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Microglial Senescence and Activation in Healthy Aging and Alzheimer's Disease: Systematic Review and Neuropathological Scoring

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 16 November 2023 and was last updated on 16 November 2023.

INTRODUCTION

Review question / Objective This systematic review looks at the various phenotypes of human microglia, particularly activated and senescent microglia, and their function in healthy aging and AD that is paradigmatic of age-related neurodegeneration. The interaction between the different microglial phenotypes, beta-amyloid, TAU protein and iron metabolism will be discussed. We propose an integrated model of genetics, phenotypical, and neuropathological signa-tures of microglial dysfunction related to neurodegeneration. Furthermore, in light of the current evidence, we highlight potential strategies to study microglial senescence (MS), and we propose a semiquantitative score system to grade microglial activation.

Rationale The greatest risk factor for neurodegeneration is the aging of the multiple cell types of human CNS. Microglial are important because they are the "sentinels" of internal and external varia-tions. Although having long lifespans, human microglia have received little interest in studies about aging and Alzheimer's disease (AD).Due to the lack in literature of specific human microglia's systematic review, we aim to emphasize microglial signatures in homeostatic brain aging and AD. Our review highlights that studies on animal models only partially clarify what happens in humans.

Condition being studied A total of 3630 cases were included in the qualitative analysis. We analyzed Healthy Controls and Azheimer's disease' post-mortem brain tissue. Specifically, we reviewed all studies according to homeostatic

brain human microglia during healthy aging and AD.

METHODS

Search strategy We performed a systematic literature search on PubMed and Scopus up to June 2023 mentioning microglial senescence (MS) and microglial activation (MA), and different phenotypes in aging healthy controls and AD, using the terms: “Microglial Senescence”, “Microglial Activation” combined with “Human” OR “Humans” AND “Alzheimer Dis-ease” OR “Alzheimer’s disease” OR “Healthy Aging” OR “Healthy Controls”. Additional articles were identified from other sources (i.e., articles cited in reviews). Those articles were imported to the PICOs portal (automation tool software) and duplicates were removed. Inclusion and exclusion criteria reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

Participant or population Healthy Controls and Azheimer's disease.

Intervention Not applicable.

Comparator Not applicable.

Study designs to be included Case-Control studies.

Eligibility criteria The eligibility for inclusion was based on human MS and MA studies, reporting genetics, phenotypical, and neuropathological tissue signatures in healthy aging and AD. Concurrently, studies that were not relevant to human MS or MA, or that presented limited data on the brain tissue samples, poorly developed methodologies, biased outcomes and insufficient sample size, were all ruled out.

Information sources Electronic databases (PubMed, Scopus, Cochrane library), contact with authors, articles cited in other reviews.

Main outcome(s) - Identify and classify various phenotypes of human microglia, particularly activated and senescent microglia, and their function in healthy aging and AD pathology
- To study and to review the interaction between the different microglial phenotypes, beta-amyloid, TAU protein and iron metabolism
- To propose an integrated model of genetics, phenotypical, and neuropathological signatures of microglial dysfunction related to neurodegeneration.

Quality assessment / Risk of bias analysis Two reviewers (AM and AG) independently assessed study quality and any discrepancies were resolved through discussion and with the expert opinion of a third reviewer (TEP). Quality of studies included in this systematic review was independently assessed by the two reviewers using the NIH Quality Assessment Tool for Case-Control studies/ Systematic Reviews and Meta-Analysis (Study Quality Assessment Tools | NHLBI, NIH, https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools.

Strategy of data synthesis Two reviewers (AM and AG) independently extracted essential information from each study, with discrepancies resolved by consensus. Data extracted included information of authors, population and methodology of the study, brain tissue conditions whether it was comparable to other studies, study findings, and significant statistical value. A qualitative synthesis of data was employed to summarize the information obtained from the selected articles. Data were summarized using descriptive statistics, with means and standard deviations for continuous variables and frequencies and percentages for dichotomous variables. A meta-analysis (or quantitative analysis) was not performed due to inadequate uniform results from the articles chosen.

Subgroup analysis Not applicable.

Sensitivity analysis Not applicable.

Language restriction English.

Country(ies) involved Italy.

Keywords human microglia; microglial senescence; microglial activation; Alzheimer’s disease; Healthy Aging; neuropathology.

Contributions of each author

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