Review article

Integrating the tools for an individualized prognosis in multiple sclerosis ☆

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ABSTRACT

Clinicians treating multiple sclerosis (MS) patients need biomarkers in order to predict an individualized prognosis for every patient, that is, characteristics that can be measured in an objective manner, and that give information over normal or pathological processes, or about the response to a given therapeutic intervention. Pharmacogenetics/Genomics in the fields of MS by now can be considered a promise. In the meanwhile, clinicians should use the information provided by the many clinical epidemiological studies performed by now, telling us that there are some clinical markers of good prognosis (female sex, young age of onset, optic neuritis or isolated sensory symptoms at debut, long interval between initial and second relapse, no accumulation of disability after five years of disease evolution, normal or near normal magnetic resonance imaging (MRI) at onset). Some markers in biological samples are considered as potential prognostic markers like IgM and neurofilaments in CSF or antimyelin and chitinase 3-like 1 in blood (plasma/sera). Baseline MRI lesion number, lesion load and location have been closely associated with a worse evolution, as well as MRI measures related to axonal damage (black holes in T1, brain atrophy, grey matter atrophy (GMA) and white matter atrophy (WMA), magnetization transfer measures and intracortical lesions). Functional measures (OCT, evoked potentials) have a potential role in measuring neurodegeneration in MS and could be very useful tools for prognosis. Several mathematical approaches to estimate the risk of short term use early clinical and paraclinical biomarkers to predict the evolution of the disease.

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1. Introduction

The word prognosis from the Greek πρόγνωση, literally foreknowing, foreseeing, is a medical term to describe the likely outcome of an illness. When applied to large statistical populations, prognostic

estimates can be very accurate, even in the field of multiple sclerosis (MS), however, it is much harder to translate this into a prognosis for an individual patient, and more "personalized or individualized" information is needed.

As clinicians, we are pragmatic professionals that must borrow any available information, from any field of Science in the interest of patients. Prognosis is one of the main issues raised by patients to their physicians. Therefore, clinicians treating MS patients need to have precise tools that will permit them to predict the exact prognosis, at an individual level, that is to say, the prognosis for the person they have in front of them at a given moment. Traditionally we have used implicit (non-explicit) decisions based on experience, but what we need actually is to use explicit decisions, based on numbers or probabilities. We need to go from population prognosis to individual prognosis. One good example today is the benefit/risk stratification in the use of NTZ after the introduction in the clinic of the JC virus antibody test.

Anyhow, we have to consider some caveats:

- Most studies are not even population based BUT hospital based and,
- Early onset multiple sclerosis (EOMS) and late onset multiple sclerosis (LOMS) usually are not included in population or hospital based studies.

Therefore, we should be very much interested on the available information on prognosis in Individualized or Personalized Medicine in MS. Trying to obtain that information, we performed a PubMed search on 10/Sept/2011 using the following strategy of search: "multiple sclerosis" AND "prognosis" that gave as result 1367 articles. A second search on "personalized medicine" AND "multiple sclerosis" arose only 12 articles, 6 of them on Pharmacogenetics; by searching "individualized medicine" AND "multiple sclerosis": 6 articles were found (3 on Pharmacogenetics); by using "personalized medicine" AND "multiple sclerosis" AND "prognosis": 1 article; and finally by using "individualized medicine" AND "multiple sclerosis" AND "prognosis": 1 article was found.

This single article is authored by Pablo Villoslada [1]. He underlines the fact that the pursuit of personalized medicine requires the development of biomarkers to predict disease course, monitor disease evolution, stratify patient subgroups by disease activity and to predict and monitor response to therapies. He acknowledges the fact that "the ability of neurologists to make an accurate prognosis is very limited", "a situation perceived by patients as one of their biggest concerns" and concludes by saying that "Indeed, it may currently be necessary to readdress the bias in research towards clinical validation rather than discovery in order to promote translational research and improve patient's quality of life".

2. The concept of biomarker

Biomarkers are highly needed in Medicine. A biomarker is a characteristic that can be measured in an objective manner, and that gives information over normal or pathological processes, or about the response to a given therapeutic intervention. Biomarkers can be classified in four groups [2]:

- Biomarkers with diagnostic value that permits to identify patients with a disease, discriminating between healthy and sick individuals.
- Biomarkers with predictive value, that permits to predict the possibility to develop a disease before the appearance of clinical symptoms
- Biomarkers with prognostic value, that give information on the possible course of the disease
- Biomarkers of response that predicts the response to therapeutic interventions and its possible adverse effects.

In the case of MS, there are many challenges to biomarker discovery and validation: MS has a high variability from the immunologic, neuropathologic, clinical, imaging and therapeutic points of view. We do not have a good definition for therapeutic response and frequently MS changes are subclinical. Also the correlations with markers like MRI are modest at best.

3. Prognostic biomarkers in MS

Pharmacogenetics/Genomics in the fields of MS by now can be considered a promise, but the appearance of new chips like Ion Torrent chip [3], that supports 1.2 million DNA-testing wells at a real low cost and the possibility to have a new version with 11 million different single nucleotide polymorphisms (SNPs) appearing soon, makes the promise something with tremendous probabilities of being a reality in the very next future. Probably, in a matter of months to one year, we will be able to predict the response to some drugs like interferons or glatiramer acetate. In view of today's genetic knowledge we must consider the fact that probably epigenetic modifications could be more important for prognostic purposes, but we must await until the field is more developed.

3.1. Clinical epidemiology (exacerbations, disability progression)

In the meanwhile, clinicians should use the information provided by the many clinical epidemiological studies performed by now, telling us that there are some clinical markers of good prognosis (female sex, young age of onset, optic neuritis or isolated sensory symptoms at debut, long interval between initial and second relapse, no accumulation of disability after five years of disease evolution, normal or near normal magnetic resonance imaging (MRI) at onset. Poor prognosis will be conferred by the opposite facts: male sex, older age and multifocal CIS at onset, efferent system affected at debut, high relapse rate in the first 2–5 years, abnormal initial MRI with high number of lesions and large lesion load (Table 1) [4].

Clinical variables, relapses and EDSS progression are considered important for clinicians, as it has been shown as the existence of a EDSS increase after relapses [5], and the fact that prognosis of MS, as shown by EDSS progression, is linked to the number of relapses in the first 2 years [6], and the fact that once reached EDSS 4, disability progression is independent of the initial prognostic factors [7,8].

An interesting approximation to the prognosis of MS has been done by using the global multiple sclerosis severity score (MSSS), in which scores generated from 9892 European patients have been tabulated and used for prognostic purposes. The MSSS for an individual patient is ascertained by finding the column corresponding to the patient's EDSS and the row corresponding to the number of years since the onset of multiple sclerosis. Deciles are color coded to show the pattern of disease progression at different disease durations [9]. It has not been validated.

Other similar approaches have been done in several independent cohorts, in which case, time to reach EDSS 6.0 has been used as a prognostic threshold: London Ontario cohort: 15 years [6]; Lyon cohort 20 years [10] and British Columbia cohort 28 years [11], showing the variability of the disease, along the time, most probably related to the diagnosis of more benign cases lately.

Another aspect to focus prognosis is to consider that MS is a severe disease and keeping oneself aware that benign forms are rare, as the majority of patients showing a benign course (EDSS < 3) at 10 years progress to more severe forms at 20 years [12].

A final aspect is the ethnic background, having been proved that non-whites have a worse prognosis [13].