

Disentangling Age-Related and Disease-Specific Upper Cervical Cord Atrophy in Multiple Sclerosis

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BACKGROUND AND AIMS

Spinal cord atrophy has been consistently reported in multiple sclerosis (MS), and represents a key predictor of clinical disability and disease progression.¹⁻³ Mean upper cervical cord area (MUCCA), i.e., cross-sectional area measured at the level of the first two cervical segments, has

proven to be a reliable surrogate marker of cord atrophy measurement in both early and late MS.⁴ However, the distinct contributions of physiological aging versus MS-related neurodegeneration⁵ remain poorly characterized. The aim of this study¹ was to model aging trajectories of upper cervical cord atrophy in healthy controls (HC) and subsequently identify MS-specific patterns of spinal cord atrophy in a large, multicenter cohort.

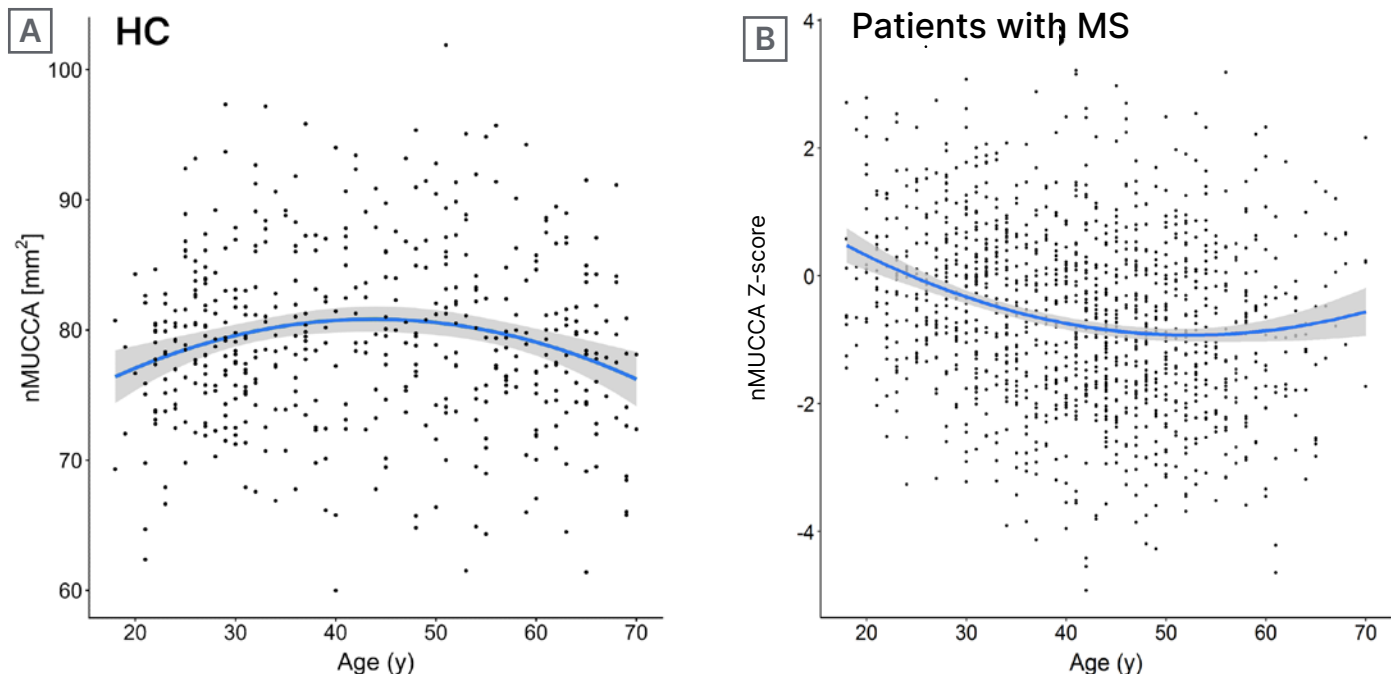
MATERIALS AND METHODS

The authors analyzed 3D T1-weighted brain MRIs and clinical data from 480 HC and 1,295 patients with MS (ages: 18–70 years). MUCCA was measured between the C1 and C2/3 intervertebral discs using the active surface method and normalized for head size (nMUCCA). Aging trajectories of nMUCCA were modelled in HC using a polynomial regression model accounting for age, age-squared, sex, scanner, and interaction terms. This model was then applied to the MS cohort generating nMUCCA Z-scores, capturing disease-specific atrophy beyond normal aging. Effect of sex and age at onset (pediatric-onset <18 years, adult-onset 18–49 years, late-onset ≥50 years) on Z-scores age dependence was evaluated.

RESULTS

In HC, nMUCCA showed a non-linear age relationship, increasing until late 30s ($p \leq 0.033$) and subsequently declining after age 50 years ($p \leq 0.008$; [Figure 1](#)). In patients with MS, nMUCCA Z-scores exhibited a non-linear decline with age: a steep reduction was observed in early adulthood, while decline attenuated up to late 40s ($p < 0.001$); deviations from age-expected values

Figure 1: Cord age.



Lifespan average nMUCCA and nMUCCA Z-score trajectories in HC and patients with MS.

A) Sex- and scanner-adjusted estimated lifespan trajectory of nMUCCA in HC, illustrating the significant non-linear relationship with age. **B)** Non-linear nMUCCA Z-score trajectory with age in patients with MS. The shaded gray area represents the 95% CI.

HC: healthy control; MS: multiple sclerosis; nMUCCA: normalized mean upper cervical cord area; y: years.

decreased in later decades (Figure 1). Sex did not significantly influence atrophy patterns in either HC ($p=0.256$) or patients with MS ($p=0.422$). Patients with pediatric-onset MS exhibited significantly lower Z-scores compared to adult-onset MS and late-onset MS ($p<0.001$), although MS-driven decline with age did not differ among onset groups. Lower Z-scores were associated with higher disability and worse structural MRI measures (ρ range = -0.355 – 0.372 , all $p<0.001$).

CONCLUSION

In MS, upper cervical cord atrophy exceeded effects of normal aging, especially during

early adulthood and midlife, suggesting that the relative contribution of normal aging increased with age, while disease-specific atrophy predominated early, independent of sex. Differences across onset groups largely reflected disease duration. Upper cord atrophy was associated with disability, supporting its role as a sensitive biomarker of MS-related neurodegeneration beyond aging.

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