EPI-01 Amyotrophic lateral sclerosis in Africa: a multi-center cohort study, ALS and related syndromes under the tropics (TROPALS) collaboration

J Luna1, M Diagana1,2, LA Aissa3, R Gouider4, F Henning5, A Basse6, AAK Balogou7, T Agba8, D Houinato1,9, A Millogo1,10, B Hamidou1, P-M Preux1, P Couratier1,11, B Marin1, Collaboration Tropals1

1INSERM UMR1094, Tropical Neuroepidemiology, University of Limoges, Institute of Neuroepidemiology and Tropical Neurology, CNRS FR 3503 GEIST, Limoges, France, 2CHU de Nouakchott, Nouakchott, Mauritania, 3Laboratoire de recherché en Neurosciences, CHU Mustapha, Algiers, Algeria, 4Department of Neurology Razi Hospital, La Manouba, Tunis, Tunisia, 5Division of Neurology, Centre for Research in Neurodegenerative Disease, Stellenbosch University, South Africa, 6Department of Neurology, CHNU Fann, UCAD, Dakar, Senegal, 7Service de neurologie CHU, Campus Université de Lomé, 8Université de Lomé, Togo, 9Laboratory of Chronic and Neurologic Diseases Epidemiology, University of Abomey-Calavi, Neurology Unit, CNHU Cotonou, Cotonou, Benin, 10Service de Neurologie, CHU Souró Sanou, Bobo-Dioulasso, Burkina Faso, 11CHU Limoges, Service de Neurologie, Centre expert ALS, Limoges, France

Email address for correspondence: jaimeandreslunam@gmail.com

Keywords: clinical features, survival, Africa

Objective: We aimed to describe and compare demographics, clinical features, management and survival of ALS in Africa.

Methods: A hospital-based multi-centre cohort study was undertaken in African countries. ALS patients diagnosed from 2005 to 2017 in the participant centres were included. An ALS expert neurologist confirmed the diagnosis through medical records. Patients were categorized at diagnosis according to El Escorial revised criteria and follow-up assessments were performed. Descriptive and analytical statistics were conducted. Subgroup analyses were performed according to subcontinent, based on the United Nations Statistics Division. Survival analyses were carried out with the Kaplan-Meier method.

Results: 10 centres from 89 African countries participated. An overall 185 patients were included: 114 in Northern Africa, 30 in Southern Africa and 41 in Western Africa. A male predominance was found with a sex ratio (male/female) of 2.9 overall. Median age at onset was 54 years (interquartile range (IQR) 41–64). Western African patients had younger age at onset (47 years) compared with Northern and Southern Africa, p=0.0001. The median diagnostic delay was 12 months. Onset was bulbar in 22.7% of cases. Median ALS Functional Rating Scale Revised (ALSFRS-R) was 38 at diagnosis. 59 cases presented with atypical signs (32%), of which nearly 40% had cognitive impairment. Concerning the management, 80% had a medical or traditional treatment. However, only 47 cases had access to riluzole, mostly in Northern Africa. Overall, the median survival since diagnosis was 14 months. Longer survival was observed in Northern Africa with a median of 19 months compared with Southern Africa (11 months) and Western Africa (6 months), log rank p=0.001.

Conclusions: This is the first ALS multi-centre cohort study in African countries. Our research contributes to improving the clinical and survival understanding of ALS in Africa. However, we are aware that hospital-based studies are limited by selection bias. Further studies are needed to clarify variability in clinical features. Genetic research should also be included for a more comprehensive approach on ALS in African populations.

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EPI-02 Spatial correlation of ALS mortality and the role of environmental variables in Chile

P Zitko¹, D Valenzuela¹,², P Lillo²

¹Complejo Asistencial Barros Luco, Santiago, Chile, ²Departamento de Neurología Sur, Universidad de Chile, Santiago, Chile

Email address for correspondence: pedrozitko@gmail.com

Keywords: mortality rates, spatial correlation

Background: The evidence of spatial cluster of cases of ALS is not conclusive. Some studies have demonstrated that certain environmental variables could explain that possible spatial correlation.

Objectives: To determine the presence of spatial correlation of mortality cases of ALS among 29 Health Services areas (HAS) in Chile, over 24 years. To explore the significance of environmental variables that could explain this correlation.

Methods: A data base of 696 strata of fatal cases of ALS was built, including sex, age (4 strata), education (3 strata) and 29 geographical areas, over 24 years (1990–2013). Deaths were extracted from the national registry from the Ministry of Health. Contextual variables were estimated using a national representative socioeconomic characterization survey that has been carried out biennially since 1990. For each stratum and year the percentage of population exposed to: 1) living in a rural zone, 2) agricultural occupation, 3) mining occupation and 4) belonging to an ethnic group, was estimated. Denominators of each stratum were extracted from the inter-census estimation of the National Institute of Statistics. We estimated the ratio between observed and expected mortality rates of ALS for each geographic area, each year, and for the total period of study. Random effect and spatial dependence of neighboring areas were modeled separately through Poisson models using Markov Chain Monte Carlo procedures. Residuals of adjusted and non-adjusted models were explored. Magnitude of effect of variables are expressed as relative rate ratios (RR).

Results and discussion: Combining the information of all years, a higher risk of ALS mortality was observed in three central-north Health Services areas (range: RR 1.22 to 1.41), while a lower risk was concentrated in very north (range: RR 0.53 to 0.57) and central-south Health Services areas (range: RR 0.55 to 0.77). Observing each year separately, the clustering was not evident. The strata that were exposed to a greater level of rurality presented a higher risk for death by ALS (RR 1.11 (95% CI 1.03–1.21), by each additional 10% of rurality), independent of other co-variables. Initially, exposure to mining occupation showed lower risk (RR 0.74 (0.63–0.86) but this association was confounded mainly by the age of these strata (full adjusted RR 1.14 (0.97–1.34)). Although raw analysis showed that agricultural occupation was associated to a higher risk of ALS mortality (RR 1.34 (1.35–1.40)), the significance disappears after adjusting (RR 0.97 (0.91–1.04)). Ethnicity did not show significant association in the full adjusted model, while females presented a protective risk (RR 0.66 (0.60–0.74)). Lowest education stratum showed higher risk of death by ALS, independent of other factors.

Conclusion: In the long term, ALS mortality in Chile presents spatial correlation. At an ecological level, only rurality was associated to higher mortality by ALS independent of other variables.

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EPI-03 The incidence of amyotrophic lateral sclerosis (ALS) and its influence factors in Beijing, China, 2010–2015

S Zhou¹, S Qian¹, W Chang¹, L Wang²

¹School of Reliability and System Engineering, Beihang University, Beijing, China, ²Department of Neurology, the Third Hospital of Peking University, Beijing, China

Email address for correspondence: qiansilin@buaa.edu.cn

Keywords: incidence, influencing factors, Beijing

Background: In general, the number of persons with amyotrophic lateral sclerosis (ALS) was derived from the patient databases, and the data were normally collected through the National ALS Registry. This non-probabilistic sampling method requires the patient to register actively, while there were few studies on the method of estimating the patient population. In addition, to date no studies on the incidence of ALS in the Beijing municipality of China have been conducted. Beijing is a city with a population of nearly 21,000,000, where ALS epidemiological studies are crucial.

Objectives: Estimate the number of patients and determine the incidence and influencing factors of ALS in Beijing from 2010 to 2015.

Methods: The number of patients diagnosed with ALS between 2010 and 2015 were created from two aspects, namely, the patient visit record (including basic information and diagnostic results) of the Peking University No.3 Hospital (PUH3) and the census report (including basic information, hospital diagnosed at, treatment methods and current conditions) of Oriental Rain ALS care center (ORALS). PUH3 is the main ALS diagnostic hospital in Beijing, where patients diagnosed will choose a care center for adjuvant therapy, eg ORALS. By examining the consistency of age and gender distribution, it was demonstrated that the number of patients diagnosed at PUH3 in the visit record corresponded to the proportion of the total number diagnosed by PUH3 in the census.
report. Further, the number of ALS patients in Beijing’s other hospitals was estimated. Finally, combined with demographic data, the incidence and influencing factors of ALS were analyzed.

**Results:** A total of 3381 patients diagnosed with ALS within the 6-year period were estimated. Average yearly incidence was 2.708/100,000, where the male incidence was 3.308/100,000, and female incidence was 2.069/100,000. Male:female ratio was 1.698:1. The age distribution obeyed the 3-parameter Weibull distribution. The average age of males was 53.89 years and females was 52.42 years. There were differences in the incidence of different age groups (Chi-square = 74.360; p < 0.05). The number of patients above the age of 20 years began to rise slowly, to reach a peak at 55–60 years, and then began to fall.

**Discussion:** The incidence estimates of ALS in Beijing are consistent with findings from long established ALS registries in Europe and from some studies on incidence in Asia. Males are more susceptible to ALS than females. The ALS incidence is related to age. The incidence increased with age before the age of 60 years, and gradually decreased above 60 years. The patient age range is mainly 30–65 years. Later, the risk of the disease will decline and the cause may be related to the pathogenesis of ALS.

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**EPI-04** An odyssey in epidemiology - from snow to hill to ALS: acquired somatic mutations may trigger ALS onset

C Armon¹,²

¹Tel Aviv University Sackler School of Medicine, Tel Aviv, Israel, ²Assaf Harofeh Medical Center, Zerifin, USA

Email address for correspondence: carmel.armon@gmail.com

Keywords: causation, evidence-based methods, smoking

**Background:** Establishing mechanisms of disease causation in neurodegenerative diseases had long seemed to be beyond the pale of traditional epidemiological tools. Over the past 30 years it has become increasingly more plausible that many cases of ALS may be triggered by cumulative changes, such as accrued somatic mutations (nucleic acid changes), occurring in a single cell.

**Objective:** To demonstrate how this conclusion regarding the likely mechanisms by which many cases of ALS are triggered was derived by the systematic application of classical epidemiological principles.

**Conclusions:** Application of classical epidemiological methods supports a likely mechanism of biological onset of disease in many cases of ALS: accrued somatic mutations.

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**EPI-05** The Epidemiology of ALS in Massachusetts, 2008–2012: results from the first comprehensive capture, population-based ALS registry in the US

A Fraser¹, V Abille¹, S Paganoni², J Berry², N Atassi², D Chad², K Nicholson², R Knorr¹

¹Massachusetts Department of Public Health, Boston, USA, ²Massachusetts General Hospital, Boston, USA
Background: Community concerns relative to unusual spatial and temporal patterns in amyotrophic lateral sclerosis (ALS) prevalence, along with a largely unknown disease etiology, led to the establishment of a statewide registry for ALS in Massachusetts in 2003. Following pilot studies and methods development, the Argeo Paul Cellucci ALS Registry of Massachusetts began tracking ALS cases across the state in 2007. Designated a reportable disease in Massachusetts, ALS cases are reported annually to the Massachusetts Department of Public Health (MDPH) by hospitals, ALS clinics, and neurologists in accordance with federal and state privacy protection regulations. This first-in-the-nation registry allows for a comprehensive capture, population-based surveillance system for monitoring the occurrence of ALS and provides a unique opportunity to explore possible environmental causes of the disease. Here, we present results from 2008 to 2012.

Objectives: To determine patterns of incidence and prevalence of ALS in Massachusetts and to provide a resource for ALS researchers.

Methods: Medical records are obtained and abstracted for all patients who have been diagnosed with or evaluated for ALS in Massachusetts. All eligible cases are reviewed by consulting ALS specialists to confirm diagnosis based on El Escorial criteria. The MDPH Registry of Vital Records and the National Death Index are used to confirm any deaths. Clinical and demographic information is recorded and used by the MDPH to investigate spatial and temporal patterns of ALS in Massachusetts.

Results: From 2008 to 2012, 833 new ALS cases were reported to MDPH. The age-adjusted incidence rate was 2.3 people per 100,000 per year. The incidence of ALS increased by age until approximately age 80 years with the highest incidence rate observed for those aged 70–79 years. The male to female case ratio was 1.2. ALS prevalence and incidence will be presented by geography and stratified by other demographic variables including family history. Survival and disease progression statistics will also be presented.

Conclusion: The Massachusetts ALS Registry is the only comprehensive statewide system of reporting medically diagnosed cases of ALS in the United States. Difficulty in the diagnosis of ALS presents challenges for estimating disease rates, but systematic data collection and physician verification protocols enable consistent reporting. The Massachusetts ALS Registry is the only state government mandated registry in the United States. It has established a baseline for surveillance of a disease that is not widely tracked, particularly in the United States. Data are available for epidemiologic studies and to ALS researchers to better understand the causes of ALS. Data are available to inform patient service needs and epidemiologic studies. Researchers can apply for access with the MDPH’s IRB (Institutional Review Board).

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registries. The most common sources of information collected. Respondents have been from 32 different countries. To date, just under 1,000 responses have been collected, and we plan to make the survey answers open source so that other investigations can mine the data.

**Discussion and conclusions:** Creating a geographically diverse biorepository has unique challenges. However, these specimens will be a valuable resource for researchers who can request specimens for ALS studies.

**Keywords:** risk factors, online questionnaire, environment

We are conducting a web-based study (entitled ‘ALS Quest’) to look for risk factors for ALS/MND. The study consists of an online questionnaire, which is filled out by people both with and without ALS/MND. Community members and friends and relatives of ALS patients are encouraged to participate as controls. The questionnaire, which uses Qualtrics software, is available online at www.alsquest.org. The ALS Quest survey questions were initially based on experience from administering an Australia-wide paper-based ALS risk factor questionnaire which had over 2,000 respondents. New and modified questions were added from literature searches that implicated new risk factors and from validated ALS questionnaires generously supplied by investigators in the USA and Europe.

Survey questions include details of: occupational activities, chemical and pesticide exposures, physical activity, smoking, family sizes and medical histories, the ALS functional rating scale, index and ring finger lengths, personality types, and life event stressors. The questionnaire employs skip logic, which creates a custom path through the survey that varies based on a respondent’s answers. The questionnaire takes about 90 minutes to complete, and can be conducted in multiple sessions. Computers, tablets, and smart phones can be used to take the survey. No personally-identifiable information is sought, so all responses are anonymous.

The questionnaire has been translated into 23 languages, so it is now available in at least one official language of the majority of countries around the world. More languages are planned to be added in the near future.

The ALS Quest questionnaire was launched in 2015 and will be active for at least another 10 years, so that enough responses can be collected for between-nation comparisons. To date, just under 1,000 responses have been collected. Respondents have been from 32 different countries. The most common sources of information about the questionnaire cited by respondents have been: ALS Associations, the internet, friends, ALS patients, health professionals, community groups, Facebook, the USA CDC National ALS Registry, the Canadian Neuromuscular Disease Registry, and ALS researchers.

**Keywords:** ARREST, COSMOS, telephone-based

**Methods:** Data for ARREST are obtained via telephone over a 24-month period. Patients are recruited from the National ALS Registry and included if their symptoms began within 24 months of screening. To date, 85 patients have been enrolled.

COSMOS was a multicenter collaborative study conducted at 16 study sites. COSMOS obtained data via in-person assessments and telephone interviews. We recruited 355 patients who had symptoms for less than 18 months at baseline.
Compared to COSMOS, patients in ARREST are more likely to be white (97.4% vs. 87.9%) and have higher educational attainment (BA/BS or higher: 59.2% vs. 45.3%). Patients in both studies were similar in age, gender, and ethnicity. ARREST patients were more likely to use Medicare as their primary insurance (44.9% vs. 31.4%).

At baseline, ARREST patients have lower ALSFRS-R scores compared to COSMOS patients (34.2 ± 7.0 vs. 36.0 ± 6.7). They report longer duration of symptoms at baseline (13.6 ± 6.2 vs. 11.7 ± 4.5), but this is perhaps due to study design. A greater percentage of patients with progressive muscular atrophy enrolled in ARREST (13.3% vs. 7.9%) (ALS is most common, but other motor neuron diseases were included in both studies). Respiratory function, body mass index, region of onset, and percentage of patients that tested positive for the C9orf72 gene did not differ between the studies.

At baseline, ARREST patients scored better on word generation and exhibited less emotional lability than COSMOS patients; other cognitive and behavioral measures did not differ between the studies.

Discussion: ARREST was intended to add to the rich data collected from COSMOS. While there are some differences in demographic and baseline ALS functional parameters, these can be controlled statistically in the analytical phase. To our knowledge, this telephone-based study design is the first of its kind in ALS research and will be useful in future large-scale, population-based epidemiological studies.

Acknowledgements: Agency for Toxic Substances and Disease Registry, Centers for Disease Control and Prevention, National ALS Registry.
Background: In Sweden several hospitals care for amyotrophic lateral sclerosis (ALS) patients through specialized ALS teams, although some of the clinics only provide care for a handful of patients. As a result, the diagnostic criteria and treatment guidelines at these centers may not always be based on the most recently updated guidelines. Additionally, the research activity among the ALS teams might not be prominent and the patients from smaller hospitals are therefore not as often included in research projects or randomized clinical trials.

Objective: Our primary aim was to construct a national motor neuron disease (MND) Quality Registry in Sweden, which will assure high quality health care for all MND patients, including ALS. Our secondary aim is to create a research base by prospectively following the entire ALS population in Sweden.

Methods: The variables included in the MND Registry were jointly decided by a steering group. The layout of the registry, with a screen displaying the current and the past variables, gives the clinicians and researchers an instant overview of the temporal trend of important clinical variables. An internet based patient own reporting portal (PER) was also implemented to actively involve patients in the registration of symptoms and health status.

Results: To date around 80% of all prevalent ALS patients in Sweden (n=666), including all ALS patients of the Stockholm area (n=194), are registered in the MND Registry. ALS was the most common diagnosis registered (n=153, 78.9%), followed by primary lateral sclerosis (PLS) (n=13, 6.7%), and progressive spinal muscular atrophy (PSMA) (n=8, 4.1%). A slightly higher proportion of these patients were females (n=100, 52%), and females and males had a similar age at ALS diagnosis (61 years). Females seemed to be overrepresented in both the youngest and oldest age groups, ie <40 years, 41–50 years, and >71 years at diagnosis, although these gender differences were not statistically significant (all p values >0.05).

The vast majority of patients (n=78 males, 83.0%; n=87 females, 87.0%) had been treated with riluzole. Around half of the patients had been treated with enteral nutrition (n=98, 50.5%), and around 30% of the patients had been treated with non-invasive ventilation (n=58, 29.9%). A minority of the patients had been treated with invasive ventilation or tracheostomy (n=16, 8.2%).

Discussion and conclusion: The two main strengths of the Swedish MND Registry are the easy accessibility, via the internet and the possibility for the patients to participate through the self-reporting tool. These set-ups are not evident in the other international MND quality registries and will ensure an important contribution of the registry in both patient care and research.

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EPI-11 Total correlation explanation applied to the Irish ALS register

J Rooney, O Hardiman

Trinity College Dublin, Dublin, Ireland

Email address for correspondence: rooneyj4@tcd.ie

Keywords: incidence, structured data, survival

Introduction: Total correlation explanation (CorEx) is a new approach to discovering structure in data. The method is based on information as entropy theory and has been shown to outperform a number of alternative clustering methods (1).

Methods: All cases on the Irish ALS register from 2006 to 2014 were included. For each case, variables included were: age at diagnosis, diagnostic delay, site of onset, gender, revised El Escorial criteria, survival in months and C9orf72 status. The CorEx algorithm was applied to these data allowing for one to six latent variables with one to six different levels possible per variable. For each setting, the model was run 40 times. The overall best fit model was that which produced the highest overall total correlation.

Results: 944 cases met the inclusion criteria. The model that best explained correlation in the data from the Irish ALS register indicated four latent variables with a maximum of 4 dimensions. The four latent variables clustered as: 1) Diagnostic delay and survival, 2) Sex and site of onset, 3) Age of diagnosis and C9orf72, 4) El Escorial criteria.

Discussion: The CorEx algorithm detected structure in the data that confirms the known association of variables in the Irish ALS datasets. Further work is ongoing to explore the dimensionality of the latent variables.

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EPI-12 Epidemiological survey of SBMA in Italian north-east regions

C Bertolin, G Querin, I Martinelli, G Meo, E Pegoraro, G Sorarù

Department of Neurosciences, University of Padova, Padova, Italy

Email address for correspondence: giorgia.querin@gmail.com

Keywords: SBMA, epidemiology, Italy

Background: Spinal and bulbar muscular atrophy (SBMA), also known as Kennedy’s disease, is a rare, late
onset, X-linked neuromuscular disease. It is caused by a CAG repeat expansion localized in the first exon of the androgen receptor (AR) gene. The disease manifests clearly only in male patients, while female carriers of the mutation are usually asymptomatic, and it is characterized by slowly progressive, mostly proximal, limbs and bulbar muscle weakness and atrophy, which is associated with wide systemic involvement. The diagnosis is made through a genetic test for AR-CAG expansion. Different SBMA founder haplotypes have been described in patients from around the world and no expansion-prone haplotypes were found. SBMA is considered a very rare disease and its real epidemiology is not known. This is mainly due to the presence of minimally symptomatic patients who may not search for medical advice.

**Objective:** Aims of this study were to perform a survey of SBMA epidemiology in three north-east Italian regions and to clarify the AR-haplotype diversity in our cohort.

**Methods:** 95 patients came from the three north-east Italian regions (Veneto, Emilia-Romagna, and Friuli-Venezia Giulia) and were referred to the Neuromuscular Centre of the University of Padova between January 2006 and May 2017. For each family, pedigree structure was traced back to at least 3 generations. In search of relationships between apparently unrelated patients, we genotyped 46 SBMA families and reconstructed the haplotypes associated with the CAG repeat, defined by eight SNPs and six flanking STRs.

**Results:** 46 families for a total of 95 genetically confirmed patients were considered. Prevalence was 0.89/100,000 for the total population (95/10,584,487) and 1.84/100,000 for the male population (95/514,325). Mean incidence per year for the period 2006 through 2017 was 0.09/100,000 for the total population and 0.1/100,000 for the male population. Mean age of onset, defined as first appearance of muscular weakness, was 48.08 years +/- 10.48. The yearly mortality rate was 0.02/100,000 for the general population and 0.04/100,000 for the male population, with average age at death 75.8 +/- 5.98 years. Mean disease duration was 20.83 years +/- 11.72. We found a strong founder effect with 21% of the patients coming from the Verona district and 12% coming from the Reggio Emilia district, confirmed by molecular haplotype analysis.

**Conclusions:** This is the first study describing the epidemiology of SBMA considering such a wide population of patients. Our data confirm previous epidemiological studies conducted on small populations of patients. Nevertheless, estimation of the real distribution of the disease remains difficult since asymptomatic patients are frequent and not always undergoing genetic testing, so the disease is probably underdiagnosed and further studies are warranted to obtain complete epidemiology data.

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**EPI-13 A high-incidence cluster of ALS in the French Alps: common environment and multiple exposures**

E Lagrange\(^1\), V Bonneterre\(^2\), K Talbot\(^3\), P Couratier\(^4\), E Bernard\(^5\), W Camu\(^6\)

\(^1\)European reference center on neuromuscular diseases, Grenoble, France, \(^2\)EPEP, Grenoble, France, \(^3\)Nuffield department of clinical neuro-sciences, Oxford, United Kingdom, \(^4\)ALS Centre, Limoges, France, \(^5\)ALS Centre, Lyon, France, \(^6\)ALS Centre, Montpellier, France

**Email address for correspondence:** william.camu@sfr.fr

**Keywords:** cluster, exposome, environment

**Background:** ALS clustering is important to describe as it may be helpful for uncovering/studying potential causes of ALS.

**Objectives:** To describe a clustering of ALS cases in a small hamlet in the French Alps and discuss potential exposures in the patients’ environment.

**Cases:** Between 1991 and 2013, five ALS cases were described in the small hamlet of Montchavin, Savoie, France. Two of them were spouses. They have all lived in the hamlet since early childhood or birth. Patients were all neighbours and the hamlet comprised 200 persons living here on a regular basis.

Between 2010 and 2015, seven other cases of ALS were identified in individuals that did not originate from the village but spent a part of their life in the area. One had lived here since 2009, another spent half of his lifetime in Montchavin, two were present during holidays for more than 20 years, and two others lived in close villages and had an activity, professional or leisure, in the hamlet.

**Results:** The study of the cases did not identify any genetic/familial relationships between the patients and, when possible, a genetic analysis was performed and was negative.

For the 5 ALS patients originating from the area, given the interval of observation, 22 years, the population of 200 and the incidence of ALS, 2.5/100,000, the standardized incidence ratio=45 (p<0.00001). It does not seem possible to estimate an incidence ratio for the whole group of 12 patients in the cluster area, as the population during winter and summertime greatly increases, and for seven of them, exposure was not continuous.

**Exposures:** Common exposures were found between the 12 patients: all but one practiced sport intensively, eight had a vegetable garden, six used to eat local mushrooms, five were ski teachers, and four had a restaurant. The water used for the vegetable gardens was collected immediately downstream from the ski area where snow guns were intensively using snomax for artificial snow, with a mix containing bacteria. Among the five ALS cases originating from the area, four of them were chronically exposed to polycyclic aromatic hydrocarbons, and in two
EPI-14 Assessing cyanobacterial harmful algal blooms as risk factors for amyotrophic lateral sclerosis

N Torbick¹, B Ziniti¹, E Stommel²

¹Applied Geosolutions, Durham, USA, ²Dartmouth College, Hanover, USA

Email address for correspondence: ntorbick@appliedgeosolutions.com

Keywords: CHABs, modeling

Reoccurring seasonal cyanobacterial harmful algal blooms (CHABs) persist in many waters, and recent work has shown links between CHAB and elevated risk of amyotrophic lateral sclerosis (ALS). Quantifying the exposure levels of CHAB as a potential risk factor for ALS is complicated by human mobility, potential pathways, and data availability. In this work, we develop phycocyanin concentration (ie CHAB exposure) maps using satellite remote sensing, across northern New England, to assess relationships with ALS cases, using a spatial epidemiological approach. Strategic semi-analytical regression models integrated Landsat and in situ observations to map phycocyanin (PCN) and chlorophyl-a (chl-a) in waterbodies of >8 hectares. The spread of cyanotoxins from waterbodies to the residences of subjects was modeled using the kernel density estimation (KDE) with 1 km, 5 km, and 10 km as the bandwidth.

Results: With a bandwidth of KDE=1 km, residential exposure of ALS patients was greater than that of controls: for PCN, OR=1.0930; 95% CI=(1.0027–1.1915); and p-values=0.0432; for chl-a, OR=1.0732; 95% CI=(0.9988–1.1530); and p-values=0.0538. At bandwidth=5 km, for chl-a, OR=1.1243; 95% CI=(1.0136–1.2471); and p-values=0.0268. At bandwidth=10 km, for chl-a, OR=1.1489; 95% CI=(0.9936–1.3286); and p-values=0.0611.

Discussion and conclusion: PCN and chl-a have different spatial associations with ALS patients’ residences, indicating that the choice of measurement of cyanotoxins is important. Generally, in northern New England, the risk of ALS appears to be positively related to exposure to cyanobacteria in waterbodies.

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EPI-16 Predictors of survival among US military veterans with ALS

T Larson, P Mehta, K Horton
Agency for Toxic Substances and Disease Registry, Atlanta, USA

Email address for correspondence: thl3@cdc.gov

Keywords: military veterans, survival

Background: In many studies, military veterans appear to have an increased risk of developing amyotrophic lateral sclerosis (ALS). Our objective was to identify patient factors associated with ALS mortality among military veterans participating in the National ALS Registry, a registry recording ALS in the United States.

Methods: Subjects were veterans enrolled in the Registry via its web portal during 2010–2014 with complete data for covariates. Vital status was determined using National Death Index. Multivariate Cox proportional hazards models were fitted using the interval since diagnosis as the time variable. Covariates were sex, age at diagnosis, race (white, black, or other race), body mass index (BMI: categorized as underweight, normal, overweight, or obese), and smoking history (never, past, or current). A variable representing rate of change in the ALS Functional Rating Scale (ALSFRS) was also considered. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated for each covariate.

Results: Among 1052 registered veterans, there were 423 decedents. Mean time between diagnosis and death was shorter among veterans than registrants reporting no military service (2.5 vs. 2.8 years; p < 0.001). Being male was associated with better survival (HR 0.68, 95% CI 0.62–0.74), as was being overweight (HR 0.78, 95% CI 0.62–0.98). Compared with never-smokers, current smokers had worse survival (HR 1.29, 95% CI 0.90–1.84), and each additional year of age at diagnosis increased the hazard of death by 9% (p < 0.001). A separate model using the same covariates and the ALSFRS rate-of-change variable, restricted to 217 veterans with complete data, showed a statistically significant increase in hazard among veterans with large and/or rapid declines in patient function.

Conclusions: Several patient factors were weakly associated with survival, although later age at diagnosis and declines in ALSFRS were strongly associated with worse survival. Analysis of additional factors including environmental exposures and their potential relationship with ALS survival among veterans enrolled in the Registry should be considered.

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EPI-17 Exposure to electric shocks and extremely-low-frequency magnetic fields: the risk of amyotrophic lateral sclerosis

S Peters1,2, AE Visser1, JPK Rooney3, F D’Ovidio4, E Beghi5, A Chio4, G Logroscino5,6, O Hardiman3, H Kromhout2, A Huss2, J Veldink1, R Vermeulen2, L van den Berg1
1University Medical Centre Utrecht, Utrecht, Netherlands, 2Utrecht University, Utrecht, Netherlands, 3Trinity Biomedical Sciences Institute, Dublin, Ireland, 4University of Torino, Turin, Italy, 5IRCCS, Istituto di Ricerche Farmacologiche “Mario Negri”, Milan, Italy, 6University of Bari, Lecce, Italy

Email address for correspondence: s.m.peters-5@umcutrecht.nl

Keywords: electric shocks, electromagnetic fields, risk factor

Background: Electrical occupations have been linked to an increased risk of amyotrophic lateral sclerosis (ALS) in multiple studies. The underlying mechanism is however not clear. We explored the association between occupational exposure to electric shocks and extremely low-frequency magnetic fields (ELF-MF) and the risk of ALS in 3 population-based case-control studies.

Methods: ALS patients and population-based controls were recruited in the Netherlands, Ireland and Italy, between 2010 and 2015, as part of the Euro-MOTOR project. Lifetime occupational and lifestyle histories were obtained using structured questionnaires. We applied 2 previously developed job exposure matrices assigning low (i. background), medium or high risk of electric injuries due to shocks and exposure to ELF-MF. Odds ratios (OR) and 95% confidence intervals (CI) for ALS were estimated by logistic regression for both occupational exposures in the same model, adjusted for age, sex, cohort, smoking status and alcohol drinking.

Results: Complete occupational histories and information on confounding variables was available for 1423 confirmed ALS cases and 2851 controls. Among cases, 20% had ever been high exposed to electric shocks, and 7% had ever been high exposed to ELF-MF. Among controls, the proportions were 16% and 5%, respectively. Exposure to electric shocks and ELF-MF were only weakly correlated (Pearson correlation R = 0.37). Both ever exposure to electric shocks (OR = 1.23, 95% CI 1.05–1.44) and ELF-MF (OR = 1.15, 95% CI 0.99–1.32) were associated with ALS. No difference between the level
of exposure or a trend with duration of exposure was observed for either exposure.

**Conclusion:** Our findings support a possible independent association between occupational exposure to electric shocks and ELF-MF and the risk of ALS.

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**EPI-18 Highways of NH/VT and ALS patients: a geospatial analysis using case-control addresses and census blocks**

B Guetti¹, P Henegan¹, A Andrew¹, N Torbick², D Facciponte¹, E Stommel¹, W Bradley³

¹Dartmouth-Hitchcock Medical Center, Lebanon, USA, ²Applied GeoSolutions, Newmarket, USA, ³University of Miami, Miami, USA

**Email address for correspondence:** patricia.l.henegan@dartmouth.edu

**Keywords:** case-control, environment, runoff

**Background:** ALS has been found to occur in conjugal couples and geospatial clusters. Both of these characteristics are suggestive of environmental contributors (1). Identified clusters of cases were determined to exceed expected numbers and were both statistically and clinically significant. They concluded that the importance of scale should not be underestimated and recommended that environmental sources be explored in further studies. This investigation began to explore the recommendation, specifically the possible contribution of living near certain types of transportation facilities.

**Objectives:** To determine the spatial relationship, if any, that highways have on ALS patients compared to clinic controls. Using GIS analysis of case and control locations with road network data, proximity analyses are being conducted to calculate the mean distances between these locations and the road network for demographic groups. The mean distances for cases are then being compared to the mean distances for controls to see if the cases are different to the controls. If the cases are closer to the roads than the controls, the factors associated with the differences are being explored.

**Method:** Using case-control questionnaire data, the addresses of ALS patients and controls were geocoded. Once tested for locational accuracy, the distance to the closest highway was measured. Using TIGER street centerlines (www.arcgis.com), highways were extracted using MTFCC codes S1100 (primary) and S1200 (secondary). The analyses were done using ArcGIS on the data, that is in a NAD 1983 datum/spheroid, and projected to a UTM Zone 18 North coordinate system. There are currently 103 ALS cases and 138 control records. An additional source of control data has been created from the US Census demographic data. Population locations for two million people have been created using Census Block centroids. Control locations are then extracted from the total population using the 46 age and sex categories used by the US Census. Available census controls were assigned to known residential addresses. Mean distances and their standard deviations were generated from the individual distances for groupings of cases and controls using the US Census age and sex categories. All datasets were processed to extract the approximate DHMC (Dartmouth-Hitchcock Medical Center) and UVMC (Upper Valley Medical Center) referral areas.

**Results:** Mean distances and standard deviations have been calculated for the following sample categories: female/male questionnaire cases 60 years or older; female/male questionnaire controls 60 years or older; matched Census based population; and female/male census based controls 60 years or older. Distances from highways have been consistent. The case categories have been routinely 20–25% closer than the controls.

**Conclusion:** Early results indicate a possible relationship of ALS cases with highways.

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**EPI-19 Smoking is a risk factor for ALS in a UK population - a case control study**

S Martin¹, P Shaw², N Pearce³, C Shaw¹, K Morrison⁴, A Al-Chalabi¹

¹King’s College London, London, United Kingdom, ²University of Sheffield, Sheffield, United Kingdom, ³London School of Hygiene and Tropical Medicine, London, United Kingdom, ⁴University of Southampton, Southampton, United Kingdom

**Email address for correspondence:** sarah.martin@kcl.ac.uk

**Keywords:** smoking, risk factor, epidemiology

**Background:** The role of smoking in ALS remains controversial. On the basis of quality of evidence, smoking may be considered as an established risk factor in ALS. Meta-analysis of a broader range of studies has shown that smoking may not be a risk factor for ALS, except in
subgroups such as females. Recently, survival analysis has shown that people who smoke at onset of ALS have shorter survival than former or never smokers, and earlier age of disease onset. A population based study on the risk of smoking and ALS, also reported that lower alcohol consumption is a risk factor of ALS.

We aimed to discover whether smoking was associated with a risk of ALS in a case controlled study of people from the UK.

Methods: This was a retrospective case controlled study including people with a diagnosis of MND confirmed by a consultant neurologist. The data were collected from three centres in the UK. People diagnosed with ALS were asked about their current smoking habits and smoking history as part of a telephone interview with a trained healthcare professional. We performed a multivariate logistic regression analysis to compute odds ratios for the risk of never, former and current smoking and risk of ALS. The odds ratios were adjusted for gender, age at survey, educational attainment, cigarette pack years and alcohol consumption.

Results: The analysis was performed on complete data from 201 cases and 199 controls. The gender ratio was 56:44 male-female in the control group and 42:58 in the in the patient group. The average age was 64.5 years for controls and 63.1 years for cases. We found there was an increased risk of ALS in current smokers (adjusted OR 3.46, 95% CI 1.24–10.56, p-value 0.003), but not for former smokers. We found there was a significant association of ALS with being a former drinker (adjusted OR 4.60, 95% CI 1.99–10.94, p-value 0.004), but current or never drinking had no effect. Most survey responders who had given up drinking (60%) gave symptoms associated with the disease as the reason.

Discussion: In our study population smoking carries an increased risk of ALS. The effect of alcohol consumption on disease risk has not been confirmed by our analysis.

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EPI-20 Do people with ALS have lower index-to-ring finger length ratios (2D:4D)?

J P Kullmann, R Pamphlett
University of Sydney, Sydney, Australia

Email address for correspondence: jpar5295@uni.sydney.edu.au

Keywords: 2D:4D ratio, prenatal testosterone, online questionnaire

Objectives: The ratio of the length of the index finger (2D) to the ring finger (4D) (2D:4D) has been reported to be lower (i.e. 2D < 4D) in people with ALS than non-ALS controls. This has led to suggestions that exposure to increased prenatal testosterone, which also lowers this ratio, could be a risk factor for ALS. In an attempt to test this hypothesis, we examined 2D:4Ds from large numbers of ALS patients and controls.

Results: Unpaired t-tests with 95% confidence intervals were used to assess differences in mean 2D:4Ds. Males had significantly lower mean 2D:4Ds than females, in both ALS and control groups, for both left and right hands. However, no significant differences were found in 2D:4Ds between ALS and control groups, in either males or females, for either left or right hands. Receiver operating characteristic (ROC) curves showed no power for 2D:4Ds to predict ALS status in either males or females.

Conclusions: 2D:4Ds did not differ between ALS patients and controls in this study. This was despite the dataset being large enough to confirm the established finding of lower 2D:4Ds in males compared to females. These findings do not therefore support the hypothesis that exposure to increased prenatal testosterone is a risk factor for ALS. A putative lower 2D:4D has been proposed to explain the link between ALS and exercise, but our results indicate that other exercise-related factors need to be found to explain this association.

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EPI-21 The role of pre-morbid diabetes on developing amyotrophic lateral sclerosis

A Calvo1, F D’Ovidio1, G Costa2, A D’Errico2, P Carna2, A Chio1

1ALS Centre, ‘Rita Levi Montalcini’ Department of Neuroscience, University of Torino, Torino, Italy, 2Epidemiology Department ASL TO3, Regione Piemonte, Italy

Email address for correspondence: andrea.calvo@unito.it

Keywords: genetics, mapping

Background: The literature on the association between diabetes and amyotrophic lateral sclerosis (ALS) produced some inconsistent results. This study was developed in order to assess the role of diabetes on the risk of developing ALS.

Methods: The study population was represented by all residents in Turin (Italy) at the beginning of 1996, already present at the 1991 Census, older than 14 years (n=727,977) and followed up for diabetes and ALS occurrence from 1998 to 2014. Presence of diabetes was ascertained through 2 Piedmont regional sources: the
Diabetes Registry and the ATC Drugs Prescriptions Archive. The risk of ALS was estimated using the Piedmont and Valle d’Aosta ALS Registry (PARALS). The association of diabetes, treated as a time-dependent variable, with ALS onset was estimated through Cox proportional hazard regression models adjusted for age, gender, education and marital status.

Results: During the follow-up, 397 subjects developed ALS, 20 of whom were already diabetics before ALS onset. Diabetes identified through the Diabetes Registry or drugs prescriptions more than 1 year before ALS onset significantly decreased the risk of ALS (HR=0.26; 95% CI 0.17–0.42).

Conclusions: The study results support a protective role of diabetes toward ALS.

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EPI-22 Dysphagia in ALS: an Italian population-based study

C Moglia1, A Calvo1, A Canosa1, S Cammarosano1, U Manera1, F Pisano2, G Mora3, L Mazzini4, A Chio1

1 Department of Neuroscience, ALS Centre, Torino, Italy, 2Fondazione S. Maugeri, Veruno, Italy, 3Fondazione S. Maugeri, Milano, Italy, 4ALS Centre, Ospedale Maggiore della Carità, Novara, Italy

Email address for correspondence: cristina.moglia@gmail.com

Keywords: dysphagia, register

Aim: To define the natural history of dysphagia in a population-based series of Italian ALS patients.

Methods: A total of 1236 patients with ALS from the Piemonte/Valle d’Aosta Register for ALS, in the 2007–2015 period, were considered. Cases were classified according to the established site of onset: bulbar, upper limb, lower limb or respiratory. Disease progression was measured by the ALS-MITOS system, directly deduced from the three monthly based ALSFRS-r score assessment. The time to gastrostomy was collected using multiple sources (eg hospital discharge records and outpatient visits/calls) and it was recorded in the register.

Results: The time to reach severe swallowing involvement (MITOS-EAT=1) was significantly lower in female patients (median time of 2.06 years in females vs. 2.53 years in males; p<0.001) and it progressively increased with aging (χ² of 54.01, p<0.001). It was significantly lower in bulbar onset (median time of 1.24 years) and respiratory onset (median time of 1.36 years) patients compared to patients with upper/lower limb onset (median time of 3.18 years/4.34 years, respectively). Also, cognitive impairment was related to an early swallowing dysfunction, particularly ALS-Bi (median time 1.88 years, SD 0.63) and FTD (median time 1.58 years, SD 0.12). C9orf72 patients showed a significant swallowing impairment compared to patients carrying other genetic mutations and wild-type patients (C9 median time 1.87 years, SD 0.25 vs. wild-type median time 2.25 years, SD 0.11). 417 patients (33.3%) underwent gastrostomy in a median time of 1.86 years (SD 0.6) from onset. The gastrostomy time was significantly lower in respiratory onset patients (median time 0.79 years, SD 0.15) and bulbar patients (median time 1.67 years, SD 0.06).

Discussion: Bulbar dysfunction in ALS patients seems to be influenced by different demographic, genetic and cognitive aspects, underlining the complexity of pathological mechanisms involved in the phenotype determination.

Moreover, time to gastrostomy seems to be influenced not only by bulbar impairment (median time to PEG 1.86 years vs. MITOS-EAT=1 time 2.25 years), but also by other clinical features (ie respiratory failure, weight loss).

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EPI-23 Medical cost of ALS in Japan

A Uchino1, N Tominaga1, Y Ogino2, M Ogino3

1Kitasato university, Kanagawa, Japan, 2Hakone Hospital, Kanagawa, Japan, 3International University of Health and Welfare, Narita, Japan

Email address for correspondence: ogino@iuhw.ac.jp

Keywords: medical cost, prevalence rate, real-world database

Objective: To understand medical costs of ALS compared with other diseases in Japan through an analysis of health insurance claims data.

Methods: We analyzed a real-world data (January 2005–January 2016) containing nationwide employee health insurance claims. ALS patients were identified based on diagnosis codes. Medical costs included inpatients, outpatients, and prescription drugs, and were analyzed using data from February 2015 to January 2016. The cost per patient per month (PPPM) was calculated by dividing total medical cost by the total number of months of insurance period of ALS patients. The cost per member per month (PMPM) was calculated by dividing total medical cost by the total number of months of insurance period of all policyholders in the database.

Results: The prevalence rate of ALS was 0.01% in 2015. Mean age in these data was 46.1 years. The total PMPM cost for ALS (¥182,597; US$1,640, €1,466 as of May 2017) was higher than those for multiple sclerosis (MS) (¥24,337), Parkinson’s disease (¥84,410), myasthenia gravis (¥82,944), or rheumatoid arthritis (¥53,843). However, the total PMPM cost, which represents population-based economic impact, for ALS (¥10) was lower than those for Parkinson’s disease (¥123.0), MS (¥25.2), or rheumatoid arthritis (¥311.6) partly due to the low prevalence of MS in Japan.
Conclusions: Based on real-world database, we provided up-to-date prevalence, treatment status, and medical costs for ALS in Japan. Our results demonstrated efficacy of real-world database analysis to obtain the latest national trend of rare diseases including ALS, which may provide important information for clinicians and policymakers.

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EPI-24 Are people with ALS really nicer? An online international study of the big five personality traits

JP Kullmann, R Pamphlett, S Hayes
University of Sydney, Sydney, Australia

Email address for correspondence: jpar5295@uni.sydney.edu.au

Keywords: personality, Big Five, risk factors

Objective: Clinicians who see people with ALS often mention that they present as being particularly 'nice', with agreeable and outgoing personalities. These pleasant traits stand out particularly when considering ALS patients face a devastating disease. In an attempt to see if any evidence could be found to support these anecdotal reports of niceness, we conducted a case-control study looking for personality differences between ALS patients and non-ALS controls.

Methods: The web-based international ALS risk factor questionnaire ‘ALS Quest’ includes the Big Five Inventory of personality traits, ie agreeableness, conscientiousness, extraversion, neuroticism, and openness. ALS patients were asked to respond to the Big Five inventory in a manner reflective of their pre-diagnostic state. The Big Five factors were compared between ALS and non-ALS groups using logistic regression with odds ratios and 95% confidence intervals, controlled for age and gender.

Results: 929 respondents (355 ALS and 574 controls) met the criteria for inclusion. Odds ratios were significantly greater than one in ALS patients for agreeableness, conscientiousness, and extraversion, indicating these traits were more likely to be found in patients than controls.

Conclusion: People with ALS tend to be more agreeable, more conscientious, and more extraverted than control subjects. These factors are likely to be found more often in people with an outgoing, risk-taking personality type who may be prone to some risk factors associated with ALS, such as athleticism, head injury, and smoking. Another possibility is that genetic polymorphisms associated with these personality factors co-localise with polymorphisms that increase the likelihood of getting ALS. With the greater numbers of respondents expected for the ALS Quest survey in the future, international comparisons of personality types in ALS and controls will be able to be made.

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EPI-25 Modelling individual amyotrophic lateral sclerosis disease courses in the PRO-ACT database using the D50 progression model

N Gaur, B Stubendorff, A Rödiger, A Gunkel, M Radscheidt, B Ilse, OW Witte, J Grosskreutz

Hans-Berger Department of Neurology, Jena University Hospital, Jena, Germany

Email address for correspondence: beatrice.stubendorff@med.uni-jena.de

Keywords: PRO-ACT database, ALSFRS-R

Introduction: Evidence shows that ALS progression is curvilinear and heterogeneous. However, the routinely used progression rate (PR=(48-ALSFRS-R/disease duration)) only reflects progression at a circumscribed time-point rather than across the disease. It is crucial to develop indices that can describe individual progression over the whole disease course.

Objectives: The study aimed to develop a model that uses regularly collected ALSFRS-R scores to describe and relate to individual events within the ALS disease course and reduce noise associated with the ALSFRS-R.

Methods: We used a sigmoidal decay function to describe the transition from full health to maximum disease for patients in the PRO-ACT database (1). The model yields three parameters: D50=time taken for ALSFRS-R to drop to 24, dx=slope of ALSFRS-R decrease, relative D50 (rD50)=calculated value describing individual disease covered in reference to D50, where 0 would signify onset and 0.5 would indicate the time-point of halved functionality. D50 was used to mathematically derive disease phases: Phase I (early semi-stable phase), Phase II (early progressive phase), Phase III (late progressive phase) and Phase IV (late semi-stable phase).

Results: Using ALSFRS-R scores and disease duration from onset to ALSFRS-R date, we determined D50, dx, and rD50 for 4838 patients. The relationship between D50 and dx was highly linear (r=0.889), indicating that the entire disease course can be described using D50 alone. A significant correlation between D50 and survival was observed (r=0.654). Although significant correlations were observed between D50 and transformed (1/PR) first (r=0.601) and last (r=0.772) recorded PRs, the difference in the correlations indicates how profoundly PR can vary over time. When selecting for patients for whom model data were best fitted to actual data, we showed that riluzole treatment significantly prolonged mean D50 (43.6 vs. 40.7 months). We were also able to use rD50 to demonstrate progressive worsening of both forced and slow vital capacity for most patients. Statistical significance was set at p < 0.01.

Conclusion: D50, rD50, and dx enable comparisons between vastly different time-scales of disease courses and also enable staging of individual events, ie sampling at any given time-point can be correlated to any of the three parameters. This may aid the discovery of early prognostic
markers and bolster understanding of the pathomechanisms underlying the heterogeneity in ALS progression. rD50 offers an alternative reference point to survival, given that the latter is often a function of the quality of care the patient receives, rather than genuine disease progression.

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EPI-26 Serum creatine kinase in neuromuscular disease/post-polio syndrome (PPS)

AA Quadros¹,², MDSB Contiq¹,³; MP Mota¹, KM de Campos¹, CF Viana¹, LS Ferreira¹, CT Munhoz¹, AS Helou¹, RHB Piovesan¹, AS Oliveira¹

¹Federal University of São Paulo, São Paulo, Brazil, ²Adventist University Center of São Paulo, São Paulo, Brazil, ³Federal University of Rio Grande do Sul, Porto Alegre, Brazil

Email address for correspondence: aaiquadros@gmail.com

Keywords: creatinophosphokinase, post-polio syndrome, polio sequelae

Background: Post-polio syndrome (PPS) is a motor neuronopathy characterized by new and progressive muscular weakness, pain, and fatigue many years after the acute paralytic polio: ICD10 G14. Elevated creatine kinase (CK) levels have been reported in many neuromuscular diseases as a result of muscle damage and necrosis. Elevations of CK levels have been mentioned in other investigations of the post-polio patient population.

Objectives: We sought to measure the serum CK levels in post-polio patients (PPP) and patients with polio sequelae (PS) without evidence of new neurological compromise (Control).

Methods: We measured the serum CK level of PPP with new neurological compromises (case group) and polio sequelae patients with no evidence of new neurological symptoms (control group). Patient groups were comparable for age, gender and years since onset of poliomyelitis and since onset of PPS.

Results: A total of 141 patients, 81 PPS patients (cases) and 60 PS patients (controls) were enrolled in a Brazilian tertiary care center. Median age was 50.6 years (±6.4) for both patients and controls and the majority were females (60.3%), median years since onset of polio was 37 years (±6.2), years since PPS onset was 14.5 years (±2.4). The PPS group had substantially increased CK levels compared with the Control group, 272 IU (95% CI 230.2–314.1) vs. 130 IU (95% CI 113.4–146.9).

Discussion and conclusion: The study demonstrated markedly elevated levels of CK were present in the PPS group. Males had higher CK levels compared to females.

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