Comparing the Pathology, Clinical, and Demographic Characteristics of Younger and Older-Onset Multiple Sclerosis

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Objective: Older people with multiple sclerosis (MS) have a less active radiological and clinical presentation, but many still attain significant levels of disability; but what drives worsening disability in this group?
Methods: We used data from the UK MS Register to characterize demographics and clinical features of late-onset multiple sclerosis (LOMS; symptom onset at ≥50 years), compared with adult-onset MS (AOMS; onset 18–49 years). We performed a pathology study of a separate MS cohort with a later onset (n = 18, mean age of onset 54 years) versus AOMS (n = 23, mean age of onset 29 years).
Results: In the Register cohort, there were 1,608 (9.4%) with LOMS. When compared with AOMS, there was a lower proportion of women, a higher proportion of primary progressive MS, a higher level of disability at diagnosis (median MS impact scale 36.7 vs. 28.3, $p < 0.001$), and a higher proportion of gait-related initial symptoms. People with LOMS were less likely to receive a high efficacy disease-modifying treatment and attained substantial disability sooner. Controlling for age of death and sex, neuron density in the thalamus and pons decreased with onset-age, whereas actively demyelinating lesions and compartmentalized inflammation was greatest in AOMS. Only neuron density, and not demyelination or the extent of compartmentalized inflammation, correlated with disability outcomes in older-onset MS patients.
Interpretation: The more progressive nature of older-onset MS is associated with significant neurodegeneration, but infrequent inflammatory demyelination. These findings have implications for the assessment and treatment of MS in older people.

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Introduction

Older age at multiple sclerosis (MS) onset is more often associated with a progressive presentation, male sex, fewer clinical and radiological indicators of disease activity, and a more rapid worsening, in comparison with younger onset MS.[1,2] Current immunomodulatory treatments are less effective in older groups.[3,4] Most people with MS experience their first symptoms in their third or fourth

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decade, and disease onset after the age of 50 years has been called late-onset MS (LOMS[5]). The bifurcation of MS into young- and old-onset is in part based on earlier diagnostic criteria that excluded a possible diagnosis of MS in those aged >50 years.[5,6] There is still uncertainty regarding the pathological characteristics of MS in older individuals, including LOMS, and a better understanding is needed given the increased recognition of MS in older groups, and the effects of age in determining MS outcome and treatment response.

An older age at MS onset is strongly associated with more rapid transition to the progressive phase and a shorter time to attainment of significant disability. Current age is an important determinant of worsening disability.[7,8] The incidence and prevalence of MS in older people has increased. For example, LOMS was fourfold more prevalent in women in 2009 than in 1959, whereas the highest proportion of new MS diagnoses in UK men now occurs in the ≥45 years age group.[9,10] Older-onset MS and people with LOMS are more likely to have progressive disease at onset and be more disabled at diagnosis.[5,11,12] In those older people with a relapse-onset, motor relapses, rather than sensory relapses or optic neuropathy, are more frequently reported, whereas full recovery following an attack is less likely.[5,13–17]

There is a lack of data on treating MS in older age groups; they may be less likely to receive and to adhere to treatment, and drug effectiveness is lower,[3,12] but more evidence is needed.[1,4,18] The more progressive, rather than acute inflammatory presentation in older people suggests differing balance of underlying pathological processes, which may require different management.

The early stages of MS pathology are associated with focal inflammation, active demyelination, and tissue remodelling.[19–23] Over the course of adult-onset MS (AOMS), the frequency of active inflammatory lesions decreases, whereas large, demyelinated areas of white and grey matter, chronic inflammation, and a compartmentalized immune response are more common.[20,24–26] Neurodegeneration is associated with age-related confounders, such as Alzheimer's disease and vascular pathology, in older cases of pathologically inactive MS.[27–29] There has been no study specifically designed to investigate the association between age of MS onset and later neuropathology, and little attention has been paid to LOMS.

To help us understand more about the effect of age on MS outcome, we: (i) provide a clinical and demographic description of LOMS, in comparison with AOMS; (ii) report treatment type and time to treatment; (iii) stratify patients into age brackets at onset to report how clinical and demographic details change with aging, and (iv) provide a comparative pathological description of older-onset MS. By combining longitudinal information from a large patient-reported register with quantitative neuropathology, we provide a detailed description of MS in older people, highlighting similarities and differences between later-onset MS and AOMS with regard to MS in the aging brain.

Methods

Data Source

The UK MS Register (UKMSR) is an extensive databank that captures real-world information from people living with MS across the UK. These data are collected directly from people with MS via the UKMSR website (portal data) and from NHS Specialist Treatment centres (clinical data). The UKMSR has research ethics approval from South West Central Bristol Research Ethics Committee initially as 16/SW/0194, currently 21/SW/0085. We used UKMSR Web portal data to characterize demographics and clinical features of LOMS and AOMS. Portal users are asked to complete patient-reported outcome measures at regular 6-monthly intervals. UKMSR clinical data were used to obtain disease-modifying therapy (DMT) information, and to verify self-reported onset and diagnosis dates.

Population and Outcomes

Data were downloaded from the UKMSR web portal on 17 March 2022 for individuals with a known onset date greater than age 18 years. We used the following clinical and portal data items: onset age; sex; MS type at diagnosis; initial treatment; time to treatment; first symptoms; and disability, assessed by the 20 physical questions in the Multiple Sclerosis Impact Scale (MSIS-29)[30] and by the 12-Item MS Walking Scale (MSWS-12).[31] For clinically linked participants, clinical DMT data were also collected. LOMS was defined as onset at age ≥50 years, and AOMS as onset of symptoms between 18 and 49 years. A separate analysis comparing groups with an onset age of <40, 40–49, 50–54, 55–59, and ≥60 years was then conducted to further explore patient onset age and the disease experience.

Survival analyses were conducted to estimate and compare the time to no longer being able to walk between LOMS and AOMS. Not being able to walk was defined as a minimum of 2 consecutive reports of answering "no" to the first question of the MSWS-12 "Are you able to walk unassisted in any capacity?". We created a cohort of MSWS-12 respondents, diagnosed after 2011 when the UKMSR began collecting data, who had answered a "streak" of questionnaires on the portal, ensuring no significant gaps in the data.[32] Only MSWS-12 data from the new UKMSR portal were used (August 2018 onwards).

Two underlying timescales were examined: time from disease onset and time from birth.

Post-Mortem Cohorts and Sampled Tissue Blocks

All MS samples were provided by the UK MS Tissue Bank (a registered research tissue bank; research ethics approval 18/WA/0238), Imperial College London, London, UK, with retrospectively determined clinical milestones and complete neuropathological summaries written by neurologists and neuropathologists with MS expertise. Populations in the UK MS Tissue Bank and the UKMSR are similar with significant overlap—13% of UK MS Tissue Bank donors are registered on the UKMSR. Samples of verified non-neurological disease controls were provided by the UK MS Tissue Bank and the Thomas Willis Oxford Brain Bank (research ethics approval 13/WA/0292). Sampled areas, neuroanatomically matched between cases irrespective of the presence or absence of macroscopically visible lesions, included coronal preparations of the superior frontal gyrus (sampled 1-cm rostral to the temporal pole), cingulate gyrus, thalamus occipital cortex (including the striate cortex), basal pons, cerebellum (sampled in the sagittal plain to include the white matter and dentate nucleus) and spinal cord (cervical, thoracic and lumber spinal cord). All blocks were formalin-fixed and paraffin-embedded and sectioned at 7 μm.

A total of 23 AOMS cases (15 women; mean age of onset 29 years; standard deviation [SD] 5.3 years; range 20–37 years) were selected without prior knowledge of the extent of MS-related neuropathology. Only cases with an age of first symptom onset between the age of 18 to 40 years with the full complement of brain regions of interest, and complete clinical and demographic data were included. The AOMS cohort was representative, in terms of sex distribution, MS type at onset, age at onset, and disease duration, of the wider UK MS Tissue Bank collection (Table S1).[33] A separate cohort of older-onset MS were identified (n = 18; 14 women; mean age of onset 54 years; SD 6.4 years; range 47–69 years; 7 cases with first symptom between the age of 47 and 49 years) that represented all the available cases of older-onset MS with preserved samples of brain blocks of interest in the UK MS Tissue Bank collection. A total of 13 of these cases had available spinal cord samples. Superior frontal gyrus, cingulate gyrus, and thalamus samples were available from 28 cases of non-neurological disease controls (mean age at death 64.5 years; SD 11.8 years; range 41–88 years; 8 women). Common age-related pathological confounders identified at post-mortem were categorized as features of Alzheimer's disease (including neuronal neurofibrillary tau accumulation, amyloid-β positive extracellular plaques) or vascular pathology (including hypoxic injury, small vessel disease or atherosclerosis; see Table S1 for further details).

Immunohistochemistry and Tissue Characterization

Tissue sections were stained as standard with hematoxylin–eosin and luxol fast blue, and immunohistochemically stained with anti-HLA-DR (clone cr3/43; Dako, Glostrup, Denmark), anti-myelin oligodendrocyte glycoprotein (clone Y10, in house), and anti-HuC (mouse anti-HuC/HuD, clone 16A11; Invitrogen, Waltham, MA, USA) to allow the identification of tissue architecture, inflammation, and the quantification of demyelination and neuron density.

Immunohistochemistry was performed as described[34] by the authors with diaminobenzidine (Impact DAB; Vector Labs, Newmark, CA, USA) as the chromogen. In all instances, the relevant immunoglobulin G control or the absence of the secondary detection antibody yielded no signal. Whole slide scanned images were acquired at ×200 magnification with an Aperio AT2 slide scanner (Leica Biosystems, Nussloch, Germany) for analysis in QuPath (https://qupath.github.io/,[35]).

Quantifying Demyelination

We quantified the number of demyelinated lesions and relative extent (percent) of total demyelination from the 7 sampled blocks. The percentage of gray and white matter demyelination was additionally reported for brain cortical blocks. Only lesions of deep cerebellar white matter and/or the dentate nucleus were measured and not those affecting the cerebellar cortex. The basal pons, including the pontine nuclei, and major ascending and descending tracts, was annotated for analysis. We did not differentiate between gray and white matter lesions in the spinal cord, and lesion area was reported as a proportion of the mean total cross-sectional area of the spinal cord.

Assessing the Relative Extent of Compartmentalized Inflammation

Active and chronic active (smouldering or slowly expanding) lesions were identified based on the presence of demyelinated plaques (identified on consecutively stained luxol fast blue/human leukocyte antigen and anti-myelin oligodendrocyte glycoprotein sections) either confluent with human leukocyte antigen + microglia/macrophages containing myelin lipids (active) or bordered by a rim of myelin lipid + microglia/macrophages (chronic active); according to established criteria.[20,36] Chronic inactive lesions most often presented as sharply demarcated plaques characterized by the presence of human leukocyte antigen + microglia/ macrophages at the lesion border at densities indistinguishable to the surrounding normal

appearing tissue. The presence of one or more actively (active or chronic active) demyelinating lesion in the sampled blocks defined a case as harboring "active lesions." A combined measure of relative leptomeningeal and perivascular immune cell infiltration was reported by assessing the extent of Nissl-stained infiltrates of the intact cerebral leptomeninges, and perivascular spaces from a minimum of 6 sampled blocks per case according to previously described criteria.[34] The extent of leptomeningeal inflammation was scored semiquantitatively as: absent = 0; mild (1); moderate (2); or substantial (3), to represent the largest single infiltrate observed for that case.

Measuring Neuron Density

Automated cell counting of anti-HuC^+ neurons was performed using QuPath, as previously outlined.[37] The density of HuC^+ neurons was reported in the neocortex (two rectangular regions of interest >5 mm^2 extending from layer I–VI, placed midpoint either side of a cortical sulcus), the entire annotated thalamus and basal pons, the annotated dentate nucleus and the ventral spinal cord grey matter (defined by a virtual line from the central canal to the most lateral aspect of the spinal cord). Non-neurological disease control anti-HuC cell counts were captured from available blocks of superior frontal gyrus, cingulate gyrus, and thalamus using the same criteria.

Statistical Analysis

Data cleansing and analysis was conducted using the programming language R (version 4.1.3; R Core Team, Vienna, Austria) in the RStudio environment (version 2022.2.3.492; RStudio Team) and with GraphPad PRISM 10 (GraphPad Software, San Diego, CA, USA). Most data were non-normally distributed (D'Agostino–Pearson test) and non-parametric Mann–Whitney U test (2 group comparisons) and Kruskal–Wallis and Dunn's multiplicity adjusted post-tests (three or more groups) were used. χ^2-tests and Fisher's exact tests were used to assess independence between categorical variables. Spearman's rank correlation was used to identify interdependence of variables, and Spearman r and p values were reported. Separate linear regressions were performed for each variable to examine the relationship between age at onset (as a continuous variable) and each pathological outcome measure. Each regression model included age at death and sex as covariates to account for their potential influence, and Bonferroni correction was applied to address the issue of multiple testing (statistical significance of these models was determined using $\alpha = 0.002$ (0.05/24 tests). Kaplan–Meier and Cox regression modeling were used to assess the difference in rates to losing the ability to walk unassisted. Covariates considered were age at baseline, age at diagnosis, MS type at diagnosis, and sex.

Results

Demography and Clinical Characteristics of LOMS Compared with AOMS

The UKMSR study population consisted of 17,124 people with (pw) MS, of which 1,608 (9.4%) were LOMS (Table 1). When compared with AOMS, the LOMS group had a lower proportion of women (62.8% vs 75.4%, $p < 0.001$), a higher proportion of primary progressive MS (PPMS; 39.8% vs 9.5%, $p < 0.001$), and a lower proportion of relapsing–remitting MS (RRMS; 42.5% vs 76.2%, $p < 0.001$). LOMS were more likely to self-report gait-related initial symptoms (69.9% vs 49.8%, $p < 0.001$), and fewer visual (26.9% vs 46.4%, $p < 0.001$) and numbness (58.2% vs 71.2%, $p < 0.001$) symptoms. Level of disability at diagnosis was correspondingly worse in pwLOMS (median MSIS-29-Phys score 36.7 vs 28.3, $p < 0.001$). Time from onset to diagnosis was faster in the LOMS group (1.2 vs 1.9 years, $p < 0.001$).

Disease-Modifying Therapy in People with RRMS

Only participants with RRMS were included in any DMT analyses. Proportions of pwLOMS and pwAOMS reporting DMTs were the same (44.7% vs 44.3%, $p = 0.96$; Table 1). However, pwLOMS were less likely to be on a high efficacy DMT compared with pwAOMS (17.0% vs 24.6%, $p < 0.05$). Those with LOMS were found to begin treatment earlier (median [interquartile range], 0.7 [0.3–2.4] years compared with 2.1 [0.4–7.1] years, $p < 0.001$), but this may in part be influenced by drug availability, as the average LOMS year of diagnosis (2012) was later than the AOMS group (2006). There was no difference between the two groups in the number of DMTs taken (mean ± SD, 1.19 ± 0.48 LOMS vs 1.24 ± 0.54 AOMS, $p = 0.11$). Clinical DMT data were available for 1,899 participants with RRMS. There was a broad agreement between the clinical and patient reported data (Table 1). pwLOMS were just as likely to be on a treatment (55.5% compared with 55.8%, $p = 0.96$), but were less likely to be taking a high efficacy DMT compared with pwAOMS (15.0% vs 28.5%, $p < 0.05$).

Time to Substantial Disability

Of the 1,361 participants who had a streak of MSWS-12 data, 1,067 were AOMS and 294 were LOMS. When using time from onset as the underlying timescale, walking time (defined as time from onset to reporting a minimum of 2 consecutive reports of no longer being able to walk) was significantly shorter in the LOMS group ($p < 0.001$, log-rank test). The median survival time in the LOMS group was 17.77 years (95% CI 16.54–NA), and was 40.75 years in the AOMS group (95% CI 35.13–NA; Fig. 1). A Cox regression model adjusting for MS type and

TABLE 1. Demographics and Clinical Characteristics of People With Late-Onset Multiple Sclerosis and Adult-Onset Multiple Sclerosis

Population parameter	Total	AOMS (<50)	LOMS (50+)	*p*
n (%)	17,124 (100.0)	15,516 (90.6)	1,608 (9.4)	
Mean age at onset, yr (SD)	35.06 (10.1)	33.05 (8.2)	54.50 (4.3)	<0.001
Sex (F), *n* (%)	12,698 (74.2)	11,689 (75.4)	1,009 (62.8)	<0.001
MS type at diagnosis (RR/SP/PP/unknown), *n* (%)	12,483 (73.1) /1,040 (6.1)/2,105 (12.3)/ 1,454 (8.5)	11,801 (76.2)/914 (5.9)/1,466 (9.5)/1,297 (8.4)	682 (42.5)/126 (7.9)/639 (39.8)/157 (9.8)	<0.001
First symptoms (walking/vision/numbness), *n* (%)	8,847 (51.7)/7,634 (44.6)/11,977 (69.9)	7,723 (49.8)/7,202 (46.4)/11,041 (71.2)	1,124 (69.9)/432 (26.9)/936 (58.2)	<0.001, <0.001, <0.001
Median time to diagnosis, yr (IQR)	1.8 (0.6–5.5)	1.9 (0.6–6.0)	1.2 (0.5–2.9)	<0.001
Median MSIS-29-Phys at diagnosis, *n* (IQR)	3,401, 28.3 (11.7–51.7)	2,934, 28.3 (11.6–50.0)	467, 36.7 (18.3–55.8)	<0.001
Portal DMT data in pwRRMS				
Reported taking a DMT *n* (%)/Initial treatment, highly active *n* (%)	5,538 (44.4)/1,337 (24.1)	5,233 (44.3)/1,258 (24.6)	305 (44.7)/52 (17.0)	0.96, <0.05
Median time to DMT, yr (IQR)	1.9 (0.4–6.9)	2.1 (0.4–7.1)	0.7 (0.3–2.4)	<0.001
No. DMTs taken, mean (SD)	1.24 (0.54)	1.24 (0.54)	1.19 (0.48)	0.11
Clinical DMT data in pwRRMS				
On DMT *n* (%)/current treatment, high efficacy/moderate efficacy/unknown, *n* (%)	843 (55.7)/231 (27.5)/608 (72.4)/<5 (0.1)	783 (55.8)/222 (28.5)/557 (71.4)/ <5 (0.1)	60 (55.5)/9 (15.0)/51 (85.0)/0 (0.0)	0.96, <0.05

Level of disability at diagnosis is measured using the MSIS-29-Phys. DMT reporting amongst pwRRMS on the MS Register portal shows type of initial treatment (high efficacy vs moderate efficacy), time from onset to first DMT, total number of DMTs reported. Clinically reported DMT data show number currently on active DMT and type of initial DMT. Unknown is due to blinded clinical trial. Significant differences were determined using the χ^2-test, *t* test or Mann–Whitney *U* test.

DMT = disease-modifying therapy; PP = primary progressive; pwRRMS = people with relapsing–remitting multiple sclerosis; RR = relapsing–remitting; SP = secondary progressive.

sex (age at baseline was not significant in the univariate analysis and, therefore, not included in the multivariate analysis) showed that from disease onset, the risk of losing walking ability was 2.25-fold higher in the LOMS group (HR 2.25, 95% CI 1.32–3.82, $p < 0.001$; Table 3).

However, when considering age as the underlying timescale (time from birth), walking time was found to be significantly shorter in the AOMS group (median age at not-walking 70.80 years, 95% CI 69.20–NA vs 77.18 years, 95% CI 77.18–NA, $p < 0.001$, log-rank test; (Fig. 1). A Cox regression analysis adjusting for age at baseline and age at diagnosis (other covariates were not significant in the univariate analysis) showed that from birth, pwLOMS had a 49% reduced risk of losing walking ability (HR 0.51, 95% CI 0.28–0.91, $p < 0.001$; Table 3), compared with AOMS.

Age at Onset Epochs

We then separated onset age into 5 groups (<40, 40–49, 50–54, 55–59, ≥60 years; Fig. 2; Table 2). This revealed a shift toward more men ($p < 0.001$), a shift in MS type with more PPMS diagnoses and fewer RRMS ($p < 0.001$), and a shift in initial symptoms toward more walking symptoms, and fewer visual and sensory symptoms with

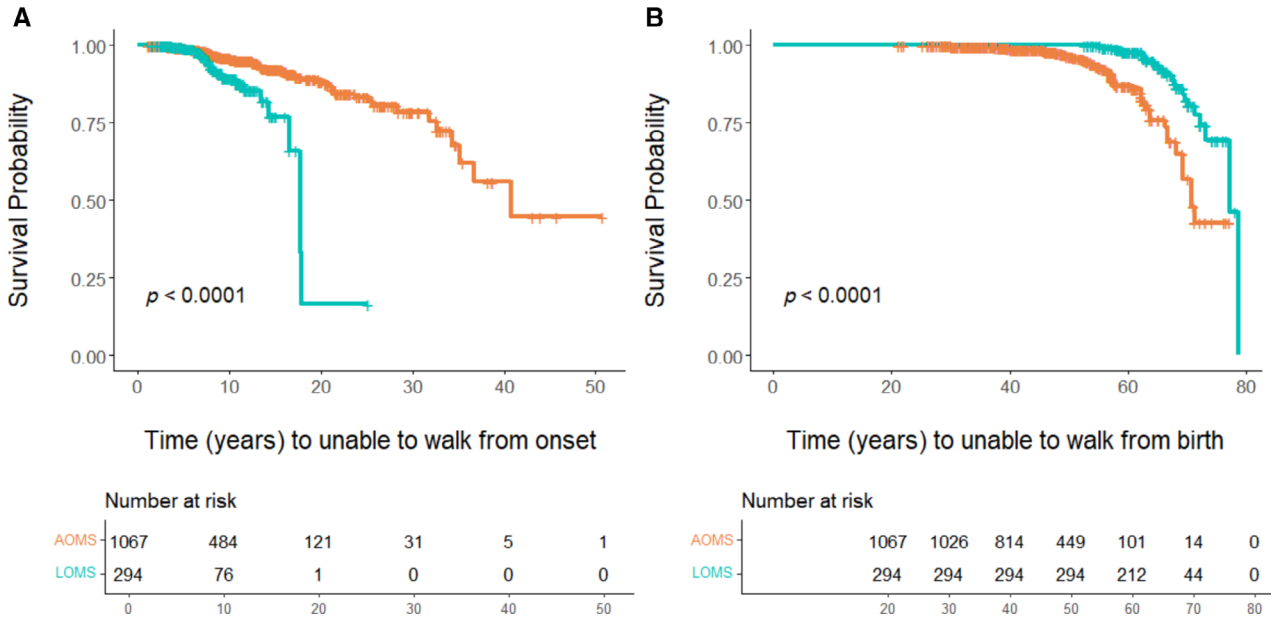

Figure 1: In comparison to the adult-onset MS (AOMS) group, the late-onset multiple sclerosis (LOMS) group attain significant disability sooner from onset but at an older age. (A) Using time from onset as the underlying timescale, walking time (time from onset to losing walking ability) was significantly shorter in the LOMS group ($p < 0.001$, log-rank test). (B) Using age as the underlying timescale (time from birth to losing walking ability), walking time was significantly shorter in the AOMS group ($p < 0.001$, log-rank test). [Color figure can be viewed at www.annalsofneurology.org]

an older onset age ($p < 0.001$). This continuum was also present in the MSIS-29-Phys at diagnosis, rising with age of onset (from 26.7 in the <40 years age group up to 38.3 in the ≥60 years age group, $p < 0.001$). Time from diagnosis to initial DMT was reduced with an increased onset age ($p < 0.001$), but there was no significant difference in initial treatments between groups.

Demyelination Affecting the White Matter was Greatest in AOMS

Cases with an old age at MS onset (see Table S1) more frequently presented with confounding age-related neurodegenerative or vascular pathologies at post-mortem in comparison with AOMS (comparing the frequency of coexistent pathology between young and old-onset MS; $p = 0.0087$ Fisher's exact test). Age-related confounding pathology was reported in 18 of 28 control cases. The frequency of age-related confounders was not different between controls and old-onset MS (10/16; $p = 0.758$), but were more frequently observed in controls in comparison with younger MS (5/23 cases with coexistent pathology; $p = 0.0043$, Fisher's exact test).

The extent of demyelination averaged across all sampled blocks (white and gray matter areas combined) was greater in younger-onset MS (12.3% vs 7.7%; $p = 0.037$; Fig. 3). Specifically, the extent of demyelination was greater in the total cingulate gyrus and spinal cord of AOMS compared with old-onset MS (Fig. 3A–E). Spinal lesions were observed in 21 of 23 AOMS and 9/11 older-MS onset cords, accounting for 15.8% and 5.0% of the measured spinal cord cross-sectional area, respectively ($p = 0.009$; Fig. 3E). Cortical grey matter lesions were frequently observed in both groups and represented a greater proportion of the total lesion load in older-onset MS (46/80 lesions in late-onset MS and 90/276 AOMS lesions categorized as cortical gray matter lesions of all lesions; $p < 0.0001$, Fisher's exact test). The relative area of total cortical grey matter lesions was not different between groups (comparing percentage of cortical gray matter lesion area of total measured cortical grey matter per block; Fig. 3F). The extent of white matter demyelination of subcortical white matter was different in those same cingulate (11.6% vs 0.8%; $p = 0.0013$) and occipital blocks (12.3% vs 4.0%; $p = 0.0490$; Fig. 3G), and more AOMS blocks contained subcortical white matter lesions (36/54 vs 12/54 sampled blocks with ≥1 white mater lesion; $p = 0.0047$, Fisher's exact test).

An Older Age at Onset is Characterized by Fewer Active Lesions and a Lower Relative Extent of Compartmentalized Inflammation in Comparison to Younger-Onset MS

Cases of older-onset MS were less likely to harbor ≥1 actively demyelinating lesion (classified as active or chronic active; HR 0.09, 95% CI 0.02–0.39, $p = 0.001$; Fig. 3B, H), and presented with a lower relative extent of leptomeningeal and perivascular inflammation (median

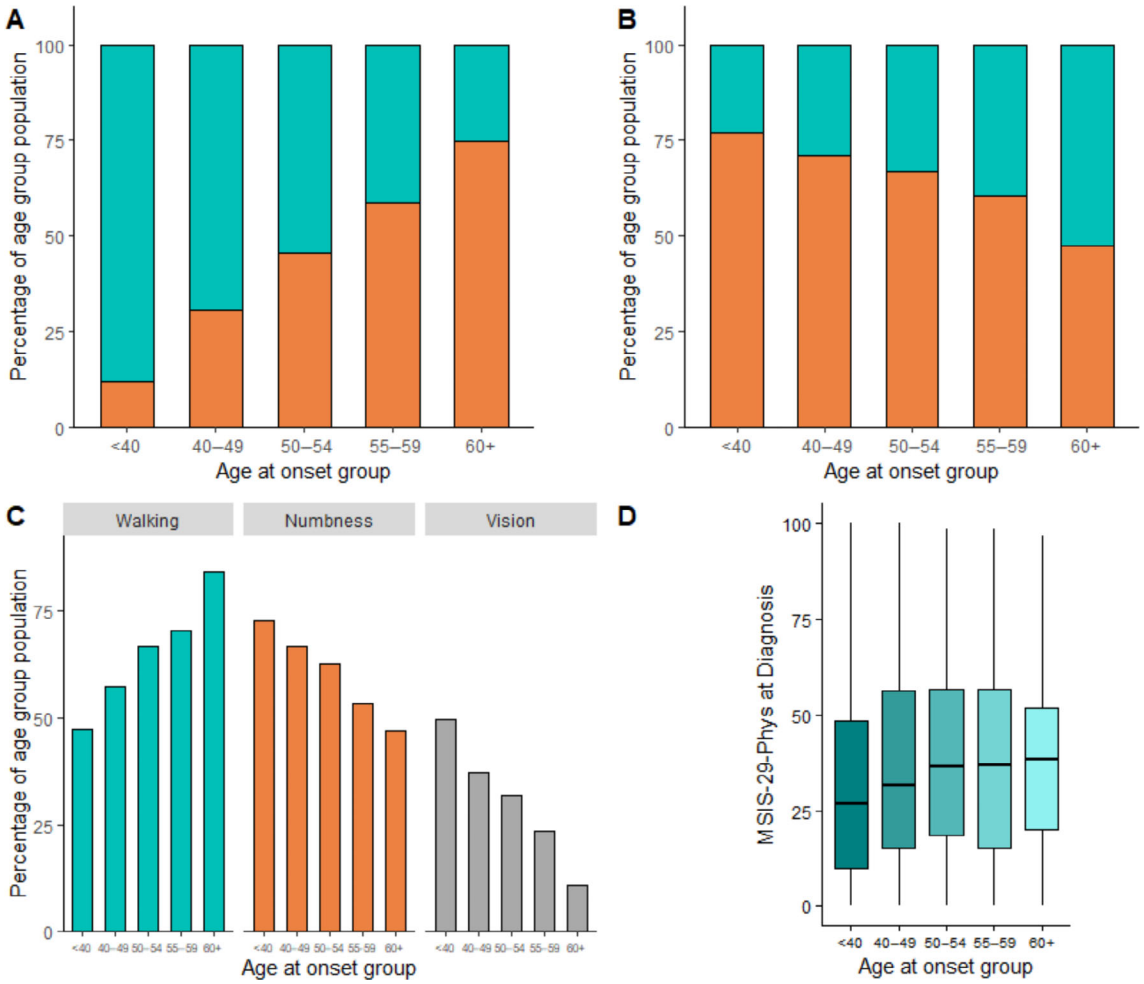

Figure 2: The clinical characteristics of multiple sclerosis (MS) defined by age of onset epochs. (A) Percentage of population per age group with either a relapsing–remitting or a progressive diagnosis, showing a shift in MS type at diagnosis towards more progressive diagnoses with an older onset age (relapsing–remitting, upper; progressive, lower; $p < 0.001$). (B) Percentage of population per age group who are male or female showing an increase in number of males as age at onset increases (male, upper; female, lower; $p < 0.001$). (C) Percentage of population per age group reporting initial walking, numbness and vision symptoms. More people reported initial walking symptoms, and fewer people reported initial numbness and vision symptoms with increasing age at onset ($p < 0.001$ for all 3 comparisons). (D) Boxplots showing median normalized Multiple Sclerosis Impact Scale (MSIS-29-Phys) score at diagnosis. Average score increased with an increased age at onset ($p < 0.001$). Significant differences were determined using the χ^2-test or Kruskal–Wallis test. [Color figure can be viewed at www.annalsofneurology.org]

rating of 1 vs 2 for meningeal and perivascular infiltration, $p = 0.025$; Fig. 3C, I) in comparison with AOMS.

An Older Age at MS Onset is Associated With a Reduced Neuron Density That Correlates With Disability Outcomes

We quantified the density of HuC^+ neurons in the same AOMS and older-onset MS blocks (Fig. 4 and Tables 4 and 5). Neuron density in both AOMS and older-onset MS was significantly reduced compared with controls (Fig. S1, representing a 19.7%–54.7% reduction in neuron density, $p < 0.001$ for all comparisons). Although AOMS was associated with greater inflammation and white matter demyelination, neuron density in older-onset MS was unchanged (superior frontal, occipital gyri, dentate nucleus, pons, spinal cord) or reduced (cingulate, thalamus), in comparison with AOMS (Fig. 4A–D; equivalent to a 14.9% and 15.6% reduction in mean neuron density for cingulate and thalamus, respectively; $p < 0.05$ in both instances). We included 7 MS cases in the older-onset group with a disease onset between the ages of 47 and 49 years due to limited numbers of true LOMS autopsy cases. We did not note a difference in any of the pathological variables assessed between these cases and LOMS (n = 11, age of onset ≥50 years; Table S2).

When analyzing age at onset as a continuous variable, and adjusting for both age at death and sex, we found a significant negative effect of onset age on neuron density in the thalamus and pons (Table 5). For each 1-year increase in age at onset, neuron density decreased

TABLE 2. Comparison of Demographic and Clinical Characteristics and Disease-Modifying Therapies When Stratifying Age at Onset Into Further Epochs

Population parameter	Onset age (yr) <40	40–49	50–54	55–59	≥60	*p*
n (%)	11,616	3,900	962	444	202	
Mean age at onset, yr (SD)	29.4 (5.8)	43.9 (2.8)	51.7 (1.4)	56.6 (1.4)	63.2 (3.5)	<0.001
Sex (F), *n* (%)	8,921 (76.8)	2,768 (71.0)	644 (67.0)	269 (60.6)	96 (47.5)	<0.001
MS type at diagnosis (RR/SP/PP/unknown), *n* (%)	9,350 (80.5)/601 (5.2)/690 (5.9)/946 (8.1)	2,451 (62.8)/313 (8.0)/776 (19.9)/351 (9.0)	474 (49.3)/70 (7.3)/327 (34.0)/87 (9.0)	163 (36.7)/40 (9.0)/194 (43.7)/47 (10.6)	45 (22.3)/16 (7.9)/118 (58.4)/23 (11.4)	<0.001
First symptoms (walking/vision/numbness), *n* (%)	5,488 (47.2)/5,751 (49.5)/8,445 (72.7)	2,235 (57.3)/1,451 (37.2)/2,596 (66.6)	641 (66.6)/306 (31.8)/604 (62.8)	313 (70.5)/104 (23.4)/237 (53.4)	170 (84.2)/22 (10.9)/95 (47.0)	<0.001, <0.001, <0.001
Median MSIS-29-Phys at diagnosis, *n* (IQR)	2037, 26.7 (10.0–48.3)	897, 31.7 (15.0–56.3)	276, 36.5 (18.3–56.7)	125, 36.7 (15.0–56.7)	66, 38.3 (20.0–51.6)	<0.001
Reported taking a DMT, pwRRMS only, *n* (%)/initial treatment, high efficacy, *n* (%)	4,026 (43.1%)/457 (11.4%)	1,113 (45.4%)/104 (9.3%)	219 (46.2%)/21 (9.6%)	63 (38.7%)/8 (12.7%)	18 (40.0%)/<5 (5.6%)	0.11, 0.31
Median time to DMT, yr, (IQR)	2.3 (0.4–8.0)	1.2 (0.3–4.2)	0.7 (0.3–2.5)	0.8 (0.3–2.3)	0.35 (0.3–1.0)	<0.001

DMT data is reported for pwRRMS only. Significant differences were determined using χ^2-test, Fisher's exact test or Kruskal–Wallis test.
DMT = disease-modifying therapy; PP = primary progressive; pwRRMS = people with relapsing–remitting multiple sclerosis; RR = relapsing–remitting; SP = secondary progressive.

by 1.7 cells/mm^2 in the thalamus ($p < 0.001$) and 2.8 cells/mm^2 in the pons ($p < 0.001$). In healthy controls, no relationship was found between age at death and neuron density in the thalamus, superior frontal, or cingulate gyrus when adjusting for sex.

Neuron density in the thalamus, a brain region with significantly lower neuron density in all cases of MS, was modestly associated with demyelination (lesion area; Spearman $r = -0.55$, $p = 0.031$) and compartmentalized inflammation in AOMS ($r = -0.53$, $p = 0.02$), but not in older-onset MS (all $r < 0.28$, $p > 0.35$; Fig 4E–H), suggesting a partial disconnect between neurodegeneration and demyelination and compartmentalized inflammation in the thalamus in MS with a late onset.

Correlation analysis revealed neuron loss and lesion area, especially affecting the thalamus, but also affecting the cerebellar dentate nucleus, basal pons, and spinal cord, to be associated with more severe disease, including shorter overall disease duration, in AOMS (Table 5, significant associations marked in bold text). In contrast, only neuron density, but not lesion area, significantly associated with measures of disease severity in the later-onset group ($r > 0.48$, $p < 0.05$).

Discussion

We have coupled a large population-scale study of people with LOMS, using a comprehensive registry cohort, with neuropathology findings from a related UK national population, to create a detailed demographic, clinical, and biological picture of the disease when it develops in later life. Our findings underline that MS that presents in older people represents a change in the balance of the underpinning biological variables toward a more neurodegenerative, less inflammatory, and less demyelinating disease in comparison

TABLE 3. Cox Regression Models for Time to Reaching Severe Disability (at Least 2 Consecutive Reports of No Longer Being Able to Walk Unassisted on the MSWS-12)

		Time since onset		Time since birth	
Group variable		**Univariate**	**Multivariate**	**Univariate**	**Multivariate**
LOMS group (ref: AOMS)	LOMS	**3.20 (2.00–5.30)*** **	**2.25 (1.32–3.82)** **	**0.25 (0.15–0.41)*** **	**0.51 (0.28–0.91)***
Age at baseline score (yr)		1.00 (0.99–1.00)	N/A	**0.52 (0.46–0.58)*** **	**0.53 (0.46–0.61)*** **
Age at diagnosis (yr)		1.00 (1.00–1.00)	N/A	**0.71 (0.66–0.76)*** **	0.99 (0.90–1.09)
Sex (ref: F)	Male	**1.90 (1.20–2.90)** **	1.35 (0.85–2.13)	0.98 (0.63–1.50)	N/A
Progressive (ref: No)	Yes	**2.80 (1.80–4.20)*** **	**2.09 (1.32–3.32)** **	1.1 (0.71–1.70)	N/A

Values are presented as hazard ratio (95% CI). N/A is used where variable was not significant at univariate analysis and therefore not included in the multivariate analysis (*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; significant associations shown in bold).
AOMS = adult-onset multiple sclerosis; LOMS = late-onset multiple sclerosis.

with MS in younger individuals. This may explain why older people with MS do not respond as well to current immunomodulatory therapies in comparison with younger people, and suggests they may benefit from different management.[1,2]

The Clinical, Demographic, and Pathological Picture of MS in Older Groups at Onset

It is no longer uncommon for people to develop the first symptoms of MS over the age of 50 years.[12] The proportion of LOMS in our cohort was 9.4%, which is similar to other recent nationwide findings and higher than previously recognized,[5,12,13,38] presumably reflecting the changing clinical and diagnostic landscape.[39] The female:male ratio is reduced in pwLOMS, although more women are still affected. Age has a profound impact on the risk of progressive-onset MS or the transition to secondary progression.[7,40] PwLOMS were more likely to present with a progressive form of the disease at onset, were more likely to report motor dysfunction, and be more disabled at diagnosis. These findings are in line with previous reports.[5,11–13,38]

TABLE 4. Linear Regressions Examining the Association between Onset Age as a Continuous Variable and the Neuropathological Outcome Measures, While Adjusting for Age at Death and Sex

Brain region	Neuron density (neurons/mm^2)	Total demyelination (%)	Grey matter lesions (%)	White matter lesions (%)
SFG	−1.958	0.146	0.378	−0.094
Cingulate	−2.594	−0.269	−0.228	−0.298
Thalamus	**−1.660*** **	0.135	0.135	N/A
Occipital	−2.198	0.162	0.502	−0.154
Cb DN	0.371	0.103	N/A	0.069
Pons	**−2.754*** **	−0.074	−0.074	N/A
Spinal cord	0.026	0.040	N/A	N/A

Beta coefficients and p values quoted (*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; significant associations shown in bold, significant at Bonferroni corrected $\alpha = 0.002$).
Cb DN = cerebellar white matter and dentate nucleus; SFG = superior frontal gyrus.

TABLE 5. Clinical-Neuropathological Correlates Indicate Neuron Density, but not Lesion Area, is Associated with Disease Severity in Later-Onset Multiple Sclerosis

	Neuron density					Lesion area				
Brain region by group	**Onset to prog**	**Onset to WC**	**Prog to death**	**Age died**	**Disease duration**	**Onset to prog**	**Onset to WC**	**Prog to death**	**Age died**	**Disease duration**
AOMS										
SFG	0.144	0.285	0.121	−0.042	0.147	−0.214	−0.149	0.097	−0.213	−0.138
Cingulate	−0.007	−0.233	0.248	−0.046	−0.025	0.051	−0.104	−0.168	−0.223	−0.102
Thalamus	**0.587****	**0.445***	**0.469***	**0.638****	**0.805*****	−0.466	**−0.615****	−0.245	**−0.751*****	**−0.595****
Occipital	0.032	0.103	0.329	0.237	0.344	−0.194	−0.236	−0.425	**−0.493***	**−0.486***
Cb DN	−0.220	0.053	**0.501***	0.145	0.136	−0.332	**−0.566****	−0.276	**−0.632****	**−0.515***
Pons	**0.541****	**0.665****	0.121	**0.438***	**0.594****	−0.163	−0.388	−0.376	**−0.657****	**−0.546***
Spinal cord	−0.137	0.080	**0.466***	0.064	0.034	−0.157	−0.355	**−0.442***	**−0.590****	**−0.499***
Later-onset										
SFG	0.082	−0.074	−0.250	−0.124	−0.164	−0.296	−0.400	0.140	0.090	0.103
Cingulate	0.299	0.143	0.173	0.031	0.315	−0.333	−0.108	0.244	0.144	0.126
Thalamus	0.512	−0.094	−0.212	**0.623***	**0.492***	−0.252	−0.407	0.122	−0.361	−0.209
Occipital	0.400	0.454	0.303	−0.061	0.048	−0.248	−0.115	0.142	−0.341	−0.208
Cb DN	−0.344	−0.063	−0.303	−0.255	−0.412	0.161	−0.390	−0.395	−0.237	−0.101
Pons	**0.567***	**0.761***	0.232	**0.477***	**0.600***	0.255	0.101	0.422	0.094	0.382
Spinal cord	−0.111	0.291	0.234	−0.002	−0.074	−0.188	−0.402	−0.342	−0.210	−0.019

Comparing quantitative measures of neuron density and lesion area per region of interest with retrospectively determined clinical milestones for AOMS and later-onset MS, respectively. Time from first symptom onset to progression (prog), wheelchair (WC), time from progression to death, and overall disease duration are reported (in years). Spearman correlation r values and unadjusted p values quoted (<*0.05; **0.01; ***0.001; significant associations shown in bold).

AOMS = adult-onset multiple sclerosis; Cb DN = cerebellar white matter and dentate nucleus; LOMS = late-onset multiple sclerosis; SFG = superior frontal gyrus.

We found the rate at which pwLOMS reach a marker of severe disability (no longer being able to walk unassisted) was approximately twofold higher than pwAOMS. Similar results have been found in other studies. For example, pwLOMS have been found to reach Expanded Disability Status Score 6 (requiring an aid to walk ~100 m) at a faster rate than those with a younger age at onset.[12,38] However, when examining age as the underlying timescale (time since birth), the rate was higher for those with an earlier onset. This indicates that although pwLOMS experience a higher rate from onset, the risk of losing walking ability at any given age is in fact higher in pwAOMS, which is likely attributable to their longer disease duration.

In parallel, we conducted a quantitative neuropathological analysis of MS with a wide range of ages at first symptom onset. We observed a shift between the balance of inflammation, demyelination, and neuron density, with age of onset. Our AOMS cohort was characterized by far more frequent and extensive white matter demyelination, but a similar extent of cortical lesions, which represented by far the greatest lesion type in our older-onset pathological group. Of interest, the spinal cord was less affected by demyelination in older-onset cases. Large-scale neuropathology has revealed a higher incidence of cortical lesions in men, although it remains unclear whether this correlates with larger lesion areas. Additionally, men showed a greater proportion of chronic active lesions compared with

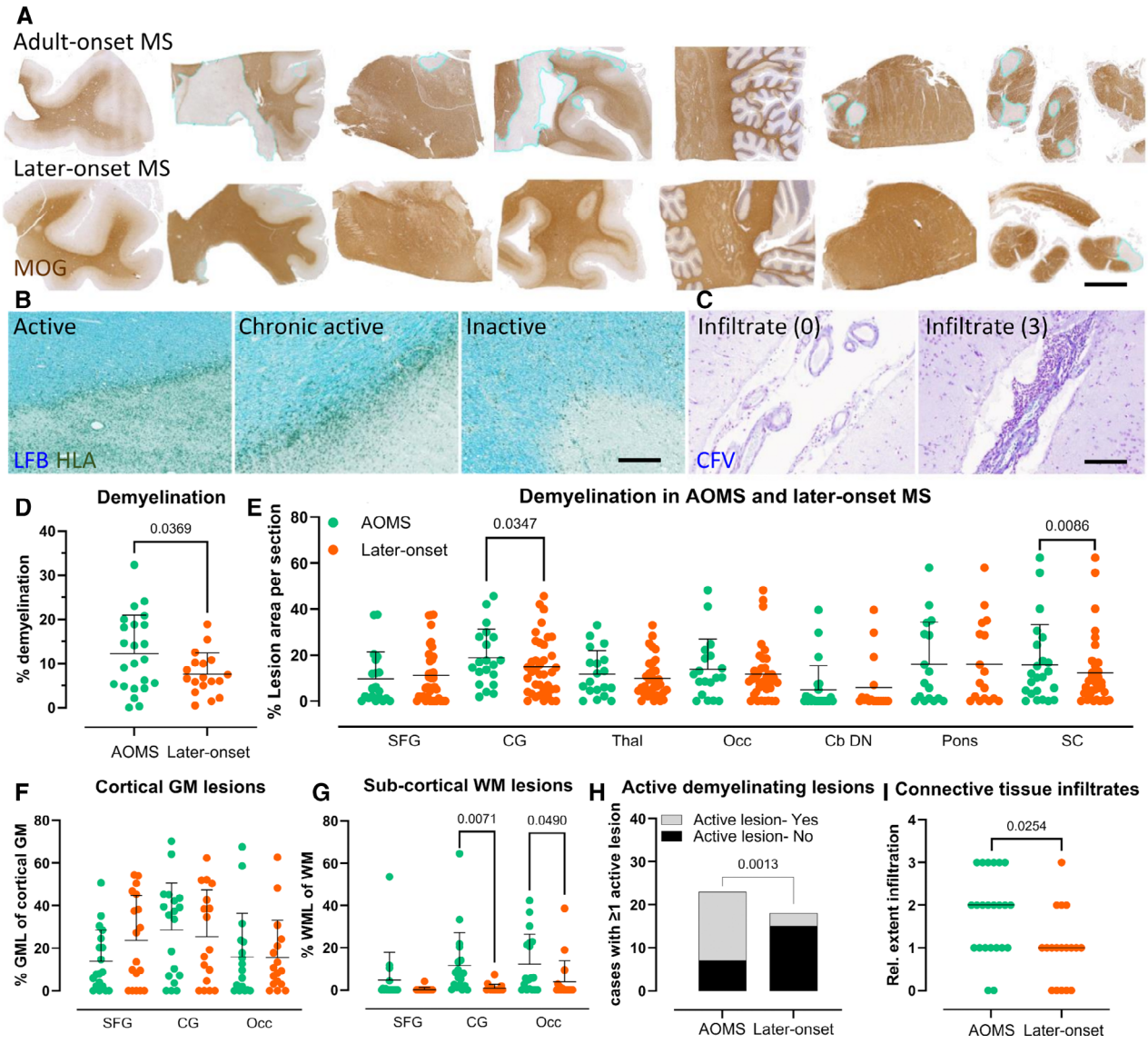

Figure 3: Multiple sclerosis (MS) with an older age at onset is characterized pathologically by fewer and less active demyelinating lesions, and reduced compartmentalised inflammation in comparison with adult-onset MS (AOMS). (A) Comparing demyelination (cyan annotations) between systematically sampled blocks of forebrain, thalamus, cerebellum, pons, and spinal cord from AOMS (case MS389, female, relapse-onset, 28 years disease duration) and older-onset MS (case MS529, male, progressive onset, 24 years duration of disease). (B,C) The presence of active (active or chronic active demyelinating) lesions and a semiquantitative rating of meningeal and perivascular cellular infiltration (from 0 = none, to 3 = substantial) was reported for each case. (D,E) The relative area of demyelination per block, per case, between later-onset MS and AOMS was compared. The relative area of (F) demyelinated cortical gray matter was unchanged, whereas the area of (G) demyelinated subcortical white matter, sampled from the same blocks, was reduced. (H) Fewer cases of later-onset MS presented with ≥1 active (active or chronic active) demyelinating lesions and (I) the relative extent of compartmentalised inflammation (rated 0–3) was also reduced. Cb DN = cerebellum and dentate nucleus; SC = spinal cord; SFG = superior frontal gyrus; Thal = thalamus. Kruskal–Wallis and Dunn's multiple comparison post-test. Each data point equals mean value per block or per case. Scale bars: A = 1 cm; B, C = 100 μm. [Color figure can be viewed at www.annalsofneurology.org]

women.[36] Our cohort of late-onset MS happened to consist mainly of women (14/18). Consequently, a more representative LOMS cohort, in terms of sex distribution, may show an even higher prevalence of cortical lesions and a greater number of cases with active lesions than reported here. This pathological picture of tissue injury focused on the forebrain gray matter and not the white matter in older-onset cases, has implications for the monitoring and treatment of MS in older groups. Assays of neuroaxonal and tissue injury, such as circulating levels of neurofilament light chain and glial fibrillary acidic protein, could be informative in clinical practice alongside neuroimaging.[41] Whereas standard radiological measures of new inflammatory lesions or of white matter lesion load might

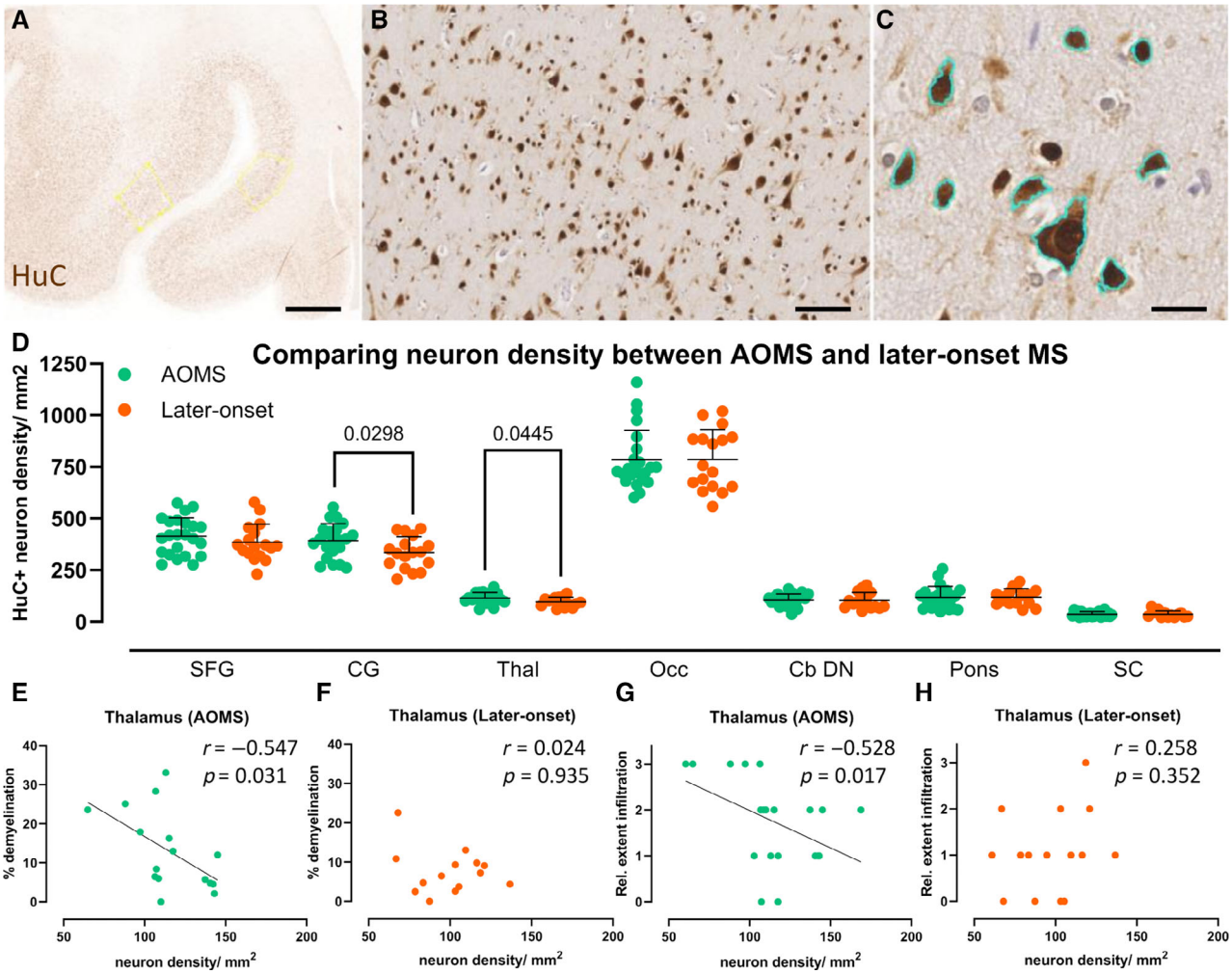

Figure 4: Later-onset multiple sclerosis (MS) is characterized by significant neuronal loss that is partly independent of the extent of demyelination and inflammation. (A–C) Neuron density was quantified in the same systematically sampled blocks used for the quantification of demyelination (HuC+ neurons identified in whole scanned sections and automatically counted per region of interest (highlighted). (C) Example of positive cells outlined by cyan mask. (D) The density of HuC$^+$ neurons per mm^2 was similar between adult-onset MS (AOMS) and later-onset MS except for in the cingulate gyrus and thalamus. When comparing neuron density in the thalamus, we saw a modest correlation between neuron number and (E) the extent of demyelination and (G) compartmentalized inflammation in AOMS, (F, G) that was not evident for the later-onset cases; Spearman correlation analysis, Spearman *r* and *p* values reported. Each data point represents the mean value for that block/case. Cb DN = cerebellum and dentate nucleus; SC = spinal cord; SFG = superior frontal gyrus; Thal = thalamus. Kruskal–Wallis and Dunn's multiple comparison post-test. Scale bars; A = 2 mm, B = 100 µm, C = 25 µm. [Color figure can be viewed at www.annalsofneurology.org]

be less insightful in comparison with measures of whole brain or regional tissue atrophy in this group.

Neuron loss is a significant contributor to regional brain atrophy.[42] In the older-onset MS group, neuron density in the thalamus and basal pons were the best correlate of disease severity, where, for example, a reduced neuron density strongly correlated with a shorter duration of disease irrespective of onset age. Damage to the thalamus represents an important indicator of past, present, and future disease severity, and is driven by innate immunity, including complement activation, and by more distal events in the well-connected long-tracts.[37,43] Therefore, monitoring thalamic atrophy could be instructive in older individuals newly diagnosed with MS, as it is for pediatric and AOMS groups, where it has been shown to be prognostic for later disability worsening.[44–46]

Our new data suggest that an older onset is linked to an already reduced neuron density equivalent to a 1%–2% per 1-year increase in onset age, when corrected for sex and age at death. This suggests MS with a delayed onset may be preceded by a prolonged prodromal phase culminating in a more neurodegenerative disease at breakthrough. Microscopically, PPMS does not differ from SPMS in terms of lesion quantity or lesion activity.[36] Clinically, PPMS can be viewed as SPMS without the earlier RR phase.[47] Our discovery that individuals with a late onset of MS experience a greater degree of neuron loss and higher disability levels at the time of diagnosis aligns

with the idea that MS represents a single disease influenced by age, environmental factors, and genetics. The reasons why acute inflammatory episodes occur in most people with MS, or why some people may be protected from an earlier onset, need investigating.

Although age of onset can be viewed as a proxy for disease duration, this association is complex. For example, an active and rapidly worsening disease starting in a young person, such as in those characterized by the presence of meningeal follicle-like structures at post-mortem, is associated with significant neuronal loss and an early death.[48,49] In contrast, we showed that a relatively short disease course in those with an older age at onset is associated with fewer relapses, an inactive pathology, and a reduced white matter lesion load at death. Aging will play a more prominent role in dictating disease length in these older cases. To investigate the impact of neuronal loss on disease outcomes in both younger- and older-onset groups matched for disease lengths, it would be necessary to include younger cases with shorter disease durations, which would not be representative of the typical AOMS course.

The number of apoptotic neurons is greatest in areas of MS gray matter demyelination in comparison with myelinated gray matter.[50] Although white matter lesion area was reduced in old-onset MS, the extent of gray matter demyelination was not different to AOMS, suggesting local MS-specific pathological processes in the gray matter contribute to neuronal loss. Nevertheless, comorbid conditions, such as vascular or metabolic disease or coexistent features of Alzheimer's pathology, may contribute to neurodegeneration in older cases.[27–29] These confounding pathologies, which were more commonly reported in our older MS and control donors in comparison with AOMS, would further the neuronal loss that underlies the rapid accumulation of disability of the older-onset group. Identifying and treating the comorbidities that most effect MS progression could have a profound impact on an individual's quality of life.

We believe that there is a continuum in the changing clinical pattern of MS with age, and that an arbitrary age-dictated cutoff, or the labeling of individuals with LOMS, is not a useful way to approach this complex interaction between disease and age. We were able to show the changing course of MS in cohorts whose onset ranged from age <40 years through to ≥60 years due to excellent coverage of the data. By stratifying cases in this way, we showed a continual shift with age in almost all clinical and demographic variables investigated. The view of MS as a clinical continuum is supported by neuropathology, which interprets the course of MS as a changing balance of key pathological variables, rather than distinctly different pathological states representing the different clinical stages.[24,36,51] Our pathological findings are in broad accordance with this view, where we noted a shift from a more active and focal demyelinating disease of the white matter toward a more progressive, neurodegenerative disease focused on the gray matter. These findings suggest that progression in old-onset MS is principally driven by demyelination and neuron loss in the gray matter, in combination with age-related confounders, and smouldering lesion activity in the white matter and compartmentalized inflammation play a less prominent role than in younger cases. To address this question of the changing balance of pathologies with age, we could in future analyze larger autopsy cohorts representing MS-onset in young, middle-aged, and older groups.

When comparing DMT prescription in LOMS and AOMS RRMS participants, there was no difference in the number of people reporting being on treatment. However, pwLOMS with RRMS were less likely to be prescribed a high-efficacy treatment than pwAOMS. Variance in DMT availability may be a potential confounder due to differences in time of diagnosis in pwLOMS and pwAOMS. However, given that the average year of diagnosis of the LOMS group is more recent than the AOMS group (2012 vs 2006), the true difference between rates of high-efficacy DMT prescribing between younger and older-onset MS could be underestimated in the present study. The majority of participants on a high-efficacy treatment were treated with ocrelizumab or natalizumab. Treatment with either of these drugs in the UK requires evidence of active lesions on magnetic resonance imaging.[52] Therefore, this finding suggests that pwLOMS are less likely to have inflammatory lesions. In support of this analysis, our unbiased tissue sampling showed that white matter lesions were a minor component of all those lesions identified in the older-onset cohort, and that cases with active lesions were uncommon. Previously, neuroradiology,[53] biochemistry,[54] and neuropathology[28] have shown a relative age-associated reduction in new incident lesions, central markers of inflammation and neuro-axonal degeneration. All told, these reports support current efforts to identify cohorts that may be suitable for de-escalating or discontinuing immunomodulatory treatment,[55,56] which are less effective in older people[3].

Strengths and Limitations

We described a large and well cataloged population of MS that includes one of the largest LOMS cohorts on record. The primary source of data used in the present study is self-reported, coming directly from pwMS via the UKMSR portal. However, participants can verify their diagnosis by uploading a clinic letter to the website. The validity of this data can also be confirmed using "linked

data", which come from participants in the portal population who have also consented at their hospital, and has been shown to be highly analogous to the clinical (validated) population.[57] We did not investigate comorbidities in the patient population, which may influence MS progression. We felt that the role of age-related confounders could be best addressed in the autopsy cohort, where those coexistent pathologies present at death and impacting on the central nervous system could be described. An analysis of the lifetime burden of comorbid conditions in younger and older pwMS would be warranted given the evidence presented here and in the literature.

This work further benefits from the addition of a cohort of autopsy samples from a similar UK population that, for the first time, reports the burden of pathology in cohorts with a young- or old-age of MS onset. The study was not designed to look at the effect of age-related confounding pathologies, which do play a role in disease processes relevant to progression. Age-related confounders were noted at a similar frequency in the control group, where age of death was not related to neuron density in our analysis. In comparison with MS, where relative neuron loss can be 20%–50% of age-matched controls, the small reduction in neuron density seen with normal aging[58] may not have been detectable in our modestly sized study.

Conclusions

By combining nationwide registry-led data, clinical linked data, and neuropathology, we showed that developing MS in later life is associated with a quantitative difference in the burden of clinical disease, and the extent of neurodegeneration, demyelination, and inflammation, in comparison with MS that manifests in younger people. The shifting pathological, demographic, and clinical picture of MS with age of onset indicates that the binary stratification of patients based on age at onset is not a particularly relevant clinical descriptor. Importantly, we showed that an older age of MS onset is linked to a reduced neuron density, irrespective of sex or age at death and that neuron density, and not the extent of inflammation or white matter demyelination, was the best correlate of disease severity. The present findings have implications for the monitoring of MS in older people, given that disease worsening is disconnected from the hallmarks of new inflammatory attacks and new lesions in this group.

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Author Contributions

S.K., R.M., J.N., R.N., O.P., W.O.P., and O.W.H. contributed to the conception and study design; all authors contributed to the acquisition and analysis of data; S.K., R.M., J.N., R.N., O.P., W.O.P., and O.W.H. prepared figures and wrote the first draft; all authors reviewed the final submitted version.

Potential Conflicts of Interest

Nothing to report. The UK MS Register is primarily funded by the MS Society.

Data Availability

The original contributions presented in this study are included in the article and supplementary material, further inquiries can be directed to the corresponding authors.

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