Supplementary Data 1.

Case Demographics

	Age	Sex	PMI	A	C	B	Braak	Clinical Assessment	COD	RACE
Control AD										
1	88	F	9.00	1	1	1	Stage I	No Cognitive Disorder	Arteriovascular sclerotic disease	Caucasian
2	87	M	8.00	1	0	1	Stage I	No Cognitive Disorder	Cardiac Arrest;Atherosclerotic Disease	Caucasian
3	86	F	37.00	1	0	1	Stage II	No Cognitive Disorder	urethral cancer, heart murmur	Caucasian
4	89	F	4.55	1	1	1	Stage I-II	No Cognitive Disorder	Coronary Artery Disease;Atrial fibrillation;Hypertension	Caucasian
5	96	F	6.00	0	1	1	Stage I-II	No Cognitive Disorder	Generalized atherosclerosis	Caucasian
6	91	F	18.66	0	0	1	Stage I	No Cognitive Disorder	End Stage Congestive Heart Failure	Caucasian
7	92	F	22.30	1	0	1	Stage II	No Cognitive Disorder	Atherosclerotic Heart Disease	Caucasian
8	72	M	17.25	0	0	1	Stage I	No Cognitive Disorder	Atherosclerotic Coronary Artery Disease , Ischemic Cardiomyopathy	Caucasian
9	72	M	17.66	0	0	0	Stage 0	No Cognitive Disorder	Acute Myocardial Infarction;Diabetes Mellitus	Caucasian
10	73	M	20.50	2	0	1	Stage I	No Cognitive Disorder	Atherosclerotic Heart Disease, Cardiomyopathy, Diabetes	Caucasian
11	74	F	34.9	1	0	1	Stage I	No Cognitive Disorder	chronic kidney disease	Caucasian
12	67	F	25.95	1	0	1	Stage 1	No Cognitive Disorder	Atherosclerotic Coronary Artery Disease, Tobacco Abuse, Hypertension	Caucasian
13	94	M	23.40	2	0	1	Stage 1	No Cognitive Disorder	Congestive Heart Failure	Caucasian
14	90	F	24.30	1	1	1	Stage II	No Cognitive Disorder	Cardiac Arrest;Respiratory Arrest;Unspecified Natural Causes;Cardiovascular Diseae	Caucasian
15	93	M	16.88	1	1	1	Stage I-II	No Cognitive Disorder	Cardiac Arrest;Atherosclerotic Disease	Caucasian
16	72	M	24.28	1	0	0	Stage 0	No Cognitive Disorder	Acute Myocardial Infarction due to Hypertensive Arteriosclerotic Cardiovascular Disease	Caucasian
17	102	F	10.30	0	0	1	Stage II	No Cognitive Disorder	Failure to thrive	Caucasian
Mean	84.588		18.88							
Intermediate AD										
1	92	M	12.00	3	3	2	Stage III-IV	Moderate	Acute Renal Failure	Caucasian
2	90	F	8.48	2	3	2	Stage III	MCI	Acute Renal Failure	Caucasian
3	90	F	22.12	2	3	2	Stage III-IV	Severe	Advanced Dementia;vascular	Caucasian
4	91	F	15.00	3	2	2	Stage III	MCI	Lung cancer	Caucasian
5	79	F	18.28	2	3	2	Stage III	Moderate	Cardiac Arrest;Atherosclerotic Disease	Caucasian
6	82	M	17.60	2	3	2	Stage III-IV	Moderate	Cardiac Arrest;Atherosclerotic Disease	Caucasian
7	94	F	18.45	2	2	2	Stage III-IV	MCI	Cardiopulmonary Arrest	Caucasian
8	82	M	18.22	2	2	2	Stage III-IV	Moderate	Cardiac Arrest;Vascular Dementia	Caucasian
9	87	M	13.91	2	3	3	Stage V-VI	Moderate	Sepsis due to urinary tract infection	Caucasian
10	80	M	10.53	3	2	3	Stage V-VI	MCI	Cardiac Arrest;Atherosclerotic Disease	Caucasian
11	78	M	14.51	2	2	2	Stage III-IV	Moderate	Cardiac Arrest;Atherosclerotic Disease	Caucasian
12	78	F	6.00	2	2	2	Stage III-IV	Moderate	Cardiac Arrest;Atherosclerotic Disease	Caucasian
13	79	F	6.40	1	3	3	Stage V-VI	Severe	Cardiac Arrest;Atherosclerotic Disease	Caucasian
14	66	F	44.25	3	3	2	Stage III-IV	Moderate	Urinary Tract Infection	Caucasian
15	83	M	15.12	2	2	2	Stage III-IV	Moderate	Liver Failure	Caucasian
16	77	F	10.75	2	2	2	Stage III	Moderate	Cardiac Arrest;Atherosclerotic Disease	Caucasian
17	90	F	13.25	2	1	2	Stage III-IV	Moderate	Lung Cancer	Caucasian
Mean	83.412		15.58							

PMI=postmortem interval; Yr=year; A Score=Aβ immunopositivity, Thal Phase; C Score=neuritic plaque density, CERAD; B Score=Neurofibrillary tangles; COD= Cause of Death; AD= Alzheimer's disease; M = male; F = female; No Cognitive Disorder ≥ 62 % on Modified Telephone Interview for Cognitive Status (TICS-M) score; MCI=Mild Cognitive Impairment (TICS-M score 61-54%); Moderate=Moderate dementia (TICS-M score 53-36%); Severe=Severe dementia ; Case data published in Vontell, Regina T et al. "Identification of inflammasome signaling proteins in neurons and microglia in early and intermediate stages of Alzheimer's disease." *Brain pathology (Zurich, Switzerland)* vol. 33,4 (2023): e13142. doi:10.1111/bpa.13142

Intermediate AD pathology is defined as the presence of sparse to moderate diffuse and neuritic beta-amyloid plaques (i.e., 6-20 neuritic plaques per 1 mm2) and moderate hyperphosphorylated tau-positive NFTs (e.g., neuropathology scores of B2 or B3; Braak III-IV) seen in the CA1-CA3 regions of the hippocampus.

A review of Immunohistochemical procedure.

All slides were incubated overnight at 4°C in a solution of either, mouse anti-Ng-2 (gift from UGOT, 1.5 µ g/ml), mouse anti-MAP2 (0.5 µg/ml; Sigma), mouse anti-pTau (AT-8; 0.5 µg/ml; Sigma), mouse anti-Tau (GT-38; 0.1 µg/ml; Abcam), polyclonal rabbit anti-Synaptophysin (0.6 µg/ml; Abcam)or mouse anti-beta Amyloid (0.2 µg/ml; Sigma) in PBS. The next day, sections were exposed to biotinylated horse-anti-mouse IgG (15 µg/ml; Vector Laboratories) or goat-anti-rabbit IgG (15 µg/ml; Vector Laboratories) in PBS for 1 h followed by avidin-biotin complex for 1 h (1:200, ABC; Vector Laboratories). Reactions were visualized with 3,3 -diaminobenzidine (MilliporeSigma) for 10 min. Finally, the sections were dehydrated, cleared in xylene, and cover slipped. As negative low AD, we performed staining in the absence of the primary antibodies and no specific staining was identified in these preparations.

A review of Immunofluorescence Labelling procedures

The mouse monoclonal primary Ng antibody (1.5 µg/ml) was compatible with the humanized antibody anti-ASC (0.1 µg/ml) mixed in a cocktail solution. Sections were pretreated as described above and blocked in 5% goat serum for 20 min before the primary antibodies were applied and incubated overnight at 4°C. Following primary antibody incubation, sections were rinsed three times in PBS, for 3 min each time before these secondary antibodies were added. The samples were finally soaked for 1.5 h in PBS containing the following secondary antibody cocktail: goat anti-mouse IgG conjugated to Alexa Fluor 488 (4 µg/ml; Invitrogen, Eugene, Oreg., USA) and goat anti-human IgG conjugated to Alexa Fluor 546 (4 µg/ml; Invitrogen).

To co-label the Ng with incompatible markers, such as, mouse anti-ASC (B-3; Santa Cruz Biotechnology, Santa Cruz, CA.), the monoclonal antibodies were applied separately. Thus, after the sections were blocked in 5% goat serum for 20 min, the anti-Ng and human ASC cocktail was applied and incubated overnight at 4°C. The sections were rinsed three times in PBS, for 3 min each time and were soaked for 1.5 h in PBS containing goat anti-mouse IgG conjugated to Alexa Fluor 488 (4 µg/ml; Invitrogen) and goat anti-human IgG conjugated to Alexa Fluor 546 (4 µg/ml; Invitrogen) followed by several rinses in PBS and postfixation in 4% paraformaldehyde for 20 min. The marker mouse anti-ASC (0.4 µg/mL), which stains the microglia as previously described in 23was conjugated to Alexa Fluor 647 (4 µg/ml; Invitrogen) and the slides were incubated for 3hrs, then the sections were rinsed in several changes of PBS and postfixed in 4% paraformaldehyde for 10 mins. Finally, the sections were placed under a coverslip using ProLong Gold antifade

A overview of formulas and details used to quanitify the staining results.

Ng, MAP2, Tau (GT-38) and Synaptophysin staining was performed by RV in the hippocampal sub regions including the the Dentate Gyrus (DG); CA3; CA2 and CA1. For the Ng, MAP2 and GT-38 counts, three contours from each region of interest (ROI) were taken from the CA1, CA2, CA3, the subiculum, and the adjacent DG, which encompassed an average area of 3.2 mm2 per region using the Image-Pro Premier (Media Cybernetics) program

For each region, the CA scans encompassed all layers of the strata. Tissue scans were reviewed (by RV) to ensure that counts had met the criteria to avoid duplication of counts (e.g., an area containing an Ng or MAP2-positive nucleus [>10 µm2] connected positive processes. In a pilot study, we confirmed that the counting profile described previously counted the correct number of labeled cells and nuclei (using an ImageJ cell counter). Estimation of number density was performed by applying the following formula:

$N=(\Sigma Q^-)/V$

Where N is the total number of cells or clusters per volume of brain region; ΣQ– is the number of counted cells; and V is the volume of regions of interest per sampling frame.

The Ng morphological changes were ascertained by using a circularity measure, which was calculated by the equation:

$4A/Pi*MaxFeret2$

Where A = area and MaxFeret=the distance between two parallel tangential lines (Media Cybernetics); a value of 0 indicates a flat (line) object, a value of 1 indicates a perfect circular object.

The staining synaptophysin data was obtained from software-derived annotations that accurately identified immune-positivity and the software efficiently identified the percent area stained using the formula:

% Stained Area=(sum(area of stained with synaptophysin)/(ROI area))*100

Each of the ROIs area was limited to 1mm2 to normalize the data.