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Annual Report 2021
Swiss Pediatric Inflammatory Brain Disease Cohort Study

For the Swiss Pediatric Inflammatory Brain Disease Cohort Study:

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2 Summary

EN:

«The Swiss Pediatric Inflammatory Brain Disease Cohort Study: A nationwide population-based registry to enhance epidemiological knowledge and improve care of pediatric onset MS and related disorders»

The Swiss Pediatric Inflammatory Brain Disease Cohort Study (Swiss-Ped-IBrainD) has a registry at its core. We are currently building this registry to systematically collect medical data on pediatric patients suffering from inflammatory brain diseases (IBrainDs) such as multiple sclerosis (MS).

Our focus is on collecting extensive information on the diagnosis, disease course, and treatment of the included diseases. These data will come together to generate an accurate, high resolving image showing which areas of the diseased children's lives are affected and to what extent.

However, the registry is not just a simple data collection, it is a dynamic structure that promotes the communication and collaboration of the participating centers. It fosters a network of specialists in the field, who will not only help to gather knowledge but also to implement the acquired knowledge in the best interest of their patients. **We aim to improve the medical care as well as the quality of life of children affected by IBrainDs**.

We have achieved all the targets set for the year 2021:

- All clinics that have agreed to participate in the Swiss-Ped-IBrainD have been opened for patient recruitment. We initiated every site with a kick-off meeting attended by the executive office, the clinical lead, and the local study team.
- We have found a suitable validated questionnaire for our first survey study. We plan to include additional questions on patient perception of the diagnostic process, since this influences therapy adherence in adults.
- We held a first annual meeting with all local principal investigators. The meeting resulted in the formation of the Swiss-Ped-IBrainD Task Force. The Swiss-Ped-IBrainD Task Force discusses challenging cases from the clinics on a bimonthly basis.

DE:

«Die Schweizerische Pädiatrische Kohortenstudie zu entzündlichen Hirnerkrankungen: Ein landesweites Register mit dem Ziel, Multiple Sklerose und verwandten Erkrankungen bei Kindern besser zu verstehen und zu behandeln»

Die schweizerische pädiatrische Kohortenstudie zu entzündlichen Hirnerkrankungen (Swiss-Ped-IBrainD) hat als Kernstück ein Register. Wir bauen dieses Register derzeit auf. Darin werden medizinische Daten von Patienten gesammelt, die als Kind an einer entzündlichen Hirnerkrankungen (IBrainDs) wie Multipler Sklerose (MS) erkrankt sind.

Unser Augenmerk liegt auf Daten zur Diagnose, dem Krankheitsverlauf und der Behandlung der verschiedenen IBrainDs. Aus diesen Daten soll ein genaues, hochauflösendes Bild von der Situation der Betroffenen in der Schweiz entstehen.

Das Register ist aber nicht nur eine einfache Datensammlung. Es ist eine dynamische Struktur, die den Austausch und die Zusammenarbeit der beteiligten Spitalzentren fördert. Wir pflegen ein Netzwerk von Fachleuten. Diese helfen dabei Wissen zu schaffen und setzen das erworbene Wissen im besten Interesse ihrer Patienten um. **Unser Ziel ist es, die medizinische Versorgung und die Lebensqualität von Kindern mit IBrainDs zu verbessern**.

Wir haben alle für das Jahr 2021 gesetzten Ziele erreicht:

- Alle Kliniken, die sich zur Teilnahme am Swiss-Ped-IBrainD bereit erklärt haben, sind für die Patientenrekrutierung geöffnet. Alle Standorte wurden mit einem Kick-off-Meeting initiiert, an dem das Swiss-Ped-IBrainD Team, inklusive klinische Leitung, und das lokale Studienteam teilgenommen haben.
- Wir haben einen geeigneten, validierten Fragebogen für unsere erste Fragebogenstudie gewählt. Zusätzliche planen wir Fragen zur Wahrnehmung des Diagnoseprozesses durch die Patienten anzufügen, da diese die Therapietreue bei Erwachsenen beeinflusst.
- Wir haben ein erstes jährliches Treffen mit allen lokalen Prüfärzten abgehalten. Das Treffen führte zur Gründung der Swiss-Ped-IBrainD Task Force. Die Swiss-Ped-IBrainD Task Force bespricht alle zwei Monate schwierige Fälle aus den Kliniken.

FR:

« L'étude de cohorte suisse sur les maladies inflammatoires du cerveau à l'âge pédiatrique : Un registre national pour mieux comprendre et traiter la sclérose en plaques et maladies apparentées chez les enfants ».

L'étude de cohorte suisse sur les maladies inflammatoires du cerveau à l'âge pédiatrique (Swiss-Ped-IBrainD) repose sur un registre. Nous sommes en train de mettre en place ce registre pour lequel nous recueillons des données médicales de patients atteints de maladies cérébrales inflammatoires d'origine pédiatrique (IBrainDs), comme la sclérose en plaques.

Notre objectif est de recueillir des informations détaillées relatives au diagnostic, à l'évolution de la maladie et au traitement des différentes IBrainDs. Ces données sont collectées afin de dresser un état des lieux précis de la situation des personnes concernées en Suisse.

Le registre n'est toutefois pas un simple recueil de données, mais une structure dynamique qui facilite la communication et la collaboration entre les centres participants. Il favorise un réseau de spécialistes du domaine, qui contribueront non seulement à rassembler les connaissances, mais aussi à les mettre en œuvre dans le meilleur intérêt de leurs patients. **Notre objectif est d'améliorer les soins médicaux ainsi que la qualité de vie des enfants atteints de IBrainDs.**

Nous avons atteint tous les buts fixés pour l'année 2021 :

- Toutes les cliniques qui ont accepté de participer au Swiss-Ped-IBrainD ont été ouvertes au recrutement de patients. Nous avons initié chaque site lors d'une réunion de lancement à laquelle ont participé les représentants du registre, la direction clinique et l'équipe d'étude locale.
- Nous avons sélectionné un questionnaire approprié et validé pour notre première enquête. Nous allons y inclure des questions supplémentaires sur la perception du processus diagnostique par les patients, un facteur qui influence grandement l'adhésion au traitement chez les adultes.
- Nous avons organisé une première réunion annuelle avec tous les investigateurs principaux locaux. Cette réunion a résulté dans la constitution de la Swiss-Ped-IBrainD Task Force qui discute tous les deux mois des cas difficiles provenant des cliniques.

3 Background

Pediatric onset MS and other IBrainDs are severe diseases affecting children and adolescents in a period of essential brain development. This possibly leads to a variety of focal neurological deficits as well as early cognitive impairment. In turn, the cognitive impairment may pose additional difficulties to everyday life and impact school performance and vocational achievements.

Timely diagnosis and treatment initiation as well as individually tailored management are important for a favorable disease course. However, the diagnosis of the different IBrainDs can be challenging, especially in young children, since their first acute inflammation is often accompanied by unspecific symptoms common to all IBrainDs. A systematic assessment of similarities and differences between clinical signs, symptoms, and diagnostic workup of different IBrainDs will enable faster and more reliable diagnosis.

Furthermore, neither epidemiological data nor information on health care management and disease outcome of pediatric IBrainD patients exist in Switzerland. Therefore, we are setting up a national registry, which will allow a deeper understanding of pediatric IBrainD epidemiology, clinical presentation, and management. Ultimately, the registry will improve the care of children suffering from an IBrainD in Switzerland.

4 Description of the Swiss-Ped-IBrainD Registry

4.1 Organizational Structure

The Swiss-Ped-IBrainD is run by an overall lead and an executive office in close collaboration (Table 1). The clinics are the university and cantonal hospitals who have agreed to participate in the Swiss-Ped-IBrainD. Figure 1 is an overview of the organizational structure of the Registry.

The overall lead of the registry is currently shared between the clinical lead and a legal representative at the ISPM. They share the overall responsibility for the registry as well as the making of directional decisions. In the near future, we plan to install a steering board. The steering board will include pediatric neurologists from participating clinics to complement the overall lead of the registry.

The executive office represents the operative part of the registry. It organizes various tasks such as the development and curation of documents (study plan, patient information, case report forms, standard operating procedures, etc.), set-up of the electronic database (RedCap), collection of data, submission of documents to the ethics committee, management of the finances, preparation of legal documents (e.g., study agreements), and maintenance of ways of dissemination.

The clinics have the fundamental task of recruiting patients for the registry and providing data/data access to the executive office.

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Table 1: Registry staff and participating clinics

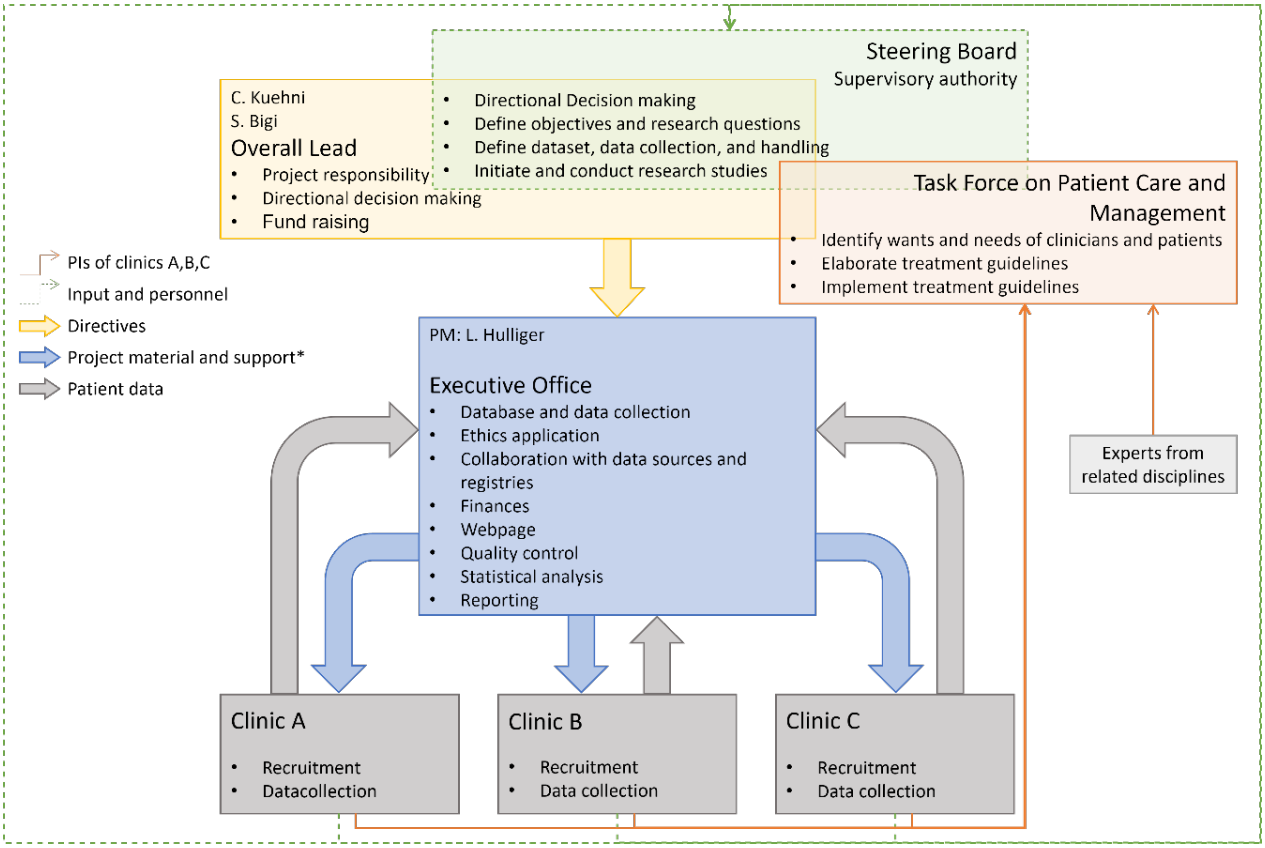

*Figure 1: Organizational structure of the Swiss-Ped-IBrainD. *The executive office shares gained knowledge with the clinics and provides a basis for future studies, which may be initiated by the clinics.*

At the end of 2021, we founded the «Swiss-Ped-IBrainD Task Force». The task force consists of the local principal investigators of the participating centers and additional members from complementing disciplines such as pediatric neuroradiology and neuropsychology.

The purpose of the task force is to discuss challenging cases from the sites and to develop and implement treatment guidelines. The pediatric IBrainD patients thus benefit directly from the knowledge exchange within this expert panel.

4.2 Objectives

The registry pursues the following goals:

1) Gathering representative, population-based epidemiological data on pediatric IBrainDs in Switzerland.

2) Monitoring treatment, clinical course, education, social aspects, and outcomes of pediatric IBrainD patients.

3) Providing a platform to facilitate research, national and international collaboration and exchange of knowledge between experts.

The registry thus addresses the increasing requests for medical trial participation and promotes the exchange with existing adult registries (e.g., Swiss MS Registry).

4.3 Inclusion/Exclusion Criteria

The following patients qualify for inclusion: All patients living and/or treated in Switzerland living with an IBrainD specified in Table 2 with an onset before the age of 18.

Demyelinating diseases
Optic neuritis
Transverse myelitis
Acute disseminated encephalomyelitis
Multiple sclerosis
Neuromyelitis optica spectrum disorders
Antibody-associated diseases
Anti-NMDA-R associated autoimmune encephalitis
Anti-GAD65 associated autoimmune encephalitis
Anti-AMPA-1/2 associated autoimmune encephalitis
Anti-Lgi-1 associated autoimmune encephalitis
Anti-CASPR-2 associated autoimmune encephalitis
Anti-GABA-1/2 associated autoimmune encephalitis
Onconeuronal antibody (Hu, Ri, Yo, Amphiphysin, CRMP-5, Ma-1, Ma-2, SOX-1) associated autoimmune encephalitis
Hashimoto encephalopathy
Other IBrainDs
CNS vasculitis
CNS sarcoidosis
CNS Lupus
Rasmussen's encephalitis

Table 2: Included IBrainDs

Excluded are patients with:

1) Neurological symptoms due to infectious diseases of the CNS

2) Genetic/metabolic causes of central demyelinating diseases

3) Neurological symptoms due to Guillain-Barré-Syndrome

4.4 Registration of Patients and Collection of Medical Data

Pediatricians, pediatric neurologists, neurologists, specialists in rehabilitation, and primary care physicians at the participating centers are responsible to identify children with the listed IBrainDs (see Table 2) during regular medical consultations. Upon identification, treating physicians inform patients and their parents orally and in writing about the Swiss-Ped-IBrainD. Patients who do not attend regular consultations (e.g., because they are no longer treated for their IBrainD, have transitioned to adult care, have relocated, etc.) and can therefore not be informed by the physician are sent an invitation to participate. Patients (and their legal representatives if applicable) who want to participate must give their informed consent. Once a patient consents to participate, his/her medical data will be entered in the database of the registry.

The diagnostic workup and treatment of patients continue as usual and are independent from participation; no examination will be carried out specifically for the Swiss-Ped-IBrainD.

Medical data is collected through the following sources:

- Medical records and reports
- Oral/written information from treating physician
- Oral/written information from patient/family
- Routine statistics and other medical registries
- Questionnaires for patients and families

The data collection focuses on diagnostic data, follow-up data, and data on relapses.

4.5 Ethics Approval / Data Protection

The Swiss-Ped-IBrainD project (title: «Swiss Pediatric Inflammatory Brain Disease Cohort Study», project number: 2019-00377) has been approved by the ethics committees of Bern, the Ethikkommission Nordwest- und Zentralschweiz (EKNZ), the Ethikkommission Ostschweiz (EKOS), and the ethics committee of Zürich. In 2021 the Swiss-Ped-IBrainD has additionally been approved by the remaining ethics committees of Lausanne, Geneva, and Bellinzona.

The transmission, storage, and analysis of health-related personal data within this project follow the current Swiss legal requirements for data protection and the Human Research Ordinance Art. 5. Data is always pseudonymized for analysis.

Health-related personal data are strictly confidential. They are handled with uttermost discretion and are only accessible to authorized personnel. Direct access to source documents for purposes of monitoring, audits, or inspections is permitted.

The data protection concept of ISPM ensures the secure handling of all sensitive data at ISPM and within Swiss-Ped-IBrainD. All employees are subject to the duty of confidentiality.

4.6 Funding

The Swiss-Ped-IBrainD is financed through third-party funds. The initial fundraising yielded 380’000 CHF. In 2021 the Swiss-Ped-IBrainD has been awarded further funding of 121’000 CHF.

We differentiate between peer-reviewed funding and other funding.

Peer-reviewed funding

Our only peer-reviewed support comes from the Swiss MS Society. They provided us with a generous grant for the years 2020/2021.

Other funding

The PedNet Bern has supported the project in its beginning with a start-up aid.

Roche Pharma (Switzerland) Ltd and Novartis Pharma Schweiz AG are further sponsors of the project. In 2021 we added Sanofi-Aventis (Schweiz) to our list of supporters from the pharmaceutical industry.

Additionally, the Fondation Johann Dürmüller-Bol has donated money to the Swiss-Ped-IBrainD for the coverage of material costs. The Swiss MS Society offered additional funding achieved through donations.

5 Achievements of the Swiss-Ped-IBrainD 2021

The Swiss-Ped-IBrainD is a long-term project with a stepwise development. In our research plan we have defined the main goals for the first five years (2020-2024).

The declared goals for the year 2021 were:

1) All sites initiated

2) First questionnaire developed

3) First annual meeting held

All sites initiated

All sites have been initiated. This means that all clinics who have agreed to participate are open for patient recruitment. We met with the principal investigators and study teams of all sites to initiate the screening and search of patients meeting the inclusion criteria of the Swiss-Ped-IBrainD. For that occasion, we compiled the study documents in Investigator Site Files. The Investigator Site Files include the site-specific patient information and informed consent forms as well as documents describing the inclusion procedure. During the initiation meeting we discussed patient screening, patient and parent information, informed consent procedure, and inclusion.

We are currently establishing individual patient recruitment and data collection workflows with every site. The heterogeneity of the participating sites (including differences in structure, clinic information system, team sizes, patient emergence, etc.) calls for tailored approaches with different levels of support by the executive office. All procedures conform with the study plan.

First questionnaire developed

Next year we want to conduct a survey study on the quality of life of children with MS and other IBrainDs. We have decided to first use a validated instrument for that purpose. One of the advantages of using a validated instrument is data comparability – which is important (particularly in the field of rare diseases) since we want to compare our results with those of other countries and contribute to the overall picture. We have therefore refrained from developing our own questionnaire. However, we plan to add questions about the experience of the diagnostic process.

First annual meeting held

We held the first annual meeting with all local principal investigators on November 12, 2021. The meeting led to the formation of the «Swiss-Ped-IBrainD Task Force». The purpose and constitution of the task force are detailed in section 4.1.

Further achievements

Beyond reaching our goals for the year 2021, we have started recruiting patients and collecting data. Until now, patient screening has yielded 181 potential participants, 50 of whom have already consented to participate in the Swiss-Ped-IBrainD registry. Preliminary results suggest pediatric onset MS to be the most common pediatric IBrainD in Switzerland.

We have also kept working on the Swiss-Ped-IBrainD RedCap database; Last year we established the variables of interest (reflecting the events of registration, diagnosis, follow-up, and relapse) and programmed our database accordingly. This year, after thorough testing we have set the database to "production" mode and are now entering the collected medical data of all those patients who have agreed to participate in the Swiss-Ped-IBrainD registry.

The presentation of the Swiss-Ped-IBrainD registry at the 46th annual meeting of the «Gesellschaft für Neuropädiatrie» which resulted in the publication of the congress abstract in the journal Neuropediatrics[1] was a further achievement of 2021.

6 Outlook

The declared goals for the year 2022 are:

1) Data collection initiated at all sites

2) First questionnaire distributed

3) Study protocol submitted for publication

We have further been invited to present the Swiss-Ped-IBrainD at the 14th European Paediatric Neurology Society Congress at the end of April/beginning of May 2022.

We also need to continue raising funds to secure the continued existence of the Swiss-Ped-IBrainD.

7 Acknowledgements

We would like to thank all the participants and their families for taking an interest in the registry and allowing us to access their data. We are further very thankful to the local principal investigators for their collaboration and effort to advance the project.

We are also very grateful to the patient organization Swiss MS Society not only for their financial support but also for their inspiring commitment to the cause.

Further we express our thanks to Roche Pharma (Switzerland) Ltd, Novartis Pharma Schweiz AG, Sanofi-Aventis (Schweiz), the Fondation Johanna Dürmüller-Bol, and the PedNet Bern for funding us.

8 References

1. Bigi S, Bauder F, Mori AC, et al. The Swiss Pediatric Inflammatory Brain Disease Cohort Study: Setting up a National Registry for Children and Adolescents with Pediatric Onset MS and Related Disorders. *Neuropediatrics.* 2021;52(S 01):P1.21.