بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ
Treatment personalization in multiple sclerosis

Baghbanian S.M. M.D
Assistant professor of Neurology
MS Fellowship
Mazandaran University Of Medical Science
Introduction

- Multiple sclerosis is a multifocal demyelinating disease with progressive neurodegeneration caused by an autoimmune response to self-antigens.
- The result of both genetic predisposition and environmental triggers.
- Patients with clinically isolated syndrome (CIS) have a variable chance of conversion to RRMS.
- Some patients progress from RRMS to irreversible progressive disability called secondary progressive multiple sclerosis (SPMS).
- 10–15% of patients exhibit progressive disease after initial symptoms without relapses termed primary progressive multiple sclerosis (PPMS).
- Early therapeutic intervention delays long-term disease progression.
Multiple Sclerosis in Iran:  
A Demographic Study of 8,000 Patients and Changes over Time

Mohammad Ali Sahraian\textsuperscript{a, b} Saeideh Khorramnia\textsuperscript{a} Mina Mohammad Ebrahim\textsuperscript{a} Zahra Moinfar\textsuperscript{a} Jamshid Lotfi\textsuperscript{c} Hossien Pakdaman\textsuperscript{d}

\textsuperscript{a}Sina MS Research Center, Sina Hospital, and \textsuperscript{b}Department of Neurology, Sina Hospital, Tehran University of Medical Sciences, \textsuperscript{c}Iranian MS Society, and \textsuperscript{d}Department of Neurology, Shahid Beheshti University of Medical Sciences, Tehran, Iran
Abstract

Background: Iran was formerly considered to be located in a low prevalence zone for multiple sclerosis (MS). During the last decade the number of patients has increased. This study was conducted to estimate the prevalence of MS in the capital city of the country. Methods: We re-evaluated the files of all patients who had registered at the Iranian Multiple Sclerosis Society during a 10-year period. Results: 8,146 patients (72.3% female, 27.7% male) with a female-to-male ratio of 2.60 had registered. Mean age of disease onset was 27.24 (SD: 8.32). A relapsing-remitting pattern was recognized in 84.9% of the patients. The number of new registrations tripled from 2002 to 2008 and the female-to-male ratio increased from 2 to 3.12. The prevalence of MS in Tehran is estimated to be at least 51.9 per 100,000. Visual impairment was the main presenting symptom. Conclusions: It seems that the prevalence of MS has increased to a medium-to-high risk level in Iran.
Why biomarkers are important?

- Ruled out other differential diagnosis
- Confirmed diagnosis
- Prediction of conversion to definite MS from CIS
- Prediction of disease course, aggressive MS, RRMS to SPMS, PPMS
- Selection of effective drug
- Prediction of treatment response.
- Prediction of treatment complications
Biomarkers currently in clinical use

• OCBs in CSF is predictive of conversion from CIS to multiple sclerosis.
• testing for OCBs still represents a useful tool for
  • Ruling out other possible diagnoses.
  • Prognostication of CIS conversion.
• Progressive multifocal leukoencephalopathy (PML) emerged as a rare adverse event from natalizumab treatment.
• PML is caused by reactivation of a latent John Cunningham virus in immunocompromised individuals.
• making John Cunningham virus antibodies an extremely useful clinical biomarker for assessing the risk of PML.
Potential biomarkers

• CNS neurofilaments (Nfl) levels in CSF are increased in both RRMS and progressive multiple sclerosis.
  • Nfl is increased at all disease stages, but fluctuates consistent with clinical course and the presence of active lesions.
  • Nfl levels could be a prognostic biomarker for an aggressive disease course and high risk for secondary progression.
  • Correlate with treatment response.

• CD163 is a monocyte/macrophage specific membrane marker.
  • Increased sCD163 levels in the blood and the CSF of multiple sclerosis patients.

• (Chitinase-3-like 1) is an activation marker for glia, macrophages, levels in the CSF were found to be significantly higher in CIS patients that converted to multiple sclerosis
  • Correlated with shorter time to multiple sclerosis conversion.
  • More rapid progression.
Con,

- Osteopontin (OPN) is an early activation marker on T cells with a role in T-cell costimulation and interferon (IFN)-g expression.
  - Significantly higher in multiple sclerosis blood and CSF.
  - Correlated to disease severity and relapse rate.
  - High levels of OPN in the CSF also correlated to disease severity in PPMS.
  - Disagreement on OPN levels as a prognostic biomarker of disease severity.
Biomarkers associated with disease course and activity

- The increased mRNA expression levels observed in peripheral blood cells discriminative between RRMS, SPMS from PPMS.
- The kynurenine pathway involved in the breakdown of the essential amino acid tryptophan upregulated in the CSF of primary progressive MS.
- Proteomic study in which two-dimensional electrophoresis was applied to CSF samples
  - The vitamin D-binding protein,
  - The apolipoprotein E
    - Discriminate between MS patients with aggressive and benign disease courses.
  - The calcium-binding protein secretogranin-1 decreased in the CSF during the disease course compared with the early phases of MS.
- B-cell-activating factor (BAFF)
  - Significantly increased in plasma samples from stable MS patients compared with relapsing patients.
- Heavy chain subunit of neurofilaments were associated with more severe disability progression
Biomarkers of disease conversion

- Gadolinium enhancing lesions at CIS
- OCBs in the CSF
- Predictive biomarkers of subjects with high risk of progression to multiple sclerosis
Treatment response biomarkers to IFNb

- At the genetic level, an intronic variant of solute carrier family 9, subfamily A (SLC9A9), a gene encoding a Na+ – H+ exchanger found in endosomes, was associated with the nonresponse to IFNb.

- **SLC9A9** expression was **down regulated** in peripheral blood cells from MS patients with more activated lymphocyte profile and at **increased risk for relapses**.

- the NLR family, pyrin domain containing 3 (**NLRP3**) inflammasome as response biomarker to IFNb.
  - mRNA expression levels for NLRP3 and its target IL-1b, were **upregulated** in peripheral blood cells from **nonresponders** to IFNb.
Treatment response biomarkers to GA

• the increased mRNA expression levels of response gene to complement 32 (RGC-32) and FasL and decreased expression of IL-21 observed in peripheral blood cells from responders compared to nonresponders.

• Among these three genes, RCG-32, had associated the best estimates of detecting a good response.
Treatment response biomarkers to Natalizumab

- an increase in the number of circulating hematopoietic stem and progenitor cells (CD45lowCD34+) was associated with clinical remission in patients treated with natalizumab and proposed as response biomarker.

- the mean percentage of lymphocytes over a period of 10 natalizumab administrations was significantly higher in responders.

- Oxysterols are oxidized derivatives of cholesterol that were found to be reduced in the CSF of MS patients by the effect of natalizumab.
Biomarkers of risk for progressive multifocal leukoencephalopathy (PML)

• the presence of lipid-specific IgM oligoclonal bands and the decreased risk for PML in patients treated with natalizumab.

• the L-selectin (CD62L) expressed by CD4+ T cells as a potential biomarker for PML risk.
Treatment response biomarkers to Fingolimod

- **Reductions in the NF-L levels** after 1 year of treatment with fingolimod were associated with improvements in relapse and MRI outcomes
Genetics

• Genome-wide association studies (GWASs) using single nucleotide polymorphisms (SNPs) from the Hap Map project allowed the use of an unbiased approach in scanning the whole genome and identifying SNPs associated with disease.

• A GWAS with over 9000 cases of multiple sclerosis identified an additional 29 novel susceptibility loci.

• To date, approximately 1000 patients with progressive multiple sclerosis have been investigated in GWASs, and those subjects cannot be differentiated from patients with relapsing remitting multiple sclerosis (RRMS).

• GWASs only identify variants associated with susceptibility to disease.
Thanks for your attention.