lump these cases either with AD thus identifying a case with a lower level of precision- "possible AD" rather than "probable AD"- or lumping

them with the vascular category as done in a recent paper [9].

The way such cases are classified is important in view of recent observations: 1- vascular dementia may present insidiously with diffuse involvement of the white matter in a pattern sometimes impossible to differentiate from AD with neuroimaging; 2- this subcortical involvement is more frequent than once thought; 3- pathological studies show a coexistence of markers of both diseases in up to 20% of patients. Since degenerative dementia, i.e AD, appears only after a certain threshold is reached, VaD may contribute to lower this threshold.

With these observations in mind recent epidemiological studies will be described.

1.1.1 Prevalence studies

Earlier European studies have been described above. A review of the best studies was published in 1991[10]. A crossnational comparison is available for Sweden, Finland, UK and Italy. Age-specific prevalence varied from 0.5% at age 60-69 to 2.2-4.6% at age 70-79, to 3.6-16.3% at age 80-89. Figures showed higher prevalence in men than in women especially in Italy where prevalence was twice as much in men (see Table 1). These latter observations are based on few subjects. Rates from Cambridge, UK, at age 80-89 were 2.8% for women and 3.5% for men. Based on more than 1000 subjects, these figures would appear more reliable. The rates across countries are comparable at age 75-79 for men. Prevalence varied among other age groups by as much as 3-4 fold. Notably, trends of decreasing prevalence in the oldest individuals (i.e. > 85years) could indicate a

diagnostic bias in this age group.

Prevalence data from the Canadian Study on Health and Aging (CSHA) have been published recently[11]. This study will be described in more detail below. Prevalence for men was higher than for women in all age groups. For the age groups 65-74, 75-84 and > 85 proportions in men were 0.8, 3.1 and 5.2% respectively. Comparable figures for women were 0.4, 1.9 and 4.6% respectively (Table 1). These proportions do not differ substantially from the European studies except perhaps from the Italian study carried out in Appignano[10]. These proportions are based on observations of 10,000 subjects randomly selected from most large communities in the 10 provinces. They are precise with a coefficient of variation of 8.0%.

Recent studies have looked more precisely at prevalence in subjects > 85 years old[12]. A Swedish study found a prevalence of 14% for VaD, almost the same in women and men[13]. In the CSHA prevalence was lower but steadily increased with age[14]. It was 3.4% at age 85-89, 4.6% at age 90-94 and 6.7% over age 95. Prevalence for all types of dementia (i.e. AD plus VaD and "other type of dementia") was similar in both studies. However, the relative proportion of AD vs VD, differed in the two studies. In Gothenburg, Sweden, the ratio of AD to VD was close to 1 whereas the ratio was 5.4 in Canada.

1.1.2 The relative proportion of VaD vs AD

The different proportion of AD vs VaD in the CSHA, as compared to the Swedish study, is difficult to explain. Since both studies used DSM-III criteria it is possible that these

Table 1 Prevalence of vascular dementia in different countries as a function of age (%)

	Men			Women		
age-group	65-74	75-84	>85	65-74	75-84	>85
country						
Canada CSHA [11]	0.8	3.1	5.2	0.4	1.9	4.6
Holland Ott et al[15]	0.3	3.1	2.2	0.2	2.0	4.9
Finland Sulkava et al[10]	2.2	3.9	3.9	1.7	4.7	1.8
		70-79	80-89		70-79	80-89
United Kingdom O'Connor et al [10]		1.8	3.5		1.5	2.8
Italy Rocca [10]		4.8	16.3		2.2	9.2
Sweden Hagnell et al [10]		4.6	4.8		2.6	7.0

criteria leave much room for interpretation. This has been observed by others[16]. Because the proportions of demented subjects were high, 30% in both studies, such a high prevalence would tend to blur the difference between AD and VaD. This is especially true in a group of frail individuals where the examination is difficult to carry out. Also, both pathologies are very frequently found at autopsy. An interaction between the two is probable.

These explanations do not eliminate the difference between the two countries. Variability in the AD/VaD ratio is seen in younger individuals across different countries. Japan for instance has a higher rate of VaD than AD. A recent study from Hisayama, Japan, shows that the ratio was closer to one [17]. The latter study also showed a higher prevalence rate for AD than for VaD for subjects over 85. Stated differently, in the CSHA study, AD accounted for 64% of all dementia, and VaD for 19%. Corresponding figures for the Rotterdam study were 72% for AD and 16% for VaD.

A Chinese study conducted in Shanghai revealed that AD accounted for 65% of all dementias[18]. Most European studies showed similar rates for AD and VaD in the age group 70-79; however, AD becomes more prevalent after age 80 years. In Canada the AD/VaD ratio was 1.6 at age 65-74, 2.8 at 75-84 and 5.4 over age 85.

1.1.3 The importance of "mixed cases"

Few epidemiological studies have separated VaD from Mixed (MIX) cases. Mixed refers to the coexistence of two pathologies in the same patient, AD and VaD. The ratio of VaD/MIX was 2:1 in Italy but 16:1 in Cambridge[10]. This is in marked contrast to hospital case series which show a ratio close to 1. This exemplifies the importance of clear diagnostic criteria. As mentioned above there are no criteria allowing separation of these two groups.

1.1.4 Incidence

Few studies have looked at the incidence of VaD. Fukunishi in Japan [19]found an annual incidence of VaD of 0.4% for all subjects over 65. In a Swedish study [20]the annual incidence rates in men were 0.44% at age 65-70 and 2.1% at age 80-89. Rates for women were 0.12 and 1.7% respectively. In Mannheim, Germany, the annual incidence rate for VaD was 0.44% over the age of 65 [21]. The Cambridge Project for Late Life shows an annual rate of 1.2% over the age of 75 [22]. These rates are somewhat comparable across the different countries.

1.1.5 Survival

Data on survival are important because of the effect on prevalence. According to one study, 3 year mortality was 42% for AD but 67% for VaD[13]. Mölsä et al[23] showed a 6-year survival rate of 11.9% for VaD and 21.1% for AD.

1.1.6 Risk factors and clinical studies

Studies already described above were helpful in identifying the following risk factors for vascular dementia: involvement of the left hemisphere, the number of strokes, the total volume of infarcted tissue, bilaterality of lesions as well as involvement of the white matter[24]. The implication of the dominant hemisphere, mostly from vascular lesions in the territory of the anterior or the posterior cerebral artery, has been described[25]. Vascular risk factors are also associated with the risk of dementia although their contribution is not as strong. High blood pressure seems to contribute most. Hypertensive patients are more prone to develop ischemia because of increased resistance and a steeper pressure drop over a stenosis or occlusion[25]. Hypertensive patients are at risk of presenting with cognitive impairment whether or not there is associated white matter involvement[24]. Control of blood pressure has been shown to improve cognition in at least one study[26]. Measurement of blood pressure in epidemiological studies is subject to difficulties. First, a history of hypertension is probably more important than recent hypertension. Second, low blood pressure has been implicated as a risk factor for cognitive impairment[26]. Measurement of the presence of vascular risk factors from a questionaire as done in our study seems to be an acceptable method[25]. Kappa values, measuring interrater agreement for a positive history of hypertension, diabetes or myocardial infarct were 0.81, 0.81, and 0.90 respectively. Others studies have implicated previous myocardial infarct[27], diabetes [25] or large artery atherosclerosis as risk factors[24].

Other clinical observations commonly associated with the risk of dementia are the presence of gait disorder [28] and urinary incontinence. Gait disorder for instance seems to

be present in all of our 26 patients with vascular dementia according to DSM-IIIr criterion. Even though clinicians were asked to describe any modification of gait, only one third were able to visually pick up this abnormality in a standard neurological examination[28]. The nerve fibers involved in gait have a frontal periventricular route which is in accordance with the theory of a frontal-subcortical disconnection.

The study by Tatemichi et al from a cohort of ischemic stroke survivors at the Columbia-Presbyterian Medical Center will be described in more detail, since it is similar to our pilot study[29].

In this study 1511 admissions were initially screened for cerebrovascular disease. After excluding hemorragic strokes, transient ischemic attacks, strokes that were too severe, and patients less that 60 years old, 658 ischemic strokes were left. From this cohort 222 patients were excluded because they were unsuitable for testing (severe aphasia, clouding of consciousness, etc) patients were finally assessed. Another group of 139 subjects was not sudied because of refusal (93) early discharge or moving to another area. Finally, 46 patients initially enrolled during the acute phase of stroke were not available for study 3 months later, either because of death, too severe medical comorbidity, refusal or migration.

All remaining 251 patients were studied 3 months after stroke by a neurological exam and a neuropsychological test battery. Diagnostic classification was obtained by consensus between the examining neurologist and the neuropsychologist. The choice of 3 months follow up was justified by an earlier observation[27] that most patients who become demented do so within a few weeks of their stroke. This study used DSM-IIIr criteria for diagnosis of VaD. They used predetermined cutoff scores for each of the subtests.

This study represents the largest cohort of consecutive stroke patients that has been studied in such a detailed manner. It was found that 26.3% of patients were demented at 3 months after stroke, and, after excluding a case history compatible with a history of Alzheimer's disease, 16.3% seemed to have a vascular dementia compared to only 3.2% in the control group. In the latter, dementia was observed mostly in the older individuals and was mostly of the AD type. The non-demented stroke survivors were then followed longitudinally. Thirty-six cases developed dementia (longest follow-up = 52 months) for an annual incidence of 8.4%[30]. The following etiologies were proposed as possible explanations: 1) 8 cases developed dementia after a new stroke compatible with the diagnosis of "multi-infarct dementia"; 2) 6 cases had medical events similar to hypotensive episodes suggesting an association with what is referred to as a "hypoperfusion dementia"; 3) 6 cases were borderline at entry suggesting an association with a lower intelligence. Such an association between low intelligence or lower education has been observed for Alzheimer's disease as well as for vascular dementia[24]; finally , 4) 12 cases had no explanation for their new dementia. It may be that they had progressive but silent cerebrovascular disease or an underlying degenerative dementia unmasked by the stroke event. Only autopsy of a large cohort will confirm these assumptions.

The problem of the coexistence of AD and VaD has been mentioned before. In the New York study, 36% of demented cases at 3 months met criteria for "AD plus cerebrovascular disease"[29]. With longer follow-up 1/3 (12/36) of new dementia had a pattern that looked like a degenerative dementia. It is likely that both entities contribute synergically to the appearance of dementia in a high proportion of cases. Scheinberg[31] has proposed that the combination of AD and VaD may represent the most common form of dementia. This

remains to be proven. This observation will have to be taken into account when studying VaD. The use of specific criteria, in order to exclude AD, will decrease sensitivity thus underestimating the contribution of vascular events.

The question of whether large artery lesions contribute more to dementia than do small vessel lesions will be discussed in the following sections. Hachinski et al noted, as did Fisher, that "cerebrovascular dementia is a matter of strokes large and small"[32]. Even though they coined the term "multi-infarct dementia", they observed that multiple small infarcts, in association with hypertension, is one of the commonest causes of dementia. The relative importance of both pathophysiological mechanisms probably depends on the type of population studied. In a population of ischemic stroke survivors[29], or from a multicenter stroke registry[27], large vessel strokes were significantly associated with the risk of dementia. In the study by Tatemichi et al[29], the risk of dementia after stroke was increased 9 times compared to the controls. A similarly increased dementia risk was observed in survivors of lacunar strokes[33]. Lacunes were responsible for 43% of vascular dementia in one study[34]. What is most important? In the study by Gorelick et al [35] the predictors of dementia in a logistic regression study were left cortical infarction and diffuse enlargement of the left ventricle. For Liu et al[36] dementia was related to total white matter lesion (WML) area, left WML area, right WML age, left cortical infarction area, left parietal infarction area and total infarction area, in that order.

1.2 Contribution of Pathology

Neuropathological contribution to the study of vascular dementia has been very important. The lack of unbiased population studies, however, is one of the main reasons why this knowledge fails to guide us. Pathological studies will be examined here for their contribution to: 1) broadening the scope of the disease, 2) introducing the concept of frontal white matter rarefaction, 3) validating clinical diagnostic criteria, 4) showing how to differentiate AD from VaD, and 5) identifying the important subgroup of "mixed" etiology.

The following paragraphs can be skipped without loss of comprehension of further discussion. The main conclusions of this section are the following: 1- For some authors, small vessel lesions (including incomplete white matter infarct) represent the most common pathological substrate for dementia[37-39], although this is controversial; 2- cases of pure AD may not be as common a type of dementia as once thought; 3- the correct identification of pure cases of AD or VaD from mixed cases seems very difficult. These questions will be examined again in the section on neuroradiology, neuropsychology and clinical findings. The main question is: how good are we in differentiating the 2 main causes of dementia, namely AD and VaD?

1) The study of Tomlinson et al published in 1970[2] was the first to identify a threshold level for which differentiation of VaD from AD was possible. Where the volume of tissue loss was more than 100 cc, the etiology of dementia was most certainly vascular since

there was no overlap with controls[2]. There was some overlap when the total volume of infarct was between 50 and 100 cc. In the following decade these observations on the importance of the volume of infarct were not challenged. However, the paper by Tomlinson et al is based on a small number of pure vascular lesions (6 cases). In addition there were 4 cases with a mixed pathology (AD + vascular changes) and 11 cases with high normal values for both AD and vascular changes. The conclusion is that vascular lesions were frequent, even in Alzheimer cases, but had to involve a fairly large part of the brain to be considered as the etiology of the dementia. The pursuit of an etiology for Alzheimer's disease in the following 15 years tended to exclude cases with stroke, therefore slowing research in this area. Indeed Tomlinson et al had observed a large proportion (28%) with mixed etiology. Lack of clear guidelines for separation of cases into either AD or VaD according to pathological examination is a problem that is still present today.

A more recent study by del Ser et al[40], looking at cases with pure vascular changes at autopsy, showed that there was a great deal of overlap in the volume of infarct between those with dementia (near 30 cc) and those without (near 10cc). This is considerably less than in the Tomlinson study. A factorial analysis identified 3 variables which accounted for 58% of the variance of the main component (referred to as "mental deterioration"), namely: 1- total volume of infarct, 2- a lacunar state, 3- gliosis and demyelination of white matter. The last 2 concepts have received considerable attention over the past 15 years. Both were described at the turn of the century by Marie in 1901[41], and Binswanger in 1894[1], with various synonyms: Binswanger's disease, progressive subcortical vascular

encephalopathy, etc. Both were considered very rare until recently. The development of neuroimaging was instrumental in resurrecting these syndromes.

In a study of 30 autopsy cases presenting at least 6 lacunes (mean=12), Ishii et al[42] showed that lacunes were mostly distributed in the frontal subcortical white matter and to a much lesser extent in the basal ganglia and posterior white matter. At the macroscopic level, large coronal sections showed incomplete softening of the white matter. The latter observation is reminiscent of what is found in Binswanger's disease and it can be said that the two conditions (basal ganglia infarct and white matter disease) coexist in most patients, only the proportion of the two varying. Thus only our operational definition allows these two conditions to be separated.

2) The susceptibility of white matter to microscopic lesions is highest in the frontal periventricular area. Other studies also identified a predominant loss of nerve fibers in the frontal white matter[43] as well as the corpus callosum[44]. The involvement of these regions fits well with the theory of a subcortical dementia. It is therefore unusual to see aphasia, apraxia or agnosia in this type of dementia; rather a disconnection syndrome is seen. The same pathogenetic phenomenon, disconnection of fibers, explains other symptoms of these patients such as urinary incontinence and loss of control of the legs i.e gait apraxia.

3) Pathological studies were instrumental in verifying the accuracy of the clinical diagnosis of VaD. Erkinjuntti et al conducted such a validation study[45]. Out of 233 autopsy cases with dementia, 27 had the diagnosis of VaD. It was found that 23 fulfilled neuropathological criteria for VaD whereas 3/27 had both AD and VaD. The accuracy of

a clinical diagnosis of VaD approaches 85%. This is as good as that seen for AD[46] diagnosis. Earlier studies were not as accurate however. In the study by Erkinjuntti et al, the volume of infarcted tissue for the MID cases was 39 cc whereas it was 6 cc in the mixed cases.

Pathological studies also helped us to refine our sets of clinical criteria for identifying VaD and more specifically multi-infarct dementia (MID). MID, a concept introduced by Hachinski's et al [3], describe the association between multiple infarcts and clinical corrrelates. The Hachinski' s Ischemic Score (IS), using 13 items[3], operationalize this concept. In the Erkinjuntti study[45] the items that discriminated AD from VaD were: abrupt onset, a stepwise deterioration, fluctuating course, somatic complaints, a history of strokes, focal neurological signs and symptoms. A recent meta-analysis published only as an abstract looked at 262 cases of dementia, all autopsied. Five items differentiated AD from MID (one form of VaD). The IS had a sensitivity of 90% and a specificity of 88%. The differentiation of MID from mixed cases however, had a sensitivity of 92% and a specificity of 18%[47]using autopsy results as the gold standard.

4) Most studies found poor accuracy when differentiating mixed cases (AD + MID) from pure MID[45,47]. Obviously the importance of this observation varies according to the frequency of the mixed cases. In a recent autopsy series of consecutive cases from Sweden[37] Brun found that only 28 of 175 dementia cases had pure AD, 63 cases had mixed AD + vascular, and 59 cases had pure vascular changes. Viewed from another angle, 40/175 had a large vessel infarct (isolated or combined with other Alzheimer'

degenerative changes) compared with 96/175 with small vessel infarct or incomplete white matter infarction, a process similar in physiopathology to the small vessel infarcts (see above).

5) What is the frequency of the mixed cases? The literature in general reports a frequency of 10-20%. The study of Brun had 35% (63/175) of cases with mixed etiology. The presence of incomplete white matter infarction, as well as a small number of lacunar infarctions, has been rejected by most authors as the etiology of a dementing process. They are regarded as coincidental by most, since the relationship between Alzheimer's pathological changes and dementia is well established, whereas the relationship between white matter changes and dementia is more complex. This is even more complex in view of the frequent finding of white matter changes on NMR imaging. To complicate matters further, Alzheimer's disease is frequently associated with amyloid angiopathy[48] which is responsible for similar pathological changes[49]. Hypertension contributes to white matter changes even in Alzheimer`s disease[50]. Some authors also described a microvascular pathology in Alzheimer's disease[51,52].

Because there is no accepted pathological gold standard[53] the foundation the clinical and radiological criteria rests upon appears controversial. Any research protocol on vascular dementia must adhere to strict definitions whether or not they are valid. For the sake of comparison of studies there is much to gain if all investigators would use the same criteria.

1.3 Contribution of Neuroimaging

We will try in this section to see if the use of CT scan or MRI can help us discriminate between the two most common types of dementia.

Modern classification of dementia requires the use of imaging data (see below for research criteria on the vascular dementias). While MRI is more sensitive than CT for stroke, it is less specific, more costly, and less available. The use of CT scan is accepted in epidemiological studies.

Timing is important. It has been observed that only 50% of CT are positive during the first 48 hours after a stroke[54]. CT's are used acutely to eliminate the presence of a hemorrhagic condition or the presence of a tumor. Some have found that CT may miss significant ischemic lesions responsible for a dementia syndrome[55].

Recent sets of research criteria for vascular dementia (VaD) include the results of CT or MRI. Some, such as the NINDS-AIREN [16], look for at least one vascular lesion; others, such as the California State criteria[56], require at least two lesions,. Others like the DSM-IV or the ICD-10 do not require input from neuroimaging. Recent criteria for the diagnosis of VaD [16] require an anatomic as well as a temporal relationship between the imaging data and the clinical symptomatology in order to establish a relationship.

The presence of one or many infarcts is not sufficient for a diagnosis of VaD. Indeed, it

has been said that there are no pathognomonic CT or MRI findings in VaD[16]. CT images of strokes may be seen as coincidental lesions in Alzheimer's disease[57] as well as in normal volunteers. According to some authors, patients with cerebrovascular disease do not differ on the basis of their CT whether they have dementia or not[58]. Most, however, recognize the role of multiple infarcts[3] in causing dementia.

More recently the interest has shifted toward the role of subcortical lesions such as lacunes and white matter lesions. These lesions can be easily identified with modern neuroimaging. The use of imaging was helpful in characterizing and supporting the role of white matter lesions as a specific entity[59]. The spectrum of this entity encompasses Binswanger's disease at one end and incomplete white matter infarction at the other extreme. In the past few years, neuroimaging identified almost universally white matter lesions in vascular dementia on CT[60] but also in AD or controls, especially in studies using MRI[61]. Most studies however showed a gradation with VaD presenting increased amount of infarcts or lucencies[62-64] compared to AD patients.

Leukoaraiosis (LA) is a term applied to these abnormalities of white matter on CT or MRI (see definition[65]). It is associated with cognitive decline in some studies[36,66-69] but not in others[61,68,70-74]. In most studies the clinical correlates are those of a subcortical dementia[66,74,75]. Some studies have suggested a form of disconnection syndrome as there is involvement of fibers without frank signs of infarction in the corpus callosum[44] or parieto-occipital lobes[70,76]. Involvement of the white matter is probably the most frequent cause of vascular dementia[38] as already mentioned in the previous section. Its presence on

neuroimaging, however, is not specific as too many conditions may cause it[77-81].
LA contributed marginally to the variance of cognitive decline in some studies that were positive[82]. Many individuals presenting with the association of LA and dementia do not have a history of stroke. Studying a pure population of strokes may underestimate this physiopathological mechanism. Some have proposed two types of lacunes: those that are associated with symptoms such as stroke, and those associated with dementia and LA[83]. Finally, recent studies have shown a decrease of regional cerebral blood flow associated with LA[84-87] which supports the vascular hypothesis.

In conclusion, there is considerable overlap on CT or MRI between AD and VaD. The location of lesions, their size, the total number of infarcts as well as the relationship of a lesion to the clinical presentation of a patient are all helpful for diagnosis. Many would regard an incidental stroke on CT or MRI as purely coincidental.

1.4 Contribution of neuropsychology

The use of a neuropsychological battery for the diagnosis of vascular dementia has been advocated by most authors in recent years. It is currently recognized however that a specific battery for VaD has yet to be developed and validated[16].This brief review will address the following issues: a) Pathophysiological mechanisms ; b) Are there specific tests that allow differentiation of VaD from AD? c) What is the frequency of abnormalities in different subgroups of vascular patients?, d) For current state of knowledge about

neuropsychological testing in VaD see appendix 6.

a) Pathophysiology. Many authors have looked at the relationship of VaD and abnormal cognition from the point of view of an abnormality in the fronto-subcortical system[88-95]. This is not surprising considering the body of knowledge already described in the section on neuroradiology or neuropathology. The cardinal features of subcortical dementia according to Cummings[96] are memory deficits, difficulty in executive function, slower information processing, mood and personality changes.

Finally there is a need to look at normally functioning individuals who may have leukoaraiosis on neuroimaging. There is still controversy in this area. A study by Rao et al[71] did not find any difference in individuals with and without LA . The subjects were young and the investigators excluded most subjects at risk such as the elderly and hypertensives[71]. Other studies have found cognitive deficits in subjects harboring LA[97,98]. It has been suggested that subtle deficits in these patients indicate that their brain is at risk of developing a dementia.

b) Are there any tests that differentiate AD from VaD? A recent review by Almkvist reveals that there is not much difference between the two conditions from the point of view of neuropsychological testing[88]. This point was supported by an earlier study from Erkinjuntti et al[99]. There is thus no difference in general cognitive ability, syntax, verbal comprehension, visuospatial functions, primary and semantic memory[99]. However, there are differences in scores on tests related to a) motor functions such as speech, finger

motor coordination and b) executive functions manifested in planning and inductive thinking. These deficits are caused by dysfunctions of the frontal lobes or related subcortical structures[88,89,100] (see appendix 9).

It is important therefore in investigating stroke patients to include testing of frontal lobe function.

c) What is the frequency of involvement in different subgroups? Loeb[33] and Wolfe[90] have found a prevalence of approximately 25% for dementia in lacunar stroke patients. In a group of unselected ischemic stroke patients Tatemichi et al[29] showed that 26% had dementia, where 16% had dementia attributed to stroke and 10% seemed to have coexisting Alzheimer's dementia. In a companion article, Tatemichi et al showed that 78% of their ischemic stroke survivors evaluated at 3 months failed one or more items of a neuropsychological battery, compared to 40% of controls. On the other hand if the cut-off is failure with 4 items or more, 35% of stroke patients but only 3.8% of controls were identified. In another study the frequency of impairment in orientation (27%) and figure copying tasks (26%) were similar[101].

In conclusion for this section: 1- there is no single test that would allow correct classification along the line of specific neuropsychological syndromes, at least not for epidemiological studies; 2- the spectrum of stroke presentation is vast, so must be the spectrum of neuropsychological tests; 3- batteries that do not use tests for frontal lobe

function will underestimate the prevalence of abnormalities in VaD.

1.6 Saguenay stroke registry

The Saguenay region has a population of 172,000, comprised mostly of 3 urban areas Chicoutimi (60,000), Jonquière (60,000) and La Baie (30,000). Other smaller communities make up 22,000 people in a territory covering 45,500 square kilometers, most of it inhabited.

The Saguenay stroke registry was launched in October 1991. Funded for 1-year by the local administrative medical body CRSSS-02, it still continues its operation. Objectives were to provide descriptive epidemiologic data such as incidence of transient ischemic attack (TIA) , first-ever stroke and recurrent stroke, subtype classification, etc. At the start of the study a notification system was implemented in the region where hospitalized patients would be identified by the head nurse who, within 72 hours, would notify the research team in one of 3 ways; two pagers (main investigator, nurse coordinator) or by use of an answering machine. All physicians in the region were contacted by mail. A letter explained the study, and notification means were specified. The investigator provided cerebrovascular consultation for those requiring it. Other cases were reported to the other 3 neurologists working in the area. All 4 neurologists, including the investigator, practice at the same hospital. Other cases were identified at the Doppler laboratory. Finally, we collected admission sheets for all patients at the 3 hospitals. Because our ethics committee, in 1994, required that we waited for notification before establishing contact with a

patient, some cases were never seen. We confirmed their diagnosis by looking at hospitals charts, without further data collection.

The database for the first 18 months of data collection has been analyzed[102]. The annual incidence for first-ever stroke was 121/100,000 , similar in men and women. In total , 315 first-ever strokes were observed over that period. As observed in all other countries, rates dramatically increased with age. Falling rates in the very old would indicate underreporting which was not observed here. Most cases were hospitalized (95%). Ten percent of cases were not reported to the registry which means that data, for these patients, were collected retrospectively at the hospital archives from chart review. All other cases had contact with the nurse coordinator.

We found a high rate of CT scanning (85%). After excluding patients on the following criteria: no CT scan (15%), hemorrhagic stroke (14%), death before 3 months (26%), no notification to the registry (9%), age below 50 years (6%), a total of 142 patients, or 45%, are lost. The number sum to more than 100% because some patients may have more than one cause for exclusion. Thus, 10 patients per month would be available for the study. Patients for the current study on cognitive changes after stroke were obtained from the registry at the time of hospitalization. A proactive approach was used as much as possible in order to recruit cases within the boundary limitations established by our ethics committee.

Chapter 2

Study objectives

This is a pilot study on the prevalence of cognitive impairment after an ischemic stroke. Patients were taken from a population-based registry of stroke. In order to determine the feasibility of a larger study our objectives were:

1- a) to measure the frequency of fully eligible ischemic stroke patients obtained from a regional stroke registry

b) to determine the frequency of protocol violators among the fully eligible patients.

2- to demonstrate the INTER-RATER reliability of:

a) measurement of deficits in cognitive domains

b) diagnosis in cognitive status changes

3- to estimate the frequencies of ischemic stroke patients who present 3 months after a stroke with:

a) no cognitive impairment in any of 8 studied subdomains

b) cognitive impairment but no dementia

c) dementia.

Chapter 3

Methodology

3.1 Assembly of inception cohort

3.1.1 Patient recruitment

Our cases were recruited while they were hospitalized and recovering from stroke. For more severe stroke cases, especially those with aphasia, their recovery was followed by keeping in touch with speech therapists who would, 2 months after the incident stroke, inform us of their potential for neuropsychological testing. A few patients with moderate-severe aphasia during the initial phase of stroke may thus have been recruited.

We applied the following definitions:

INCLUSION criteria: all subjects to be studied had to be a resident of the Saguenay region, be a survivor of an ischemic stroke and older than 50 years.

EXCLUSION criteria: all stroke subjects who did not have CT scan examination, those who refused to provide consent, those living alone or without any proxy respondent able to answer a questionaire, those with a too severe stroke or when the aphasia was too severe (according to the Montreal-Toulouse test), hemorrhagic stroke or transient ischemic attack.

FULLY eligible patients: meet inclusion criteria, no exclusion criteria.

PROTOCOL VIOLATORS (data loss)

We labelled protocol violators patients discharged too early (not seen by study team), those not available at 3 months, those studied outside the time window (3 months ± 2 weeks), those whose performances were affected by a recent new medical event other than acute stroke and those unable to complete one or more subitems of the CSHA protocol. This protocol includes a nurse questionnaire, neurological exam, and a neuropsychological battery (see below).

We aimed to see all patients at 3 months post stroke ● 2 weeks. Most patients came to hospital, some to a downtown clinic and some were seen in their homes in order to minimize refusal. In one session 1-3 patients were evaluated. Our nurse coordinator met the family member in order to administer the CAMDEX questionnaire[103], a questionnaire on activities of daily living, as well as the CED score for depression after stroke[104].

3.1.1 Phase I (the first 10 cases)

We evaluated our first case in September 1994. After the first 10 cases, we had time to complete a consensus form for the first 5 cases. A low level of agreement between the 2 neurologists, as well as the two teams, made us slightly modify our protocol. Because one neurologist used the 3MS tool and the second avoided using it to prevent recall, it was thought that this could explain part of the disagreement. A modified scale, here referred to as the mod-3MS, was developed. The type of questions and degree of difficulty were thought to be similar, i.e. it seemed valid at face value. We did not have time to validate it

because recruited patients had to be seen during the same period.

3.1.2 Phase II (the next 26 cases)

We elected, before starting our protocol, to study a total of 35 cases mainly for cost reasons. Since 10 cases were seen before modifying our protocol, 26 more cases were evaluated. They were evaluated as described below. Our main analysis will thus concentrate on those 26 cases.

3.1.3 Sample size

Because of costs, no more than 36 subjects were evaluated in this study. Since this is a pilot study that number seemed appropriate.

3.2 Ethical review

Our protocol was accepted by the local Ethics Committee in the Spring of 1994. One restriction was that we had to await notification before establishing contact with patients. We frequently asked head nurses at the 3 hospitals if any patient with stroke were currently hospitalized and then contacted the attending physician.

3.3 Clinical evaluation

3.3.1 Instrumentation

At the time this study was planned, early 1994, it was decided to use the DSM-IIIr criteria for diagnosis of dementia (cf appendix 5).More recent guidelines for diagnosis of VaD, NINDS-AIREN for instance [16] had barely been published and were not validated. Also,

NINDS-AIREN criteria require neuroimaging input for diagnosis of VaD. Because of lack of funding it was not possible to do CT scan studies 3 months after a stroke preventing us from using these criteria. Also, it was thought important to use an approach that had been used by others and the CSHA's protocol seemed particularly suited for that. Although this protocol was used in a population survey, instead of a stroke population such as ours, it is important to use similar tools in studies on dementia for the sake of comparability. The CSHA protocol had been tested on more than 10,000 subjects in Canada, probably the largest dementia prevalence study in the world.

The different tests used in the neuropsychological battery of the CSHA protocol were chosen for the following reasons [105]: 1- they were structured around the DSM-IIIr criteria, 2- they were familiar to psychometricians, 3- their validity were established, 4- norms were available, 5- a French version was available. During the course of the study, one CSHA team, based in Montreal, was to establish norms for a French- speaking population. A review of neuropsychological tests used in the diagnosis of VaD shows that no specific battery has been accepted in the literature (appendix 9). It was decided to simply use the whole CSHA neuropsychological battery (cf. below). It was not pretested in our stroke population. After collecting data on individual tests, the CSHA protocol ask the neuropsychologist to provide a preliminary working diagnosis based on the results of all psychometric tests.

The CAMDEX instrument is also used for diagnosis of mental impairment in the elderly [103]. The CSHA protocol uses only a subscale (section H) for evaluating the item "B4" (personality) and"C" (interference from work) of the DSM-IIIr. This questionnaire, applied by the research nurse, is completed by an informant. This section is not an

instrument but used here only to answer one question: "Is there a significant impairment in the individual's work or activities of daily living to support a diagnosis of dementia?". There is no norm for this questionnaire although several questions are asked. Therefore it will not appear in the statistical analysis.

The diagnosis of AD and VaD is made possible by excluding other potential causes of dementia. A neurological clinical examination is therefore conducted by experienced clinicians. Here two neurologists examined all cases. Their clinical approach has not been standardized since no such instrument exists in the literature. Thus, they both tried to evaluate the presence of rule-in criteria such as impairment in individual cognitive domain, and significant impairment in level of functioning (the latter justify a diagnosis of dementia).

One particular potential cause of dementia is the presence of a depression. It is important to identify depression after stroke since its prevalence was estimated at 41%[104]. The latter study validated a twenty item, self-administered questionnaire, for detection of depression after stroke (CED-S)[104].

The CED-S instrument was not used in the CSHA but chosen here because of its validity in a population of stroke survivors. We translated it and used it without further validation. This seemed acceptable at face value because simple question were asked such as: "I am happy", "I am afraid","my sleep is bad","my appetite is bad". Scores go from 0 to 4 based on whether symptoms are absent, or present for less than 1 day, 1-2 , 3-4, or 5-7 days a week[104]. Also, four questions asked to the informant, about the presence of depression, were obtained from the CAMDEX questionnaire.

3.3.2 Neurological evaluation

After having seen the research nurse, patients were evaluated by the first neurologist in a second room while the second neurologist would see the next patient in a third room. After 30 minutes patients would rotate from one examiner to the next. The neurologist reviewed results from the CAMDEX questionnaire, applied a standard neurologic questionnaire, a physical examination as well as the 3MS or modified-3MS, and met the family proxy in order to enquire about changes in cognitive performance of the patient. The 3 MS represents a more elaborate screening tool than the well known Mini Mental State[106,107]. The tool has been validated in a French Canadian population[108]. At the end of the session the neurologists completed a scoring sheet similar to the consensus team (cf appendix 1), thus deciding if there was involvement in individual domains, and made a preliminary diagnosis using DSM-IIIr criteria.

3.3.3 Neuropsychological testing

The neuropsychological battery of the CSHA is described below[11,105]. We obtained permission from individual agencies as well as authors to use, free of charge, all tests. Our psychologist participated in the CSHA in 1991 so she had experience in applying that battery. The battery was applied by a single psychologist to all patients in a single session lasting 2-3 hours. The battery was well tolerated by patients and families except in two patients who had to be tested in two sessions because of tiredness. Different items were occasionally not answered because of high level of difficulty in the face a demented patient. In the CSHA study the neuropsychological battery was not applied if the score on the 3 MS was below 50, indicating a too severe dementia.

We used the CSHA norms for scoring individual tests. A single set of norms for both English and French Canada was used in 1991[105]. A recent study has shown that norms differ between English and french Canadian (Meunier and Ska. November 1996. Unpublished). These results, obtained after phase 1 of the CSHA, were not available to us at the start of our study. Although cut-offs on some particular tests were lower for French Canadian, the frequency of diagnosis of dementia was less in the latter group. Norms used by the CSHA's study are described in appendix 4 as well as a sample of corrected norms for French Canada as obtained in November 1996. For patients younger than 60-65 years we used norms of the next age group that was available. For some sub-tests younger patients did better but for most other tests the performance of younger patients was comparable to older ones (cf. appendix 4). There were thus 10 patients in phase 2, age 54-64, for whom norms of the next age group were applied.

CSHA Neuropsychological battery

A- Memory	Buschke cued recall
	Wechsler memory scale:
	information subset
	Rey auditory-verbal learning test
	Benton visual retention test (revised)
	WAIS-R Digit Span
	Working Memory Test
B1- Abstract thinking	WAIS-R Similarities (Short Form)
B2- Judgement	WAIS-R Comprehension (Short Form)
B3- Aphasia	Token Test (11 items)
	Lexical Fluency (Words)
	Semantic Fluency (Animals)
Apraxia	Buschke Visual Component
Construction	WAIS-R Block Design (Short Form)
	Clock test
B4- Personality	CAMDEX history
C- Interference with work, social activities or personal relationships	CAMDEX history

We also added Trail-Making A and B.

3.3.4 Consensus meeting

At the next level a consensus diagnosis was established according to the form used at the CSHA[11](see collection forms in appendix 1). The original tool was used unmodified except for adding a category in the subgroup with cognitive impairment but no dementia. Another category, "two or more domains affected without dementia", was added to the existing category " cognitive impairment in one domain". The goal here is to compare the ratings of two consensus teams both constructed around a neurologist who saw the patient and a neuropsychologist looking at the result of psychometric tests. This is the way consensus is established in the literature. We are somewhat limited in the availability of personnel in the region. Only one psychologist was available. That person thus applied all psychometric tests and participated in the consensus neeting, as a neuropsychologist, with the first neurologist. The investigators were paired in the following way: consensus 1 represented the effort of neurologist 1 with the neuropsychologist (using psychometric tests) who met monthly. Consensus 2 consisted of neurologist 2 (MB), who travelled to Québec city with the results of the same psychometric tests and met with Dr Rémi Bouchard a cognitive neurologist, co-investigator in the CSHA. Dr Rémi Bouchard who was the only rater not examining the patients. He played the role of a second neuropsychologist. All raters were blind to the evaluation made by the others.

3.3.5 Diagnosis of dementia

All sets of criteria for diagnosis of vascular dementia were reviewed. More recent sets of criteria are consensus derived and based on recent literature. Since the forms were based on the DSM-IIIr criteria, it was difficult to use criteria that were not based on the working

tools. Also it was felt important to test fully the tools that were used in the CSHA[11]. The criteria for DSM-III-R diagnosis of vascular dementia are as follows: a) dementia (impairment in memory plus one other sphere; significant decline from a previous level of functioning), b) stepwise deterioration, c) focal signs or symptoms, d) evidence of cerebrovascular disease (history, physical, radiological). Most stroke patients would meet easily criteria b-d. As for dementia, we were more conservative and looked for involvement in memory plus two or more spheres. Judging whether there is a significant decline from previous functioning may be difficult, as it is an intuitive call in some cases.

As specified by these criteria there is no need to demonstrate on CT the presence of significant stroke or multiple lesions. This is helpful in our protocol since some patients had CT testing acutely at a time when this test is still negative. According to the DSM-IIIr criteria all raters had to provide a final diagnosis. In the CSHA study the diagnosis of dementia depend on a consensus obtained by a multidisciplinary team (neurologist, neuropsychologist, and history obtained from the family). Clinical diagnosis by neurologists is only a step in the process, and subject to more variability because no standardised tests are applied.

3.4 Prevalence of impairment in different cognitive domains

The approach taken for diagnosis included a step for identification of impairment at the domain level. Several tests were used by the neuropsychologist to probe all different domains (see section 3.2.2).The neurologist, using a more intuitive approach, could use one or more tests. In general , however, the neurologist relied mostly on items taken from

the screening instrument (3MS or mod 3MS).

3.5 Data handling and statistical analysis

All forms were kept in the office of the nurse coordinator. Data entry was done by the investigator using Paradox for Windows.

Statistical analysis was done using SPSS for Windows.

Frequency in percentages was used to evaluate the occurrence of protocol violators in phase 1 and 2 put together or the number of fully eligible subjects taken from a population of cerebrovascular patients. Frequency of involvement in individual domains is provided for phase 2 only.

3.5.1 Testing agreement

Agreement was tested at the domain level (criterion of DSM-IIIr) as well as with diagnosis. For inter-rater agreement Kappa statistics[109,110] was used when testing for agreement on dichotomous data (involvement of individual cognitive domains) between three examiners taken 2X2 (2 neurologists and one neuropsychologist), as well as between the two consensus teams. It is obvious that agreement between two neurologists, or worse, between a neurologist and neuropsychologist, is not a direct comparison because they used different tools. We nevertheless tested agreement at this level in an exploratory manner.Values of Kappa below 0.40 indicate poor agreement, between .40 to .75 fair to good agreement, and above 0.75 excellent agreement.

At the level of diagnosis, a weighted Kappa for multiple categories was calculated

according to Fleiss[109] using a hand calculator. The following weights for multiple Kappa was used (according to Fleiss and Cohen the intraclass correlation coefficient is identical to weighted kappa provided the weights are taken as below):

$$Wij = 1 - \frac{(i-j)2}{(k-1)2}$$

We calculated Intraclass Correlation Coefficient (ICC) for classification at the diagnostic level since cases were classified in 4 ordinal categories (no cognitive impairment, one cognitive sphere, two or more spheres-but no dementia; dementia). The ICC as an estimate of agreement is comparable to a weighted Kappa[111]. Standard one-way ANOVA was calculated twice in order to partition the variance between subjects raters and error. The ICC model (2,1), according to Shrout and Fleiss[112,113], was chosen. This model would allow us to generalize our findings to other neurologists as if our 3 raters had been chosen randomly. An alternative model (3,1) assumes that the raters are fixed. This model would give slightly higher values. It may be of interest since in our milieu the same 3 researchers may be chosen again for future studies. Paired t-tests for comparison of the 3MS score with modified-3MS was calculated.

3.5.2 Other instruments

We do not present results from the CAMDEX questionnaire since we used only a subscale

of the instrument to qualify for a criterion of the DSM-IIIr. Also, the CED-S was abandoned after 10 patients since all patients scored low value on depression. It was thought that its sensitivity was too low in our population.

Scoring of neuropsychological tests was done using norms based on 3 age groups: 60-69, 70-79, and over 80 years. Scores were used to rule-in criterion for cognitive impairment when a deviation of 2 SD was seen . Statistical analysis of neuropsychological test results was not planned at first since we were not testing hypothesis on this aspect (results for these tests are provided in appendix 3).

Chapter 4

Results

4.1 The stroke population under study.

4.1.1 Frequency of eligible subjects.

We believe that our patients were obtained from a truly population-based stroke registry. The number of missed cases is not known but is probably less than 10% since most hospitalized cases were counted.

We present in Table 2 a distribution of all cerebrovascular cases that were seen during the recruitment period from June 24 1994 to January 13 1995.

We enumerated 68 cases of ischemic incident stroke during the observation period. The exclusion of 35 cases as non-cerebrovascular shows that our approach for detection of cases was sensitive. Twenty-seven cases not meeting entry criteria were distributed as follows: 5 were less than 50 years, 3 did not have a CT scan, 14 died during the first 3 months and 5 had a stroke that was too severe. We studied 36/41 of truly eligible cases; 4 patients refused and 1 could not be reached after discharge from hospital.

The proportion of ischemic stroke patients studied (36/68 or 53%) is close to our prediction before the start of the study. The total number of all stroke cases during the study period was less than predicted (see Saguenay stroke registry above). It is possible that a lower incidence during the summer and autumn months explains this fluctuation.

4.1.2 Frequency of protocol violators

Among the 36 cases studied in phase 1 and 2, there were two cases who did not have a CAMDEX questionaire (in one case ,# 24, no family member was available; case # 32 died a few days before evaluation). Two cases were not available for study by the neuropsychologist (one moved without notice, case # 33; the other was judged to be too severe, case # 24). One case was considered too severe at the consensus to arrive at a diagnosis (case # 33). One neurologist could not complete the 3 MS in two cases considered to be too severe (cases # 22 and 37). Finally, 7 cases were evaluated outside our preestablished time window of 90 days ±2 weeks. They were seen at most 10 days outside this time range and this can be considered acceptable. There were thus 6 cases for which part of our protocol could not be applied. Major protocol deviation was seen for one case only. This patient, # 33, had moved and could not be studied by the neuropsychologist. He was labeled as cognitively impaired by one neurologist and as suffering from vascular dementia by the other neurologist. There was no consensus diagnosis established for this particular case since he was not evaluated by the neuropsychologist. This last case is the only patient that was lost to follow-up. All other cases represent partial data loss.

Considering the patients in phases 1 and 2, the frequency of truly eligible cases who underwent the full protocol is 30/41 (73% of our total population) or 20/26 (77% for our patients in phase 2). In the analysis a minor protocol deviation, namely mild delay in evaluation, was not included because that could be resolved in the future with a better budget and greater availability of personnel

Table 2. Distribution of 206 cerebrovascular cases seen in the Saguenay region over a 7 month period.

NOT ELIGIBLE	
False diagnosis	35
Hemorrhagic stroke	20
Recurrent stroke	24
Living out of region	11
Transient ischemic attack	48
EXCLUSION	
Less than 50 years old	5
No CT scan done	3
Death within 3 months post-stroke	14
Stroke too severe	5
TRULY ELIGIBLE	
Refused	4
Not reached	1
Studied	36

4.1.3 Description of study population (phase II)

In the second phase of the study 18 men (mean age= 71.3) and 8 women (mean age= 68.3) were evaluated. The youngest individual was 53 and the oldest 86 years old. There were 3, 10, 6 and 7 individuals in the following age categories 50-59, 60-69, 70-79 and ≥ 80. Using the classification of the TOAST [114,115]study the following final diagnoses for these cases were: 2 cases of large artery atherothrombosis, 3 cases of cardioembolic stroke, 6 cases of lacunes and 15 cases with ischemic stroke of unspecified etiology (10 cases with negative workup, and 5 cases with incomplete work-up). The average Barthell score, obtained for most patients at 3 months, was 88. There were 20/24 cases who scored above 70 indicating a good level of functional recovery.

A translation of a well validated scale for depression after stroke was used without pilot tested in our stroke population. Our nurse had difficulty in obtaining meaningful answers to several subitems. Notes from examining neurologists as well as some individual questions from CAMDEX were therefore used to identify depression. Only 4 cases presented depressive symptomatology at the time of examination. It was believed not to explain the cognitive impairment except for one case. The CAMDEX questionnaire was, for our purpose, deceptive. It correlated poorly with diagnostic classification. An Intraclass Classsification Coefficient between consensus diagnosis and total score on 6 questions of the CAMDEX intellectual decline subsection was 0.19 for team 1 and 0.14 for team 2 both showing poor concordance.

4.2 Interrater agreement.

4.2.1 Degree of agreement between 3MS and mod-3MS.

As mentioned above, neurologist 1 applied the 3MS scale and neurologist 2 used a modified version (mod-3MS). This new scale was not validated because time was lacking. This is important since impairment in the cognitive domain is derived from scores in subitems. For example, 3MS asks the patient to name 10 four-legged animals in 30 seconds. This type of test is standard in neuropsychological testing and seemed to be sensitive in detecting cases of vascular impairment, especially of the frontal type. The mod-3MS asks the patient to generate 8 colors instead. This seems an easier task. Using 3MS, two patients could not be scored because they were too severe. Also, two patients had low scores (27 and 49). Subjects scoring below 50 in the CSHA were not submitted to neuropsychological testing because of severity. With mod-3MS scores for those four patients were respectively 23,58, 42 and 59.

The correlation coefficient between 3MS score and mod-3MS was 0.91. Mean score for 3MS was 70/100 (SD= 15) and 78.6/100 (SD= 13.5) for mod-3MS. The means were statistically different when tested using a paired t-test ($p < .001$). This 8 point difference (95% CI= -11.4;-5.8) could have introduced a serious bias. That this did not happen is shown by the classification of cases. There were 15 cases tested with 3MS who scored below 80 (a threshold for cognitive impairment) and only 12 with mod-3MS. This did not prevent the neurologist using mod-3MS from diagnosing 6 cases as being demented whereas only 3 cases were diagnosed as such by the user of 3MS. The interpretation of individual items of this scale was left totally to the judgment of the neurologist since no

normative data for subitems of that scale exist.

4.2.2 Degree of agreement on cognitive domains

We examined agreement at two levels: a) between individual raters and b) between two consensus team (consensus 1 vs consensus 2). The results shown in tables 3 and 4 are disappointing. There was no or poor agreement in almost all categories. There was agreement only for involvement of long term memory between neurologist 1 and 2 and for apraxia and aphasia at the consensus level.

Table 3. Agreement between individual raters according to Kappa statistics. Neurologist 1 vs neurologist 2 (N1 vs N2), neurologist 1 vs neuropsychologist (N1 vs Ps), neurologist 2 vs Neuropsychologist (N2 vs Ps). Results from phase II (N=26).

Domain	N1 vs N2 Kappa	N1 vs Ps Kappa	N2 vs Ps Kappa
short term memory	0.22	0.39	0.16
long term memory	0.62	0.07	0.08
apraxia	0.33	-0.16	0.39
agnosia	-	-	-0.06
aphasia	0.38	0.12	0.25
judgment	0.29	0.13	0.31
abstraction	0.30	0.24	0.48
visuospatial	-0.12	-0.10	-0.20

Table 4. Agreement between the 2 consensus teams (C1= neurologist 1 with neuropsychologist; C2= neurologist 2 with Dr Rémi Bouchard using the scores of the neuropsychologist). Results from phase II (N=26).

Domain	C1 vs C2 kappa
short term memory	-0.15
long term memory	0.22
apraxia	0.56
agnosia	-
aphasia	0.56
judgment	0.31
abstraction	0.36
visuospatial	-0.16

4.2.3 Degree of agreement on diagnosis of changes in cognitive status

We describe the agreement for classification of these cases as to whether there was no cognitive impairment, involvement in one sphere (i.e. one domain), in two or more spheres, or dementia (Table 6). In order to compute an intraclass correlation coefficient (ICC) we excluded 2 cases that were thought to be too severe to be evaluated according to one team. Also, the diagnosis "AD with stroke" on the one hand and "vascular dementia" on the other were put together, since there were too few cases in either category. The ICC (calculation describedin Table 5) was .64 and represents a good agreement. For comparison only, a weighted Kappa (K= .62) was computed with individual weights estimated according to the method of Fleiss (see section 3.5.1)[109]. Although this method is not equivalent, and was used here only for comparison, it provided values in the same range of agreement.

Table 7 shows the frequency of involvement in individual domains for patients in phase 2, while table 6 is a 4X4 table comparing diagnosis between the two neurologists. A comparison of table 8 (N1 vs N2) vs table 6 (consensus level C1 vs C2) shows a better agreement in the latter. Thus, agreement is better between consensus teams (a tandem neurologist-neuropsychologist) than between individual neurologists. It seems likely that the input of the neuropsychological battery was substantial in reducing the variability[105]. An alternative is the possibility that a consensus per se is the method of choice for diagnosis, or a combination of the above. One has to mention the poor agreement at the diagnostic level between individual raters. The ICC for neurologist 1 vs 2 was .51 whereas the ICC between both neurologists and the neuropsychologist were respectively 0.059 and 0.229 very poor indeed.

Table 5. Computation of Intraclass Correlation Coefficient (ICC)- model (2,1)[113] based on repeated analysis of variance of k=2 raters (2 consensus teams) and 24 patients. Scores from the consensus teams were entered as follows: 0= no involvement; 1= impairment in one cognitive sphere; 2= impairment in two or more spheres but no dementia; 3= dementia.

Source of variance	df	SS	MS
Between subjects	23	17.67	0.76
Within subjects			
Between raters	1	.0833	.0833
error	23	3.91	.170

$$ICC(2,1) = \frac{BMS - EMS}{BMS + (K-1)\,EMS + \frac{K\,(RMS-EMS)}{n}}$$

$$= \frac{.7681 - .170}{.7681 + 1\,(.170) + \frac{2\,(.083 - .170)}{24}}$$

$$= .64$$

Table 6. Agreement at the consensus level C1 vs C2 for diagnostic classification.

Consensus 2 degree of involvement Consensus 1	no changes	one sphere	two or more	Vascular dementia	Alzheimer + stroke
no cognitive impairment	0	1	0	0	0
one sphere	0	2	2	0	0
two or more spheres	0	2	11	2	1
Vascular dementia	0	0	1	1	0
Alzheimer's disease and	0	0	0	0	1
too severe to be studied	0	0	0	1	0

Table 7. Distribution of cognitive impairment according to 2 neurologists.

patient number	impairment coded by neurologist 1	impairment coded by neurologist 2
13	memory short memory long abstract aphasia	memory short
14	memory short	-
15	memory short abstract	memory short
17	-	-
18	memory short abstract	memory short abstract apraxia
19	memory short abstract	memory short
20	-	memory short
22	memory short aphasia	memory short abstract aphasia visuospatial

23	memory short abstract aphasia	memory short abstract aphasia visuospatial
24	memory short abstract aphasia apraxia	memory short abstract aphasia apraxia
25	-	-
26	memory short	memory short abstract aphasia visuospatial
29	-	memory short memory long apraxia
31	memory short abstract aphasia	memory short

32	memory short memory long abstract judgment aphasia apraxia	memory short memory long abstract aphasia apraxia visuospatial
33	memory short memory long abstract judgment	memory short memory long abstract judgment aphasia apraxia
35	memory short abstract	aphasia
36	memory short memory long abstract aphasia	memory short memory long abstract judgment aphasia apraxia agnosia

38	memory short judgment	memory short aphasia visuospatial
40	memory short memory long aphasia visuospatial	memory short memory long abstract judgment aphasia apraxia
42	-	memory short
44	memory short memory long aphasia	memory short memory long
45	memory short aphasia	memory short aphasia apraxiavisuospatial
46	memory short aphasia apraxia	memory short apraxia visuospatial
47	memory short	memory short apraxia

Table 8. Diagnostic comparison between two neurologists.

neurologist 2 neurologist 1	not impaired	1 domain	≥ 2 domains	dementia
no cognitive impairment	2	2	1	
1 domain	2	1	1	
2 or more domains	1	4	3	3
dementia			2	1

4.3 Frequency of cognitive deficits

4.3.1 Involvement at the domain level.

The level of agreement between two neurologists or two consensus teams was higher in frequently involved domains, and less in those involved rarely or very often as shown above. Table 9 shows the frequency of cognitive impairment in different domains according to all raters. Some, like short term memory (87%), were frequently involved. Aphasia and abstract reasoning are impaired in about half of patients. Some raters had a high sensitivity for detection in certain domains. Specificity can hardly be evaluated in view of the lack of a gold standard.

It seems likely that cut-off scores for the neuropsychologist would have been lower, i.e. the frequencies would have been less, since norms for a French Canadian population have lower cut-offs[105](Meunier and Ska November 1996). At the consensus level, the other rater, i.e. neurologist, provided input that raised threshold for detection of impairment. In most cognitive domains the neuropsychologist sensitivity was higher.

Table 9. Frequency distribution in cognitive domains according to all possible raters.

individual raters / individual domains	N1 (%)	N2 (%)	Psychol (%)	Consens C1 (%)	Consens C2 (%)
short term memory	20/25 (80%)	22/26 (84.6%)	20/23 (86.9%)	20/23 (86.9%)	20/23 (86.9%)
long term memory	6/25 (24%)	7/26 (26.9%)	20/23 (86.9%)	15/23 (65.2%)	7/23 (30.4%)
apraxia	3/24 (12,5%)	10/26 (38.5%)	5/22 (22.7%)	7/23 (30.4%)	5/23 (21.7%)
agnosia	9/24 (37.5%)	1/26 (3.8%)	2/24 (8.3%)	1/23 (4.3%)	0/23 (0%)
aphasia	11/25 (44%)	12/26 (46%)	20/24 (83.3%)	12/23 (52.2%)	15/23 (65.2%)
judgment	3/21 (14.3%)	3/26 (11.5%)	8/24 (33.3%)	5/23 (21.7%)	4/23 (17.4%)
abstract	11/24 (45.8%)	9/26 (34.6%)	11/24 (45.8%)	10/23 (43.5%)	7/23 (30.4%)
visuospatial	1/25 (4%)	8/26 (30.8%)	8/21 (30.1%)	2/23 (8.7%)	8/23 (34.8%)

4.3.2 Frequency of impairment at the diagnostic level

Again there was no gold standard. Owing to the small sample size these rates are not precise. One method is to average the results from two consensus teams, especially for power calculation in future studies. Based on results shown in table 6 it can seen that team 1 identified 2 cases of VaD whereas team 2 identified 4, for an average of 3 out of 26 cases studied (11.5%). Total number of dementia cases was 3 for team 1 and 6 for team 2 and the average was 17.3%. Similarly 21 out of 26 cases (80%) had involvement in two or more cognitive domains.

Chapter 5

Discussion

5.1 The study population

5.1.1 Was it a population-based study?

We think that our results are based on a truly population-based study. Only 5 cases that were eligible were missed and only minor deviations from the protocol were observed in this pilot study. Only one previous study looked at a total population, and it did not use an elaborate neuropsychological battery[101]. The study of Tatemichi et al[29] looked at a population of consecutive hospitalized stroke survivors. They observed a 21% rate of refusal to participate, twice as much as in our study. Moreover 33% were found unsuitable for dementia testing because of severe stroke, impairment of consciousness or severe comorbid disease. No one would argue now that these cases are worth studying for dementia since they represent a subgroup with severe handicap. In this study 27/68 (28%) ischemic strokes were excluded on similar grounds, but two more cases with moderate aphasia, according to one neurologist, could have been exluded. This proportion is similar to Tatemichi et al[29].

The stroke registry follows an approach that is recognized as ideal for morbidity statistics[116]. Its success is based on collection of data from multiple sources (hospitalization, private office, vascular laboratory and hospital discharge lists). The registry was implemented in 1991 according to the guidelines of Malmgren et al[117] for an ideal stroke registry. Namely it should : 1- be prospective; 2- study a population whose denominator is known; 3- have complete coverage; 4- have a neurological examination

performed early; 5- have a high autopsy rate. According to Lilienfield[116], the success of this type of registry depends on maintaining the interest of cooperating physicians and hospitals. At the time of our pilot study in 1994, one hospital in the region decreased its level of collaboration so that most patients at that center were not seen during the acute phase of stroke. Although it is not possible to evaluate the frequency of non-hospitalized cases, this is probably a minor proportion of the stroke population. In our region up to 95% of all strokes were hospitalized in 1992.

We also encountered a large number of cases with stroke of unknown origin. Incomplete work-up could be the explanation for these. The Stroke Data Bank also observed a high number (40%) of strokes of undetermined origin[118].

5.1.2 What is the frequency of data loss?

We aimed to evaluate the frequency of protocol violators in order to determine if a larger study is feasible. There were 20/26 (77%) patients in phase 2 who completed the full protocol. As mentioned above seven cases were not included in this computation because they were studied up to 10 days late since it is believed that it did not produce bias. We tried to accommodate our patients as much as possible. Although consensus diagnosis could be derived, even when some tests were not realized (i.e. CAMDEX questionnaire, 3-MS, etc.), this is not ideal since one may want to apply different sets of diagnostic criteria and test their effect on sensitivity. These problematic cases are probably excluded from analysis by other authors. Thus, 4 out of 6 protocol violators were judged too severe by one or the other rater. One died before being seen by one rater and one could not be traced after moving away. There is not much one can do in these cases.

5.2 Interrater agreement

5.2.1 What was wrong with the identification of impairment at the domain level?

We observed very a low rate of agreement, as measured by the Kappa statistic, between 2 raters. Similarly low agreement was seen at the consensus level for individual domains. This was observed despite an agreement on final diagnosis above 0.60 using either Kappa or ICC (see Table 5). In the CSHA comparisons were made between diagnosis of no dementia/dementia between clinicians, neuropsychologists and consensus teams. Kappa values for French Canada varied between 0.41 and 0.76. The worst scores were obtained for institutionalized individuals who may resemble the more severe cases of stroke survivors in our study. In the CSHA study there were no comparisons of the ability of a clinician and a neuropsychologist in identifying deficit in individual cognitive domain. Not only are the tools different but the purpose is not the same: the neuropsychologist, using high sensitivity tools, serves in ruling in criteria, whereas the clinician looks for reasons to explain the involvement as well as to provide a differential diagnosis.

Although the methodology of Kappa statistics has been criticized, it remains in widespread use today[119]. It has been said that it gives a low value in homogenous populations, i.e. a low Kappa value in situations of high prevalence[120] or low prevalence[121]. This applies to certain of our domains which were scored positive either very frequently (short term memory) or almost never affected (agnosia). Shrout et al[119] have analyzed the different sources of variation in these type of studies and grouped them as follows: 1- difficulty during the information gathering phase of the study (information variance), 2- instability

of the clinical phenomenon being measured by the diagnostician (occasion variance), 3- the use of idiosyncratic sets of diagnostic criteria (criterion variance), i.e. 2 diagnosticians having different concepts of a disorder, 4- careless, inconsistent, incompetent inference on the part of the clinician, 5- constant bias.

Although all raters here have between 6 and 8 years of practice, it can be said that this is not sufficient to guarantee valid diagnoses. Both neurologists participated in a community-based study on Alzheimer's disease (IMAGE)[122]. The level of accuracy, close to 85% (study unpublished), for diagnosis of AD in this community project, compared with pathology, is similar to that found elsewhere in the literature. The neurologists were not tested for reliability at the item or domain level, so that it is possible that they had different ways of conducting neurological examinations. One main weakness of the protocol was the lack of training as well as standardization of the neurological exam.

Other authors have observed a tendency for clinicians to use 'best guesses' to resolve issues that are not clearly specified or when the individuals can not be classified according to written criteria[123-127]. Agreements, even by experts, are less than commonly assumed[125,128].

The level of agreement on cognitive status changes seems very good compared to agreement at the level of individual domains. It is likely that the diagnostic approach for individual domains is different than the one involving a global diagnosis. This suggests that clinicians work better with an intuitive approach regarding a final diagnosis, but do poorly in agreeing on the presence of individual components.

5.2.2 Agreement was low on memory involvement.

Low agreement on memory involvement in an elaborate neuropsychology battery is attributable to the commonly observed poor performance of subjects in this domain according to Teng et al[129]. Teng is the first author of the methodology paper on the 3MS screening tool that was used in this study[106]. The frequency of involvement of memory in our study was much higher than that found in the literature. Wade et al, in a study of 186 individuals taken from a community-based stroke registry, studied memory involvement at 3 months. They found difficulty in immediate logical memory in 29% and with immediate visual recall in 39%[130]. Tatemichi et al[131] found abnormal scores in about 20% for most memory subtests in a population of ischemic strokes seen at 3 months. Zaudig et al, in the SIDAM protocol[132], found some of their lowest Kappa on immediate memory (K=0.47), where there was a high failure rate. When they used failure in one out of 18 questions for choosing impairment in the memory domain, Kappa was -0.05 showing the importance of not using too sensitive, unspecific criteria. Using a different set of criteria (failure of 2 items out of 18) they observed better agreement (Kappa=0.79).

5.2.3 Criticisms of the DSM-IIIr criteria.

The low agreement on cognitive impairment in most individual domains mentioned above is not surprising in view of the fact that there are no cutoffs specified in the 3MS. Normalized scores have been published based on age and education for the Mini-Mental State[133]. No such norms were available for the 3MS, as obtained from a large community, prior to the launching of the CSHA. Obviously there are no guidelines for dividing the total score into individual domains, although this was attempted with a similar tool

(SIDAM)[132]. This study described pilot testing of a screening battery presenting 55 questions to subjects. This corresponds to the length of time the two neurologists in our study spent with our patients. Agreement in the SIDAM study was between psychiatrists scoring an individual session of data gathering seen by all raters whereas in our study, data was collected in individual sessions. The SIDAM tends to reduce variance. The latter study also prespecified cut-off scores for all items. Interviewers were not allowed to ask any questions other than those found in the questionnaire. One would thus expect a better result on reliability, although validity can't be assessed with this approach. Thus, agreement was good or excellent for most domains, criteria or diagnoses. Agreement was lowest for diagnosis of cerebrovascular dementia (Kappa=0.64) although a low base rate could partly explain this observation.

In the previous decade many authors have criticized the use of DSM-III criteria in the field of dementia[126,134,135]. They observed poor specification of criteria , lack of appropriate cut-offs, failure to use information from proxies, failure to recognize that dementia is distributed on a continuum scale (i.e. no specification for severity)[135]. There is too much interpretation left to the investigator in deciding involvement at the criterion level such as 1) when to decide if there is an intellectual loss, 2) when there is sufficient memory loss, or 3) when there is sufficient change in social functioning.

As mentioned above, the two neurologists were free to decide when to call for failure in a particular domain, using whatever tests he/she found helpful. It is not surprising that a low level of agreement was found at the domain level.

5.2.4 Why would 2 neurologists disagree on diagnosis?

We observed a low level of agreement between two neurologists diagnosing the absence or presence of cognitive impairment, or dementia. This is even more surprising than what can be found at the domain level. Most of the explanations offered above could apply here. Again poor specification of criteria would bring diagnosticians to disagree purely on interpretation. On the other hand recognition of the most severe diagnosis, vascular dementia, should be agreed upon more often. The sources of discrepancy can be found with the clinical description in appendix 5. The most common explanations for disagreement were whether a patient was testable or not because of aphasia, whether there was a significant impairment of social function and finally whether the intellectual deficits were enough to qualify for a diagnosis of dementia.

It appears obvious that the DSM-III criteria are not helpful in resolving these difficulties. This has been observed by recent reviewers[16] and recent consensus on vascular dementia have been put forward to replace the non-specific criteria of the DSM-III criterias. Neurologists appear to be better in differentiating AD from VaD than in deciding whether there is vascular cognitive impairment without dementia or very mild dementia. That the latter questioning is not the most crucial issue has been mentioned by Hachinski[136], since both populations are at risk of evolving to a more severe dementia syndrome and could benefit from treatment at an earlier stage.

The use of recently published NINDS-AIREN criteria[16] has been described[137]. Agreement between 4 neurologists taken 2 by 2 shows Kappa for agreement on vascular dementia between 0.46 and 0.72. The investigators used a case review of 42 demented cases which

were interpreted and compared in six 2X2 comparisons.

This study cannot be compared to ours for several reasons: 1- we looked at cognitive impairment on a spectrum from a population of strokes, whereas they looked at classification of dementia in a series where all cases were demented, 2- both neurologists in our study examined all patients; in the study by Lopez et al [137]only printed case summaries were used. It can be said nevertheless that recent criteria for diagnosis of VaD don't offer the kind of precision one would desire for study of drug treatment for instance. Definitely, more research is needed.

The main take home lesson is that reliability of diagnosis of dementia by a neurologist is poor to moderate when carried alone and has to be supplemented by psychometric testing. We observed that the addition of neuropsychological data brings more stability to the diagnosis. There was much better agreement at the consensus level than between individual raters. This is not surprising since the use of a neuropsychological battery is recommended in recent diagnostic criteria[16,56].

The theory behind agreement has been around for many decades. Its use in psychology and psychiatry has been widespread. Only recently has it been used in neurology[137-139]. Although the use of Kappa has its detractors and its limits[140] it is nevertheless accepted as a solid technique. So is the use of the intraclass coefficient.

Recent publications have emphasized the possibility of low agreement among experts in fields as diverse as radiology[125], pathology[128] or cardiology[141]. Publications in the field of psychology-psychiatry have shown high levels of agreement using the intraclass

coefficient[142,143]. Our low agreement will require a rethinking of the methodology or the use of different tools.

5.3 What is the frequency of cognitive impairment or dementia at 3 months?

We tried to avoid calculating rates in this small study. In order to calculate power in future studies one needs to make the following observations. After excluding isolated memory deficits (since the specificity of this observation seems to be low), and averaging results from the two consensus teams, we found in a population of 26 patients 12 cases with involvement in more than one domain (including memory or not), 3 vascular dementia (one team found 2 cases the other team found 4) , and 1.5 cases (one team found 1 the other found 2) of Alzheimer's type dementia with stroke. Corresponding rates would thus be 46% for cognitive impairment in more than one domain, 11.5% for vascular dementia, 5.8% for AD with CVD. These rates are close to Tatemichi et al[29] who found a frequency of 26% for dementia 3 months after ischemic stroke in a population of survivors who were aged 60 years and above. In our study, 4 cases, who were between 50 and 59, were included. A similar rate of 15.9% was observed in the Stroke Data Bank[27]. In the New York study there was one third of cases for which the etiology was related to AD, a proportion similar to ours.

An Italian study, published as yet only as an abstract, found that out of 94 testable ischemic stroke patients at 3 months, 16% had dementia and 75% had "no significant cognitive impairment"[144]. This categorical statement and the lack of recognition of mixed pathology seems difficult to understand.

We observed high rates of failure for memory subtests (see Table 7) , see discussion below. Although this may be artefactual, others have observed frequent involvement of memory after stroke. Memory was affected in only 20% of the New York study[29] and 29-39% in the study by Wade et al[130]. In our study involvement in apraxia was founf in 21 to 30%, agnosia 0 to 4%, aphasia 55 to 65%, judgment 17 to 21%, abstract thinking 30 to 45%, and visuospatial domain in 9 to 34%. Here the two numbers represent the frequency of involvement according to both consensus teams. Corresponding rates by Tatemichi et al[131]were 13-32% for language , 16-25% for visuospatial, 16-20% for abstract thinking. Although these rates are not totally comparable, they point to a high frequency of involvement in these patients. Specificity was not calculated here since there is no gold standard.

5.4 Which diagnostic criteria should be adopted?

We mentioned above the reliability of recent research criteria. In Table 10, a summary of publications on this aspect of inter-rater agreement, including our study, is included. It must be said that validity is not addressed since there is no gold standard and pathological verifications of these criteria have not yet been done. In two studies[137,145] reliability was tested with printed case summaries, a situation which is far from real life. Neverthelesss, all studies found a Kappa value of around 65% for diagnosis of VaD which is acceptable. The SIDAM approach shows that DSM-III- r (or more recent DSM-IV and ICD-10 criteria) can be used if standardization of data collection is used.

This brings us to the important aspect of sensitivity of these criteria. In a recently

published German study[146], 167 patients with probable dementia were examined and classified according to 4 different sets of criteria for VaD (DSM-IV, ICD-10, ADDTC, NINDS-AIREN, see abbreviations in appendix 10) . The sensitivity of each tool varied by a factor of 4 where 45 cases were classified as VaD according to DSM-IV but only 12 cases according to NINDS-AIREN. Only 5 cases met criteria of all 4 sets. Thus, some diagnostic criteria have high sensitivity (DSM-IV), others have high specificity (NINDS-AIREN).

One source of disagreement was related to subjects with borderline cognitive deficits. Another source was related to the most frequent subtype of VaD, namely white matter disease, which was seen in 42% of subjects. One major difficulty is that the latter group usually lack the focal neurological signs that are central to the clinical diagnosis of VaD. Another source of difficulty is the finding that 30% of subjects diagnosed as VaD according to DSM-IV did not have any infarct on CT scan and that 31.1% of these subjects also met the criteria for Alzheimer's disease. The possibility that there is a high proportion of mixed disease was alluded to in the background section.

In order to identify better criteria for VaD it seems likely that further work is necessary. For comparability across nations and for increased sensitivity, simpler criteria like DSM-IV should be used in a larger study. Nothing prevents us from using all sets of criteria simultaneously and then comparing results.

In the German study[146] no MRI was done so it is not possible to fully test the sensitivity of the Californian criteria (ADDTC)[56]. In the latter, MRI is suggested for diagnosis of VaD.

Table 10. Inter-rater agreement on diagnosis of vascular dementia according to different studies

Study	references	# of cases	Printed cases vs real patients?	research criteria	Kappa
Baldereschi	[145]	51	printed	ICD-10	0.66
Lopez	[137]	42	printed	NINDS-AIREN	0.42-0.72
Zaudig	[132]	60	real	SIDAM protocol DSM-IIIr ICD-10	 0.64 0.64
Our study		26	real	DSM-III	0.61 weighted Kappa

5.5 How to diagnose mild dementia?

This is a crucial question at the heart of the difficulties that was encountered in this study. As mentioned by Hachinski[147] we need to identify cases at an early stage where treatment can be instituted. On the other hand, at a low threshold for detection, specificity is low. This was shown in an international study sponsored by WHO looking at the cross-national reliability of DSM-IIIr and ICD-10 criteria[145]. They found no agreement (Kappa = 0.10) on diagnosing "cognitive impairment". That it can't be agreed upon does not negate its usefulness as a concept. In a study in Mannheim, Germany, the most powerful predictor of dementia was the identification of cognitive impairment from a screening instrument[21]. Tobiansky et al[148] have also shown that subjective memory impairment increases the risk of dementia and of depression fourfold and twofold respectively.

The diagnostic disagreements are due mainly to the difficulties in differentiating mild dementia from cognitive impairment. On the other hand inter-rater agreement on 3 levels of severity (mild, moderate, severe) of a dementia syndrome showed a Kappa of 0.42[145]. Similar agreement fell significantly (Kappa= 0.26) after merging moderate and severe dementia, i.e. there is a difficulty in recognizing mild dementia.

Establishing a theshold is always arbitrary. Brayne et al[149] have shown that the distribution of changes in MMSE scores in older individuals (over 75 years) is unimodal, showing that cognitive decline is universal in aged individuals. Here one can see a similarity with hypertension. Although the benefit of treating severe hypertension is well proven, it is only when intervening in mild and moderate hypertension that one can have an impact on the community.

5.6 Level of education

This variable may have importance in our study when using standardized neuropsychological tests that have established norms in a population different than ours. The average educational achievement in our sampled population was 8.2 years. In our sample, half of all studied individuals had a primary level of education compared to 26% in the Rotterdam study[15]. Education plays an important role in screening tests such as MMSE even though they were designed to minimize this effect. Low education is also a risk factor for VaD. In the Rotterdam Study[15] the lowest quintile of education was associated with VaD. In the study from Mannheim, vascular dementia was seen exclusively in housewives and unskilled manual workers[21]. There is no explanation yet, but it is possible that people with less education have more risk factors for vascular disease (eg. smoking, untreated hypertension, dyslipidemia). That education may have played a minor role is shown by a study from the CSHA. It was observed that the prevalence of dementia in French Canada was not higher than in English Canada despite a significant difference in education achievement, 7.0 vs 10.4 years respectively [105].

Chapter 6

Conclusion

We have shown in our pilot study that a population-based stroke registry can be used to identify those who present dementia at 3 months post ischemic stroke. In an ideal study 33% of patients with cerebrovascular presentation would be eligible for the study. About 40% of these would be excluded on the basis of severity of motor deficits, aphasia or because they did not have a CT scan during the acute phase. Among 26 cases who participated in phase 2 of this study there were 6 cases of protocol violation. In two cases, one of the evaluators could not see the patient. In two cases, the patient was judged to have too severe neurological impairment to obtain meaningful results.

We observed poor agreement between two experienced neurologists using an intuitive method but classifying patients according to DSM-IIIr criteria. When using consensus diagnosis on the other hand, with the help of neuropsychological evaluation, acceptable agreement was seen. More stringent criteria would have to be applied and a review of the recent literature shows that this is feasible.

We observed a prevalence of dementia after stroke of 17.5% where 2/3 seemed to be related to VaD, similar to what is found in the literature. There were 80% of patients who showed impairment in more than one cognitive domain. Our study thus showed high sensitivity in identifying cognitive deficits at the expense of low interrater reliability. Although one can synthesize current knowledge and use all current technological support, there is no ideal study in this field. This is because there is no current set of criteria for VaD that has been validated. It all depends on the objectives of the study. An

epidemiological study may require a greater sensitivity at the cost of specificity, or vice versa. Research in this field is recent and ongoing. In the following section a grant application based on our clinical set-up is presented.

Chapter 7

Grant proposal

Prevalence of dementia and cognitive impairment 3 months after an ischemic stroke or transient ischemic attack. Comparison of a referral hospital with a population based stroke registry.

1. Background.

We have seen in the past decade a resurgence of the interest in vascular dementia (VaD). This entity is still in the process of being defined, its mechanisms being unraveled and research diagnostic criteria being identified[16,56]. From earlier terms such as "arteriosclerotic dementia", "Binswanger's disease"[1] to "multi-infarct dementia"[3] our knowledge has evolved, although there is a lot of confusion regarding the relative contribution of these different entities.

It is known that VaD represents the second cause for dementia, after Alzheimer's disease (AD), in a proportion varying from 10% up to 50% depending on the country or the age group[13,150]. It is also recognized that an important group of patients have a mixed disease composed of AD plus VaD, the proportion of which is subject of controversy but estimated conservatively at 10-20%.

Epidemiological studies from Europe and Canada have shown that the prevalence of VaD (after averaging results of some studies) is close to 0.5% at age 60-69, 2.5% at age 70-79, and 4-15% over age 80[10,11]. These measures are quite imprecise owing to the unproven reliability of research tools. It seems important to measure this entity more accurately

since remedial action could be taken quickly. Indeed, this type of dementia is amenable to therapy[16].

There have been few community studies aimed at measuring its prevalence or more rarely its incidence. Since VaD represents heterogenous categories, being the result of many types of infarcts "large and small"[3], it seems logical to study it with a pure population of stroke patients. Only then would it be possible to characterize more fully the different subtypes. Tatemichi et al[29] looked at 251 survivors of an incident ischemic stroke who were evaluated 3 months after the event. This hospital based series identified a high rate of dementia in testable subjects. Thus, about 16% were thought to present one form or the other of VaD whereas close to 8% had a type of dementia resembling Alzheimer's disease. There was a significant proportion of these patients who, although they were not demented, presented some form of cognitive impairment on neuropsychological testing[131]. The characterization of this important subgroup, the cognitively impaired-but-not-demented, has been neglected by recent guidelines for diagnosis of VaD[16,151]. This is unfortunate since this group represents a population at risk and should receive our attention before irreversible damage occurs[151].

Hachinski and Bowler[151] observed that recent guidelines do not include an obligatory classification into subgroups. The recent ICD-10 criteria for VaD partly include subgroups in the classification[152-154] as follows: a) dementia of acute onset, b) multi-infarct dementia, c) subcortical dementia, d) mixed cortical and subcortical, e) others and f) unspecified. Only type c and d represent true etiological subgroups. Type (a) relates more to mode of onset and type (b) to mode of progression, a rather heterogenous classification. Similar

types of pathophysiological mechanisms have been described in two recent consensus conferences on VaD. The NINDS-AIREN sets of criterias do not include these categories in the final diagnosis[16].

Validation of these criteria remains to be done[155]. A recent study looking at reliability found good agreement between observers with a Kappa value of approximately 0.60[137]. This study used printed case summaries and does not tell us much about the reality of testing in the real world.

1.1 Saguenay stroke registry.

We will use a methodology implemented for a community-based stroke registry for collection of cases. The registry started in 1991 and is based on a system of notification linking all 3 local hospitals. Entry of non-hospitalized patients occurs via outpatient clinic, private practice of neurologists who all collaborate on this project, Doppler lab, etc. Our contact rate has been high in the past. A 10% non-notification rate, which can be verified via study of hospital admission logs, was observed. According to our ethics committee we could not study patients, for whom we were not notified. Nevertheless, there is a mean of estimating this proportion, namely by following admission lists for the target diagnosis at the 3 hospitals.

<u>1.2 Prevalence of cognitive impairment after an ischemic stroke in the Saguenay region-a pilot study.</u>

We conducted a pilot study in 1994 aimed at testing the tools of the Canadian Study on Health and Aging (CSHA)[11]. Thirty six consecutive eligible survivors of a first-ever

ischemic stroke were obtained from the Saguenay stroke registry. They were studied 3 months after stroke with a neuropsychological battery, a neurological examination and a nurse interview using the CAMDEX questionnaire[103], a scale for depression[104], etc. According to the CSHA protocol[11] dating back to 1991, all observers specify whether there is involvement in a particular domain of cognition (memory, language, praxis, etc). A diagnosis is then made (whether the patient is normal, cognitively impaired in one domain, two or more domains, or is demented). Demented patients are subclassified as AD, AD with cerebrovascular disease (CVD), and VaD. Note that AD plus CVD is referred to as MIXED cases by other authors. VaD patients are further classified in i) acute onset, ii) multi-infarct, iii) subcortical, iv) mixed cortical and subcortical. A tandem team neurologist- neuropsychologist then classifies patients as to whether there is involvement at the domain and diagnostic level.

Although proportions based on such a small study are unstable (results of two consensus teams were averaged), it was estimated that twelve percent(12%) of patients had VaD, six percent (6%) had AD associated with CVD, and forty-six percent (46%) had cognitive impairment in more than one domain. Similar rates for dementia have been observed by others[27,29,144]. In a substudy on reliability, we found an acceptable level of agreement at the consensus level for final diagnosis (Intraclass correlation coefficient ICC=0.64). This occured despite low level of agreement between 2 neurologists at the domain as well as the diagnostic level. Poor operationalization of DSM-III criteria[16,126,134,135], which were used in our study, have been observed by others. The lack of standardization of the neurological examination, the absence of norms for subitems (i.e. the domains) of a screening tool that was used (3MS)[106], the relative difficulty in deciding whether a

borderline case was demented or cognitively-impaired-but-not-demented, whether a mild-moderate dysphasia explained a poor performance in most tests, high prevalence of involvement on memory (i.e. non specific cut-offs), low prevalence in other domains (i.e. agnosia) all contributed to the poor agreement among our raters (2 neurologists and one neuropsychologist). In that study poor agreement between 2 raters for involvement at the domain level (Kappa between 0 and .62) was observed. In the current study effort will be invested in standardization of methodology as well as better training of raters.

1.3 Recent studies.

Most recent studies have used consensus diagnosis[16,29]. Our study also found a higher degree of concordance after consensus, justifying its use in this proposal. A recent study tested the value of an extended screening tool for dementia, the SIDAM questionnaire[132]. This questionnaire is based on 55 questions administered over 30 minutes. It incorporates all questions of the very well known Mini-Mental Status and operationalizes the diagnosis of dementia according to DSM-IV and ICD-10. This tool showed good results for interrater agreeement with Kappa = 0.6 at the domain, criterion or diagnostic level. Kappa for VaD was 0.63. This tool, translated into several languages but not French, will be used here by a neurologist, after translation, as a supplement to a standard neurological exam. The other side of testing is the neuropsychology battery. Most accept now that there is no standard battery that is validated for this type of patient[16]. The range of domain involvement is as vast as in AD yet it does not necessarily follow that the same tests will have similar validity and sensitivity. VaD had a lesser degree of involvement in memory and language[89]. It is also believed that a large proportion of VaD patients suffer from a

form of disconnection syndrome between frontal lobes and subcortical structures[93,96]. White matter changes and lacunes form the substratum of this entity[93]. These individuals are described as being more apathetic, have almost universal difficulty in concentration and attention, have slowness in information processing, lack initiative, have poor motor executive functions, and have poor strategy for resolution of complex constructional tasks[93,96,156,157]. A neuropsychological battery would need to probe these domains[100,158].

The problem of overlap between AD and VaD. The failure of current approaches to separate the mixed group from either AD or VaD is shown by the low specificity of the Hachinski's Ischemic Score [47]. There is also much overlap between AD and VaD using neuroimaging[61] or neuropsychology[88]. The ICD-10 criteria, like others, have provisions for diagnosing concurrent AD and VaD. The criteria seem to have high specificity for identifying mixed disease at the cost of sensitivity.

Choosing diagnostic criteria. How did we choose our tools knowing the difficulties with current research criteria for VaD? We can set our goals first and then decide which set to use. We would like to : 1) use known criteria in order to facilitate comparison with others, 2) recognize and evaluate the large cohort of patients presenting cognitive impairment but no dementia, 3) use criteria that are not too sensitive on neuroimaging since in our region MRI is not available, and because CT scanning, performed in the acute phase of stroke, is often negative in ischemic stroke[54], 4) categorize our patients into pathophysiological subgroups, 5) be able to adapt the protocol for individual patients like those with mild-moderate dysphasia, old age, tiredness due to co-morbid disease, low education, right-

hand paralysis, etc. The DSM-IV and ICD-10 criteria could represent an advantage for our study[66]. Cases will also be classified according to NINDS-AIREN guidelines[16]. The latter classification is known to have low sensitivity but high specificity[146] for VaD. Although these sets of criteria provide different estimate of prevalence they will all be used in order to compare results with other studies which may use any of those sets. With advances in this field it will be possible to analyze our results accordingly.

2- OBJECTIVES

1) To measure the prevalence of a) dementia, and b) "cognitive impairment but no dementia" after both a TIA or a stroke and according to different sets of criteria: DSM-IV, ICD-10 and NINDS-AIREN. These results will be obtained after pooling data from 2 centers: hôpital de l' Enfant-Jésus in Québec city (a large referral hospital) and the Saguenay stroke registry.

2) To estimate the difference in these proportions between the 2 centers

3) To estimate the relative proportion of etiologic subgroups for VaD according to i) ICD-10, then ii) our own classification: a) the strategic cortical infarct, b) strategic subcortical infarct, c) multi-infarct, d) multiple lacunes, e) white matter disease, f) mixed cortical and subcortical.

4) To identify factors associated with the risk of the 2 major types of dementia (AD and VaD) as well as cognitive impairment after stroke and TIA.

3- Methodology

3.1- Case detection

We will obtain patients from the Saguenay stroke registry[102]. This registry allows rapid notification to the research team via several means including pager, answering machine and a research nurse collecting admission sheets for the target diagnosis. There are 3 hospitals in the region one of which is Chicoutimi hospital where the researchers have quick access to patients, since all neurologists collaborate on the study. Hôpital de La Baie has few admissions for acute stroke. Hôpital de Jonquière collaborated well with the registry in the first 3 years, but interest then declined so that in the past year a high rate of non-notification (1/3) was observed. This could be circumvented by reestablishing contact with key personnel. Our Ethics Committee requires that an attending physician notify us first before contacting the patient. This does not prevent us from actively pursuing cases. In our pilot study, admissions on wards were followed without being aware of the name of patients. Then, the attending physician was called and ask permission to see his/her patient. Cases will also be obtained via the outpatient clinic. It is harder to estimate the proportion of non-notification for transient ischemic attack. Many such cases do not reach medical attention and most are not hospitalized. Some cases will be detected several weeks after their event (via hospital archives review, Doppler lab, etc). If they can still be seen at 3 months post event, they will be included. In any case all efforts will be made to count the number of non-participants in the study. Hospitalized cases in Québec city will be collected prospectively using an acute stroke treatment log already in use at that center. The nurse coordinator is responsible for obtaining consent at the end of hospitalization or at a later date. The way contact with these patients or their families is established,

including the use of a consent form, will ensure that the study meets ethical standards for inclusion of unable subjects.

3.2- Inclusion and exclusion criteria:

INCLUSION * Saguenay arm: resident of Saguenay region

Québec arm: all hospitalized patient at hôpital de l'Enfant-Jésus

* survivors of an ischemic stroke or TIA

* age ≥ 50 years

EXCLUSION * no CT scan

* refusal to provide consent

* no proxy respondent

* too severe stroke

* aphasia too severe (Montreal-Toulouse test as applied by speech therapist)

* death within 3 months

* hemorrhagic stroke

Effects of selection criterias.

In our pilot study covering a period of 7 months 158 cases with probable stroke event were evaluated. The following were not eligible: 35 cases with false diagnosis, 20 hemorrhagic strokes, 24 recurrent strokes, 11 were living outside the region. A total of 68 first-ever ischemic strokes was counted. Five cases younger than 50, 3 cases in whom a

CT scan was not done, 14 cases dying within 3 months of their stroke, and 5 cases deemed too severe were excluded. Among truly eligible cases 4 patients refused to participate and one could not be reached. Of 36 cases who were studied 7 could not complete one part or the other of the protocol. In only one case was the missing information thought to be important (a patient could not be evaluated by the neuropsychologist after a change of address).

3.3- Evaluation at 3 months.

Although unproven, this time mark has been proposed by recent investigators[16,27]. It is a time when most improvement has occurred, although individual cases still get functional improvement between 3 and 6 months. The interest in such a study tends to fall beyond that period and survival becomes an issue. Patients who did not provide consent will be contacted by phone, and for all an interview will be scheduled at their convenience. Rare cases will be studied at home in order to minimize refusal. In our pilot study (Phase II) 20 out of 26 cases were studied at 3 months ± 2 weeks.

Although much experience was gained during our pilot study, a run of 20 more subjects will be used in order to standardize our methodology and apply correctly the definitions (see below). Raters (one neurologist and a neuropsychologist) will review the diagnostic process against a panel of 4 experts assembled only for this training phase. This panel will be considered as a golden standard for the training phase.

3.3.1 Research nurse evaluation.

The nurse coordinator at both centers is responsible for obtaining consent at the end of hospitalization for a stroke or TIA. For recruiting unable subjects, guidelines used in the

field of dementia research will be used . Thus a family proxy will also provide consent. At the 3rd month visit the nurse will apply several validated scales in a 1 hour interview. The following will be used: Barthell index, CED scale for depression after stroke[104], CAMDEX[17]. The interview will occur at the same time of the day , around 10:00-12:00 AM.

3.3.2 Neurologist exam.

A participating neurologist will apply a standard neurological examination as well as the SIDAM questionnaire[132]. The neurologic examination specifically detects signs that are known to be associated with a diagnosis of VaD or AD. Collection sheets for involvement at the domain, criterion and diagnostic levels will be completed. All clinical data from the previous hospitalization will be available. The family proxy will also be met and strong emphasis put on identifying any change from previous level of functioning. In the hour after seeing a patient, the neurologist will classify the patient according to the guidelines of the 3 sets of criteria. At that time the neurologist will decide on the most likely etiological subtypes of VaD. This decision is somewhat empirical as these subclassifications have not yet been validated.

We will use a semi-quantitative and intuitive question in order to evaluate the level of mental deterioration of the patient under study. Family relatives will be asked to describe the current level of mental function, in percentage, where 100% represents the level prior to the stroke.

3.3.3- Neuropsychology. In our pilot study no subtest could not be completed except in cases with mild-moderate aphasia or cases with more severe attention deficit. It is planned to use the CSHA battery[11] again since we gained experience with it. More tests for attention and for frontal lobe functions will be used. Therefore, the auditory continuous performance test and the visual continuous performance test for attention[100], the Stroop color test[100,159], the Mattis motor performance subtest, the WAIS-R picture arrangement and WAIS-R object assembly[89], the Porteus Maze test[93,100], as well as unstructured tasks, such as the Cookie theft picture test from the Boston Aphasia Test and the Lezak Tinker Toy assembly test, as suggested by Mendez and Mendez[158], will be added. The whole battery should be completed in 2-21/2 hours. In rare cases it will be completed in two interview sessions. Norms for the CSHA battery's tests have been established for a French Canadian population (Marchand & Ska, November 1996, unpublished).

3.4.4- Definitions

We will use the following definitions:

Cognitive impairment in one domain: performance below 2 standard deviations compared to a similar age group in that particular domain.

Cognitive impairment in two domains or more: again, 2 SD below norms for the test; does not meet criteria for functional impairment at home justifying the label of dementia.

Dementia: see definitions of dementia according to DSM-IV, ICD-10 [152-154] and NINDS-AIREN criteria (appendix 5,6,7). At the end of the session, the rater, using available sets of criteria, will classify the patient according to those 3 sets. For ICD-10 criteria impairment at 3 months, instead of 6 months, will be used.

For the memory criterion we will require an impairment in 50% of the tests below 2 SD. For other domains a failure in 2 out of 3 tests, at 2 SD, will be required.

Consensus diagnosis: Twice a month both neurologist and neuropsychologist will meet and classify their cases according to the 3 sets of criteria using all material at hand. In case of disagreement, a third neurologist with experience in dementia testing will be included in the discussion and a rating will be decided by majority vote. Attention will be paid to the source of disagreement. A primary diagnosis will be provided for patients for whom data are complete. A secondary diagnosis will be provided for those with missing or unknown data (eg. suboptimal neuropsychological testing may occur because of right hand paralysis).

3.5- Neuroimaging. A review of the field of neuroimaging suggests that MRI could be more useful than CT scanning. However, there is no pathognomonic finding in most cases, and, since MRI is not available for routine use in our region, CT scan will be used.

All patients will be called around the 3rd month mark for CT scanning. Scans will be scored blindly by a radiologist, using the exam that was performed the closest to the 3-month evaluation in case of repeated testing. In rare cases, only the acute stroke period exam will be available. A radiologist with experience in this type of study will rate the presence of stroke(s)(which site is involved, total volume of infarct), leukoaraiosis, atrophy and ventricular enlargement according to the CSHA-2 protocol (unpublished).

3.6- Statistical analysis

Data handling . All forms will be processed at Chicoutimi Hospital. Cases with missing

data will be returned to the investigator. Paradox for Windows will be used for data entry and management.

For prediction of accrual we have assumed the following: in the Saguenay region there is a slight decrease of incident strokes in summer months. We will add 10% of patients to the number that were seen during the pilot phase. Thus, it is expected that 70 cases of incident strokes per year and 30 TIAs per year will be studied. At L'Enfant-Jésus it has been conservatively estimated that a similar number of first-ever ischemic strokes and TIAs will be seen. Over a 3 year period there will thus be 300 cases seen in the Saguenay and 300 cases in Québec city. A total of 180 cases of TIAs at both centers and 420 cases of incident strokes will be seen. It is also also assumed that 25% of strokes will be found to be demented at 3 months and 6% of TIAs. Thus we expect to find 104 dementia in strokes and only 11 cases in the TIA group. We also assume that 40% of stroke patients will show cognitive impairment without dementia.

In estimating proportions the binomial distribution will be used. With α=0.05 (two-tailed) one can estimate power with different proportions and specify a degree into which the estimate may fall. Data from both centers will be pooled to estimate the prevalence of dementia and cognitive impairment.

estimated proportion %	Δ variation	N	Power
.25 ±.08	0.17-0.32	420	.84
.40 ±.08	.32-.48	420	.84
.08 ±.04	.04-.12	420	.74
.06 ±.04	.02-.10	180	.30

It is thus possible to estimate with confidence a proportion of dementia of 25±8% and cognitive impairment of 40 ±8%. However, estimates of subtypes of dementia and proportion of dementia after a TIA (based on 180 subjects) will not be precise. We will also compute 95% c.i. for the estimate. Distribution difference between the two sites will be calculated using the Chi-square test.

The next step involves testing whether there is a difference in proportions between both centers. Zar[160] describes methods for comparison of two proportions. A Fisher's exact test after correction for continuity is suggested. We calculated the required number of cases in two populations that have to be studied in order to detect a minimal difference. It can be can demonstrated that our study has 80% power to identify a difference in proportions between our two centers according to the following prevalences:

Proportion in center 1	proportion in center 2	N= required number
0.16	.25	211 patients
.30	.40	211
.18	.30	86

We can thus show a difference in prevalence of dementia (16 vs 25%) and cognitive impairment after stroke (30 vs 40%) and a relatively larger difference of cognitive impairment after a TIA (18 % vs 30%).

The third ojective relates to the frequency of different subtypes of VaD. Some subtypes (i.e. strategic infarct) are so rare that they may not be encountered in this study. Simple descriptive statistics will be used for this part of the analysis.

We will use multiple logistic regression to identify which variables (clinical, radiological) are associated with the risk of dementia vs no-dementia. The following variables will be entered into the model: age, sex, level of education, socio-economic level (1 to 5), risk factors for stroke (history of hypertension, diabetes, auricular fibrillation, coronary heart disease, smoking, TIA prior to stroke), subtypes of strokes, CT scan measures (total volume of infarct, leukoaraiosis, atrophy, ventricular dilation and localisation of strokes), initial stroke severity using the CNS scale, symptoms of cognitive impairment prior to the index stroke (as obtained from the family).

The same analysis will be repeated for a) the diagnosis of cognitive impairment after stroke, and b) cognitive impairment after a TIA.

We will visually examine the distribution of patients according to a simple question asked of family relatives as to how they can perform (in percentage) as compared to pre-stroke

level (100%). We will try to establish a cut-off score that maximizes good classification (i.e. clinical impression of dementia or not). A ROC curve will be used to derive the score with best discrimination for sensitivity and specificity.

Usefulness

Vascular dementia represents only the tip of the iceberg among vascular cognitive impairment[151]. The large subgroup of cognitively impaired but not demented has not been studied in large epidemiological studies. Recent hospital-based studies identified a high proportion of failure on test items in most cognitive domains[130,131]. Our study has several advantages over prior ones. Cognitive impairment in a population of TIAs has never been studied to such an extent. Rates from a population-based stroke registry will help us to identify more precisely the extent of the phenomenon. Since only stroke and TIA survivors are studied, it is likely that we will underestimate the true incidence of VaD, since some patient do not present with this clinical event. Prevalent strokes, not detected in our protocol, may also evolve to dementia. Later studies with follow-up of our cohort could establish the annual risk of dementia from our cohort. Our study will also examine the difference between a population-based series and a hospital one. Since the Québec hospital is fairly representative of large referral centers for strokes, on which the literature is based, it will be possible to estimate the bias this type of population introduces.
This type of study aimed at identifying new cases of vascular dementia is important from the point of view of preventive medicine. Only after 1) having validated screening tools, 2) knowing more about the epidemiology of these diseases or 3) understanding the variability among cases, can we start planning intervention measures to prevent this disease. Among

the common forms of dementia, those with a vascular etiology are the only one potentially amenable to treatment.

Appendix 1- Data collection form

ID # _____

Section H

OPINION DIAGNOSTIQUE CLINIQUE FINALE

Selectioner et encercler une seule des catégories diagnostiques :a à 'f', puis ajouter des détails lorsque necessaire. (Un diagnostic doit être posé. Votre confiance en ce diagnostic peut être indique en (k)).

a-0 ACV trop sévère

1. aphasie trop sévère
2. déficit neurologique trop sévère pour être étudie

a. Pas de trouble cognitif

b. Trouble neurologique, mais sans démence

1. délire cause_____
2. abus chronique d'alcool
3. intoxication médicamenteuse chronique

cause_____

4. dépression
5. maladie psychiatrique autre que dépression
6. troubles de mémoire associés à l'age
7. retard mental cause_____
8. atteinte dans une seule sphere
9. atteinte dans plus d'une sphère mais insuffisant pour une démence
10. autre_____

c. Maladie d'Alzheimer

1. probable
2. possible (encercler une seule)

i présentation ou évolution atypique
ii avec composante vasculaires
iii avec parkinsonisme
iv avec pathologie coexistante (voir 6)

ID _____

d. Demence vasculaire* (pointage ischémique _____) (encercler seulement un choix de 1 à 4)

1 à début soudain

2 infarctus corticaux multiples

3 sous corticale

4 mixte corticale et sous corticale

e. Autre démence spécifique (encercler seulement un choix de 1 à 6)

1 Parkinson

2 Pick

3 Huntington

4 Jacob-Creutzfeldt

5 post-trauma crânien

6 autre _____

f. Démence non-classifiable

Pour les cas dans les catégories (c) à (f) seulement

g. Maladie co-existante contribuant à la démence

1 hypothyroïdisme

2 déficience en B12

3 alcoolisme

4 autre(s) _____

_____

_____

* Voir les critères diagnostiques dans le manuel et remplir la feuille H-5, H-6.

ID _____

Tous les cas:

h. Maladie(s) co-existante(s) ne contribuant pas à la démence

_____

_____

_____

_____

_____

i. Si démence, en estimer la sévérité:

1 légère 2 modérée 3 sévère

j. Qui était présent pour atteindre le diagnostic final?

1 le/la clinicien/ne qui a vu le sujet

2 d'autre(s) clinicien(nes)

3 le/la psychométricien/ne qui a vu le sujet

4 un(e) neuropsychologue

5 l'infirmière qui a vu le sujet

6 autre _____

k. Êtes-vous confiant par rapport à votre diagnostic?

1 très confiant

2 quelque peu confiant

3 pas très confiant

4 aucune confiance

spécifiez _____

_____

_____

1. Codes d'identité de ceux présents au diagnostics final:

_____ # _____ # _____

_____ # _____ # _____

2. Est-ce qu'un follow-up médical est nécessaire? 1 oui 2 non

Si oui: 1 par un des médicins-chercheurs du site
2 par le médecin de famille
3 par un neuroloque du réseau CERAD
4 autre, spécifies _____

ID # _____

LISTE POUR VERIFICATION DES CRITÈRES DIAGNOSTICS VENANT DU DSM-IIIR ET NINCDS-ADRDA

S.V.P. compléter pour les catégories encerclées en page ( ).

Coter: 1 = oui 0 = non 9 = information insuffisante

a. DELIRE
- ____ 1 inattention
- ____ 2 désorganisation de la pensée
- ____ 3 obnubilation de la conscience
- ____ 4 anomalies de la perception
- ____ 5 perturbation de rythme veille-sommeil
- ____ 6 aug. ou dim. de l'activité psycho-motrice
- ____ 7 désorientation tempero-spatiale
- ____ 8 troubles mnésiques
- ____ 9 évolution courte avec fluctuations
- ____ 10 Début soudain (heures à jours)

b. DÉPRESSION (voir liste de questions dans la Section C)

c. DÉMENCE
- ____ 1 altération de la mémoire - à court terme
- ____ 2 altération de la mémoire - à long terme
- ____ 3 altération de la pensée abstraite
- ____ 4 altération du jugement

perturbation des fonctions supérieures
- ____ 5 aphasie
- ____ 6 apraxie
- ____ 7 agnosie
- ____ 8 difficultés visuo-spatiales
- ____ 9 altération de la personnalité
- ____ 10 interférence avec activités professionnelles
- ____ 12 interférence avec activités sociales
- ____ 13 interférence avec relations avec les autres

ID _____

4. MALADIE D'ALZHEIMER (AD) PROBABLE

___ 1 démence

___ 2 déficit dans deux ou plusieurs champs intellectuels

___ 3 détérioration progressive

___ 4 pas de trouble de l'éveil

___ 5 début entre 40 et 90 ans

___ 6 absence d'autre pathologie systémique ou cérébrale qui pourrait causer une démence

Appendix 2- Ethics approval

Hôpital de Chicoutimi

1994.06.15

Docteur Michel Beaudry
Hôpital de Chicoutimi
Chicoutimi

OBJET: Votre projet de recherche intitulé: «Prévalence des troubles cognitifs suite à un accident cérébro-vasculaire»

Cher Docteur,

Lors de sa réunion du 7 juin 1994, le comité de bioéthique a étudié votre projet de recherche ci-haut mentionné.

J'ai le plaisir de vous informer que votre projet a été jugé éthiquement acceptable par le comité de bioéthique.

Veuillez trouver, ci-joint, un extrait du procès-verbal de la réunion ainsi que la liste des membres de notre comité.

Le comité désirerait être informé des effets secondaires possibles qui peuvent survenir au cours des études et souhaitent avoir de façon périodique un compte rendu de l'évolution des protocoles de recherche en cours.

Espérant le tout à votre satisfaction, veuillez agréer, cher Docteur, l'expression de mes sentiments les meilleurs.

François BROCHET, MD,
Président du sous-comité
de bioéthique

PP/JB
Pièces jointes

Appendix 3- Letter of information and consent form

FORMULAIRE DE CONSENTEMENT (1)

ÉTUDE DE PRÉVALENCE DES TROUBLES COGNITIFS SUITE À UN ACV

Monsieur,
Madame,

Votre médecin a permis que nous vous contactions afin de solliciter votre participation à un projet de recherche. La présente recherche vise à mesurer la fréquence des répercussions physiques et mentales à la suite d'un accident cérébrovasculaire (ACV). Nous aimerions vous inviter à participer à cette étude.

L'ACV "thrombose cérébrale" amène des déficits bien connus sous forme de paralysie, difficulté à s'exprimer, troubles visuels ou instabilité à la marche. De plus en plus, les chercheurs s'intéressent à la répercussion des ACV sur la performance mentale. Par exemple, on peut observer, à la suite d'un ACV, des difficultés au niveau des tâches reliées au travail, difficulté à s'habiller ou à penser qui ne sont pas vraiment reliées à la faiblesse d'un bras ou d'une jambe par exemple. Des changements de comportement ou des troubles de mémoire sont également observés. Notre étude vise à quantifier la fréquence de ces troubles.

Pour ce faire, nous devrons attendre que les problèmes médicaux survenus lors de la thrombose soient disparus ou se soient améliorés. C'est pourquoi nous effectuerons nos entrevues trois mois après la thrombose.

Cette évaluation se fera en 2 ou 3 séances. A la première visite on appliquera un questionnaire sur vos capacités fonctionnelles. Un membre de la famille, le conjoint par exemple, devra aussi répondre à une partie du questionnaire. Cette entrevue dure à peu près 2 heures. A la deuxième visite un psychologue administrera des tests concernant vos habiletés mentales, la mémoire et la langage. Par la suite, vous serez examinés par 2 neurologues les Drs Michel Beaudry et Francine Veilleux (1 heure chacun).

Nous vous inviterons à venir à l'hôpital de Chicoutimi pour ces entrevues. Advenant le cas que vous soyez dans l'incapacité de vous déplacer les entrevues seront réaliser chez vous.. Il n'y aura aucune compensation financière pour votre participation à cette étude.

Toutes les données de l'étude demeureront confidentielles et, en aucun cas votre nom ne sera utilisé pour fin de rapport. Votre participation ou non à cette étude n'aura pas de répercussion sur les soins médicaux que vous recevrez. Vous demeurez libre de vous retirer en tout temps.

FORMULAIRE DE CONSENTEMENT (2)

J'ai lu la description du projet intitulé "Étude de prévalence des troubles cognitifs suite à un accident cérébrovasculaire". Je comprends que cette étude implique deux entrevues, la première devant être réalisée chez moi. Une infirmière me posera des questions en rapport avec mes activités récentes. Cette entrevue durera une heure.

Par la suite, il est possible que je sois invité à passer des tests administrés par un psychologue. Ces examens prendront deux heures. Je serai également examiné par un neurologue. Je comprends qu'en participant à ce projet, je demeure libre de me retirer en tout temps et qu'on maintiendra une stricte confidentialité à propos des résultats.

Je comprends également que ma participation à ce projet n'influencera en aucun lieu les soins médicaux que je recevrai.

J'accepte de participer à cette étude et j'ai signé le _____ 19__

_____
Nom du patient

_____
Nom du témoin

_____
Nom du chercheur ou son représentant

Appendix 3- Sample results for patients in phase 2 of the study as well as norms for the CSHA (unpublished). For comparison, average norms for a French Canadian population are addded for comparison only (Meunier and Ska. November 1996. Unpublished. With permission). In accordance with individual agencies standard deviation are not provided.

Buschke (age 65-74)

population tests	CSHA norms	French Canada norms 65-69	 70-74	current study 65-74 N	 N	N < 65 years N	 N
Total 1st	11.9	11.94	11.84	11.4	N=6	11.5	N=10
Total 2nd	11.9	11.94	11.97	11.1	N=6	12	N=10

Buschke (age 75-79)

population tests	CSHA norms	French Canada norms	current study N
Total 1st	11.9	11.89	11.3 N=3
Total 2nd	11.9	11.92	11.3 N=3

Buscke (age over 80)

Total 1st	11.7	11.86	10.0 N=4
Total 2nd	12.0	11.86	11.4 N=4

Appendix 3- Rey Auditory Verbal Learning Test

Men

age group	60-69 CSHA norms	French Canada 65-69	60-69 Current study	70-79 CSHA	French Canada men & women 70-74	75-79	70-79 Current study
Rey 1	5.6	4.52	3.5 N=6	6.3	4.19	4.07	2.5 N=2
Rey 2	8	6.96	5.0	8.2	7.52	6.93	4.0
Rey 3	9.9	7.70	5.8	9.6	8.29	8.02	5.0
Rey 4	10.3	9.18	5.8	10.0	9.33	9.10	5.5
Rey 5	11.3	9.64	6.5	10.8	9.67	9.39	5.5
Rec	13.9	13.95	12.8	14.2	14.00	13.63	13

Women

age group	60-69 CSHA norms	French Canada 65-69	60-69 Current study	70-79 CSHA	French Canada 70-74	75-79	70-79 Current study
Rey 1	3.04	4.52	3 N=3	6.3	see above		3.0 N=3
Rey 2	5.58	6.96	4.3	9.4			3.7
Rey 3	6.86	7.70	3	10.4			4.8
Rey 4	7.84	9.18	5	11.8			4.8
Rey 5	7.98	9.64	6	12.5			5.0
Rec	12.36	13.95	10.3	14.2			9.3

Appendix 3-

Digit span

	CSHA age 65-79	French Canada 65-69 70-74 75-79	Current study age 65 & over	Current study Age < 65
Scores	6.1	4.93 5.16 4.97	4.3 N=13	4.7 N=9

WAIS- similarities

age	CSHA	French Canada	Current study
< 65			8.0 N=9
65-69	8.5-9.0	5.61	4.3 N=3
70-74	7.7.5	5.47	4.0 N=4
75-79	6.0-7.0	6.17	3.0 N=2
80-84	5.5-6.5	5.04	5.6 N=5

Appendix 3-

Judgment (WAIS-Comprehension)

age	CSHA	French Canada	Current study	
< 65			8.8	N=10
65-69	10-10.5	7.32	4.0	N=3
70-74	9-9.5	7.75	6.0	N=4
75-79	8.5-9.0	7.33	7.5	N=2
80-84	8.5-9.0	6.82	6.0	N=5

Controlled Oral Word Association Test

education / age group	CSHA norms		Current study	
	< 12 y	12 or more	< 12 y	12 or more
< 65			8.7	31
65-69	39.25	44.16	7.5	23
70-74	36.47	41.0	13	-
75 +	35.2	39.08	8.5	18

Appendix 3-

Animal naming

education / age group	CSHA norms < 12 y	CSHA norms 12 or more	Current study < 12 y	Current study 12 or more
< 65			10.8	17.5
65-69	17.75	19.13	6.0	11.0
70-74	16.35	18.28	9.2	-
75 +	15.09	17.07	8.0	12.5

Block design

age group	CSHA -average scores	Current study	N
< 65		10.5	N=10
65-69	9.5-10.5	11.0	N=3
70-74	8-9.5	4.2	N=4
75-79	7.0-9.0	6.0	N=2
80 +	6.5-8.0	4.6	N=5

Appendix 4- DSM-III-R criteria for dementia [161]and Multi-Infarct Dementia

Criteria for dementia

A. Demonstrable evidence of impairment in short- and long term memory

B. At least one of the following:

(1) impairment in abstract thinking

(2) impaired judgment

(3) other disturbances of higher cortical function such as aphasia, apraxia, agnosia, and constructional difficulty

(4) personality changes

C. The disturbances in A and B significantly interferes with work or usual social activities or relationship with others.

D. Not occuring exclusively during the course of Delirium.

E. (1) evidence of an organic etiologic factor.

(2) in the absence of such evidence, rule out non-organic mental disorder, e.g. Major Depression

Diagnositic criteria for Multi-infarct Dementia

A. Dementia

B. Stepwise deterioration with "patchy" distribution of deficits.

C. Focal neurologic signs and symptoms

D. Evidence from history, physical exmination, or laboratory tests of significant cerebrovascular disease that is jeudged to be etiologically related to the disturbance.

Appendix 5- ICD-10 criteria for vascular dementia [162]

Criteria for dementia

G1.1 A decline in memory (mainly short term memory). It applies to both verbal and non-verbal memory

G1.2 A decline in other cognitive abilities (judgment, thinking, planning and organizing, general processing of information). Deterioration from a previous level of functioning.

G2 Absence of clouding of consciousness

G3 A decline in emotional control or motivation or a change in social behavior

G4 Change under G1 should have been present for 6 months, otherwise tentative diagnosis only.

Criteria for vascular dementia

G1 Evidence of dementia as described above

G2 Unequal distribution of deficits in higher cognitive functions, with some affected and others relatively spared.

G3 Evidence of focal brain damage with at least one of the following (spastic weakness; unilateral increase of tendon reflexes; extensor plantar response; pseudobulbar palsy)

G4 There is evidence from the history, examination, or tests, of significant cerebrovascular disease, which may reasonably be judged to be etiologically related to the dementia (history of stroke, evidence of cerebral infarction)

Appendix 6- NINDS-AIREN criteria for vascular dementia [16]

I- The criteria for probable vascular dementia include all of the following:

1. Dementia preferably established by clinical examination and documented by neuropsychological testing.

a) impairment of memory

b) impairment in two or more cognitive domains (orientation, attention, language, visuospatial functions, motor control and praxis). Deficits should be severe enough to interfere with activities of daily living and not due to the physical effect of stroke alone. Exclusion: Delirium, severe aphasia or major sensorimotor impairment precluding neuropsychological testing.

2.Cerebrovascular disease

a) Focal signs on neurological examination, **and**

b) Evidence of relevant cerebrovascular disease by brain imaging (CT or MRI) including multiple large-vessel infarcts or a single strategically placed infarct; multiple basal ganglia and white matter lacunes or extensive periventricular white matter lesions or combinations thereof.

c) A relationship between the above two disorders: onset of dementia within 3 months following a recognized stroke; abrupt deterioration in cognitive functions; or fluctuating, stepwise progression in cognitive deficits.

II- Clinical features consistent with the diagnosis

a) Early presence of a gait disturbance; b) history of unsteadiness and frequent falls; c) early urinary frequency, urgency or other urinary symptoms not explained by urologic disease; d) pseudobulbar palsy; e) personality and mood changes, abulia, depression, emotional incontinence, or other subcortical deficits including psychomotor retardation and abnormal executive function.

III- Features that make the diagnosis uncertain or unlikely:

a) Early onset of memory deficit and other cognitive functions such as language, motor skills and perception in the absence of corresponding focal lesions on brain imaging;

b) absence of focal neurologic signs, other than cognitive disturbances, and c) absence of cerebrovascualr lesions on CT or MRI.

AD with CVD: used to classify patients fulfilling the clinical criteria for possible AD and who also present clinical criteria or brain imaging evidence of relevant CVD.

Appendix 7- Cases Description

We describe here cases that presented a dementia syndrome according to one or more raters.

Case 24. This patient was rated as having vascular dementia according to both neurologists as well as at the consensus level. The neuropsychologist could not complete the test battery because the deficits were too severe. Neurologist 1 noted that the patient displayed frontal behavior and was easily discouraged. Neurologist 2 observed a frank deficit with aphasia, a right hemiparesis as well as spasticity. CT scan showed an anteroposterior hypodensity (as seen in border zone infarcts caused by carotid thrombosis). No Doppler examination was done. This represents a case of agreement between both neurologists and the consensus teams.

Case 36. This 81 year old man was rated as having vascular dementia by neurologist 1, consensus 1, and the neuropsychologist. After discussion with the family, neurologist 2 thought the patient was not demented and maintained that diagnosis at the consensus level. The stroke syndrome included a dysphasia and a facial asymmetry. One family member thought the neurological deficit lasted 4 days. On examination, neurologist 1 noted some rigidity on both sides, while neurologist 2 found it on the right side. The CAMDEX questionaire showed intellectual deficit acquired after the stroke. On cognitive examination all 3 raters found involvement in most domains. Depending on whether patchy involvement was present or not this patient may be classified as AD or VAD.

According to DSM-III this patient would be classified as vascular dementia. On the other hand, according to NINDS-AIREN the stroke syndrome was too mild and CT scanning not compatible with a VaD diagnosis. The patient would have been classified as "Alzheimer's disease with CVD". Neurologist 2 on the other hand thought that there were no significant changes in his mental ability to justify a diagnosis of dementia. There is disagreement at two levels here: 1) on the severity of involvement, and 2) whether the syndrome is degenerative or vascular-related only.

Case 40. This patient presented at the hospital with a new onset of aphasia, a right arm motor deficit as well as focal motor clonic jerk. He was found to be in atrial fibrillation so the etiology was deemed to be cardioembolic despite a negative echo cardiogram. On testing 3 months later he was found to be too aphasic according to neurologist 1 as well as the neuropsychologist. The latter observed that the patient could not repeat some words in preparation for testing short term memory, thus having too severe an aphasia. Neurologist 2 observed an important psychomotor retardation as well as a significant language problem. The mental slowing was enough to justify a diagnosis of vascular dementia. This disagreement could be resolved if all cases with moderate aphasia were excluded. This would increase specificity of diagnosis at the cost of sensitivity.

Case 45. This patient initially presented with a mild stroke. One week after hospitalization she deteriorated with decreased level of consciousness and severe motor weakness. A second CT showed a lesion in the left temporo-occipital lobes. Three months after the stroke she was still hospitalized. On examination she held a pen with her left hand because

of moderate-severe paresis on the right side. According to neurologist 1 she had 48/85 on the 3MS, the missing item being related to her inalibity to use a pen. She was found to have involvement of 2 domains. The psychologist found difficulty with memory, language and much slowing on the Trail-Making test. Consensus 1 judged her to be non-demented. Neurologist 2 found deficits in 5 domains and obtained from her sister an impression that there was an important change in her mental ability. She was therefore put in the category dementia by neurologist 2 and consensus 2.

Case 22. This patient was judged to have too severe aphasia by Neurologist 1. The psychologist also documented an important aphasia as well as difficulty with judgment and memory. The patient's spouse mentioned that after his stroke he was unable to finish whatever activity he would start. Neurologist 2 considered that the patient had vascular dementia (of acute onset). CT scanning showed a lesion in the left internal capsule with some extension beyond, compatible with a diagnosis of strategic infarct, i.e. affecting cognition.

Case 38. This patient was found to have deficits in multiple domains according to all raters, with more domains detected by the psychologist. The CAMDEX questionaire as well as one neurologist noted that the onset of deficits came only after the stroke. The neurospychologist thought on the basis of this observation that the patient had a vascular dementia. Both neurologists were convinced at the consensus level that the clinical pattern was typical of Alzheimer`s disease and thus labelled the case as "possible AD" with history of stroke. This represents a case of agreement on a diagnosis of "AD + CVD".

Case 32. This 79 year old women presented with a mild right motor stroke. At 3 months she was evaluated in her own apartment by all raters because she could not be brought to hospital by family members. She was living by herself although meals were taken in a cafeteria. Her behavior appeared to be normal except for mental slowness. She surprised both neurologists with a low performance on memory, abstraction, judgment, aphasia and apraxia. Both thought she was not demented. Team 2, looking at the results of the neuropsychological battery, thought that the impairment was severe enough to label her demented. However the psychologist did not classify her as demented, so team 1 did classify her as cognitively impaired in more than 2 spheres but not demented. This is an example of difficulty with interpretation of tests. She scored 51/100 on 3MS and 73/100 on mod-3MS which is abnormal.

Appendix 8 -Current status of neuropsychological testing in Vascular dementia

a) Frontal syndrome

Looking at the close anatomical relationship between frontal lobes and subcortical structures on the one hand and the clinical presentation of lesions in these systems on the other, at least 3 specific clinical presentations can be recognized according to Cummings. The first is an executive function deficit with difficulty in motor programming, in organizing strategies, in copying complex designs. This is evident in tasks using alternating reciprocal motor tasks and sequential motor tests. Lesion in the dorsolateral frontal lobe or reciprocal connections with the dorsolateral striatum produce these deficits.
Lesions in the orbitofrontal lobe, with reciprocal connection with the ventral striatum, produce a different syndrome presenting with irritability, lability and euphoria. Finally a third syndrome involves the medial cingulum with limbic striatum producing an apathetic state, incontinence and occasionally an akinetic mutism. Cummings does not mention lesions in the white matter but others have alluded to the possibility of a disconnection syndrome responsible for a frontal syndrome[91-93].

This has also been observed in the field of VaD [157,163]. Patients with white matter changes have a retrieval deficit, reduced verbal output, impaired set shifting, poor strategy for resolution of complex tasks, more depression, more apathy and a more variable course of cognitive decline. For instance Bennett et al[163] observed that half of Binswanger's disease cases had improved cognition on follow-up. The annual rate of decline for Binswanger's cases was 0.6 points on the MMSE scale compared to 3.9 points for AD. Coupled with a lower survival rate in vascular dementia, compared to AD, this complicates the

comparison of both entities since demented vascular patients seem to survive less than their non-demented controls.

b) Differentiation of VaD from AD. Kertesz et al identified subtests which, with discriminant analysis, could allow a good classification of AD patients (83% accuracy) or VaD patients (86% accuracy)[89]. VaD patients performed more poorly on the Mattis motor performance subtest, the WAIS-R picture arrangement subtest, the Western Aphasia Battery writing subtest, the WAIS-R object assembly subtest, and the WAB block design subtest. AD patients had more difficulty with WAB repetition subtest and a story recall subtest. Few studies looked at mixed cases. They were described as performing worse and being more agitated[95]. Mendez and Mendez found poorer performance on unstructured tests tapping frontal lobe functions in VaD compared to AD. They used the Cookie Theft Picture from the Boston Aphasia Battery (a verbal test) and the Lezak Tinker Toy assembly test[158].

c) What is the current state of knowledge on the neuropsychology of VaD? The first issue to resolve is the possibility of different syndromes. Although still controversial there seemed to be some differences between subcortical lesion syndrome (recapitulating a frontal syndrome) and a strategic cortical infarct syndrome. Three studies have looked at the effect of lacunar strokes[90,93,164]. Wolfe et al found that lacunar stroke patients had more difficulty than controls on the Stroop test, verbal fluency, and produced fewer semantic clusters on the California verbal learning test[90]. These 3 tests, sensitive to frontal lobe damage, accounted for 91% of the variance in global cognitive score. These patients were also more apathetic, showed more dysarthria and were more depressed. In another study,

factor analysis showed impairment in 3 domains: visuospatial ability, verbal memory and attention-concentration[93]. Godefroy et al examined 11 cases of infarcts in the deep lenticulostriate artery (a form of lacunar infarcts). They found that MRI was a more sensitive test than CT scan: patients with greater cognitive deficits had lesions extending either in the cortex or the surrounding white matter casting some doubts on the correlation of subcortical lesions and cognition based on CT scan studies. Patients with a pure lenticulostriate lesion had mild aphasia characterized with prominent expressive and lexicosemantic task impairments.

Other studies have described a dementia syndrome related to an isolated cortical infarct such as the angular gyrus syndrome[165], or to multiple infarcts[32]. In a study that was positive for showing a correlation between cortical infarcts and cognitive impairment, the following tests were abnormal: Benton recognition test, orientation, category, fluency, repetition and attention[131]. That the four domains affected (memory, orientation, language, attention) are tested with a simple test such as the MMS may facilitate epidemiological research. Some still believe that screening tools can be used in this type of research[16].

Although many authors now recognize that lacunar infarct represents the most frequent type of stroke[35,166], it has not been determined that lacunar strokes contribute more than cortical infarcts.

As mentioned before, cognitive impairment is related to white matter lesions[35,36,92,93,97,98], lacunar infarcts[35,90,167], ventricular enlargement (a surrogate measure for atrophy)[35,92,93,168] or cortical infarct[35,36,88,93,131].

Other important points to remember are the frequency of depressive symptomatology[90,95,156,169] and the behavioral observation such as apathy, irritability, and anxiety[95,156] which, although non-specific , have been associated with a frontal lobe type of damage.

d) Are there neuropsychological deficits associated with specific site involvement?

Thalamic infarcts have been shown to be associated with severe memory deficits[122]. These patients also showed a dysphoric mood as well as irritability and distractibility. These lesions would benefit from being studied with MRI rather than CT scan as mentioned above. Striatal lesions as part of a lacunar syndrome have been mentioned above.

White matter lesions in community controls showed an association with decreased executive function, mental speed (Trail Making A and B), and memory (Word list learning delayed recall). Another study found difficulty with immediate and delayed recall of a prose passage[97]. Demented subjects with LA did not perform worse than those without LA in the latter study. Liu et al[36] however found that white matter lesions resulted in poorer performance on a general scale (CDR scale).

Ventricular enlargement was associated with decreased global cognitive function as well as memory and executive functions in controls[92]. Demented subjects tend to have lower scores on global measures of intellectual function[93,168].

The cognitive deficits associated with cortical infarct encompass the whole neurological semiology. Specific findings are found in small case series[165]. In a larger study of consecutive stroke patients using CT scanning[93] no meaningful correlation between the anatomical site of infarction or the hemisphere involved and the results of neuropsychological testing was seen.

Appendix 9

Glossary of terms and abbreviations used

ADDTC stands for the State of California Alzheimer's Disease Diagnostic and Treatment Centers.

akinetic mutism: a condition of silent, alert-appearing immobility that characterizes certain subacute or chronic states of altered consciousness in which sleep-wake cycles have returned but externally obtainable evidence for mental activity remains almost entirely absent and spontaneous motor activity is lacking.

amyloid angiopathy: a small vessel disease related to deposition of amyloid (a glycoprotein)

angular gyrus: a convolution of the inferior parietal lobule (i.e. a sector of the brain)

apraxia: inability to carry out purposeful movements in the absence of paralysis or other motor or sensory impairment

CAMDEX: the Cambridge examination for mental disorders of the elderly.

cingulum: a bundle of association fibers which partly encircles the corpus callosum not far from the median plane, the fibers of which interrelate the cingulate and hippocampal gyri

cognitive impairment: a decrease in the operation of the mind, insufficient for a dementia

corpus callosum: an arched mass of white matter, situated at the bottom of the longitudinal fissure, and made up of transverse fibers connecting the cerebral hemispheres.

CSHA: Canadian study on Health and Aging. A large epidemiological study on the prevalence of dementia carried out in all regions of Canada

CT: Computed tomography, i.e. computer-aided pictures of the brain

delirium: a floridly abnormal mental state characterized by disorientation, fear, irritability, misperception of sensory stimuli, and often, visual hallucinations

demyelination: loss of the myelin sheaths of nerve

DSM-IV Diagnostic and Statistical Manual of Mental Disorders 4th edition. Published by the American Psychiatric Association

encephalopathy: modifications of mind state (i.e. a confusional state) related to etiologies such as infections, metabolic changes or intoxications.

executive function: consists of those capacities that enable a person to engage successfully in independent, purposive, self-serving behavior.

frontal lobe: a large part of the brain situated anteriorly and involved in motor function, planning and behavior control

gliosis: proliferation or hyperplasia of neuroglial tissue

hypodensity: (such as in white matter hypodensity) pallor of tissue.

ICD-10 International Classification of Disease. 10th revision

infarct: an area of coagulation necrosis in a tissue due to local anemia resulting from obstruction of circulation to the area.

internal capsule: a broad band of white substance that separates the lentiform nucleus and thalamus.

lacunar stroke: stroke in the territory of small perforating arterioles.

lenticulostriate artery: small artery nourishing deep nuclei of the brain (striatum and globus pallidus)

leukoaraiosis: zone of rarefaction of white matter seen as hypodensitied on CT scan or hyperintensities on NMR

limbic striatum: region of the brain involved in functioning of deep viscera, regulation of metabolism and emotion.

microvascular: small vessel.

motor executive functions: see executive functions

neuropsychological battery: a series of test, performed by the neuropsychologist, pertaining to mental function

NINDS-AIREN a joint international meeting established criteria for vascular dementia under the supervision of the Neuroepidemiology Branch of the National Institute of Neurological Disorders and Stroke (NINDS) and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (AIREN).

NMR: nuclear magnetic resonance. Used for taking precise pictures of the brain.

occipital (occipito-): posterior part of the brain involved in vision.

orbitofrontal: a subsector of the frontal lobe situated over the orbits.

parietal (parieto-) lobe: a sector of the brain involved in processing sensory afferents from the contralateral side of the body.

periventricular: situated near the ventricles these areas are rich in fibers connectings different part of the nervous systems.

semantic memory: what is learned as knowledge is "timeless and spaceless", as, for instance,the alphabet or historical data unrelated to a persons's life.

semiology: part of medicine which studies signs of disease.

SIDAM: sreening test developed by German investigators. It stands for Structured Interview for the Diagnosis of dementia of the Alzheimer type, Multi-infact dementia and dementia of other etiology according to DSM-III-r and ICD-10

subcortical: comprises different parts of the brain underneath the cortex: white matter
(connecting fibers) and deep nuclei.

transient ischemic attack (TIA): a transient neurological deficit secondary to insufficiency of circulation and lasting less than 24 hours. A warning of stroke.

ventral striatum: one subsector of a deep nuclei of the brain

visuospatial functions: ability that depends on understanding spatial relationships between objects.

white matter: all connecting fibers of the central nervous fibers. Underneath the cortex these predominate and give a white color to this region of the brain.

WAIS-R: Weschler Intelligence Scales- revised

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