The contribution of Alois Alzheimer and Oskar Fischer to the understanding of Pick’s complex

A contribuição de Alois Alzheimer e Oskar Fischer para a compreensão do complexo de Pick

Eliasz Engelhardt¹[https://orcid.org/0000-0003-4168-1992]

Arnold Pick described a series of cases with progressive aphasia, behavioural disorders, and dementia. The post-mortem examination revealed on macroscopy, beside diffuse brain atrophy, also circumscribed (lobar) atrophy of the temporal and/or frontal lobes. The histopathology was not provided. Such kind of cases were soon named after the author, being known for a time as ‘Pick’s disease’, coming to constitute a new nosological group. A time later after the original description, Alois Alzheimer and Oskar Fischer completed microscopic examination of similar cases, where the first author found, on silver impregnation, spheric neuronal inclusions, he named ‘argentophilic ball’ inclusions, while the second one identified complex cortical changes he named ‘spongiform cortical wasting’, and additionally a type of swollen cell that was named ‘ballooned neuron’. Such microscopic changes became the first histopathological markers of this group of diseases.

**Keywords:** Pick, Alzheimer, Fischer, frontotemporal dementia, argentophilic ball, spongiform cortical wasting, ballooned neuron

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1Instituto de Neurologia Deolindo Couto and Instituto de Psiquiatria, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil

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**Corresponding author address:** eliasz@centroin.net.br

**RESUMO**

Arnold Pick descreveu uma série de casos apresentando, de modo progressivo, afasia, transtornos de comportamento e demência. O exame pós-morte revelou à macroscopia, além de atrofia cerebral difusa, também atrofia circunscrita (lobar) dos lobos temporais e/ou frontais. A histopatologia não foi fornecida. Tal tipo de casos foi logo denominado segundo o autor, sendo conhecido por um período como ‘doença de Pick’, vindo a constituir um novo grupo nosológico. Alguns tempo após a descrição original, Alois Alzheimer e Oskar Fischer perfizeram exame microscópio de casos semelhantes, onde o primeiro autor encontrou inclusões neuronais esféricas à impregnação pela prata, que denominou de ‘bola argirofílica’, enquanto o segundo identificou alterações corticais complexas às quais denominou ‘perda cortical espongiforme’, além de um tipo de célula tumefita que chamou de ‘neurônio balonizado’. Tais alterações microscópicas tornaram-se os primeiros marcadores histopatológicos desse grupo de doenças.

**Palavras-chave:** Pick, Alzheimer, Fischer, demência frontotemporal, bola argirofílica, perda cortical espongiforme, neurônio balonizado
INTRODUCTION

The ‘frontotemporal dementia’/‘frontotemporal lobar degeneration’ (FTD/FTLD) concept emerged from the study of the psychiatrist Arnold Pick (1851-1924), born of German-Jewish parents in Moravia (present day part of Czech Republic). He described a series of cases of progressive aphasia, behavioural disorders, and dementia, which on the post-mortem showed uni- or bilateral ‘circumscribed or lobar atrophies’ of the frontal and/or temporal lobes, often in an asymmetric manner (1892-1906). However, the study lacked microscopic examination, and so, the underlying histopathology, and in as consequence, a better understanding of this group of diseases.\textsuperscript{1,3,4,5}

The condition received a name, as Abraham Gans first suggested the eponym ‘Pick’s atrophy’ (\textit{Picksche Atrophie}) (1922), next named ‘Pick’s disease’ (\textit{Ziekte van Pick}) (1925), the latter designation being soon reaffirmed by Kimuri Onari and Hugo Spatz as ‘Pick’s disease’ (\textit{Picksche Krankheit}) (1926). Recently, in order to maintain the original name, the FTD/FTLD designation received also the name ‘Pick’s complex’, and ‘Pick’s-lobar atrophy complex’.\textsuperscript{10}

The microscopic examination of similar cases began to appear, and Erwin Stransky is credited by authors for the first description of one case. However, his findings were apparently nearer to Alzheimer’s ‘perivascular gliosis of the cerebral cortex’ (\textit{perivaskulären Glüose der Hirnrinde}), than to a new finding (1905).\textsuperscript{11,12}

The descriptions of neuronal changes that would characterize lobar atrophy cases, which can be regarded as the first unequivocal ones were provided by Alois Alzheimer and Oscar Fischer, who published their account on the subject in the same year and month (Dec 1911).\textsuperscript{13,14}

The German psychiatrist and neuropathologist, Alois Alzheimer (1864 - 1915), in his paper “On peculiar disease cases of the later age” (\textit{Über eigenartige Krankheitsfälle des späteren Alters}), focused on a group of senile diseases cases with, as he wrote, “circumscribed atrophy to which Pick has devoted a particularly detailed study”. There, he described the histopathology of two cases, which tissue was stained with Bielschowsky’s silver technique. There, [senile] plaques lacked, but the small cortical pyramidal neurons were affected by marked changes primarily of the fibrils, “but different from those occurring in dementia senilis” (i.e., the characteristic ‘peculiar fibrillary change’ [\textit{eigentümliche Fibrillenveränderung}] [‘neurofibrillary tangles’]). These pyramidal neurons presented a peculiar fibril change in the shape of a dark ‘argentophilic ball’ (\textit{argentophile Kugel}) inclusion, next to the displaced nucleus, whose size varied from half to twice that of the nucleus, or occupying the most part of the cell. The neurons with such fibrillary pathology could be easily recognized also in alcohol-toluidine blue preparations [Nissl’s], by the ‘particular overall shape of the cell, the cap-like nucleus displaced upwards in the plasma, as well as the peculiar, dull-shining colour of the place where the argentophilic mass lies’. He provided clear illustrations of neurons with the argentophilic inclusions (1911).\textsuperscript{13} (Figure 1)

One of Alzheimer’s cases was later described and published by Georg Stertz (1926), identified as TM, a 67-year-old woman, who presented an atypical senile dementia, with behavioural disorders, and sensory aphasia. The post-mortem revealed left temporal lobe atrophy, mainly the 2\textsuperscript{nd} and 3\textsuperscript{rd} circumvolutions, and the fusiform gyrus. The microscopic examination revealed that in some places the upper cortical layers (I-III) of the atrophic gyri were more severely affected; plaques and [typical] neurofibrillary changes were not seen; numerous ‘argentophilic balls’ (\textit{argentophilen Kugeln}) inclusions in pyramidal cells, were found, as already described by Alzheimer. Additionally, very frequently, somewhat completely different cell changes were seen, namely ‘peculiar swellings’ (\textit{eigentümliche Schwellungen}) (especially in the upper layers), where the nucleus was dislocated to the side, and the centre of the cell filled by a dull stained homogeneous mass. This image was reminiscent of the ‘primary irritation’ (\textit{primäre Reizung}) described by Franz Nissl (1892).\textsuperscript{15,16}

COMMENTS

Alzheimer described the histopathology of two cases with circumscribed brain atrophy, which he regarded as similar to those of Pick. There, he observed absence of plaques and tangles, and described argyrophilic globular inclusions (‘argentophilic ball’ inclusions) with silver impregnation. He also described, with toluidine blue staining, that the cells with such fibrillary changes could be recognized by the particular shape of the cell, and a dull-shining colour of the place where the argentophilic [i.e., the ‘ball’]mass lies, which he regarded as a related counterpart (1911).\textsuperscript{13} His description permits to understand that neurons bearing the same structure (the ‘ball’) stained positively with
silver, and negatively with toluidine blue, i.e., cells with the same pathology, seen through different staining method. Later, cells with such ‘ball’ inclusions were designated ‘Pick’s bodies’.\(^1\)\(^,\)\(^7\)\(^,\)\(^18\)\(^,\)\(^19\)

However, regarding the above-mentioned cells of particular shape stained with toluidine blue, some authors presented a different interpretation, crediting to Alzheimer the description, beside the ‘argentophilic ball’ inclusions, also the [presumed] description of neurons with ‘peculiar swellings’ (as described by Stertz).\(^2\)\(^,\)\(^16\)\(^,\)\(^17\)\(^,\)\(^18\)\(^,\)\(^19\) However, there is not such report or statement in Alzheimer’s paper on the subject. He clearly described such histological presentation of Nissl-stained tissue, explaining this look as a counterpart finding in connexion with the argentophilic ball inclusions.\(^7\)\(^,\)\(^13\)

Opportune to mention that neurons with such ‘peculiar swellings’ – the ‘ballooned neuron’ forms, in the same year of Alzheimer’s account on the ‘ball’ inclusions, were first identified by the Bohemian (presently part of Czech Republic) psychiatrist Oskar Fischer (1876-1942), born into a German-speaking Jewish family.\(^2\)\(^0\) Fischer reported, besides the complex changes of the cerebral cortex he named ‘spongiform cortical wasting’, the presence of peculiar neuronal morphologies in some of the cases of lobar atrophy, described as “swelling of the ganglion cells” (Aufblähung der Ganglienzellen), in one of his cases, and ‘rounded ganglion cells’ (...Ganglienzellen...von rundlicher Gestalt...) in other cases (1911).\(^14\)

Later, cells with such characteristics were designated ‘Pick’s cells’.\(^3\)\(^,\)\(^17\)\(^,\)\(^18\)\(^,\)\(^19\)

**CONCLUSION**

Pick described a series of peculiar cases that would be recognized as a new group of disease, later known as FTD/FTLD or Pick’s complex. Alzheimer was the first to describe microscopic features of similar cases, identifying neurons with a spheric silver-stained inclusion, he named ‘argentophilic ball’, later designated as ‘Pick’s body’. Additional important microscopic findings were described by Fischer, namely, the ‘spongiform cortical wasting’ and the ‘ballooned neuron’, later known as ‘Pick’s cell’. These kind of changes became the first histopathologic identity of this group of diseases.

Thus, these three personalities, Pick, Alzheimer and Fischer, established the foundations of this new group of diseases. (Figure 2)

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**Figure 2.** The three personalities who laid the foundations of FTD/FTLD or Pick’s complex. Arnold Pick (28-04-2024) [https://commons.wikimedia.org/wiki/File:Arnold_Pick.JPG](https://commons.wikimedia.org/wiki/File:Arnold_Pick.JPG) Alois Alzheimer (28-04-2024) [https://commons.wikimedia.org/wiki/File:Alois_Alzheimer_003.jpg](https://commons.wikimedia.org/wiki/File:Alois_Alzheimer_003.jpg) Oskar Fischer (28-04-2024) [https://commons.wikimedia.org/wiki/File:Oskar_Fischer.JPG](https://commons.wikimedia.org/wiki/File:Oskar_Fischer.JPG)