

Intracranial MR Dynamics in Clinically Diagnosed Alzheimer's Disease: The Emerging Concept of "Pulse Wave Encephalopathy"

Marie Cécile Henry-Feugeas*

Department of Radiology, Bichat-Claude Bernard University Hospital, AP-HP, 46 rue Henri Huchard, 75877 Paris cedex 18, France

Abstract: As increasingly shown in neuropathological and predementia clinical studies, cognitive decline with altered intracranial dynamics can fulfill current clinical criteria of dementia of the Alzheimer's type (DAT) and there is a marked pathogenic complexity of this epidemic syndrome. Whereas structural studies only suggest the unexpected frequency of cerebrovascular changes in late life DAT, flow quantification MR sequences now offer a great opportunity of *in vivo* accurate analysis of cerebrovascular function.

Their first applications have allowed development of a modern concept of the intracranial dynamics; a complex windkessel system allows two processes that are crucial to insure brain oxygenation and nutrition, a periodic systolic marked expansion of the intracranial blood compartment within the rigid cranial cavity on the one hand, a marked dampening of the arterial pulse wave before it reaches capillary level on the other hand. This modern concept has allowed better understanding of two archetypes of windkessel failure or so-called pulse wave encephalopathy, normal pressure hydrocephalus and subcortical arteriosclerotic encephalopathy.

Dynamic MRI may now help to detect and classify distinct patterns of cerebrovascular dysfunction in DAT. This dynamic approach helps to understand the major association between aging and DAT as well as the increasingly recognized overlap between Alzheimer's pathology, normal pressure hydrocephalus and arteriosclerotic neurodegeneration. Evidence of such a great variety of disturbances in intracranial dynamics behind a single clinical syndrome of DAT can greatly impact therapeutic research on this devastating disorder.

1. INTRODUCTION

Current clinical diagnostic criteria of Alzheimer's disease (AD) mainly require a progressive loss of cognition involving memory and other cognitive functions with no other obvious cause for the decline; the commonest standardized clinical definition of dementia of the Alzheimer's type (DAT) lacks any specific biomarker of AD [1]. However, there are still clinicopathological reports suggesting a high accuracy of this old clinical definition [2]. Indeed, a post-mortem diagnosis of AD does not preclude a non-AD condition as the preponderant cause of cognitive decline. Neuropathological AD diagnosis is based on the assessment of amyloid plaques and neurofibrillar degeneration, whereas both of these Alzheimer type lesions can be extensively present in cognitively intact elderly subjects - they even seem to be particularly favoured by vascular disturbances [3-5]. Conversely, parenchymal atrophy increasingly appears to be the most closely related to cognitive status in AD [6] but is not included in current standard neuropathological criteria of AD. With better understanding of several fallacies in the initial clinicopathologic correlations, there is a growing body of evidence that the positive predictive value of a clinical diagnosis of AD may be well below the classical estimation of 71-88% and even as low as 38%, [7, 8].

Thus, besides Lewy's body dementia, disturbances in intracranial dynamics such as subcortical arteriosclerotic encephalopathy [9], altered cerebral venous outflow [10, 11] or hippocampal sclerosis [12], a condition of presumed vascular origin, can be associated with an "AD like dementia". More generally, cognitive impairment related to "silent" cerebrovascular disease (that does not include overt stroke) is more likely to fulfill the clinical criteria of DAT than those of vascular dementia [3, 13], and there is a substantial overlap between clinical definitions of AD and vascular dementia [14, 15].

Moreover, there is a pathological and clinical heterogeneity which still worsens the uncertainty surrounding the accuracy of clinical diagnostic of DAT [8]. Indeed, AD unassociated with any other pathology or "pure AD" was traditionally believed to make up between 50% and 60% of autopsy samples, but "mixed dementia" is now recognized as the most common form of dementia [3, 16].

This "mixed" substratum may contribute to several unexpected findings in late DAT; the overall burden of Alzheimer's type lesions and brain atrophy is surprisingly low and there is no longer a strong correlation between dementia severity and Alzheimer type lesions burden, entorhinal MR atrophy can be less marked and dissociated from hippocampal MR atrophy, leukoaraiosis, a white matter degeneration of presumed vascular origin, is particularly frequent and appears to parallel cognitive decline [17], anterograde amnesic syndrome does not systematically dominate the clinical pre-

*Address correspondence to this author at the Department of Radiology, Bichat-Claude Bernard University Hospital, AP-HP, 46 rue Henri Huchard, 75877 Paris cedex 18, France; Tel: + 33(1) 40 25 81 52; Fax: +33(1) 40 25 88 24; E-mail: marie-cecile.henry-feugeas@bch.aphp.fr

dementia picture and mild Parkinsonian signs can precede the dementia stage [3].

If there is increasing evidence of a previously underestimated role of cerebrovascular disease, the critical question of the respective role of AD and associated cerebrovascular disease in late life dementia is still unresolved. Indeed, cerebral microinfarcts, visible only using microscopic examinations, may be the strongest correlate of cognitive decline in elderly demented patients [18], whereas the current concept of vascular cognitive impairment remains controversial but largely based on macroscopic markers of cerebrovascular disease [19]. In the same way, there is a great variability in neuropathologic criteria of vascular dementia [9], which certainly contributes to conflicting reports on the accuracy of clinical criteria of AD (cf supra).

In this context, MRI offers a unique opportunity for a routine and accurate analysis of cerebrovascular function and thus detection of vascular cognitive impairment in late life cognitive decline. Indeed, flow quantification MR sequences are now accepted as gold standard methods for quantification of flow with error rate in the order of 3% and negligible intra and inter observer variability [20]. Conventional dynamic indicators of brain perfusion such as total cerebral blood flow can be calculated from the sum of the volumetric flow through the internal carotid arteries and vertebral arteries or basilar trunk over a cardiac cycle. More importantly, cardiac gated phase contrast MR measurements may assess changes in blood and cerebrospinal fluid (CSF) flow over time. Thus, volumetric MR waveforms over a cardiac cycle now allow a detailed analysis of the pulsatile component of both blood and CSF circulations.

2. MODERN CONCEPT OF INTRACRANIAL DYNAMICS: THE VITAL "WINDKESSEL" SYSTEM

Whereas the conventional concept of intracranial dynamics relied on bulk flow of blood and CSF, the modern concept of intracranial dynamics relies on intracranial blood and CSF pulsations and their inter relationship.

2.1. Dampening of the Periodic Expansion of the Intracranial Blood Compartment within a Rigid Cranial Cavity

The pressure and the flow rate of the blood flowing into the brain vary with time i.e. the pulse pressure and the pulse flow. Therefore, the arterial inflow into the cranial cavity is initially greater than cerebral venous and CSF outflows [21-23], there is a systolic expansion followed by a symmetrical diastolic decrease in the intracranial blood volume and thus cyclic variations in the intracranial blood volume. The intracranial space is confined by a rigid skull. Thus, any pulsatile increase in the intracranial volume induces pulsatile variations in the intracranial pressure and the so-called intracranial pulse pressure. Its amplitude depends on the amplitude of the intracranial fluid pulse volume and the relationship between intracranial pressure changes (dP) and volume change (dV) or (dV/dP), the so-called intracranial compliance. This last term can also be defined as the ability of a buffer system to accommodate a volume change [22].

To prevent a deleterious increase in intracranial pressure or even to simply physically allow systolic arterial inflow

into the cranial cavity, systolic increase in the intracranial arterial blood volume has to be rapidly compensated by an intracranial reciprocal volume decrease in other intracranial components [21-23]. Indeed, brain tissue, CSF and blood are incompressible within the physiologic pressure range. Therefore, intracranial compliance relies on complex, interdependent brain motion, CSF and venous flow which may be termed the "mobile intracranial compliance" [24].

Arterial inflow into the cranial cavity induces transient central brain displacement directed towards the more compliant spinal cavity and most importantly, an early CSF outflow from the cranial cavity [21-26]. This CSF mobile compliance requires free communication between subarachnoid cranial and spinal spaces and relies on the ability of expansion of the spinal thecal sac or spinal compliance. The contribution of ventricular CSF displacement through the aqueduct to this "CSF mobile compliance" is delayed and much more limited, at least in physiological conditions [21-26]. Finally, subarachnoid CSF pulsations promote cerebral venous outflow by direct compression of the subarachnoid veins; this "venous mobile compliance" also appears an important mechanism of dampening of the arterial pulsations within the intracranial cavity [21-26].

2.2. Dampening of the Arterial Pulse Wave Before it Reaches the Cerebral Capillary Level

The vascular windkessel effect describes the dampening of pulsatile flow brought about by vascular compliance; an almost continuous and smooth flow is obtained at the capillary level by storing part of the systolic pulse during systole, and releasing it to the capillaries during diastole. More generally, the term windkessel was historically proposed in the 19th century for a system allowing more efficient fire hose; it is now used for any process that transforms a pulsating flow into a non-pulsating continuous flow. A vascular windkessel process is a general requisite within the human body for efficient capillary exchanges [27]. Indeed, capillary exchange requires an almost continuous and smooth blood flow and thus marked dampening of the arterial pulsations generated by the heart. This so-called cushion function of the arterial tree mainly relies on the large artery wall compliance: in normal conditions, pulsatile energy is mainly absorbed in the large arteries, the most elastic arteries [27], even if arterioles also contribute -to a lesser degree - to bring down both the systemic blood pressure and the pulse pressure. The more muscular and less elastic peripheral arteries or so-called resistance arteries offer the greatest resistance to arterial inflow and represent the major site of reflection of the pulsations entering from the large arteries. Whereas the diameter of large cerebral arteries remain mainly constant under different hemodynamic conditions [28], cerebral resistance small arteries may dilate or constrict in response to dynamic perfusion pressure changes according to the so-called process of cerebral autoregulation. Thus, the pial arterioles on the surface of the cortex appear to be the major site of control of penetration of the arterial pulse wave into the downstream vascular network [29]. However, in normal conditions, a particularly low resistance perfusion to the brain and kidneys is accompanied by low wave reflection from these organs and deeper penetration of the arterial pulse wave; unlike other organs protected by marked vasoconstriction upstream,

brain and kidneys pulsate [30]. This makes both the brain and the kidneys particularly vulnerable to large artery windkessel dysfunction [30, 31].

Dependence on the CSF and venous mobile compliance is an additional specific feature of the cerebral vascular windkessel process [32, 33]. Indeed, in normal conditions, the intracranial arterial pulsations are dissipated into the subarachnoid spaces before they reach the capillary level; by CSF venting into the spinal cavity and by venous outflow from the subarachnoid veins itself induced by CSF pulsations [22, 34]. Such a diversion of the arterial pulsations from the capillary blood within the subarachnoid spaces is favoured by a peculiar characteristic of cerebral circulation; the vessels controlling parenchymal flow are predominantly located outside of the brain itself [29].

Indeed, the cortical arteries that supply the cortex and adjacent white matter - as well as the cortical veins- have a long course within the subarachnoid spaces. Thus, there is a close relationship between arterial and venous superficial pulsations [35]; an efficient diversion of the arterial pulsations from the capillary blood into CSF spaces and thus the cortical veins, protects the richly supplied brain cortical mantle, the major source of intracranial blood volume variations.

However, the long perforating medullary arteries that supply the deep white matter, the deep penetrating arterioles rising from the circle of Willis and the deep veins have a mainly intraparenchymal course. Thus, MR flow measurements show a broader deep venous systolic peak outflow which is less closely related to the arterial systolic peak than in the superficial regions [35]. Such a lower coupling between the arterial and venous pulsations in the deep brain regions suggests a lesser transmission of the arterial pulsations to the deep veins via CSF and a preferential transmission of these pulsations to the deep capillary network. Moreover, there is a close relationship between the splenium of the corpus callosum and the vein of Galen, a key structure in the deep venous system; thus, the early systolic downward motion of the corpus callosum [21] and resulting compression of the underlying vein of Galen [36] may still reduce the interactions between CSF and the deep venous system during the intracranial arterial systole. Finally, as deep perforating arteries directly rise from the circle of Willis, they are particularly vulnerable to insufficient dampening of the arterial pulsations by the large arteries [3]. All these anatomic particularities suggest a high vulnerability of deep brain perfusion to windkessel dysfunction.

In summary, the windkessel effect requires a compliant arterial tree allowing passage of the pulsations directly into the CSF. From here, the pulsations are dampened by a combination of shifting CSF into the compliant spinal canal and compressing cortical veins rendering the venous outflow pulsatile. A breakdown of any of these components will contribute to windkessel dysfunction

3. THE EMERGING CONCEPT OF PULSE WAVE ENCEPHALOPATHY

Assigning disturbances in intracranial dynamics to simple disturbances in vessels or CSF spaces bulk flow –a kind of “plumbing problem”- now appears an over simplistic

viewpoint. It will be shown that alterations in pulse wave propagation may better explain the available data.

3.1. Limits of the Bulk Flow Concept in CSF and Vascular Intracranial Disturbances

Theories based on abnormalities in the bulk flow of fluids intracranially do not accurately describe the findings of the literature.

Indeed, there is no large transmantle pressure difference in hydrocephalus; though a small or transient pressure gradient cannot be fully eliminated, these data rather suggest no evidence of a bulk CSF flow abnormality [37, 38]. In addition, non communicating and communicating chronic hydrocephalus – with and without obstruction of ventricular system respectively- appear increasingly to share common pathomechanisms [39], as underlined by the efficacy of third ventriculostomy for treating communicating hydrocephalus; though it has been advocated that this treatment can act as a by-pass of a focal obstruction through the basal cisterns [40], this unexpected efficiency supports the new hydrodynamic concept of hydrocephalus [22, 41, 42] rather than the conventional bulk flow concept of CSF dynamics.

In the same way, cerebral microangiopathies can lead to cerebral focal necrosis and hypoxia despite widely patent arteriolar lumens and thus no significant change in cerebrovascular conduit function [43, 44]. This does not preclude undetectable transient episodes of brain hypoperfusion due to impaired vasoreactivity; however, there is also no direct relationship between cerebral arterial flow rate and “silent cerebrovascular damage” (cf infra.), so that all these data converge to suggest a non hypoperfusive pathogenesis of these hypoxic changes.

Finally, metabolic brain changes similar to those resulting from arterial stenosis or occlusion can result from mere disturbances in intracranial pulse pressure [45].

Thus, parameters relating to pulsation strength, i.e. the arterial pulse pressure increasingly appear to be a more meaningful marker of disease than the mean arterial pressure [27, 46], the intracranial pulse pressure is increasingly recognized as a more meaningful parameter than the mean intracranial pressure [47]. Recognizing the major potential risk of any disturbances in the pulsatile components of intracranial CSF and blood flow led to the use of the term pulse wave encephalopathy [36, 48-50]. Analyses of these recently identified conditions are still in their infancy. However, they have allowed a better understanding of two archetypes of pulse wave encephalopathy in the elderly, subcortical arteriosclerotic encephalopathy and idiopathic normal pressure hydrocephalus. They may also help to classify the various subtypes of the heterogeneous “Alzheimer’s syndrome”.

3.2. Subcortical Arteriosclerotic Encephalopathy: From Normal Aging to Subcortical Arteriosclerotic Dementia

3.2.1. A Key Dynamic Change, the Increase in Intracranial Blood Pulsations with Large Artery Stiffening

Arterial aging i.e. arteriosclerosis is characterized by large artery dilatation and stiffening [27]. This results from

cumulative fatiguing effects of cyclic strain on the non living elastic material of the large arteries, mainly the ascending aorta [27]. Arterial hypertension and other cardiovascular risk factors may also accelerate large artery stiffening [46] and promote the onset of atherosclerosis, i.e. the association of morphological (atherosis) and functional (sclerosis) alterations of the large artery wall. Whereas arteriosclerosis does not affect large artery conduct function, it is a major cause of reduced large artery compliance and thus of increased arterial systolic pulse and decreased arterial diastolic pulse [27]. Moreover, increased aortic pulse wave velocity with aortic degeneration induces an earlier return of wave reflection from the peripheral arterioles, which increases the systolic pulse in older adults instead of the diastolic pulse in younger adults [27, 51].

Thus, large artery stiffening with arteriosclerosis is accompanied by an elevation in the amplitude of arterial pulse pressure and flow pulse [27, 51, 52] and MR flow measurements confirm an increased intracranial arterial pulse volume in the elderly [53] (Tables 1 and 2). However, in one study [54] using both clinical and MR criteria of "normal aging" instead of a single clinical definition, no significant differences in the intracranial blood pulse volume was detected between young and elderly subjects; thus, in the most "successful" form of aging, arteriosclerotic changes may be limited. As expected, more severe large artery stiffening is associated with even higher intracranial arterial pulse volume in subcortical arteriosclerotic dementia [53, 55-58].

There is an increase in the arterial pulsatility index (PI) or Gosling index with aging, which is even more severe in patients with arteriosclerotic dementia [59-61] (Tables 1 and 2). The arterial pulsatility index is often postulated to reflect the downstream vascular resistance, but it is not just a measure of vascular resistance of both proximal and distal vessels. It is a more complex integration of arterial compliance, pulsatility, and peripheral resistance, becoming progressively less influenced by arterial resistance as vascular compliance decreases [28, 62, 63].

An unexpected finding in hypertension, (a major risk factor of atherosclerosis), is higher regional cerebral blood flow in elderly patients with symptomatic atherosclerotic disease than compared to normal aging [64]. As vascular flow is inversely related to arterial resistance, a reduction would be expected by a model of increased downstream vascular resistance. This population of elderly patients with symptomatic atherosclerotic disease also demonstrated an unexpected slightly higher arterial blood flow compared to the general population [65]; in the same way, there is an association between increased pulse pressure and higher total brain perfusion [66]. All these data argue against an increased peripheral total resistance in symptomatic atherosclerosis and rather suggest a slightly overloaded autoregulatory capacity of the cerebral vessels. Thus, in a recent MR study, the mean arterial pressure divided by cerebral blood inflow i.e. the estimated cerebral vascular resistance was significantly decreased in vascular dementia [56].

Therefore, increased IP can rather be considered as a clinical biomarker of generalized atherosclerosis [67] and target organ microvascular damage [68]; it correlates with arterial pulse pressure in patients with arterial hypertension

[63, 69] and other markers of large artery stiffening including ankle brachial indices [70] and carotid intima media thickness [67].

Thus, MRI can detect advanced arteriosclerotic cerebral disease as an increase in both PI and intracranial net blood pulse volume, a cardinal feature when predicting vascular cognitive decline in the elderly [57, 58]; a single pathomechanism of markedly increased intracranial arterial pulsations with secondary capillary dysfunction may help in understanding the single clinical picture of vascular dementia whether it is a subcortical dementia or a so-called "cortical" dementia with coincident cortical strokes.

3.2.2. A Subcortical Syndrome of Deep Windkessel Dysfunction

An increase in intracranial arterial pulsations is associated with a significant increase in the straight (ST) sinus pulse volume and pulsatility in aging and vascular dementia [53, 71]. This suggests a deep capillary hyperpulsatility in these two last conditions, because the increased arterial pulsations are more likely to be transmitted to the deep venous system through the deep capillary network than via CSF.

Indeed, the already low coupling between CSF and venous pulsations in the deep regions may be still worsened by an abnormal systolic compression of the vein of Galen in aging and vascular dementia; there is an increased transmission of the arterial pulse to the brain in arteriosclerotic encephalopathy [72]. Such an increased downward pulsatile motion of the corpus callosum [21] is probably favored by the increased resistance to CSF outflow and reduced spinal compliance with aging [73]. It promotes the onset of mild repetitive trauma and gliosis along the corpus callosum splenium and a so-called "traumatic leukoaraiosis" in arteriosclerotic encephalopathy [49]. Thus, splenial leukoaraiosis appears a mandatory feature in progression to subcortical arteriosclerotic dementia [57], whereas its extent parallels cognitive decline in the elderly [74].

Decreased dampening of the arterial pulse within the deep venous territories defines a similar syndrome of deep windkessel dysfunction in aging and subcortical arteriosclerotic dementia, the age-related microvascular frontal subcortical syndrome [75]; however, this syndrome is much more severe in vascular dementia than in physiological aging. Deep grey matter and midbrain dysfunction in arteriosclerotic disease is associated with parkinsonian-like gait disturbances [76]. This syndrome of deep windkessel dysfunction also includes cognitive symptoms of fronto-striatal dysfunction with mainly executive dysfunction. Thus, gait and cognitive fronto-striatal disturbances are the earliest and typically predominant clinical changes in vascular dementia [19].

Microvascular pulsatile stress promotes chronic perivascular edema in the frail deep white matter i.e. subcortical leukoaraiosis [49, 50, 77], perivascular leakage of erythrocytes and "microbleeds" and enlargement of perivascular spaces around the penetrating striothalamic arteries in the basal ganglia. Thus, aging and arterial hypertension are the major risk factors of structural changes suggestive of deep windkessel dysfunction, including deep white matter changes [78], deep brain microbleeds [79, 80] and deep perivascular

enlargement [81]. Leukoaraiosis worsens with the increase in the arterial pulse pressure [82], intracranial arterial pulse volume and net blood pulse volume [48] and is inversely related to large artery elasticity indices [48, 50, 69, 83]. Thus, subcortical leukoaraiosis is the most common substratum of vascular cognitive impairment [78] and it is a mandatory feature to predict conversion to subcortical arteriosclerotic dementia in the elderly [57]. Interestingly, the extent of perivascular enlargement of the Virchow Robin spaces has been also correlated with arterial systolic pressure and pulse pressure [84].

Deep cerebrovascular dysfunction with large artery stiffening also explains a preferential atrophy of the white matter with physiological aging [85] and clinical arteriosclerotic microvascular disease [86]. Even more severe atrophy of the white matter in patients with advanced subcortical arteriosclerotic encephalopathy [87] may contribute to enhance periventricular pulsatile stress due to intraventricular CSF pulsations, leading to an abnormally thick “traumatic” periventricular leukoaraiosis compared to normal aging [49]. However, abnormally thick periventricular leukoaraiosis increasingly appears an even more reliable indicator of large artery stiffness, downstream capillary damage and clinical dysfunction than subcortical leukoaraiosis [3, 17, 74, 76, 88, 89]. Progressive lowering of cerebral arterial flow rates with capillary dysfunction and hypometabolism also appears related to an increase in periventricular – rather than subcortical- leukoaraiosis volumes [90]. However, there is a high correlation between both periventricular and subcortical leukoaraiosis in the elderly patients [3], whereas some conflicting results about the role of these two subtypes in terms of clinical dysfunction may also result from differences in terms of clinical tests and definition of these two subtypes [91].

Periventricular leukoaraiosis does not appear to result from hypoperfusion itself. Periventricular leukoaraiosis does not demonstrate markers of hypoxia [44], there is no correlation between periventricular leukoaraiosis and cardiac output, a measure of systemic perfusion [92] and there is no selective periventricular ischemia among patients with chronic carotid occlusion [93]. More generally, there is no linear relationship between cerebral arterial flow rate and leukoaraiosis [48, 50, 69, 94], a reduction in carotid flow rates does not induce leukoaraiosis [95] and there is no spatial concordance between leukoaraiosis and cerebral large artery territories; instead, periventricular leukoaraiosis shows a ventricular systematization [49], the bilateral symmetric subcortical white matter changes visible on MRI or CT scans mimic leukoencephalopathy from impaired deep venous outflow [96] which enhances the peculiar vulnerability of the deep venous territories to windkessel dysfunction.

Nevertheless, cerebral blood flow is coupled to brain metabolism and lower regional perfusion may be a local consequence of leukoaraiosis, whereas this form of interstitial oedema preferentially extends in frail and thus poorly supplied regions [3, 97]. Parenchymal atrophy may also contribute to a mild decrease in total cerebral arterial flow rate in symptomatic arteriosclerotic cerebral disease [65]. Thus, a lack of very high arterial flow rate appears a mandatory feature for cognitive decline in small vessel disease [57]. However, there is no marked brain hypoperfusion in vascular

dementia, at least before the end-stages [53, 56-58, 98]. Thus, qualitative and not quantitative disturbances in cerebral perfusion appear to most often underlie neuronal dysfunction in vascular dementia, reduced tissular oxygenation and hypoxia may result from replacement of the normal smooth capillary flow by an abnormal pulsatile capillary flow rather than from a reduction in blood supply [3].

Deep white matter atrophy promotes an imbalance between the amplitude of intraventricular CSF pulsations and periventricular tissular resistance to pulsatile stress and thus secondary ventricular enlargement [22, 34, 49]. The syndrome of deep windkessel dysfunction in aging and arteriosclerotic subcortical dementia also includes a mild or moderate ventricular enlargement; as expected, ventricular enlargement is correlated with periventricular leukoaraiosis in aging [99], whereas both ventricular enlargement and periventricular leukoaraiosis often accompany progression to arteriosclerotic dementia [14, 57, 58, 89].

The deep venous territories include the deep white matter but also the deep grey matter of the thalamus and striatum, the hippocampus, the cortical areas of the limbic lobe, the visual cortex and rostral brain stem [100]. Thus, besides the preferential white matter atrophy, morphologic changes in subcortical vascular dementia also include deep lacuna, hippocampal atrophy and midbrain atrophy [3, 86]. Marked striatal dysfunction also promotes atrophy along the fronto-subcortical pathways correlated with cognitive decline [101]. Neuroimaging studies may also evidence hypoperfusion in the basal ganglia in patients with left ventricular hypertrophy [102], a cardiac biomarker of arteriosclerosis, marked hypometabolism or hypoperfusion in the basal ganglia and in the frontal lobes in those with vascular dementia [103]. There are also recent reports of reduced perfusion not only in the subcortical but also in the limbic and paralimbic structures in patients with arterial hypertension [104], reduced regional brain perfusion in the occipital cortex in patients with subcortical arteriosclerotic encephalopathy [105], altered integrity of the activation-flow coupling in the occipital cortex in patients with vascular dementia [106].

3.2.3. Diffuse Cortical Windkessel Dysfunction, a Characteristic Feature of Subcortical Arteriosclerotic Dementia

Normal aging is associated with elevated arterial pulse pressures and arterial pulse volumes. In normal aging, a higher superior sagittal sinus pulse volume parallels the higher arterial pulse volume [53]. Thus, there is no significant inward redistribution of blood pulsations from CSF subarachnoid spaces to the ventricles in the healthy elderly; CSF aqueductal stroke is not elevated in the elderly subjects [55] compared to the younger adults [23]. Most importantly, the cortical capillaries and global cognition appear preserved in the elderly subjects. Thus, the elevated arterial pulsation caused by the elevated arterial pulse pressure is adequately dampened by elevated venous pulsation in normal aging (Tables 1 and 2).

In contrast, an even higher arterial pulse volume is not associated with a similar increase in the superficial venous pulse in vascular dementia [53] and this suggests inadequate venous dampening. This is in good agreement with an overloaded superficial venous capacitance, due to too high arte-

rial pulse volume and could also be favoured by an increased systemic and/or intracranial venous pressure.

Table 1. Relationship Between Physiological Factors and MR Parameters

Physiological Factors	MR Parameters
Large artery compliance (-)	Pulsatility index (+) Periventricular leukoaraiosis (=or +)
Distal vascular compliance (+)	Subcortical leukoaraiosis (= or +) Arterial pulse volume (+) Intracranial blood stroke volume (+)
Intracranial compliance (-)	Index of intracranial compliance (-) CSF stroke volume (+) / blood stroke volume (-)
Intracranial dynamic equilibrium (-)	Ventricular enlargement (= or +) Leukoaraiosis (initially + then -) Superficial venous flow rate (typically -) Deep venous flow (= or -) Total arterial flow rate (= or -)

A synergistic effect of the even higher arterial pulse and insufficient superficial venous dampening may thus contribute to diffuse cortical capillary dysfunction in subcortical arteriosclerotic encephalopathy; with diffuse cortical atrophy, cortical microinfarcts and dementia [3, 107]. Thus, diffuse confluent leukoaraiosis, a recognized substratum of vascular dementia, is associated with lower (subcortical and) cortical grey matter perfusion [108].

In severe subcortical arteriosclerotic dementia unlike normal aging, there is also an increased subarachnoid CSF outflow through the incisura [48, 53] helping to offset the insufficient venous compliance and maintaining a normal total compliance. This higher subarachnoid CSF pulse volume despite stiffened large arteries highlights the pumping role of cerebral arteriolar expansion [26]. It may be favoured by more severe brain shrinkage in advanced arteriosclerotic microvascular disease [85]. Nevertheless, a ratio calculated from aqueduct and blood strokes volumes measurements, the so-called compliance ratio, is on average increased in arteriosclerotic dementia [55]. This forced increase in subarachnoid mobile compliance prevents inward redistribution of the arterial pulsations; the aqueduct CSF pulse volume is not significantly increased in arteriosclerotic dementia [55] nor in severe arteriosclerotic cerebral microangiopathy [109].

Thus, although disturbances in intracranial pulsations play a key role in the new hydrodynamic concept of chronic hydrocephalus, it can be noticed that hydrocephalus is not systematically associated with conditions that induce an isolated increase in arterial pulsatility (such as aortic insufficiency, hypercapnia) or a reduction in CSF venting from the cranial cavity – such as spinal stenosis [110]. Indeed, onset of chronic hydrocephalus appears to be modulated by the elastic properties of the brain [111] and it rather requires at least moderate failure of all the components of the multifactorial and sophisticated windkessel system.

However, dynamic equilibrium in subcortical arteriosclerotic dementia, which is based on the increase in subarachnoid mobile compliance (Fig. 1) is particularly vulnerable in the elderly; progressively increased arterial pulse volume with large artery stiffening on the one hand [27], progressively restricted intracranial compliance with craniospinal cavity aging on the other hand [73], may induce an imbalance between intracranial arterial pulse and compliance. Therefore, Normal Pressure Hydrocephalus-like dynamic changes [112] have been reported in patients with several risk factors for stroke [109] and a subcortical arteriosclerotic encephalopathy may promote normal pressure hydrocephalus in elderly patients [22, 113].

3.3 Normal Pressure Hydrocephalus

3.3.1. A Mechanical Syndrome

Unlike subcortical arteriosclerotic encephalopathy where the total compliance was maintained, major dynamic features of normal pressure hydrocephalus (NPH) include a major insufficiency of craniospinal compliance (Fig. 2) and its corollary, a marked increase in the intracranial pulse pressure together with a normal or low-grade elevation of intracranial pressure [114] (Tables 1 and 2). Another key NPH feature is its potential reversibility with CSF derivation; an almost purely mechanical therapy, CSF derivation, may radically affect intracranial compliance, reduce intracranial pulse amplitude and reverse clinical disturbances [115].

Indeed, clinical disturbances in NPH mainly appear as mechanical consequences of the marked dynamic imbalance between intracranial arterial pulsations and compliance with high intracranial pulse pressure and forced distension of the spinal thecal sac.

Progressively decreased brain parenchyma resistance to water hammer effects and hydraulic-compression with aging certainly play a role in the variable manifestations of a reduction in intracranial compliance according to the age of the patients [116]. Nevertheless, in the elderly, the increased amplitude of the intracranial -and thus endoventricular - pulsatile pressure alone is associated with an active distension of the ventricular system [34]; this distension may contribute per se to the early and prominent clinical impairment of dynamic equilibrium in NPH [116, 117]. It is associated with a narrowing of subarachnoid spaces at least at the high frontoparietal convexity and high midline areas, probably due to the radial and mainly suprasylvian expansion of the ventricles [118].

Loss of communication between the cranial cavity and spinal canal with progressive distension of spinal thecal sac or “spinal subarachnoid block” and deterioration of cervical CSF flow appears a key determinant in the onset of the NPH clinical syndrome [112, 119]; indeed, it favours a - reversible - mechanical compression of the midbrain. This change has been recently correlated with the – reversible - gait disturbances in NPH [120]. It may contribute to the -reversible- striatal dysfunction in NPH [121]. Reduced basal ganglia and frontal perfusion has been also reported in NPH [122] and there is typically a frontostriatal cognitive dysfunction in NPH [123].

Table 2. Relationship Between Main Forms of Pulse Wave Encephalopathy and MR Parameters

Pulse Wave Encephal.	“Usual“ Aging	Subcortical Arteriosclerotic Encephalopathy (Pure Arteriosclerotic Form)	“Normal Pressure Hydrocephalus” (Pure Resistive Form)	Alzheimer’s Disease (Arteriosclerotic Form)	Alzheimer’s Disease (Resistive Form)
Type	Hypoxic + (neuronal dysfunction)	Hypoxic ++ subacute (neuronal dysfunction)	Mechanical ++ subacute (neuronal dysfunction)	Toxic ++ chronic (neuronal and synaptic loss)	Toxic ++ chronic (neuronal and synaptic loss)
Cardinal Pathogenic Features	Increased large artery pulsations (+) Increased IC pulsations (+) Hypoxic >>toxic deep capillary dysfunction Preserved IC dynamic balance	Increased large artery pulsations (++) Increased IC pulsations (++) Hypoxic>>toxic deep and cortical capillary dysfunction Preserved IC dynamic balance	Decreased IC compliance (++) Decreased IC flow pulsations Tissular compression (++)>> toxic capillary dysfunction Altered IC dynamic balance ++	Increased large artery pulsations (+) Decreased IC flow pulsations Toxic capillary dysfunction Preserved IC dynamic balance	Decreased IC compliance (+) Decreased IC flow pulsations Toxic capillary dysfunction Altered IC dynamic balance +-
Cardinal MR Features	Punctuate leukoaraiosis and thin periventricular leukoaraiosis High IP (+) High IC blood stroke (+/-) Preserved compliance index	Significant leukoaraiosis High IP (++) High IC blood stroke (++) Preserved compliance index	Marked ventricular enlargement Reduced SAS (superior convexity) Low IP Low IC blood stroke Low compliance index	Anteromesial temporal atrophy +++ High IP Low IC blood stroke Preserved compliance index	Anteromesial temporal atrophy +++ Low IP Low IC blood stroke Low compliance index
Clinical Syndromes	Deep GM >>cortical hypoxic dysfunction	Deep GM + cortical hypoxic dysfunction	Deep and infratentorial mechanical dysfunction >> cortical mechanical dysfunction	Cortical >>deep GM toxic alterations	Cortical >>deep GM toxic alterations

Abbreviations; GM for grey matter, IC for intracranial , IP for index of pulsatility, SAS for subarachnoid spaces

Thus, a mere reduction in spinal CSF volume by a spinal CSF tap test typically provides a rapid and spectacular clinical improvement in gait disturbances and this test represents a specific though not highly sensitive key step of diagnosis [124].

Interestingly, clinical disequilibrium is less improved by lumbar puncture than other gait disturbances [124]. This may reflect its closer relationship to structural aspects of ventriculomegaly, which is not usually significantly reduced, even after efficient CSF diversion in chronic hydrocephalus [125].

Impairment of brain perfusion in NPH also seems to mainly result from mechanical factors, with compressive forces upon the subarachnoid veins and periventricular tissues.

The pial and cortical veins are compressed within the constricted subarachnoid spaces in NPH [126, 127]. Indeed, collapsible subarachnoid veins are particularly vulnerable to disturbances in impedance to CSF flow through the subarachnoid space, so that altered superficial venous outflow appears a key dynamic indicator of marked insufficiency of

the intracranial compliance [39, 57, 58, 126, 127]. There is a reversible decrease in the cortical venous flow pulsatility [126] and at least a relative and reversible reduction in the superficial venous outflow rate in NPH [35, 128, 129].

The earlier onset of the superficial venous peak outflow is associated with a reversible (absolute or relative) reduction in intracranial arterial pulse volume and intracranial net blood pulse in NPH [35, 55, 130, 131]. Conversely, the often high arterial PI in elderly NPH patients is not lowered following CSF shunt and rather suggests arteriosclerotic comorbidity [126]. In the same way, impaired cerebrovascular autoregulation seems related to cerebrovascular co-morbidity in NPH patients [132].

Total cerebral arterial flow rate is closely related to superior sagittal sinus flow rate and can be reduced in NPH [35, 128]. However, the reduction in cerebral arterial inflow is typically moderate in NPH [129] and can reverse with CSF shunt or with CSF tap test [133]. Similarly, impairment in general cognitive ability is typically only moderate and reversible in NPH [113, 134].

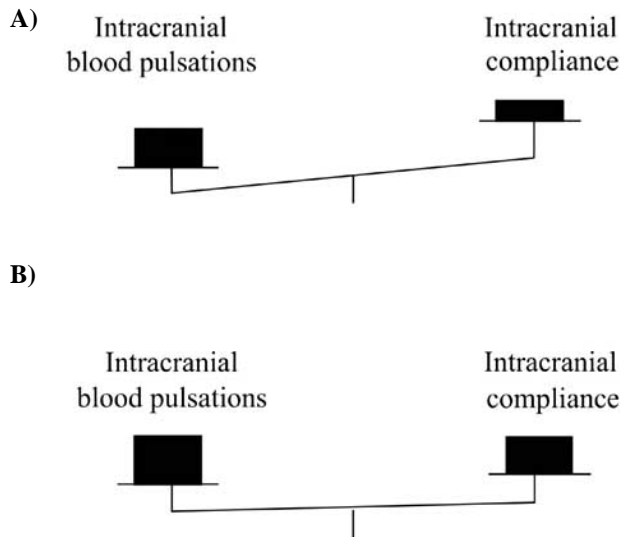


Fig. (1). Intracranial dynamics in normal adults (A) and in subcortical arteriosclerotic dementia (B).

In these two conditions, the intracranial overall dynamic equilibrium is preserved; however, there is a deleterious increase in intracranial blood pulsations with large artery stiffening and compensatory increase in the intracranial compliance in arteriosclerotic pulse wave encephalopathy

Interestingly, there is no significant change in the deep net blood pulse volume in NPH in both baseline and post shunt conditions [35]. This may reflect the mainly centrifugal expansion of the brain and most importantly, the previously underlined interaction between CSF and deep venous system. Nevertheless, periventricular white matter is compressed in NPH as indicated by a positive correlation between reduction in CBF and proximity to the ventricles; there is also a correlation between the decrease in CBF in the white matter, thalamus and basal ganglia and changes in CSF pressure [122].

3.3.2. A Wide Spectrum Of Dynamic Disturbances Behind the Single Normal Pressure Hydrocephalus Syndrome

Increased intracranial compliance with CSF shunt corrects the dynamic imbalance between intracranial compliance and arterial pulse volume that defines the NPH syndrome. However, if this syndrome predominantly results from a marked increase in the intracranial arterial pulse pressure, CSF diversion only replaces the mechanical NPH syndrome by a clinically almost similar syndrome of arteriosclerotic dementia. Indeed, midbrain, basal ganglia, frontostriatal and hippocampal dysfunction can be observed in both NPH and subcortical arteriosclerotic encephalopathy [121, 122, 135-137].

Both severe arteriosclerotic disease and a primary abnormal increase in impedance to CSF outflow can lead to disequilibrium in intracranial dynamics [113, 138]; thus there is a wide spectrum of patterns ranging from purely hydrodynamic disturbances to predominant large artery alterations in NPH [139]. Moreover, a combination of both of these pathologies most frequently underlies this syndrome. Thus, although it is relatively easy to diagnose a normal pressure hydrocephalus syndrome, there is a considerable

overlap in clinical, brain structural and dynamic features of responders and non responders NPH patients i.e. NPH patients with good outcome after CSF shunt and NPH patients with poor outcome after CSF shunt [130, 136].

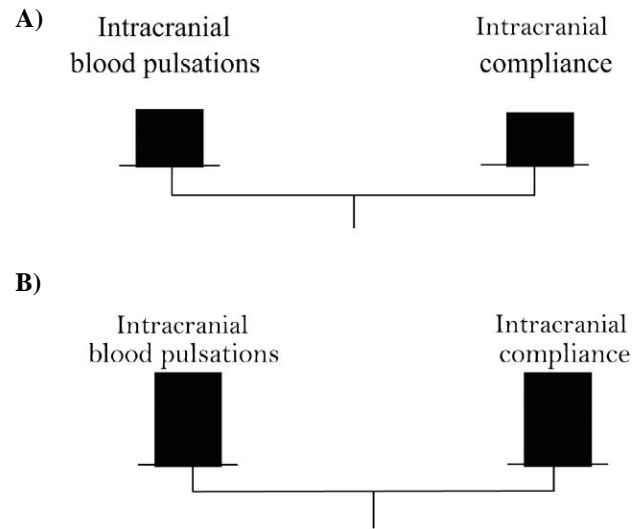


Fig. (2). Intracranial dynamics in Normal Pressure Hydrocephalus (A) resistive (C) subtype of (B) AD.

There is a marked imbalance between intracranial blood pulsations and compliance in NPH (which in this example, results from a marked reduction in intracranial compliance). There is only a mild imbalance between intracranial blood pulsations and compliance in AD, due to a moderate decrease in intracranial compliance with aging ("resistive" AD subtype); thus, there are rapidly progressive and predominantly mechanic deleterious consequences of this imbalance in NPH, but insidious and predominantly toxic deleterious consequences of this imbalance in AD.

Nevertheless, the most severe forms of dynamic imbalance seem preferentially observed when the predominant pathogenic factor is a primary increase in impedance to CSF outflow in NPH [114].

Thus, an increase in the intracranial pulse pressure appears well correlated to good clinical outcome after CSF shunt [114, 115, 134]. In the same way, the highest aqueductal flow rates or stroke volumes are most often observed in NPH patients that are later improved by CSF diversion or NPH responders patients [112, 130]. Indeed, increased amplitude of these ventricular CSF pulsations in NPH reflects a compensatory inward redistribution of the arterial pulsations due to insufficient venous and subarachnoid CSF mobile compliance. Thus, the increase in CSF aqueduct flow stroke may parallel clinical worsening [140], it is reversed by successful CSF shunt [112, 141] whereas the decrease in CSF aqueduct flow velocity following CSF tap test predicts good outcome after CSF shunt [142]. However, the relationship between this parameter and intracranial compliance is not linear and this parameter alone is most often not sufficient to predict clinical outcome [112, 130, 140, 143].

Conversely, the highest intracranial arterial pulse volumes –suggestive of marked large artery stiffening but only moderately reduced intracranial compliance- seem observed in non responders rather than responders NPH [130] and there is converging evidence that poor outcome tends to be

more frequent than good outcome in NPH patients with marked cerebrovascular disease [113,144].

Finally, recent data suggest that reversibility of dynamic disturbances with CSF tap test increasingly may be the most efficient way of predicting outcome after CSF shunt [133, 142].

4. PULSE WAVE ENCEPHALOPATHY AND THE “ALZHEIMER’S SYNDROME”

AD was originally defined and managed as a non vascular disorder. However, there is now a growing body of data showing early abnormalities of both structure and function of large arteries and cerebral microcirculation in AD [145-149] and the “Alzheimer’s syndrome” can now be associated with a wide spectrum of pulse wave encephalopathies; including pure AD (Tables 1 and 2) - or toxic pulse wave encephalopathy – as well as AD-like pulse wave encephalopathies – characterized by hypoxic and mechanic complications of windkessel dysfunction [57].

4.1. “Pure” AD, a Low Grade and Predominantly Toxic Form of Pulse Wave Encephalopathy

An imbalance between the production and clearance of amyloid beta peptide in the brain is increasingly recognized as the initiating event [150]; there is an increase in amyloid beta production in familial AD, whereas a reduced amyloid clearance in patients with large artery stiffening or increased impedance to CSF flow with aging may explain why aging is the main risk factor of sporadic AD.

Indeed, there is an increase in amyloid beta-peptide (A β) deposition in the brain with arterial hypertension [151] and hydrocephalus [152], a higher than expected coincidence of AD pathology in subcortical arteriosclerotic encephalopathy [3] as well as in NPH [113, 153]. The extent of intracranial atherosclerosis [154], arteriosclerotic small vessel changes [155] and leukoaraiosis [156] has been correlated with the extent of Alzheimer’s pathology, whereas an early microvascular breakdown is increasingly advocated in the pathogenesis of amyloid beta peptide [157]. The similar reduction in CSF turn over [153] and CSF concentrations of amyloid beta (1-42) peptide in patients with AD and idiopathic NPH [158] also supports a reduced amyloid clearance via CSF disturbances in both of these diseases.

MR analysis of intracranial dynamics differentiates two dynamic subtypes in “pure” AD, one demonstrating reminiscent features of subcortical arteriosclerotic encephalopathy, the other demonstrating reminiscent features of chronic hydrocephalus [57].

NPH is a rather acute and predominantly mechanical complication of windkessel dysfunction, subcortical arteriosclerotic encephalopathy is a subacute and predominantly hypoxic complication of windkessel dysfunction; conversely, AD appears to be a much more insidious and predominantly toxic complication of a subclinical reduction in large artery or intracranial compliance (Fig. 2).

4.1.1. A Subclinical Arteriosclerotic Form of AD

As expected from the neuropathological evidence of more severe atherosclerosis, the arterial pulsatility index is

frequently increased in AD [57, 60, 159]. However, there is no significant increase in the intracranial arterial pulse volume nor in the net blood pulse volume in AD [53, 56, 57] which suggests that the requirement for a normal arterial compliance for the pulsations to be dissipated to the CSF spaces may be lost in this form of AD. This low net blood pulse volume even appears a key dynamic feature in AD; high arterial inflow does not seem to preclude progression to dementia of the Alzheimer’s type in elderly patients with MCI, whereas low intracranial net blood pulse together with marked and predominantly left entorhinal atrophy appear required for conversion to DAT [57].

Such a lack of deeper penetration of the arterial flow pulsations into the distal vascular bed however does not preclude a deeper penetration of the arterial pressure pulsations into the distal vascular bed; thus, similar ultrastructural capillary changes have been reported in both arterial hypertension and AD [145]. This isolated pulse pressure capillary disturbances in AD may alter blood-brain barrier, promoting toxic chronic complications of arteriosclerotic disease and amyloid deposits [160] instead of the hypoxic subacute complications of arteriosclerotic disease. Indeed, as compared with the simultaneous increase in pressure and volume waves in SAE, the hemodynamic AD pattern of continuous and smooth capillary flow, necessary for capillary exchanges and oxygen extraction [3], may protect from the subacute hypoxic SAE pattern.

Nevertheless, such a lack of increased capillary pulse flow despite an altered arterial dampening in this arteriosclerotic form of AD is not normal. Indeed, this particular lack of deep windkessel dysfunction contrasts with the intermediate severity of intracranial atherosclerosis in AD compared to normal aging and vascular dementia [154]. It suggests some local disturbance counteracting the expected increase in the intracranial arterial pulse from large artery windkessel dysfunction [52] (such as very stiff distal arterioles). Such a restricted arterial pulse wave penetration into the cerebral microvascular network may result from early small amyloid aggregates associated with the microvasculature inducing constrictions along these vessels [147] or at least reduced compliance of the distal arterial tree in AD [56, 146]. Finally, it may be favoured by altered cerebrovascular reactivity priming vasoconstriction in AD [148, 160], so that an excessive vasoconstriction upstream protects the brain. Indeed, both large cerebral arteries and parenchymal vessels are densely innervated by cholinergic nerves, cholinergic enhancement increases regional cerebral blood flow in the cerebral cortex and subcortical structures whereas AD promotes an early deterioration of cholinergic neurogenic control of cerebral vessels and secondary reduction in nitric oxide activity, one of the most potent vasodilators [149]. Thus, reduced total cerebral arterial flow is a frequent and early finding in DAT [53, 56, 57, 61, 98, 159]. It is more severe than in subcortical arteriosclerotic dementia [98] and precedes neuronal disintegration; indeed, early temporoparietal hypoperfusion in AD is coupled with a local increase in oxygen extraction [145].

Thus, there is no significant increase in the deep venous pulse volume in AD compared to normal aging [53]. Such a low volume of the intracranial pulsations suggesting a least a

preservation of the capillary flow from the pulsatile stress appears in line with clinical characteristics of AD; unlike arteriosclerotic subcortical dementia, AD is not characterized by an early clinical syndrome of deep cerebral windkessel dysfunction. Indeed, there is no significant increase in subcortical leukoariosis in early onset AD i.e. "pure" AD [3] and this change is not required to predict progressive cognitive decline to AD dementia [57]. In the same way, patients having progressive amnesic MCI and AD prodementia MCI patients are characterized by low extent of periventricular leukoariosis [57,161]; thus, periventricular leukoariosis rather appears as a consequence of the delayed deep brain atrophy in AD [162]. In the same way, MR evidence of deep perivascular enlargement or deep microbleeds suggests vascular dementia rather than AD [79, 81], there is at least a relative preservation of metabolism and perfusion in the basal ganglia and in the earliest stages in the frontal lobes in AD [163]. Unlike vascular dementia, AD is characterized by a preserved integrity of the activation-flow coupling the occipital cortex before the ultimate stages of the disease [106]. Executive dysfunction, a key feature of the frontostriatal dysfunction, is at least less severe than the amnesic syndrome in AD, reflecting the delayed involvement of the frontal cortex [15, 57], whereas gait disturbances are classically absent in early AD [1, 57]; early parkinsonian-like gait disturbances rather suggest vascular mild cognitive impairment [76].

4.1.2. Subclinical Alterations in Impedance to CSF Outflow in AD or Resistive AD

CSF transmission of the arterial pulsations to the subarachnoid veins may be faster in AD as compared to elderly controls, which suggests a more severe reduction in intracranial compliance than expected from mere advancing age [130] suggesting these patients have a condition more toward the NPH end of the spectrum. However, as previously detailed, there seems to be an early limitation in the arterial pulse volume in AD (cf. supra) and this may contribute to the prevention of the onset of marked dynamic disequilibrium and NPH syndrome in AD. Thus, once again, gait disturbances, the most salient clinical features of the NPH syndrome, are usually late in pathologically verified AD and CSF tap test worsens instead of reverses the reduction in total arterial flow rate in AD [164]. In the same way, although CSF derivation may induce some improvements at the earliest stages of AD, no significant benefit was detected in the delayed stages of severe dementia [165].

Nevertheless, the aqueduct CSF stroke volume may be relatively high compared to the low intracranial arterial pulse and the index of relative intracranial compliance may be reduced in AD patients even in the prodementia stages [55, 57]. But these disturbances appear less marked than in NPH patients [55, 57], whereas mere aqueductal flow rate measurements may fail to demonstrate any significant elevation in AD [166].

Moreover, there seems to be a relative increase in the supratentorial venous pulsations in AD; the basal sinus pulsations are significantly reduced despite no reduction in total venous pulsations [53]. These findings are rather unexpected; even mild reduction in subarachnoid compliance usually leads to an early mobilization of additional capaci-

tance by compression of the frail subarachnoid veins [33, 126, 127, 167]. A potential explanation is that the massive increase in the rigidity of the mid size leptomenigeal and cortical artery wall with arteriolar amyloid deposits [146] may promote more vigorous cerebral superficial venous outflow and greater venous pulsations in the supratentorial space. Lesser alterations of the infratentorial vessels [159] with delayed arteriolar amyloid deposits [155] in AD patients with reduced intracranial arterial pulse volume may explain reduced infratentorial venous pulsations [53].

4.2. "AD with Cerebrovascular Disease"

AD with elevated white matter hyperintensities is usually considered as a subtype of AD, i.e. the so-called "AD with cerebrovascular disease". However, there is increasing evidence that cerebral amyloid angiopathy is most often not the cause of leukoariosis in aging and dementia, whereas leukoariosis may be more specifically related to arteriosclerosis than initially believed [50, 107]. Thus, leukoariosis in elderly patients predicts a pattern of metabolic decline suggestive of subcortical vascular cognitive impairment rather than AD [168]. The first detailed prodementia analysis of both intracranial dynamics and hydrodynamics and brain morphology in clinically diagnosed dementia of the Alzheimer's type also enhances the under-diagnosed contribution of subcortical arteriosclerotic disease in late life dementia [57].

Indeed, in this study, none of the MCI patients with significant leukoariosis at the prodementia stages showed the previously described dynamic AD pattern, nor the typical prodementia mesiotemporal atrophy; a predominantly left atrophy combining hippocampal and entorhinal atrophy with marked enlargement of the collateral/ rhinal sulcus [169-171]. The most frequent dynamic pattern in this subgroup was an arteriosclerotic hyperdynamic pulse wave encephalopathy (cf. supra), thus confirming a major clinical overlap between subcortical arteriosclerotic encephalopathy and clinically diagnosed AD according to NINCDS-ADRDA criteria [14, 15]. This may explain the controversial use of transcranial Doppler sonography as a tool to distinguish Alzheimer disease and vascular dementia or yet conflicting results in former studies describing cerebrovascular reactivity or blood brain barrier damage in AD [61, 77, 172-175].

CONCLUSION

The current marked heterogeneity in responses to the available pharmacologic therapies for AD and disappointing effectiveness of these therapies [176] is well explained by the increasing evidence that clinically diagnosed DAT is a heterogeneous condition rather than a uniform disease entity. Greater focus on pulse wave encephalopathy – and mainly arteriosclerotic subcortical encephalopathy – may impact therapeutic research [177] because analysis of the intracranial dynamics may allow *in vivo* method for distinguishing multiple - potentially preventable or treatable- causes for this dementing syndrome.

In the pure or predominantly AD subtype, it may be useful to detect the initiating process behind reduced clearance of toxic substance, moderate large artery stiffening or reduced intracranial windkessel dysfunction. Vascular treatments in the former case [27], early CSF shunting in the lat-

ter case [153, 165], may help to stabilize an otherwise progressive cognitive decline.

In the common dementia form of “AD with cerebrovascular disease”, use of dynamic data may help to tailor treatments to the exact cause of cognitive decline, AD or most often cerebrovascular dysfunction, despite considerable overlap in risk factors, neuropathology and current clinical definitions of these two conditions. Indeed, as previously enhanced, AD and vascular dementia show opposite dynamic patterns; the former is characterized by reduced compliance of the distal arterial tree and no syndrome of deep windkessel dysfunction, the latter is characterized by increased compliance of the distal vascular tree and deep windkessel dysfunction. There is already preliminary evidence of effectiveness of vascular therapeutic strategies [160]; however, more targeted treatments in this last AD-like condition may be used to specifically improve abnormally low large artery compliance or reduce other cardiovascular disturbances such as reduced cardiac output –and brain perfusion- or elevated venous pressure.

In conclusion, better assessment of pulse wave encephalopathy in late life dementia may provide the rationale for both current and novel therapeutic strategies and greatly impact therapeutic research in this devastating syndrome.

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