The forgotten history of Alzheimer's: remembering Oskar Fischer

La historia olvidada del alzhéimer: recordando a Oskar Fischer

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ABSTRACT

Introduction: *Alzheimer's disease (AD) is a progressive neurodegenerative pathology that affects memory and other cognitive functions. Until now, there are no curative or disease-modifying treatments, so management is focused on prevention and treatment of factors that may contribute to its evolution; pharmacological tools are scarce and have modest effects in slowing the disease. It is proposed to make a brief biography of Oskar Fischer, describe the conflict with Alois Alzheimer that is identified in scientific documents and mention the main elements of Oskar Fischer's theory.* ***Method:*** *A narrative review was carried out in the Scielo, PubMed and Lilacs databases, with the terms "Oskar Fischer" and fifteen articles published between 1906 and 2023 were found, which were summarized by the authors GS and NR. The article was subsequently reviewed by the other authors.* ***Results:*** *They were organized in sections, starting with a brief biography of the author, his interaction with Alois Alzheimer and a summary of his theory; what was described by Oskar Fischer in terms of the structures of plaques and tangles is considered one of the main pathophysiological theories of AD.* ***Conclusions:*** *Oskar Fisher made an invaluable contribution and raised classic concepts regarding AD, which, although they did not earn him recognition in posterity, have allowed subsequent research to be of great importance to rethink these concepts and include other possibilities and hypotheses, to continue deepening the knowledge of the disease.*

Keywords: *Alzheimer's disease, Oskar Fisher, Alois Alzheimer.*

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INTRODUCTION

Alzheimer's Disease is a progressive neurodegenerative pathology that affects memory and other cognitive functions. At present there are no curative or modifying treatments for the disease. So, management is mainly focused on prevention and treating factors that can contribute to the evolution of the disease, since pharmacological tools are scarce and have modest effects in slowing down the disease [1].

The current worldwide prevalence of dementia is estimated to 50 million in people older than 65 years old and it is estimated that these numbers will triple, reaching 150 million for the year 2050 [2], this mainly as a consequence of the progressive increase in aging due to the greater life expectancy of the worldwide population, as well as the increase of other risk factors such as metabolic, environmental, and personal [3].

There are different theories that seek to explain the pathology of AD, including the immune theory[4], the microglial theory [5], and the hormonal theory[6]. However, the most accepted theory is the amyloidal theory [7], which is based on the neuronal damage generated due to the accumulation of beta amyloid and Tau protein, initially in the entorhinal cortex and then in the rest of the brain [7].

Most of the investigations carried out around these theories have been done in the last 50 years, however the description of the senile plaques dates to more than 100 years. It is interesting to discuss the origins of this theory and look back on the different contributions of different scientists, some even made valuable contributions that went unnoticed in the history of Alzheimer's disease, such as the contributions made by Fischer; in this narrative review, an attempt to discuss and rescue these contributions will be made.

In this context, the following objectives have been set:
Write a short biography of Oskar Fischer.
Describe the conflict with Alois Alzheimer that is identified in scientific documents.
Mention the main elements of Oskar Fischer's theory.

Historical Context

Dementia has been recognized as a neurological disease related to age since the end of the XVIII century (e.g., Amentia Senilis described by William Cullen). In 1838, the French doctor, Jean Esquirol described with great precision the natural progression of Alzheimer's disease, starting with the deterioration of recent memory, followed by the loss of concentration, judgment and willpower, and reaching a stage of extreme aging. This later distinguishes it from other cases that present a different course, such as paralytic dementia (neurosyphilis) or early Kraepelin dementia (schizophrenia). Toward the end of the XIX century, with the advent of new staining methods and the routine use of microscopes, the described symptoms were associated with specific microscopic lesions. It was at this point that the concept of senile dementia started to diversify itself into the spectrum of conditions that today constitutes the different subtypes of degenerative dementia [8].

Alois Alzheimer is traditionally credited with the first description of the disease in 1907, after the historic case was associated with the patient August Deter, who showed cognitive deterioration, memory loss and behavioural disorders. However, it is known that other authors have made interesting discoveries in this pathology but have fallen into oblivion. Among them, the Czech psychiatrist and neuropathologist, Oskar Fischer stands out, he described the pathologic changes in patients with dementia even before Alois Alzheimer.

METHODOLOGY

A narrative revision was made in the Scielo, Pubmed, and Lilacs databases with the terms "Oskar Fischer" and fifteen articles were found that had been published between 1906 and 2023, which were summarised by the authors GS and NR. The article was then revised by the rest of the authors.

RESULTS

The results were organized in sections, starting with a brief biography of the author, his interaction with Alois Alzheimer and a summary of his theory.

A brief biography of Oskar Fischer

Oskar Fischer was a psychiatrist and neuropathologist of Czech nationality. He was born in Slaný on 12 April 1876, where he culminated his primary and secondary studies, subsequently he studied at the University of Prague and Strasbourg

where he graduated in medicine in 1900. He completed studies about dementia and was part of Dr. Arnold Pick's team, whom was a pioneer in the typification of frontotemporal dementias (10). He died on 28 February 1942 [11].

In 1907 Fischer described the presence of "miliary sclerosis" (currently senile plaques) as the principal marker of senile dementia [11]. Additionally, during his investigations, he pointed out that their origin was infectious, although he did not clarify the causal agent [12]. In spite of this, his contributions were unknown for many years and were recognized through studies carried out and documented that have been registered in the history of medicine of the city of Prague.

Relation with Alois Alzheimer

During this time, two schools that competed in the study of dementia can be distinguished. The one in Munich (represented by Emil Kraepelin and his disciple Alois Alzheimer) and the one in Prague, where Arnold Pick and Oskar Fischer stood out. While Alzheimer and Fischer had scarce contact between them, in the same year that Alois made his publications, Oskar Fischer published his observations of 16 patients, in which he described the presence of plaques of dark colour in some areas of the brain and affirmed that these were the cause of the behaviours in some patients diagnosed with senile dementia [14].

Although these plaques and other neuronal changes in patients with dementia had been previously described [15,16], the descriptions made by Fischer [14] and those made by Alzheimer [17] were more complete and were related to a larger number of dementia cases, and even included illustrations **(figure 1)**.

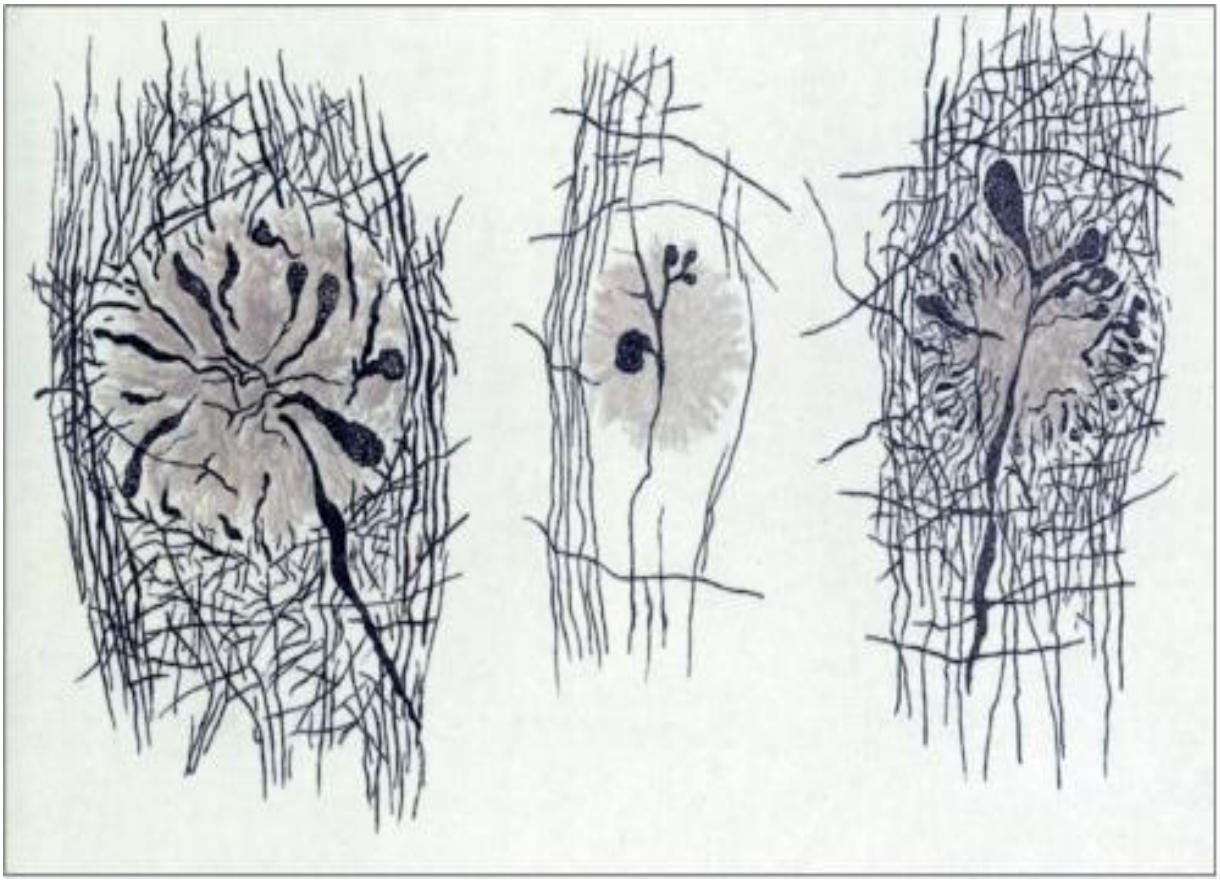

Figure 1. "Neural plaque" adapted from Goedert (11)

It is believed that the lesser recognition of Oskar Fischer is due to on the one hand the discrepancy of his theories in regard to those proposed by Alzheimer, and on the other the political power of the latter's school [11,18].

Alzheimer did not disagree with Fischer, with respect to the presence of plaques or neurofibrillary tangles but to the relation of the origin of these, given that Alzheimer doubted that their presence had an infectious cause. Likewise, Alzheimer also did not consider the case he described of August D., of "presenile" dementia and the case described by Fischer had to do with the same pathology. Based on these data, it is suggested that Alois Alzheimer's boss (Emil Kraepelin), would have been ahead of Fischer by naming the disease, Alzheimer's Disease in his psychiatry manual [19].

Principal elements of Oskar Fischer's theory

In his first publication, Fischer described that the cerebral plaques found were a product of an infection caused by an actinobacteria similar to tuberculosis, which was later named Streptothrix[14]. In other subsequently published articles, he also described the neurofibrillary tangles and compiled various drawings that detailed their characteristics **(figure 2)**. In figure 2 an example of how Fischer studied the cerebral cortex in senile dementia is illustrated; He used various staining techniques that included Bielschowsky's silver, in his observations he offered the first description of what is currently known as neuritic plaque.

Fischer did not believe in the glial origin of the plaques, rather he referred to them as inclusions of unknown origin and variable sizes, that had a diameter of 10 µm to 12 µm; He observed that the smallest plaques had a compact aspect and were encrusted in the normal neuropil and as the plaques grew in size, they generally consisted of a nucleus surrounded by a crown that was accompanied by a great number of abnormal neurites. The general aspect of the mature plaques reminded Fischer of the histological aspect of actinomycosis *("actinomyces Druse")* and he though those neural changes were similar to certain structures of the developing nervous system [11].

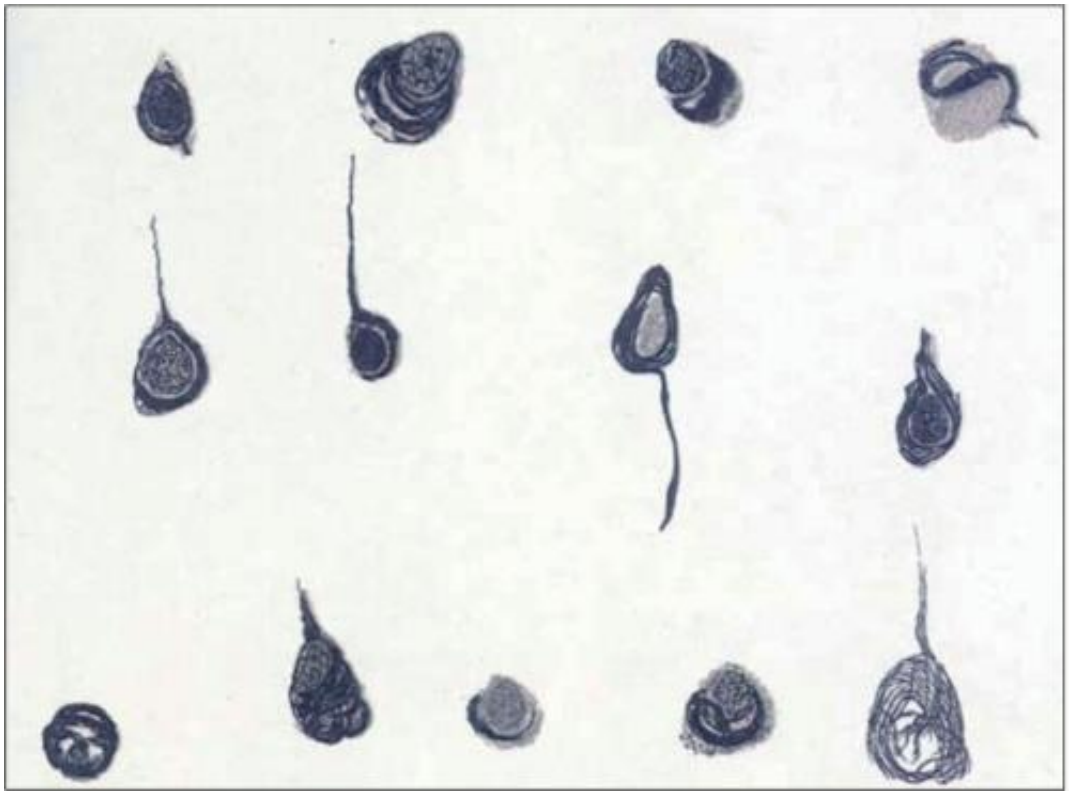

Figure 2. "Neurofibrillary tangles" adapted from Goedert (11)

As was previously mentioned, Oskar Fischer observed the change in size of the plaques, a change that he associated with the different stages of the disease; He identified that these plaques in their majority concentrated in the cortical grey matter of the frontal cortex, followed by the temporal cortex and observed that there was a smaller concentration in the thalamus, the striatum, and the cerebellum but, there was none in the brain stem nor in the spinal cord.

Basing himself on morphologic criteria, Fischer distinguished eight types of plaques that could also be classified as stages. So that, stage I consisted of small stellate fibrous structures embedded in the normal neuropil. With time, many of these structures which Fischer named, "Morgensterne" (stars of the morning), seemed to fuse (stage II) and displace the normal-appearing neurites that fold in on themselves. Stage III is characterized by an increase in size of the plaque and the presence of abnormal material outside of the stellated structures, giving them a radial aspect. The plaques in Stage IV are described as wheels with a star-shaped nucleus attached to a fibre sphere through various surfaces. Subsequently, the biggest plaques form a stage V, which are homogeneous in appearance and seem to be constituted by a thick fibrous material. Stage VI is specifically related to the connection of the plaque with the blood vessels; in this stage Fischer described examples of perivascular deposits and the presence of an abnormal material throughout the vascular walls which caused their destruction, thereby providing the first example of "cerebral amyloid angiopathy"[11].

In stage VII, he described the presence of a fine fibrous material within the plaque, which he interpreted as a sign of destruction. Finally, in stage VIII a massive and diffused infiltration was described in the cortical grey matter, which appeared to be the same fibrous material found on the borders of the most mature plaques and he observed that the ganglion cells within these infiltrations seemed to degenerate.

Fischer believed that stages I-V were a continuum from the early clinical phase up to the late phase of the disease, and he found a close relationship between the duration of the disease and the stage of the plaque, so that the longer the duration of the disease, the more antique the plaques. He associated stages I-III with a median duration of the disease of approximately 6 months, stages III and IV with an average duration of 19,5 months and stages IV and V with a mean duration of 37 months. Fischer was not sure where stages VI and VII fit in but opted to classify them as late stages. Alternatively, he considered stage VIII a stage in which the brain tissue was unusually sensitive to the deposit of fibrous material, in which approximately 50% of the plaques were associated with anomalous mace-shaped neurites and most of them were stage V, some stage IV and stage III **(Figure 3)**.

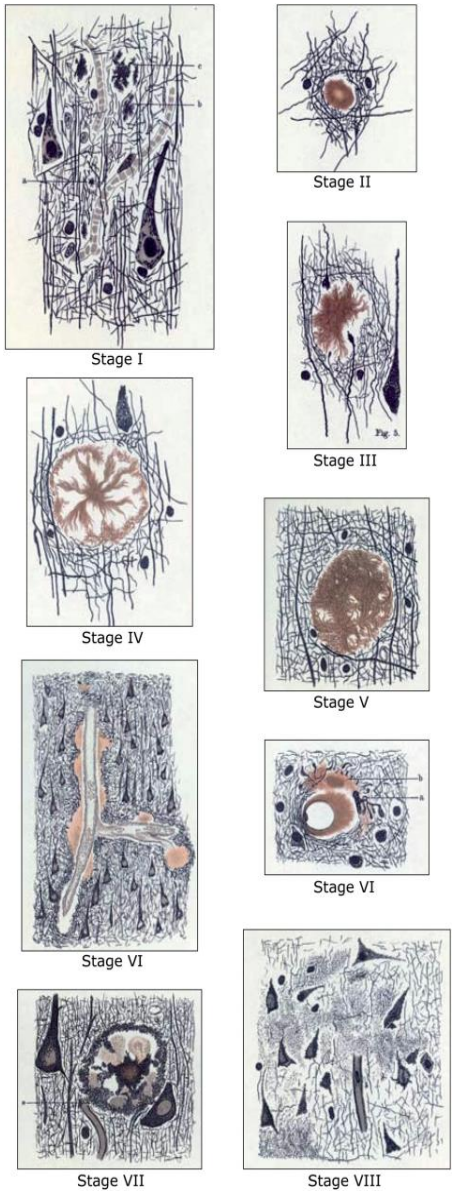

Figure 3. "Stages of the disease" adapted from Goedert (11)

Discussion

Currently, what Oskar Fischer described in terms of the structures of the plaques and tangles is considered as one of the principle pathophysiological theories of Alzheimer's Disease. Although at the moment, the infectious hypothesis is not the most accepted, other authors describe microbial infections that contribute to the pathological process [20].

CONCLUSIONS

Oskar Fischer made an invaluable contribution to neuroscience and put forward classic concepts with respect to Alzheimer's disease, although they did not give him recognition in posterity, they have allowed and continue to allow subsequent investigations, the great importance of rethinking these concepts and the inclusion of other possibilities and hypothesis, such as the inflammation, the immune and the infectious to continue to deepen the understanding of the disease.

On par with Alzheimer, he described the pathological substrate of the disease, although, Alzheimer thought it was a rare disease with a precocious start, while Fischer more accurately, considered it the principal substrate of senile dementia. Alzheimer accepted the idea that atheromatous disease was the main cause of senile dementia [21].

Despite the extensive effort of investigations to determine the etiology and cure for Alzheimer's, there is still a long road to cover, which is why it is important to keep investigating and deciphering the different mechanisms by which the disease develops, in order to produce treatments that will allow to stop or slow down its evolution.

Given the scarce advancement in the models used for the comprehension of the disease, it is useful to go back to the roots and study classic authors such as Oskar Fischer, since the exploration of other perspectives to understand this pathology allows the opening to new therapeutic paths and the generation of ideas for future investigations.

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