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The Swiss Primary Hypersomnolence and Narcolepsy Cohort study (SPHYNCS): Study protocol for a prospective, multicentre cohort observational study

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Abstract

Narcolepsy type 1 (NT1) is a disorder with well-established markers and a suspected autoimmune aetiology. Conversely, the narcoleptic borderland (NBL) disorders, including

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narcolepsy type 2, idiopathic hypersomnia, insufficient sleep syndrome and hypersomnia associated with a psychiatric disorder, lack well-defined markers and remain controversial in terms of aetiology, diagnosis and management. The Swiss Primary Hypersomnolence and Narcolepsy Cohort Study (SPHYNCS) is a comprehensive multicentre cohort study, which will investigate the clinical picture, pathophysiology and long-term course of NT1 and the NBL. The primary aim is to validate new and reappraise well-known markers for the characterization of the NBL, facilitating the diagnostic process. Seven Swiss sleep centres, belonging to the Swiss Narcolepsy Network (SNaNe), joined the study and will prospectively enrol over 500 patients with recent onset of excessive daytime sleepiness (EDS), hypersomnia or a suspected central disorder of hypersomnolence (CDH) during a 3-year recruitment phase. Healthy controls and patients with EDS due to severe sleep-disordered breathing, improving after therapy, will represent two control groups of over 50 patients each. Clinical and electrophysiological (polysomnography, multiple sleep latency test, maintenance of wakefulness test) information, and information on psychomotor vigilance and a sustained attention to response task, actigraphy and wearable devices (long-term monitoring), and responses to questionnaires will be collected at baseline and after 6, 12, 24 and 36 months. Potential disease markers will be searched for in blood, cerebrospinal fluid and stool. Analyses will include quantitative hypocretin measurements, proteomics/peptidomics, and immunological, genetic and microbiota studies. SPHYNCS will increase our understanding of CDH and the relationship between NT1 and the NBL. The identification of new disease markers is expected to lead to better and earlier diagnosis, better prognosis and personalized management of CDH.

KEYWORDS
biomarkers, electrophysiology, excessive daytime sleepiness, hypersomnia, sleep–wake disorders

1 | INTRODUCTION

An estimated 5% of the general population suffers from excessive daytime sleepiness (EDS) and/or hypersomnolence (H) (Ohayon, 2011). In about 1%–2% of the population, EDS/hypersomnolence is due to so-called central disorders of hypersomnolence (CDH). CDH includes a group of sleep disorders in which EDS is the primary complaint, without comorbid conditions causing disturbance of nocturnal sleep or circadian rhythm disorder being the reason for EDS. To date, these disorders are mostly classified according to the International Classification of Sleep Disorders 3rd edition (ICSD3) published in 2014 (American Association of Sleep Medicine, 2014). The following disorders are included amongst others in the group of CDH: narcolepsy with cataplexy (narcolepsy type 1 [NT1]), narcolepsy without cataplexy (narcolepsy type 2 [NT2]), idiopathic hypersomnia (IH), insufficient sleep syndrome (ISS), and hypersomnia associated with a psychiatric disorder (American Association of Sleep Medicine, 2014).

NT1 is a relatively well-defined disorder with known specific and sensitive markers and a suspected autoimmune pathology that most likely leads to degeneration of hypocretin-producing neurons. All other central disorders of hypersomnolence have ill-defined diagnostic criteria with overlapping signs and symptoms and little is known about their pathophysiology (Fronczek et al., 2020; Lammers et al., 2020). In clinical practice, EDS without cataplexy presents a common diagnostic challenge, resulting in changing, incorrect or missing diagnoses. Especially difficult is the diagnostic procedure in EDS patients with psychiatric disorders and ambiguous electrophysiological findings (Barateau et al., 2017; Plante, 2017). Consequently, patients receive wrong or no treatment despite serious symptoms with severe impairment of their quality of life, even though therapeutic options would exist. Therefore, a better definition of disorders of the narcoleptic borderland (NBL), including NT2, IH, ISS and EDS associated with psychiatric diseases, is urgently needed (Fronczek et al., 2020; Lammers et al., 2020). Furthermore, the evolution of NT1 and NBL over time is an important and so far not well-studied research question. NT1 typically does not show remission and is currently considered a lifelong disease. However, it is at present not well understood if different forms of narcolepsy in terms of their natural history and evolution exist (Bassetti et al., 2019). From clinical experience the existence of different narcolepsy-course subgroups has been postulated: acute versus chronic or progressive narcolepsy (Bassetti et al., 2019; Pizza et al., 2014). Thus, studies are needed to clarify the natural history and evolution of NBL patients. Patients with NT2 may evolve to NT1, often within weeks or months, although sometimes only after

decades (Andlauer et al., 2012; Pizza et al., 2014; Sturzenegger & Bassetti, 2004). In 2018, Latorre et al. were able to detect autoreactive T-cell clones in patients with NT1 and in one patient with NT2, who later developed cataplexy (Latorre et al., 2018). HLA positivity and diminished cerebrospinal fluid (CSF) Hcrt-1 levels may represent predictors for the subsequent development of cataplexy. Recent studies reported frequent remissions or changes of diagnosis and results of ancillary findings (e.g., multiple sleep latency test [MSLT]) in NBL patients (Kim et al., 2016; Trotti et al., 2013).

The Swiss Primary Hypersomnolence and Narcolepsy Cohort Study (SPHYNCS) will investigate the clinical picture and long-term course of NT1 and the NBL with the goal to tie up the loose ends and facilitate the diagnostic process for CDH in the future.

2 | METHODS/DESIGN

2.1 | Study Design

The SPHYNCS is a prospective, national, multicentre cohort study for systematic evaluation of clinical presentation and course of NT1 and the NBL. Data from multimodal assessments, combining classical and new methods (Figure 1), are collected in a large database. Next to a hypothesis-driven approach, the SPHYNCS will additionally employ a data-driven, stepwise approach, which will allow reassessment and sharpen our understanding of the narcoleptic borderland by recognizing its underlying immunological and pathophysiological mechanisms.

2.2 | Aims and hypotheses

Our primary aim is to establish and validate new and reappraise well-known methods and markers for the characterization of the NBL. The primary hypothesis is that NT1 and some NBL patients differ from control subjects with respect to different properties. Those are (1) clinical signs and symptoms, (2) autoreactive immune cells, (3) genetic markers such as HLA types, (4) CSF hypocretin-1, (5) proteomic/peptidomic profile, (6) the gut microbiome, (7) parameters from conventional electrophysiological sleep–wake studies, (8) vigilance tests and (9) activity patterns resulting from ambulatory sleep–wake studies (Figure 1). Our secondary aim is to reassess the pathophysiological understanding of the NBL and synthesize the collected information with the help of machine learning algorithms. The hypothesis is that combined information from established and new technologies will result in novel disease markers or marker profiles reshaping the NBL and facilitating the diagnostic process (Figure 2). Our third aim is to predict the evaluation and course of

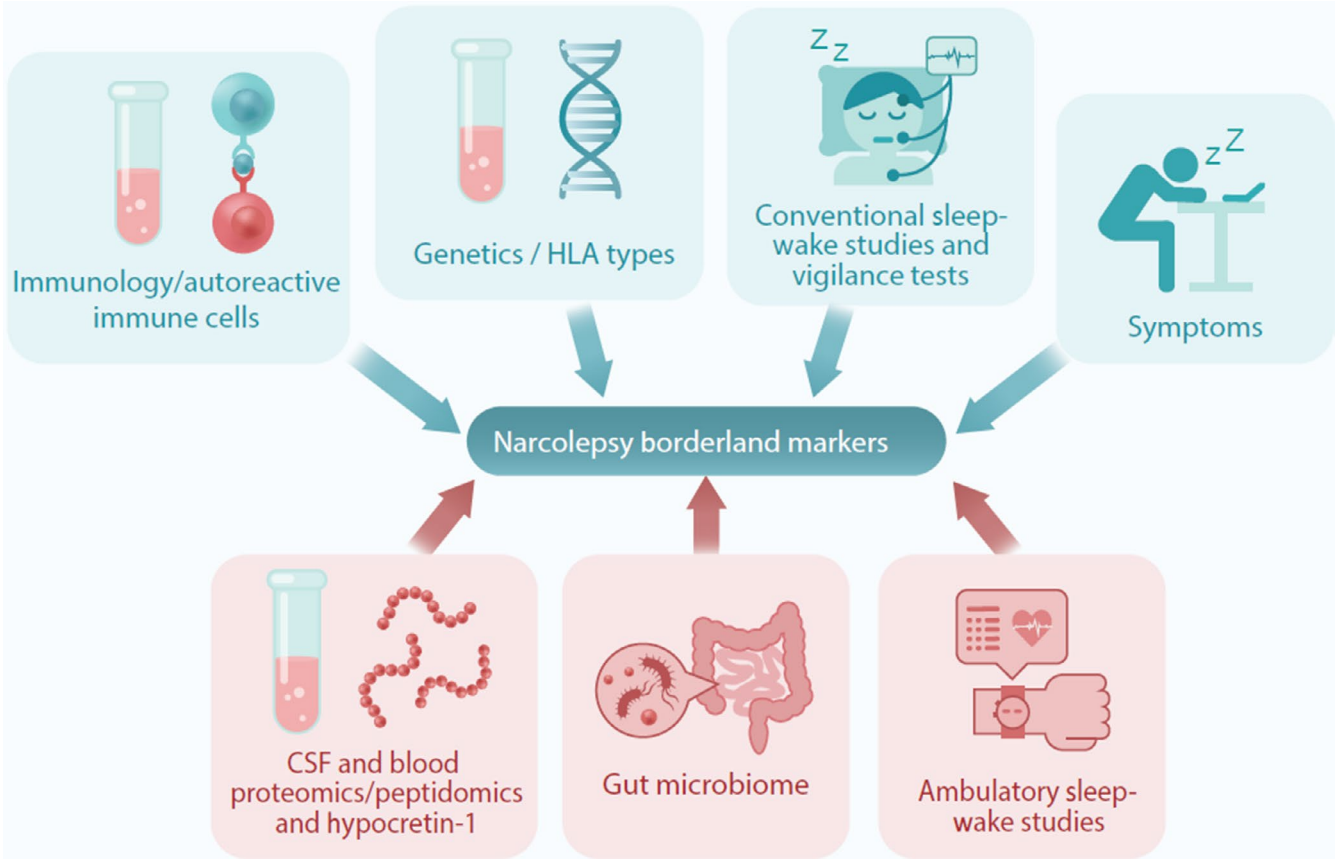

FIGURE 1 Multimodal study design with the aim to identify novel markers for the narcoleptic borderland (NBL). Established methods (i.e., genetic, immunological and electrophysiological) are combined with new technologies (highlighted in red) in order to validate both well-known and novel disease markers and marker profiles

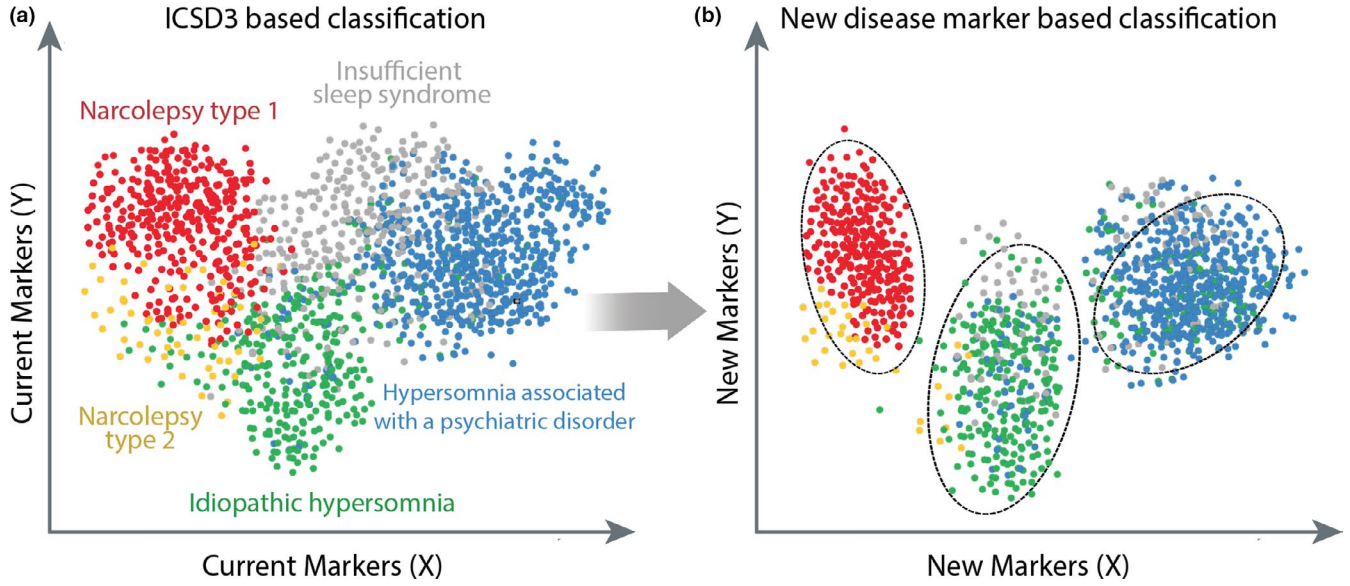

FIGURE 2 The reclassification of the narcoleptic borderland. Hypothetical distribution of patients (dots representing patients, colours according to the current ICSD3 classification). Individuals with similar disease marker profiles co-locate in a two-dimensional graph based on dimension reduction algorithms such as principal component analysis (PCA) or t-distributed stochastic neighbour embedding (t-SNE). (a) Based on the current ICSD3 criteria (only a few markers), patients present with partly overlapping signs and symptoms, complicating the diagnostic process. (b) A major aim of the SPHYNCS is to identify new disease markers and marker profiles, enabling the assignment of individuals to a diagnostic group. This could potentially lead to a new disease classification, which is indicated by three hypothetical disease groups (simplified illustration)

CDH. Our tertiary hypothesis is that there are markers or marker profiles, which allow predicting disease progression (Figure 3).

2.3 | Setting

In a first pilot phase, which started in February 2020 in the Bern and Barmelweid centres, the study protocol has been tested and revised according to clinical and study requirements and feasibility. Feasibility has been confirmed following the inclusion of six patients and controls. In November 2020, the study was started in further Swiss sleep centres.

The following study centres, belonging to the Swiss Narcolepsy Network (SNaNe, www.snane.ch), have agreed to participate in the study (in alphabetical order): Bad Zurzach (Sleep Center); Barmelweid (Clinic and Sleep Center); Basel (Sleep Center); Bern (Sleep Center and University Hospital Inselspital); Lugano (Sleep Center and Neurocenter of the Southern Switzerland, Regional Hospital (EOC)); St. Gallen (Sleep Center and Cantonal Hospital); and Zürich (Sleep Center and University Hospital Zürich). More centers in both Switzerland and Europe have expressed their interest in participating.

2.4 | Sample size estimates

Our intended sample size is based on retrospective numbers of patients per year who have been given a relevant diagnosis in the participating sleep centres and on power analyses for different subsamples (= diagnostic groups). We intend to include over 500 study participants and 100 control subjects during a recruitment phase of 3 years. In a follow-up phase of another 3 years, the clinical course of study participants will be observed. Based on our estimates, each diagnostic group will contain at least 50 individuals.

2.5 | Definitions

Excessive daytime sleepiness (EDS): complaints of abnormal daytime sleepiness with inability to stay awake during daytime and/or recurrent (voluntary or involuntary) napping and at least one of the following complaints attributed to EDS: ESS > 10, impaired sustained attention, automatic behaviours, memory/attention deficits, sleep drunkenness (American Association of Sleep Medicine, 2014; Lammers et al., 2020).

Hypersomnolence (H): complaints of abnormal high sleep needs with estimated/subjectively reported sleep duration/need of > 11 h/24 h, adapted to normal changes in sleep time for variability across cultures (American Association of Sleep Medicine, 2014).

2.6 | Study population

The study population includes subjects referred to the outpatient clinic/sleep centre of one of the study sites for further investigation due to complaints of EDS and/or H as defined above and/or

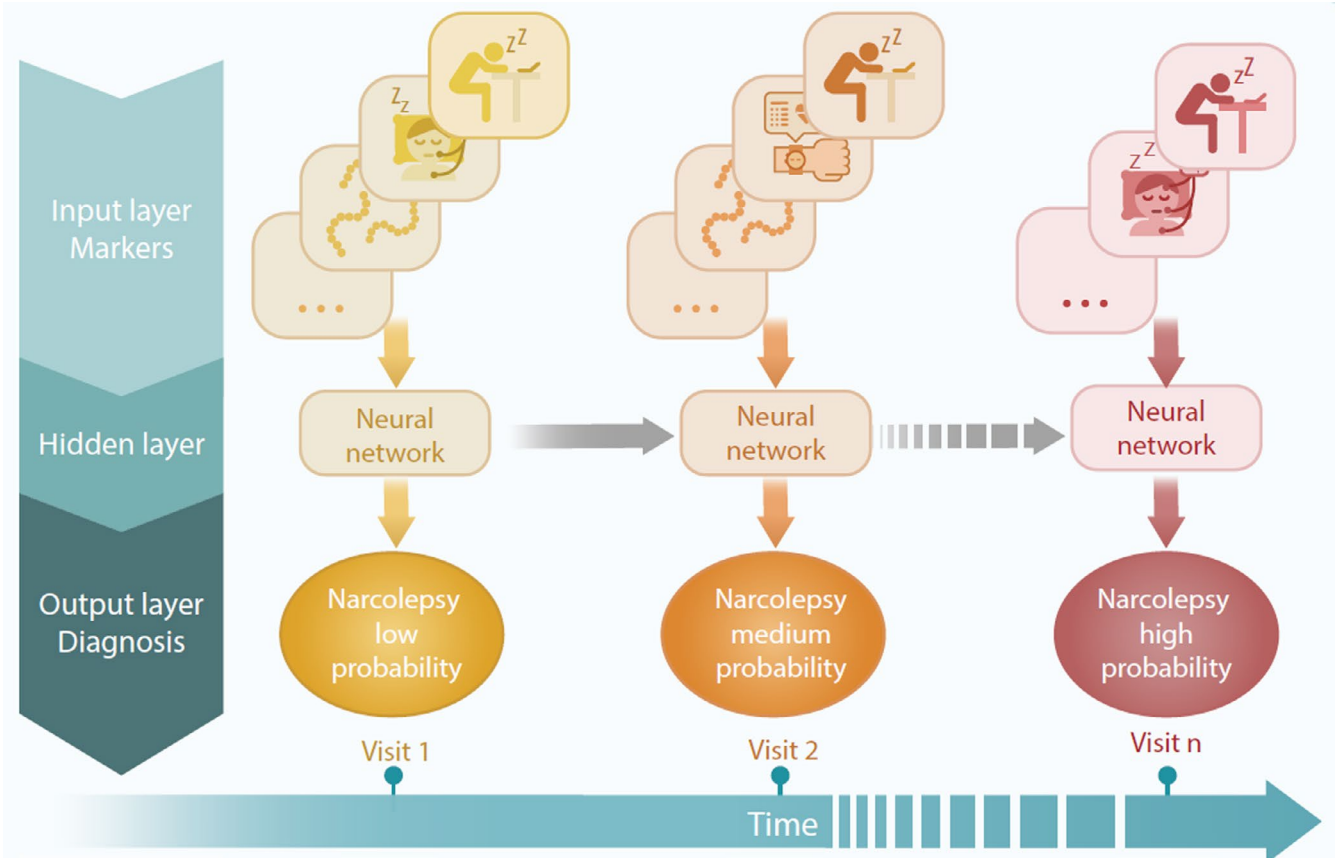

FIGURE 3 Schematic neural network approach for prediction of disease progression: longitudinal data from the SPHYNCS study are fed into a long short-term memory (LSTM) network or similar. For each time point (study visit, «n» indicating an indefinite number of visits), disease markers (here exemplified by the respective icons introduced in Figure 1) will be used as input layer. At each time-point, new input will be consolidated with information from previous time-points. The LSTM network integrates the longitudinal data to produce a diagnosis with predictive power increasing over time (here exemplified by stronger colours and increase of the probability for one diagnosis as new symptoms develop over time)

suspected CDH fulfilling inclusion/exclusion criteria. The control population includes subjects with complaints of EDS and/or H due to severe sleep-disordered breathing (SDB), resolved after therapy with positive airway pressure (PAP), as well as healthy controls. A prospective and consecutive enrolment of patients with subjective complaints of EDS and/or H, presenting daily or almost daily for at least 1 month prior to the consultation, ranging from 16–70 years, will take place after signing written informed consent. Fulfilling the diagnostic criteria for a specific CDH is not mandatory to be included. Exclusion criteria comprise the existence of other disorders/conditions considered to be the cause of EDS/H on clinical grounds, such as other sleep disorders, including untreated or non-satisfactorily treated obstructive or central sleep apnea, non-compliance with treatment, neurological disorders and medical disorders, as well as unstable psychiatric disorders or chronic use of antibiotics or immune-modulatory drugs. The control group comprises proportionally age- and sex-matched patients with sleep-disordered breathing and a documented apnea–hypopnea index (AHI) >30/h, and EDS with a mean sleep latency ≤ 8min in MSLT with documented subjective and objective improvement of EDS within 3 months of positive airway pressure treatment. Non-compliance with PAP therapy and central sleep apnea as well as lack of improvement of EDS represent exclusion criteria. A healthy control (HC) group will be recruited by an advertisement on the websites of the participating sleep centres and will consist of proportionally age- and sex- matched volunteers without subjective or objective EDS and/or H.

2.7 | Collection of information

Patients in the CDH group will be evaluated for inclusion and exclusion criteria in a screening phase, integrated into the clinical routine and including electrophysiological assessments, followed by a study inclusion visit (Figure 4). After enrolment, a study visit for biosampling will take place. Thereafter, study participants in the CDH group will be seen after 6, 12, 24 and 36 months. Control study subjects with SDB will undergo the same screening procedure and be included in the study at the start of the PAP treatment. There will be a final study inclusion visit 3 months after initiation of PAP treatment and one follow-up visit 12 months thereafter. HC participants will get a complete electrophysiological examination after giving their signed informed consent. They will be finally

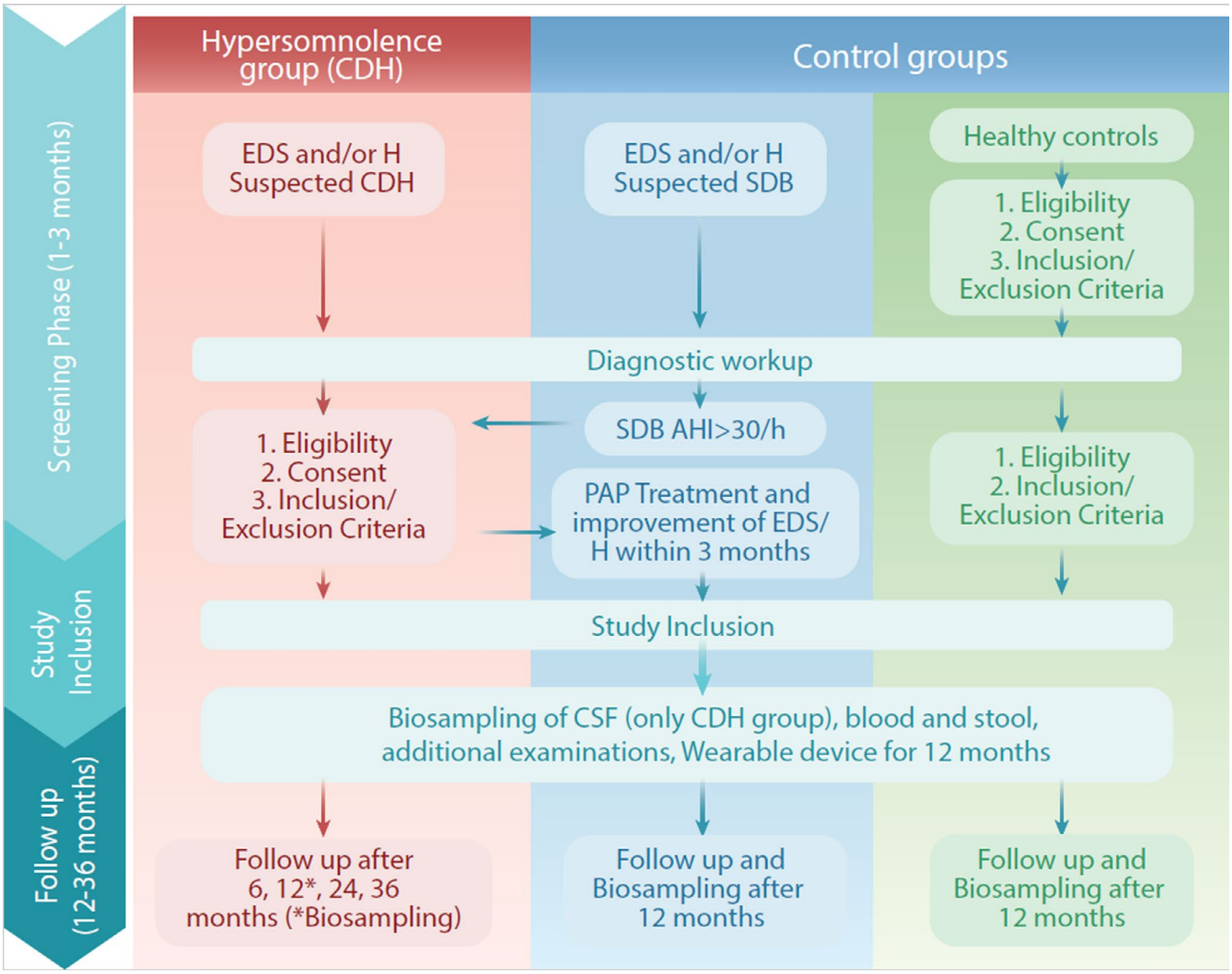

FIGURE 4 Study flow chart. The diagnostic work-up is the same for all three groups (1. group with central disorders of hypersomnolence [CDH]; 2. group with sleep disordered breathing [SDB]; 3. healthy control group) and includes 14 days of actigraphy (day 1 to day 14), polysomnography (day 12), multiple sleep latency test (day 13) and maintenance of wakefulness test (day 14), the psychomotor vigilance task (PVT, day 13 and 14) and the sustained attention to response task (SART, day 13). AHI, apnea–hypopnea index; CDH, central disorders of hypersomnolence; CSF, cerebrospinal fluid; EDS, excessive daytime sleepiness; H, hypersomnolence; PAP, positive airway pressure; SDB, sleep-disordered breathing

included if electrophysiological examinations do not show any exclusion criteria. Thereafter, there will be one follow-up visit after 12 months.

2.8 | Assessments

Clinical assessments in the CDH group and SDB control group will be performed within routinely scheduled clinical visits. All participants, including healthy controls, will have a full examination (clinical signs and symptoms and neurological examination if clinically indicated) and fill out questionnaires at different time-points. Electrophysiological assessments include polysomnography (PSG), which allows the participants to sleep until 10:00 AM at the latest, a multiple sleep latency test (MSLT) and a maintenance of wakefulness test (MWT). Two weeks of actigraphy and a sleep diary allow assessment of the total sleep time over 24 h, prior to and including the days of PSG (day 12), MSLT (day 13) and MWT (day 14). Actigraphy and vigilance tests, the psychomotor vigilance task (PVT) and the sustained attention to response task (SART), will be performed on the days of the MSLT and MWT, at the 12- (all groups) and 36-month (only CDH group) follow-up visits, and at any time-point when clinically indicated. At inclusion and after 12 months, a structured neuropsychiatric interview takes place, performed by either a trained clinician, psychologist or study nurse. If clinically indicated, data from magnetic resonance imaging (MRI) scans will be used for the study. During the first year after inclusion, the participants will be asked to wear a watch-like wrist device (FitBit®) for long-term activity recordings. From the wearable device, parameters on sleep and wake times and

information about vital parameters and physical activity will be collected. Participants can operate it with the application provided by the manufacturer.

In the control group with SDB, 3 months after start of PAP treatment, improvement of EDS and/or H will be assessed by clinical interview and normalization of the Epworth Sleepiness Scale (ESS), as well as repeated electrophysiological examinations under PAP therapy, if clinically indicated. Compliance with PAP therapy, defined by usage of the device on ≥ 70% of nights and ≥ 4 h per night in the last 90 days, as well as residual AHI will be assessed by read-out of the PAP device.

2.9 | Biosampling

Biosampling will take place at inclusion and after 12 months. Blood and stool samples will be collected at both times. CSF will be collected only once at inclusion and only in the CDH patient group. All samples will be processed immediately according to a standardized protocol. All samples will be frozen at −80°C and stored at the Liquid Biobank (LBB, www.biobankenbern.ch), Inselspital, Bern, until further analysis in batches.

The following parameters will be examined: immunological markers (phenotyping, T-cell-receptor sequencing, T-cell library and B-cell response (Latorre et al., 2018)), proteomic/peptidomic profiles in CSF and blood (Aebersold & Mann, 2016), hypocretin measurements with the currently used technique (radioimmunoassay) and with a novel mass spectrometric approach, genetic markers (genetic studies to define protective and predisposing HLA types (Tafti et al., 2016)), and microbiome profiles in stools (Figure 1).

2.10 | Questionnaires

Two sets of validated and non-validated questionnaires will be handed out to study participants repeatedly at predefined timepoints, in the primary language of study participants. Those include the Epworth Sleepiness Scale (Johns, 1991), Fatigue Severity Scale (FSS) (Valko et al., 2008), Narcolepsy Severity Scale (NSS) (Dauvilliers et al., 2017), Idiopathic Hypersomnia Severity Scale (IHSS) (Dauvilliers et al., 2019) and the Swiss Narcolepsy Scale (SNS) (Sturzenegger et al., 2018). Within the study protocol, some new translations of existing questionnaires will be linguistically validated.

2.11 | Database

All data from this trial are collected electronically using a dedicated central electronic data capturing system (REDCap). All questionnaires will be distributed as online surveys and directly entered electronically into the database.

2.12 | Data monitoring

Trial progress, data quality and timelines will be monitored centrally by a data manager and a study coordinator. Special attention will be paid to patient safety and protection of trial data confidentiality by each participating study centre's principal investigator and study team.

2.13 | Data analysis

The primary analysis will be performed after the last patient has completed the study. Interim analyses may be considered during the course of the study for administrative or exploratory scientific purposes. The primary analysis population will include all recruited subjects, whereas specific analyses will focus on subgroups of interest (e.g., based on ICSD3 diagnoses). For example, pursuing our primary aim to validate known and identify new NBL markers, we will test if hypocretin-responsive CD4 + T-cell clones are more frequent in NT1 patients and other diagnostic groups than in healthy controls. For the endpoint hypocretin-responsive CD4 + T-cell clones in NT1 patients versus controls, a significant difference has already been shown in a small sample ($n = 9$ for NT1 patients and $n = 6$ for controls; Latorre et al., 2018). Assuming a minimal number of 50 for each diagnostic group and the healthy controls, respectively, we will be able to show medium to large effects in between-group comparisons of continuous variables. Specifically, an effect size of 0.56 would be detectable with 80% power using a one-sided t test at the 5% level, even in the case of a 20% dropout rate (namely two groups with a sample size of 40 each). Due to the heterogeneity of the data collected in this study, each data type will be pre-processed and analysed by experts in the field considering the respective state-of-the-art methods (see Bader et al., 2020; Latorre et al., 2018; Stephansen et al., 2018; Tafti et al., 2016; Yilmaz et al., 2019; Zhang et al., 2018)).

In order to pursue our secondary aim, namely to reshape the NBL, we will integrate the marker profiles from the different data sources. Figure 2a shows a hypothetical visualization of the marker-based NBL landscape as obtained with unsupervised dimension reduction algorithms such as principle component analysis (PCA) or t-distributed stochastic neighbour embedding (t-SNE; Van Der Maaten & Hinton, 2008). Figure 2b shows a hypothetical new classification based on the marker-based stratification of individuals. Challenges such as data dimensionality, heterogeneity, stratification, outliers and missing data will be addressed by exploring appropriate approaches, including machine learning based algorithms (Mirza et al., 2019; Wainberg et al., 2018). For example, inspired by our previous work on clinical features and quality of life in narcolepsy, we will apply stochastic gradient boosting (SGB), a decision tree-based ensemble learning method that can incorporate mixtures of numeric and categorical variables (Zhang et al., 2018).

Finally, we will pursue our tertiary aim, the marker-based prediction of disease progression. Making use of the longitudinal information from the study participants' follow-up visits, we will use

techniques such as long short-term memory (LSTM) networks or similar to improve disease prognosis (Metwally et al., 2019), as schematically illustrated in Figure 3. As state-of-the-art methods may further evolve until the end of the study, the named methods serve as examples and may be subject to change.

2.14 | Funding

The study is an investigator-initiated research project. The project leader is financially supported by a Swiss National Fonds project funding grant (Project Number 320030_185362) and by two non-product-related investigator initiated study grants from UCB Biopharma SRL (IIS-2017-120409) and Jazz Pharmaceuticals (IST-18-10975). Biobanking is supported by a cohort funding grant (DLF Bern Biobank Call 2017).

2.15 | Ethical considerations and registry

The study and a first amendment have been approved by the local ethical committees (2019–00788). Before inclusion, patients will give written informed consent. The study is registered at http://www.clinicaltrials.gov and identified by NCT04330963.

3 | DISCUSSION

The International Classification of Sleep Disorders 3rd edition describes definite criteria for the diagnosis of central disorders of hypersomnolence (American Association of Sleep Medicine, 2014). These criteria are mainly based on clinical features and MSLT findings (American Association of Sleep Medicine, 2014). In most CDH, especially in NBL patients, pathophysiology is not well understood and in routine clinical practice these clinical and electrophysiological findings are often inconclusive (Fronczek et al., 2020; Lammers et al., 2020; Mayer & Lammers, 2014; Trotti et al., 2013) and render it extremely challenging to make a clear diagnosis. For this reason, diagnoses may change over time and many patients need years to receive a correct diagnosis. As a result, they are prevented from receiving therapeutic options and are left alone with their significantly life-impairing symptoms.

The SPHYNCS is the first prospective, large-scale study including a broad variety of patients with both NT1 and diseases from the NBL and has the goal to solve these diagnostic challenges. Its comprehensive approach overcomes certain limitations of previous studies on CDH. Strengths of the study are the inclusion of patients with different CDH aetiologies, but also of patients with symptoms of EDS and/or H, not fitting into the current diagnostic groups. The described stepwise assessments of immunological, genetic and proteomic/peptidomic and microbiome data will allow new and partly unbiased insights into the pathophysiology of the NBL. As shown for NT1 (Latorre et al., 2018), such investigations are promising on their own. Applied to a larger cohort of NBL patients, and in combination, they will provide better understanding of the disease immunopathology and potential role of the gut microbiome and hopefully lead to new disease markers allowing an earlier and more precise diagnosis. The study uses new digital wearable devices, which offer the opportunity for continuous monitoring of people's rest and activity patterns, including sleep/wake behaviour and assessment of simple and complex activities. Ambulatory sleep–wake studies have the advantage of examining people in their normal sleep environment, are cheaper and are practical for long-term observations, compared with conventional polysomnography in sleep laboratories. Machine learning tools are suitable for integrating and reclassifying heterogeneous information and will help to characterize and, if necessary, reclassify the NBL by defining new disease markers or marker profiles (Figure 2).

The study protocol is demanding, but feasible, as our experience at the two starting sites has shown. To address the complexity of the study, the SPHYNCS is supported by a large team of experts in different fields, and has national and international collaborations. As the study protocol needs to be integrated into clinical routine, meet the requirements of several study sites and addresses different research questions, some limitations may arise due to feasibility aspects. The collection of datasets that are as complete as possible is important to the SPHYNCS, but rejection of single procedures in the clinical routine or in the study context does not automatically lead to exclusion from the study, but only from certain sub-analyses. The SPHYNCS consortium also considered providing an abridged version of the protocol to allow further sleep centres to join the study. As this study addresses the evolution of CDH, a limitation is the restricted follow-up time of 36 months, which does not allow detection of changes in diagnoses after this period. We are exploring a future study to fill this gap and to provide an additional time-point for follow-up to the SPHYNCS cohort.

The results of this study are expected to change current diagnostic criteria, improve our understanding of aetiology, pathophysiology and evolution, and provide new targets and opportunities for prevention and treatment of this not infrequent and debilitating group of diseases.

CONFLICT OF INTEREST

No conflicts of interest declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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