

TOPICAL REVIEW

The tangled story of Alois Alzheimer

Zilka N, Novak M

*Institute of Neuroimmunology, AD Centre of Excellence, Slovak Academy of Sciences, Bratislava, Slovakia.
michal.novak@savba.sk*

Abstract

In 1907, Bavarian psychiatrist Alois Alzheimer, who is considered to be a founding father of neuropathology, was first to describe the main neuropathologic characteristics of the peculiar disease in the brain of a woman showing progressive dementia when she was in her early 50s. Using a newly developed Bielschowsky's silver staining method, Alzheimer observed degenerating neurons with bundles of fibrils (neurofibrillary tangles) and miliary foci of silver-staining deposits scattered over the cortex (senile plaques). In 1910 Emil Kraepelin (Alois Alzheimer's superior) coined the term "Alzheimer's disease" to distinguish the presenile form of dementia from the more common senile variant. Alzheimer's findings were followed up, and soon a number of reports of similar cases appeared in the literature. During the time, both pathological hallmarks of Alzheimer's disease became the gold standard for post-mortem diagnosis of the disease. One hundred years later, dementia of Alzheimer's type is considered to be one of the most devastating illnesses of old age. Despite intensive research the cause of the disease still remains elusive (Fig. 2, Ref. 17).

Key words: Alzheimer's disease, Alois Alzheimer, Augusta D, neurofibrillary tangles, senile plaques.

Alois Alzheimer was born in June 14, 1864 in Markbreit am Main in Southern Germany. He commenced the study of medicine in Berlin, where he attended the anatomy class of famous pathologist Wilhelm von Waldeyer (1836–1921), who coined the term neuron. Then he continued his education at medical schools in Tübingen and Würzburg, where he graduated in 1887 (Kircher and Wormstall, 1996). In the same year he defended his doctoral thesis, on the wax-producing ceruminous glands. The work was based on experimental research performed in the laboratory of the famous Swiss physiologist and histologist Rudolf Albert von Köelliker (1817–1905), who published the first report on Camillio Golgi's silver staining technique (Thomas and Isaac, 1987, Burns et al, 2002). In December 1888 Alzheimer was appointed as a clinical assistant at the Municipal Mental Asylum in Frankfurt am Main, where Emil Sioli was director (Bick, 1994). Here he commenced his education in psychiatry and neuropathology and later he was promoted to senior physician. It was in Frankfurt where Alzheimer began his long and productive collaboration with neurologist Franz Nissl (1860–1919), who came to the Asylum in 1889 (Bick, 1994). They became close friends working with patients during daytime and discussing scientific topics over the microscope at evenings and nights (Graeber, 2005). They collaborated on researching the

pathology of the nervous system, studying in particular the normal and pathological anatomy of the cerebral cortex. Together they published the six-volume work *Histologic and Histopathologic Studies of the Cerebral Cortex* (Histologische und histopathologische Arbeiten über die Grosshirnrinde).

In 1902 Emil Kraepelin, leading German psychiatrist of the time, invited Alzheimer to his Psychiatric department of Heidelberg University and promised him the post of a scientific assistant. Thus he could work again with Nissl, who had moved to the same place in 1895. In 1903, Alzheimer accompanied Kraepelin to the Ludwig-Maximilians University in Munich, where Kraepelin became the head of the Psychiatry Department (O'Brien, 1996, Burns et al, 2002). Emil Kraepelin was an early interdisciplinarian who interconnected brain research with psy-

Institute of Neuroimmunology, AD Centre of Excellence, Slovak Academy of Sciences, 845 10 Bratislava, Slovakia

Address of correspondence: M. Novak, Institute of Neuroimmunology, Slovak Academy of Sciences, Dubravská 9, SK-845 10 Bratislava, Slovakia.

Acknowledgement. The authors wish to thank Professor Manuel Graeber, University Department of Neuropathology, Imperial College London and Hammersmith Hospitals Trust, for reading the manuscript.

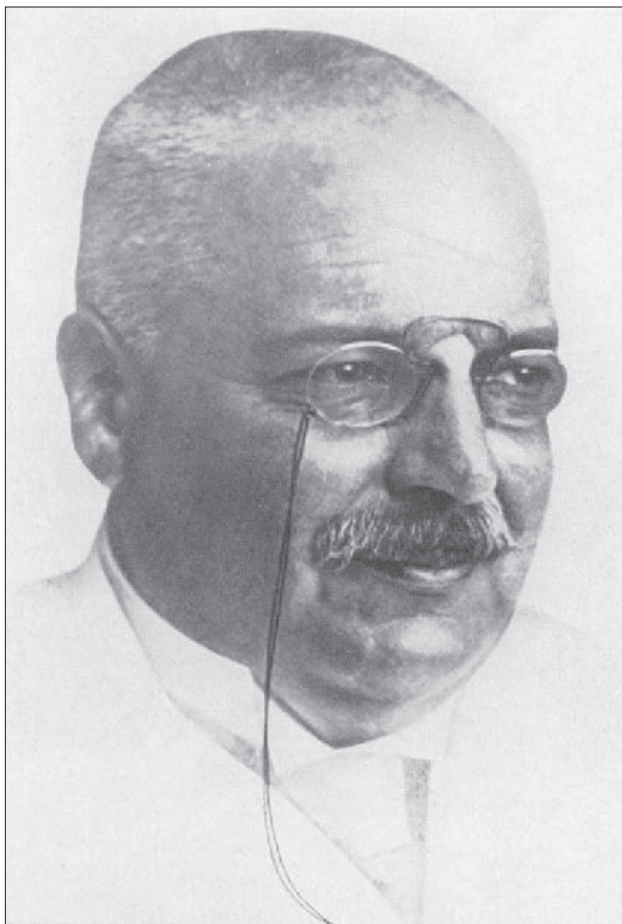


Fig. 1. The original portrait of Alois Alzheimer (in Graeber, 2005). Figure by courtesy of the Prof. Manuel Graeber.

chiatry. He was convinced that neuropathological research was fundamental for psychiatry and therefore he initiated the setting up of a special anatomical laboratory. Alois Alzheimer established this “Anatomical Laboratory” on the third floor of the Royal Psychiatric Clinic, headed by him until 1912 (Graeber, 1999, Graeber and Mehraein, 1999). Alzheimer’s research laboratory gained international reputation and became very soon the Mecca for students from all over the world and a meeting place for several important researchers such as Ugo Cerletti, Francesco Bonfiglio and Gaetano Perusini from Italy, Hans Gerhardt Creutzfeldt, Alfons Maria Jakob and Fritz Lewy from Germany, F. Lotmar from Switzerland and others (Bick, 1994). Alzheimer was the careful and dedicated laboratory worker with a wonderful gift for describing microscopical findings. Robert Gaupp, the head of the psychiatry department in Tübingen University wrote about him: “Alzheimer was a man with a clear head and unusual creative powers who took greatest pains over his work and had a strong sense for scientific truth.” (Graeber, 2005).

At the 37th Meeting of Southwest German Psychiatrists held in Tübingen in November 1906, Alzheimer presented the clinical and neuropathological findings on a woman aged 51 years

suffering from an ‘unusual disease of the cerebral cortex’ (Eine eigenartige Erkrankung der Hirnrinde) which caused memory loss, disorientation followed by depression and hallucinations. Pathological examination revealed atrophy and specific lesions which he described as a “paucity of cells in the cerebral cortex and clumps of filaments between the nerve cells”. Alzheimer’s report on his patient Augusta D. was published in the following year. It was not a full size paper but rather a short abstract summarizing his presentation at the meeting (Alzheimer, 1907, Alzheimer et al, 1995). The paper did not contain any illustrations, first drawings of plaques and tangles were published by Alzheimer later in his comprehensive article on the histopathology of Alzheimer’s disease (Alzheimer, 1911), where he provided a review of the histopathological spectrum of Alzheimer’s disease ranging from “plaque only” to “tangles and plaques” forms (Graeber et al, 1997, 1998).

Alzheimer’s findings were followed up, and soon a number of reports of similar cases had appeared in the literature. Solomon Fuller summarized clinical and pathological reports from 12 other cases that had been published within 5 years (Bick, 1994). In 1910 Emil Kraepelin in his influential Textbook of Psychiatry (Psychiatrie: Ein Lehrbuch für Studierende und Aerzte) proposed naming the disease condition after Alzheimer (Holstein, 1997, Berchtold and Cotman, 1998). In the Textbook he stated: “The clinical interpretation of this Alzheimer’s disease is still unclear”. Although the anatomical findings suggest that we are dealing with a particularly serious form of senile dementia. The fact is that this disease sometimes starts as early as in the late forties”

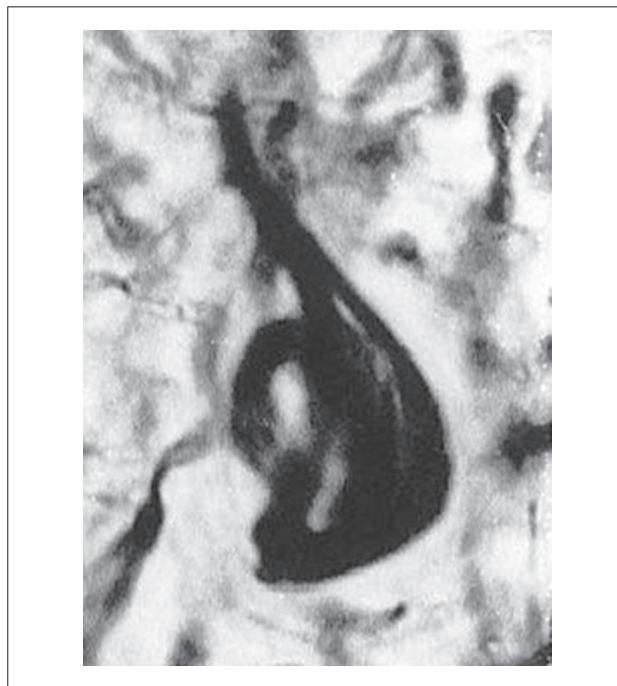


Fig. 2. A neurofibrillary tangle, first described by Alois Alzheimer in Augusta D’s brain (in Graeber, 2005). Figure by courtesy of the Prof. Manuel Graeber.

(Burns et al, 2002). The age of his first patient became significant in the development of this new brain disease. Relatively rare Alzheimer's disease was separated from senile dementia and accepted as a diagnostic category. This classification remained intact until the last third of 20th century (Holstein, 1997). Some authors claim that Kraepelin's decision to separate a presenile form of dementia from senile one and to put the name of Alzheimer's disease for the former one was most probably inspired by political reasons rather than by exact scientific data (Boller and Forbes, 1998). The novel neuropathological features that Alzheimer described consisted of both tangles and plaques. However the widespread presence of plaque pathology in the brain of his patient was very similar to those seen in patients with senile dementia. It was Oscar Fischer from the Prague group led by Arnold Pick, who extensively described plaques in cases of senile dementia and suggested that this neuropathological hallmark could be considered as a marker for senile dementia. It has been speculated that final decision of Kraepelin to describe novel disease category was largely due to an academic rivalry between the neuropathological schools located in Munich and in Prague (Graeber et al, 1997, Berchtold and Cotman, 1998, Boller and Forbes, 1998). Others claimed that the Kraepelin's idea came from the controversy over functional versus organic bases of mental diseases (Bick, 1994, Moller and Graeber, 1998). Nowadays, the majority of authorities no longer limit the term Alzheimer's disease to presenile cases.

Alzheimer made fundamental contributions to understanding other diseases such as vascular dementia, Huntington's chorea, syphilis, brain tumors and epilepsy. Alzheimer spent in Munich almost 10 fruitful years. He became an internationally respected authority and made significant contributions to the field of neurohistopathology. On July 16, 1912, King Wilhelm II of Prussia signed the certificate of Alzheimer's appointment as full professor of psychiatry and director at the Psychiatric and Neurologic Institute of the Silesian Friedrich-Wilhelm University in Breslau. Alzheimer accepted the invitation and left Munich. Already on the way to Breslau Alzheimer caught a severe cold complicated by endocarditis and had to be hospitalised immediately upon arrival. Alzheimer continued his research there for the next three years, dying of rheumatic endocarditis in a uraemic coma in December 19, 1915 at the age of 51 (Burns et al, 2002). Alzheimer's many years of research and work serve as the foundation for today's extensive search for a cure of the disease that bears his name.

References

- Alzheimer A.** Über eine eigenartige Erkrankung der Hirnrinde. *Allg Z Psychiat* 1907; 64: 146—148.
- Alzheimer A, Stelzmann RA, Schnitzlein HN, Murtagh FR.** An English translation of Alzheimer's 1907 paper, „Über eine eigenartige Erkrankung der Hirnrinde“. *Clin Anat* 1995; 8 (6): 429—431.
- Alzheimer A.** Über eigenartige Krankheitsfälle des späteren Alters. *Z Gesamte Neurol Psychiat* 1911; 4: 356—385.
- Berchtold NC, Cotman CW.** Evolution in the conceptualization of dementia and Alzheimer's disease: Greco-Roman period to the 1960s. *Neurobiol Aging* 1998; 19 (3): 173—189.
- Bick KL.** The early story of Alzheimer disease. From: Terr RD, Katzman R, Bick KL (Eds). *Alzheimer disease*. Raven Press, New York 1994: 1—7.
- Boller F, Forbes MM.** History of dementia and dementia in history: an overview. *J Neurol Sci* 1998; 158 (2): 125—133.
- Burns A, Bzrne J, Maurer K.** Alzheimer's disease. *Lancet* 2002; 360: 163—165.
- Graeber MB, Kosel S, Egensperger R, Banati RB, Muller U, Bise K, Hoff P, Moller HJ, Fujisawa K, Mehraein P.** Rediscovery of the case described by Alois Alzheimer in 1911: historical, histological and molecular genetic analysis. *Neurogenetics* 1997; 1 (1): 73—80.
- Graeber MB, Kösel S, Grasbon-Frodl, E, Möller HJ, Mehraein P.** Histopathology and APOE genotype of the first Alzheimer disease patient, Auguste D. *Neurogenetics* 1998; 1: 223—228.
- Graeber MB, Mehraein P.** Reanalysis of the first case of Alzheimer's disease. *Europ Arch Psychiat Clin Neurosci* 1999; 249: 10—3.
- Graeber MB.** No man alone: the rediscovery of Alois Alzheimer's original cases. *Brain Pathol* 1999; 9 (2): 237—240.
- Graeber MB.** Alois Alzheimer. 2005, IBRO web page /http://www.ibro.info/Pub_Main_Display.asp?Main_Id=34.
- Holstein M.** Alzheimer's disease and senile dementia, 1885—1920: An interpretive history of disease negotiation. *J Aging Studies* 1997; 11: 1—13.
- Kircher, T, Wormstall, H.** Origin of Alois Alzheimer's interest in neurohistology. *Amer J Psychiat* 1996; 10: 1369—1370.
- Moller HJ, Graeber MB.** The case described by Alois Alzheimer in 1911. Historical and conceptual perspectives based on the clinical record and neurohistological sections. *Europ Arch Psychiat Clin Neurosci* 1998; 248 (3): 111—122.
- O'Brien Ch.** Auguste D. and Alzheimer's disease. *Science* 1996; 273: 28.
- Thomas M, Isaac M.** Alois Alzheimer: a memoir. *TINS* 1987; 8: 306—307.

Received June 29, 2006.
Accepted September 2, 2006.