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Retrospective Evaluation of Neuropathologic Proxies of the Minimal Atrophy Subtype Compared to Corticolimbic Alzheimer Disease Subtypes

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Abstract

Background: Alzheimer's disease (AD) is neuropathologically classified into three corticolimbic subtypes based on the neurofibrillary tangle distribution throughout the hippocampus and association cortices: limbic predominant, typical, and hippocampal sparing. In vivo, a fourth subtype, dubbed "minimal atrophy", was identified using structural MRI. **Objective:** The objective of this study was to identify a neuropathologic proxy for the neuroimaging-defined minimal atrophy subtype.

Methods: We applied two strategies in the FLorida Autopsied Multi-Ethnic (FLAME) cohort to evaluate a neuropathologic proxy for the minimal atrophy subtype. In the first strategy, we selected AD cases with a Braak IV tangle stage because of the relative paucity of neocortical tangle involvement compared to Braak>IV. Braak IV cases were compared to the three AD subtypes. In the alternative strategy, typical AD was stratified by brain weight and cases having a relatively high brain weight (>75th percentile) were defined as minimal atrophy.

Results: Braak IV cases (n=37) differed from AD subtypes (limbic predominant [n=174], typical [n=986], and hippocampal sparing [n=187] AD) in terms of having the least years of education (median 12 years, group-wise p<0.001) and the highest brain weight (median 1140 grams, p=0.002). Braak IV cases most resembled the limbic predominant cases owing to their high proportion of *APOE ε4* carriers (75%, p<0.001), an amnestic syndrome (100%, p<0.001), as well as older age of cognitive symptom onset and death (median 79 and 85 years, respectively, p<0.001). Only 5% of Braak IV had amygdala predominant Lewy bodies (the lowest frequency observed, p=0.017), whereas 32% had coexisting pathology of Lewy body disease which was greater than the other subtypes (p=0.005). Nearly half (47%) of the Braak IV sample had coexisting limbic-predominant age-related TDP-43 encephalopathy neuropathologic change. Cases with a high brain weight (n=201) were less likely to have amygdala predominant Lewy bodies (14%, p=0.006) and most likely to have Lewy body disease (31%, p=0.042) compared to those with middle (n=455) and low brain weight (n=203).

Discussion: The frequency of Lewy body disease was increased in both neuropathologic proxies of the minimal atrophy subtype. We hypothesize that Lewy body disease may underlie cognitive decline observed in minimal atrophy cases.

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Keywords

Atypical Alzheimer's disease; minimal atrophy Alzheimer's disease; Lewy body disease; Alzheimer's disease subtypes

Abbreviations

AD = Alzheimer's disease

Braak IV = Braak neurofibrillary tangle stage IV

FLAME = FLorida-Autopsied Multi-Ethnic

Introduction

Neuropathologic hallmarks of Alzheimer's disease (AD) accumulate in a spatiotemporal manner.[1, 2] Abnormal accumulation of extracellular amyloid-β plaques is first observed in the neocortex before progressing to the limbic areas, diencephalon, brainstem, and cerebellum, as described by Thal amyloid phases.[2] Amyloid-β topographic distribution remains relatively consistent across autopsied AD cases.[3]

Neurofibrillary tangles first accumulate in the locus coeruleus and transentorhinal cortex, before affecting the hippocampus, and eventually involving the neocortex, with the primary cortices being the last affected according to Braak tangle stages.[1, 4] Tangle distribution is less uniform than that of amyloid-β. Using a mathematical algorithm to examine the topographic distribution of corticolimbic tangles, we previously identified three neuropathologic subtypes of AD: limbic predominant, typical, and hippocampal sparing.[5-7] The limbic predominant subtype shows significant tangle accumulation in the hippocampus while the cortex is relatively spared. In contrast, the hippocampal sparing subtype is characterized by disproportionate neocortical tangle burden with relative sparing of the hippocampus. Falling between these two extreme phenotypes is typical AD, which exhibits a tangle distribution across hippocampal and cortical regions as reflective of Braak tangle staging system.[1, 5] Beyond differences in tangle distribution, these neuropathologically-defined subtypes also differ in demographic, genetic, and clinical features. Limbic predominant AD cases are older at cognitive symptom onset, are more likely to carry the *APOE ε4* allele, and typically exhibit an amnestic clinical phenotype.[5] In contrast, hippocampal sparing AD cases have a younger age at cognitive symptom onset, are less likely to carry the *APOE ε4* allele, and more often exhibit non-amnestic clinical phenotypes.[5, 7]

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Studies utilizing structural MRI have supported these neuropathologic subtypes in vivo by investigating areas of regional atrophy across the brain.[8-13] MRI-measured atrophy correlates with tangle density in corresponding brain regions.[8] In limbic predominant AD cases, the amygdala and hippocampus show the most volume loss, whereas in hippocampal sparing AD cases, cortical grey matter atrophy is most remarkable.[8] In addition to the neuropathologically-defined limbic predominant, typical, and hippocampal sparing AD subtypes, a fourth subtype, dubbed "minimal atrophy", was identified using neuroimaging.[11] Individuals categorized with this minimal atrophy AD showed impairment on cognitive testing, but lacked significant atrophy on MRI.[9-11, 14] A meta-analysis by Ferreira *et al*.[10] showed that individuals with minimal atrophy had an intermediate age at cognitive symptom onset (mean of 70 years) and less dementia severity based on the Mini-Mental State Examination and Clinical Dementia Rating scale Sum of Boxes despite lower mean levels of education, compared to individuals with neuropathologically-defined subtypes.[10]

A recent study including antemortem MRI and postmortem neuropathology data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort aimed to investigate the neuropathology of the AD subtypes.[15] The study concluded that compared to the hippocampal sparing AD subtype, the limbic predominant AD subtype was associated with a higher Thal amyloid phase, higher neuritic plaque density, and greater limbic-predominant age-related TDP-43 encephalopathy neuropathologic change.[15] However, since individuals could not be categorized into subgroups or categorical subtypes due to the small cohort size (n=31), the study was not designed to provide clear insights into the etiology of minimal atrophy.

Therefore, the minimal atrophy AD subtype has yet to be neuropathologically characterized. The objective of this study was thus to identify a neuropathologic proxy for the minimal atrophy subtype, in order to continue the search toward understanding the neuropathologic and associated phenotypic expression of this neuroimaging-defined subtype. To do so, we created a "minimal atrophy" proxy using two strategies. For the "main strategy," minimal atrophy cases were defined as cases with a Braak tangle stage IV (Braak IV) and compared to the operationally defined neuropathologic subtypes of AD (Braak>IV). For the alternative strategy, typical AD cases were stratified by brain weight. Cases with the highest brain weight were used as a proxy for minimal atrophy AD and compared with middle and

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lowest brain weight cases. We analyzed the demographic and clinicopathologic characteristics of the neuropathologic proxy for minimal atrophy AD using both strategies.

Materials and Methods

Study Samples

The FLorida Autopsied Multi-Ethnic (FLAME) cohort[16] was updated through May 27th, 2020, by querying the Mayo Clinic brain bank for individuals who came to autopsy in the State of Florida, USA. The FLAME cohort consists of individuals self-identifying as Hispanic/Latino, Black/of African descent, and non-Hispanic White/of European descent; hereafter referred to as Hispanic decedents, Black decedents, and White decedents, respectively. Of the 3,503 decedents identified, 109 were excluded for lack of neuropathologic report, and 899 were excluded because the primary study source documented was not affiliated with State of Florida memory disorder clinic referral services. The final 2,495 FLAME-2020 decedents, with age at death ranging between 37 and 104 years, were queried for neuropathologically diagnosed AD. To ensure uniformity, we excluded cases that were not diagnosed by our standard neuropathologist (D.W.D). We also excluded cases with a primary diagnosis of non-AD neurodegenerative disorder (e.g., amyotrophic lateral sclerosis,[17] corticobasal degeneration,[18] Creutzfeldt-Jakob disease,[19] frontotemporal lobar degeneration,[20] globular glial tauopathies,[21] multiple system atrophy,[22] Pick's disease,[23] progressive supranuclear palsy[24]), coexisting hippocampal sclerosis of a TDP-43 etiology,[25] missing data on tangle count, and known genetic mutations. The final sample size of AD cases was 1,384.

Standard Protocol Approvals, Registrations, and Patient Consents

All brains were acquired with appropriate ethical approval, and the research performed on postmortem samples was approved by the Mayo Clinic Research Executive Committee (IRB# 16-003061).

Neuropathologic Procedures and Clinical History

All cases underwent standardized neuropathologic examination by a single board-certified neuropathologist (D.W.D). The fixed hemisphere of each brain was weighed and doubled to obtain the total brain weight in grams. Specific brain regions were dissected and studied for gross

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and microscopic pathology using the Dickson sampling scheme.[16] Five-micron thick paraffin-embedded sections were cut and stained to assess AD neuropathologic changes. The topographic distributions of neurofibrillary tangles and senile plaques were evaluated using thioflavin-S immunofluorescence imaging using an Olympus BH2 fluorescence microscope to assign the Braak tangle stage[1] and Thal amyloid phase,[2] as previously described.[3] AD subtypes were classified using tangle counts from the hippocampus (CA1, subiculum) and association cortices (superior temporal, inferior parietal, and middle frontal), as previously described.[5] The AD subtype algorithm evaluates the relative distribution of corticolimbic tangle densities to classify AD cases as limbic predominant, typical, or hippocampal sparing and is further described in section "AD subtype classification".[5-7] To provide visual representation of tangle distribution, we converted tangle counts from available brain regions (eMethods, eFigure 1).[9, 26-28] Coexisting Lewy-related pathology,[7, 29, 30] TDP-43 pathology,[31] and cerebrovascular disease[32, 33] are further described in eMethods. History was retrospectively abstracted from clinical records made available by brain bank participants or family members (eMethods).[16]

AD Subtype Classification

Figure 1 shows the cohort breakdown of each strategy used to investigate the neuropathologic proxy of minimal atrophy. The cohort selection started with the original neurofibrillary tangle subtype classification (i.e., limbic predominant, typical, and hippocampal sparing).[5] Original inclusion criteria allowed for cases with a Braak stage >IV. To operationally classify AD subtypes as limbic predominant, typical, or hippocampal sparing, the previously described algorithm compares the individual hippocampal and cortical measures with the expected medians to assess relative sparing or relative predominance of tangle pathology.[5-7] This information is then combined with the hippocampal-to-cortical ratio to ensure that extreme phenotypes (limbic predominant and hippocampal sparing) lie outside the 75th and 25th bounds.[5] Cases with a Braak tangle stage of IV were databased as early AD. Therefore, Braak IV cases were omitted when developing the AD subtype algorithm to identify tangle patterns in advanced disease. We expected relative preservation of brain weight in the context of neurodegeneration. Thus, we categorized AD cases with a Braak tangle stage of IV as the neuropathologic proxy for the neuroimaging-defined minimal atrophy subtype.

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We performed an alternative strategy to further examine neuropathologic features of the minimal atrophy subtype. We sought to utilize the most representative phenotype (typical AD) to evaluate minimal atrophy through stratification of brain weight. We excluded cases lacking data on brain weight, resulting in 859 cases to be assessed for the alternative strategy. Typical AD cases with a high brain weight, i.e., brain weight greater than the 75th percentile (n=201, brain weight range: 1130–1540 grams), represented the minimal atrophy proxy group and were compared with typical AD cases with a brain weight between the 25th to 75th percentile range (n=455, brain weight range: 920–1120 grams) and those with a brain weight below the 25th percentile (n=203, brain weight range: 560–900 grams).

Comparison with Previous Studies on Minimal Atrophy

Results from the two strategies used in the current study for the neuropathologic proxy of minimal atrophy AD subtype were compared to results reported in the meta-analysis by Ferreira *et al.*[10]

Statistical Analysis

Continuous variables were summarized with the sample median (25th percentile, 75th percentile). Categorical variables were summarized with number and percentage of patients. Comparisons of continuous variables across groups were made using Kruskal-Wallis rank sum test and comparisons of continuous variables between groups were made using Wilcoxon rank sum test. The association between categorical variables were tested using Fisher's exact test. Post-hoc tests also used Fisher's exact test. P-values<0.05 were considered as statistically significant and all statistical tests were two-sided. Statistical analysis was performed using R Statistical Software (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria).

Data Availability

All requests for raw and analyzed data and related materials, excluding programming code, will be reviewed by Mayo Clinic's Legal Department and Mayo Clinic Ventures to verify whether each request is subject to any intellectual property or confidentiality obligations. Any data and materials that can be shared will be released via a Data Use/Share Agreement or Material Transfer Agreement.

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Results

Table 1 shows the demographic, and clinicopathologic features of the Braak IV, limbic predominant, typical, and hippocampal sparing AD cases. For a better comparison between the groups, the features are illustrated in Figure 2. Using the main strategy described in the methods section "AD subtype classification", our cohort (n=1,384) consisted of 37 Braak IV cases, 174 limbic predominant, 986 typical, and 187 hippocampal sparing AD cases. The Braak IV cases, the neuropathologic proxy for the minimal atrophy subtype, consisted of a nearly equal male-to-female ratio (group-wise $p<0.001$), had the least years of education (median 12 years, $p=0.002$), and a high frequency of the *APOE ε4* allele (75%, $p<0.001$) compared to the other subtypes. Clinically, Braak IV cases had a late-onset of cognitive decline (median 79 years, $p<0.001$), a slower annual decline on the Mini-Mental State Examination (-0.6 points, $p<0.001$), and lacked atypical clinical syndromes (0%, $p<0.001$). A clinical diagnosis of Lewy body dementia was met in 17% of Braak IV cases ($p=0.378$). Neuropathologically, Braak IV cases had a relatively high brain weight (median 1140 grams, $p<0.001$), which is in line with the minimal atrophy aspect. Braak IV cases did not reach a maximum Thal amyloid phase (phase 4, $p<0.001$) and showed a similar severity of cerebrovascular pathology as the other subtypes based on Kalaria score (4 points, $p=0.054$). Amygdala predominant Lewy bodies was observed in only 5% of Braak IV cases ($p<0.017$), and coexisting Lewy body disease was present in 32% of cases, which was the most among all subtypes ($p=0.004$). The presence of Lewy body disease subtypes is further specified in eTable 2. Nearly half of cases in the Braak IV group had limbic-predominant age-related TDP-43 encephalopathy neuropathologic change (47%, $p<0.021$). Braak IV cases showed a similar frequency of moderate-to-severe cerebral amyloid angiopathy in the visual cortex as the other subtypes (22%, $p=0.117$).

The demographic and clinicopathologic findings for the limbic predominant subtype revealed greater frequency of females (67%) and *APOE ε4* carriers (74%) as well as older age at cognitive symptom onset (median 78 years) and death (median 86 years) than in the other subtypes. Decline on the Mini-Mental State Examination was slow with -1.2 points per year and clinical syndrome was seldom atypical (1%) in this subtype. Amygdala predominant Lewy bodies was found in 26% of cases and Lewy body disease in 22% of cases. The limbic predominant subtype showed the highest frequency of limbic-predominant age-related TDP-43

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encephalopathy neuropathologic change (56%) among all subtypes. A moderate-to-severe score for cerebral amyloid angiopathy was observed in 32% of cases.

Typical AD was observed equally in men and women with a median of 14 years of education, of which 64% carried an *APOE ε4* allele. The age at onset (median 71 years) and death (median 81 years), the annual decline on the Mini-Mental State Examination (-1.4), and the presence of atypical clinical syndromes (9%) fell between those with hippocampal sparing and limbic predominant AD. Amygdala predominant Lewy bodies was present in 19% of cases and Lewy body disease in 24% of cases. More than half of the typical cases had limbic-predominant age-related TDP-43 encephalopathy neuropathologic change (54%) and more than a third had a moderate-to-severe score for cerebral amyloid angiopathy (36%).

The hippocampal sparing AD subtype was more common in men (64%), were more highly educated (median 16 years), and less likely to be an *APOE ε4* carrier (47%) than the other three subtypes. The hippocampal sparing subtype had a younger age at onset (median 64 years) and death (median 72 years), a more rapid annual decline on the Mini-Mental State Examination (-4.4) and was more likely to have an atypical clinical syndrome (35%) than the other subtypes. Hippocampal sparing AD cases had the highest frequency of moderate-to-severe cerebral amyloid angiopathy (41%) and lower frequencies of amygdala predominant Lewy bodies (16%), Lewy body disease (13%), and limbic-predominant age-related TDP-43 encephalopathy neuropathologic change (34%).

Braak IV cases were most comparable to those of the limbic predominant subtype because of the high frequency of *APOE ε4* allele carriers, older age at cognitive onset and death, and slower annual decline on the Mini-Mental State Examination. The low frequency of amygdala predominant Lewy-related pathology (5%) but high frequency of Lewy body disease (32%) differentiated Braak IV cases from the other subtypes. Table 2 compares the demographic and clinicopathologic characteristics of the Braak IV neuropathologic proxy for minimal atrophy to those of the minimal atrophy subtype defined by Ferreira *et al* (eResults).[10]

For our alternative strategy to identify a neuropathologic proxy for the minimal atrophy subtype, 201 typical AD cases with a high brain weight and thus less atrophy (i.e., brain weight >75th percentile, range: 1130–1540 grams) were compared with 455 typical AD cases with expected brain weight (i.e., brain weight within 25th–75th percentile, range: 920–1120 grams) and 203 typical AD cases with lower brain weight or more atrophy (brain weight <25th percentile,

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range: 560–900 grams). Table 3 details the demographics and clinicopathologic characteristics of typical AD cases stratified by brain weight. Results are illustrated in Figure 3. High brain weight cases were disproportionally male (80%, p<0.001) and had the most years of education (median 16 years, p=0.010) compared with middle and low brain weight cases. The *APOE ε4* allele frequency (62-66%) did not differ across groups (p=0.789). Clinically, cases with higher brain weight were older at symptom onset (median 72 years, p<0.001), had the shortest disease duration (median 7 years, p<0.001), and the highest final Mini-Mental State Examination score (median 16 points, p=0.002) compared with the other brain weight groups. Atypical clinical syndromes (6–11%) were infrequent in the typical AD group, (p=0.121). However, the group with higher brain weight was more frequently clinically diagnosed with Lewy body dementia (22%, p<0.001). The group with the highest brain weight had the lowest Braak tangle stage (stage V, p<0.001) and the lowest score for cerebrovascular pathology measured by Kalaria score (4 points, p=0.001). Similar to the Braak IV cases of the main strategy, the typical cases with a high brain weight showed the lowest frequency of amygdala predominant Lewy bodies (14%, p=0.005) but the highest frequency of Lewy body disease (31%, p=0.045). The presence of Lewy body disease is further specified in eTable 3. Limbic-predominant age-related TDP-43 encephalopathy neuropathologic change was frequent in the high brain weight group (41%) but less than that observed in the other brain weight groups (p=0.029). The high brain weight cases also showed an increased frequency of moderate-to-severe cerebral amyloid angiopathy (45%, p=0.002) in the visual cortex compared with the other cases. To contextualize the typical AD with high brain weight neuropathologic proxy, we compare demographics and clinicopathologic characteristics to the minimal atrophy subtype defined by Ferreira *et al.*[10] (Table 2, eResults). Given that men have a higher brain weight than women,[34] we further sub-stratified the results for each sex individually. These results are shown for women in eTable 4 and for men in eTable 5, and further elaborated upon in eResults.

Although we did not observe any Black or Hispanic decedents among Braak IV cases, we further substratified by self-reported ethnoracial status to evaluate overall proportion of AD subtypes (p=0.246, see eTable 6). Chi-square test did not find an observable difference in proportion of neuropathologically-defined AD subtypes with typical AD being consistently found to have the largest number of individuals. Application of the alternative strategy using brain weight bins did find a difference overall when comparing ethnoracial groups (p<0.001, see

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eTable 7). However, the frequency of minimal atrophy surrogate in high brain weight cases did not appear to differ substantially.

Discussion

Investigating neuropathologic proxies of minimal atrophy subtype revealed that these individuals are less likely to be college educated, more likely to have an older onset of cognitive symptoms, have a lower frequency of amygdala predominant Lewy bodies, and have a higher frequency of coexisting Lewy body disease.

To operationalize, we employed two strategies to classify "minimal atrophy" outside the context of MRI. Evaluation of Braak IV cases minimized cortical involvement of tangle pathology. Alternatively, we stratified typical AD cases by brain weight to recapitulate less atrophy in the context of advanced AD (i.e., Braak>IV). Braak IV individuals had a higher brain weight than individuals with other AD subtypes, and therefore, experienced minimal atrophy before death. Furthermore, Braak IV cases had the least years of education, consisted equally of men and women, and had—together with limbic predominant cases—the highest frequency of the *APOE ε4* carriers. Moreover, Braak IV cases exhibited a shorter disease duration, suggesting there was less time for atrophy to occur than in other subtypes. These demographic and clinical characteristics of the Braak IV cases align with those of the minimal atrophy subtype as described in the meta-analysis of Ferreira *et al.*[10] Others have suggested that minimal atrophy cases may have less cognitive reserve in the context of fewer years of education,[10] which may lead to a greater vulnerability to pathology or to the effects of neuropathology on cognitive function.[11, 27, 35]

The Braak IV cases differed from the minimal atrophy individuals of the meta-analysis in their median age at onset. Braak IV cases were 79 years at onset, whereas minimal atrophy individuals were 70 years at onset.[10] The age at onset in the meta-analysis study was two years older in the hippocampal sparing group and five years younger in the limbic predominant group compared to the corresponding groups in our study. This difference may be due to cohort-specific characteristics as the present study investigated neuropathologically diagnosed AD cohort. The meta-analysis included both antemortem and postmortem cohorts.[10] Antemortem cohorts are often prospectively acquired with recruitment age cutoffs and use neuroimaging to

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define AD subtypes without autopsy confirmation. Although a broad age range was examined, autopsy cohorts may be skewed by individuals willing to donate their brain tissue.[36] Although we did not observe Black or Hispanic decedents among Braak IV cases in the main strategy, we may be sampling individuals with more advanced pathology in our underrepresented groups. The alternative strategy did not detect disproportionate ethnoracial differences in the high brain weight group.

Our two neuropathologic proxies for minimal atrophy differed regarding some observations of coexisting pathologies. Braak IV cases had a similar frequency of cerebrovascular disease and limbic-predominant age-related TDP-43 encephalopathy neuropathologic change, but less moderate-to-severe cerebral amyloid angiopathy than the other defined subtypes. In contrast, typical AD cases (Braak >IV) with a high brain weight had less cerebrovascular disease and limbic-predominant age-related TDP-43 encephalopathy neuropathologic change and were more likely to have moderate-to-severe cerebral amyloid angiopathy compared to cases with middle and low brain weight. Interestingly, both strategies showed lower scores for Braak tangle stage and Thal amyloid phase, lower frequency of amygdala predominant Lewy bodies but increased frequency of Lewy body disease for minimal atrophy proxies. Both minimal atrophy proxies showed substantial cognitive decline indicated by the 16 points on their final Mini-Mental State Examination, much lower than the dementia cutoff of 24 points.[37] Unlike amygdala predominant Lewy bodies, the presence of Lewy body disease correlates well with cognitive decline.[30, 38] However, Lewy body disease pathology is not associated with cortical atrophy.[13, 39] Therefore, the addition of Lewy body disease to the AD pathology may partly explain the observed cognitive decline along with the minimal atrophy subtype, which is supported by a previous study that found that Lewy body dementia was more frequent in the minimal atrophy group.[40] The coexistence of cerebrovascular disease, limbic-predominant age-related TDP-43 encephalopathy neuropathologic change, or cerebral amyloid angiopathy may additionally contribute to cognitive decline.[41, 42] The individual effect of the aforementioned coexisting pathologies on cognition may be relatively small.[41] However, the combinatorial effect of cerebrovascular disease, limbic-predominant age-related TDP-43 encephalopathy neuropathologic change, and cerebral amyloid angiopathy, in addition to the Lewy body disease and the AD neuropathologic change on cognitive decline, is likely to be synergistic rather than additive.[43, 44]

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The data on which the minimal atrophy subtype is defined was mostly derived from the AD Neuroimaging Initiative (ADNI).[10, 45] By design, the ADNI cohort consists mainly of cases with a typical phenotype and only a few with extreme phenotypes such as hippocampal sparing AD. Therefore, to facilitate comparisons, we employed an alternative strategy to identify a neuropathologic proxy for minimal atrophy by stratifying typical AD cases based on brain weight. The group of typical cases with a relatively high brain weight represented the minimal atrophy proxy. Although typical cases with a high brain weight differed in demographic and clinical characteristics from Braak IV and minimal atrophy cases from the meta-analysis by Ferreira et al.,[10] the neuropathologic proxy for minimal atrophy obtained by the alternative approach demonstrated that Lewy body disease distinguishes minimal atrophy proxy from other cases. The alternative strategy is, in our eyes, less optimal than our main strategy as brain weight is affected by sex. Although the exact brain weights for each sex differ over the years, the average brain weight (±1200 grams) of women is consistently lower than that of men (±1350 grams).[34, 46, 47] Our observation that the typical cases with a higher brain weight consisted of 80% men was thus not a surprise. To investigate if the increased presence of Lewy body disease observed in the high brain weight group was sex specific, we sub-stratified the analysis for women and men. We observed that a clinical diagnosis of Lewy body dementia was more common in men with typical AD and a high brain weight than men with other brain weights. Although not significant when assessed for men and women separately, the high brain weight groups showed lower frequency of amygdala predominant Lewy bodies but increased frequency of Lewy body disease. Even if the ideal approach for identifying a neuropathologic proxy for the minimal atrophy subtype lies in the middle of our chosen strategies, coexisting Lewy body disease seems to be a probable factor for the cognitive decline in minimal atrophy cases.

It is important to note that the minimal atrophy designation is based upon neurodegeneration as assessed by MRI,[10] whereas the neuropathologically-defined subtypes are based upon the relative corticolimbic tangle distribution in the hippocampus and association cortices.[5] Although neurodegeneration and tangle burden are tightly correlated,[48] these two factors are not the same. Recognized limitations thus exist in implementing a neuropathologic approach to investigate findings from neuroimaging studies. A strength of the current study is the cohort size of the neuropathologic proxy for minimal atrophy (n=37 for Braak IV and n=201 for typical AD with high brain weight). However, the current study is limited to the evaluation of

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autopsied individuals that lacked antemortem MRI; thus, we cannot be sure that the neuropathologic proxies defined in the current study truly reflect the neuroimaging-defined minimal atrophy subtype. A second limitation is that the weight of fixed hemispheres was doubled to achieve total brain weight. This approach does not account for the asymmetrically affected brains that can be observed in atypical clinical syndromes,[26-28] which may result in inaccurate brain weight estimations in those groups with high presence of atypical clinical syndromes.

In conclusion, our data suggest that other proteinopathies that are less associated with cortical atrophy (e.g., Lewy body disease) may explain the cognitive decline in minimal atrophy cases. Minimal atrophy individuals were suggested as a therapeutic target to represent individuals early in the disease course. However, our findings warrant caution in that approach without recognizing the underlying contributing neuropathologies.

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Tables

Table 1. Demographics and clinicopathologic characteristics of Braak IV Alzheimer's disease cases compared to those of operationally defined Alzheimer's disease neuropathologic subtypes.

Characteristics	Braak IV (n=37)	Alzheimer's disease subtypes			p-value
		Limbic predominant (n=174)	Typical (n=986)	Hippocampal sparing (n=187)	
Demographics					
Women, %	17/37 (46%)	117/174 (67%)*	539/984 (55%)	67/187 (36%)	<0.001
Education, years	12 (12,16)	14 (12,16)	14 (12,16)	16 (12,17)*	0.002
APOE ε4^{+}, %	18/24 (75%)	90/122 (74%)	465/726 (64%)	65/139 (47%)*	<0.001
Clinical findings					
Age at onset, years	79 (75,82)	78 (72,81)	71 (64,77)***	64 (56,71)***	<0.001
Disease duration, years	8 (6,9)	9 (7,12)*	9 (6,12)	8 (6,10)	0.001
Mini-Mental State Examination					
Time final test to death, years	1.6 (2.1,0.8)	1.2 (2.1,0.6)	1.6 (2.3,1.0)	1.9 (2.4,1.5)*	0.052
Final score, points	16 (11,22)	18 (8,21)	13 (7,20)	8 (5,16)*	0.015
Annual decline, points	-0.6 (-0.8,0.2)	-1.2 (-2.5,-0.5)	-1.4 (-3.4,-0.2)	-4.4 (-6.1,-2.8)**	<0.001
Atypical clinical syndromes, %	0/29 (0%)	2/148 (1%)	79/842 (9%)	60/168 (35%)***	<0.001
Lewy body dementia, %	5/29 (17%)	16/148 (11%)	113/842 (13%)	16/168 (10%)	0.378
Neuropathology					
Age at death, years	85 (83,90)	86 (82,90)	81 (75,86)***	72 (65,80)***	<0.001
Brain weight, grams	1140 (1060,1210)	1035 (940,1120)***	1020 (920,1120)***	1040 (960,1140)**	<0.001
Braak tangle stage (0–VI)	IV (IV,IV)	VI (V,VI)***	VI (V,VI)***	VI (V,VI)***	<0.001
Thal amyloid phase (0–5)	4 (3,5)	5 (5,5)***	5 (5,5)***	5 (5,5)***	<0.001
Kalaria CVD score (0–10)	4 (2,6)	4 (2,7)	4 (2,6)	4 (2,5)	0.054
Lewy-related pathology					
Incidental, %	1/37 (3%)	2/174 (1%)	3/986 (0.3%)	2/187 (1%)	0.062
Amygdala predominant, %	2/37 (5%)	45/174 (26%)**	191/986 (19%)*	31/187 (17%)	0.013
Lewy body disease, %	12/37 (32%)	39/174 (22%)	241/986 (24%)	25/187 (13%)**	0.004
LATE-NC, %	14/30 (47%)	22/39 (56%)	144/265 (54%)	25/73 (34%)	0.021
CAA moderate-to-severe, %	8/37 (22%)	49/152 (32%)	310/863 (36%)	63/153 (41%)	0.117

The Braak IV group represents the minimal atrophy proxy using the main strategy. Values indicate median and interquartile ranges, or percentages. Kruskal-Wallis test with post-hoc Wilcoxon rank sum test used for continuous measures and Fisher's exact test with post-hoc Fisher's exact test for discrete variables. * $p<0.05$, ** $p<0.01$, and *** $p<0.001$ for post-hoc pairwise comparisons using Braak IV as the reference group. Abbreviations: CAA=cerebral amyloid angiopathy; CVD=cerebrovascular disease; LATE-NC=limbic-predominant age-related TDP-43 encephalopathy neuropathologic change; mm=millimeter.

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Table 2. Comparison of demographic and clinicopathologic characteristics between the Braak IV, typical Alzheimer's disease with high brain weight, and minimal atrophy subtype as reported in Ferreira *et al*.[10]

Characteristics	Main strategy	Alternative strategy	Meta-analysis
	Braak IV (n=37)	**Typical w/ high brain weight (>75th; 1130 – 1540 grams)** (n=201)	**Minimal atrophy**
Demographics			
Women, %	≈ 46%	↓ 20%	≈ 53%
Education, years	↓ 12	↑ 16	↓ 12
Clinical findings			
APOE ε4^{+}, %	↑ 75%	≈ 62%	≈ 66%
Age at onset, years	↑ 79	↑ 72	↓ 70
Disease duration, years	≈ 8	↓ 7	---
Mini-Mental State Examination			
Time final test to death, years	≈ 1.6	≈ 1.4	---
Final score, points	↑ 16	↑ 16	↑ 23.8
Annual decline, points/year	↓ -0.6	≈ -2.1	---
Atypical clinical syndromes, %	↓ 0%	≈ 6%	---
Lewy body dementia, %	↑ 17%	↑ 22%	---
Neuropathology			
Age at death, years	↑ 85	≈ 80	---
Brain weight, grams	↑ 1140	↑ 1220	---
Braak tangle stage (0-VI)	↓ IV	↓ V	---
Thal amyloid phase (0-5)	↓ 4	↓ 5	---
Kalaria CVD score (0-10)	≈ 4	↓ 4	---
Lewy-related pathology			---
Incidental, %	≈ 3%	≈ 0%	---
Amygdala predominant, %	↓ 5%	↓ 14%	---
Lewy body disease, %	↑ 32%	↑ 31%	---
LATE-NC, %	≈ 47%	↓ 41%	---
CAA moderate-to-severe, %	≈ 22%	↑ 45%	---

The data is reported in medians. Values for Braak IV are compared to the neuropathologic subtypes of limbic predominant, typical, and hippocampal sparing Alzheimer's disease (Table 1), for typical with high brain weight to typical with middle and lower brain weight (Table 3), and for minimal atrophy to the other subtypes from the Ferreira meta-analysis.[10] ↑ indicate increased value; ↓ decreased value; ≈ similar value; --- not assessed. Abbreviations: CAA=cerebral amyloid angiopathy; CVD=cerebrovascular disease; LATE-NC=limbic-predominant age-related TDP-43 encephalopathy neuropathologic change; w/=with.

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Table 3. Demographics and clinicopathologic characteristics of operationally defined typical Alzheimer's disease subtypes stratified by brain weight.

Characteristics	High brain weight (>75th; 1130 – 1540 grams) (n=201)	Middle brain weight (25th-75th; 920 – 1120 grams) (n=455)	Low brain weight (<25th; 560 – 900 grams) (n=203)	p-value
Demographics				
Women, %	40/201 (20%)	262/455 (58%)***	174/203 (86%)***	<0.001
Education, years	16 (12,16)	14 (12,16)	12 (12,16)**	0.010
APOE ε4^{+}, %	112/180 (62%)	238/372 (64%)	109/166 (66%)	0.789
Clinical findings				
Age at onset, years	72 (67,78)	72 (66,77)	68 (60,74)***	<0.001
Disease duration, years	7 (5,10)	9 (7,12)***	12 (9,15)***	<0.001
Mini-Mental State Examination				
Time final test to death, years	1.4 (1.9,0.7)	1.8 (2.3,1.1)*	1.9 (2.5,1.4)	0.019
Final score, points	16 (10,20)	12 (6,18)*	8 (2,11)**	0.002
Annual decline, points/year	-2.1 (-4.0,-0.6)	-1.3 (-2.4,-0.2)*	-2.4 (-3.9,-0.1)	0.040
Atypical clinical syndromes, %	11/194 (6%)	48/445 (11%)	20/203 (10%)	0.114
Lewy body dementia, %	42/194 (22%)	57/445 (13%)**	14/203 (7%)***	<0.001
Neuropathology				
Age at death, years	80 (75,85)	81 (76,86)	81 (74,87)	0.091
Brain weight, grams	1220 (1160,1260)	1020 (960,1080)***	840 (800,880)***	<0.001
Braak tangle stage (0-VI)	V (V,VI)	VI (V,VI)***	VI (VI,VI)***	<0.001
Thal amyloid phase (0-5)	5 (5,5)	5 (5,5)*	5 (5,5)***	<0.001
Kalaria CVD score (0-10)	4 (2,5)	4 (2,6)	5 (4,6)***	0.001
Lewy-related pathology				
Incidental, %	0/201 (0%)	2/455 (0.4%)	0/203 (0%)	1.000
Amygdala predominant, %	28/201 (14%)	104/455 (23%)**	54/203 (27%)**	0.005
Lewy body disease, %	62/201 (31%)	99/455 (22%)*	53/203 (26%)	0.045
LATE-NC, %	26/64 (41%)	80/141 (57%)*	38/60 (63%)*	0.029
CAA moderate-to-severe, %	83/183 (45%)	134/390 (34%)*	46/166 (28%)**	0.002

The high brain weight group represents the minimal atrophy proxy using the alternative strategy. Values indicate medians and interquartile ranges, or percentages. Kruskal-Wallis test with post-hoc Wilcoxon rank sum test used for continuous measures and Fisher's exact test with post-hoc Fisher's exact test for discrete variables. * $p<0.05$, ** $p<0.01$, and *** $p<0.001$ for post-hoc pairwise comparisons using high brain weight as the reference group. Abbreviations: CAA=cerebral amyloid angiopathy; CVD=cerebrovascular disease; LATE-NC=limbic-predominant age-related TDP-43 encephalopathy neuropathologic change; mm=millimeter.

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Figure legends

Figure 1. Cohort breakdown for both strategies applied to identify a neuropathologic proxy for the "minimal atrophy" Alzheimer's disease subtype (dotted line). For our main strategy, we selected cases with Braak tangle stage IV as the minimal atrophy proxy and compared these to the pre-existent neuropathologic subtypes of limbic predominant, typical, and hippocampal sparing Alzheimer's disease. For our alternative strategy, typical Alzheimer's disease cases were further stratified based on brain weight. Typical cases with a relatively high brain weight (>75th percentile) were assigned as the minimal atrophy proxy and compared to the other typical Alzheimer's disease groups with middle (25th–75th percentile) and low brain weight (<25th percentile). Abbreviations: Braak IV= cases with Braak tangle stage IV; n=number; w/o=without.

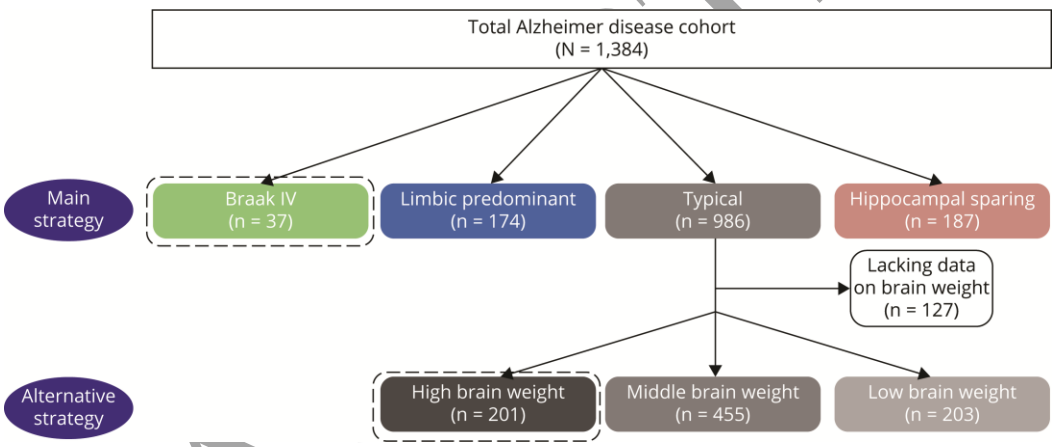

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Figure 2. Demographic, clinical, genetic, and neuropathologic features of Braak IV and the neuropathologically-defined Alzheimer's disease subtypes. Alzheimer's disease cases with a Braak tangle stage of IV (Braak IV) represent the neuropathologic proxy for minimal atrophy (dotted line). They are compared to limbic predominant, typical, and hippocampal sparing Alzheimer's disease cases. Brain illustrations visualize the corticolimbic patterns of tangle burden, with dark blue indicating high tangle burden and yellow indicating low tangle burden. Please note that no specific numbers were provided for visual purposes for the categories 'age at onset' and 'syndrome.' The amygdala predominant Lewy bodies category refers to Lewy-related pathology predominantly observed in the amygdala. The CAA category refers to a moderate-to-severe score for CAA on thioflavin-S-stained sections of the visual cortex. Abbreviations: ALB=amygdala predominant Lewy bodies; CAA=cerebral amyloid angiopathy; LATE-NC=limbic-predominant age-related TDP-43 encephalopathy neuropathologic change; LBD=Lewy body disease.

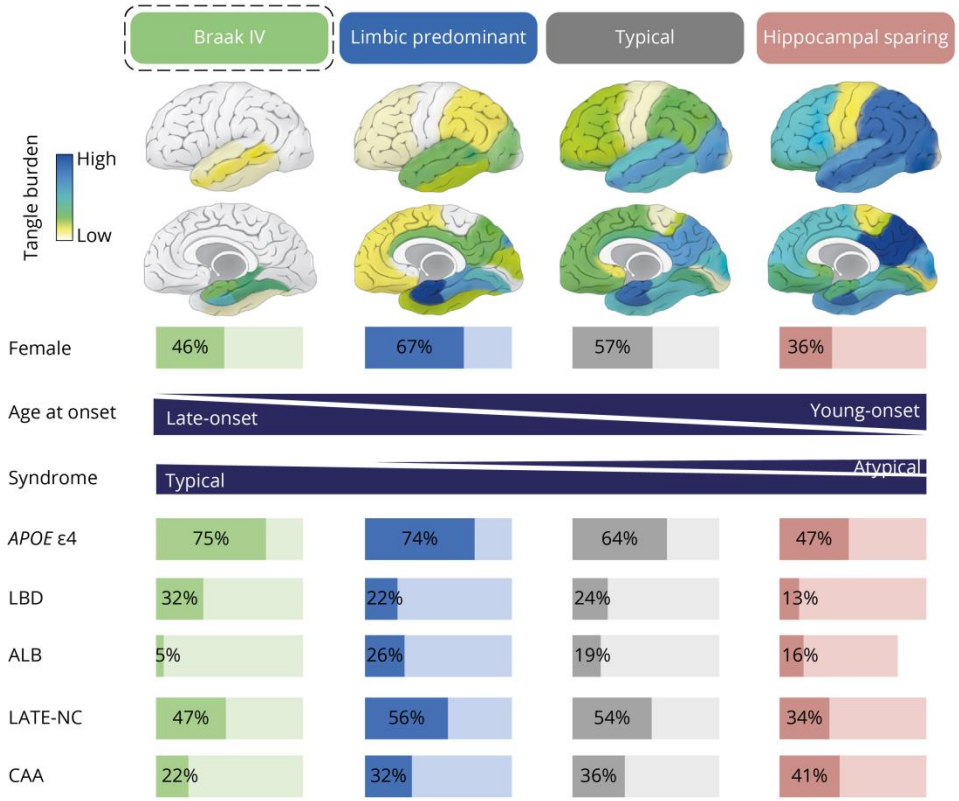

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Figure 3. Demographic, clinical, genetic, and neuropathologic features of the alternative strategy to investigate a proxy for Alzheimer's disease minimal atrophy. The typical Alzheimer's disease subtype was stratified based on brain weight. Cases with a high brain weight (i.e., >75th percentile) were designated the minimal atrophy proxy and compared with cases that had a middle (i.e., 25th–75th percentile) and a low brain weight (i.e., <25th percentile). Brain illustration visualizes the corticolimbic patterns of tangle burden, with dark blue indicating high tangle burden and yellow indicating low burden. Please note that no specific numbers were provided for the categories 'age at onset' and 'syndrome' for visual purposes. The amygdala predominant Lewy bodies category refers to Lewy-related pathology predominantly observed in the amygdala. The CAA category refers to a moderate-severe score for CAA on thioflavin-S stained sections of the visual cortex. Abbreviations: AD=Alzheimer's disease; ALB=amygdala predominant Lewy bodies; CAA=cerebral amyloid angiopathy; LATE-NC=limbic-predominant age-related TDP-43 encephalopathy neuropathologic change; LBD=Lewy body disease.

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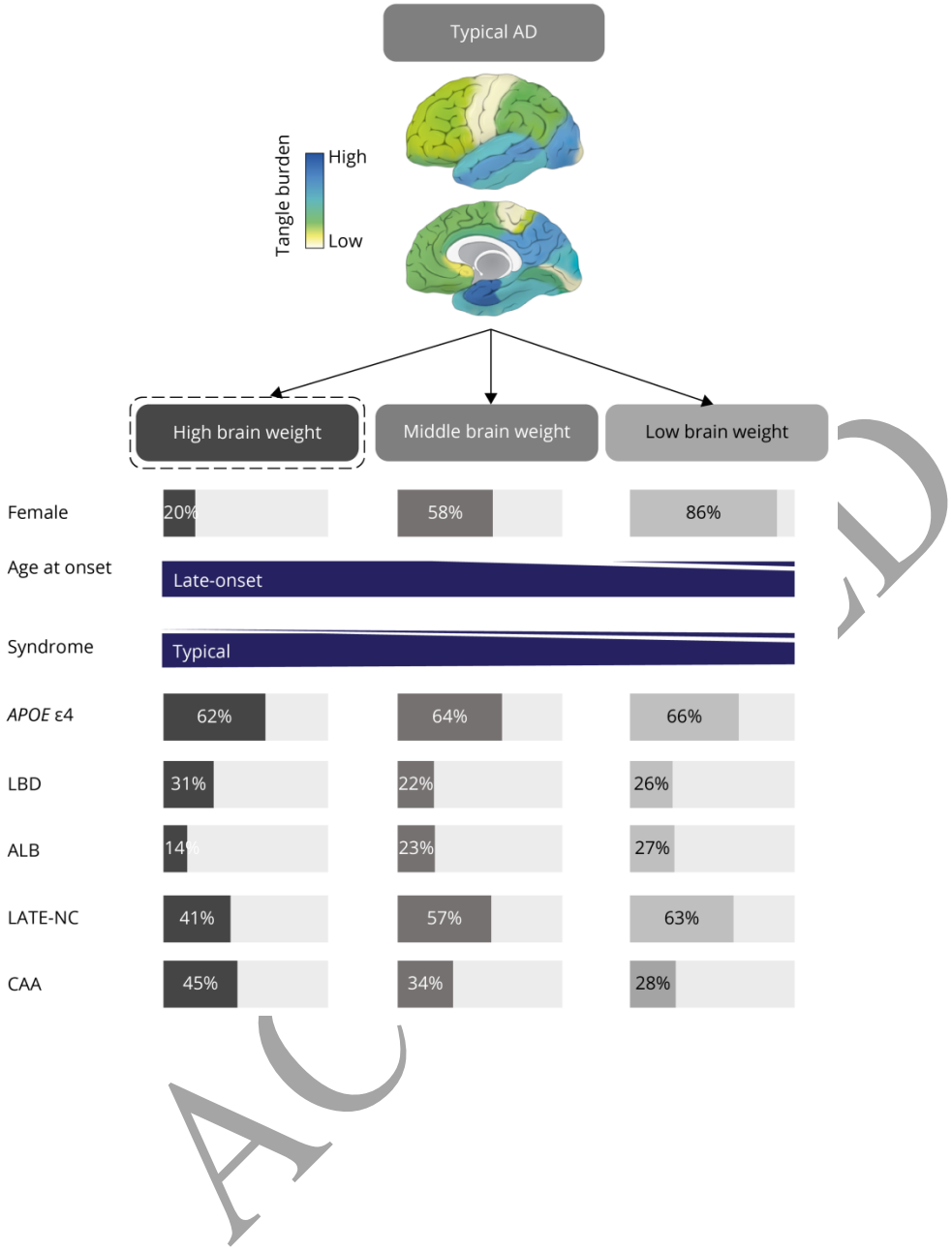

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Retrospective Evaluation of Neuropathologic Proxies of the Minimal Atrophy Subtype Compared to Corticolimbic Alzheimer Disease Subtypes

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