NISCI

Nogo Inhibition in Spinal Cord Injury

EMSCI

# Newsletter 2022

## EMSCI Network

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the grant agreement No 681094,and is supported by the Swiss State Secretariat for Education, Research and Innovation (SERI) under contract number 15.0255.

Schweizer Paraplegiker Stiftung

Wings for Life Spinal Cord Research Foundation

## Dear valued EMSCI and NISCI colleagues,

I hope this newsletter is findig you well and as you can see for the first time we have a combined **EMSCI and NISCI newsletter.**

For the most of us this seems logical (almost overdue) as NISCI is basically one of the several successful outputs from EMSCI. We are now looking at **2 decades of EMSCI** with a very impressive ongoing data collection which is internationally truly unique. And more than this our scientific outcomes with more than **100 peer reviewed papers** paved the way to consider and put into action of a very modern and sophisticated trial protocol, that will have a strong impact onto the field.

Of course such endeavors are always good for some surprises and this holds true also for our **ongoing NISCI trial**. Based on the parallel group design of the study (predefined outcome cohorts) the envisioned randomization did not work out per plan and we have to extend our trial by a max of 3 months to increase the numbers of serum treated patients. The number of serum tested patients is still lower than planed (we aimed for 78 patients) but is crucial, as only from these patients we can learn, if the drug intervention is improving outcomes. This is inducing several administrative challenges and we hope to manage these in time.....fingers crossed!

We anticipate to have **first scrutinized outcomes by summer 2023** and will circulate and discuss them first within the NISCI/EMSCI network.
We hope you will find interest in this newsletter and please feel free to provide any feedback that comes to mind.

**With very best greetings and sincere thanks to all your efforts and support,**
**Armin**

## NISCI update

Despite the inhospitable and turbulent last two years during the COVID-19 pandemic, the NISCI study centers have managed to continue actively enrolling patients in the study. All of you have contributed to our success. This outstanding performance has meant that we are already on schedule to enter the home stretch.
What else is there to report and what has happened since the last newsletter in September 2019?
From 26-27 September 2019, we had the pleasure of being guests at the Study Centre in Heidelberg for a GA meeting. We would like to thank Norbert Weidner and his team and all of you who contributed to this very revealing and productive meeting. A short update of the site readiness and the new study centers was given. Furthermore, Rainer Abel reported about his experience of the 1st patient screening and inclusion in Germany. In the evening we enjoyed a nice walk through the old town of Heidelberg and a delicious dinner in a lovely restaurant.

Already during the last meetings before 2019, there were repeated discussions of increasing the allocation 1:1 to 3:1. At the same time, we realized that we would not be in a position to complete the study according to plan. Therefore, we were able to come up with a mitigation strategy to change the allocation to 3:1 when we asked for a study extension. Thanks to all the efforts on the part of the CROs and the sponsor both requests were approved and quickly implemented at the end of 2020. During this time all further study sites could be successfully initiated and randomize their first patients.
The first Data Safety Monitoring Board (DSMB) was held in February 2021 followed by the second meeting in March this year. All efforts to get an approval for the site in Italy were not successful due to specific requests by the national authority (AIFA). The final decision to drop Italy was made in September 2021.
As we were unfortunately not able to plan any meetings on site, we held them virtually. The first webinar was carried out in April 2020 while the lockdown prevailed in all participating countries and thus in the study centers. The main focus here was on the extension of the trial and the introduction of the new allocation. Updates and main goals of WP 2/3/4 were given.
This meeting was followed by three more webinars, one of which was within the framework of the DMGP as part of the annual EMSCI meeting. The meetings continued to focus on the progress of the study and the inclusion of patient numbers, the development of biomarkers in the WPS and the intensive good cooperation with all sites and the CROs, as well as the imminent end of the study. At our last meeting on 6 April, the necessary number of patients in the verum-group was also addressed and the necessary measures were discussed. In the meantime, we have already indicated to our officer in Brussels that we have a further 6 months extension of the trial in mind. This would not only allow us to take full advantage of the EU's financial resources but also to reach the specified number of patients. We do not yet know when the target number of patients will be reached, but we hope that this will be the case as early as summer 2022. Until the end of September at the latest we can include patients in the NISCI trial.

I'd like to emphasize once again how good the cooperation with the study centers is. Thanks to this we are so successful.

**I wish you all continued success**
**Andrea**

NISCI
Nogo Inhibition in Spinal Cord Injury

## Fluid biomarker development in spinal cord injury

Norbert Weidner, Christian Schuld, Andreas Hug
Spinal Cord Injury Center
Heidelberg University Hospital

A core element, which was added to the NISCI clinical trial aims to analyze serum and cerebrospinal fluid (CSF) from SCI patients enrolled in the phase II trial to identify protein based biomarkers which are correlated with the clinical outcome of SCI patients and which may allow to identify responders or non-responders to the pharmacological therapy with the anti-NOGO-A antibody (NG-101). To enable not just fluid biomarker development, but in addition pharmacokinetics and immunogenicity analyses high quality serum and CSF samples are collected, processed, shipped, and stored in the Heidelberg Cardio Biobank (Tanja Weis) which serves as the NISCI core biobank. To ensure highest sample quality detailed standard operating procedures related to shipping, sample processing, documentation and storage were established. The proteomics analyses are done by the Medical Proteome Center in Bochum (Katrin Marcus, Katalin Barkovits).

To identify marker proteins that allow to measure the response to the therapeutic intervention or to serve as outcome predictors, mass spectrometry (MS) based quantitative proteomic analyses are performed. Prior to analysis, proteins present in a sample are enzymatically cleaved to peptides. Subsequently, the peptide concentration is determined by amino acid analysis, which ensures that the same quantities are analyzed in the MS-based analysis. In the MS based measurement, a complexity reduction of the peptide mixture is performed by ultra high liquid chromatography (UHPLC) followed by mass spectrometric analysis, where the resulting peptide ions are measured in the mass spectrometer to obtain MS1 spectra. For accurate identification of the peptide sequences and the resulting proteins, the ion masses of the MS2 spectra resulting from peptide fragmentation are used within database analyses. In addition to protein identification, the underlying information from the MS1 spectra is used for quantitative analysis. This is based on the measured intensities of protein-specific peptides, from which the abundance of the respective proteins can be calculated. For the proteomic analysis, a sufficient number of defined high quality CSF samples are analyzed to ensure the generation of a statistically reliable set of data. For the identification of potential marker proteins, the proteomic dataset is being comprehensively analyzed using bioinformatics and biostatistical approaches. Established methods such as principle component analysis (PCA), cluster analysis and multivariate statistics are used for the evaluation and interpretation of the MS datasets.

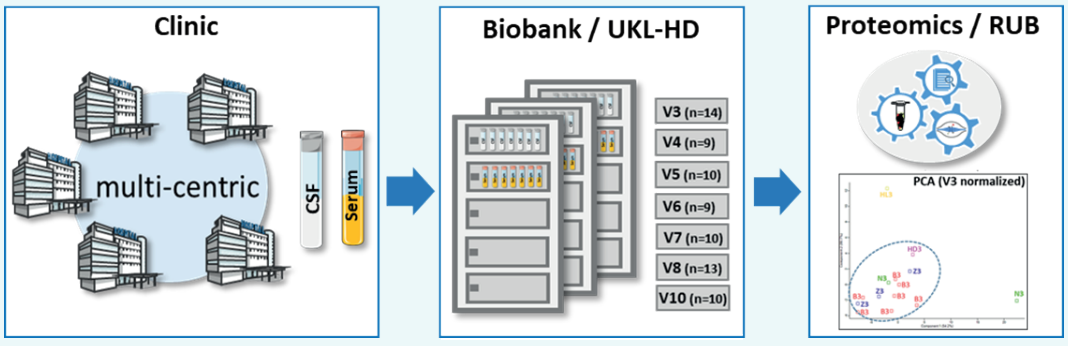



**Figure 1:** Overview preliminary proteome study. Biomaterial (CSF and serum) from the clinical sites is stored at the biobank and selected samples from visit 3 to visit 10 were transferred for proteome analysis. PCA of the proteomic data showed no significant clinic-dependent clustering.

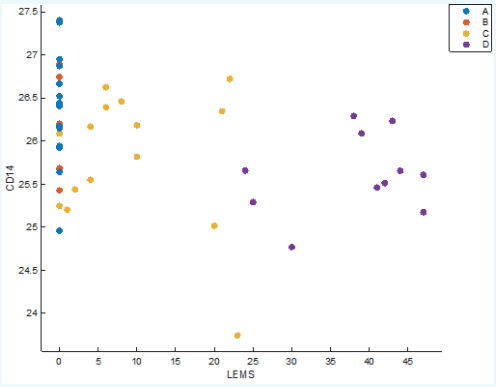



**Figure 2:** CD14 abundance in relation to AIS grade and LEMS.

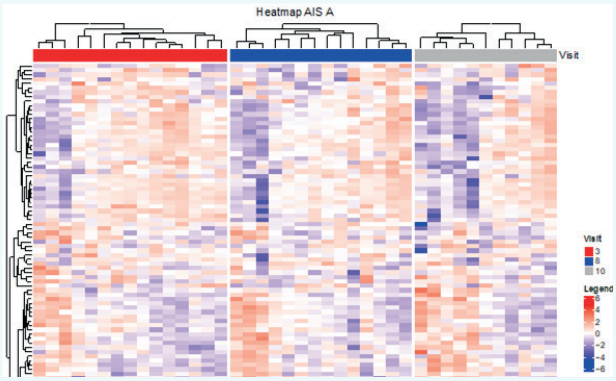



**Figure 3:** Abundance of detected proteins (each row represents a different protein) in AIS A subjects (each column represents a single patient) at three consecutive time points (V3,V8,V10). RED color coded fields stand for relatively higher abundance, BLUE color coded fields for relatively lower abundance (referenced to the mean abundance of each protein).

Currently, 919 CSF and serum samples of 59 patients have been shipped to the Biobank. After processing (centrifugation, aliquoting, documentation) a total of 12.747 aliquots from serum and CSF samples are available in store. The aim of a first analysis was to check the quality of the multicentric samples. 75 CSF samples from 5 different study sites were analysed. The evaluation of the data set using PCA showed that there was no clinic-dependent clustering and that the sample quality for quantitative proteomic analyses was sufficient. In addition, evaluation of the data set showed that previously described SCI related proteins were detected, e.g., transferrin, neurofilament, and cathepsin D.

In a second step, CSF aliquots from time points between 1 and 3 months after injury (visits V3, V8 and V10) from 49 patients were shipped to Bochum for subsequent proteomics analyses. Mass spectrometry analysis confirmed the absence of clustering of samples indicating excellent quality of the samples. Within the data set over 300 proteins were identified and 100 proteins could be used for differential quantitative analysis (proteins present in all samples no missing value). By comparing the proteome profile of the different visits significantly differential proteins could be identified. In respect to the correlation of protein-based biomarkers with clinical outcome parameters, neurological outcome parameters were selected. Comprehensive analysis is underway. As an example, the expression of CD14 as a marker for macrophages and microglia shows a clear correlation with parameters reflecting injury severity such as AIS grade and lower extremity motor score (LEMS; Fig.2). Respective findings – inflammatory reactions increase with increasing injury severity - confirm the excellent quality of fluid samples and the reliability of the employed protein detection method (mass spectrometry).

In order to better better comprehend proteomics datasets, "heat maps" displaying protein abundance together clinical assessments including neurological recovery, pain presentation, structural changes, lab chemistry results are being generated, which will help to identify promising proteins or protein clusters to be investigated more thoroughly (Figure 3).

Ongoing analyses have incorporated a MS-based method for candidate protein validation, which will be conducted with serum and CSF samples of the complete study cohort in order to evaluate the suitability of protein candidates as outcome and or therapy response prediction biomarkers.

## Neuroimaging biomarker

Maryam Seif

The neuroimaging biomarker is one of the main WPs in the NISCI clinical trial which is aimed at developing and applying magnetic resonance imaging (MRI) as a sensitive biomarker to treatment effects and potential adverse effects of the anti-Nogo-A antibody treatment. We have developed and applied a quantitative MRI protocol in cervical cord and brain in the NISCI trial. We use the MRI images acquired at baseline and 1 month and 6-months following the injection, from NISCI patients to investigate group differences and the trajectory of lesion changes over time. The anatomical MRI protocol consisted of standard sagittal T1-weighted, sagittal T2-weighted, and axial T2-weighted clinical scans obtained at the lesion level (Fig. 4). The brain protocol consists of different microstructural MRI, sensitive to myelin and iron integrity of the tissue. To date, 111 SCI patients have been scanned for at least one time-point, applying the developed quantitative MRI protocol.

Lesion segmentation is performed manually by an experienced rater. We delineate the lesion on the midsagittal slice from sagittal T2-weighted scans. This enables us to assess the lesion area, its rostro-caudal lesion length, anterior-posterior lesion width and ventral and dorsal tissue bridges, the sum of both reflecting the total width of tissue bridges (i.e., hypointense regions between the relatively hyperintense adjacent cystic cavity within the spinal cord and the cerebrospinal fluid (Pfyffer D & Vallotton K 2020 JNNP). The interim results including a sub group of the available data showed the trajectory of lesion area and lesion length over time. The lesion area is significantly decreased with the rate of 0.08 mm/day, p=0.01) and the lesion length was decreased over time with the rate of 0.01 mm/day (p=0.09).

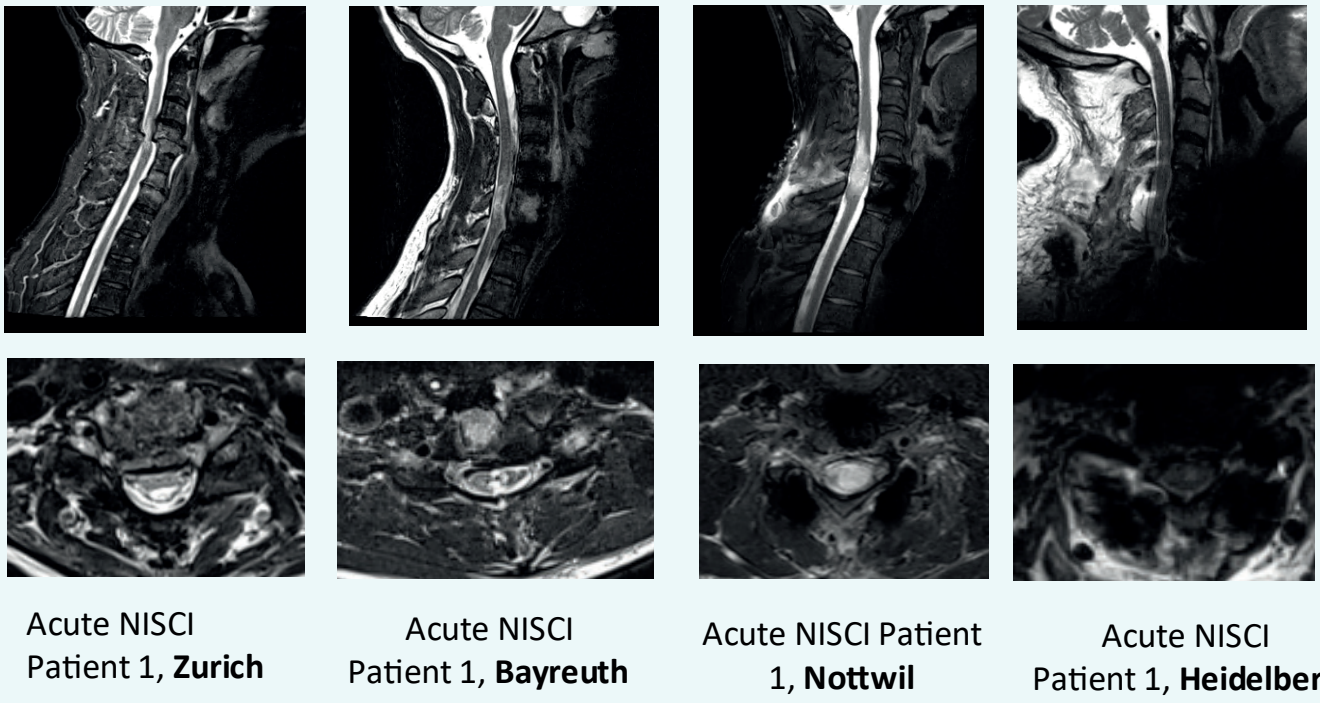



**Figure 4:** Overview of the lesion bridges at baseline ←14 days post SCI in NISCI patient with traumatic cervical spinal cord injury. Sagittal and axial T2-weighted scans show the cervical cord lesion from SCI patient recruited in Zurich, Bayreuth, Nottwil and Heidelberg.

## Characterizing walking patterns in patients with a spinal cord injury using wearable inertial sensors

Charlotte Werner, Armin Curt

An accurate gait assessment during rehabilitation can give an insight into the recovery of motor functions, possibly predict functional outcomes, and provide guidelines for individualized rehabilitation goals. This is of special interest for patients with a spinal cord injury (SCI), because depending on the severity and location of the injury the symptoms vary widely resulting in diverse gait deficits.

In today's clinical routine, mainly simple gait tests are performed to assess walking, e.g. the six minute walking test (6MWT), providing only the average walking speed as an outcome. In other neurological disorders like stroke and Parkinson's disease, movement sensors have been shown to be a good compromise between clinical gait tests and the so-called gait laboratories to assess also the qualitative properties of walking [1]. The application of movement sensors are less time and resource consuming than marker-based gait laboratories, but they still provide spatio-temporal parameters like stride length and duration, gait phases, and speed.

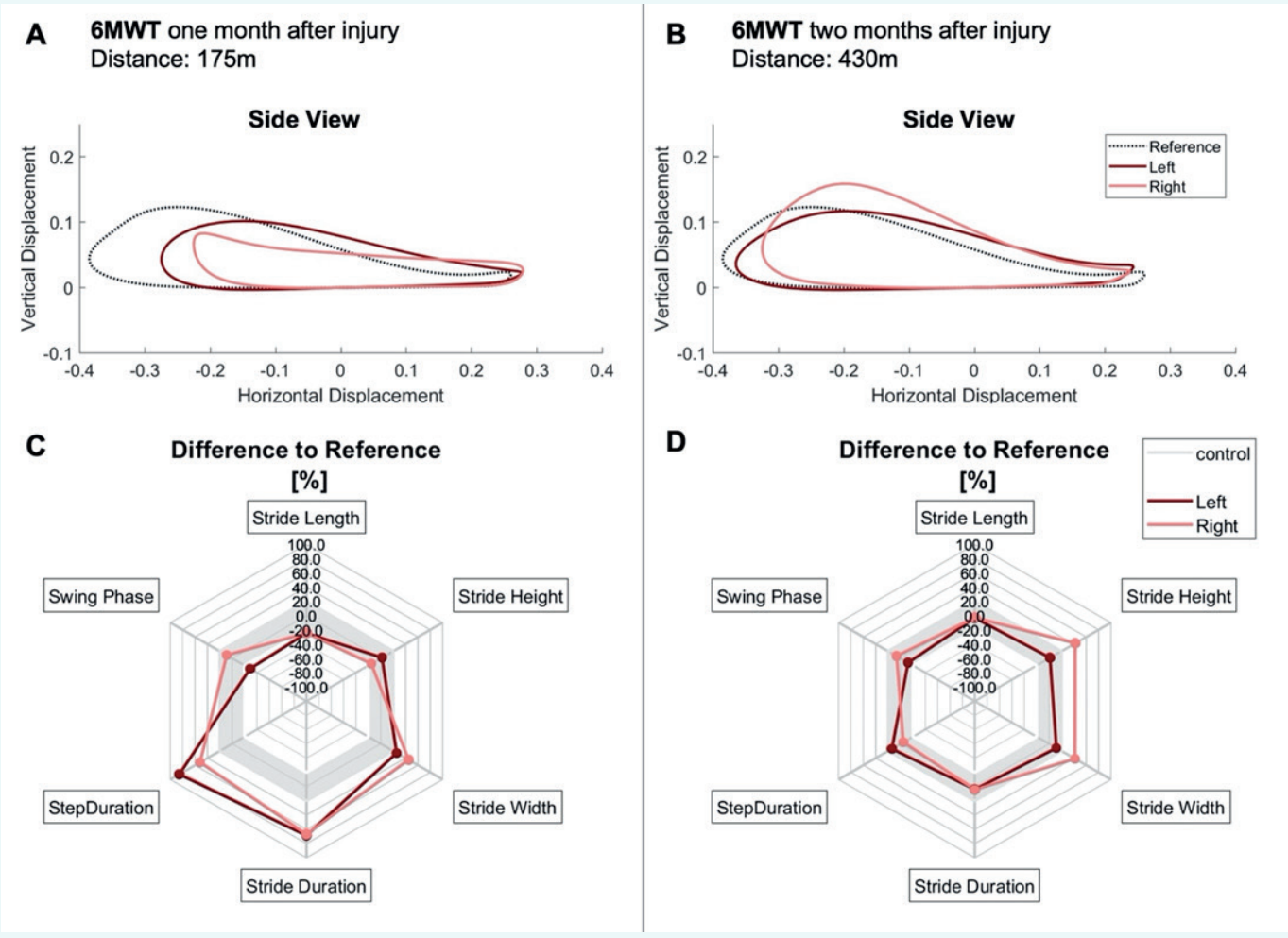



**Figure 5:** Sensor-based gait analysis of a SCI patient performing the 6MWT. Side view of the left and right ankle trajectories during a gait cycle A) one month and B) two months after the injury. Spatio-temporal parameters in comparison to reference data of healthy controls C) one month and D) two months after the injury.

Recently, the Sensor Technology group of the University Hospital Balgrist developed and validated a sensor-based gait analysis specifically for patients with a SCI [2]. The proposed algorithm uses shank- mounted inertial sensors and automatically personalized thresholds to detect steps and gait events according to the individual gait profiles. The method was validated in SCI patients and healthy controls walking on an instrumented treadmill while wearing reflective markers for motion capture used as a gold standard. The algorithm performed similarly well for the two cohorts and is robust enough to cover the diverse gait deficits of SCI patients, from slow (0.3 m/s) to preferred walking speeds. Furthermore, we demonstrated that a sensor-based gait analysis can complement the 6MWT for patients with a SCI by providing information on the gait pattern [3].

One example of spatio-temporal parameters of a SCI patient performing the 6MWT one month after injury is shown in Figure 5 A and C. Clearly, the ankle trajectory is for both left and right side different to reference data from healthy individuals. The patient walks with an increase stride and step duration as well as decrease stride length. Further, especially in the right side an increased stride width and reduced stride height is observed indicating compensatory movements. One month later (Figure 5B and 5D) the patient shows are more physiological walking pattern. However, an abnormal stride height and width is still observed for the right side.

In future projects we want to investigate how gait patterns change during rehabilitation and how this is related to clinical scores such as the lower extremity motor scores and sensibility measures. We hypothesize that wearable inertial sensors can help to better describe the impact of sensory-motor deficits for functional tasks such as walking. The results will be a step towards a more personalized and deficit-oriented therapy using state-of-the art rehabilitation technology.

Refences:

[1] F. A. Storm, A. Cesareo, G. Reni, and E. Biffi, "Wearable inertial sensors to assess gait during the 6-minute walk test: A systematic review," Sensors (Switzerland), 2020, doi: 10.3390/s20092660.

[2] C. Werner, C. A. Easthope, A. Curt, and L. Demkó, "Towards a mobile gait analysis for patients with a spinal cord injury: A robust algorithm validated for slow walking speeds," Sensors, 2021, doi: 10.3390/s21217381.

[3] C. Werner, S. Schneider, R. Gassert, A. Curt, and L. Demko, "Complementing Clinical Gait Assessments of Spinal Cord Injured Individuals using Wearable Movement Sensors," in Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS, 2020, doi: 10.1109/EMBC44109.2020.9175703.

## Neuro-urological management in patients with spinal cord injury

Veronika Birkhäuser and Thomas M. Kessler

Spinal cord injury (SCI) usually results in neurogenic lower urinary tract dysfunction (NLUTD). The site and nature of the lesion in the neurological axis determine the type of lower urinary tract dysfunction (Figure 6), which is reflected in the patient's symptoms. [1,2]

The aims of the neuro-urological management are to preserve upper urinary tract function, to control urinary tract infection, to improve quality of life, and to maintain a low-pressure bladder that is both continent and capable of emptying completely and to avoid complications such as urethral strictures, calculus disease, hydronephrosis, and renal failure. [1,2]
The cornerstone of lower urinary tract assessment is history taking. Keeping a bladder diary is a highly useful tool in clinical practice since it provides an objective measure of lower urinary tract symptoms mirroring day-to-day reality. Physical examination includes the abdomen, flanks and external genital organs, as well as sensation and reflexes in the urogenital area and testing the function of the anal sphincter and the pelvic floor (Figure 7). Urinalysis and urinary culture, free uroflowmetry (when possible) and measurement of post-void residual are also part of the basic neuro-urological assessment.

Video-urodynamic investigation is crucial to assess detrusor and bladder outlet function and it is essential for clinical decision making. Generally accepted risk factors jeopardizing the upper urinary tract are high detrusor pressure during storage phase due to low compliance bladder and/or detrusor overactivity combined with detrusor sphincter dyssynergia (DSD). Urethro-cystoscopy combined with bladder washing cytology is used to detect urethral and bladder pathologies (e.g. urethral

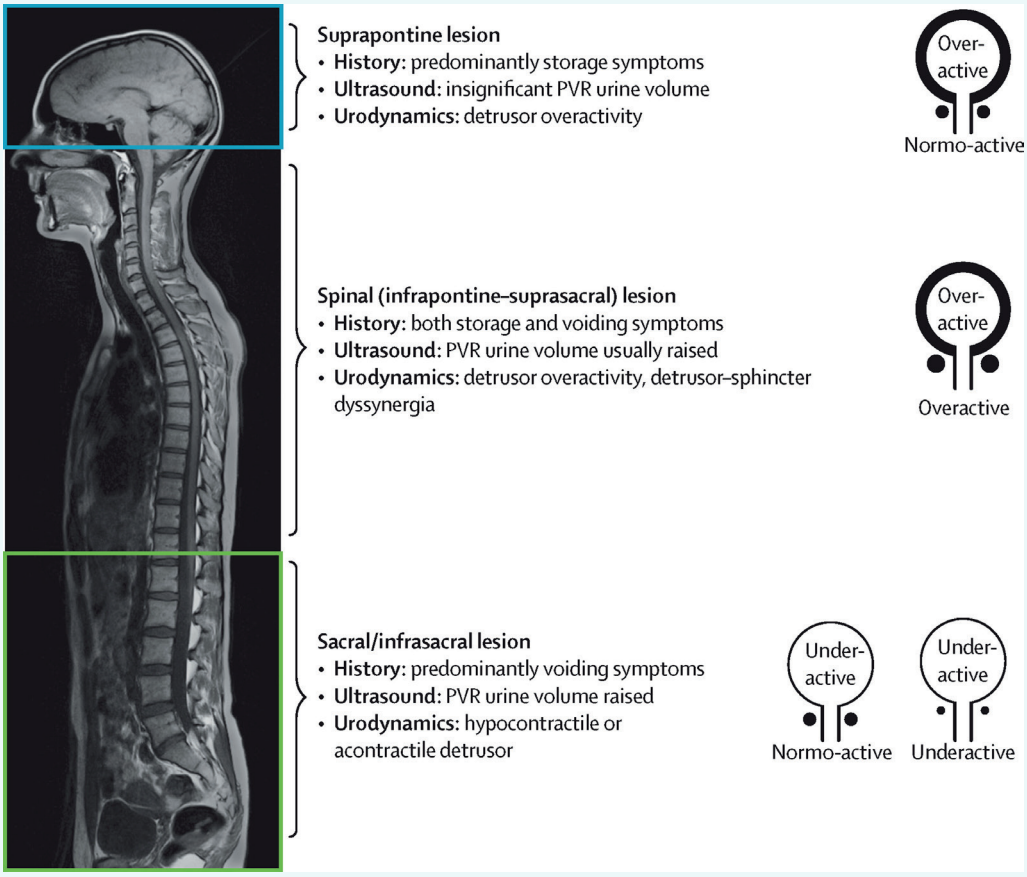
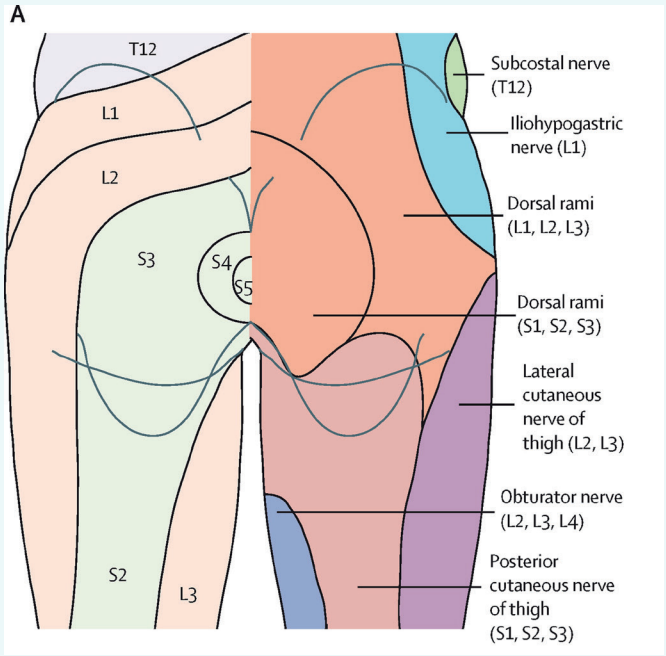
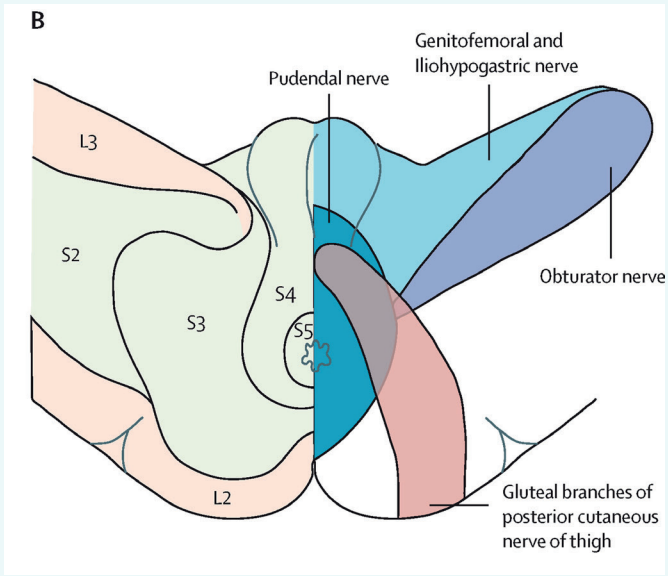



**Figure 6:** Patterns of lower urinary tract dysfunction following neurological disease (with permission from [1]).



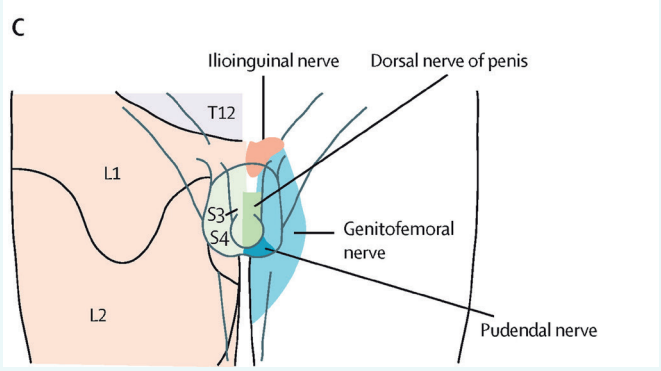
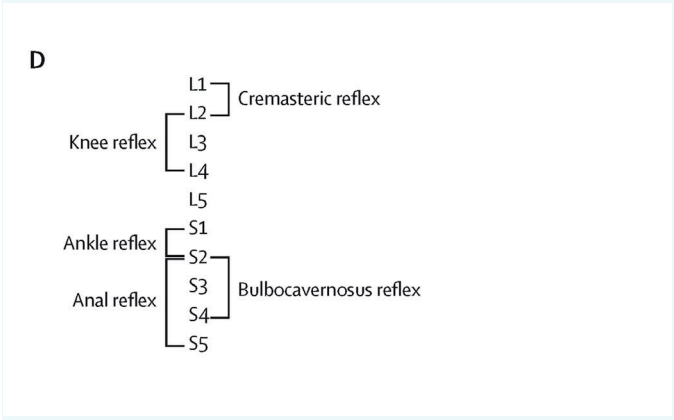




**Figure 7:** Lumbosacral dermatomes, cutaneous nerves, and reflexes (with permission from [1]).




stricture, bladder stones, bladder tumors, etc.).

Serum creatinine and estimated glomerular filtration rate (eGFR) are useful for the initial evaluation of renal function. However, due to the reduced muscle mass after SCI serum creatinine levels may be misleadingly low for long-term monitoring and serum cystatin c seems to be a more accurate marker of renal function, although high-level evidence studies are lacking. The most accurate measurement is still isotopic GFR.

In daily practice, the neuro-urological management is based on the clinical and urodynamic dysfunction pattern. In patients with detrusor overactivity, the therapeutic concept is to convert the overactive into a normoactive or underactive detrusor. Therefore, antimuscarinics are the pharmacological treatment of choice. For refractory neurogenic detrusor overactivity, intradetrusor onabotulinumtoxinA injections are a highly effective, minimally invasive, and generally well-tolerated treatment. In the case of failed onabotulinumtoxinA treatment, patients are candidates for more invasive therapies (e.g. augmentation, cystectomy with continent or incontinent urinary diversion).

In the case of stress urinary incontinence due to low bladder outlet resistance, electrical stimulation of the pelvic floor can help to restore urinary continence in patients with incomplete lesions. In some patients, the implantation of a sub-urethral sling or an artificial urinary sphincter may become necessary.

In patients with an underactive/acontractile detrusor and/or with DSD, intermittent self-catheterization is recommended to assist bladder emptying. Passive voiding by abdominal straining (Valsalva manoeuvre) or, particularly, by suprapubic downwards compression of the lower abdomen (Credé manoeuvre) is not recommended since it creates un-physiological and high intravesical pressure, which puts the upper urinary tract at risk. Nevertheless, some patients are not able and/or not willing to perform intermittent self-catheterization and therefore an indwelling transurethral or suprapubic catheter is potentially the only alternative.

In SCI patients, regular follow-up is essential since NLUTD is often not stable. The EAU Guideline on Neuro-Urology2 provides strong recommendations to perform urodynamic investigation as mandatory baseline diagnostic intervention, to instigate further, specialized, investigation in the case of any significant clinical changes, to perform a physical examination and laboratory urinalysis every year. Also, the upper urinary tract should be assessed at regular intervals. However, due to a lack of high-level evidence studies on uniform follow-up schedules, a rather individualized, patient-tailored approach is needed for this special patient population to achieve an optimum quality of life and to protect the upper and lower urinary tract.[1,2]

Refences:

[1] Panicker JN, Fowler CJ, Kessler TM. Lower urinary tract dysfunction in the neurological patient: clinical assessment and management. Lancet Neurol 2015; 14:720-32.

[2] Groen J, Pannek J, Castro Diaz D, Del Popolo G, Gross T, Hamid R, Karsenty G, Kessler TM, Schneider M, t Hoen L, Blok B. Summary of European Association of Urology (EAU) Guidelines on Neuro-Urology. Eur Urol 2016; 69:324-33.

# EMSCI at RadboudUMC

## Letter from Martin Pouw, successor of Henk van de Meent in Nijmegen

**Dear EMSCI members,**

Thank you for the opportunity to become the EMSCI coordinator in the RadboudUMC. As Henk van de Meent is leaving our hospital, he suggested to ask you if I could be his successor. I am very honored you agreed and will do my utmost to continue and widen our long lasting partnership.

A short introduction:
I finished my PhD in 2014 and in several studies, I have used the EMSCI data. For an orthopaedic surgeon, I am thus quite familiair with the ins and outs of the EMSCI and obviously I am currently working as a spine surgeon in both the RadboudUMC and the Maartenskliniek SCI-rehab center. This gives me the opportunity to have a full insight in the "chain of dedication" concerning tSCI management, acute care up to the complete rehab program.

I'm looking forward to being an active member of the EMSCI community again and I'm looking forward to some interesting discussions during the EMSCI meetings!

Lastly, I would like to take this opportunity to thank Henk again for all his time and effort he has put in the EMSCI project! In addition, I would like to thank all the EMSCI members for their continuous effort in making the EMSCI such a great project!

**Kind regards,**
**Martin Pouw**

## Who we are

### EMSCI Management

| | | |
|---|---|---|
| Project responsibility | A. Curt | armin.curt@balgrist.ch |
| Coordination | M. Schubert | martin.schubert@balgrist.ch |
| Database | R. Rupp | ruediger.rupp@med.uni-heidelberg.de |
| Datamanager | R. Koller | rene.koller@balgrist.ch |
| Research Manager | M. Bolliger | marc.bolliger@balgrist.ch |

| Active centers | PI | Coordination | Coordination |
|---|---|---|---|
| Barcelona | Dr. J. Vidal | J. Benito | jbenito@guttmann.com |
| Basel | PD Dr M. Hund | I. Debecker | i.debecker@rehab.ch |
| Bayreuth | PD Dr. R. Abel | M. Mayer | michaela.mayer@klinikum-bayreuth.de |
| Berlin (UKB) | Dr. M. Gössling | M. Gössling | Malte.Goessling@ukb.de |
| Halle | Dr. K. Röhl | F. Röhrich | frank.roehrich@bergmannstrost.com |
| Heidelberg | Prof. N. Weidner | R. Rupp | ruediger.rupp@med.uni-heidelberg.de |
| Hessisch-Lichtenau | Dr. M. Saur | D. Ehmer | zftp-aufnahme@lichtenau-ev.de |
| | | N Rohleder | nrohleder@lichteau-ev.de |
| Karlsbad-Langensteinbach | Dr. C. Fürstenberg | G. Bihlmaier | georg.bihlmaier@srh.de |
| Kreischa | Dr. K. Anders | V. Skotta | vincent.skotta@klinik-bavaria.de |
| Murnau | Dr. D. Maier | O. Mach | omach@bgu-murnau.de |
| Nijmegen | Dr. M. Pouw | D. Reijnen-Nabuurs | diane.reijnen-nabuurs@radboudumc.nl |
| Nottwil | Dr. M. Baumberger | D. Hersche | dario.herrsche@paraplegie.ch |
| | | A. Bulloni | agata.bulloni@paraplegie.ch |
| Pavia | Dr. A. o Nardone | C. Pavese | chiara.pavese@icsmaugeri.it |
| Prague | Dr. J. Kriz | V. Hysperska | veronika.hysperska@fnmotol.cz |
| Rome | Dr. G. Scivoletto | G. Scivoletto | g.scivoletto@hsantalucia.it |
| Sion | Dr. X. Jordan | X. Jordan | xavier.jordan@crr-suva.ch |
| Toledo | Dr. A. Gil-Agudo | M. Alcobendas | malcobendas@sescam.jccm.es |
| Tübingen | Dr. A. Badke | C. Gonser | cgonser@bgu-tuebingen.de |
| Udine | Dr. L. Lattuada | E. Bizzarini | emiliana.bizzarini@asuiud.sanita.fvg.it |
| Ulm | Dr. Y.-B. Kalke | V. Armbruster | verena.armbruster@rku.de |
| Wien | Prim. Dr. K. Gstaltner | A. Seis | astrid.seis@auva.at |
| Zürich | Prof. A. Curt | I. Lerch | irina.lerch@balgrist.ch |
| | | A. Linke | anita.linke@balgrist.ch |

### Associated member

| | |
|---|---|
| Berlin Charité | Prof. J. Schwab |

### Coperation partner

| | |
|---|---|
| ASCIS (Austria) | Prim. PD. Dr. Georg Mattiassich & Prim. Univ. Prof. Dr. Thomas Freude<br>Coordination: B. Zehentner - barbara.zehentner@pmu.ac.at |

**Passive centers and canditates can be found at: www.emsci.org/members**

NISCI
Nogo Inhibition in Spinal Cord Injury

EMSCI

# Save the date

## DMGP annual meeting
22-25.06.2022 in Bad Wildungen

## ISCoS Annual Scientific Meeting
15-18 September 2022 - Vancuver Convention Cerntre -Canada

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the grant agreement No 681094,and is supported by the Swiss State Secretariat for Education, Research and Innovation (SERI) under contract number 15.0255.

Schweizer Paraplegiker Stiftung

Wings for Life
Spinal Cord Research Foundation