

Long-term Prognosis of Multiple Sclerosis in Untreated Patients and Patients Treated with First Generation Immunomodulators

Helen Tedeholm

Department of Clinical Neuroscience and Rehabilitation,
Institute of Neuroscience and Physiology at
The Sahlgrenska Academy

ABSTRACT

The course of multiple sclerosis (MS) is extremely variable. A limited number of demographic and clinical variables at MS onset were described to predict time to the onset of irreversible disability. However, there is no general consensus concerning the power and long-term range of these predictors. Although pivotal trials of interferon beta and glatirameracetate in relapsing-remitting MS demonstrated a reduced relapse rate, it is not clear whether the onset of secondary progression is postponed by means of treatment. Long-term randomized control trials are of several reasons not possible to accomplish. The only option is observational studies.

In this thesis the long-term prognosis was determined in a 50-year follow-up in the geographically and temporally defined “Gothenburg Incidence Cohort” (onset 1950-64, $n=305$). A Kaplan-Meier survival analysis showed that the median time to secondary progression was 14 years, to EDSS 6 (gait with a cane) 25 years and EDSS7 (wheelchair bound) 48 years. A score of combined onset predictors provided an estimate of the time to disability with a hazard ratio in the order of magnitude 2-4 (*paper I*).

Further, we investigated whether first generation immunomodulating drugs in the relapsing remitting phase delay the time to secondary progression. We explored the predictors as tools to adjust for imbalance between treated patients and historical controls. We compared the time to secondary progression between treated patients from the Swedish National MS Registry (disease onset 1995–2004, $n = 730$) and untreated patients from the Gothenburg Incidence Cohort ($n = 186$) within a 12-year survival analysis. The treated patients exhibited a significant longer time to secondary progression than the historical controls (hazard ratios: men, 0.32; women, 0.53) (*paper II*).

In order to obtain an individual prediction of the risk of secondary progression we investigated predictors associated with relapses throughout the course. We used Poisson regression to estimate the individual current risk of secondary progression at any point during the relapsing-remitting course. The average annual risk of secondary progression was 4.6 %. An algorithm including current age, a severity score of the last attack and the time elapsed since the attack predicted the yearly risk of secondary progression within the range 0.1-15%. This algorithm is now web-based (<http://msprediction.com>) and may be used for stratification of patients in future studies (*paper III*).

Keywords: Multiple Sclerosis, Long-term Prognosis, Predictors, therapy, immunomodulators, historical controls,

ISBN: 978-91-628-9220-3

Available online: <http://hdl.handle.net/2077/36905>

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Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska Akademin vid Göteborgs Universitet kommer att offentligen försvaras i hörsal Ivan Östholm, Medicinaregatan 11, Göteborg, Måndagen den 8 december 2014 kl 13.00

av

Helen Tedeholm

Fakultetsopponent: Dr.Med. Nils Koch-Henriksen
Institut for klinisk medicin, Neurologisk afdelning
Aarhus Universitet, Aalborg Danmark

Avhandlingen baseras på följande delarbeten:

- I. Tedeholm H, Skoog B, Lisovskaja V, Runmarker B, Nerman O, Andersen O.
The outcome spectrum of multiple sclerosis: disability, mortality and a cluster of predictors.
Submitted manuscript
- II. Tedeholm H, Lycke J, Skoog B, Lisovskaja V, Hillert J, Dahle C, Fagius J, Fredrikson S, Landtblom A-M, Malmeström C, Martin C, Piehl F, Runmarker B, Stawiarz L, Vrethem M, Nerman O and Andersen O.
Time to secondary progression in patients with multiple sclerosis who were treated with first generation immunomodulating drugs.
Multiple Sclerosis Journal. 2012; 19(6): 765–774.
- III. Skoog B, Tedeholm H, Runmarker B, Odén A, Andersen O. **Continuous prediction of secondary progression in the individual course of multiple sclerosis.**
Multiple Sclerosis and Related Disorders. 2014; 3(5): 584–592



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