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The European Narcolepsy Network (EU-NN) database

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Keywords

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SUMMARY

Narcolepsy with cataplexy is a rare disease with an estimated prevalence of 0.02% in European populations. Narcolepsy shares many features of rare disorders, in particular the lack of awareness of the disease with serious consequences for healthcare supply. Similar to other rare diseases, only a few European countries have registered narcolepsy cases in databases of the International Classification of Diseases or in registries of the European health authorities. A promising approach to

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identify disease-specific adverse health effects and needs in healthcare delivery in the field of rare diseases is to establish a distributed expert network. A first and important step is to create a database that allows collection, storage and dissemination of data on narcolepsy in a comprehensive and systematic way. Here, the first prospective web-based European narcolepsy database hosted by the European Narcolepsy Network is introduced. The database structure, standardization of data acquisition and quality control procedures are described, and an overview provided of the first 1079 patients from 18 European specialized centres. Due to its standardization this continuously increasing data pool is most promising to provide a better insight into many unsolved aspects of narcolepsy and related disorders, including clear phenotype characterization of subtypes of narcolepsy, more precise epidemiological data and knowledge on the natural history of narcolepsy, expectations about treatment effects, identification of post-marketing medication side-effects, and will contribute to improve clinical trial designs and provide facilities to further develop phase III trials.

INTRODUCTION

Narcolepsy is currently classified into narcolepsy type 1 (NT-1) and type 2 (NT-2) according to the new International Classification of Sleep Disorders (ICSD-3; American Academy of Sleep Medicine, 2014) that was released in 2014. NT-1, formerly known as narcolepsy with cataplexy (NC), is a well-defined clinical disease, presenting with disabling daytime sleepiness, a transient loss of muscle tone triggered by emotions (cataplexy), and optional symptoms such as disturbed night sleep, hypnagogic hallucinations and sleep paralysis. The tight association with HLA DQB1*06:02 haplotype and low or undetectable hypocretin-1 (orexin A) levels in the cerebrospinal fluid (CSF) support the idea that NT-1 represents a specific entity with suspected autoinflammatory/autoimmune aetiology. By contrast, the neurobiology and aetiology of narcolepsy without cataplexy (NT-2) is much more controversial (Baumann *et al.*, 2014), and NT-2 may even encompass different entities presenting with a similar clinical phenotype. The current definition of NT-2 relies on patients' complaints of daytime sleepiness confirmed by objective tests, i.e. short sleep latency (≤ 8 min) together with \geq two sleep-onset rapid eye movement (REM) periods (SOREMPs) either in the multiple sleep latency test (MSLT) or MSLT and polysomnography (PSG), in the absence of other causes of daytime sleepiness such as insufficient sleep syndrome, delayed sleep phase syndrome or sleepiness related to attention deficit-hyperactivity disorder.

Narcolepsy affects approximately 0.02–0.05% of various populations in European, USA and Asian countries, and qualifies by its low prevalence rate as an orphan disease. Orphan diseases are known to have a strong impact on European healthcare systems as they constitute about 6000–8000 different disease types affecting 6–8% of the population (Background Paper on Orphan Diseases for the 'WHO Report on Priority Medicines for Europe and the World' – 7 October 2004).

Narcolepsy shares many typical features with other rare diseases, in that a relatively common but unspecific symptom, such as sleepiness, conceals the specific underlying aetiology. Similar to many rare diseases misdiagnoses, long diagnostic delays and lack of awareness of the disease are common. As awareness of the disease is essential for nearly all aspects of healthcare delivery, patients with narcolepsy face profound medical problems both at individual and institutional levels, including lack of appropriate information on the disease and inappropriate healthcare services. Patients with narcolepsy are confronted with improper healthcare quality and experience a low quality of life (Jennum *et al.*, 2012). Finally, typical for all orphan diseases is the fact that only a few randomized clinical trials, post-approval safety and effectiveness studies exist. Considering these limitations, alternative strategies are required to improve the situation of patients with narcolepsy. One of the most promising strategies is to establish a close interaction and collaboration among experts in the field, and the integration of multicentre activities. A distributed expert network will allow a more global approach to rare diseases as opposed to the scattered research efforts of single centres that gain only minor attention in the scientific community. Large electronic databases are key instruments for the promotion of coordinated research in the field of rare diseases as they are appropriate to pool scarce data from different centres. Indeed, most of the current clinical knowledge in human narcolepsy is based on datasets of single centres or rare multicentre cohorts. Single-centre datasets are frequently characterized by a limited number of patients, and are biased due to the absence of standardized diagnostic procedures for data acquisition. Hence, generalization of study results into larger patient populations is difficult. The European Narcolepsy Network (EU-NN) is an association of leading European Sleep Centers, which launched the first European web-based database for narcolepsy and related disorders. Here, the structure of the database is introduced.

The following sections describe, how data acquisition is achieved by standardized and predefined diagnostic procedures. Then, a descriptive overview of the first 1079 cases is provided, and sleep diagnoses (according to ICSD-3 criteria) and clinical features presenting at time of inclusion are reported. Finally, future perspectives and developments of the database are discussed.

THE NEED FOR RESEARCH IN THE FIELD OF NARCOLEPSY

Recent advances in research in narcolepsy have led (with no doubt) to major achievements in diagnostic certainty and a better understanding of the neurobiology of NC. In particular, the discovery of the pivotal role of hypocretins/orexins was a milestone (de Lecea and Sutcliffe, 1999; Nishino *et al.*, 2000; Sakurai *et al.*, 1998). Regarding the aetiology of NT-1, the very strong association of narcolepsy with certain HLA types (especially DQB1*06:02; Hor *et al.*, 2011; Tafti *et al.*, 2014) as well as the observed increase of incidence of narcolepsy after the adjuvanted H1N1 vaccine in Europe or the H1N1 epidemic in China indicate that NT-1 may be of autoimmune origin (Dauvilliers *et al.*, 2013; Partinen *et al.*, 2012; Poli *et al.*, 2013). Also, findings on autoantibodies (Bergman *et al.*, 2014; Cvetkovic-Lopes *et al.*, 2010) support an autoimmune aetiology of NT-1. New discoveries have been considered in recent revised classification of sleep disorders (American Academy of Sleep Medicine, 2014), in that the diagnostic value of two biomarkers, hypocretin deficiency and a SOREMP on nocturnal PSG, has been strengthened. NT-1 can be diagnosed on the basis of excessive daytime sleepiness (EDS) associated with hypocretin deficiency, meaning that strictly speaking cataplexy is no longer a mandatory symptom of the disease. When unambiguous cataplexy is present and hypocretin is not available, diagnosis of NT-1 needs to be confirmed by established MSLT criteria (short sleep latency ≤ 8 min and ≥ 2 SOREMPs). A nocturnal SOREMP episode is now of equal diagnostic significance to a SOREMP on the MSLT (Andlauer *et al.*, 2012). By contrast, the diagnostic criteria of NT-2 have not essentially changed compared with previous classifications due to the lack of specific biomarkers. Diagnosis of NT-2 still requires established MSLT criteria (again with the option that nocturnal SOREMP on the preceding PSG may replace a SOREMP on the MSLT), a constellation that is frequently seen in various clinical conditions, especially in chronic sleep disorders presenting with EDS, such as insufficient sleep syndrome, circadian misalignment, sleep apnoea syndrome, intake of psychotropic drugs or even among normal population without EDS (Goldbart *et al.*, 2014; Morrish *et al.*, 2004; Singh *et al.*, 2006).

Although typical cataplexy in adulthood (Overeem *et al.*, 2011) and a children-specific phenotype of cataplexy (Plazzi *et al.*, 2011) has been described in detail, narcolepsy often remains undiagnosed or diagnosis is delayed for years or decades in patients with mild or atypical cataplexy. Also, a

validated severity index of cataplexy by frequency, duration or intensity of attacks is not yet available. Narcolepsy may thus remain underdiagnosed (Dodel *et al.*, 2007; Ozaki *et al.*, 2012; Vignatelli *et al.*, 2011) due to variations in disease severity with incomplete or atypical presentation of symptoms (Overeem *et al.*, 2011). The spectrum of narcolepsy is not clearly described, and the entities of monosymptomatic narcolepsy, idiopathic hypersomnia and sleepiness associated with psychiatric disorders warrant further characterization. The consideration that insufficient sleep is a public health epidemic underlines the potential overlap of narcolepsy with behavioural-induced conditions (Centers for Disease Control and Prevention, Morbidity and Mortality Weekly Report, 4 March 2011; www.cdc.gov).

HOW TO PROCEED?

A common problem for rare diseases is that epidemiological data are not available because these patients are not systematically registered in databases coded according to the International Classification of Diseases as developed by the World Health Organisation (WHO) or in registries of the European health authorities. These registries are frequently used as tools adapted to count patients, and healthcare institutions often resort to these registries to plan healthcare services. This problem is well recognized and documented in the WHO Report on Priority Medicines for Europe and the World as stated 'Unfortunately, the epidemiological data that are available are inadequate for most rare diseases to give firm details on the number of patients with a specific rare disease. [...] Many rare diseases are summed up as "other endocrine and metabolic disorders" and as a consequence, with few exceptions, it is difficult to register people with a rare disease on a national or international basis, and in a reliable, harmonized way'. Thus, a first and important step to coordinate collaborative efforts is to create a database or a patient registry that allows collection, storage and dissemination of data on narcolepsy and related disorders in a systematic and comprehensive way. It is important to note that such databases must focus on specific aspects and particular characteristics of narcolepsy in order to identify disease-specific adverse health effects and to track the changing needs of narcolepsy in healthcare delivery.

Multicentre prospective databases are appropriate to fulfill this aim and have many advantages to pool scarce data of rare diseases. A major advantage is that continuous data entry by multiple specialized centres according to predefined standardized procedures ensures data collection unbiased for specific outcome parameters as defined in clinical pharmacological studies. Clinical datasets are suitable to initiate cooperative projects that help to gain insight in many medical, epidemiological and socioeconomic aspects of narcolepsy, among others the most important are as follows. (i) Establishing natural history; continuous patient entry will include patients without pharmacological and/or non-pharmacological treatments. These rare but unique data (when

merged together from many centres) will contribute to a better understanding of the natural history of narcolepsy, and are appropriate to delineate differences between subtypes of narcolepsy. Knowledge on the natural course of disease is especially important to establish a clear phenotype characterization by summarizing changes of clinical presentation over time. (ii) Initiation of European research collaboration; scarcity and complexity of narcolepsy has always been a challenge for single centres to collect extensive patients' data. As a result many single-centre databases exist, each of them with local data structure that prevents merging data to a global European-wide project. Multicentre prospective databases will provide a solid basis for international research collaborations with much higher visibility and scientific impact, including availability of biosamples from patients to organize educational and expertise resources. (iii) Assessing clinical effectiveness and monitoring safety in outcome surveys; international multicentre prospective data carry important outcome information of treated patients. As these data are usually collected independently and outside of interventional protocols of pharmacological studies, they usually well represent clinical effectiveness of treatments. Thus, ongoing data collection of 'real world' patients is essentially valuable to monitor the effectiveness of orphan drugs in addition to studies that precede marketing authorization of the drugs. The same is true for safety issues when gathering evidence of possible side-effects in post-marketing studies. (iv) Influencing healthcare policies and resources; obtaining European-wide data is absolutely necessary to gain impact on governmental representatives when lobbying for improved care. Prospective databases when guided by predefined data assessment criteria will fulfill high quality requirements via standardization. Pooling multicentre data from many European countries will help to provide an overview of the global situation in Europe, and comparison among different European countries is useful for identifying specific national needs for medical care delivery.

EU-NN

The EU-NN is a large European network of clinicians and scientists dedicated to promote research on narcolepsy founded in 2008 in Zurich, Switzerland. The objective of the association is the promotion of the European scientific research in narcolepsy, hypersomnias and related fields, and the optimization of medical care for patients by improving diagnostic and therapeutic measures. The major goals of EU-NN are:

- to gain a better insight into narcolepsy and related hypersomnias by pooling the resources of European narcolepsy centres;
- to enhance patient care by improving diagnostic and therapeutic options;
- to create a more efficient cooperation between the centres, and a better doctor to patient, and patient to patient communication;
- to initiate and perform scientific projects in basic and clinical research as well as research in healthcare in the areas mentioned above;
- to publish research results, guidelines and recommendations for socio-legal aspects and unmet needs;
- to improve the medical care of affected patients by coordinating basic and clinical research in the field of hypersomnias.

Membership to EU-NN is by using published procedures at <https://www.narcolepsy-network.eu/>. Only institutions or persons with particular competence and experience in the management of patients with narcolepsy may qualify as EU-NN members upon approval by the EU-NN board. Currently, 27 centres across 13 European countries and Switzerland participate in the European Narcolepsy Network. Centres include university hospitals, public hospitals and specialized centres for sleep medicine (listed in alphabetic order in Table 1).

THE EU-NN DATABASE

The EU-NN database was launched by EU-NN to provide a central tool to collect and store clinical and paraclinical data of narcolepsy including surrogate markers, and to standardize clinical, biological and genetic information from narcolepsy and related disorders. A key structure of the database is a web-based protected data entry. All EU-NN members had longstanding experience in the management of narcolepsy, and could propose clinical and paraclinical data. A database task force (RK, SO, GJL, ChB) coordinated all inputs and determined the database structure. Early members, such as MP, CB, GM and RO, have particularly been involved. Final inclusion into the database was based on consensus decision by all members. The same procedure was applied when defining the standardized procedures of data acquisition. The task force put a strong effort on evaluation of standardized data acquisition as it was considered a prerequisite of data comparability between centres.

Table 1 EU-NN centres

Country	No. of centres
Czech Republic	1
Denmark	2
Finland	1
France	2
Germany	3
Italy	3
the Netherlands	2
Poland	1
Portugal	2
Slovak Republic	1
Spain	4
Switzerland	4
United Kingdom	1
Total	27

For the children's database, two additional physicians (ML and GP) with longstanding experience in childhood narcolepsy were asked to assist the task force in database development, which is ready to be launched. During an initial dummy phase the task force carefully evaluated the feasibility of data entry and identified any problems of database structure. After that a beta version was made available to all EU-NN members to enter cases in a pilot phase. The purpose of the second phase was to prove accessibility and to test efficient operation of the database.

Data structure and standardization

The EU-NN database contains two types of data, a mandatory and an optional dataset. The mandatory dataset consists of a minimum of data that needs to be completed. Mandatory data carry an essential amount of information on the current status of disease that is considered as necessary to ensure data quality. Mandatory data fields are highlighted in red colour and remain in red until completion for better visibility. Completion of all other optional data is strongly desired for the sake of complete information. The EU-NN database is designed as a prospective database. Regular follow-ups are essential to assess outcome evaluation and to identify factors that influence various outcome parameters. Only complete mandatory datasets will label a case as a 'validated' case, and only validated cases qualify for further follow-up visits and subsequent data analysis. If a mandatory dataset remains incomplete the case will not be considered for data analysis.

One important data feature of the EU-NN database is that any data field is strictly related to symptoms rather than to (existing) definitions or diagnosis. For example, instead of asking for 'typical', 'atypical', 'complete' or 'incomplete' cataplexy, information on 'involved body parts', 'duration' and 'frequency' of attacks is requested, and these fields need to be filled in by predefined drag and drop answers (e.g. frequency '<1/year', '<1/year-1/month', '1/month-1/week', '1/week-1/day', '>1/day'). This procedure strictly follows the basic idea of scientific databases to collect raw data and to prevent inadequate data interpretation at the early stage of data acquisition. Instead, the clinician's interpretation is also assessed by additional data fields explicitly asking for levels of certainty, for example the certainty of typical cataplexy according to the clinician's judgement is graded as 'possible', 'probable', 'definite'. This data structure offers various data stratification options for subsequent data analysis.

Quality control

High data quality is challenging when collecting data from multiple centres, and directly indicates the reliability of a database. To achieve high data quality the task force has developed several tools. (i) Data consistency control: at data entry various implemented algorithms check for data consistencies. These algorithms are easily applicable and effective tools to avoid transcription mistakes during data entry. An

illustrative example is the rare situation when cataplexy is accompanied by normal hypocretin 1/orexin A CSF levels. In this case a plausibility warning will pop up that needs to be actively confirmed or rejected. (ii) Mandatory and optional datasets: a minimum of data has been classified as mandatory. (iii) Definitions and standardizations: in total, 82 data field definitions and 11 procedures have been compiled by the task force. Definitions have been allocated to each data field and are displayed when hovering over a symbol (indicated by a '?') with the computer mouse. Thus, convenient accessibility to definitions has been made possible during data entry.

Data access policy, ethics and security specifications

The EU-NN database contains sensitive patient information about narcolepsy that requires high data security standards. The EU-NN has established a policy for data access, data ownership, publication- and authorship rules, ethical guidelines and data security, which has been sent to all EU-NN members. Each centre has to apply for ethical approval by a national Institutional Review Board before entering patients. As EU-NN members will transfer sensitive patient information via a web-application, confidentiality and protection of these data is guaranteed by several steps. (i) Each centre has access to its own data by a personal and protected password. After personal access to the database all other data remain invisible. (ii) Anonymous data are realized by allocation of a centre-specific patient-code, facilitating identification by the local institution only. (iii) Data are entered via a standardized security line and stored according to international security guidelines. All communication between clients (web-browsers) and the server is SSL-encrypted according to the current standards implemented in web-browsers. The central database server is hosted at a professional data-centre offering high availability and security (NU-Dateautomaten GmbH, Automatisierte internetgestützte Netzwerklösungen, Rathausstraße 2 A-6900 Bregenz, Austria).

Statistical analysis

To compare frequencies/proportions, the z-test or chi-square test ($\alpha = 0.05$) were used. For testing the differences between the means, t-test, respectively, one-way ANOVA were used. Statistical significance was considered significant when $P < 0.05$. Normal distribution was tested for all populations and results using statistical tests accordingly.

CURRENT STATUS OF THE DATABASE

As of May 2015, the EU-NN database contained 1079 patients (over 16 years old) from 18 different European centres: Prague (Czech Republic), Helsinki (Finland), Montpellier (France), Munster and Schwalmstadt (Germany), Bologna (Italy), Leiden and Heeze (the Netherlands), Warsaw (Poland), Porto (Portugal), Barcelona, two Madrid

centres (Spain), Barmelweid, Bern, Lausanne, Lugano (Switzerland) and Kosice (Slovak Republic).

More than two-thirds of the cases ($n = 739$) are validated, the majority of them ($n = 423$; 56%) were drug free. A definite diagnosis is indicated in 710 validated cases. Besides NT-1 ($n = 542$), NT-2 ($n = 120$), unspecified narcolepsy or narcolepsy due to medical conditions ($n = 3$), hypersomnias ($n = 38$), behaviourally induced insufficient sleep syndrome ($n = 2$), or sleep disorders associated with conditions classifiable elsewhere ($n = 5$) have also been included.

Overall, the median age of the patients entered in the present database is 39.5 years (range 16–94 years), with a slight predominance for men (56%). The body mass index (BMI) was significantly different between NT-1, NT-2 and hypersomnia patients, NT-1 patients having the highest BMI (NT-1: $27.5 \pm 5.7 \text{ kg m}^{-2}$; NT-2: $25.8 \pm 4.3 \text{ kg m}^{-2}$; Hy: $25.7 \pm 5.4 \text{ kg m}^{-2}$, independent samples median test, $P = 0.003$). The course of the disease is documented as follow-up data. Information about the first follow-up visit was added for 173 patients, but also information about successive follow-up visits is provided (second follow-up visit $n = 82$; third follow-up visit $n = 45$, fourth or more $n = 37$).

NT-1

The mean age of patients diagnosed with NT-1 was 42 ± 0.9 years for women and 44 ± 1.4 years for men ($n = 542$, with 307 men). BMI was higher in men compared with women ($28.2 \pm 4.9 \text{ kg m}^{-2}$ for men versus $26.6 \pm 6.4 \text{ kg m}^{-2}$ for women, $P = 0.001$). In 24 cases, cataplexy was the first symptom, while for the rest the first symptom was EDS. No gender differences for diagnostic delay (10.4 \pm 0.8 years in men versus 9.8 \pm 0.8 years in women; Fig. 1), and age at sleepiness or cataplexy onset were found. Episodes of irresistible daytime naps were present both in treated and drug-free patients (77% versus 84%) and, as a consequence, patients scheduled naps [52% of treated patients and 47% of *de novo* (drug-free) patients scheduled one nap per day, while 28% of treated patients and 34% of drug-free patients had no scheduled naps]. No differences were found in the presence of sleep paralysis or disturbed nocturnal sleep between treated and *de novo* patients (Fig. 2), while hypnagogic hallucinations were more frequent in drug-free patients (chi-square, $P < 0.001$). Cataplexy was definitely present in 85.5% of included cases. The frequency of cataplexy was higher in drug-free patients (53.0% versus 44.4%, chi-square, $P < 0.001$), but there were no differences between Epworth Sleepiness Scale (ESS) scores between these two groups (Fig. 3).

NT-2

A gender effect was observed in NT-2 ($n = 120$), with 73% ($n = 89$) of the patients being men. The median age was 36 years (range 18–85 years), and shorter diagnostic delay

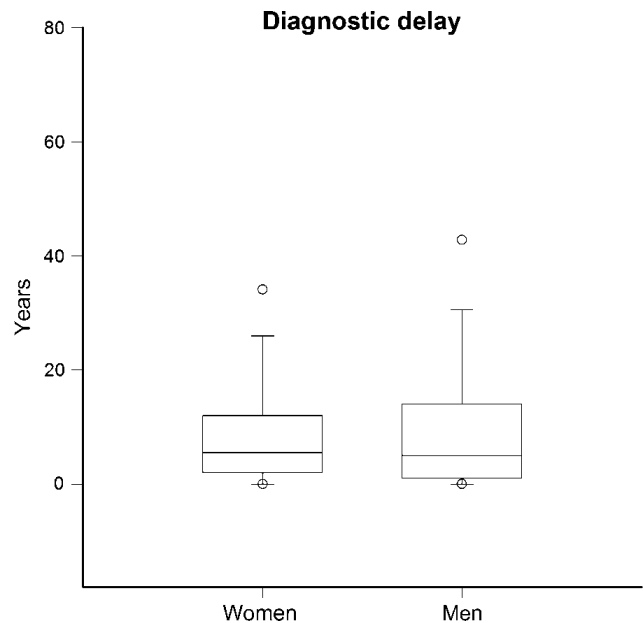


Figure 1. Median diagnostic delay for men and women diagnosed with NT-1

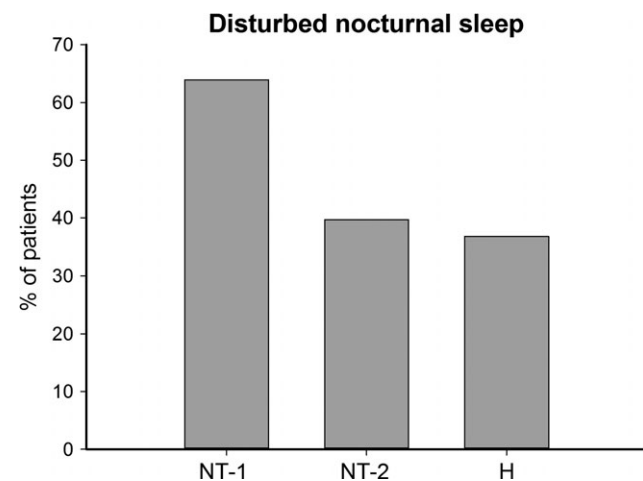


Figure 2. The prevalence of disturbed nocturnal sleep among patients included in the database.

(8.1 \pm 9 years, *t*-test, $P = 0.04$). Daytime sleepiness as measured by the ESS was similar to patients with NT-1. To cope with EDS, 36.8% of the patients scheduled one nap per day with a mean duration of 60 min. Disturbed nocturnal sleep was reported by 41% of the patients, significantly lower than for patients with NT-1 ($\chi^2 = 22.058$; $P < 0.001$). Sleep paralysis was present in 23% of NT-2 and patients with unspecified narcolepsy, and hypnagogic hallucinations were present in 31% of them. The proportion of NT-2 patients declaring sleep paralysis and hypnagogic hallucinations was significantly lower compared with NT-1 ($z = 4.659$ and 4.161, respectively, $P < 0.001$).

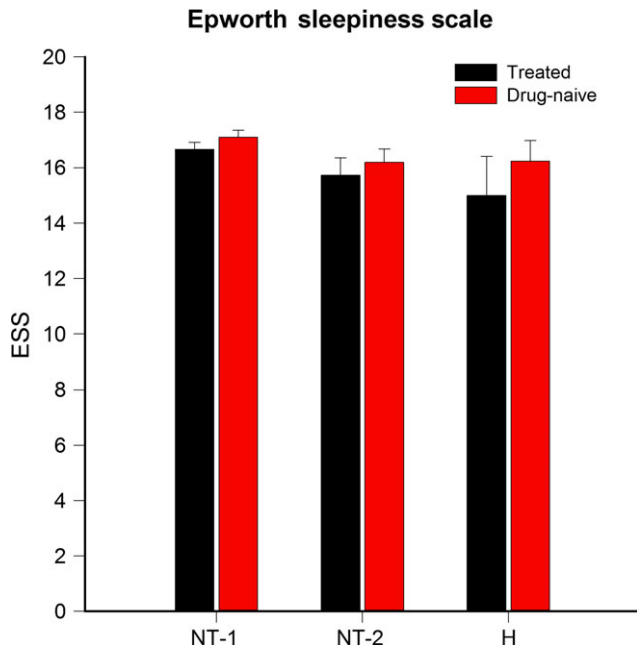


Figure 3. Epworth Sleepiness Scale (ESS) scores at diagnosis, for drug-free and treated patients. Black bars represent treated patients, red bars represent drug-free patients.

Other hypersomnias

Opposite to NT-2, 69% ($n = 26$) of idiopathic or recurrent hypersomnia patients ($n = 38$) were female, and one-third of the patients reported disturbed nocturnal sleep. Sleep paralysis and hypnagogic hallucinations were rarely reported by these patients. The ESS scores were similar to those obtained in NT-1, NT-2 or patients with unspecified narcolepsy.

CONCLUSIONS AND PERSPECTIVES

The EU-NN database is the first European multinational, multicentre database that will prospectively collect data from patients with narcolepsy and other hypersomnias in European countries. The database is unique in its standardized data acquisition and its control for high data quality. Because the lack of reliable and representative data on narcolepsy is a key problem for patients, family members, researchers, physicians and other healthcare representatives, this structured database is urgently needed. Similar to other rare diseases, narcolepsy requires a long-term monitoring to identify patients' specific needs to coordinate efforts of different stakeholders involved in management of the disease.

The purpose of this paper is to introduce the structure and usefulness of such a standardized prospective database. Also, survey results of the first 1079 patients collected from 13 European countries are presented to show that most of the descriptive statistics of the population in the dataset are comparable with published results from retrospective

datasets, indicating that so far mainly typical cases have been entered into the database. Patients presented at a typical age and had a long delay of diagnosis of NT-1 in both males and females. As already shown in previous retrospective datasets, disturbed nocturnal sleep and increased BMI were more prevalent in NT-1 compared with NT-2 and Hy in the prospective data. Remarkably, sleepiness as measured by ESS was similar in treated and in drug-free patients in all groups (NT-1, NT-2 and Hy), while only frequency of cataplexy decreased in treated NT-1 patients, indicating the urgent need for improved treatment options against sleepiness. The next steps are detailed data analyses using this continuously growing dataset. Future analyses should focus on identification of distinct narcoleptic phenotypes by stratifying data according to various sets of clinical or paraclinical parameters (e.g. HLA positivity versus HLA negativity; typical cataplexy versus atypical cataplexy, etc.) and identification of specific markers for narcolepsy or related disorders. Data correlations in longitudinal data will help infer knowledge on the course of different phenotypes. These analyses of prospective long-term follow-up cases will provide more profound insights into the factors determining variation in severity of the disease. Of special clinical interest are follow-up examinations of drug-free patients to determine responses to medication and co-morbidities. Once sufficient data on other hypersomnias and NT-2 have been collected, it will be possible to further delineate the spectrum or the phenotypical borderland of narcolepsy by evaluating the existence of clinical homogenous groups and their aetiological neurobiology. As EDS is the common complaint of many hypersomniac patients, phenotypic characterization of various types of EDS is an ambitious but promising new approach to identify distinct entities of hypersomnias. A better phenotypic discrimination of EDS will require other and more specific parameters than existing MSLT criteria. The discovery of new biomarkers will be of major importance for the scientific progress in the field of hypersomnia, not only because of their diagnostic value in the differential diagnosis of diseases, but also because of their potential contribution to explain underlying pathophysiologies. The EU-NN database plays an important role in the attempt to identify potential biomarkers as it offers a rich source of clinical and paraclinical data from different European countries. The advantage of international data from different geographical locations is a better generalizability of results as clinical and paraclinical data are known to vary with the population background due to genetic or environmental factors. Therefore, single-centre or even a large national dataset are more biased to demographic background than datasets from geographically dispersed populations. This option is a useful tool to get a quick overview of potential projects and may help to organize coordinated research projects among EU-NN centres with respect to expertise and resources. Based on the experience of the adult database, the EU-NN task force has recently developed a childhood database on narcolepsy and related disorders. A childhood database is of special interest

because it will cover a wide range of age-specific and developmental aspects of narcolepsy. Data in children will also help to evaluate therapeutic interventions close to disease onset. By launching both an adult and a childhood web-based database for narcolepsy and related disorders, two complementary key instruments will be available for the systematic collection and dissemination of data on narcolepsy. These databases are promising tools to allow promotion of coordinated research and the development of optimal long-term care of narcolepsy at an individual and community level.

AUTHOR CONTRIBUTIONS

Two database taskforces (adult database: RK, ChB, GJL, SO and a children's database: RK, ChB, GJL, SO, GP and ML) realized the development of the databases by coordinating proposals of all EU-NN members and designed the database structure. GL and RK have analysed the data. RK wrote the manuscript. All EU-NN members revised the manuscript.

CONFLICTS OF INTEREST

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