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Motor Neuron Disease Population-Based Registry in Egypt: Where Do We Stand?

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Abstract
Background: There is a growing body of evidence indicating that the worldwide distribution of amyotrophic lateral sclerosis (ALS) is far from uniform. This is evident through variations in the epidemiology, genetics, and phenotypical characteristics of ALS and other motor neuron diseases (MND) across different regions. However, comprehensive ALS epidemiological studies are still lacking in many parts of the world, especially in Africa. Therefore, we propose the establishment of a population-based register for ALS/MND in Egypt, an important part of Africa with a population of more than 100 millions of people. ***Summary:*** Given Egypt's distinctive social and demographic characteristics, it is highly recommended to employ specific, recently developed epidemiological techniques for assessing the prevalence and incidence of these diseases within the country. By utilizing these methods, we can gather invaluable data that will contribute to a deeper understanding of ALS and enable us to effectively address its impact on the population of Egypt. ***Key Messages:*** Our goal with this pioneering ALS/MND population-based register in Egypt is to define the burden of ALS in this part of Africa and to increase the chances for this consanguineous population to get access to modern individualized genetic therapies. Additionally, we aspire to uncover potential environmental factors and gene-environment interactions that contribute to the development of ALS. This knowledge of MND individual and group risk in Egypt will not only open doors for interventions but also provide opportunities for future research and discovery.

Significance of Epidemiological Studies beyond Europe and North America

The worldwide standardized incidence rate of amyotrophic lateral sclerosis (ALS) was estimated to be 1.68 per 100,000 person-years (95% CI: 1.50–1.85), yet it varied with sex, age, and geography [1]. Genetic factors linked to populations' ancestries, along with environmental and lifestyle factors, seem to play a significant role in the occurrence of ALS and the variation in incidence, prevalence, and mortality across different populations and geographical areas. Nevertheless, epidemiological research on ALS is currently lacking in large regions of

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the world, specifically in Africa, the majority of Latin America, Eastern Europe, and South and Central Asia.

The global, regional, and national burden of motor neuron diseases (MND) was analyzed for 195 countries and territories from 1990 to 2016 as part of the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2016. The distribution of MND among countries with different sociodemographic indexes (SDI) showed that high SDI countries, especially North America, Western Europe, and Australasia, had the highest burden (48.9%), followed by high-middle SDI countries (15.2%), and then the low SDI countries (2.6%). SDI is a composite indicator of development status based on a single country's education, fertility, and gross product [2]. The age-standardized incidence increased by 13% in the high SDI groups but was stable for the other groups [3]. This could be explained by improved survival due to medical advancements, definite diagnosis, case ascertainment, and robust surveillance systems. ALS research and clinical trials in the USA and Europe also increased public awareness about MND. Intriguingly, the MND burden in the high-income Asia Pacific region was lower than what was reported for other countries in the same SDI level, in addition to differences in genetic and clinical characteristics, such as age at onset, disease duration, and clinical subtype if compared to Europe. Thus, the MND burden must be influenced by factors other than socioeconomic status. Interestingly, none of the 84 risk factors quantified in GBD could explain the geographical heterogeneity of MND burden, suggesting a role of race, ancestral origin, and unmeasured risk factors [4–6]. The prevalence and incidence of MND in South Australia were considerably higher than global estimates [7], while other studies reported lower ALS incidence and prevalence outside populations of European origin. Studies in the USA showed higher ALS rates in Caucasians of non-Hispanic ancestry than those of Hispanic, African, and Asian ancestry [8–10]. The recent studies by the Latin American Epidemiology Network for ALS (LAENALS), focusing on three populations with varying degrees of ethnic and genetic admixture, Chile, Cuba, and Uruguay, showed significantly lower mortality rates in the mixed population than in whites and blacks [11, 12]. Population-based mortality studies in Cuba [13] and Ecuador [14] support the hypothesis that ALS occurrence is lower in admixed populations from Latin America compared to other ethnics. Other studies performed in the USA [15–17] and the UK [18] reported a lower mortality among "non-white" than "white" patients. A comparison of ALS patients from Uruguay and Limousin in France revealed that mean ages at onset and diagnosis were significantly lower in Uruguay compared to Limousin (61 vs. 66 years), and Uruguay patients demonstrated more advanced disease at diagnosis, and shorter median survival from time of diagnosis (19 vs. 28 months) [19]. Moreover, differences between the Cuban and Irish genetic signature in terms of known ALS-associated genetic variants were reported [20]. Overall, these studies further support the nonuniform distribution of ALS worldwide and the role of ancestry.

Current Knowledge about ALS in Africa

Africa is characterized by its expansive landmass and rich cultural heritage. The continent boasts numerous ethnic groups, each with its unique traditions, languages, and customs. Furthermore, Africa's population exhibits remarkable racial diversity, encompassing various phenotypes and genetic backgrounds. Additionally, a wide range of religious beliefs and practices thrives across the continent, including Christianity, Islam, traditional African religions, and various other faiths.

Characteristics of ALS among African Populations

Population-based studies on ALS are still lacking on the African continent. The few studies on ALS in African populations were mostly case series that vary in methods, sample sizes, and collected data. Marin and colleagues highlighted some specific characteristics related to phenotype and prognosis after reviewing 35 studies on ALS among Africans across different geographic areas and ethnicities [21]. The male predominance was remarkable, with a median male-to-female sex ratio (SR) of 2.75. Although the same observation was reported in Europe and USA some decades ago [8], the SR has changed in Europe, and it is now approaching unity [22, 23]. Beyond the demographic development [23], this change in the SR has been attributed to changes in the exposure of females to possible environmental factors, such as smoking [24]. It remains to be confirmed whether the higher SR in African ALS patients is real or is due to sex-driven different access to specialized neurological care.

The most striking finding in Africa is the early onset of classic ALS with an estimated overall mean age at the onset of 50 years [21], corresponding to roughly 1 decade earlier than Caucasians and Japanese [22]. However, the mean age at onset varies between clinical series across Africa, ranging from 40 years in some countries [21] to almost 60 years in others [25]. Similarly, younger age at

onset was reported in African-American patients (55 years) when compared to Caucasian-American patients (61 years) [26]. Juvenile forms of ALS/MND have been reported across African countries [21, 27, 28], yet a clear definition with an agreed cutoff age is necessary for future epidemiological studies. The early-onset age observed in non-European populations may suggest an age-related shift in vulnerability threshold in non-Europeans who develop the disease.

None of the African studies addressed the incidence and mortality of ALS/MND. A recent prospective incidence study of ALS/MND in South Africa reported a crude incidence rate of 1.09 per 100,000 person-years. The overall age- and sex-adjusted incidence rate (ASAIR) was 1.67. The highest ASAIR was found in the European ancestry group (2.62), while the lowest ASAIR was in the African ancestry group (0.56). The age-specific incidence rates peak approximately 10 years earlier in people of African ancestry, compared to European and mixed ancestry, and reach a plateau after the age of 50 years [29]. African survival data are scarce due to difficulties in the follow-up, and no studies addressed prognostic factors for African ALS patients [21]. Collectively, these findings support the previously reported lower ALS frequency in people of African and Asian ancestry compared to whites [4, 5, 8, 10]. Large-scale population-based studies are needed to assess the clinical and epidemiological features of ALS among various African (and Asian) populations compared to other ancestral populations.

The first multicenter, hospital-based cohort study investigating ALS in Africa was published in 2019 within the TROPALS Collaboration (Etude Epidémiologique de la Sclérose Latérale Amyotrophique sous les Tropiques: http://www.tropals.unilim.fr/) [30]. The study included 185 ALS patients from nine Northern, Western, and Southern African centers. A standardized questionnaire and a homogeneous methodology were used to describe and compare the sociodemographic and clinical features, treatments, prognoses, and, for the first time, the survival times. Overall, SR was 2.9, and the median age at onset was 53 years, which agrees with the previous reports [21]. Bulbar onset was found in 22.7% of the patients, supporting the previous observation that bulbar ALS is more dominant in European than in African and Asian populations [4–6, 31]. The median survival time was 14 months from diagnosis and 35 months from disease onset, which is similar to data from Europe and North America, showing a median survival time of 13–25 months (since diagnosis) and 25–35 months (since onset) [6].

ALS Management in Africa

A multidisciplinary approach is essential for the optimum management of ALS patients. The availability and affordability of such multidisciplinary care were analyzed in eight African countries within the TROPALS collaboration [32]. Although continuous evaluation of respiratory function is a crucial pillar of ALS management, respiratory specialists were lacking in half of the centers, and palliative care was available in only three of the centers assessed. Riluzole was available in four out of nine centers but was unaffordable; its price was highly variable across African countries, and the cost was either partially or totally covered by patients. Previous studies reported that only 26.3% of African ALS patients received riluzole [30]. Taken altogether, the support of governments and health-insurance systems is crucial for a better disease outcome. A recent study comparing South Africa and Portugal reported that noninvasive ventilation was introduced in half of Portuguese but only a quarter of South African patients, and none of the South African patients used riluzole, while 100% of Portuguese patients did. These differences in care could contribute to the significantly higher mortality rates in the South African cohort at both 12 months (35% vs. 16%) and 24 months (63% vs. 39%) [25].

Feasibility of Establishing an MND Registry in Egypt

Egypt, located at the northeastern corner of Africa, has been a crossroads of civilizations, serving as a bridge between Africa, Asia, and Europe. Ancient Egypt itself witnessed interactions with neighboring cultures, including Nubians, Greeks, Persians, Romans, and Arabs. These interactions left lasting imprints on Egypt's cultural landscape, contributing to its diversity. Egyptians, primarily of Arab descent, form the majority, while Nubians, Berbers, and Beja people contribute to Egypt's ethnic diversity. The historical interactions and migrations across the Mediterranean and Red Sea have contributed to Egypt's racial diversity, reflecting a blend of Arab, Mediterranean, African, and Middle Eastern influences. Islam is the predominant religion, with significant Christian communities, including Coptic Christians tracing their roots to ancient Egypt. Egypt stands as a testament to the complexities and interconnections of human civilizations, offering opportunities for cross-cultural and no doubt first-cousin marriage for study, and reflecting the diverse heritage and contributions that have shaped the African continent as a whole.

The Methodology: The Reconstructed Cohort Design

Estimating the incidence of rare diseases like ALS using traditional cohort studies is not feasible due to the requirement of a large participant pool (many millions of subjects) to be visited in person and to diagnose only a few cases. The diagnostic process is particularly difficult because specialized expertise in MND to have an accurate diagnosis is needed. Continuously monitoring disease occurrence during follow-up visits can be complicated and expensive, especially without sufficient funds. A cost-effective alternative is the use of a "reconstructed" cohort design to estimate the incidence of rare diseases [33]. This approach involves creating a theoretical cohort by collecting case information from a well-defined geographic area through a surveillance system supported by an effective referral network connecting all healthcare system levels, from primary to tertiary care. Given the low prevalence of ALS, it is reasonable to assume that all individuals in the specified region are at risk of developing ALS, excluding the few existing cases. The incidence rate is then calculated as the ratio between the number of diagnosed cases (numerator) and the total time individuals in the reference population was at risk during the study period (denominator). The reconstructed cohort method was used in different parts of the world, lastly to estimate the incidence of FTLD-associated disorders in Europe [34]. The proposed registry will be constructed after obtaining IRB approval and patients will be asked to give their informed consent for inclusion of their data in the registry.

The Denominator: Census Data in Egypt

The reliability of the information provided by any registry depends on the quality of the data collected. According to the reconstructed cohort design, the denominator is based on the statistics of the regional demographics at a certain point in time. Thus, without proper census data, the estimation of prevalence and incidence is not feasible. In Egypt, the Central Agency for Public Mobilization and Statistics (CAPMAS) in the Ministry of Planning is responsible for generating population census data made available for public use in Arabic and English (https://www.capmas.gov.eg/). The administrative division of Egypt comprises 27 Governorates that are subdivided into districts (http://www.citypopulation.de/en/egypt/admin/). Demographic information is provided for each district within the respective governorate [35]. These census data are produced at 10-year intervals; the upcoming updates will be generated in 2027.

Expertise in Neuromuscular Diseases in Egypt

Including all incident cases in the numerator is crucial for accurately determining ALS incidence in the area of interest and ensures a complete identification of the disease phenotypic spectrum, including those that might be overlooked otherwise. In highly populated countries like Egypt, with currently around 105 million inhabitants (https://worldpopulationreview.com/countries/egypt-population), accurately determining the number of ALS cases can be methodologically challenging. The goal of our population-based study is not to cover all Egypt, but to select specific geographic areas characterized by the presence of a center specialized in neuromuscular diseases and to choose the surrounding geographical areas where a complete case ascertainment is highly likely.

Multiple data sources are necessary to capture all potential incident cases, which is especially difficult for complex diseases like ALS, requiring specialized knowledge and experience in the field of neuromuscular disorders [36]. According to the World Health Organization (WHO), there is a global shortage of adult neurologists (0.43 per 100,000 population), with the lowest numbers observed in the African Region (0.04 per 100,000 population) and in low-income countries (0.03 per 100,000 population) in comparison to high-income countries (median of 4.75 per 100,000 population) [37]. Data on the number of neurologists in Egypt are unavailable. However, a survey of middle- and high-income Arab countries revealed that most neurologists are concentrated in large cities, resulting in varied patient-to-neurologist ratios ranging from 35,000 to over 2 million. Most neurologists had received extensive training in neurology and or passed specialty exams, and the majority had all or part of their training abroad [38]. Across 50 African countries, only Egypt and Algeria had more than 200 neurologists, and only six countries, including Morocco, Nigeria, South Africa, and Tunisia, had 30–200 neurologists [39]. Postgraduate training programs in neurology exist only in a minority of European countries and are limited in many countries, including Egypt, highlighting the need for improvement in medical education [40]. The scarcity of neurologists in certain countries increases the likelihood of nonspecialist primary care providers managing neurological patients, leading to delays in diagnosis, inadequate treatment, and poorer outcomes in terms of quality of life and mortality rates.

Despite the availability of numerous public and private healthcare providers in Egypt, only a few specialized neuromuscular centers exist. The Neuromuscular Unit of Ain Shams University (NMU-ASU), in the capital city Cairo, is the only specialized and comprehensive unit of

MND in Egypt. It was established in 1996 by the Neuropsychiatry Department and includes specialized laboratories for histopathology, immunohistochemistry, and genetic analysis, in addition to a biobank for muscle biopsies and biological samples. It is a referral tertiary center for all neuromuscular disorders, including ALS patients from all over Egypt and from the neighboring countries. The myology clinic serves around 50 outpatients weekly. This unit conducted many research studies on various neuromuscular disorders, including congenital neuromuscular disorders, Duchenne/Becker muscular dystrophy, limb-girdle muscular dystrophy, inflammatory myopathies, osteomalacic myopathy, myasthenic disorders, ALS, spinal muscular atrophy (SMA), and hereditary neuropathies and hereditary ataxias. The unit also attracted national and international collaboration and recently became one of the leading centers for gene therapy of SMA. Moreover, it offers young neurologists and researchers regular training in the field of neuromuscular disorders. Recently, two other centers became available for MND patients. Nasser Institute for Research and Treatment, one of the specialized medical centers of the Ministry of Health (MOH), was assigned as a treatment center for SMA patients within the frame of the presidential initiative to treat children with SMA at the state's expense. In addition, the International Medical Center (IMC) is a high-standard hospital with a specialized ALS multidisciplinary clinic established in 2019. It offers care for MND patients, especially gene therapy for SMA patients.

The Area

The main eligibility criterion for registries is a residency in a specific geographic region. Based on the low incidence rate of ALS, a region with at least one million residents is needed for a 1-year study, although regions with 3–5 million residents are preferable [33].

We are trying to build up a system based on the reconstructed source population sampling from different geographical areas in Egypt starting our project from Cairo. The capital city, Cairo, is the third largest urban area in the Islamic World and the largest city in Egypt. Cairo is a major city, as the second largest city of Alexandria is only 30% of Cairo's size. Cairo currently hosts over 10 million inhabitants and spread over 453 km^2. People living in Cairo benefit from a good infrastructure, with good access to both public and private entities of Egypt's healthcare system. The high number of inhabitants, the good infrastructure, and the accessibility to specialized centers for neuromuscular diseases make Cairo a suitable region for establishing an MND register. In addition to the capital city Cairo, our initiative also includes 4 other governorates with active neuromuscular centers, namely Alexandria (5.5 million individuals), Dakahlia (around 7 million individuals), Assiut (around 5 million individuals), and Gharbia (5.4 million individuals). The demographic characteristics of the five governorates are detailed in Table 1.

The Network for Counting the Numerator: Network of Neuromuscular Centers

In a population-based disease registry using a reconstructed cohort design, collecting incident cases involves identifying a network of diagnostic facilities to which individuals diagnosed with or suspected of having the targeted disease are referred for confirmation. The selection of these facilities is determined by the specific characteristics of the disease in question and the healthcare system within the defined geographic region.

The Healthcare System in Egypt

The healthcare system in Egypt is diverse, consisting of public and private providers. Various public entities, such as Ministry of Health (MOH), Ministry of Higher Education (MOHE), and other ministries' hospitals (e.g., Aviation, Defense, Interiors), participate in delivering health services. The main focus of the MOH is to provide primary, preventive, and curative care through its healthcare facilities, while other public healthcare providers primarily concentrate on delivering secondary and tertiary healthcare services. Alongside service provision, the MOH plays a crucial role in formulating national health policies and regulating the healthcare sector in areas such as finance, private and public service provision, and the pharmaceutical sector. However, the Ministry of Social Solidarity (MOSS) plays a vital role in bolstering the healthcare system by offering comprehensive support and assistance to persons with disabilities, including MND like SMA and ALS. The MOSS has spearheaded the "We will deliver to you" campaign that aligns with Egypt's commitment to ensure the rights of individuals with disabilities, provide them with essential services, and raise awareness among all societal groups about their rights. This initiative aims to issue one million integrated services cards to individuals with severe disabilities and critical cases across the governorates of the Republic. Moreover, the MOSS has taken charge of an extensive campaign to regulate and govern electronic donations, which are utilized to acquire expensive medications for rare diseases, including neurodegenerative diseases like SMA (https://www.moss.gov.eg/).

Table 1. Demographic details of the five governorates included in the establishment of a motor neuron population-based registry in Egypt

Governorates included in the study	Inhabitants (in million)		Sex distribution		Age distribution	
			male, %	female, %	below 50	above 50
Cairo	Total: 9,437,698		52	48	Urban 7,713,387	1,724,311
	Urban 9,437,698	Rural –			Rural –	–
Alexandria	Total: 5,163,441		51.4	48.6	Urban 4,184,798	910,350
	Urban 5,095,148	Rural 68,293			Rural 61,513	6,780
Dakahlia	Total: 6,491,898		50.9	49.1	Urban 1,519,944	315,370
	Urban 1,835,314	Rural 4,656,584			Rural 3,946,464	710,120
Assiut	Total: 4,383,116		51.7	48.3	Urban 969,756	165,197
	Urban 1,134,953	Rural 3,248,163			Rural 2,860,265	387,898
Gharbia	Total: 4,999,487		51.1	48.9	Urban 1,138,850	266,368
	Urban 1,405,218	Rural 3,594,269			Rural 3,024,078	570,191
All governorates studied	Total: 30,475,640		Mean %	Mean %	Urban 15,526,735	3,381,596
	Urban 18,908,331	Rural 11,567,309	51.42	48.58	Rural 9,892,320	1,674,989
Total Egypt	Total: 94,694,016		Mean %	Mean %	Urban 33,653,129	6,482,974
	Urban 40,136,103	Rural 54,557,913	51.5	48.5	Rural 48,353,161	6,204,752

Numbers are based on 2017 statistics report [31].

In Egypt, public university hospitals have a multifaceted role, encompassing education, research, and healthcare services, making them integral to the healthcare landscape. These hospitals are often the preferred choice for many Egyptian patients due to the widespread belief that the presence of academic staff within the hospital premises ensures a higher quality of care. This perception holds particular significance in Egypt, where most of the population belongs to low- and middle-income economic strata. Consequently, the presence of large public hospitals assumes strategic importance in the effective delivery of public services. According to the latest data from CAPMAS, public facilities provided 75% of Egypt's available hospital beds, 93,267 out of 124,361. Public university hospitals, which fall under the authority of the MOHE, serve as secondary and tertiary care facilities. Egypt hosts more than 20 medical faculties [41] and 115 hospitals and medical centers in State universities (https://mohesr.gov.eg/en-us/Pages/univ-hostpitals.aspx). Unlike MOH facilities, university hospitals are known for their advanced technology and specialized medical expertise. Among these university hospitals, Cairo University Hospital is the oldest and stands out as the largest, housing over 5,000 beds.

Regarding the private healthcare sector in Egypt, many physicians who work in governmental hospitals also manage their private practices. The collaboration and integration between the private and public sectors play a vital role in facilitating the incorporation of the private healthcare system into the network of public entities.

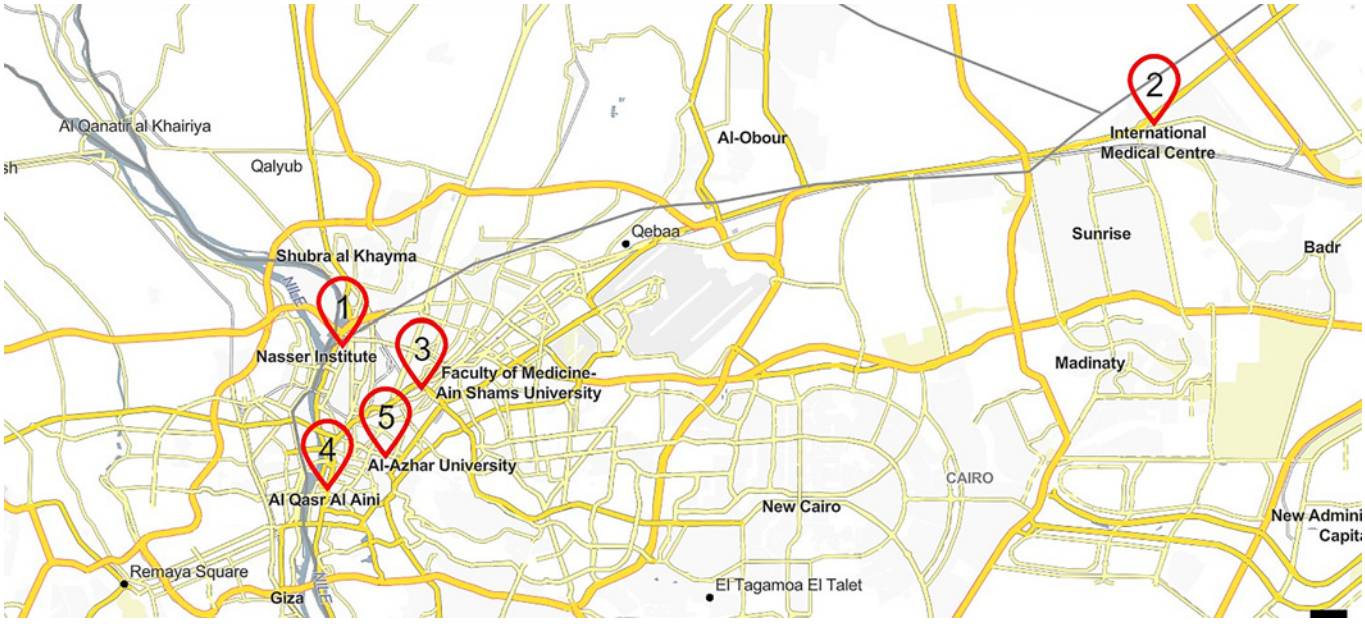

Fig. 1. Map of Cairo, showing the five neuromuscular clinical centers involved in the establishment of a motor neuron population-based registry in Egypt.

The MND Network in Cairo

To maximize the identification of MND cases, a well-designed network for population-based studies is crucial. Starting in Cairo, our proposed network (Fig. 1) includes an effective referral system that seamlessly links all healthcare services, facilitating comprehensive data collection and analysis for population-based studies. Nasser Institute for Research and Treatment is one of the specialized medical centers of the Ministry of Health and Population. It was assigned as a treatment center for SMA patients within the presidential initiative to treat children with muscle atrophy at the state's expense. The MOHE university hospitals are represented by the University Hospital of Ain Shams University, to which the NMU-ASU belongs, and Kasr Al Ainy Hospital, which belongs to Kasr Al Ainy Faculty of Medicine, Cairo University. In addition, Al-Azhar University is under the responsibility of the Central Administration of Al-Azhar Institutes, a department of the Supreme Council of Al-Azhar. Al-Azhar University is the only public higher education institution outside the jurisdiction of the MOHE. The International Medical Center (IMC) is a Military hospital, one of the largest tertiary healthcare hospitals in the Middle East. The IMC is part of the Armed Forces Medical Service Department, providing healthcare services to military personnel and privately insured local and international patients. The Egyptian Armed Forces established this large, high-standard hospital with American expertise and cooperation. It follows an international standard of patient care, utilizing Egyptian and American patient care team management. It has an ALS clinic and offers specialized care for MND patients, especially gene therapy for SMA patients.

The MND Network outside Cairo

In addition to the five neuromuscular centers based in Cairo, four active centers in university hospitals located outside Cairo, with expertise in diagnosis and treatment of neuromuscular disorders, will participate in our study (Fig. 2). Alexandria Neuromuscular Unit is a part of the Neurology Department at Alexandria University (northern coast of Egypt) and comprises a weekly neuromuscular clinic with a neurophysiology unit. Mansoura (capital city of Dakahlia Governorate, Northern Egypt) Neuromuscular Unit is part of the Neurology Department at Mansoura University and comprises a weekly neuromuscular clinic with a neurophysiology unit and neuromuscular ultrasonography. Assiut (Upper Egypt, in southern Egypt) Neuromuscular Unit is part of the Neurology Department at Assiut University and comprises a weekly neuromuscular clinic with a neurophysiology unit and a neuroepidemiology unit that is experienced with door-to-door epidemiological studies on neurodegenerative and neuromuscular disorders [42, 43]. Tanta (capital city of Gharbia Governorate, between Cairo and Alexandria) Neuromuscular Unit is part of the

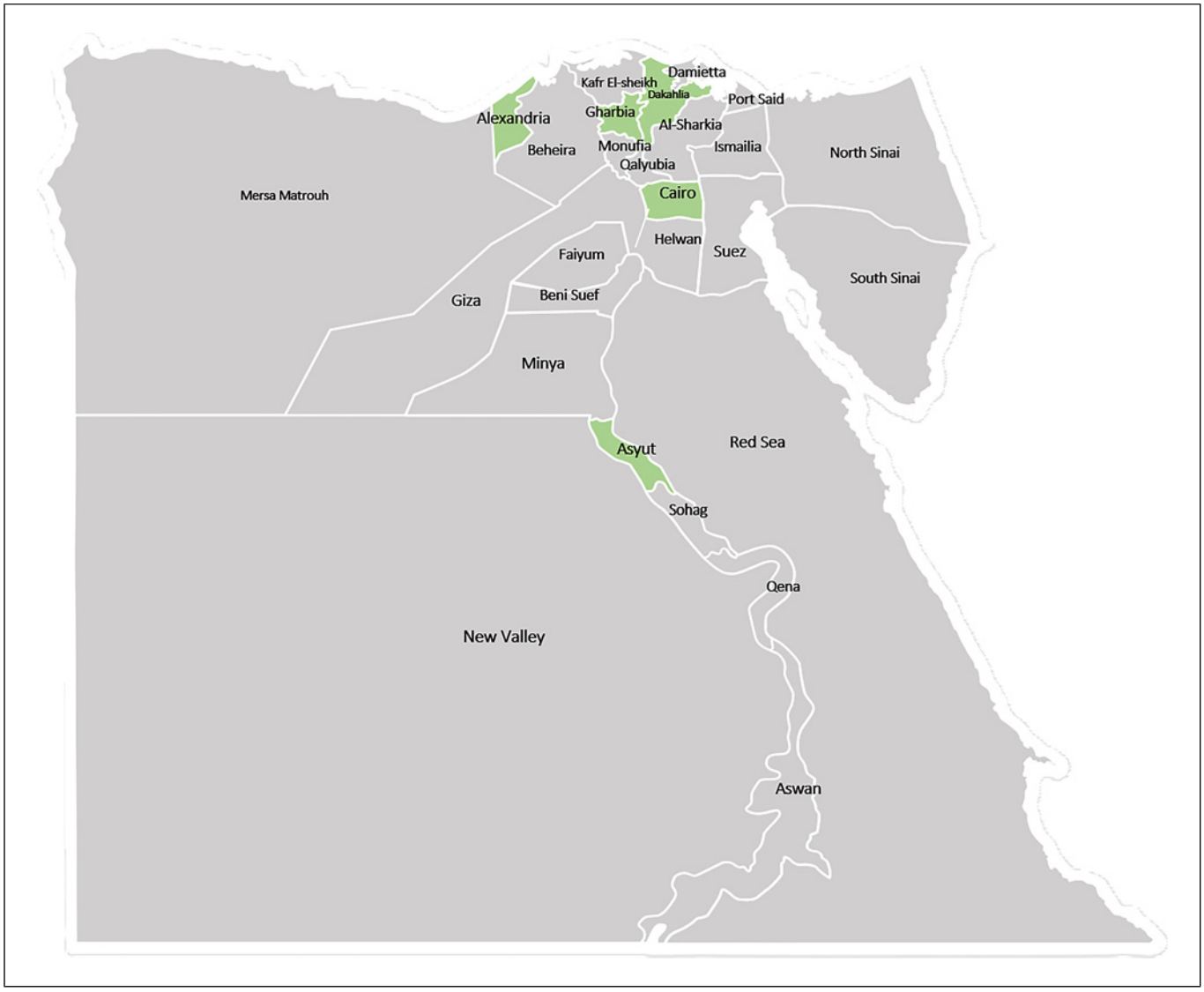

Fig. 2. Map of Egypt, showing the five governorates involved in the establishment of a motor neuron population-based registry in Egypt.

Neurology Department at Tanta University and comprises a weekly neuromuscular clinic with a neurophysiology unit and neuromuscular ultrasonography.

Our Approach

The starting steps of building up a population-based registry with a reconstructed cohort design are two. First, the network of the tertiary centers mentioned above has been built. Second, the identification based on the knots of the network will include the surrounding geographic areas with likely complete case ascertainment and perfect knowledge of the sex and age distribution of the source population. We have established the first step in 2018, where the NMU-ASU initiated the construction of a hospital-based register after receiving the ethical approval from the Ethics Committee of Ain Shams University (FMASU MS67/2018). The register encompasses a cohort of more than 180 ALS patients. The comprehensive assessment of these patients includes clinical evaluation and laboratory, neurophysiological, and radiological examination. Patients' management was conducted in the same hospital's daycare, in-patient, and intensive care units. Furthermore, the NMU-ASU showcased its dedication to international collaboration and standardization by participating in the Ulm International Meeting on ALS and FTD-Genetic and Metabolic Epidemiology in 2020.

Standardized questionnaires for future interpopulation comparison were consolidated during the conference and fruitful discussions were held on establishing international ALS registers, enabling future interpopulation comparisons.

Previous Experience with Registries in Egypt

In Egypt, the most robust experience with registries is in the field of cancer. The National Cancer Registry Program (NCRP) is the first to report cancer incidence rates on the regional and national levels in Egypt. It was established in 2007 through a protocol of cooperation between 3 ministries: Communication and Information Technology (MCIT), Health (MOH), and Higher Education and Scientific Research (MHE). The NCRP stratified Egypt into three geographical regions: Lower, Middle, and Upper Egypt. Three governorates were considered for registration purposes, each representing one of these regions. Due to logistic difficulties, this population-based registration did not cover the capital city, Cairo. However, the central registry in the National Cancer Institute, Cairo University, captured patient data from the governorates covered by the program diagnosed by or referred to the Institute [44].

The incidence rates were calculated using data from cancer patients residing in the selected governorate and treated in major cancer care facilities within and outside the governorates to maximize case ascertainments. The denominator was based on the 2006 census data of the regions studied (https://censusinfo.capmas.gov.eg/Metadata-ar-v4.2/index.php/catalog/1337). National incidence rates were then estimated through computer models using the regional incidence rates [44].

Characteristics of ALS in Egypt

Currently, relying solely on patients and their families for information collection poses challenges in terms of tediousness, incompleteness, and potential misinformation. This is especially true when gathering accurate medication and family history for neuromuscular diseases or other neurological disorders. Obtaining data related to disease progression, life expectancy, and causes of death becomes even more difficult, as maintaining regular follow-up contact with patients and their families can be challenging. Transporting patients in advanced disease stages for follow-up visits presents additional hurdles. Additionally, the psychological impact of revealing an ALS diagnosis without offering curative treatments demotivates patients and caregivers from seeking further medical assistance. However, with the hope of future therapeutic advances for ALS and the availability of new drugs for patients in Egypt, we anticipate a shift in the perspective of patients and caregivers.

In NMU-ASU, questionnaires have been used to collect clinical and epidemiological data for ALS patients. Biological sample collection protocols have also been implemented. ALS diagnosis follows standard evaluations such as EMG and MRI studies and is based on El-Escorial diagnostic criteria after examination by experienced neurologists. Recently, the two most widely used clinical scales, the revised ALS functional rating scale (ALSFRS-R) and the Edinburgh Cognitive and Behavioral ALS Screen (ECAS), were validated for Arabic/Egyptian-speaking patients. For the ALSFRS-R validation, 162 Egyptian ALS patients were enrolled at NMU-ASU and the ALS clinic at IMC [45]. For the ECAS validation, patients were enrolled at NMU-ASU [46]. These scales have shown good reproducibility and validity among Egyptian ALS patients and are currently used in clinical practice and research for evaluating Arabic-speaking patients. However, for a multicenter ALS registry, a limited number of well-defined variables should be established for successful data management. This will help in creating a simple, user-friendly web-based registry. A minimal data set will be shared with different centers involved in the MND register.

Comparison with EU Population-Based Registries

In Europe, long-standing collaborative efforts have led to the development of successful population-based registries. The European ALS Consortium (EURALS) was established by the European Neuromuscular Center (ENMC) after the creation of country-based registries in Scotland, England, Ireland, and selected regions in Italy. EURALS provides a database for ALS patients from participating countries and updates on sporadic and familial ALS epidemiology. The Swabia register, an ongoing regional register in Southwest Germany, covers a target population of 8.4 million residents. It began in 2010 and included a case-control study with over 400 cases and 800 controls. Since then, more than 200 patients per year have been recruited and followed up, achieving a register completeness rate

Table 2. Comparison of the main characteristics of ALS patients residing in Cairo versus ALS patients residing outside Cairo

Disease characteristics	Cairo residents	Non-Cairo residents
Percentage	58.3% (*N* = 105)	41.7% (*N* = 75)
Age at onset (mean±SD)	40.44±14.75	37.64±13.44
Time from onset to diagnosis, months (mean±SD)	23.29±22.95	27.97±29.47
Onset spinal/bulbar, %	77.8/22.2	74.5/25.5
ALSFRS-R at diagnosis (mean±SD)	33.68±8.39	32.74±9.22
Male-to-female ratio	2.36	3.07

of over 80%. Biomaterials have been collected from over 70% of participants [47].

The hospital-based register of NMU-ASU comprises around 200 ALS patients, with familial cases representing 18%, being higher than the commonly reported 5–10%. Preliminary data reveal remarkable differences in basic patient characteristics compared to Swabia register and EURALS. The male predominance is more striking in Egypt than in Europe, with an SR of 3.7 despite an SR close to 1 in the general population (49.4% females and 50.6% males) (https://datareportal.com/reports/digital-2023-egypt). According to the Swabia register, the mean age at onset is around 65 years and the age-adjusted incidence peaks at the age of 70–75 years with an SR of 1.1 [48]. According to EURALS, ALS incidence peaks at 75–79 years of age for women and 70–74 in men, with an SR of 1.2 [22, 49]. The mean age at onset according to the NMU-ASU register is 42 ± 13.61, and it is still not clear why the onset of ALS is much earlier in Egypt than in European populations [46], knowing that the median age of the Egyptian population is 24.2. The average diagnostic delay was 12 months, ranging from 6 to 36 months, which is longer than the time to diagnosis in Europe and North America being generally 10–16 months [50]. This diagnostic delay could be attributed to several factors, including the initial misdiagnosis of this clinically heterogeneous disease by non-experienced clinicians and the lack of specialized centers for MND. Based on a small Egyptian study comprising 30 ALS patients [45], the average diagnostic delay was 20.7 ± 21.1 months for women versus 17.6 ± 13.6 months in men, and limb onset, female gender, and young age at onset correlated with an increased mean time to diagnosis. Moreover, bulbar-onset patients were diagnosed earlier than limb onset patients (mean lag of 8.2 ± 2.57 months vs. 22.95 ± 17.6 months, respectively) [45]. According to the NMU-ASU register, classical phenotype (spinal or bulbar) represents nearly 90% of all phenotypes. Consanguinity, encountered in 34% of the cases, increases the likelihood of early-onset cases and the discovery of novel homozygous mutations [27].

In complex diseases like MND, it is fundamental to consider the heterogeneity of disease characteristics in population-based settings. Variations in the genetic background (ancestry), along with epigenetic factors, are evident to produce phenotypic divergence that encompasses age at onset/diagnosis, sex ratio, and disease onset, and even extends to comorbidities. Meta-analysis of population-based studies reflecting ten subcontinents showed a significantly higher incidence of bulbar ALS coupled with shorter survival time in Northern Europe compared to other European subcontinents and other parts of the globe. Male predominance was consistent across different populations; nevertheless, the higher the SR, the younger the onset of ALS [6]. According to the database of the NMU-ASU, 58% of ALS patients who visited the unit in the past years have lived in Cairo. The remaining ALS patients who have lived outside Cairo were distributed as follows: 37% from the Nile Delta region in Lower Egypt (Northern Egypt), where the Nile River spreads out and drains into the Mediterranean Sea, 43% from Middle Egypt, 14% from Upper Egypt (Southern Egypt), and 6% from the Suez Canal region (Eastern Egypt) that connects the Mediterranean coast and the Red Sea. Preliminary data from NMU-ASU show that ALS patients residing outside Cairo are characterized by a younger age at onset (37.6 years), a higher percentage of bulbar onset (25.5%), a longer mean time to diagnosis (28 months), a higher SR (3.07), and a slightly lower ALSFRS-R score (32.7) when compared to ALS patients residing in Cairo (40.4 years, 22.2%, 23 months, 2.36, and 33.7, respectively) (Table 2). This divergence of valuable disease characteristics within populations could be largely masked in the case of reports and case series. Nevertheless,

these differences may be explained by referral bias, with younger male patients investing more effort and finances to reach a tertiary clinic.

Limitations

We are aware that solving the problem of under diagnosis is challenging. In every survey on chronic diseases, we consistently encounter quotes from patients who have never received a proper diagnosis. According to the 2017 Statistics Report, approximately 42.4% of the population (around 43.6 million individuals) resides in urban areas. However, due to the diverse characteristics of healthcare systems worldwide, under ascertainment of cases in rural areas will likely remain a limitation. We aim to ensure that our sample is adequately representative. Our initiative involves nine centers located in five different governorates, which represents approximately 32% (around 30 million individuals) of Egypt's total population. Among these five governorates, Cairo and Alexandria are predominantly urban cities, while the remaining three governorates have a mix of urban and rural areas (Table 1). We have therefore the possibility to compare urban and rural areas in our study.

Conclusions

In many parts of the world, across North and South America, Europe, and Asia, the sustainable collaboration between clinical centers, regions, and countries has enabled the creation of platforms to study the natural history of ALS and its clinical and epidemiological characteristics [51, 52]. If the political intention that Africa will have the same opportunity to access Health Care as other populations in the world will ever become a reality, an epidemiological understanding of the specific diseases is the prerequisite. Descriptive epidemiology needs a new approach based on the advancement of diagnostic criteria, including both clinical and biological characteristics. This needs to be pursued in high-, medium-, and low-income countries to have early biological diagnosis of the disease [53]. This is true not only for basic data like disease incidence and prevalence but also for a deeper understanding of the genetics and environmental factors contributing to the local phenotype. It is well known that genetic advances have not involved African populations yet [54]; however, genetically based therapeutic interventions [55–58] are powerful tools to reduce the burden of genetic disease-causing factors. MND are different worldwide [3, 6, 13]. However, region-specific environmental factors are also important. In Africa, ALS mimics such as neurolathyrism (caused by consumption of *Lathyrus sativus* [59]) and cassava-associated MND such as Konzo [60] are prominent examples. The role of nutrition and metabolism in the pathogenesis of ALS postulates that malnutrition and catabolism are risk factors for ALS that can be used to implement preventive measures.

This initiative presents a unique opportunity to alleviate the burden of ALS in Egypt through collaborative efforts and gain valuable insights into the pathogenesis and potential therapeutic options for ALS and other MND worldwide. Therefore, an Egyptian population-based registry for MND initiative – which could be politically supported – offers.

1. The opportunity to survey and identify the burden of the dreadful disease ALS in Egypt, where the disease has a presumably young- or middle-aged onset. In this context, we aim to determine the individual and group risk of MND in Egypt.
2. The increasing hope for the consanguineous population to access modern individualized genetic therapies, such as nusinersen and onasemnogene abeparvovec for the recessive disease SMA or gene-based therapy for ALS.
3. The chance to identify environmental factors that are not only crucial for the population of Egypt but also of general importance for preventive interventions, which might modify the epidemiology of ALS worldwide.

This new research initiative will significantly improve our understanding of the diseases and their causes in Egypt and worldwide.

Collaborators Participating to the Registry

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

N.H., A.L., W.A., G.L., and N.F. substantially contributed to the conception and design of the work. O.O. and R.S. contributed to the acquisition, analysis, and interpretation of the data. All authors contributed in drafting the work. A.L., G.L., and N.F. critically reviewed the work for important intellectual content. All authors gave their final approval of the version to be published and agreed to be accountable for all aspects of the work.

References

1 Marin B, Boumédiene F, Logroscino G, Couratier P, Babron M-C, Leutenegger AL, et al. Variation in worldwide incidence of amyotrophic lateral sclerosis: a meta-analysis. Int J Epidemiol. 2017;46(1):57–74. https://doi.org/10.1093/ije/dyw061

2 Moore KA, Vandivere S, Redd Z. A socio-demographic risk index. Soc Indic Res. 2006; 75(1):45–81. https://doi.org/10.1007/s11205-004-6398-7

3 GBD 2016 Motor Neuron Disease Collaborators. Global, regional, and national burden of motor neuron diseases 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2018; 17(12):1083–97. https://doi.org/10.1016/S1474-4422(18)30404-6

4 Daria T, Müller K, Oidovdorj G, Baatar K, Boldbaatar P, Sarangerel J, et al. Genotypes of amyotrophic lateral sclerosis in Mongolia. J Neurol Neurosurg Psychiatry. 2019;90(11):1300–2. https://doi.org/10.1136/jnnp-2019-320640

5 Dorst J, Chen L, Rosenbohm A, Dreyhaupt J, Hübers A, Schuster J, et al. Prognostic factors in ALS: a comparison between Germany and China. J Neurol. 2019;266(6):1516–25. https://doi.org/10.1007/s00415-019-09290-4

6 Marin B, Logroscino G, Boumédiene F, Labrunie A, Couratier P, Babron M-C, et al. Clinical and demographic factors and outcome of amyotrophic lateral sclerosis in relation to population ancestral origin. Eur J Epidemiol. 2016;31(3):229–45. https://doi.org/10.1007/s10654-015-0090-x

7 Luker J, Woodman R, Schultz D. The incidence and prevalence of motor neurone disease in South Australia. Amyotroph Lateral Scler Frontotemporal Degener. 2023; 24(3–4):195–202. https://doi.org/10.1080/21678421.2022.2108326

8 Cronin S, Hardiman O, Traynor BJ. Ethnic variation in the incidence of ALS: a systematic review. Neurology. 2007;68(13): 1002–7. https://doi.org/10.1212/01.wnl.0000258551.96893.6f

9 Roberts AL, Johnson NJ, Chen JT, Cudkowicz ME, Weisskopf MG. Race/ethnicity, socioeconomic status, and ALS mortality in the United States. Neurology. 2016;87(22):2300–8. https://doi.org/10.1212/WNL.0000000000003298

10 Rechtman L, Jordan H, Wagner L, Horton DK, Kaye W. Racial and ethnic differences among amyotrophic lateral sclerosis cases in the United States. Amyotroph Lateral Scler Frontotemporal Degener. 2015;16(1–2): 65–71. https://doi.org/10.3109/21678421.2014.971813

11 Hardiman O, Heverin M, Rooney J, Lillo P, Godoy G, Sáez D, et al. The Latin American epidemiology network for ALS (laenals). Amyotroph Lateral Scler Frontotemporal Degener. 2022;23(5–6):372–7. https://doi.org/10.1080/21678421.2022.2028168

12 Vélez-GóMEZ B, Perna A, Vazquez C, Ketzoian C, Lillo P, Godoy-Reyes G, et al. LAENALS: epidemiological and clinical features of amyotrophic lateral sclerosis in Latin America. Amyotroph Lateral Scler Frontotemporal Degener. 2024;25(1–2): 119–27. https://doi.org/10.1080/21678421.2023.2271517

13 Zaldivar T, Gutierrez J, Lara G, Carbonara M, Logroscino G, Hardiman O. Reduced frequency of ALS in an ethnically mixed population: a population-based mortality study. Neurology. 2009;72(19):1640–5. https://doi.org/10.1212/WNL.0b013e3181a55f7b

14 Luna J, Preux PM, Logroscino G, Erazo D, Del Brutto OH, Boumediene F, et al. Amyotrophic lateral sclerosis mortality rates among ethnic groups in a predominant admixed population in Latin America: a population-based study in Ecuador. Amyotroph Lateral Scler Frontotemporal Degener. 2019;20(5–6):404–12. https://doi.org/10.1080/21678421.2019.1587632

15 Noonan CW, White MC, Thurman D, Wong L-Y. Temporal and geographic variation in United States motor neuron disease mortality, 1969-1998. Neurology. 2005;64(7): 1215–21. https://doi.org/10.1212/01.WNL.0000156518.22559.7F

16 Brand D, Polak M, Glass JD, Fournier CN. Comparison of phenotypic characteristics and prognosis between black and white patients in a tertiary ALS clinic. Neurology. 2021;96(6):e840–4. https://doi.org/10.1212/WNL.0000000000011396

17 Qadri S, Langefeld CD, Milligan C, Caress JB, Cartwright MS. Racial differences in intervention rates in individuals with ALS: a case-control study. Neurology. 2019;92(17): e1969–74. https://doi.org/10.1212/WNL.0000000000007366

18 Elian M, Dean G. Motor neuron disease and multiple sclerosis among immigrants to England from the Indian subcontinent, the Caribbean, and east and west Africa. J Neurol Neurosurg Psychiatry. 1993;56(5):454–7. https://doi.org/10.1136/jnnp.56.5.454

19 Gil J, Vazquez MC, Ketzoian C, Perna A, Marin B, Preux PM, et al. Prognosis of ALS: comparing data from the Limousin referral centre, France, and a Uruguayan population. Amyotroph Lateral Scler. 2009; 10(5–6):355–60. https://doi.org/10.3109/17482960902748686

20 Ryan M, Zaldívar Vaillant T, McLaughlin RL, Doherty MA, Rooney J, Heverin M, et al. Comparison of the clinical and genetic features of amyotrophic lateral sclerosis across Cuban, Uruguayan and Irish clinic-based populations. J Neurol Neurosurg Psychiatry. 2019;90(6):659–65. https://doi.org/10.1136/jnnp-2018-319838

21 Marin B, Kacem I, Diagana M, Boulesteix M, Gouider R, Preux PM, et al. Juvenile and adult-onset ALS/MND among Africans: incidence, phenotype, survival: a review. Amyotroph Lateral Scler. 2012;13(3):276–83. https://doi.org/10.3109/17482968.2011.648644

22 Logroscino G, Traynor BJ, Hardiman O, Chiò A, Mitchell D, Swingler RJ, et al. Incidence of amyotrophic lateral sclerosis in Europe. J Neurol Neurosurg Psychiatry. 2010;81(4):385–90. https://doi.org/10.1136/jnnp.2009.183525

23 Rosenbohm A, Peter RS, Erhardt S, Lulé D, Rothenbacher D, Ludolph AC, et al. Epidemiology of amyotrophic lateral sclerosis in Southern Germany. J Neurol. 2017;264(4):749–57. https://doi.org/10.1007/s00415-017-8413-3

24 Alonso A, Logroscino G, Jick SS, Hernán MA. Association of smoking with amyotrophic lateral sclerosis risk and survival in men and women: a prospective study. BMC Neurol. 2010;10:6. https://doi.org/10.1186/1471-2377-10-6

25 Braga AC, Gromicho M, Pinto S, de Carvalho M, Henning F. A comparative study of South African and Portuguese amyotrophic lateral sclerosis cohorts. J Neurol Sci. 2020;414:116857. https://doi.org/10.1016/j.jns.2020.116857

26 Kazamel M, Cutter G, Claussen G, Alsharabati M, Oh SJ, Lu L, et al. Epidemiological features of amyotrophic lateral sclerosis in a large clinic-based African American population. Amyotroph Lateral Scler Frontotemporal Degener. 2013;14(5–6):334–7. https://doi.org/10.3109/21678421.2013.770030
27 Fahmy N, Müller K, Andersen PM, Marklund SL, Otto M, Ludolph AC, et al. A novel homozygous p.Ser69Pro SOD1 mutation causes severe young-onset ALS with decreased enzyme activity. J Neurol. 2023;270(3):1770–3. https://doi.org/10.1007/s00415-022-11489-x
28 Kacem I, Sghaier I, Peverelli S, Souissi E, Ticozzi N, Gharbi A, et al. Genotype-phenotype correlation in Tunisian patients with amyotrophic lateral sclerosis. Neurobiol Aging. 2022;120:27–33. https://doi.org/10.1016/j.neurobiolaging.2022.08.002
29 Henning F, Heckmann JM, Naidu K, Vlok L, Cross HM, Marin B. Incidence of motor neuron disease/amyotrophic lateral sclerosis in South Africa: a 4-year prospective study. Eur J Neurol. 2021;28(1):81–9. https://doi.org/10.1111/ene.14499
30 Luna J, Diagana M, Ait Aissa L, Tazir M, Ali Pacha L, Kacem I, et al. Clinical features and prognosis of amyotrophic lateral sclerosis in Africa: the TROPALS study. J Neurol Neurosurg Psychiatry. 2019;90(1):20–9. https://doi.org/10.1136/jnnp-2018-318469
31 Abdulla MN, Sokrab TE, el Tahir A, Siddig HE, Ali ME. Motor neurone disease in the tropics: findings from Sudan. East Afr Med J. 1997;74(1):46–8.
32 Luna J, Jost J, Diagana M, Ait Aissa L, Tazir M, Ali Pacha L, et al. Clinical management and disease-modifying treatment for amyotrophic lateral sclerosis in African hospital centers: the TROPALS study. Amyotroph Lateral Scler Frontotemporal Degener. 2022;23(3–4):279–83. https://doi.org/10.1080/21678421.2021.1961806
33 Logroscino G, Kurth T, Piccininni M. The reconstructed cohort design: a method to study rare neurodegenerative diseases in population-based settings. Neuroepidemiology. 2020;54(2):114–22. https://doi.org/10.1159/000502863
34 Logroscino G, Piccininni M, Graff C, Hardiman O, Ludolph AC, Moreno F, et al. Incidence of syndromes associated with frontotemporal lobar degeneration in 9 European countries. JAMA Neurol. 2023;80(3):279–86. https://doi.org/10.1001/jamaneurol.2022.5128
35 Arab Republic of Egypt - General Census for Population. Housing and establishments 2017. EGY-CAPMAS-CENSUS-2017. Available from: https://censusinfo.capmas.gov.eg/metadata-en-v4.2/index.php/catalog/621
36 Traynor BJ, Codd MB, Corr B, Forde C, Frost E, Hardiman O. Amyotrophic lateral sclerosis mimic syndromes: a population-based study. Arch Neurol. 2000;57(1):109–13. https://doi.org/10.1001/archneur.57.1.109
37 Atlas: country resources for neurological disorders. 2nd ed. Geneva: World Health Organization; 2017. Available from: https://apps.who.int/iris/bitstream/handle/10665/258947/9789241565509-eng.pdf. Accessed July 30, 2023.
38 Benamer HTS. Neurology expertise and postgraduate training programmes in the Arab world: a survey. Eur Neurol. 2010;64(6):313–8. https://doi.org/10.1159/000321425
39 Kissani N, Liqali L, Hakimi K, Mugumbate J, Daniel GM, Ibrahim EAA, et al. Why does Africa have the lowest number of Neurologists and how to cover the Gap? J Neurol Sci. 2022;434:120119. https://doi.org/10.1016/j.jns.2021.120119
40 Tamás G, Fabbri M, Falup-Pecurariu C, Teodoro T, Kurtis MM, Aliyev R, et al. Lack of accredited clinical training in movement disorders in Europe, Egypt, and Tunisia. J Parkinsons Dis. 2020;10(4):1833–43. https://doi.org/10.3233/JPD-202000
41 Abdelaziz A, Kassab SE, Abdelnasser A, Hosny S. Medical education in Egypt: historical background, current status, and challenges. Health Prof Educ. 2018;4(4):236–44. https://doi.org/10.1016/j.hpe.2017.12.007
42 El-Tallawy HN, Khedr EM, Qayed MH, Helliwell TR, Kamel NF. Epidemiological study of muscular disorders in Assiut, Egypt. Neuroepidemiology. 2005;25(4):205–11. https://doi.org/10.1159/000088674
43 El Tallawy HNA, Farghaly WMA, Metwaly NA, Rageh TA, Shehata GA, Elfetoh NA, et al. Door-to-door survey of major neurological disorders in Al Kharga District, New Valley, Egypt: methodological aspects. Neuroepidemiology. 2010;35(3):185–90. https://doi.org/10.1159/000314345
44 Ibrahim AS, Khaled HM, Mikhail NN, Baraka H, Kamel H. Cancer incidence in Egypt: results of the national population-based cancer registry program. J Cancer Epidemiol. 2014;2014:437971. https://doi.org/10.1155/2014/437971
45 Rashed HR, Tork MA. Diagnostic delay among ALS patients: Egyptian study. Amyotroph Lateral Scler Frontotemporal Degener. 2020;21(5–6):416–9. https://doi.org/10.1080/21678421.2020.1763401
46 Soliman R, Rashed HR, Moustafa RR, Hamdi N, Swelam MS, Osman A, et al. Egyptian adaptation and validation of the Edinburgh Cognitive and Behavioral Amyotrophic Lateral Sclerosis Screen (ECAS-EG). Neurol Sci. 2023;44(6):1871–80. https://doi.org/10.1007/s10072-023-06639-6
47 Nagel G, Unal H, Rosenbohm A, Ludolph AC, Rothenbacher D; ALS Registry Study Group. Implementation of a population-based epidemiological rare disease registry: study protocol of the Amyotrophic Lateral Sclerosis (ALS)–registry Swabia. BMC Neurol. 2013;13:22. https://doi.org/10.1186/1471-2377-13-22
48 Uenal H, Rosenbohm A, Kufeldt J, Weydt P, Goder K, Ludolph A, et al. Incidence and geographical variation of Amyotrophic Lateral Sclerosis (ALS) in Southern Germany: completeness of the ALS registry Swabia. PLoS One. 2014;9(4):e93932. https://doi.org/10.1371/journal.pone.0093932
49 Beghi E, Pupillo E, Zoccolella S; European Amyotrophic Lateral Sclerosis Consortium EURALS. 148th ENMC international workshop on the scientific contributions of the EURALS consortium on amyotrophic lateral sclerosis. Neuromuscul Disord. 2009;19(5):379–81. https://doi.org/10.1016/j.nmd.2009.02.008
50 Richards D, Morren JA, Pioro EP. Time to diagnosis and factors affecting diagnostic delay in amyotrophic lateral sclerosis. J Neurol Sci. 2020;417:117054. https://doi.org/10.1016/j.jns.2020.117054
51 Cook SF, Rhodes T, Schlusser C, Han S, Chen C, Zach N, et al. A descriptive review of global real world evidence efforts to advance drug discovery and clinical development in amyotrophic lateral sclerosis. Front Neurol. 2021;12:770001. https://doi.org/10.3389/fneur.2021.770001
52 Rechtman L, Brenner S, Wright M, Ritsick M, Rahman F, Han M, et al. Impact of the national amyotrophic lateral sclerosis registry: analysis of registry-funded research. Ann Clin Transl Neurol. 2022;9(11):1692–701. https://doi.org/10.1002/acn3.51660
53 Logroscino G, Urso D, Tortelli R. The challenge of amyotrophic lateral sclerosis descriptive epidemiology: to estimate low incidence rates across complex phenotypes in different geographic areas. Curr Opin Neurol. 2022;35(5):678–85. https://doi.org/10.1097/WCO.0000000000001097
54 Bentley AR, Callier SL, Rotimi CN. Evaluating the promise of inclusion of African ancestry populations in genomics. NPJ Genom Med. 2020;5:5. https://doi.org/10.1038/s41525-019-0111-x
55 Mendell JR, Al-Zaidy S, Shell R, Arnold WD, Rodino-Klapac LR, Prior TW, et al. Single-dose gene-replacement therapy for spinal muscular atrophy. N Engl J Med. 2017;377(18):1713–22. https://doi.org/10.1056/NEJMoa1706198
56 Wurster CD, Ludolph AC. Nusinersen for spinal muscular atrophy. Ther Adv Neurol Disord. 2018;11:1756285618754459. https://doi.org/10.1177/1756285618754459
57 Miller T, Cudkowicz M, Shaw PJ, Andersen PM, Atassi N, Bucelli RC, et al. Phase 1-2 trial of antisense oligonucleotide tofersen for *SOD1* ALS. N Engl J Med. 2020;383(2):109–19. https://doi.org/10.1056/NEJMoa2003715
58 Miller TM, Cudkowicz ME, Genge A, Shaw PJ, Sobue G, Bucelli RC, et al. Trial of antisense oligonucleotide tofersen for *SOD1* ALS. N Engl J Med. 2022;387(12):1099–110. https://doi.org/10.1056/NEJMoa2204705
59 Ludolph AC, Hugon J, Dwivedi MP, Schaumburg HH, Spencer PS. Studies on the aetiology and pathogenesis of motor neuron diseases. 1. Lathyrism: clinical findings in established cases. Brain. 1987;110(Pt 1):149–65. https://doi.org/10.1093/brain/110.1.149
60 Howlett WP, Brubaker GR, Mlingi N, Rosling H. Konzo, an epidemic upper motor neuron disease studied in Tanzania. Brain. 1990;113(Pt 1):223–35. https://doi.org/10.1093/brain/113.1.223