SWISS PRIMARY HYPERSONIA NARCOLEPSY COHORT STUDY (SPHYNCS)

INTRODUCTION

Background

An estimated 5% of the general populations suffers from excessive daytime sleepiness (EDS) and/or hypersomnolence. Following sleep disordered breathing the so-called "central disorders of hypersomnolence" (CDH) or "primary hypersomnnias" are the second most common cause of EDS. Narcolepsy with cataplexy (NT 1) is a well defined form of CDH with specific and sensitive biomarkers (HLA-markers, cerebrospinal fluid hypocretin-1 levels, sleep onset REM episodes during sleep-wake recordings). Etiologically, recent data suggest an underlying autoimmune process leading to a progredient loss of hypocretinergic and an increase of histaminergic neurons in the hypothalamus. Therapeutically, few observations suggest a role for (early) immunomodulatory treatments. Other forms of CDH including narcolepsy type 2 (NT2), idiopathic hypersomnia (IH), insufficient sleep syndrome (ISS), hypersomnia in long sleepers (with relative ISS), and hypersomnia associated with psychiatric disturbances (but without a definite psychiatric disorder, non-organic hypersomnia, NOH) are less well defined.

In the absence of validated biomarkers their diagnosis is often difficult and their etiology unknown. The natural course and best treatment options for these conditions remain also unclear.

Main objectives

1) reassessment of the “narcolepsy borderland” through the identification of biomarkers for CDH (and comparison with those for NT1)
2) better understanding of the etiology (immunological, genetic, environmental, psychosocial factors) of CDH and the relationship to NT1

Patients and methods

Patients with CDH will prospectively be recruited and follow up from 5-8 sleep centers (see below) belonging to the recently constituted Swiss Narcolepsy Network (SNaNe). We expect to recruite over 2 years about 150 patients/year (in about 40-50 patients CSF are expected to be available, as well).

Detailed data on patient history (including onset and course of disease, comorbidities, vaccination status) and electrophysiological data (PSG, MSLT, MWT, SART, -week actigraphy, see below) will be obtained as part of routine clinical assessement (general informed conset).

After signing a specific (written) informed consent 40 ml of blood will be drawn, processed (plasma, buffy Coat, PBMC) and stored in our biobank. In cases where a lumbar puncture is performed within the clinical routine (or for study purposes) an extra amount of 3-5ml CSF will be drawn and stored.

In sleep centers outside Bern samples (plasma, buffy coat, CSF) will be immediately processed and stored at -80°C. Batches of frozen samples will be sent to the Inselspital for stockage.

All clinical and neurophysiological data will be monitored, reviewed and approved centrally review/consensus committee).

All centers will be assisted by a study monitoring team.

All data will be entered in a RedCap Database (a module of the EU-NN database maaged by the Clinical Trails Unit in Bern, PD S. Trelle). This database will be accessible for all participating sleep centers.

Biosamples will be stocked in the DLF liquid biobank of the Inselspital (Prof. M. Fiedler).

Biomarkers will be determined/measured in collaboration with Prof. M. Fiedler (Bern), Prof. M. Tafti (Lausanne) and Prof. F. Sallusto (Bellinzona/Zurich)

Potential impact

This is the first world-wide prospective, large scale study on CDH. The results are expected to have an impact on:

1) current diagnostic criteria
2) our understanding on etiopathogenesis and course
3) prevention and treatment of this not uncommon group of disorders.

SYNOPSIS

Name of Sponsor:	Swiss Narcolepsy Network (SNaNe), the Swiss excellence/reference center for the management of narcolepsy/primary disorders of hypersomnolence (CDH)
Name of (Principal) Investigator:	Claudio L. Bassetti
Co-Investigators:	Ramin Khatami, Zhongxing Zhang, Barmelweid-Bern
	Federica Sallusto, Daniela Latorre, Bellinzona-Zürich
	Mehdi Tafti, Jose Haba-Rubio, Lausanne
	Mauro Manconi, Lugano-Bern
	Philipp Valko, Christian Baumann, Zürich
	Arto Nirkko, Lucern (in discussion)
	Martin Strub, Basel (in discussion)
	Sigrid von Manitius, St. Gallen (in discussion)
	Johannes Mathis, Martin Fiedler, Carlo Largiadèr, Bern
Coordinating study team:	Maya Ringli, Anelia Dietmann, Panos Bargiotas, Markus Schmidt, Sebastian Ott, Bern
Study design:	Prospective, multicenter, multimodal, non-interventional
Number of sites:	Bern, Barmelweid, Zurich, Lugano, Lausanne (planned) St. Gallen, Lucerne, Basel (in discussion)

Study objectives:

Primary objective:

Reassessment of the “narcolepsy borderland” through the identification of biomarkers for CDH (narcolepsy with and without cataplexy (NT1 and NT2), idiopathic hypersomnia,

periodic hypersommnias, insufficient sleep syndrome/long sleeper, non-organic hypersomnia).

Secondary objective(s):

Better understanding of the etiology (immunological, genetic, environmental) of CDH and the relationship to narcolepsy with cataplexy (NT1).

Population:

From a sleep-center based cohort patients will be chosen according to the following criteria:

Inclusion criteria : patients with a new diagnosis of CDH

1) age 4-80y
2) Informed consent
3) CDH diagnosed according to intern. criteria (ICSD 3)

Exclusion criteria: patients of other cases of EDS/hypersomnia according to a systemic approach including :

1) Structured interview/clinical examination
2) Questionnaires (sleep, wake, psychiatry, QoL,…)
3) Video-Polysomography
4) MSLT
5) 2-week actigraphy

Ancillary tests (labor, brain MRI, psychiatric investigation) will be performed only if clinically indicated.

Study duration per patient will be limited to baseline assessments. There will be at least 1 follow-up visit at 6 months.Follow-ups at 2-4 years to be scheduled (follow-up grant).

Efficacy variables:

Primary efficacy variables:

Primary variables will be the following biomarkers in blood and cerebrospinal fluid:

1) Cellular and humoral immunological markers (incl. Tcells, antibodies (incl. MOG, anti-aquaporin/anti-neuronal antiboides), cytokine/chemokine profile, incl. masscytometry based analysis
2) Genetic factors (incl. protective HLA markers)
3) CSF measurements (incl. oligoclonal bands, hypocretin, histamine, NF, tau, beta-amyloid), using also mass spectrometry analysis not applicable

Secondary variables :

1) clinical data
2) neurophysiological data

Specific assessments/tools/scales:

1) Clinical data (incl. scales*)
2) PSG data
3) Vigilance data (incl. MSLT, MWT and SART)
4) Actigraphy data

*Epworth Sleepiness Scale, Fatigue Severity Scale, Swiss Narcolepsy scale, BDI, Narcolepsy Severity Scale, SF-36

Study flow chart (schedule of assessments):

- Informed consent*
- Clinical visit, questionnaires*
- Neurophysiological examinations*
- Collection of biosamples
- At least 1 follow-up visit at 6 months*

*these assessemnts are part of the clinical routine/clinically indicated

Statistical methods:

The nature of the study is exploratory (unbiased approach).

SCIENTIFIC COMMUNICATION PLAN

Type of scientific communication:	Original research
Meeting/conference:	European/World meetings of sleep/neurology societies
Anticipated dates:	See start/end of project

REQUESTED SUPPORT

Estimated costs for 2 years (total: 600'00):

Ethical approval: 10'000

Databank creation/management (extra-module of EU-NN databnak): 50'000

Study coordination: 40'000

Patients' fees (1000/patient): 150'000

Biosamples' collection, transport, stockage: 140'000

Study monitoring: 40'000

Central neurophysiological scoring/statistics: 60'000

Biosample analyses: 100'000

Meetings, travel costs: 10'000

Other sources of funding

Bern Biobank Call DLF: obtained (50'000)

IRB Internal Grant: obtained (50'000)

European Sleep Foundation/SNaNE: obtained (10'000)

IRC Grant Bern, fall 2016 (submitted)

Novartis, summer 2017 (submitted)

Insel-Grant, fall 2017 (planned)

JAZZ Pharmaceuticals Inc. fall 2017 (planned)

Horton Foundation, 2018 (planned)

Tropos Foundation, 2018 (planned)

ABREOC, 2018 (planned)

SNF (Sinergia), 2018 (planned)

RELEVANT LITERATURE

1. *American Academy of Sleep Medicine, 2014*
2. *Barateau L, Lopez R, Arnulf I, et al. Neurology, 2017*
3. *Bassetti CL, Dauvilliers Y, Adamantidis A, et al. Brain 2017 (close to submission)*
4. *Dauvilliers Y, Evangelista E, Lopez R, et al. Ann Neurol 2016*
5. *Dauvillliers Y, Beziat S, Pesenti C, et al. Neurology 2017*
6. *Giannoccaro MP, Waters P, Pizza F. Sleep 2017*
7. *Hartmann FJ, Bernard-Valnet R, Queriault C, et al. J Exp Med 2016*
8. *Hirtz C, Vialaret J, Gabelle A, et al. Sci Rep 2016*
9. *Jennum J, Pedersen OL, Bahl JMC, et al. Sleep 2017*
10. *Jennum P, Kornum BR, Issa NM, et al. Neurology, Neuroimmunol Neuroinfl 2016*
11. *Jennum P, Ibsen R, Petersen ER, et al. Sleep Med 2012*
12. *Kallweit U, Schmidt M, Bassetti CL. J Clin Sleep Med 2017*
13. *Kallweit U, Bassetti CL. Exp Op Pharmacol 2017*
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17. *Kretschmar U, Werth E, Sturzenegger C, et al. JSR 2016*
18. *Latorre D, Kallweit U, Armetani E, Manconi M, Khatami R, Tafti M, Bassetti CL, Sallusto F. Nature or Nature Med 2017 (close to submission)*
19. *Lecendreux M, Churlaud G, Pitoiset F, et al. PlosOne 2017*
20. *Peraita-Adrados R, Romero-Martinez J, Guzman-D. JA, et al. Sleep Med 2017*
21. *Pizza F, Vandi S, Liguori R, et al. Neurology 2014*
22. *Tafti M, Lammers GJ, Dauvilliers Y, et al. Sleep 2016*
23. *Van der Heide A, van Schle MKM, Lammers GJ, et al. Sleep 2015*