Earlier onset and shorter survival of amyotrophic lateral sclerosis in Jewish patients of North African origin
A clue to modifying genetic factors?

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Abstract
Amyotrophic lateral sclerosis (ALS) is a multifactorial disease, with many genetic and environmental factors contributing to its outcome. The population of Israel is comprised of immigrants from all over the world as well as by Arabs. People with different ethnic backgrounds who live in the same environment provide a unique opportunity to analyze genetic and environmental influences on ALS.

We performed a retrospective analysis of 374 sporadic ALS patients whose origin was European in 211, North African in 53, Oriental in 43, Balkan in 19, Arab in 9, and Yemenite in 7, comparing their age at disease onset, gender, disease form at onset, survival, smoking habits, cognitive dysfunction and apolipoprotein E genotype.

Patients of North African origin were significantly younger and had a shorter duration of disease relative to their age compared to other ethnic groups, adjusted for age. The difference between the patient groups might be related to a genetic burden in North African patients and warrants further investigation.

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1. Introduction
Amyotrophic lateral sclerosis (ALS) is most probably a multifactorial disease, with many genetic and environmental factors contributing to the clinical presentation. It is relatively equally distributed in North America and Europe, with an incidence of 1–2 cases per 100000 people per year [1–3]. A few geographic clusters of ALS cases were reported, the main ones being in the islands of Guam in the Western Pacific [4] and in the Kii peninsula of Japan [5]. The incidence of ALS in Israel was reported to be lower than that of North America and Europe [6], but this figure is probably artifactual due to incomplete patient assessment in the past. Data from a recent population-based survey are not available, but the annual incidence of ALS appears to be similar to the figure quoted in the North American and European studies.

Survival after the first appearance of symptoms is short, with a reported mean of 2–5 years [7–9]. A variety of prognostic factors have been associated with a shorter survival, including older age at onset, female sex, onset with bulbar rather than limb weakness, and short time from first symptoms to diagnosis [10–15]. Smoking was positively associated with ALS [16].

Ethnic differences as a modifying factor, which may influence disease onset and prognosis, were only sparsely evaluated outside geographic cluster areas. Elian and Dean [17] noted that immigrants to England from the Indian subcontinent, Caribbean and Africa have fewer ALS diagnoses on their death certificates than would ordinarily be expected from the English population. They raised
The apolipoprotein E (APOE) allele status was determined in a subgroup of patients and those data were published elsewhere [19]. The APOE status, where examined, was included in the present data set.

We included only patients who fulfilled the revised El Escorial diagnostic criteria for probable or definite ALS [20] at their last clinical evaluation. Patients with a positive family history of ALS were excluded, since the genetic burden probably overweighs any modifying factor in those cases.

Patients were classified into seven ethnic groups: European (Ashkenazi) excluding Balkan countries, Balkan, North African, Oriental, Yemenite, Arabs living in Israel and mixed/others. The ethnic group of each patient was determined by the origin of both parents. In some cases, in which the parents or grandparents immigrated to another geographic area from their origin, the farthest known ethnic relationship was used for classification.

Comparisons between the patient groups were performed using one-way analysis of variance and chi-square tests, as appropriate. Since the comparison between groups regarding age at onset was significant, pairwise comparisons between groups were performed using Ryan–Einot–Gabriel–Welsh multiple range test. Survival between the groups was compared using the Kaplan–Meier method. A multivariate analysis of factors influencing survival was performed using the Cox proportional hazard model. The Ashkenazi ethnic group was considered as the reference group for origin. The model compared differences between seven ethnicity groups after adjustment for the following co-variates: disease form at onset, age at onset, smoking, gender, education. All statistical tests were performed using a SAS system for Windows, release 8.02.

3. Results

Among 374 patients included in the study, the breakdown of ethnic origin was 211 European, 53 North African, 43 Oriental, 19 Balkan, 9 Arab, 7 Yemenite and 32 others. The Yemenite patient group was the smallest, representative of the proportion of this ethnic group in the Israeli population, and their epidemiologic data were rather different from those of the other patient groups (less males, prolonged survival), so it was felt that this subgroup of patients is too small in order to provide reliable epidemiologic data. The group defined as “others” included 21 Jewish patients whose parents were of different origins and 11 non-Jewish–non-Arab patients.

The comparative data of each group and of the entire patient cohort are given in Table 1. Patients in the different groups (excluding the Yemenites) were not significantly different in their gender distribution, disease form at onset, smoking habits, frequency of cognitive dysfunction, and APOE status (chi-square tests). A higher proportion of patients in the European group had a high school education than in the other groups ($p<0.0001$, chi-square test). The
main positive finding in this comparison was that patients of North African and Arab origins were significantly younger, while patients of Balkan and European descent were significantly older (Ryan–Einot–Gabriel–Welsh multiple range test for pair-wise comparisons between groups).

The Kaplan–Meier survival curves of the seven ethnic groups showed poorer survival of patients of Balkan origin as compared to longer survival of Arab, Oriental and Yemenite patients (Fig. 1), but the differences between the groups were only marginally significant \((p = 0.05\) for all groups, log-rank test).

Younger patients are supposed to have a more prolonged survival, as compared to older ones, and bulbar patients have usually a poorer prognosis as compared to patients with limb-onset disease, therefore we performed a multivariate analysis of all ethnic groups using the Cox proportional hazard model, taking into account the age at onset, gender, disease form at onset, pack-years of cigarettes smoked and education. Only the age at onset and being of North African and Balkan origin showed a significant correlation with survival \((p < 0.0001, p < 0.05\) and \(p < 0.05\), respectively). The \(APOE\) status was not included in this model, as data were not available for all patients.

4. Discussion

The results of the present study show that in spite of a relatively homogenous incidence of ALS outside the Pacific clusters, the disease characteristics may vary within different patient populations, giving rise to a more aggressive disease, with earlier onset and more rapid progression. This was clearly demonstrated in our patients of North African Jewish origin. These findings are concordant with those reporting differences between Caucasians and African Americans in the United States \([10,12,18]\) and among immigrants to England versus English-born patients \([17]\). A previous epidemiological survey in Israel described similar clinical features of ALS, but did not differentiate between patients of various ethnic origins \([21]\).

The difference between groups could stem from various causes, such as the environment or the genetic burden, or it could be an artifact of patient referral. Specifically, patient referral bias could be a factor if older North African and Arab patients would be less able to reach the tertiary clinic. Given that the health system in Israel is mainly government funded and all inhabitants have access to it, a referral bias is not very likely in this setting. A referral bias would also not explain the shorter survival in North African Jewish, but not in Arab patients. Nevertheless, it should be borne in mind that this is a referral clinic based series, and bears the possible biases typically encountered in such a study. Unfortunately, there are no epidemiological population-based data on the incidence of ALS in different ethnic groups in Israel, therefore we cannot assess the effect of patient selection to the tertiary center in this study.

The shorter survival of patients of North African origin is an important finding, even though its statistical significance is moderate: the failure to reach a higher level of significance
stems from the fact that this patient group has an earlier age at onset and so a longer survival is expected [11].

We did not collect data about the socioeconomic background of the patients. The socioeconomic status could influence to some extent end-of-life decisions, such as timing of tracheostomy or percutaneous enterogastrostomy. Instead of this variable, we used schooling years, although it has to be kept in mind, that the correlation between schooling and socioeconomic status is not necessarily high. Education by itself, independently of socioeconomic background, could have an influence on end-of-life decisions and therefore on survival. Schooling was not homogeneously distributed in the various patient groups, with a higher proportion of patients with a greater level of education in the group of European origin. Nevertheless, this difference did not express itself as a factor influencing survival in the Cox analysis.

Environmental factors appear in our opinion not to significantly influence the results of this study, because Israelis of different ethnic origins are integrated residentially, vocationally and socially and, as such, would be exposed similarly to toxins or infectious agents or other exogenous influences, although we cannot rule out that differences in socioeconomic status or education could imply also a different exposure to still unknown environmental toxins or infectious agents, possibly during early life.

Patients had access to the same health system, particularly a similar proportion of patients in all groups performed life-prolonging procedures, as percutaneous enterogastrostomy and initiation of non-invasive ventilation, and the timing of the procedures relative to disease status was similar. All patients have free access to riluzole as well.

Thus, it is possible that the reason for the difference found between these groups is a genetic predisposition. The North African Jewish population had formed a closed community for many hundreds of years, with almost no mixing from outside, compared to the European Jews, who are genetically much more heterogeneous. Therefore, it is highly likely that there is a genetic susceptibility factor in the North African patients that negatively influences the onset and progression of ALS.

A rare form of juvenile-onset, recessive ALS was described previously in non-Jewish patients of North African origin, mainly from Tunisia, with linkage to chromosome 2q [22] and 15q [23]. These patients have usually very early onset of disease ranging from 8 to 18 years and slow progression over more than 10 years. Therefore, our patients, who presented with an only slightly lower mean age at onset, but a large spectrum of ages, ranging from 27 to 73 years, and fast progression, are probably not part of the juvenile ALS syndrome.

Patients of Arab origin had the lowest mean age at onset compared to other ethnic groups, but their survival after first symptoms was relatively long, as expected in this age group. As this ethnic group was small, a referral bias of younger patients or underdiagnosis in the elderly in this population cannot be ruled out.

Patients of Balkan origin had also a relatively poor survival, but they formed the oldest group in this series, so their age probably explains at least partly the poor survival, although the statistical analysis suggests that there might be further modulating factors in this population.

One of the known susceptibility genes for ALS is the APOE ε4 genotype, which may predict an earlier age at onset and a more rapid progression with shorter survival [19,24,25]. The APOE allelic status was analyzed in a subgroup of patients with representatives from all ethnic groups and did not indicate any significant relationship with a specific ethnic origin. Other susceptibility genes for ALS have been described during the last few years and may warrant further attention in this population.

In conclusion, this investigation on a large series of ALS patients revealed that Jewish patients of North African origin have a significantly younger age at onset and a relatively shorter survival after first symptoms of ALS. Specific genetic susceptibility factors in this population that negatively influence disease onset and progression are suspected and have to be further identified. Ethnic differences should also be sought in other epidemiological series, possibly with multinational comparisons, in order to determine populations with an increased susceptibility to a more benign or more fulminant course of disease. In the long run, analysis of such differences could lead to a better understanding of genetic and environmental influences on occurrence and progression of ALS.

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References