A New Visual Scale to Assess White Matter Hyperintensities Within Cholinergic Pathways

Mikolaj Pawlak, MD; Jaroslaw Krejza, MD, PhD

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E  neral networks of the human cerebral cortex responsible for attention, memory, and emotions are modulated by cholinergic input from the 4 overlapping Ch1–Ch4 cell groups of the basal forebrain.1–2 Cholinergic neurons of the medial septal nucleus (Ch1 cell group) and the vertical limb nucleus of the diagonal band (Ch2) provide the major cholinergic input to the hippocampus. Cholinergic neurons of the horizontal limb nucleus of the diagonal band (Ch3) provide the major cholinergic input of the olfactory bulb, and cholinergic neurons of the nucleus basalis of Meynert (nbM-Ch4) provide the principal cholinergic input of the remaining cerebral cortex and amygdala. Trajectories of these cholinergic fibers in white matter have been described recently in humans.2

Cholinergic system damage leads to cognitive decline,3 thus, it is expected that the magnitude and extent of the damage will correlate with the degree of decline. White matter hyperintensities (WMHs) are encountered frequently on magnetic resonance (MR) scans of normal elderly people as well as in patients with various types of dementia. These hyperintensities are presumably related to small infarcts and lacunes caused by cerebrovascular disease.4 Therefore, their spatial relationships with the cholinergic system should be taken into account in addition to the number of lesions, their size, and volume, while trying to quantify the contribution of WMH to the cognitive decline.

The Cholinergic Pathways Hyperintensities Scale (CHIPS) proposed by Bocti et al,5 unlike previously published scales,6–9 takes into account the spatial relationships of WMHs and cholinergic pathways projecting from the nucleus basalis of Meynert. Bocti et al visually assessed the degree of WMH load on selected MR axial slices located in specific anatomic structures containing cholinergic tracts. Furthermore, because fibers entering the cerebral hemispheres from lower brain centers radiate fan-like through the cerebral white matter to the cortex, their density per unit of brain tissue volume decreases along the way from their source to destination. This specific fiber density in the white matter is also addressed in the CHIPS by assigning a factor from 1 to 4 for each subsequent MR axial slice starting at the base of the brain.

Bocti et al5 selected patients with Alzheimer disease to validate the CHIPS most likely because not only is the cholinergic system affected in this disease, but WMHs are also common. It is still not clear though what the contribution of WMHs is to cognitive impairment in Alzheimer disease. Nevertheless, the CHIPS can have practical value in these patients because it might be possible to determine the degree of cholinergic fibers damage and more precisely evaluate progression of structural changes in clinical trials. The study showed that the CHIPS score in patients with Alzheimer disease is better associated with cognitive functions, as measured with the Mattis dementia rating scale,10 than a score obtained with age-related white matter changes rating scale, a scale commonly used in clinical practice.6

The CHIPS does not take into consideration the whole cholinergic system involved in cognitive processes. It focuses only on pathways originating from nucleus basalis of Meynert, whereas white matter lesions in other parts of cholinergic system can also influence cognition.1

Furthermore, visual perception of WMHs depends on selected window settings, which are usually a matter of personal preferences, and MR acquisition protocols. These factors can increase inter-rater and inter-rater variability, whereas high reproducibility is crucial for any visual scale to become widely used in the clinical setting. Admittedly, Bocti et al5 demonstrate high reproducibility of the CHIPS as determined with very high interclass correlation coefficient. However, it is important to note that assessment of reproducibility with this coefficient has certain shortcomings. The value of the interclass correlation coefficient is dependent on the variability between raters and within the rater. If the measurement bias attributable to the rater or within-rater variance is smaller with respect to the between-raters variance, the value of the coefficient will be high. The opposite is also true, although less likely in the Bocti et al study. If variance between raters is small, but within-rater variance is very high, the value of the coefficient will be low.11

Another approach that might also be considered in assessment of reproducibility of such scales is Located Latent Class Agreement approach proposed by Uebersax.12 The idea of this approach is that observed ratings (manifest variables) are attributable to unobserved factors (latent variables). It assumes that there is a set of case subtypes, which may represent gradations of disease severity, corresponding to discrete location on the latent trait continuum and accounting for a certain proportion of cases. The model allows for elucidation of 3 potential sources of disagreement. First, ratings may disagree because 1 rater threshold in assessment of white matter lesions can be systematically higher or lower.
than another’s; in this case, we consider observers as differently biased. Second, observers may differ in rating category definitions in some cases, despite that categories are provided a priori. Third, there is a random measurement error attributable to various sources of “noise.”

The CHIPS is a novel scale designed to semiquantitatively measure the WMH load within the cholinergic neurotransmitter system on MR scans. The scale may be more sensitive to damage to the cholinergic system than the currently used scales. However, its practical usefulness in evaluation of degree and progression of the damage remains to be determined.

References
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