

## Multiple Sclerosis Risk After Optic Neuritis: Final Optic Neuritis Treatment Trial Follow-up

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This article included the results of the final follow-up study to the landmark Optic Neuritis Treatment Trial (ONTT) from 1992 (see wk 13). The original ONTT showed that treatment with IV methylprednisolone, followed by an oral prednisone taper, in acute isolated optic neuritis (ON) accelerates the recovery of vision but does not improve the eventual visual outcome. Later, a 1997 follow-up study reported the 5-year risk of multiple sclerosis (MS) in these same ONTT patient cohorts, and showed a 5-year cumulative probability of 30% regardless of treatment. Even later, this 2008 follow-up study was conducted to provide the final results for the risk of developing MS in the original ONTT cohorts, after 15yrs of follow up.

**Experimental design and statistical analysis:** The original ONTT was a multicenter, randomized controlled trial that enrolled 457 patients aged 18-46 years with acute, unilateral ON. The ONTT randomized these patients into 3 treatment groups: IV methylprednisolone, oral prednisone, and oral placebo (see wk 13 summary for details). Standardized, unenhanced baseline brain MRIs were performed at enrollment. Because this follow-up study examined the risk of MS development, they excluded the enrolled ONTT patients who were diagnosed as having either probable or definite MS at the time of trial entry. As such, for the purpose of this follow-up study, there were 389 eligible patients analyzed, all of which had acute unilateral ON without an initial diagnosis of probable or definite MS. Data was complete for only 300 patients (77%) at the 15-year follow-up point, but a few patients who were unable to be examined had details verified over telephone.

**Results:** Overall, the results of this follow-up study found that the aggregate, cumulative probability of developing MS by the 15-year follow up time point (after an episode of acute ON) was 50%. In patients with 1 or more lesions on a baseline brain MRI, the probability was 72% as opposed to only 25% in patients with no brain lesions. Notably, there were no significant differences in the risk of developing MS between the 3 original ONTT treatment groups (e.g. treatment with or w/o IV steroids). Of note, the time interval to developing MS also seemed to differ based on the number of baseline MRI lesions, and the risk of developing MS was highest in the first 5 years. Specifically, the probability of developing MS was 42% in the first 5 years in patients with +1 baseline brain lesion vs. 16% in patients with no brain lesions. At 6-10yrs, the probability of developing MS in patients with +1 baseline brain lesion was 30%, and it was 32% at 10 to 15 years after the initial optic neuritis event. This was compared to 9% and 2%, respectively, in patients with no brain lesions. Among patients with no brain lesions on MRI, baseline factors associated with a LOWER risk for MS development included male sex (women had a 3x higher risk), optic disc swelling at the onset of visual loss, and atypical features of ON including disc or peripapillary hemorrhages, retinal macular exudates, absence of pain, and either a reduction of vision or no light perception. Among patients with MS who completed the 15-year examination, the degree of disability as assessed by the EDSS score was not related to the number of brain lesions on baseline MRI. The authors also noted that the use of disease modifying therapies among these patients with and without baseline brain lesions was also similar.

**Conclusion:** In summary, the overall 15-year risk of developing MS after an episode of acute, unilateral ON was 50% and strongly correlated to the presence of demyelinating lesions on baseline MRI scan. The risk appeared to be much higher if there was at least 1 lesion on a baseline brain MRI (72% vs. 25% without lesions). The risk of developing MS in patients with at least 1 lesion on a baseline brain MRI also appeared to be relatively consistent throughout the 15 years of examination; in patients without any brain lesions, the risk of developing MS was greatest within the first 5 years and then sharply declined. This longitudinal study of MS risk in patients who presented with ON is clinically useful when risk-stratifying and counseling patients.

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