

A Historical Review of the Concept of Vascular Dementia: Lessons from the Past for the Future

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Summary: The history of senile dementia begins in the Greco-Roman period with basic concepts of senility by Pythagoras and Hippocrates. During the Middle Ages, the main contribution was by Roger Bacon in 1290. The first textbook of neurology, *De cerebri morbis*, by Jaso de Pratis (1549), included a chapter on dementia ("De memoriae detrimento"). In the 17th century, Thomas Willis recognized intellectual loss with aging. In the 19th century, Philippe Pinel removed chains from the mentally ill; his student Esquirol wrote the first modern classification of mental disease, including senile dementia. In 1860, Morel recognized brain atrophy with aging. The modern history of vascular dementia began in 1896, when Emil Kraepelin in his textbook *Psychiatrie* included "arteriosclerotic dementia" among the senile dementias, following the ideas of Otto Binswanger and Alois Alzheimer, who had differentiated clinically and pathologically arteriosclerotic brain lesions from senile dementia and from neurosyphilitic general paresis of the insane. Binswanger's and Alzheimer's contributions are reviewed in detail. **Key Words:** History of medicine—History of neurology—Thomas Willis—Alois Alzheimer—Otto Binswanger—Emil Kraepelin—Senile dementia—Vascular dementia.

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—E.G. Clark (1955)

Recently, Berchtold and Cotman (1998) reviewed the rich history of dementia during the Greco-Roman Period (7th century B.C.). Important figures during that period included Pythagoras who defined the *senium* as the period of life after age 63 when the body declines and there is regression of mental capacities. Hippocrates' concept of four cardinal body fluids or *humours* persisted well into the middle ages. With age the brain would become "dry and cold" predisposing the elder to melancholy (*melas*, black; *chole*, bile) and to mental decline. Plato, Aristotle, Cicero, and Galen considered mental decline an inevitable part of old age.

During the Middle Ages, lack of anatomical knowledge limited the development of accurate concepts. For instance, in 1290, Roger Bacon mentioned a brain with three ventricles, memory being stored in the posterior one, thought and judgment in the middle one, and imagination in the anterior ventricle. However, he wrote accurately that "old age is the home of forgetfulness." According to van Gijn (1998), the first textbook of neurology, *De cerebri morbis*, written by Iason Pratensis (Jaso de Pratis) and published in 1549 in Basle, included a chapter on dementia, "De memoriae detrimento," which followed immediately the chapter on stroke, "De apoplexia." Jaso de Pratis studied medicine in Louvain and the Low Countries, and practiced general medicine, like his father before him, in the town of Zierikzee, in the Rhine delta.

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the first time in the 1681 translation of Willis's book. In this book, Willis "set forth, among other things, a method for the removal and dissection of the brain; a new numbering and grouping according to function of the cranial nerves, which greatly improved on the old Galenic system; extensive descriptions of the basal ganglia, brain stem, and cerebellum; and detailed schemes of the vagal and sympathetic nerves supplying the viscera" (Feindel, 1983). Willis also wrote one of the earliest textbooks on nervous diseases, *Pathologia Cerebri* (1667), which contains a striking description of general paresis. Finally, Willis' *London Practice of Physick* (1685) recognized that some people "become by degrees dull . . . by the mere declining of age." Toward the end of the century, in 1776, William Cullen first classified senile dementia as a medical entity, *Amentia senilis*.

In the 19th century, Philippe Pinel succeeded in his view that madness was not a crime but a disease, removing the chains from the mentally ill. His student Esquirol, who wrote the first modern classification of mental disease, stated: "senile dementia results from the progress of age . . . commences with feebleness of memory, particularly recent memory; and attention . . . becomes impossible." Morel, in 1860 wrote that "loss in brain weight—a constant feature in dementia—is also present in ageing" (quoted in Berchtold and Cotman, 1998).

FIRST CONCEPTS OF VASCULAR DEMENTIA

The modern history of vascular dementia began in 1910, when Emil Kraepelin, in his landmark textbook *Psychiatrie*, separated from the group of senile and pre-senile dementias (*Das senile und präsenile Irresein*), a form he called "arteriosclerotic insanity" or "arteriosclerotic psychosis" (*Das arteriosklerotische Irresein*). This concept was based on the clinicopathological correlations undertaken by Otto Binswanger (1893, 1894, 1908) and Alois Alzheimer (1894, 1895, 1898, 1899, 1902) with the main purpose of separating from syphilitic dementia paralytica—then, a leading cause of dementia and mental illness—other forms of dementia (Mast et al., 1995).

The historical evolution of the early concepts of vascular dementia can be found in a review titled "New Studies on Senile Dementia and Brain Diseases Caused by Atheromatous Vascular Diseases" [Neuere Arbeiten Über die Dementia senilis und die auf atheromatöser Gefässerkrankung basierendenn Gehirnkrankheiten] written by Alzheimer in 1898 in the *Monatsschrift für Psychiatrie und Neurologie*. He begins his review as follows:

Senile dementia has not been the object of clinical and histological studies in recent years to the same

degree as paralytic dementia. Nevertheless one can report on a number of studies which, on the one hand have opened up some new and interesting aspects for us, and on the other have substantially deepened our knowledge of their symptomatology and anatomic pathology. These studies, in fact, have not dealt with senile dementia in the narrow sense, but with mental disorders of senility, which often are associated with atherosclerosis of the vascular system. . . .

Alzheimer then acknowledged the role of Kraepelin, who recognized that some forms of depression in the elderly may be a manifestation of senile dementia. Alzheimer wrote:

Kraepelin in the new edition of his manual [1896] has presented melancholia as a disease etiologically linked with the beginning regression; apart from this, amongst the depressive states he recognizes the depressive states of periodic depressive insanity, and constitutional depression. [. . .] Ziehen [1895] has written about periodic melancholia in menopause. It certainly cannot be doubted that constitutional periodic insanity also could first appear in the involutional period. Still, melancholia of the involutional period (in Kraepelin's sense) also sometimes tends to assume a periodic character, even if not with such regular intervals. Finally, one observes cases of melancholia which after a long interval of mental health recur in a second attack, in which the mental defect soon comes to the foreground and progressive senile dementia follows. One cannot draw a sharp boundary between melancholias of the involutional period which end with recovery and those which end up in senile dementia.

Alzheimer also analyzed some forms of senile dementia that present with psychomotor agitation, as follows: "Kraepelin's delirious diseases of old age may be unique expressions of senile brain degeneration. On the basis of histologic examinations I must endorse this view of Kraepelin. [. . .] Noetzli and Kraepelin are in accord that often febrile diseases such as influenza, bronchial inflammation, etc. give rise to the appearance of the first manifestations of senile dementia."

Regarding the cause of senile dementia, Alzheimer noted that he no longer accepted the popular notion that vascular lesions were essential:

With regard to the fundamental anatomic origin of senile dementia, there is certainly unanimity as to the fact that atheromatous degeneration of the brain vessels is of essential importance for the development of senile brain atrophy. Some authors appear to believe

that a second element of some nature must be added in order to explain the process. Noetzli believes that senile dementia parallels arteriosclerotic kidney. With this he certainly is saying that arteriosclerosis of the brain vessels is the direct cause of senile dementia. I myself earlier regarded this concept as correct. But then, I examined a case which had to be called presenile dementia in which I found severe atrophic processes on the ganglion cells, but also rather insignificant atheromatous vascular changes. This case appears to me to speak against Noetzli's concept.

Alzheimer was not referring to his now-famous first patient Auguste D., who only until November 25, 1901 was to be admitted to the Hospital for the Mentally Ill and Epileptics in Frankfurt am Main, where Alzheimer was working as a resident at the time when he wrote this review. Auguste D. died on April 8, 1906, 3 years after Alzheimer had moved to Munich (Maurer et al., 1997). Also to his credit, in 1907, when he first described the typical neuropathological changes of Alzheimer disease in the brain of this 51-year-old woman with severe cortical atrophy and minimal arteriosclerosis of the cerebral vessels, Alzheimer (1907) recognized that "we are dealing with a peculiar, little-known disease process" not vascular in origin. Kraepelin (1910) first included "Alzheimer's disease" as a form of presenile dementia in the 8th edition of his book.

Alzheimer's (1898) review described some of the morphological features considered typical of senile dementia, such as loss of brain weight and "widespread degeneration of ganglionic cells of the cortex." He then reviewed the advances made in the understanding of the several forms of vascular dementia described earlier and independently by Binswanger and by himself. Alzheimer wrote:

Apart from typical senile dementia, particularly in recent years, we have come to learn various clinically and histologically characteristic disease pictures more precisely, in which the atheromatous vascular degeneration represents the most important of the disease processes and for that reason has also been the most frequently observed in old persons. Almost all appear by the end of the forties or in the fifties. Depending on their appearance in early or late age, they cause differential diagnostic difficulties vis-à-vis [syphilitic] paralysis or senile dementia.

FIRST CLINICAL FORMS OF VASCULAR DEMENTIA

According to Alzheimer (1898, 1902), he and Binswanger were the first to describe several forms of vascular dementia.

Arteriosclerotic Brain Degeneration

In 1902, Alzheimer reviewed the topic "Mental Disorders of Arteriosclerotic Basis" before the Jahresversammlung des Vereins des Deutschen Irrenärzte [the Annual Meeting of the Society of German Psychiatrists]. He wrote: "In Germany, at the conference of German Psychiatrists in Dresden in 1894, Binswanger and this reviewer [Alzheimer] first described arteriosclerotic brain degeneration [atrophy] and emphasized the need to differentiate it from [syphilitic] paralysis."

In his 1898 review, Alzheimer wrote the following regarding the clinical picture:

First to be mentioned here is arteriosclerotic brain degeneration, which Binswanger and this reviewer described, simultaneously and similarly in its essential points. Arteriosclerotic brain degeneration almost exclusively appears at the beginning of the fifties. Differential diagnosis from [syphilitic] paralysis often offers difficulties in the clinical aspect. This disease form in shorter or longer episodes (lasting months to years) finally leads to severe dementia. The type of dementia, however, usually is strikingly different from paralytic dementia. More substantial remnants of the original personality remain intact much longer, so that the patients even at a late point often show a relatively large degree of insight and judgment and a conspicuously orderly behavior, which appears to be severely disturbed only during the often sudden appearance of exacerbations. The mood is mostly murky and despairing. Often, disease consciousness is retained into the late stages of the disease. Certainly quite justifiably Binswanger conjectured that this striking difference from paralysis is caused by the differing anatomic basis. [Syphilitic] Paralysis is a diffuse process while in the focally appearing arteriosclerotic dementia extensive brain regions can perform their functions for still a long time.

The pathological lesions of arteriosclerotic brain degeneration were described as follows:

Autopsy shows . . . widespread atheromatosis of the vascular system, atheromatous changes in the kidneys and the liver, and a high-degree arteriosclerosis of the blood vessels. The brain exhibits a substantial loss of weight. Breaches in vessel continuity are generally very broad. In the immediate vicinity of the vessels even macroscopically one can see the brain substance colored light gray to reddish brown and slightly sunken in many places on the cortex and medulla, especially in the area of the stem [basal] ganglia and the inner capsule. The cortex is indistinctly pale gray, slightly narrowed, the stratification is unclear. The medulla is

dirty white to grayish white. The ventricles are regularly dilated. The microscopic examination enables an easy differentiation from [syphilitic] paralysis and shows that we are not dealing with a diffuse, but rather a focal disease. The pigmentary cell degenerations and vascular changes intrinsic to senility are often to be found dispersed everywhere, even if not to a high degree. High-degree atheromatously degenerated vessels, which are often tangled and present wide continuity breaches in which granular cells, lymphoid elements, plaque and crystalline pigment are accumulated, are to be found at the midpoint of the focal changes in the medulla as in the cortex. In the vicinity there are substantial densifications of the glia and astrocyte accumulations . . . sclerosis and calcification of the vessels can be demonstrated. The myelinated fibers are reduced both in the cortex (tangential fiber layer) and in the medullary rays, as well as in the deep medulla in the area of the disease foci.

Lesions included in arteriosclerotic brain atrophy most likely included multiple lacunar strokes ("disease foci" in basal ganglia, internal capsule, and white matter of the centrum ovale), as well as *état criblé*, associated with severe arteriosclerosis of small and large blood vessels.

Chronic Progressive Subcortical Encephalitis

Alzheimer (1898) also recognized that Binswanger had described in 1894 the disease that now bears his name (Blass et al., 1991; Förstl et al., 1991). In his 1902 lecture Alzheimer said: "Binswanger, in addition to arteriosclerotic brain atrophy, also described a chronic diffuse subcortical encephalitis, of which he says that in it a strong arteriosclerosis of the brain arteries is also evident, so that the suggestion arises to attribute the subcortical fiber loss to nutrition disorders caused by the arteriosclerosis. . . . Later, this reviewer [Alzheimer] described two other types of disease, a perivascular gliosis and a senile cortical atrophy, as caused by arteriosclerosis."

Perivascular Gliosis of the Brain Cortex or Senile Cortical Atrophy

Alzheimer's (1898) description is consistent with granular atrophy and laminar necrosis, as follows: "The histologic examination shows very extraordinarily characteristic picture. The individual foci exhibit a wedge-like form, with the broad side sitting on the surface of the cortex, the apex of the wedge lies in the fourth or fifth cortical layer. The site of an older focus gives away its position on the surface of the gyrus by a small indentation. In the middle of the focus one can always find a degenerated vessel."

Dementia Postapoplexiam

Alzheimer (1898) considered it as the result of pre-existing "arteriosclerotic hemispheric foci," rather than caused by large strokes (Mast et al., 1995).

CONCLUSION

Alzheimer and Binswanger had correctly concluded that "arteriosclerotic dementia" represented a large clinicopathological spectrum, and this concept was appropriately conveyed by Kraepelin in his textbook. The lesions illustrated in Kraepelin's (1910) chapter on "Das arteriosklerotische Irresein" included arteriosclerotic brain degeneration, characterized by multiple lacunar strokes and *état criblé* associated with severe arteriosclerosis of small vessels; and senile cortical atrophy (perivascular gliosis), with granular atrophy and laminar necrosis. Also, Kraepelin's book provided probably the first illustration of Binswanger disease.

However, "arteriosclerotic dementia" incorrectly became synonymous with senile dementia, and it was widely held that cortical atrophy in the elderly resulted from progressive decrease in cerebral perfusion leading to hypoxic neuronal death. This idea prevailed until the mid-1970s, when it became clear that Alzheimer disease was the main cause of cerebral atrophy and senile dementia.

However, the pendulum is swinging back and the importance of vascular lesions in Alzheimer disease is being increasingly recognized. Moreover, not only is Binswanger disease rapidly becoming one of the most commonly recognized forms of vascular dementia, but also Binswanger-type periventricular white matter lesions are found in more than half of the patients with Alzheimer disease. At the closing of the 20th century, it is a fitting tribute to recognize the contributions of Alzheimer and Binswanger, two leading figures of senile dementia research in the 19th century.

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