

# Report on the 1<sup>st</sup> International Razavi Multiple Sclerosis Congress Held in Mashhad, Iran, September 18<sup>th</sup> - 20<sup>th</sup>

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## Abstract

From September 18<sup>th</sup> - 20<sup>th</sup>, 2015, the 1st international Razavi multiple sclerosis congress was held in Mashhad, Iran. The meeting was designated as a platform especially for young scientists to get internationally connected, discuss recent scientific findings and develop further ideas for strategic collaborations between Germany and Iran. Physicians and scientists from research groups working in Muenster (Germany), Tehran, and Mashhad attended the meeting to discuss their latest findings in Multiple Sclerosis. The meeting was very well organized in a stimulating environment and demonstrating the developments of Razavi hospital, Razavi neuroscience center, and the working environment in Mashhad, Iran.

**Keywords:** Multiple Sclerosis, Iran, Neurology

## 1. Purpose of the Meeting

Razavi neuroscience center was established to improve diagnostic and treatment strategies of neurological disorders. In this regard, the 1<sup>st</sup> international Razavi multiple sclerosis (MS) congress was held in Razavi hospital to discuss recent scientific findings and development in different aspects of MS. Considering special pattern of MS in different regions of Iran, this congress was designed to discuss further ideas on pathophysiology, diagnosis, and treatment of MS.

## 2. Summary of Presented Findings

The latest findings concerning the epidemiology of multiple sclerosis (MS) in Iran were presented. Interestingly, there is a huge difference in the incidence of MS depending on the specific region of Iran. In regions like Tehran or Isfahan, the incidence of MS is much higher than in other regions of the country. Major environmental factors are considered to contribute to the onset and progress of MS; this is an interesting finding because sun exposure and correlated vitamin D levels cannot explain this difference in incidence. Obviously a modern lifestyle in bigger cities contributes to the incidence but also to the early diagnosis of MS while less urban regions seem to show lower incidences.

Following this presentation, the latest data concerning the pathophysiology and immunology of MS were discussed. From very basic aspects of innate and adaptive immunity, it was underlined the important role of T and B lymphocytes for the initiation and effector phase of MS. Furthermore, the latest findings concerning the role of T cell differentiation, impact of regulatory T cells concepts of migrational capacity, impact of the blood-brain-barrier, and major mechanisms of new drugs in MS therapy were discussed. Following up on this topic, the German guidelines for the diagnosis of MS were presented. The role of prognostic factors like gender, age, the time between a first and a second relapse as well as the number of inflammatory lesions in the first MRI scan in MS was emphasized. In the next step, new treatment options for MS focusing on the anti-CD25 antibody aalizumab, anti-CD52 antibodies such as alemtuzumab and follow up substances as well as on substances interfering with T cell transmigration via the blood-brain-barrier were presented. Vatalizumab, a new monoclonal antibody interacting especially with activated T cells, was named as a potential novel treatment of MS.

The symposium was then followed by case presentations from Germany and Iran. Several patients were introduced, especially interesting cases of Devic syndrome. This disease is much more common in Iran compared to Germany. In addition, some cases and underlined the impor-

tance of early treatment, the different treatment options for mild and moderate MS disease courses as well as options for highly active forms of MS were presented. The case report session was highly interactive and it was an opportunity not only for postdocs and experienced physicians but also for younger students to discuss about clinical presentations and differential diagnosis of MS.

The first session of the second day of this international congress was dedicated to MS and latest research findings. The session was opened by presentation of the immune modulatory properties of bone marrow-derived mesenchymal stem cells in experimental autoimmune encephalomyelitis (EAE). EAE was introduced as a valuable tool mimicking relevant aspects of the human disorder MS. Besides the results from the animal model and the disease course, data were presented from flow cytometry experiments, proliferation assays as well as cytotoxicity assays concerning the role of mesenchymal stem cells for immune responses in EAE. The next presentation was held focusing on the role of melatonin in the treatment of MS. An overview of the literature concerning the role of melatonin in MS was presented and a concept how severity of the disease could be influenced by circadian rhythm and therefore melatonin levels warranting further investigations in human MS patients was developed. It was suggested that a good approach would involve cerebrospinal fluid (CSF) analysis for melatonin levels correlating these findings with EDSS development of the patients. Then, a very interesting data concerning the role of cyclic AMP (cAMP) in the cuprizone model of demyelination was discussed. It was demonstrated western blot and histochemistry results implicating a beneficial effect of cAMP in the mouse model of demyelinating disorders leading to a reduction in caspase-3 activity as well as to a modulation of the Bcl-2/Bax system. Within this project it was so far not possible to differentiate between different cells of the central nervous system and it was discussed that it is of particular interest to further investigate the role of regulatory T cells within this system to further delineate the mechanism of cAMP action. Interestingly enough, cAMP modulation resulted in an improved behavior of the animals as pointed out in open field experiments. In the next presentation, the role of methadone and its effects on neuro inflammation and disease severity in EAE was discussed. It was pointed out that methadone leads to a significant modulation of T lymphocytes as indicated in MOG-recall assays at day 31 after immunization. While treatment with methadone had only a non-significant effect on the disease maximum, it resulted in a clear and major impact during the effector phase of the disease. In this project it would be interesting to investigate the effects of methadone on the blood-brain-barrier and especially on brain cells. Thereby  $\mu$  opioid receptor

expression should be analyzed on splenocytes, T cells and dendritic cells and it was discussed that methadone should also be applied in a therapeutic setting starting treatment after animals already developed first signs and symptoms of the disease.

In the second session of this day, Prof. Meuth introduced Muenster University and the translational concept which is followed in the department of neurology. The overall goal is to train clinician scientists and medical doctors, who are also interested in basic science. Following this introductory speech, the latest results concerning grey and white matter demyelination in the already mentioned cuprizone mouse model of demyelinating disorders have been shown. In vitro data obtained from experiments performed in collaboration with Muenster as well as from Mashhad and Tehran Universities were presented. It has been that cuprizone treatment leads to different network behavior in the thalamocortical system not only in vitro and ex-vivo brain slice preparations but also in in-vivo recordings of freely behaving animals. White matter lesions can be restored due to remyelination, while grey matter lesions seem to be of major impact in the given mouse model. Following this presentation Then, a project showing a clear interaction between the coagulation system and inflammation was introduced. This project was focused on the particular role of the plasmatic coagulation factor FXII in human and murine inflammation. FXII is able, via binding to its receptor CD87, to modulate cAMP levels of dendritic cells. These increased cAMP levels result in the production of pro inflammatory cytokines like IL-6, which in turn leads to the differentiation of naïve T cells into TH17 cells. Following this hypotheses, knock-out animals for FXII show an ameliorated disease course in the EAE model. This session was closed by a presentation from Muenster University focusing on the role of the co-stimulation factor NKG2D in MS and Myositis. Here it has been shown that inflamed muscle cells are able to express the ligands of the NKG2D receptor and are susceptible to NKG2D-mediated lysis. The expression of this signaling pathway is highly IL-15 dependent indicating new therapeutic avenues for inflammatory myopathies.

The third session of this day was opened by a presentation demonstrating first data concerning the coincidence of MS and headache in Mashhad. A correlation between MS and headache which was not dependent on the disease course of MS was reported. It was recommended to establish a second cohort of patients suffering from tension headache to make comparison between patients with MS plus headache, other headache patients and healthy controls. In the next presentation, the Razavi cancer research center and brain bank was introduced. It was pointed out that the Razavi hospital is going to establish a cancer cen-

ter, which will be opened soon and of a large brain bank including healthy control samples but also samples from patients suffering from brain tumors will be available. In an interesting next presentation, the activities of the Shefa neuroscience research center was presented and pointed out the technical possibilities in the research center to demonstrate potential strategies and ways to collaborate between Mashhad, Tehran, and Muenster. A possibility to establish cell cultures with human brain cells derived from adult brains was then form this center was presented. This project started approximately six months ago and showed already promising results. It has been shown that it is possible to extract stem cells from surgical materials and that these cells can be differentiated in cell cultures showing expression of GFAP indicating astrocytes and approximately 10% of all cells expressed MAP2, an indicator of neuronal cells. This project is of great interest and it was heavily discussed within the group. It was recommended to further characterize these neuronal cells using especially electrophysiological methods. This last session was concluded by a discussion among all scientists and students to establish strategies and ways how collaboration between Germany and Iran can be facilitated within the next months.

### 3. Conclusion and Future Research

In summary, this first international Razavi multiple sclerosis congress 2015 was regarded by all attendees as a very useful platform to discuss projects, exchange ideas and promote younger students in the field of neuroimmunology and neuroscience. It was concluded that there should be a follow up meeting to see how these potential collaborations develop and people discussed advantages one might have by using a collaborative strategy to address unmet needs in biomedical research leading to the identification of new molecular targets in MS, to define new treatment options and to develop new model systems like human brain cell cultures derived from neurosurgical material.

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### Footnotes

**Authors' Contribution:** Manuela Cerina, Tobias Ruck, Ali Gorji, and Sven G. Meuth on behalf of the speakers of the 1<sup>st</sup>

international Razavi multiple sclerosis congress wrote the paper. All authors read and approved the final manuscript.

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