



Workshop report

## 127th ENMC International Workshop: Implementation of a European Registry of ALS Naarden, The Netherlands, 8–10 October 2004

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### 1. Aim of the meeting

The aim of the meeting was to establish a database for the prospective collection of epidemiological information on patients diagnosed with ALS in Europe. In other words, the establishment of a pan European ALS register. The data collection will be performed pursuing two major objectives: 1. To recruit a large population-based sample of patients with ALS. This will be achieved by merging the information collected by the existing national and regional registries from Italy, Ireland, England, and Scotland; 2. To collect baseline information on newly diagnosed patients from Spain, Serbia, and other countries where population-based registries are not yet available. This data will be utilized in recruiting for parallel studies and therapeutic trials.

### 2. Background

Amyotrophic lateral sclerosis (ALS) is a rare neurological condition (overall annual incidence rate in Europe 0.4–2.5 per 100,000) [1–7] with severe prognosis and death within 3–5 years from diagnosis [8–10]. Several community studies have been performed to study the incidence and characteristics of ALS in Europe. These include surveys from well-defined populations [4–7] and studies from population-based regional [3] and national registries [1,2]. Although these registries provide fairly high and homogeneous incidence rates, they have insufficient power to study risk factors with low exposure levels, because of

the small sample size. In addition, large numbers of patients with newly diagnosed ALS from different countries are needed to study the quality of care of the disease in different health care settings and to make sufficient patient numbers available for therapeutic trials recruitment. For these reasons, studies from larger populations obtained by merging data from multiple sources represent a major and logical step in the evolution of ALS epidemiology.

### 3. Problems with the implementation of multi-center population-based registries for epidemiological studies for ALS

#### 3.1. Diagnosis of ALS

The diagnosis of ALS is based on the presence of upper and lower motor neuron impairment, the detection of symptom progression over a limited period of time, and the exclusion of other conditions that may mimic ALS. Several diagnostic criteria have been devised for ALS [2,11,12]; however, most of them have been used in single studies and none has undergone a formal validation process, which prevents meaningful comparisons across studies. The El Escorial criteria (ECC) are the only diagnostic criteria having widespread use and has being assessed for validity and reliability [13]. According to these criteria, an ALS patient can be classified as definite, probable, possible, or suspected ALS based on the impairment of upper and/or lower motor neuron and on the number of involved regions (bulbar, cervical, thoracic, lumbo-sacral) (Table 1).

The advantages of the ECC include a high specificity when they are used in the selection of patients for clinical trials. By contrast, the ECC are difficult to apply in clinical practice, they are excessively rigid, and they assume ALS is a single disease entity. The overall burden of disease is not assessed and the four CNS regions are given equal

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Table 1  
El Escorial criteria for the diagnosis of amyotrophic lateral sclerosis (ALS) (13)

The diagnosis of ALS requires the presence of each of the following:  
(1) Lower motor neuron (LMN) signs by clinical, electrophysiological, or neuropathological examination in one or more of four regions (bulbar, cervical, thoracic, lumbo-sacral)  
(2) Upper motor neuron (UMN) signs by clinical examination in one or more of the four regions  
(3) Progression of signs within a region or to other regions

Definite ALS=UMN+LMN signs in three regions. Probable ALS=UMN+LMN signs in two regions with UMN signs rostral to LMN signs. Possible ALS=LMN signs in one region or UMN signs in two or three regions, such as monomelic ALS, progressive bulbar palsy, and primary lateral sclerosis. Suspected ALS=LMN signs in two or three regions, such as progressive muscular atrophy, and other motor syndromes.

weighting, thus preventing the EEC from having prognostic significance. Furthermore, some patients may be excluded if they are in the early stage of the disease or they have atypical features.

The reliability of the ECC has been recently tested through evaluation of medical records and was found to be modestly reliable in the hands of neurologists with different background and experience [14]. Specific training significantly improved the reliability of the diagnostic criteria, concordance remaining poor only at the lowest levels of the diagnostic certainty ('suspected ALS'). The ECC were revised (the Airlie-House criteria) by dropping the category 'suspected ALS' and introducing a novel category ('probable laboratory-supported ALS') based on the results of the electrophysiological examination [15] (Table 1). Although the reliability of the revised criteria has been found to be similar to the ECC [16], they are also less reproducible because they include more diagnostic categories. In addition, patients with early symptoms (i.e. 'suspected' ALS) are excluded, preventing assessment of the full spectrum of the disease for prognostic studies. This approach excluded less severe disease varieties (which may be more responsive to investigational treatments).

In conclusion, even with these limitations, the ECC are the logical choice as ALS diagnostic and classification criteria for a population-based registry. However, proper training of the assessors is required, and detailed follow-up of patients falling into the lower levels of the diagnostic certainty, to confirm the appropriateness of the diagnosis and exclude ALS mimic syndromes or other clinical conditions.

### 3.2. Assessment of environmental risk factors and gene-environment interactions

Several environmental risk factors have been implicated as putative causes of ALS [17] including mechanical trauma, activity-related exposures (welding, agriculture, leather, rubber, solvent, chemicals, lead, mercury, aluminum, selenium, manganese and iron), electrical trauma, ionizing radiations, smoking, alcohol consumption,

chemicals, and magnetic fields; pathogenic mechanisms have been postulated for some of these exposures. Long-term exposure to electromagnetic fields may result in the production of autoantibodies against calcium channels disrupting calcium homeostasis [18].

Lead exposure has long been associated with motor neuron disease and since the early historical reports, several studies have suggested a possible link between the two conditions [17]. Lead can cause peripheral neuropathy and encephalopathy in humans, with a dose-effect relationship existing between blood levels and clinical findings [19]. Lead concentrations are elevated in the anterior horn cells of ALS patients previously exposed to high levels of lead [20] and may cause upper motor neuron degeneration in predisposed individuals.

Lead mimics calcium and exerts its toxic action through several mechanisms, ranging from alteration of energy metabolism, to complex changes in neurotransmitters [19]. The possibility of genetic susceptibility implying higher lead body burden [21] and thus linking ALS with lead exposure has been recently investigated [22] but further studies are needed.

Prolonged inorganic mercury intoxication may lead to an ALS-like syndrome, which may be reversible when the toxic agent is withdrawn [23]. Similar effects on anterior horn cells can be found in patients exposed to selenium, which may act through activation of free radicals and antioxidant enzymes (like superoxide-dismutase) or even provoke genomic DNA alteration [24].

For aluminum and manganese, geochemical and pathological data from Western Pacific endemic areas suggested a role in ALS/Parkinson-Dementia-Complex. Aluminum organic and inorganic compounds administered by different routes provide an experimental model of progressive motor neuron degeneration with intraneuronal aggregation of neurofilaments in several animal species [25].

Metal-triggered protein aggregation and misfolding could be a common mechanism in various neurodegenerative diseases, including ALS [26,27].

Chronic exposure to solvents may produce progressive muscular atrophy, particularly in individuals with a family history of neurodegenerative disorders and thyroid dysfunction [28]. Heavy physical activity and trauma may provoke or accelerate motor neuron degeneration in predisposed individuals [29].

Despite a considerable literature, none of the putative risk factors has been found to fulfil the correct requirements for a cause-effect relationship. Finding a correlation between a risk factor or brain abnormality and ALS does not necessarily establish a causal association. In order for a given variable to be considered a risk factor for a disease, the association should require the satisfaction of the following conditions [30]: 1. Temporal sequence: the exposure must precede the disease in time; 2. Strength: a greater risk of disease is present among those exposed compared to those non-exposed; and the larger the difference of the exposure the greater the

strength of the association; 3. Consistency: the association should be reproducible in different populations and under different conditions; 4. Biological gradient: the evidence of a dose-response effect; 5. Biological plausibility: the association between the disease and exposure should be consistent with a recognized biologic mechanism. The lack of evidence in support of a cause-effect relationship between ALS and the reported exposures may be explained by the poor design of the published studies, most of which do not qualify for class I or class II studies based on suggested standard EBM criteria [31]. Regardless of the type of exposure, individual susceptibility may be implicated through concurrent clinical conditions (eg, osteoporosis or hyperparathyroidism) or simply through an altered genetic background; thus, ALS may be the consequence of a complex interaction between genetic and environmental factors.

It has long been recognized that ALS sometimes aggregates within kindreds, which often suggests autosomal dominant inheritance. There are also reports of apparent geographical aggregations of sporadic ALS in Italy and the United Kingdom [32,33]. This yields a genetic explanation for an observation at first thought to have an environmental basis. While such occurrences suggest a truly familial and genetically determined illness, this view has not always been universally accepted. There were those who argued that this reflects common environmental exposure rather than genetically determined disease.

Epidemiological research has thus yielded a wide range of confusing potential leads. However, rather than introducing unwanted confusion, they may hold important lessons: 1. There might be no unitary pathogenic mechanism for ALS; 2. The clinical syndrome of ALS might be a final common pathway with multiple and diverse triggers; 3. As no more than 20% of familial ALS is linked to a SOD1 mutation [34], a multiplicity of factors, some environmental, may be implicated; 4. ALS might occur in genetically susceptible individuals.

To date, the interaction of gene and environment has not been carefully studied in the pathogenesis of ALS. It is possible that exposure to a particular environmental agent leads to motor neuron degeneration in individuals with specific genotypes that convey susceptibility. Individuals with different genotypes will not develop the phenotype, even after prolonged exposure to the same environmental toxin. The ability to detect gene-environment effect is limited by the small sample size of published studies and the use of different methods of ascertainment of the risk factors (which prevents pooling and comparability of data from different studies). Only studies with adequate design performed in large population-based samples may throw some light on genetic and exogenous risk factors and their complex interactions.

### 3.3. Validity of multicenter studies

Multicenter studies are a valuable tool for assessing the distribution and causative risk factors of a rare disease. Compared to studies done in a single institution, multicenter studies have an increased power, assess more properly the heterogeneity of the disease (demographics, spectrum, exposures) in the general population. However, multicenter studies imply multiple investigators with different background and training, multiple instruments, and challenges in communication. In addition, random noise (i.e. interacting and confounding variables) may be randomly distributed across centers, leading to loss of power and decreased precision. A more important issue is that the implementation of the study protocol may vary across centers. This can lead to an incorrect assessment of the distribution of the disease and of its relation with a given exposure.

The existing ALS national and regional registries have different referral sources for ascertaining ALS cases (Table 2). The type of referral sources are largely dictated

Table 2  
Study areas, populations and modalities of case ascertainment

Geographic area	Population (in million)	Source of Patients						
		Hospital records	Administrative data (DRGs)	GPs	Neurologists	Neurophysiology Units	Treatment files	Other
England (London)	0.8	+	+		+	+	+	+
England (Preston) (*)	1.8				+			
France (Limousin)	0.8	+			+			
Ireland (*)	5.0			+	+	+	+	
Israel	6.5	+			+	+		
Italy (Lombardia) (*)	5.0	+	+		+	+	+	
Italy (Piemonte) (*)	4.3	+	+		+			
Italy (Puglia) (*)	4.0	+			+			
Russian Federation	28.6	+	+	+	+		+	
Scotland (*)	5.1				+			
Serbia (Belgrade)	1.6	+			±	±		
Spain (Madrid)	1				±	±	±	

(\*) Population-based registry. Regions or local areas in parentheses.

by the organization of the health care systems within each country. In addition, the populations may differ in their age and socio-cultural structure and the use of different languages complicates collection of the required demographic and analytical epidemiological information.

Standardization of the measurement methods is a prerequisite to performing a pan European multi-center epidemiological study. This entails the following: (a) Inter-observer agreement should be measured before the onset of the study; all sources of disagreement should be detected and discussed; (b) All observers should be trained and certified; (c) Questionnaires used to collect information on risk factor exposures should be refined; (d) Inter-observer agreement should be tested through a pilot study by using the adopted measurement methods before and after training.

Ideally, a single person (a neurologist specializing in ALS) should be nominated for each site, who should verify that each patient entered in the database conforms to the diagnosis of ALS as defined by the ECC. A clinical panel should be also elected to discuss disputable cases (ALS vs. other clinical conditions) and for the attribution of the cases to the ECC diagnostic categories.

#### 4. Data to be collected

A successful data management in a multicenter registry of ALS is based on the collection of a minimum number of variables. The choice should be based on a limited number of goal-directed, strictly defined and comprehensive variables to be collected in a simple, user-friendly, web-based registry. The principal goals of multicenter community-based registries are: (a) To share information and merge epidemiological and clinical data using population-based series of patients; and (b) To test hypotheses on the etiology and pathogenesis of ALS. For these reasons, a series of demographic and clinical variables are required for a correct definition of the spectrum of the disease and a number of exploratory variables should be identified to investigate the putative etiology and pathogenesis of the disease.

Demographic and clinical (disease) variables to be collected by the pan European ALS registry include main clinical features of the disease such as age at symptom onset, gender and site of onset. Place of residency (urban vs. rural) and place of birth will also be collected. A detailed occupational history (including occupational exposures) should be collected and coded according to standard classification systems.

The exploratory variables are selected to investigate pre-defined hypotheses. Therefore, information should be collected on diet, recreational substances, drugs, hormonal and reproductive variables, life habits, trauma, and family history of ALS and other neurodegenerative disorders.

Diet should be referred to the year preceding the clinical onset of the disease and should be investigated by using a food frequency questionnaire, computing the energy intake

in calories, and calculating the premorbid body mass index (BMI).

Recreational substances should include cigarette smoking, alcohol intake, and use of illicit drugs, with period, dose and time relationship to ALS onset. Leisure activities should be also coded when investigating physical exercise. These should include sport participation, with indication whether professional or amateur, and specification of type, duration, and period.

Physical activity should be then quantified using common standards. History of trauma should be investigated in detail, with type (mechanical/electrical/other), severity, time relation to ALS onset, and anatomical site.

The recent observation that the incidence of ALS is increased among veterans of the Gulf war suggest that military service should be accurately described, with details on deployment and missions in foreign countries. Other recreational activities as well as environmental (home) exposures (e.g. high power lines, use of wells) should be also investigated, with type, period and duration. Women should give details about their reproductive history. Family history of ALS and other neurodegenerative disorders should be collected, with information from first and second-degree relatives.

#### 5. Design of a population-based case-control study

A correct interpretation of the cause-effect relationship between a given exposure and a disease is based on several assumptions, which include: (1) A correct diagnosis of the disease under scrutiny (see above); (2) The representativeness of the cases and the controls; (3) A sizable target population, from which cases and controls can be identified in sufficient numbers, estimated through adequate power calculations.

Several methods of case ascertainment have been identified, leading to different levels of case selection. Patients with ALS may be identified when symptoms bring them to medical attention, there is an easy access to medical care, a correct diagnosis is made by an experienced physician, and they are willing to participate in the study.

Patients identified through national or regional registries are the source of representative ALS cases because they provide a clear definition of the population-time experience (well-defined geographic boundaries and calendar periods) and a full roster of cases. To exclude subjects who might have moved to the study area for the management of their disease, care should be taken to enroll patients with ALS in whom the diagnosis has been made for at least one year or resident of the area of the study for at least one year. Controls must be then selected among people who approximate the exposure prevalence of the population generating the cases. Failure to select controls not reflecting the exposure prevalence of the general population may bias the study results toward an

over- or an under-representation of the given exposure. Controls may be identified through different sources, including neighbors, people traced by random digit dialing, spouses/best friends, hospitalized patients, or people included in the rosters of the physician who referred the case. For the pan European register, the best strategy could be to select controls from the rosters of the general practitioners having in charge the ALS case. Controls should be resident of the same area of residency of the cases and should be matched for age and sex. The assessment of the exposures in the cases and controls should be performed as indicated in the section on data collection.

## 6. Inclusion criteria, diagnosis and phenotype

Every patient to be registered in the pan European ALS register should fulfill the ECC 1 for suspected, possible, probable or definite ALS. This requires the presence of upper and/or lower motor-neuron impairment in at least one region of the CNS and documented retrospective evidence of progression over a 6 month period. The phenotype of eligible patients must then be classified according to selected demographic (age, gender, ethnicity, marital status) and clinical variables (bulbar vs. spinal onset, BMI), to be used to identify distinct phenotypes. The choice not to use the Airlie-House criteria [15] reflects the need to retain suspected ALS among the cases to be registered, which are extremely useful for epidemiological and prognostic purposes. Our goal is to characterize different phenotypes (spinal vs. bulbar ALS, familial ALS, cognitive impairment present or absent).

Cognitive decline should be mentioned when present and classified according to the most recent criteria for fronto-temporal dementia [35].

## 7. Data to be included in the database and modalities of data collection

The structure of the database is flexible and permits links with other (national or local) data sources (Table 3). Accessibility is granted using Internet Explorer 6. Personal outputs in English are possible for any center. The database will be accompanied by a guide, which will explain in simple terms the modalities of collection of each variable. The structure of the database will permit storage and retrieval of data changing with time. Any change will be saved along with the position of the collector and the date of change. The variables subjected to time-dependent changes (e.g. El Escorial categories) will be recorded with the presumed date of change.

The modalities of data collection will be tested with the first cases to be registered (pilot study).

Table 3

List of variables to be included in the pan European register

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Demographic
Center
Patient's I.D. (initials)
Date and place of birth
City of residency
Education
Family history
Family history of ALS (with number of affected relatives)
Twin status (with zygosity)
Family history for Parkinson's and Alzheimer's disease
Personal history
Type of symptom onset (bulbar vs. spinal vs. general)
Motor neuron symptoms (fasciculations, cramps, motor findings)
Diagnostic work-up
ENG/EMG
Imaging (optional)
Clinical and electrophysiological findings at diagnosis by region and upper/lower motor neurons
Date and type of diagnosis (ECC)
Functional disability (ALS-FRS-R score)
Management (with dates)
Drugs
Enteral nutrition
Non-invasive ventilation
Tracheostomy
Status at registration
Dead/Alive
Date of death
Autopsy (optional)
Stated biological material
DNA samples
CSF
Muscle/nerve biopsies
Other

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## 8. Confidentiality and privacy issues, data property

Confidentiality and privacy will be preserved by adopting the following measures: (1) Each patient will be identified in the database by code. The list of patient names corresponding to the codes will be stored in a separate encrypted database. Only members of the steering committee will have access to the encrypted database and all logins will be recorded. (2) Obtaining an informed consent from patients (with documentary evidence retained in the center files); (3) Identifying a strict number of persons who are entitled to have access to the database and examine the individual patient data; (4) Adopting strict measures to prevent access to data by non-authorized persons.

A Steering Committee has been formally elected, represented by the coordinators of the existing registries (Beghi, chairman; Chiò, Hardiman, Logroscino, Mitchell, Swingler), by a statistician (to be appointed) and by a genetic epidemiologist (Traynor). Other persons have been included in the European registry as members (Al-Chalabi, Couratier, Esteban, Stevic, Skvortsova). Additional members from other groups/countries will be included upon request, provided that they represent active or planned population-based registries or wide clinical series from secondary or

tertiary centers. A data processor has been also identified (Millul) who will verify the completeness and the quality of the recorded information and who will monitor the registration procedure. The members of the steering committee will have access to the recorded data and will exert a control on every scientific product prepared as a group by the pan European register members.

Individual members may disseminate their national data provided proper disclosures are made to the steering committee. The entire procedure for the activation of the pan European register will conform to the EU directives.

### 9. Validation of the quality of data registration

A strategy to test the reliability of data registration is an essential element to establishing the pan European ALS register as each participating country may adopt differing strategies for case ascertainment according to the organization of the local health care system, each national controller will undergo a validation process. A number of patients will be randomly chosen from each participating country. The clinical information obtained from these cases will be entered on a structured questionnaire adapted from the Italian (Lombard) register. The latter data will serve as the basis to test inter-rater reliability.

### 10. Case-control study

A population-based case-control study will be the first research project of the pan European register. The principal aim of the case control study will be to test the hypothesis that sustained physical activity is a risk factor for ALS. This hypothesis will imply the identification of genetic susceptibility through DNA sampling and correct quantification of physical activity (using standardized quantitation of metabolic units). Enduring/professional sports will be noted as such and accompanied by years of activity. Trauma will be registered only if leading to medical intervention with indication of any eventual complication. A 1:2 case-control ratio will be selected. Cases and controls will be age and sex-matched. Controls will be (tentatively) randomly selected from the lists of the affiliates of the local general practitioners. The study design will be defined in a written protocol, which will be prepared in the next months and submitted for publication in a scientific journal.

### 11. Geographic areas and overall sample population

The following countries and populations (in millions, M) will be included in the European database: Scotland (5.1M), Ireland (5M), England (Preston 1.8M), England (London 0.8M), Italy (Lombardy, Piemonte/Valle D'Aosta, Puglia 13.3M), Serbia (Belgrade 1.6M), Spain (Madrid 1M), France (Limousin 0.8M), and Israel (6.5M). The inclusion

of patients from 14 regions of the Russian Federation (total population 28.6M) is under consideration.

On this basis, the overall target population will include 35.9 million persons (25.2 million from population-based registries; Table 2). Given a 2 per 100,000 per year incidence rate, the expected number of patients with ALS to be registered will be approximately 600–700 each year, of whom 500–600 will be available for epidemiological studies.

### 12. Parallel studies

Approximately 10% of ALS is familial (i.e. several members of the same family are affected), while the remaining 90% of cases are sporadic (i.e. patients do not have a family history of ALS) [36]. A variety of genes and genetic loci have been implicated in the pathogenesis of familial ALS, but the genetics underlying sporadic ALS remains elusive. Complex genetic patterns (i.e. more than one gene acting in each individual or gene-environment interactions) may play a role in sporadic ALS, but identification of genetic susceptibility or risk modifying genes is complicated by ascertainment bias, problems with phenotype assessment, lack of follow-up of phenotype, and development variation. Twin studies may provide an answer to the relative contribution of genetic and environmental factors to the etiology of disease.

The primary objective of a twin study in ALS is to evaluate the relative contribution of genetic and environmental factors to the pathogenesis of this disease by comparing concordance rates for ALS disease in monozygous (MZ) and dizygous (DZ) twins. MZ twins share identical genomes, whereas DZ twins share 50% of their genomes (similar to nontwin siblings). A 100% concordance rate among MZ twins and a 25–50% concordance rate among DZ twins would suggest that the disease is entirely determined by genetic factors, such as a mendelian inherited mutation. MZ concordance rates less than 100% indicate a significant environmental contribution to disease.

Twins are ascertained using the ALS population-based registries. Both twins are re-examined to assess diagnostic accuracy and zygosity. Caring neurologist reports, medical record examination, and direct interview of the families of the ALS cases may all contribute to the definition of case, control and twin status. Zygosity may be determined by questionnaire and by DNA analysis. Given a population at risk of 25.2 million persons (see above) and an expected number of about 500–600 patients with ALS per year, assuming a 1:80 twin pregnancies, ALS may occur each year in 6–7 twins, one third of whom will be MZ.

### 13. Other group activities

They will include a systematic review of the major risk factors for ALS, and a study of the correlation between ALS and selected occupational exposures. The study protocols

will be submitted to funding agencies (E.U., N.I.H.) and private institutions as grant proposals in the next few months. Slightly different study protocols will be prepared, to be submitted to separate funding agencies: (1) Case-control study on ALS and professional sports (E.U. PF-6); (2) Case-control study on ALS, professional sports, physical exercise, and trauma (N.I.H.). Population-based studies of ALS in twins might be submitted to ALS Lay Associations or other private agencies. The methodological reports will include the following tentative issues (proposed main authors in parentheses): (1) Relevant methodological issues in descriptive and analytic epidemiology of ALS (Logroscino, Traynor); (2) How to investigate professional sport activities and other environmental risk factors in ALS (Chiò, Herrero, Mitchell, Swingler); (3) Design and methods of a case-control study on professional sports, physical exercise, and trauma in ALS (Beghi, Hardiman); (4). Systematic review of the major risk factors for ALS (Mitchell, Chiò, Herrero, Logroscino). Other members of the pan European register are encouraged to join the main authors in the preparation of the manuscripts.

#### 14. Meeting attendants

Ettore Beghi (Milano and Monza, Italy)(chairman),  
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Members of the EURALS also include:

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