ABSTRACT. Alois Alzheimer is best known for his description of the pre-senile neurodegenerative disease named after him. However, his previous interest in vascular brain diseases, underlying cognitive and behavioral changes, was very strong. Besides describing the Arteriosclerotic atrophy of the brain and the arteriosclerotic subtype of Senile dementia which he viewed as main forms of vascular brain diseases, he also identified and described a series of conditions he considered subforms. These may be divided, as suggested by the authors of the present paper, into 3 groups: gliosis and sclerosis, subcortical atrophies, and apoplectic. The subforms of the three groups present characteristic neuropathological features and clinical, cognitive and behavioral manifestations. These provide the basis, together with part of the main forms, for the contemporary condition known as Vascular Cognitive Impairment.

Key words: Alzheimer, brain vascular disease, arteriosclerosis, vascular subtypes, Vascular Cognitive Impairment.

INTRODUCTION

Alois Alzheimer (1864-1915), psychiatrist and neuropathologist, became renowned for his description of a new disease that carries his name.1 However, his previous remarkable studies on brain vascular disorders underlying cognitive, behavioral and neurological manifestations, became forgotten. He intensively studied the subject, resulting in important conferences and lectures as well as in a few papers on the theme, published between 1894 and 1902. These studies contributed to establish key knowledge on what has become incorporated into the present status on the subject – the Vascular Cognitive Impairment spectrum.2,3

Besides the two main dementia forms, Arteriosclerotic atrophy of the brain (arteriosklerotische Atrophie des Gehirns) and Senile dementia (senile Demenz), both examined by the authors in previous papers,2,3 Alzheimer identified and described a series of conditions (diseases) related to atheromatous vascular degeneration of the brain arteries which he designated “subforms”. He was...
able to distinguish these processes according to their location and spread of the brain changes, manifested by cortical and/or subcortical clinical symptoms.\textsuperscript{4,5} Besides the cases considered as typical subforms, he also mentioned the presence of mixed cases, mainly of vascular nature or more rarely, combined with syphilitic pathology, sometimes hampering the interpretation of a given case.\textsuperscript{9}

The vascular subforms described and named by Alzheimer may be divided, here as proposed by the authors of the present paper, into 3 groups: gliosis and sclerosis, subcortical atrophies, and apoplectic. These subforms may also be regarded as focal and diffuse conditions (Table).

Hereunder, the characteristics of these subforms will be considered as condensed excerpts of Alzheimer’s descriptions, relevant for the present approach, extracted and brought together from his several writings, and excluding conditions extraneous to the present scope (Box 1, Box 2, and Box 3).

### Table. Alzheimer and vascular brain diseases (Alzheimer [1894-1902]).\textsuperscript{4,9}

<table>
<thead>
<tr>
<th>Main forms</th>
<th>Subforms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arteriosclerotic atrophy of the brain (arteriosklerotische Atrophie des Gehirns) (Alzheimer, 1894, 1902)\textsuperscript{11}</td>
<td>• Perivascular gliosis (perivascularäre Gliose) (Alzheimer, 1896, 1897, 1899, 1902)\textsuperscript{5,6,9}</td>
</tr>
<tr>
<td>Senile dementia (senile Demenz) (Alzheimer, 1898, 1902)\textsuperscript{4,9}</td>
<td>• Perivascular gliosis (perivascularäre Gliose) (Alzheimer, 1896, 1897, 1899, 1902)\textsuperscript{5,6,9}</td>
</tr>
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</tr>
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</tr>
<tr>
<td>Subcortical atrophy group</td>
<td>Senile dementia (senile Demenz) (Alzheimer, 1898, 1902)\textsuperscript{4,9}</td>
</tr>
<tr>
<td>Arteriosclerotic brain degeneration (arteriosklerotische Hirndegeneration) (Alzheimer, 1898, 1899)\textsuperscript{7,9} (described by Alzheimer and Binswanger)</td>
<td>• Arteriosclerotic brain degeneration (arteriosklerotische Hirndegeneration) (Alzheimer, 1898, 1899)\textsuperscript{7,9} (described by Alzheimer and Binswanger)</td>
</tr>
<tr>
<td>Chronic progressive subcortical encephalitis (Encephalitis subcorticalis chronica progressiva)</td>
<td>• Chronic progressive subcortical encephalitis (Encephalitis subcorticalis chronica progressiva)</td>
</tr>
<tr>
<td>Arteriosclerotic atrophy of the hemispheric white matter (arteriosklerotische Atrophie des Hemisphärenmarks) (Alzheimer, 1899)\textsuperscript{9}</td>
<td>• Arteriosclerotic atrophy of the hemispheric white matter (arteriosklerotische Atrophie des Hemisphärenmarks) (Alzheimer, 1899)\textsuperscript{9}</td>
</tr>
<tr>
<td>Apoplectic group</td>
<td>Apoplectic dementia (Dementia apoplectica) (Alzheimer, 1898)\textsuperscript{2} [or]</td>
</tr>
<tr>
<td>Apoplectic dementia (Dementia apoplectica) (Alzheimer, 1898)\textsuperscript{2}</td>
<td>• Apoplectic dementia (Dementia apoplectica) (Alzheimer, 1898)\textsuperscript{2}</td>
</tr>
<tr>
<td>Post-apoplectic dementia (Dementia post apoplexiænt) (Alzheimer, 1902)\textsuperscript{5}</td>
<td>• Post-apoplectic dementia (Dementia post apoplexiænt) (Alzheimer, 1902)\textsuperscript{5}</td>
</tr>
</tbody>
</table>

### Box 1. The gliosis and sclerosis group, comprising subforms described and named by Alzheimer (condensed excerpts).

**Perivascular gliosis** (perivascularäre Gliose). Characterized by severe arteriosclerosis of brain vessels and marked glial proliferation, with disseminated focal lesions in the cortex and white matter, restricted to one or more gyri, or single brain lobes, and expressed clinically as cortical focal disease (hemianopia, aphasia, cortical deafness, hemiplegia). Mild retraction or greater coarseness of a given gyral surface, on macroscopic neuropathology, and focal lesions with degeneration and loss of ganglion cells [neurons] and of myelinated fibers, on microscopy.\textsuperscript{5,6,9}

**Perivascular sclerosis** (perivascularäre Sklerose). Previous description reiterated, with the assumption that it would be the cause of Perivascular sclerosis, due to stenosis of one larger arterial branch, with restriction of the necessary nutrition of the territory it supplied, and followed by the above-mentioned changes.\textsuperscript{5}

**Perivascular gliosis of the cerebral cortex** (perivascularäre Gliose der Hirnrinde). Characterized by arteriosclerotic focal lesions and marked glia proliferation, unevenly distributed throughout the entire cerebral cortex. Small depressions on the cortical surface, with finely or coarsely granulated texture, on gross examination. Individual foci with wedge-shaped appearance, the broader side facing the surface, and the peak reaching the 4th or 5th cortical layer, on microscopy. Older foci evolving occasionally to small softenings, with a degenerated vessel in its central part, where the ganglion cells appeared destroyed, and the astrocytes replaced by coarse glia fibers.\textsuperscript{7}

**Perivascular sclerosis of the cerebral cortex** (perivascularäre Sklerose der Hirnrinde). Seemingly a related condition to the previous subform which, depending on the affected site, can resemble clinically Senile dementia (e.g., Perivascular gliosis of the frontal lobe), or a slowly developing focal brain disease (cortical paralysis, aphasic symptoms, cortical deafness or blindness). Gross examination of the gyri proves unremarkable, where the severity of the cortical changes can be easily overlooked.\textsuperscript{7}

**Senile gliosis of the cerebral cortex** (senile Rindenverödung). Due to disease of the short vessels from the pia mater entering the cerebral cortex, causing small wedge-shaped foci in the superficial cortex, with the base oriented toward the cortical surface, besides deeper cortical foci. Destroyed ganglion cells and myelinated fibers replaced by a dense glia felt [gliosis]. Foci often situated in clusters, in the supply territory of a larger artery, the more superficial related to punctate retraction on the cortical surface.\textsuperscript{9}
The gliosis and sclerosis group.

Interpreted, and some of the findings, in contemporary terms, commented upon, pathophysiological correlates provided, condensed excerpts of Alzheimer’s subforms will be compiled.

Here, the main features of the above-described condensed excerpts of Alzheimer’s subforms will be commented upon, pathophysiological correlates provided, and some of the findings, in contemporary terms, interpreted.

The gliosis and sclerosis group. This group includes focal or diffuse vascular subforms, according to the lesion spread. In all subforms of this group, severe arteriosclerosis and glial proliferation constitute the neuropathological hallmark features, the degenerated vessels producing nervous tissue injuries. The lesions (foci) may have subcortical and cortical distribution as in the first two subforms, and subcortical distribution and/or cortical wedge-shaped lesions in the remaining ones. All display small or punctate retraction and mild or coarse granulation on the cortical surface, being circumscribed or extensive and diffuse, according to the underlying pathology. The difference among these subforms has more of a quantitative than a qualitative nature. As expected, the clinical manifestations depend on the location and extent of the neuropathological injuries. The retraction and granulated cortical surface...
changes, described in the subforms featuring superficial lesions, were interpreted by Román as consistent with “granular atrophy of the cerebral cortex”.10 The subcortical foci appear to fit better, in present day terms, with “small infarcts” or with “microinfarcts”,11 while the cortical wedge-shaped foci were more recently identified in autopsies as “cortical microinfarcts”, described as minute foci with neuronal loss, gliosis, pallor, or more cystic lesions, considered an important neuropathological correlate of cognitive impairment and a contributor to dementia development, which escapes detection by conventional magnetic resonance imaging due to their small size. They are found in all brain regions, possibly more so in the cerebral cortex.13-16

Subcortical atrophy group. This group includes mainly diffuse vascular subforms. Alzheimer8,9 considered that the Arteriosclerotic brain degeneration (described by Binswanger and Alzheimer) differed in essence only in degree compared to the Arteriosclerotic atrophy of hemispheric white matter (described by Alzheimer), and Binswanger’s Chronic progressive subcortical encephalitis. He emphasized that the main cause of the disease, in all three conditions, was the severe arteriosclerotic diseases of the long vessels of the deep white matter [penetrating arteries], with its resultant secondary degeneration. However, such extensive damage of white matter as seen in Binswanger’s subform, is only rarely reached in the other forms. Thus, Alzheimer apparently suggested that these three subforms represented a spectrum differing only in a quantitative manner in relation to the extent of the white matter lesions.8,9

Binswanger’s original description17 was quoted partially by Alzheimer (1898). Later, Alzheimer described the subform thoroughly (1902), possibly based on his own material, presenting a somewhat different macroscopic account, and adding the missing microscopic findings. Nonetheless, both emphasized the extensive deep white matter degeneration, sparing of the cortical intrinsic myelinated fibers, the gyral core white matter, and the immediately subcortical short association fibers [U fibers], in typical cases. Both stressed a loss of the associative linking between particular cortical sensory and motor areas, responsible for some of the clinical manifestations.7,9,17 It must be emphasized that Binswanger’s description was based on an atypical case.18,19 Despite the atypicality, Binswanger’s observation was insightful, with a detailed description of the course of the case, followed for almost ten years, summarized by the main symptoms (initial motor aphasia, followed by paraphasia, dysgraphia, paralexia and dyslexia, memory deficit, among others). Binswanger’s macroscopic description revealed a severe loss of white matter in the parietal and temporal lobes, especially on the left side, and severe atrophy of the frontal cortex. The progress of the disease corroborated the pattern of white matter loss, particularly the conduction pathways between language centers and those of related functions (object images, acoustic language, reading and writing, and motor language centers). According to this destruction of associative fibers, the aphasias comprise characteristics of transcortical and intercentral conduction aphasia (conduction aphasia, Wernicke’s Leitungsaphasie), besides other symptoms, as claimed by Binswanger. The further evolution of the ailment clearly indicated that the fiber loss was not restricted only to the brain regions cited. The final mental decay indicated that the entire hemispheric white matter was affected, bilaterally, with damage and destruction of numerous pathways.17 This description reveals the complex connections of the language centers, and the resultant symptoms compatible with the language-related disconnection syndromes studied today,20,21 highly frequent in vascular brain diseases.

This subform suffered numerous criticisms over time,22 but despite these the condition survived as a disease entity until the present day, maintaining the designation given by Alzheimer,9 and later ratified by several authors.11,24,25 It is noteworthy that Durand-Fardel (1854) had previously described a similar condition he named atrophie interstitielle du cerveau (interstitial atrophy of the brain).12

Considering the quantitative differences among the subcortical subforms, already acknowledged by Alzheimer,9 probably all of the group merged with Binswanger’s, to give the surviving one. Further details on the condition, as described by Binswanger, already partially presented,18 will be reviewed at a later date.

In present day terms, these subforms appear to represent the “Subcortical Ischemic Vascular Disease”, having Binswanger’s disease as the clearest expression.21,26

The apoplectic group. This group represents mainly focal disorders, at least in the beginning. Followed, in cases that evolve to dementia, by the appearance of more diffuse manifestations. Apoplexies are of longstanding familiarity, dating back to the pioneer studies of Johann Jakob Wepfer (1620-1695) in Historiae apoplecticorum (1658), and of Thomas Willis (1621-1675), who described Post-apoplexy dementia in De Anima Brutorum (1672). Later, several works appeared, most notably Durand-Fardel’s Traité du Ramolissement du Céophage (1843).12,27

Engelhardt E, Grinberg LT Alzheimer: vascular brain diseases subforms 309
Binswanger, in 1894, had already made a brief comment on the clinical features of Post-apoplectic dementia. Alzheimer’s contribution was in the form of microscopic description of these lesions, borrowing the clinical account from Beyer (1896). He attributed the cause to hemispheric arteriosclerotic foci, and not only to apoplexy alone. Additionally, he stated that this assumption was corroborated by dementia symptoms prior to the apoplectic episode. This early observation on the issue was, much later, verified many times.

Summing up, the above-presented subforms of athromatous vascular degeneration of the brain arteries studied by Alzheimer, as a suggestion, are divided into 3 groups, appear to be related to neuropathological as well as clinical, cognitive and behavioral manifestations, which provided the basis, together with part of the main vascular forms presented in earlier papers, for the contemporary condition designated “Vascular Cognitive Impairment”, with its varied underlying neuropathological correlates and clinical nuances.

Acknowledgement. The authors are grateful to Mrs. Melanie Scholz, librarian, Institute for History of Medicine, Charite, Berlin, Germany, for kindly supplying the digitalized versions of Alzheimer’s publications on vascular diseases of the brain.

Author contributions. Eliasz Engelhardt drafted the manuscript, and both authors critically revised the manuscript.

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