Dear Colleagues,

It is with great pleasure that we invite you to this year’s 25th anniversary edition of the MS State of the Art Symposium. The symposium is organized by the Swiss MS Society and its Medico Scientific Advisory Board.

The first symposium was held in 1999 at the University Hospital of Zurich, with the main theme «Diagnosis and Therapy of Multiple Sclerosis». Today, diagnosis and therapy are still among the focal aspects of MS research, but fortunately, numerous milestones have been achieved since then. We will look ahead and dedicate this special edition to «25 Years – Moving Forward Together for People with MS».

We are very honoured to announce that there will also be a «first» at this anniversary symposium: The first «Swiss MS Society Research Prize» will be awarded at the symposium. This prestigious prize is endowed with CHF 100'000 and will be awarded to an outstanding MS researcher in Switzerland. With this award, the Swiss MS Society would like to make a further contribution to the promotion of excellent MS research in Switzerland.

The morning session features internationally renowned speakers such as Alberto Ascherio (USA) on the Epstein Barr Virus, Cristina Granziera (Basel) and Jens Kuhle (Basel) on the Swiss MS Cohort, as well as Andrew Chan (Bern) on MS Medication and Treatment.

During the coffee and lunch breaks you will have the opportunity to view the Poster Presentations of the researchers currently funded by the Swiss MS Society, and discuss their projects.

The afternoon session, with two sets of parallel Workshops, will address specific topics relevant to daily practice, and encourage you to ask your own questions and engage in the discussion.

On behalf of the organisers and speakers, we hope that the programme meets your interest, and are looking forward to meeting you for this special event in Lucerne.

PD Dr. med. Sandra Bigi
Head of the Programme Committee and Member of the Steering Committee of the Medico Scientific Advisory Board

Patricia Monin
Director of the Swiss Multiple Sclerosis Society
Dear Colleagues,

On behalf of the Swiss Neurological Society (SNS) it is a great pleasure to welcome you to the 25th Anniversary of the MS State of the Art Symposium!

Multiple Sclerosis (MS) is a very important topic for Swiss Neurology, involving many colleagues in hospitals and private practices.

The development of effective treatments with excellent tolerability for MS patients in the last 30 years, including a steadily growing number of substances and the possibility of autologous stem cell transplantation, is an impressive example of the overwhelming therapeutic progress in neurology.

We are very proud to announce that the SNS and the Swiss MS Society decided to enter a formalized partnership in 2021 which has already been fruitful.

We have already pursued a number of common and successful actions and the SNS is grateful and happy to support the activities of the Swiss MS Society with respect to optimized patient care, medical specialist training, and continuing education.

The topic of the symposium «25 Years – Moving forward together for People with MS» is of high importance and clinically relevant for all neurologists treating MS patients, and the speakers cover a large number of aspects important for neurologists in hospitals and private practices.

I wish you a very interesting, enjoyable meeting!

Prof. Dr. med. Peter Sandor
President Swiss Neurological Society
General Information

Date
Saturday, January 28, 2023, 09.30 – 16.00

Venue
KKL Luzern, Europaplatz 1, CH-6005 Lucerne

Programme Committee
Sandra Bigi, Luzern; Pasquale Calabrese, Basel; Andrew Chan, Bern; Adam Czaplinski, Zurich; Britta Engelhardt, Bern; Cristina Granziera, Basel; Robert Hoepner, Bern; Jens Kuhle, Basel; Caroline Pot, Lausanne; Anke Salmen, Bern

Organisation
Swiss Multiple Sclerosis Society and its Medico Scientific Advisory Board

Contact
Swiss Multiple Sclerosis Society
Josefstrasse 129, CH-8031 Zurich
symposium@multiplesklerose.ch

Credits
The Swiss Neurological Society awards 6.0 credit points.

www.ms-state-of-the-art.ch
symposium@multiplesklerose.ch
## Contacts

### Programme Committee and Chairpersons

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<tr>
<th>Name</th>
<th>Institution</th>
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<tr>
<td><strong>Sandra Bigi</strong></td>
<td>Cantonal Hospital of Lucerne, Children’s Hospital Lucerne, University of Bern, Institute of Social and Preventive Medicine</td>
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<tr>
<td><strong>Claire Bridel</strong></td>
<td>Geneva University Hospital, Service of Neurology</td>
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<td><strong>Pasquale Calabrese</strong></td>
<td>University of Basel, Neuropsychology &amp; Behavioural Neurology Unit</td>
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<td><strong>Andrew Chan</strong></td>
<td>University Hospital Bern, Inselspital, Department of Neurology</td>
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<td><strong>Adam Czaplinski</strong></td>
<td>Bellevue Medical Group, Clinic for Neurology Hirslanden</td>
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<td><strong>Britta Engelhardt</strong></td>
<td>University of Bern, Theodor Kocher Institute</td>
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<td><strong>Cristina Granziera</strong></td>
<td>University Hospital Basel and University of Basel, Translational Imaging in Neurology (ThINK) Basel, Department of Biomedical Engineering, University Hospital Basel and University of Basel, Neurologic Clinic and Policlinic, MS Center, and Research Center for Clinical Neuroimmunology and Neuroscience Basel (RC2NB)</td>
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<tr>
<td><strong>Caroline Pot</strong></td>
<td>Laboratory of Neuroimmunology, Neuroscience Research Centre and Service of Neurology, Department of Clinical Neurosciences, Lausanne University Hospital and University of Lausanne</td>
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<td><strong>Anke Salmen</strong></td>
<td>University Hospital Bern, Inselspital, Department of Neurology</td>
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Speakers (Lectures)

Alberto Ascherio
– Harvard T.H. Chan School of Public Health, Boston (USA)

Andrew Chan
– University Hospital Bern, Inselspital
  Department of Neurology

Cristina Granziera
– University Hospital Basel and University of Basel
  Translational Imaging in Neurology (ThINK)
  Basel, Department of Biomedical Engineering
– University Hospital Basel and University of Basel
  Neurologic Clinic and Policlinic, MS Center,
  and Research Center for Clinical Neuroimmunology
  and Neuroscience Basel (RC2NB)

Jens Kuhle
– University Hospital Basel and University of Basel
  Neurologic Clinic and Policlinic, MS Center,
  and Research Center for Clinical Neuroimmunology
  and Neuroscience Basel (RC2NB)

Speakers (Workshops)

Pasquale Calabrese
– University of Basel
  Neuropsychology & Behavioural Neurology Unit

Cristina Granziera
– University Hospital Basel and University of Basel
  Translational Imaging in Neurology (ThINK)
  Basel, Department of Biomedical Engineering
– University Hospital Basel and University of Basel
  Neurologic Clinic and Policlinic, MS Center,
  and Research Center for Clinical Neuroimmunology
  and Neuroscience Basel (RC2NB)

Jens Kuhle
– University Hospital Basel and University of Basel
  Neurologic Clinic and Policlinic, MS Center,
  and Research Center for Clinical Neuroimmunology
  and Neuroscience Basel (RC2NB)

Myrta Kohler
– Eastern Switzerland University of Applied Sciences, St. Gallen
– Clinics of Valens

Laura Leponiemi
– Bellevue Medical Group
  MS Care Nurse

Viola Marchi
– Person affected by MS, Bern

Johanna Oechtering
– University Hospital Basel and University of Basel
  Neurologic Clinic and Policlinic,
  MS Center, and Research Center for Clinical Neuroimmunology
  and Neuroscience Basel (RC2NB)

Axel Regeniter
– Medica Laboratory, Zurich
## MS Researcher Poster Presentations

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<td>Anke Salmen</td>
<td>University Hospital Bern, Inselspital Department of Neurology</td>
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<td>Regula Steinlin Egli</td>
<td>Practice for Neurology and Rehabilitation, Binningen</td>
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<td>Maria Isabel Vargas Gomez</td>
<td>Division of Neuroradiology, Diagnostic Department, Geneva University Hospital and Faculty of Medicine of Geneva</td>
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<td>Viktor von Wyl</td>
<td>University of Zurich Epidemiology, Biostatistics and Prevention Institute &amp; Institute for Implementation Science in Health Care</td>
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<td>Barbara Widmer</td>
<td>Cantonal Hospital of Aarau MS Consultation</td>
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<td>Sandra Bigi</td>
<td>Cantonal Hospital of Lucerne, Children’s Hospital Lucerne Department of Child Neurology</td>
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<td>University of Bern Institute of Social and Preventive Medicine</td>
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<td>Sarah Bolt</td>
<td>University Hospital Zurich Department of Neurology</td>
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<td>MS Care Consultation</td>
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<td>Ilaria Callegari</td>
<td>University of Basel Department of Biomedicine Clinical Neuroimmunology Lab</td>
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<td>Giulio Disanto</td>
<td>Ente Ospedaliero Cantonale, Lugano Neurocenter of Southern Switzerland</td>
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<td>Nadine Domnik</td>
<td>ETH Zurich Rehabilitation Engineering Laboratory</td>
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<td>Sarah Guimbal</td>
<td>University of Bern Theodor Kocher Institute</td>
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<td>Christina Haag</td>
<td>University of Zurich Epidemiology, Biostatistics and Prevention Institute &amp; Institute for Implementation Science in Health Care</td>
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<td>Benjamin Victor Ineichen</td>
<td>University Hospital Zurich Department of Neuroradiology</td>
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<td>Samuel Jones</td>
<td>Laboratory of Neuroimmunology, Neuroscience Research Centre, Department of</td>
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<td>Clinical Neurosciences, Lausanne University Hospital and University of Lausanne</td>
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<td>Vasileia Kalaitzaki</td>
<td>University of Zurich, Institute of Laboratory Animal Science</td>
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<td>Antonios Katsoulas</td>
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<td>Zina-Mary Manjaly</td>
<td>Schulthess Clinic, Zurich, Department of Neurology, ETH Zurich, Department</td>
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<td>Amandine Mathias</td>
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<td>Inês Pereira</td>
<td>Translational Neuromodeling Unit, University of Zürich &amp; ETH Zurich</td>
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<td>Maximilian Pistor</td>
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<td>Jessica Rebeaud</td>
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«25 Years – Moving Forward Together for People with MS»

9.30 – 10.00  Coffee and Gipfeli

Session 1

Chairpersons:
Caroline Pot, Lausanne
Claire Bridel, Geneva

10.00 – 10.15  Christoph Lotter, Zurich
Welcome from the Swiss MS Society

10.15 – 10.45  Alberto Ascherio, Boston (USA)
Epstein-Barr Virus as the Leading Cause of MS:
Epidemiological Evidence and
Potential Mechanisms

10.45 – 11.15  Jens Kuhle, Basel & Cristina Granziera, Basel
Swiss MS Cohort: Achievements and Next Steps

11.15 – 11.45  Coffee Break
MS Researcher Poster Presentation

Session 2

Chairpersons:
Sandra Bigi, Luzern
Britta Engelhardt, Bern

11.45 – 12.15  Andrew Chan, Bern
MS Medication and Treatment:
Achievements in the past 25 years

12.15 – 13.00  Award Ceremony
«Swiss Multiple Sclerosis Society
Research Prize»

13.00 – 14.15  Lunch Break
MS Researcher Poster Presentation
A potential role of the Epstein-Barr virus (EBV) in multiple sclerosis has been suspected for many years, because of the similarity in the epidemiology of MS and that of infectious mononucleosis, which is a common manifestation of primary EBV infection in adolescents and adults, but there was no definitive proof of causality.

In a longitudinal study based on a source population of over 10 million young adults, we demonstrated that EBV negative individuals do not develop MS, unless they first become infected with EBV. EBV infection also precedes the elevation of serum neurofilament light chains, an early marker of neurodegeneration in MS, and a screening of antibodies against the entire human virome revealed that only antibodies to EBV peptides are enriched in MS. Collectively, these results establish EBV infection as the leading cause of MS.

I will further discuss the potential mechanisms by which EBV can cause MS and the implication for MS prevention and treatment.

**Alberto Ascherio**

«I graduated in medicine at the University of Milan in 1978. After practicing medicine and public health in Latin America and Africa for several years I moved to Boston, where I received a doctoral degree in epidemiology in 1992 and joined the faculty at Harvard. My current research is primarily devoted to finding the causes of multiple sclerosis and other neurodegenerative diseases.»
Cristina Granziera
«I obtained an MD at Padova University Medical School (Padova, Italy) in 2001, a PhD in Neuroscience at Lausanne University in 2007 and the Swiss Neurology board in 2010. In 2011, I was appointed as lecturer at Lausanne University, where I was promoted to senior lecturer in 2014. In 2015, I joined the Massachusetts General Hospital (MGH) and Harvard Medical School (Boston, USA) as assistant professor in Radiology and assistant in Biomedical Engineering. Since 2018, I hold my current position as a senior consultant neurologist in the department of neurology of the University Hospital Basel and as professor in neurology and biomedical engineering at the University of Basel, and as a steering committee member of the «Research Center for Neuroscience and Neuroimmunology (RC2NB)» in Basel.»

Jens Kuhle
«I obtained my MD from the Eberhard-Karls University in Tübingen (Germany) and specialised in neurology and neuroimmunology at the University Hospital Basel. I was appointed as Head of the Multiple Sclerosis Centre at the University Hospital Basel in 2018. I currently work as a senior consultant neurologist and a professor of Neurology. I am the Principal Investigator for the Swiss MS Cohort Study, a national academic network dedicated to biomarker and outcome research in MS.»
Swiss MS Cohort: Achievements and Next Steps

The Swiss MS Cohort (SMSC) consortium was established in 2012 and includes eight Swiss MS centres (five university and three cantonal hospitals). Its purposes are the expansion of disease understanding and translation into clinically applicable diagnostic and therapeutic tools for persons with MS by collecting 6-monthly or annually prospective long-term clinical and radiological data, and biological samples for discovery and validation of novel biomarkers. The SMSC is one of the largest clinical MS research databases of its type across Europe and Northern America with 1'578 patients prospectively recruited (median follow-up time 5.9 years of 11'133 visits) and has developed in this profile critical expertise in the standardization and integration of high quality clinical data (i.e. patient examinations are performed by Neurostatus® certified examiners in >90% of the cases), imaging data, and over 265'000 biofluid samples (96.9% coverage of all visits, as of May 2022) (cerebrospinal fluid (CSF), serum/plasma/whole blood) have been banked.

The SMSC has established data quality control mechanisms including automated and manual data querying, and once yearly, on-site source data verification monitoring visits at all participating centres. The continuous analysis of MRI scans is led by Cristina Granziera.

The SMSC is source for high impact original papers with relevance for clinical practice, and more than 10 ongoing projects of which several supported by the Swiss National Science Foundation.

Cristina Granziera  
→ University Hospital Basel and University of Basel  
  Translational Imaging in Neurology (ThINK) Basel, Department of Biomedical Engineering
→ University Hospital Basel and University of Basel  
  Neurologic Clinic and Policlinic, MS Center, and Research Center for Clinical Neuroimmunology and Neuroscience Basel (RC2NB)

Jens Kuhle  
→ University Hospital Basel and University of Basel  
  Neurologic Clinic and Policlinic, MS Center, and Research Center for Clinical Neuroimmunology and Neuroscience Basel (RC2NB)

Notes
The approval of Interferon-beta 1b for multiple sclerosis in the 1990s as the first evidence-based disease modifying therapy (DMT) heralded a new era in the management of MS. Major progress in basic research, technical advancements (e.g. MRI) and innovative clinical study designs have led to the rapid development of new therapies with different modes of action and application routes. Meanwhile, several orally or parenterally administered substances are approved not only for relapsing MS, but also for progressive disease forms. Likewise, treatment goals have changed: whereas early on a moderate reduction of the relapse rate was considered a breakthrough, meanwhile we discuss «no evidence of disease activity» or «disability improvement» as attainable study endpoints.

The paradigm change of disease modifying therapy already at earliest clinical disease stages in the early 2000s was based on the histopathological demonstration of irreversible tissue destruction early during the disease. About 20 years later, we have only recently seen the results of the first randomized controlled treatment study in radiologically isolated syndrome. Also, identification of «progression independent of relapse activity» already during relapsing disease leads to a broadening of treatment targets early during the disease. Given the need for early therapeutic intervention, over the decades several modifications of diagnostic criteria aimed at sensitive detection of the disease (i.e. using MRI) with a careful balance for specificity. Newer modifications of diagnostic criteria will detail the role of the optic nerve in the diagnostic process. In a close interplay between different research areas, a conceptualizing context of the pathophysiological underpinnings of progressive MS is emerging. Also here we hope that therapeutic trials will corroborate our hypotheses generated from basic research, similar as has been the case in relapsing MS. Still, also in the

Andrew Chan
«I act as Head of the Medical Division Neuro (Depts. Neurology, Neurosurgery, Neuroradiology), Inselspital, University Hospital of Bern. After studying medicine and obtaining a doctorate at the University of Hamburg, I completed my specialist training at the University of Würzburg and continued my professional development as Senior Physician at the Universities of Göttingen and Bochum. I have published widely in the field of MS, including papers on molecular markers of disease progression and risk of immunotherapy, treatment optimization and patient monitoring. I have been the principal investigator for several clinical studies in MS. I have also been involved in the development of national treatment guidelines.»

MS Medication and Treatment: Achievements in the past 25 Years

The approval of Interferon-beta 1b for multiple sclerosis in the 1990s as the first evidence-based disease modifying therapy (DMT) heralded a new era in the management of MS. Major progress in basic research, technical advancements (e.g. MRI) and innovative clinical study designs have led to the rapid development of new therapies with different modes of action and application routes. Meanwhile, several orally or parenterally administered substances are approved not only for relapsing MS, but also for progressive disease forms. Likewise, treatment goals have changed: whereas early on a moderate reduction of the relapse rate was considered a breakthrough, meanwhile we discuss «no evidence of disease activity» or «disability improvement» as attainable study endpoints.

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early 2020s we face major unmet medical needs. Thus, recovery of already existing fixed neurological
disability and – as a prerequisite «protection» – can still not be achieved with current medications. Also,
in clinical practice symptomatic therapy often fails due to tolerability issues, and areas with high need
such as fatigue are not even well characterized from a clinical point of view.
However, given more recent technological and methodological advances, major progress also for these
unmet needs are to be expected if the pace of developments over the past decades can be maintained.

Andrew Chan
– University Hospital Bern, Inselspital
  Department of Neurology

Notes
The Swiss Multiple Sclerosis Society has a long standing tradition of supporting MS research. In the past 22 years, MS-related research projects throughout Switzerland were funded with over CHF 30 Mio.

In recognition of outstanding research accomplishments in the field of Multiple Sclerosis and to encourage promising future research projects, the Swiss MS Society decided to award the «Swiss Multiple Sclerosis Society Research Prize», starting in 2023.

The prize is endowed with CHF 100’000 and will be awarded every two years to a researcher at a Swiss institute or clinic.

Award applications are evaluated by a group of experts including a patient representative. Members of this year’s Research Prize Evaluation Committee are:

- Renaud Du Pasquier, Lausanne
- Adriano Fontana, Zurich
- Ludwig Kappos, Basel
- Irene Rapold, Winterthur
- Myriam Schluep, Lausanne

This year’s award will be presented at the MS State of the Art Symposium.
Gemeinsame Jahrestagung 2023
Schweizerische Neurologische Gesellschaft
Schweizerische Gesellschaft für Neurochirurgie
Gastgesellschaft:
Schweizerische Gesellschaft für Verhaltensneurologie

Réunion Annuelle Conjointe 2023
Société Suisse de Neurologie
Société Suisse de Neurochirurgie
Société Invitée:
Société Suisse de Neurologie Comportementale

23.-24. November 2023
Kongresshaus Zürich
sng-sgnc2023.congress-imk.ch

3. Neurologisches Pflegesymposium
3ème Symposium neurologique en soins

IG-NOPPS
Interessengruppe des Neurochirurgischen OP-Personals Schweiz
Association of neurosurgical nursing staff Switzerland
## Workshops

| Workshop A | 14.15 – 15.00 | Myrta Kohler, St. Gallen  
Viktor von Wyl, Zurich |
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<tr>
<td><strong>Digital Technologies – Solutions for People with MS and Health Care Professionals?</strong></td>
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<td>Apps, sensors, or virtual reality offer exciting opportunities for MS management improvement and self-empowerment of persons with MS. What will it take to implement digital tools into routine care? We will discuss wishes, needs, and pain points of different stakeholders in an interactive format. This workshop is organized jointly by the members of the Digital Advisory Board.</td>
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| Workshop B | 14.15 – 15.00 | Johanna Oechtering, Basel  
Axel Regeniter, Zurich |
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<td><strong>CSF diagnostics in MS – Essentials and News: What the Neurologist needs to know</strong></td>
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<td>CSF diagnostics in MS has experienced a revival with the return of oligoclonal bands to the McDonald criteria 2017. We will discuss the diagnostic/prognostic value and pathophysiological implications of well-known and emerging candidates like Kappa free light chains, antigen-specific indices and intrathecal IgM production.</td>
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| Coffee Break |
| 15.00 – 15.15 |

| Workshop C | 15.15 – 16.00 | Pasquale Calabrese, Basel  
Anke Salmen, Bern |
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<td><strong>Integrative Care Concepts in MS – What do Patients need besides the Medical Treatment?</strong></td>
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<td>With this workshop, we want to assess and address different perspectives of what is needed in a comprehensive MS treatment besides the medical treatment. We will hear from patients, nurses and therapists and look forward to a lively discussion with presenters and participants.</td>
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| Workshop D | 15.15 – 16.00 | Cristina Granziera, Basel  
Maria Isabel Vargas Gomez, Geneva |
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<td><strong>Advanced MRI Biomarkers and Gadolinium-based Contrast Agents Use for Clinical Routine</strong></td>
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<td>We will discuss the most recent advances in diagnostic and prognostic magnetic resonance imaging (MRI) biomarkers in MS patients as well as their current translation to clinical practice. Also, we will explain the advantages, disadvantages and risks of using gadolinium-based contrast agents for the diagnosis and monitoring of MS patients.</td>
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| Farewell Apero |
| 16.00 |

MS State of the Art Symposium 2023
Apps, sensors, or virtual reality offer exciting opportunities for Multiple Sclerosis management improvement or self-empowerment of persons with MS. Bringing such tools into clinical routine can be challenging. Are clinical settings and health systems ready for a scale-up of digital tools? How can health care providers and persons with MS manage the multitude and magnitude of digital data? What support is required to bring digital health tools to success?

Our interactive workshop will examine success factors and challenges for implementing digital tools into real-world MS management. The workshop will kick off with 2-3 short digital health project presentations, with a focus on challenges and lessons learned. The second workshop part explores the needs and expectations of health care providers and persons with MS for digi-
tal health tools in an open discussion format. Finally, we will discuss whether and how regular exchanges or intensified collaborations could be fostered between persons with MS, health care providers, and academic digital health researchers to move digital health research and care forward.

This workshop is organized jointly by the members of the Digital Advisory Board.

Myrta Kohler
– Eastern Switzerland University of Applied Sciences
– Clinics of Valens

Viktor von Wyl
– University of Zurich
  Epidemiology, Biostatistics and Prevention Institute & Institute for Implementation Science in Health Care

Notes
CSF diagnostics in multiple sclerosis (MS) has experienced a revival with the return of oligoclonal IgG bands to the McDonald criteria 2017. Oligoclonal bands reflect the chronic and persistent humoral immune response and remain the central element of CSF diagnostics in multiple sclerosis. They are present in up to 95-98% of MS patients and are therefore a pathognomonic and relevant biomarker for diagnosing MS. However, differences in the sensitivity as well as technical (dis-)advantages of the available methodologies need to be considered. While oligoclonal IgG bands serve mainly as a diagnostic biomarker, an intrathecal immunoglobulin (IgM synthesis, present in about 20-25% (according to Reiber formula) of MS patients appears to be a highly predictive biomarker. An IgM synthesis is associated with earlier conversion from clinically isolated syndrome (CIS) to MS and also beyond higher disease activity and severity. Recent studies suggest pathophysiological relevance: IgM is the strongest complement-activating immunoglobulin and the increase in disease activity and severity might be perpetuated via activation of the classical complement pathway. The chronic humoral immune response in MS

Johanna Oechtering

«I am a consultant neurologist at the MS centre and neurology department of the University Hospital Basel. I accomplished my specialization in neurology at Charité Berlin before moving to Basel in 2018 to intensify my research activities. My main scientific focus is the chronic humoral immune response in the cerebrospinal fluid (CSF) and associated pathophysiological implications in MS as well as other relevant biomarkers in CSF and blood.»

Axel Regeniter

«I am a medical doctor working in a laboratory with a special focus on CSF diagnostics. My 30-year experience with CSF methodology and result interpretation cumulated in a recent book publication that recaps the current state of knowledge and interpretation. I further developed a graphical knowledge-based system, «Visual MDI Lablink» with a CSF module to assess and visualize normal and pathological analytical results in CSF. I am an active board member of the German Society for CSF Diagnostics.»

Workshop B

CSF diagnostics in MS – Essentials and News: What the Neurologist needs to know

CSF diagnostics in multiple sclerosis (MS) has experienced a revival with the return of oligoclonal IgG bands to the McDonald criteria 2017. Oligoclonal bands reflect the chronic and persistent humoral immune response and remain the central element of CSF diagnostics in multiple sclerosis. They are present in up to 95-98% of MS patients and are therefore a pathognomonic and relevant biomarker for diagnosing MS. However, differences in the sensitivity as well as technical (dis-)advantages of the available methodologies need to be considered. While oligoclonal IgG bands serve mainly as a diagnostic biomarker, an intrathecal immunoglobulin (IgM synthesis, present in about 20-25% (according to Reiber formula) of MS patients appears to be a highly predictive biomarker. An IgM synthesis is associated with earlier conversion from clinically isolated syndrome (CIS) to MS and also beyond higher disease activity and severity. Recent studies suggest pathophysiological relevance: IgM is the strongest complement-activating immunoglobulin and the increase in disease activity and severity might be perpetuated via activation of the classical complement pathway. The chronic humoral immune response in MS
is further characterized by a polyclonal B-cell response with production of multiple antibodies, e.g. measles, rubella and varicella (MRZ reaction). This polyspecific immune response is a valuable tool to better differentiate MS from similar demyelinating entities like MOG-antibody-disease (MOGAD).

Cytokine CXCL-13 is an emerging prognostic biomarker in MS with main involvement in recruitment and activation of B- and T-lymphocytes. Last but not least it is a current matter of debate if the measurement of free kappa light chains in CSF might even serve as an alternative to the determination of oligoclonal IgG bands.

We will review the existing literature and discuss the potential, pathophysiological background, technical specialties and limitations of these CSF biomarkers.

Johanna Oechtering  
- University Hospital and University of Basel  
  Department of Neurology &  
  Multiple Sclerosis Centre and Research Center  
  for Clinical Neuroimmunology and  
  Neuroscience (RCZNB)

Axel Regeniter  
- Medica Laboratory, Zurich
Integrative care is a concept that utilizes evidence-based approaches to conventional medical care by expanding current MS-treatment standard onto symptomatic therapies that are still not firmly established in traditional care approaches, though some evidence exists. Hence, this approach incorporates also daily habits and practices, such as diet and exercise, in order to treat and also prevent disease.

This approach blends conventional medicine, lifestyle, and also wellness approaches in order to treat the whole person. By doing so the integrative approach is practiced through a supportive, not paternalistic, clinician-patient relationship.

This workshop will present some current integrative approaches from different perspectives by integrating the view and needs from a person with MS together with a MS-Nurse perspective and also a physiotherapeutic approach.
Cristina Granziera
«I obtained an MD at Padova University Medical School (Padova, Italy) in 2001, a PhD in Neuroscience at Lausanne University in 2007 and the Swiss Neurology board in 2010. In 2011, I was appointed as lecturer at Lausanne University, where I was promoted to senior lecturer in 2014. In 2015, I joined the Massachusetts General Hospital (MGH) and Harvard Medical School (Boston, USA) as assistant professor in Radiology and assistant in Biomedical Engineering. Since 2018, I hold my current position as a senior consultant neurologist in the department of neurology of the University Hospital Basel and as professor in neurology and biomedical engineering at the University of Basel, and as a steering committee member of the «Research Center for Neuroscience and Neuroimmunology (RC-2NB)» in Basel.»

Maria Isabel Vargas Gomez
«I am radiologist and neuroradiologist, head of the Diagnostic Neuroradiology unit, Vice-chairman of Neuroradiology Division and Professor of the Faculty of Medicine of the Geneva University. I have an expertise in diagnostic neuroradiology. My areas of interest are the optimization of imaging technics particularly the MRI applied to different diseases such as multiple sclerosis, epilepsy, tumours, spinal cord and peripheral nerves.»
Workshop D
Advanced MRI Biomarkers and Gadolinium-based Contrast Agents Use for Clinical Routine

We will discuss the most recent advances in diagnostic and prognostic magnetic resonance imaging (MRI) biomarkers in MS patients as well as their current translation to clinical practice. Also, we will explain the advantages, disadvantages and risks of using gadolinium-based contrast agents for the diagnosis and monitoring of MS patients.

Cristina Granziera
– University Hospital Basel and University of Basel, Translational Imaging in Neurology (ThINK) Basel, Department of Biomedical Engineering,
– University Hospital Basel and University of Basel, Neurologic Clinic and Policlinic, MS Center, and Research Center for Clinical Neuroimmunology and Neuroscience Basel (RC2NB)

Maria Isabel Vargas Gomez
– Division of Neuroradiology, Diagnostic Department, Geneva University Hospital and Faculty of Medicine of Geneva

Notes
Assistenz für Familien mit pflegenden Angehörigen

Bei der Versorgung von zu Hause lebenden Menschen mit hohem Pflegeaufwand nehmen pflegende Angehörige eine Schlüsselstellung ein! AsFam unterstützt Pflegende Angehörige bei der Pflege Zuhause und steht mit ihrem Fachwissen an ihrer Seite.

www.asfam.ch
MS Researcher
Poster Presentations

The Swiss MS Society supports research projects in the field of Multiple Sclerosis with considerable financial contributions. A selection of current projects is displayed during the coffee and lunch break of the symposium. Do not miss the opportunity of viewing these posters and discussing the projects with the researchers.

Poster No 1-10: ground floor
Poster No 11-20: first floor
Background — In neuromyelitis optica spectrum disorder (NMOSD), recurrent optic neuritis leads to potentially irreversible impairment. Pathogenic antibodies against aquaporin 4 (AQP4-IgG) are present in the majority of patients. With high abundance of AQP4 water channels, the retina might be a primary target of AQP4-IgG. Human organotypic retina cultures (hORC) retain an in vivo-like tissue architecture to investigate the intraretinal pathology in response to AQP4-IgG.

Methods — Human retinas were obtained from post-mortem donors and 50 mm² explants cultured in porous transwell cell culture inserts. After 7-8 days in vitro (DIV), AQP4-IgG + human serum (HuS), isotype (Iso-)IgG + HuS, no treatment or detergent (Triton-X) was added for 24h prior to formalin-fixation and cryo-embedding. Supernatant was collected for longitudinal analysis of cell death (Lactate dehydrogenase, LDH assay). Retinal cross sections were stained (hematoxylin/eosin, glutamate synthetase, glial fibrillary acidic protein, AQP4, human IgG).
**Results** — Treatment with AQP4-IgG and human serum did not affect retinal layer thicknesses or cell death measured by lactate dehydrogenase release. Binding of human IgG was detected in antibody-treated cultures with differential patterns between AQP4- and Iso-IgG. Involvement of Müller cells is still being investigated.

**Conclusions** — hORC are viable over the observed div without an increase of cell death upon AQP4-IgG binding. This may be in line with the recognized course of events in spinal cord lesions where astrocytic lysis is described in advanced demyelinating lesions. Early signs of NMOSD pathology include morphological changes rather than death. This is currently being investigated in our system.

_Jana Remlinger_

− University Hospital Bern, Inselspital
  Department of Neurology
**Background** — Data on sex differences in Multiple Sclerosis therapy efficacies are sparse despite clinical importance. Sphingosine 1-Phosphate (S1P) Receptor (S1PR) Modulators (S1PRMs) are a class of treatment for MS targeting S1PRs located on lymphocytes surface leading to decreased egress from lymph nodes. With this work, we aim to investigate the sex-specific aspects of S1PRM efficacy.

**Methods** — To investigate the effect of sex on S1PRM treatment efficacy, we used the MS mouse model myelin oligodendrocyte glycoprotein peptide 35-55 experimental autoimmune encephalomyelitis (MOG35-55 EAE). C57BL/6Jr wild-type mice of both sexes were treated for 20 days from immunization with Fingolimod (FTY) dissolved in condensed milk or control orally. Mice were scored daily on a 10-point scale. Spinal cord S1PR1 T cell expression was histologically assessed.

**Results** — In vivo, when stratifying the results by sex, FTY was more effective in male compared to female mice; indeed, no male mice showed any signs of disease when treated with FTY (mean cumulative EAE score: females (n=11) mean: 0.6, 95%-Confidence interval (CI): 0.4-0.9, males (n=5) mean: 0, 95%-CI: 0-0;
Mann-Whitney U Test (MWT) \( p=0.001 \). Membrane located S1PR1 expression by CNS infiltrating CD3+ T cell was higher in females FTY-treated compared to control-treated mice (FTY group mean: 3.2, 95%-CI: 3.2-3.4, control group mean: 2.9, 95%-CI: 2.8-3.0; MWT \( p<0.001 \)). This difference was not observed in male mice.

**Conclusions** — Own, unpublished investigations pointed towards age and sex differences in S1PRM treatment efficacy in people with MS, being the rationale for this experiment. Sex may affect the efficacy of FTY treatment in MOG35-55 EAE. An exceptional high rate of male mice not sick during treatment has to be considered as a confounder. Reasons for sex differences remain unclear. One plausible mechanism might be the differential expression of S1PR1 with higher receptor expression in female mice.

*Maximilian Pistor*

– University Hospital Bern, Inselspital

  Department of Neurology
03 | Antonios Katsoulas

Unexpected role of Toll-like Receptors in experimental autoimmune encephalomyelitis (EAE)

**Background** — Multiple Sclerosis is a multifactorial disease of autoimmune nature that affects a significant proportion of the population. Many environmental factors influence the disease progression, which also depends on each patient's genetic profile. The interaction of these factors in triggering the disease is still unclear but Pattern recognition receptors (PRRs), which coordinate the innate immune response, may have a significant role in MS development.

**Methods** — Previous work of our lab, with mice deficient in multiple toll-like receptors (TLR23479 KO) or adaptor molecules (Myd88/Trif-/-, TRAM-/-, TLR3-/-) as well as combinations of them (Myd88/Tlr3-/- and Myd88/Tram-/-), identified some unexpected involvements of specific TLR-signaling in CNS autoimmunity using the experimental autoimmune encephalomyelitis (EAE) model (active and passive), as well as multiparametric flow cytometry for cellular population analysis.

**Results** — Using a quintuple knockout mouse model, TLR23479, our lab has previously shown that abrogating Toll-like receptor (TLR) signalling has surprisingly no consequences on EAE. Downstream of TLR, signal is processed by two adaptor molecules: MYD88 and TRIF. As the quintuple knockout still develops EAE, it is possible that MYD88 and TRIF have a regulatory effect over each other. Using a Myd88/Trif-/-, we showed that the double
deficiency reverts the resistance to EAE observed in Myd88-/-, suggesting a feedback mechanism that keeps the highly proinflammatory and potentially damaging activation of MYD88 under the control of TRIF. Only TLR3 and TLR4-TRAM signal through TRIF. Thus, our aim was to dissect which of these branches, TLR3 or TLR4-TRAM, conveys the regulatory role of TRIF over MYD88. Crossing Tlr3-/- and Tram-/- to Myd88-/- and studying disease progression and major immunological cell populations of the double knockouts (Myd88/Tlr3-/- and Myd88/Tram-/-), showed that absence of TRAM signalling but not of TLR3 signalling (in addition to MYD88) can revert the EAE resistance seen in Myd88-/- mice.

**Conclusions** — The aforementioned results suggest that the TRIF signalling pathway has a regulatory role over Myd88. Moving forward, our aim is to explore this regulatory mechanism and use it as a possible treatment option for EAE and ultimately MS.

_Antonios Katsoulas_
— _University of Zurich_

_Institute of Laboratory Animal Sciences_
Peptide-coupled RBCs as treatment for autoimmune diseases – dissecting the mechanisms of immune tolerance induction

**Background** — Induction of antigen-specific immune tolerance is one of the most specific ways of reverting the abnormal immune reactions commonly seen in autoimmunity. Our group has developed an antigen-specific therapy for the treatment of Multiple Sclerosis which involves the coupling of autologous red blood cells (RBCs) with a cocktail of seven MS immunodominant peptides from three myelin proteins. A recent phase Ib clinical trial in MS patients demonstrated its safety and tolerability and provided evidence for induction of immune tolerance in patients. Prior data suggest an indirect mechanism of immune tolerance induction, where peptide coupled RBCs (pcRBCs) are phagocytosed and processed by tissue-resident macrophages of the liver and the spleen, which present the antigens in a tolerogenic way. Here, we aim to elucidate the mechanism of action of this antigen-specific therapy.

**Methods** — We have established a reliable protocol for the in-situ digestion of mouse liver and the subsequent isolation, as well as phenotypic characterization of non-parenchymal cells, primarily liver macrophages, with flow cytometry.

**Results** — So far, we have identified a CD11b+F4/80+ cell population, other than the CD11b+F4/80hi population of tissue-resident macrophages (Kupffer cells), which appears in the liver of mice, 2, 5 and 17 hours post intravenous injection of pcRBCs, and coincides with an increase in CD11b+F4/80- monocyte and a
decrease in Kupffer cell numbers. All three populations seem to be able to phagocytose the injected pcRBCs, with Kupffer cells being the predominant phagocytosing population. Upon erythrophagocytosis, the Kupffer cell population seems to acquire a tolerogenic phenotype, displayed by the reduction in CD80 and MHCII molecules, while the newly appearing CD11b+F4/80+ cells seem to resemble the Kupffer cell population, as shown by the expression of MHCII, PD-L1 and the engulfment receptor TIM4.

**Conclusions** — Collectively, we have successfully established a model system for the study of peptide-coupled cell-mediated immune tolerance. Moreover, we have phenotypically characterized the liver myeloid cell compartment, and have identified the involvement of Kupffer cells in peptide-coupled cell phagocytosis. Moving forward, our focus will lie on the in-depth phenotypical and transcriptional characterization of the phagocytosing populations, with the end goal of understanding the establishment of peptide-coupled cell induced immune tolerance.

_Vasileia Kalaitzaki_  
- _University of Zurich_  
- _Institute of Laboratory Animal Science_
Background — Upper limb sensorimotor impairments in persons with Multiple Sclerosis (pwMS) lead to decreased quality of life and independence. To personalize therapy methods and improve rehabilitation outcomes, it is essential to better understand impairment profiles and monitor their progression. However, conventional assessments only poorly capture upper limb sensorimotor deficits, limiting their systematic application. Technology-based assessments are a promising approach to extract digital health metrics that could be used to better describe upper limb deficits, predict their evolution during recovery, provide easy to understand feedback to patients and clinicians, and eventually help decision-making.

Methods — We proposed the Virtual Peg Insertion Test (VPIT) as an upper limb goal-directed technology-based assessment, and evaluate here its feasibility in a cohort of 170 pwMS who received therapy at the Kliniken Valens. In a cross-sectional analysis, we evaluated the ability of the VPIT metrics to sensitively capture different impairment profiles and monitor meaningful disease-related changes in sensorimotor function. Additionally, we performed a statistical comparison of VPIT metrics between pwMS and a reference sample of able-bodied participants.

Results — We observed that pwMS performed significantly worse in grip force and movement velocity than able-bodied participants. The VPIT metrics all showed movement abnormalities for pwMS in com-
comparison to able-bodied participants, but high inter-subject variability could be observed. We used mixed effect models to understand the relation between task completion time of the VPIT and abnormal movement patterns or hand grip forces. There we could identify movement smoothness, decreased speed, and impaired force control as the main influencing factors for performance in the VPIT.

Conclusions — We could show that the digital health metrics of the VPIT partly correlate with conventional clinical assessments while allowing to capture individual movement abnormalities more sensitively. These promising findings underline the potential of the VPIT for being used in clinics for assessing upper limb sensorimotor function in pwMS with mild or moderate symptoms. Next, building on the collected data, prediction models will be developed and used to predict therapy outcomes. These predictions could then be provided to therapists as well as patients to support decision making and increase motivation for therapy.

Nadine Domnik
– ETH Zürich
  Rehabilitation Engineering Laboratory
Background — Magnetic resonance imaging (MRI) has insufficient specificity for underlying tissue pathology. This is particularly important for Multiple Sclerosis, demonstrating a heterogeneous range of focal pathology, among them inflammation, demyelination, and neurodegeneration. Correlating neuroimaging features to their tissue substrate could not only provide key insights into disease pathogenesis but could also enhance the specificity of MRI. However, the procedure of correlating imaging features to tissue pathology is highly tedious and no standardised methods exist. Thus, we aimed at developing and validating a tool to facilitate correlation of brain MRI features to corresponding tissue pathology.

Methods — We developed a compoundable, water-proof, and fully MRI-compatible container with an imprinted 3D coordinate system, customised on the negative of 109 averaged brains.

Results — Pilot studies of 6 whole human brains, fresh or formalin fixed, confirmed functionality and efficiency of the Brainbox. Common imaging features such as perivascular spaces, periventricular white matter lesions and anatomical brain structures like the Hippocampus were successfully and efficiently correlated to their corresponding tissue counterpart using the built-in 3D coordinate system.
Conclusions — These proof-of-principle experiments underline the feasibility and usability of our Brainbox, both from a time and from an accuracy perspective. With this, the Brainbox can contribute to improved specificity of MRL. Based on gathered experience from these pilot studies, we now plan to extend our study to systematically investigate correlations between imaging and pathology features in Multiple Sclerosis.

Benjamin Victor Ineichen
– University Hospital Zurich
  Department of Neuroradiology
**Background** — Multiple sclerosis is widely regarded as an autoimmune disease driven by autoreactive immune cells infiltrating the brain and inducing inflammatory demyelinating lesions. CD8+ T cells are the most predominant lymphocytic population in these lesions and are clonally expanded suggesting an antigen-driven proliferation. How these CD8+ T cells interact with brain cells to mediate damage is still unclear and no CNS auto-antigen has yet been formally identified. Our objective is to screen for the presence of autoreactive CD8+ T cells recognizing autologous neurons and astrocytes.

**Methods** — To screen for neuron and astrocyte-reactive CD8+ T cells in an unbiased manner, we have implemented protocols to differentiate neurons and astrocytes from human induced pluripotent stem cells (hiPSCs). Using these cells, we have designed a fully autologous co-culture assay between CD8+ T cells and hiPSC-derived neurons and astrocytes. First, an initial expansion step is performed where ex vivo peripheral blood mononuclear cells (PBMCs) and HLA-I enhanced neurons or astrocytes are cultured together for a total of 10 days. Second, after the 10-day expansion, CD8+ T cells are isolated and incubated overnight with freshly prepared HLA-enhanced neurons and astrocytes to perform antigenic restimulation. Finally, to detect activated CD8+ T cells, an IFN-γ secretion assay is performed. The presence of activated CD8+ T cells is then assessed by flow cytometry.
**Results** — First, we have generated hiPSCs for a cohort of 6 healthy donors (HDs) and 9 MS patients that we can differentiate into neurons and astrocytes. We demonstrate that our hiPSC-derived neurons and astrocytes are capable of: 1. Upregulating HLA class I expression upon exposure to IFN-γ and TNFα; 2. Eliciting successful expansion and activation of antigen-specific CD8+ T cells through HLA-mediated presentation of endogenously expressed antigens. Additionally, preliminary results show that CD8+ T cells from MS patients, taken at the time of a relapse, do recognize auto-antigens expressed by neurons and astrocytes.

**Conclusions** — Overall, we now have at hand a co-culture system allowing us to successfully expand and detect autoreactive CD8+ T cells from any MS patient and HD directly from ex vivo PBMCs. This now paves the way for us to assess the neuron and astrocyte-specific CD8+ T cell response in our cohort of MS patients and compare with the CD8+ T cell response in HDs. Ultimately, our novel hiPSC-based model will offer unique perspectives in identifying TCRs (and ultimately antigens) that would be specifically pathogenic in MS patients. Based intervention that is well embedded in the context. Further research on effectiveness is planned.

Samuel Jones
– Laboratory of Neuroimmunology, Neuroscience research Centre,
  Department of Clinical Neurosciences,
  Lausanne University Hospital and University of Lausanne
Background — Discovery of CNS-reactive autoantibodies has profoundly changed clinical practice and therapeutic approaches in neurology and psychiatry. Nevertheless, about 10% of the patients developing autoimmune limbic encephalitis, a classical symptom associated with the presence of CNS-reactive autoantibodies, remain seronegative for all currently known CNS antigens. Here, we developed a cell-based assay to screen for the presence of novel CNS-specific antibodies in sera and cerebrospinal fluid (CSF) using neurons and astrocytes derived from human-induced pluripotent stem cells (hiPSC).

Methods — Human iPSC-derived astrocytes and neurons were incubated with paired serum and CSF of 229 patients suffering from inflammatory neurological diseases (IND) encompassing 54 MS patients and 53 patients with non-IND (NIND). IgG bound to hiPSC-derived CNS cells were detected using a combination
of fluorescently-labeled antibodies. IgG-associated fluorescence intensity (FI) measures and microscopy observations were automated. Serum or CSF were defined as positive using a ROUT test with a FDR at 2% on quantified FI. IgG reactivity to CNS cells was further analyzed by flow cytometry.

**Results** — We identified antibodies recognizing hiPSC-derived CNS cells in 64/282 (22.7%) study patients including 32 on astrocytes only, 28 on neurons only, and four on both cell types. CNS reactive antibodies were found mostly in the CSF (40/64) including six positive in both serum/CSF. Antibodies were detected in 3/53 NIND (5.6%) vs 61/229 IND (26.7%), the latter category including eleven patients who had known CNS-reactive antibodies (Hu, Ri, AK5, LGI-1, NMDAR, AQP4, GFAP) detected in routine laboratory. We further found astrocyte- or neuron-reactive IgG in 20.5% and in 13% of MS patients respectively. Microscopy and flow cytometry analyses further confirmed these results.

**Conclusions** — Our hiPSC-based CBA allows discovery of new CNS-reactive antibodies. Such a potent tool opens new perspectives in identifying new CNS antigens targeted in MS pathogenesis as in antibody-mediated diseases of the CNS.

_Amandine Mathias_
- Laboratory of Neuroimmunology,
  Neuroscience Research Centre and Service of Neurology,
  Department of Clinical Neurosciences,
  Lausanne University Hospital and University of Lausanne
Extracellular vesicles from JCV-infected human astrocytes: paving the way towards biomarker discovery for progressive multifocal leukoencephalopathy

**Background** — Progressive multifocal leukoencephalopathy (PML) is a devastating demyelinating disease of the central nervous system (CNS) caused by JC polyomavirus (JCPyV). The virus normally resides in a benign state in more than 50% of the adult population, however, in rare cases of severe or selective immune suppression, such as multiple sclerosis, patients receiving strong disease-modifying therapies (DMTs), JCPyV is able to establish a lytic infection of astrocytes and oligodendrocytes, resulting in rapid demyelination. The only means to halt disease progression is the reconstitution of the immune response in the brain, i.e. stopping DMTs. PML thus presents two major issues, 1. Irreversible neurological damage has already often occurred by the time of diagnosis; and 2. Stopping DMTs presents a major risk of MS rebound. For this reason, there is a dire need for biomarkers to identify patients who will develop PML. Extracellular vesicles (EVs) are lipid bilayer-delimited particles that are released by all cell types and found in all body fluids. Since EVs reflect the state of their cell of origin, we believe that brain-derived EVs found in the blood might provide a valuable source of biomarkers for identifying patients that are at risk for PML development.
**Methods** — EVs were isolated from JCPyV-infected and non-infected human induced pluripotent stem cell (hiPSC)-derived astrocytes at different time points post-infection and analysed by liquid chromatography tandem mass spectrometry (LC-MS/MS). As controls, we assessed the proteomic profiles of infected and non-infected astrocytes themselves as well as EVs isolated from astrocytes stimulated with TNFα and IL-1β.

**Results** — First, EVs isolated from JCPyV-infected cells were shown to have a distinct proteomic profile as compared to EVs from non-infected cells, with an enrichment in proteins involved in RNA splicing, chromosome organization and the cell cycle. Second, we show that EVs do represent the changes observed within the cells upon infection. Last, the profile of EVs from infectious conditions was sharply contrasting with the proteomic profile of EVs derived from cytokine-stimulated astrocytes, which contain more immune-related proteins.

**Conclusions** — EVs from JCPyV-infected astrocytes have a distinct proteomic profile suggesting that brain-derived EVs might help identifying early changes happening in astrocytes in the context of PML and distinguish them from the changes happening upon inflammation, i.e. MS relapses. This study paves the way to use EVs as new biomarkers for early stratification of patients at-risk of developing PML.

Larise Oberholster
- Laboratory of Neuroimmunology,
- Neuroscience Research Centre,
- Department of Clinical Neurosciences,
- Lausanne University Hospital and University of Lausanne
Background — Multiple sclerosis and its animal model, experimental autoimmune encephalomyelitis (EAE), are demyelinating diseases of the central nervous system (CNS). Both are mediated by autoreactive CNS-specific T cells activated in the periphery that enter the CNS. Gut microbiota is an emerging environmental factor involved in MS and its implication in MS pathogenesis must be further characterized. We hypothesize that myelin-specific Th17 cells acquire encephalitogenic properties by interacting with the gut microbiota during colonic lamina propria infiltration in the EAE adoptive transfer model.

Methods — We used a broad-spectrum antibiotic cocktail to unravel the effects of the gut microbiota in the EAE Th17 cell adoptive transfer model and characterize immune cells from the colon and the brain by flow cytometry and RNA sequencing. Next, we treat myelin-specific Th17 cells with microbiota-derived metabolites from mouse fecal filtrates to decipher their specific effect on the encephalitogenic properties of myelin-specific Th17 cells by flow cytometry.
Results — Antibiotic treatment attenuates EAE adoptive transfer disease and reduces CNS-specific Th17 cells infiltration in the CNS. It decreases the pathogenic signature of Th17 cells and their expression of the pro-inflammatory cytokine IFNγ and of the chemokine receptor CXCR6. Gut-derived fecal filtrates treatment of myelin-specific Th17 cells enhances their pathogenicity by increasing CXCR6 and IFNγ expression in a microbiota-dependent manner. Furthermore, their adoptive transfer increases EAE disease severity.

Conclusions — We propose that the interaction between adoptively transferred Th17 cells and microbiota-derived metabolites induces a pathogenic switch in the colon and enhances their migratory abilities leading to increase neurological disease severity.

Jessica Rebeaud
– Laboratories of Neuroimmunology, Neuroscience Research Center and Service of Neurology,
Department of Clinical Neurosciences,
Lausanne University Hospital and University of Lausanne

Die Fachmagazine des medEdition Verlags:
BrainMag, GastroMag, MédMag, OncoMag, PraxisMag und SkinMag.

medEdition
**Background** — Registries and cohorts are established sources of data to provide real-world evidence. Up to now, they have only scarcely been used for prospective, randomized assessments of diagnostic and/or therapeutic interventions in MS. Serum neurofilament light chain levels (sNfL) are associated with future disease activity and are increasingly used as a treatment response marker. The aim of this study is to evaluate the superiority of personalized care strategies vs. usual care in relapsing-remitting (RR)MS.

**Methods** — The Multiple SCLerosis pRagmatIc Platform Trial (MultiSCRIPT) is a multicenter, 1:1 randomized trial embedded in the Swiss MS Cohort (SMSC). MultiSCRIPT is a learning system that aims at creating an evolutionary approach of care for persons with MS. Innovative interventions are cyclically evaluated within the same trial platform. Here, we present the architecture of MultiSCRIPT with the first evaluation cycle on the trial platform. The first cycle will be a comparison of intensive biomarker monitoring with sNfL vs. current usual care. We plan to
include 915 RRMS patients. In the intervention group, 6-monthly monitoring of sNfL together with information on relapses, disability, and MRI will inform more personalized treatment decisions based on pre-specified treatment guidelines developed in a Delphi-process involving patients and clinical experts. The control group will receive usual care with 6- or 12-monthly visits. The primary outcomes are evidence of disease activity (EDA3) and quality of life (QoL) at month 24. The intervention will be considered superior to usual care if either more patients have no EDA3, or their health-related QoL increases. Secondary outcomes include relapses, disability worsening, MRI activity, serious adverse events and health economic outcomes.

**Results** — This study started in August 2022 and will recruit participants from the SMSC [n=1561 patients; 84% RRMS; mean age 41 yrs (IQR:33-50); disease duration 6.9 yrs (IQR 2.1; 14.1); median EDSS 2.0 (IQR:1.5-3.5)].

**Conclusions** — This platform trial allows continuous learning cycles of evaluation, merging randomized trial methodology with prospective real-world cohort data collection, generating knowledge and informing the selection of new interventions to be tested in subsequent cycles. MultiSCRIPT promises to foster better personalized MS treatment and care strategies, at low cost and with rapid translation to clinical practice aiming to treat patients as little as possible but as much as necessary at the right time.

Özgür Yaldızlı
– University Hospital Basel and University of Basel
  Neurologic Clinic and Policlinic, MS Center, and Research Center for Clinical Neuroimmunology and Neuroscience Basel (RC2NB)
Background — Histopathological studies have identified immunoglobulin (Ig) deposition and complement activation as contributors of CNS tissue damage in Multiple Sclerosis. Intrathecal IgM synthesis is associated with higher MS disease activity and severity, and IgM is the strongest complement activating immunoglobulin.

Methods — To investigate if complement activation (CA) is increased a) in clinically isolated syndrome (CIS) and MS patients, b) especially in those with an intrathecal IgM synthesis; and to determine associations with c) Expanded disability status Scale (EDSS) score, the MS Severity Score (MSSS) and d) neurofilament light chain (NfL) levels in cerebrospinal fluid (CSF). Complement components (CC) and CA products levels were quantified in plasma and CSF of 112 patients with CIS, 127 MS patients (90 relapsing-remitting, 14 primary-progressive, 23 secondary-progressive), as well as in 31 inflammatory neurological disease and 44 symptomatic controls. Levels were compared by linear regression, adjusted for age, sex and albumin quotient.

Results — a) In CIS/MS, CSF (but not plasma) levels of C3a, C4a, Ba, Bb were increased, e.g. PPMS had 85% and 53% higher C3a and C4a levels than symptomatic controls (both p<0.01).

b) CSF levels of C3a, C4a, Ba, Bb, C1q were increased along CSF Ig-categories in CIS/MS, i.e. were highest in patients with an additional intrathecal IgM synthesis: increase for C3a 128%; C4a 50%; Ba 37%; Bb 55%;
C1q 21% (all p<0.01) compared to patients without any intrathecal Ig synthesis.
c) In CIS doubling of C3a and C4a in CSF was associated with 0.31 (p=0.016) and 0.32 (p=0.041) increased
EDSS scores at lumbar puncture. Similarly, doubling of C3a and Ba in CIS/MS was associated with 0.61
(p<0.01) and 0.74 points (p=0.016) increased future MS disease severity scores (MSSS).
d) In CIS/MS CSF levels of C3a, C4a, Ba and Bb were associated with increased CSF Neurofilament light
chain (NfL) levels: e.g. doubling of C3a was associated with an increase of 54% (p<0.0001) of NfL levels.

**Conclusions** — Compartmentalized early cascade complement activation is increased in CIS/MS, especially
in presence of an intrathecal IgM synthesis and correlates with EDSS, future MSSS and NfL levels, pointing
towards an important pathophysiological role. Complement inhibition might be a novel therapeutic option
for attenuating disease severity in MS.

**Johanna Oechtering**
- University Hospital Basel and University of Basel
  Neurologic Clinic and Policlinic,
  MS Center, and Research Center for Clinical Neuroimmunology and Neuroscience Basel (RC2NB)
Background — Persistent intrathecal immunoglobulin production, mainly of the IgG subtype, detected as oligoclonal bands, is a diagnostic hallmark of Multiple Sclerosis, which can be found in up to 98% of MS patients. Up to 25% of patients show additional persisting intrathecal IgM synthesis, which, unlike their blood counterpart, show a high degree of somatic hypermutation, suggesting an antigen driven production. Despite intensive investigations, the antigenic stimulus that initiates or perpetuates B cell activation and intrathecal immunoglobulin production in MS patients is still a matter of debate. The aim of our study was to identify the target antigen of intrathecally produced CSF IgM antibodies.

Methods — Two independent cohorts (n = 360 for cohort 1; n = 200 for cohort 2) of MS patients and control CSF samples were screened in a blinded fashion by flow-cytometry for antibody binding on a panel of nervous system related cell lines. B cells from prospectively collected CSF were sorted, single cells expanded and immunoglobulin genes from wells resembling the cell specific binding pattern of the original CSF sample were sequenced. Heavy and light chain sequences were then used to produce CSF derived monoclonal IgM, which were used for immunolabeling of mouse striatum, mouse cerebellar slices and human MS brain lesions.
Results — In each cohort, we identified CSF IgM binding to a Peripheral Neuro-Ectodermal Tumor (PNET) cell line in 10% of MS donors and less than 1% of controls, independently from intrathecal IgM synthesis. We sorted and expanded 1040 single B cells from a CSF sample with this IgM reactivity and produced 5 recombinant IgM with the same cell-line specificity. One of these IgM clones (M16) showed myelin specific labelling of the striatal bundles after injection into mouse brain. Mouse cerebellar cultures were labelled by M16 in a cell specific pattern. Staining of human MS brain lesions showed labelling of neurons and foamy macrophages. Experiments for identifying the target antigen of M16 are ongoing.

Conclusions — These data suggest that intrathecal IgM synthesis in MS might not only be a sign of an increased inflammatory response but also hint at an antigenic trigger for intrathecal IgM production.

Nicholas Sanderson
– University of Basel
  Department of Biomedicine, Clinical Neuroimmunology Lab

Ilaria Callegari
– University of Basel
  Department of Biomedicine, Clinical Neuroimmunology Lab
Background — Blood-brain barrier (BBB) breakdown is amongst the earliest pathological hallmarks observed in Multiple Sclerosis. The mechanisms leading to BBB dysfunction are incompletely understood and are generally thought to be a consequence of the autoimmune neuroinflammatory process in MS. We challenge this view and ask if intrinsic alterations in BBB endothelial cells manifested at the genetic or epigenetic, transcriptional, and ultimately phenotypic level cause or contribute to altered BBB function in MS.

Methods — We made use of human induced pluripotent stem cells (hiPSCs) derived from 3 healthy controls (HC) and 4 MS patients and differentiated them using a newly established extended endothelial cell culture (EECM) protocol into EECM-brain microvascular endothelial cell (BMEC)-like cells as an in vitro model of the BBB. We performed transcriptional profiling of HC and MS-derived EECM-BMEC-like cells stimulated or not with TNF-α and IFN-γ by RNA sequencing.
**Results** — The RNA sequencing analysis showed 438 and 282 differentially regulated genes in unstimulated and stimulated EECM-BMEC-like cells derived from HC and MS patients, respectively. Reactome Pathway analysis identified a strong modulation of the Semaphorin-4D (SEMA4D) signalling pathway in unstimulated MS-derived EECM-BMEC-like cells compared to the controls. Our ongoing studies confirm expression of SEMA4D and its downstream effectors, RHOB and ROCK2 in EECM-BMEC-like cells and a contribution of this signalling pathway in junction maturation.

**Conclusions** — Our study suggests that SEMA4D and its downstream effectors may contribute to junctional impairment of the BBB in MS.

*Sarah Guimbal*

– University of Bern

  Theodor Kocher Institute
Background — Multiple Sclerosis has been mainly researched from a clinical perspective, with diagnosis, treatment and medication (change) as key milestones. However, every story of a person with MS is unique and shaped by distinct experiences and challenges. Here we present the project «My life with MS» conducted by the Swiss MS Registry (SMSR), developed in close cooperation and through the initiative of persons with MS. We examined (1) which general categories of life events persons with MS perceived as central in terms of the nature and progression of their MS across their life course and (2) how those life events resonated emotionally in hindsight.

Methods — In total, 1039 persons with MS participated in the «My life with MS» study, which was nested in the SMSR. Participants were invited to describe their story of their life with MS by writing free-text entries on self-selected key events into an electronic data capturing system or in paper questionnaires. For each event, participants provided keywords and were asked to describe the event itself, its consequences, the support they received, what was helpful and what they would advise others in a similar situation. Individuals then completed survey measures on quality of life, MS type and symptoms, medication, disease course, and treatment. For the text analysis, we first automatically translated all text entries into English. We then implemented topic modelling («latent dirichlet allocation») to identify overarching topics underlying the text descriptions. For fine-grained sentiment analyses (i.e., sadness, fear, anger, joy, surprise), we again used pretrained language models.

Results — Individuals reported a total of 4’309 unique MS-related events. Topic modelling analysis revealed eight distinct event themes: (1) «diagnosis», (2) «medication / treatment», (3) «relapses / child», (4) «work», (5) «birth, health», (6) «partnership & MS», (7) «rehab / wheelchair», and (8) «injection, symptoms». Sentiment
of the text entries was predominantly negative, with sadness and anxiety being the most frequent emotions. However, individuals also documented a significant number of positive events, particularly in the categories «birth, health» and «partnership & MS».

**Conclusion** — The «My life with MS» project sheds light on the lived experience of a life with MS by analysing large-scale text data in which participants describe central MS-related, often in great detail. Both directly related to the disease and personal life events are mentioned. Our findings thus suggest that a more holistic perspective on persons with MS is needed to understand the far-reaching impact of MS on their daily lives and to support them comprehensively.

**Viktor von Wyl**  
- University of Zurich  
  Epidemiology, Biostatistics and Prevention Institute &  
  Institute for Implementation Science in Health Care

**Christina Haag**  
- University of Zurich  
  Epidemiology, Biostatistics and Prevention Institute &  
  Institute for Implementation Science in Health Care
16 | Mina Stanikić

Real-world experiences of persons with multiple sclerosis with the Covid-19 vaccination

**Background** — Despite strong recommendations for coronavirus disease 2019 (Covid-19) vaccination by multiple sclerosis organizations, some persons with MS (pwMS) remain vaccine hesitant. The Swiss MS Registry conducted a survey to explore Covid-19 vaccine hesitancy and self-reported side effects and changes in MS symptoms following vaccination in adult pwMS.

**Methods** — Self-reported data were analysed cross-sectionally. Multivariable logistic regression models with sex, age and MS type as fixed confounders were used to explore participant characteristics associated with Covid-19 vaccine hesitancy. Variable selection was performed on the subset of complete cases. Multivariable logistic regression using 20 multiply imputed datasets was performed for comparison.

**Results** — Of 849 respondents, 73 (8.6%) were unvaccinated. Hesitation to vaccinate was most often a personal preference (N=42, 57.53%). Factors negatively associated with vaccine hesitancy included older age (OR=0.96 per year of age, 95% CI [0.94, 0.99]) and regularly seeing healthcare professionals (OR=0.24, 95% CI [0.07, 0.79]). Being underweight (OR=3.73, 95%CI [1.28, 10.88]) and having a clinically isolated syndrome (OR=5.29, 95% CI [1.09, 24.74]) were positively associated with vaccine hesitancy. Imputed full sample analysis yielded similar findings. Of 768 participants who provided information, 320 (41.2%) and 351 (45.2%)
reported side effects after the first and the second vaccine dose, respectively. After a median [interquartile range] of 250.5 [222.2, 312.0] days since the first vaccination, 11 (3.4%) participants reported they were still not recovered from side effects at the time of data collection. Changes in MS symptoms were reported by 49 (6.3%) participants after the first and 67 (9.0%) participants after the second vaccination and were most often described as increased or new-onset fatigue (N = 17/49 (34.7%) after the first and N = 21/67 (31.3%) after the second dose). Resolution of MS symptom changes was not systematically surveyed.

**Conclusions** — Covid-19 vaccine hesitancy was low among surveyed pwMS. The risk of vaccine hesitancy was higher in younger pwMS and those without regular contact with healthcare professionals. Side effects of vaccination in pwMS were mild and non-persistent, and MS symptoms rarely changed after vaccination.

*Mina Stanikić*

— *University of Zurich*

*Epidemiology, Biostatistics and Prevention Institute*
Specialist clinic for MS rehabilitation and neurological rehabilitation. Switzerland’s leading provider of robot-assisted movement therapy.
Background — The MS Advanced Practice Nurse (APN)-led outpatient consultation service at the University Hospital Zurich was established in 2010. The APN consultations are planned additional to physician appointments to support in person-centered endorsement, self-management and education as well as coordination of the treatment process. The MS care consultation was scientifically evaluated in 2018. The poster presents the adjustments based on the results of the evaluation.

Methods — The multi-method evaluation included a retrospective descriptive data analysis, a survey, individual interviews and focus group interviews. The quantitative and qualitative results were merged for an integrated analysis. The analysis was guided by the PEPPA-PLUS matrix, which considers the perspectives of different stakeholders such as patients and families, the APN team and other professionals/organizations, and the healthcare system.

Results and adjustments — Based on the results we adjusted processes with an impact on many stakeholders involved. Patients and families emphasized in the interviews that they missed continuous care and they desired a familiar contact person as well as a central telephone number. Chiefly the desire to have a personal contact was strong. Therefore, telephone availability of the APNs was increased from three to five days a week and patients were regularly seen by one of the two APNs before the medical consultations. The APNs reported a high administrative workload covering up to 35% of the daily tasks. Reorganizing internal processes and outsourcing of administrative work (e.g. planning appointments) created more capacities for patient contact. Thereupon,
the number of people with contact to the MS care consultation increased from n=376 (2017) to 763 (2021) and the number of face-to-face contacts increased from n=315 (2017) to n=1081 (2021). Internal and external professionals reported a lack of contact and direct personal communication with the APNs. We therefore established regular meetings.

**Conclusions** — The PEPPA-PLUS framework supported our understanding of the results and helped to adjust the APN-led outpatient consultation service at different levels. We believe that the changes improved the care for patients and families, but also for the professionals involved. Further research should examine the impact of the adjustments on patient outcomes and should also consider the perspective of the health care system, which was not covered by our evaluation.

Sarah Bolt
- **University Hospital Zurich**
  - Department of Neurology, MS Care Consultation

Esther Stadelmann
- **University Hospital Zurich**
  - Department of Neurology, MS Care Consultation
**Background** — Fatigue is one of the most frequent symptoms in Multiple Sclerosis and has a major impact on quality of life. At present, there do not exist any clinical tests that could guide treatment. As a consequence, therapy currently proceeds in a trial-and-error fashion. Since fatigue most likely has a heterogeneous pathophysiological basis, individualised treatment would require that we can detect the specific disease mechanism in each patient. Several potential disease processes have been identified that might be expressed variably (and possibly in combination) across persons with MS (PwMS), incl. (i) reduced monoaminergic projections from brainstem nuclei, (ii) diminished strength of orexinergic projections from the lateral hypothalamus, and (iii) altered interoception.

**Methods** — In the FAMRI study, we obtain functional readouts that reflect the above pathophysiological mechanisms and investigate how well these measures explain the variability of fatigue across PwMS. To this end, structural and functional MRI (fMRI) and physiological measures (incl. sleep) will be obtained from PwMS (N=75) with variable degrees of fatigue. In order to assess brainstem projections, hypothalamic projections, and connections within the cortical interoceptive network, respectively, we will conduct fMRI analyses of «resting state» functional connectivity and use novel methods for whole-brain effective (directed) connectivity analyses. Furthermore, we will use structural MRI techniques sensitive to tissue damage (quantitative T2), examine abnormalities of interoception and autonomic regulation with questionnaires and physiological measures, and investigate the contribution of low sleep quality to fatigue with actigraphy.
Results — Applying statistical analyses and machine learning to these measures, we will test whether (i) individual levels of fatigue can be explained by a combination of readouts reflecting the proposed pathophysiological mechanisms, (ii) which of these measures shows the strongest relation to individual fatigue levels on its own, (iii) whether local tissue damage in regions of interest correlates with fatigue, and (iv) which functional connections across the whole brain correlate with fatigue levels.

Conclusions — If a clear relationship between any (or several) of the readouts reflecting the proposed pathophysiological mechanisms and fatigue levels were found, this could provide a basis for testing whether imaging-based treatment selection could support individualized therapy of fatigue in MS.

Inês Pereira
- Translational Neuromodeling Unit
  University of Zürich & ETH Zurich

Zina-Mary Manjaly
- Schulthess Clinic, Zurich
  Department of Neurology
- ETH Zurich
  Department of Health Sciences and Technology
Background — Some disease modifying treatments impair response to SARS-CoV-2 vaccines in multiple sclerosis (MS), potentially increasing the risk of breakthrough infections. We aimed to investigate longitudinal SARS-CoV-2 antibody dynamics and memory B cells after 2 and 3 mRNA vaccine doses, and their association with risk of COVID-19 in MS patients on different treatments over 1 year.

Methods — Prospective observational cohort study in MS patients undergoing SARS-CoV-2 mRNA vaccinations. Anti-spike IgG titers were measured by chemiluminescence microparticle immunoassay. Frequencies of spike-specific memory B cells were measured upon polyclonal stimulation of peripheral blood mononuclear cells and screening of secreted antibodies by ELISA.

Results — We recruited 120 MS patients (58 on anti-CD20, 9 on S1P-modulators, 15 on cladribine, 24 on teriflunomide and 14 untreated), and collected 392 samples up to 10.8 months after two vaccine doses. As compared to untreated patients, anti-CD20 antibodies ($\beta=-2.07$, $p<0.001$) and S1P-modulators ($\beta=-2.02$, $p<0.001$) were associated with lower anti-spike IgG, while teriflunomide and cladribine were not. Anti-spike IgG decreased with months since vaccine ($\beta=-0.14$, $p<0.001$), independently of treatments. Within anti-CD20 patients, anti-spike
IgG remained higher in those with greater baseline B cell counts, and were not influenced by post-vaccine anti-CD20 infusions. Anti-spike IgG increase after a 3rd vaccine was mild on anti-CD20 and S1P-modulators. Spike-specific memory B cell responses were weaker on S1P-modulators and anti-CD20 than on teriflunomide and influenced by post-vaccine anti-CD20 infusions. Risk of COVID-19 was predicted by the last measured anti-spike IgG titer before infection (OR=0.56, 95%CI=0.37-0.86, p=0.008).

Conclusions — Post-vaccine anti-spike IgG titers decrease over time regardless of MS treatment, and are associated with breakthrough COVID-19. Both humoral and specific memory B cell responses are diminished on S1P-modulators. Within anti-CD20 treated patients, B cell count at first vaccine determines anti-spike IgG production, whereas post-vaccine anti-CD20 infusions negatively impact spike-specific memory B cells.

Giulio Disanto
– Ente Ospedaliero Cantonale, Lugano
  Neurocenter of Southern Switzerland
Background — Pediatric-onset multiple sclerosis (POMS) is a severe disease affecting children in a period of essential brain development. Timely diagnosis and treatment initiation minimize neurological sequelae and improve outcomes. However, POMS diagnosis can be challenging since its clinical presentation overlaps with that of other inflammatory brain diseases (IBrainDs). We aim to systematically assess POMS and related diseases through the national Swiss-Ped-IBrainD registry. Here we report our first-year experience after initiating all study centers.

Methods — Multicentric observational cohort study; inclusion criteria: patients with a pediatric-onset IBrainDs living or treated in Switzerland; exclusion criteria: patients with 1) infectious CNS diseases; 2) genetic/metabolic causes of CNS demyelination; 3) neurological symptoms due to Guillain–Barré–Syndrome. The informed consent of the patient/legal guardian(s) is required to collect the full dataset. A minimal dataset (gender, age, diagnosis, status, cause of death) is collected after informing the patient/legal guardian(s) of the registry.

Results — All 11 study centres have been initiated. So far, we have identified 243 eligible participants and collected the minimal dataset of 180 patients (113 females, 63%). POMS (83, 46%) is the most common diagnosis, followed by acute disseminated encephalomyelitis (23, 13%), and optic neuritis (19, 10%). Currently, 75 patients/
families have consented to participate. Diagnostic data of a patient subset (n=50) including 22 (17 female, 77%) with POMS, 9 (5 female, 56%) with optic neuritis, 7 (4 female, 57%) with acute disseminated encephalomyelitis, and 12 (7 female, 58%) with diagnoses n < 5, revealed a median age at symptom onset of 12.7y (7.7-14.9) and a median age at diagnosis of 13.0y (7.9-15.0). The most common initial symptoms among these patients were visual deficits, nausea/vomiting, and headaches.

Conclusions — We have successfully started to characterize our patient population on a national level. The different clinic information systems of the study centres have rendered patient screening time-consuming, necessitating the implementation of centre-specific recruitment and data collection workflows. We expect to complete first comprehensive epidemiological data over the next year. Furthermore, we will launch a nested, patient-centred survey study in 2023.

Sandra Bigi
– Cantonal Hospital of Lucerne, Children’s Hospital Lucerne
  Department of Child Neurology
– University of Bern
  Institute of Social and Preventive Medicine
We thank you for your participation in the symposium.

See you next year at the 26th MS State of the Art Symposium, Saturday, January 27, 2024.

Kind regards
Swiss Multiple Sclerosis Society
«At times, the pain is unbearable»

Multiple Sclerosis can affect anyone, and it progresses individually. In Stéphane’s case, severe pain in legs and arms define his life with MS.

The Swiss Multiple Sclerosis Society has been supporting persons with MS for more than 60 years. Join us in the effort to allow them a better quality of life: www.multiplesclerosis.ch