The modifiers of amyotrophic lateral sclerosis survival and clinical trial design

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Abstract

Amyotrophic lateral sclerosis (ALS) patients with different median survival also show a different progression speed. Genetic studies identified several genes associated with an increased risk and/or shorter survival of ALS. In the present review, we discuss some issues critical for the definition of survival and identification of prognostic factors of ALS. More studies are needed to exclude confounds and find the true intrinsic risk factors affecting the disease onset and/or the prognosis of this disease. We propose that some mutated genes may act more as survival modifiers than as risk factors. Recruiting a homogeneous group of patients based on their genetic background is another approach that should be considered when drafting the inclusion criteria during the trial design. This approach may facilitate the development of therapies for ALS.

Keywords: ALS: Amyotrophic lateral sclerosis; NIPPV: Non-invasive Positive Pressure Ventilation; C90r72: Chromosome 9 open reading frame72; TARDBP: TAR DNA-binding protein 43 gene; FUS: Fused in Sarcoma gene; SOD1: Superoxide dismutase 1; KIFAP3: Kinesin-associated protein 3; CX3CR1: C-X3-C Motif Chemokine Receptor 1; UNC13A: Unc-13 homolog A; CAMTA1: calmodulin binding transcription activator 1; SMN1: Survival Motor Neuron 1; ATAXN2: gene encoding protein Ataxin-2; ALSFRS-R: ALS Functional Rating Scale-Revised; PEG: percutaneous endoscopic gastrostomy; SNV: single nucleotide variation

Review

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that affects upper and lower motoneurons resulting in progressive weakness of voluntary muscles and death from respiratory failure. Arthur [1] estimated that the number of people with ALS will increase from 222,801 in 2015 to 376,674 in 2040. The prognosis is highly heterogeneous entailing large differences in the speed of progression of the disease. It is unknown why some patients with ALS deteriorate much faster, or survive for a shorter period, than others. Because of the different survival and progression speeds, the factors associated with the speed of progression have to be taken into account during the design of the clinical trial design. There is also a geographic difference in survival. Therefore, clarifying the survival and true surrogate factors for stratification will facilitate clinical trial design and the global development of therapies for patients affected by ALS.

Our literature analysis revealed that the median survival varies according to the individual and the region of origin. The median survival in Europe and North America is approximately 3 years, with individual studies ranging from 20 to 50 months, and 10–20% of patients with ALS survive more than 10 years [2]. The median survival in Asia, excluding Japan and Brazil, ranges from 66 to 116 months, which is approximately twice the median survival measured in most of Europe and North America [3–29]. Japan’s median survival (22.8 to 37 months) is similar to the survival observed in Europe [3–29]. The variability of ALS onset indicates that a time-dependent exposure to a combination of genetic and environmental risk factors may be involved in the pathogenesis of ALS. Whether this region-specific survival is also influenced by these factors needs further research and analysis (Table 1).

When comparing the median survival of patients with ALS obtained from different studies, one important issue to consider is the definition of survival. Two possible starting points can be defined: either the onset of the disease or the diagnosis. Similarly, two endpoints (the death or the use of non-invasive ventilation, or tracheostomy) can be defined. Indeed, the use of non-invasive ventilation or tracheostomy can greatly prolong survival. Sancho [30] reported that non-invasive ventilation prolonged the survival by a median of 15 months. The median survival after tracheostomy has been reported to be 30 months [31], which is almost equal to the reported overall median survival of patients with ALS. In Japan, invasive ventilation and tracheostomy extended median survival by 74 months, while non-invasive ventilation extended survival by 48 months, when compared with a non-ventilation-supported group [32]. The major reasons on whether to use non-invasive ventilation or tracheostomy can depend on the willingness of patients or their relatives and their economic status and not necessarily the severity of disease. Indeed, developing an international registry of ALS with a standard protocol for coding the geographic data relative to the median survival is an emerging objective yet to be accomplished.

In terms of the prognostic factors associated with survival in patients with ALS, old age and bulbar onset have been consistently reported as an indication of a worse clinical outcome than younger age and limb onset. The influence of sex and delayed on the prognosis

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diagnosis are still controversial [2,33,34,22]. Respiratory onset is also a negative prognostic factor [35,36] although non-invasive ventilation can significantly improve survival [37]. Interestingly, the lower frequency of bulbar-onset and younger onset in Chinese patients with an extended survival supports these findings [22]. In terms of therapeutic factors, riluzole may improve median survival by several weeks and it also improves the quality of life [38,39]. In addition to the therapeutic factors, riluzole may improve median survival by several weeks and it also improves the quality of life [38,39]. In addition to the genetic background to the pathogenesis of ALS has not been well characterized and further the contribution is limited because of the low frequency of mutation in sporadic cases. Most patients do not carry any of the mutations of the genes aforementioned. The variability observed in both the in survival and onset.

About 85–90% of ALS cases are sporadic, while 10–15% has a family history. Sporadic ALS is considered to be a complex disease with multiple genetic risk factors contributing to its pathogenesis. Mutations of 126 genes have been shown to be associated with ALS. Identification of genes that co-occur frequently may provide relevant insight into the underlying mechanism of motor neuron degeneration. The most commonly identified genes to be associated with a high risk of ALS are C9orf72 (chromosome 9 open reading frame72), TARDBP (TAR DNA-binding protein 43 gene), FUS (Fused in Sarcoma gene), and SOD1 (superoxide dismutase 1). Other genes that have been found to be rarely associated with ALS include KIFAP3 (Kinesin-associated protein 3), CX3CR1 (C-X3-C Motif Chemokine Receptor 1), UNC13A (Unc-13 homolog A), CAMTA1 (calmodulin binding transcription activator 1), SMN1 (Survival Motor Neuron 1), and ATAXN2 (gene encoding protein Ataxin-2). Although these genes showed higher frequency in patients with ALS than in healthy controls, however these mutant genes are present in less than 50% of all ALS patients. As shown in Table 2 [39-56], the mutation of SOD1 accounts for the occurrence of 4–20% of familial ALS and 1-5% of sporadic cases, C9orf72 accounts for 8.3-33% of familial ALS and 0.3-6.5% of sporadic cases, mutations in TARDBP account for 5–10% while mutations in FUS for 5% of familial ALS. The most frequent four genes in familiar ALS account for about 2–6% in sporadic ALS which represents 85-90% of all ALS cases. The remaining mutant genes are very rare in ALS. The contribution of the individual’s genetic background to the pathogenesis of ALS has not been well characterized and further the contribution is limited because of the low frequency of mutation in sporadic cases. Most patients do not carry any of the mutations of the genes aforementioned. The relatively low frequency of these genes in sporadic ALS suggests that the pathogenesis is triggered by an interaction between genes and environmental factors. However, this hypothesis requires further experimental support. However, we know that patients with ALS are heterogeneous, i.e., they display an elevated variability in the speed of the disease progression and the prognosis. We therefore speculate that differences in genetic factors provide the molecular basis for the variability observed in both the in survival and onset.

| Continent | Author | Median survival(range) |
|-----------|--------|------------------------|
| Europe    | Chiodrano [3], 2013 | 40.8m (26.4-72.6), Italy |
|           | marinbad [4], 2016     | 25m (23-34), north europe |
|           | marinbad [4], 2016     | 30m (25-34), western europe |
|           | Zoccoliella s [5], 2008 | 28m, Italy |
|           | Milia a [6], 2005      | 39.2m, Italy |
|           | Tynesesob [7], 1991    | 28m, Norway |
|           | magnus t [8], 2002     | 37-58, German |
|           | diujs v [9], 2000      | 52m, Belgium |
|           | Sanjuan-lopez p [10], 2014 | 28m, Spain |
|           | Bandetti di poggio[11], 2013 | 45m, Italy |
|           | Gordon ph [12], 2012   | 40.0m, France |
|           | Borghero [13],2014     | 50.4m, Italy (27.6-120m) |
|           | yoshida s [14], 1986   | 23.8m, Japan |
| Asia      | kahana e [15],1984    | 56m, Israel |
|           | Sajjadi M [16],2010    | 48m, Iran |
|           | lee etc [17], 2013     | 66.6m, Taiwan |
|           | Nalini a [18],2008     | 114.8m, India |
|           | kanai k [19], 2012     | 37m, Japan |
|           | furuijuma-yiyoono c [20], 2014 | 18.26m, Japan |
| North America | Chen lu [21], 2015 | 74m, China |
|           | mcguire v [22], 1996   | 32m, north america |
|           | norris f [23], 1993    | 39.5m, north america |
|           | marinbenoit[4],2016    | 26.2m,america |
|           | del Aguila MA [24],2003 | 32 m, north america |
|           | cetin b [25], 2015     | 22.m,america |
|           | pauliekeno S7[26],2015 | 31.2m, America |
| South America | loureirotemp [27] ,2015 | 49m, brazil |
|           | Moura MC [28]          | 45.7m men and 36.9m women |

| Table 1. Median survival of ALS in countries. |
| Gene | Author, Country | Frequency in ALS (%) |
| C9orf72 | Ratti a[3],2012 | fALS 23.9 | sALS 5.1 |
|        | OGAKI[40],2015, JAPAN | fALS 0 | sALS 0.4 |
|        | Houlhi[41], 2016, China | fALS 8.3 | sALS NA |
|        | He j[42], 2015, China | fALS NA | sALS 0.3 |
|        | Ozoguz a[43],2015, Turkey | fALS 18.3 | sALS 3.1 |
|        | Bertoliln [44], 2014, Italy | fALS 22 | sALS 5 |
|        | Borghero[13],2014,Italy | fALS 33 | sALS 6.5 |
|        | Abramicheva [45],2015,Russia | fALS 15 | sALS 2.5 |
|        | Milecopmas [46],2010,France | fALS 46 | sALS 8 |
| SOD1   | Houlhi [41], 2016, China | fALS 20 | sALS 1.9 |
|        | Ozoguz a [43],2015, Turkey | fALS 12.2 | sALS 0 |
|        | Canossa a[47],2014, Italy | fALS 13.6 | sALS 0.7 |
|        | Kwon M[48], 2012,Korea | fALS 77.8 | sALS 1.2 |
|        | Milecopmas [46],2010,France | fALS 12.4 | sALS NA |
|        | Borghero [13],2014,Italy | fALS 4 | sALS 0 |
| TARDBP | Corrado [49], Italy,2009 | fALS 2.7 | sALS NA |
|        | Ida A, 2010[50], Japan  | fALS 0.29 | sALS NA |
|        | Kamada[51],2009, | fALS 0.33 | sALS 0 |
|        | zozuy[52],2012,China | fALS NA | sALS 0.73 |
|        | Ozoguz a [44],2015, Turkey | fALS 3.7 | sALS NA |
|        | Milecopmas [46],2010,France | fALS 4 | sALS NA |
|        | Borghero[13],2014,Italy | fALS 25 | sALS 19.3 |
| FUS    | Houlhi [41],2016,China | fALS 13.3 | sALS 0 |
|        | Syrnan[53],2011, Spain | fALS 8 | sALS NA |
|        | Waibel[54],2010, German | fALS 2.4 | sALS NA |
|        | Dreepper [55],2009, Germany | fALS 6.9 | sALS NA |
|        | Corrado [49], 2009, Italy | fALS 4.4 | sALS NA |
|        | Van darnme [56],2010,Belgium | fALS 2.9 | sALS NA |
|        | Milecopmas [46],2010,France | fALS 4 | sALS NA |
|        | Ozoguz a[44],2015, Turkey | fALS 5 | sALS NA |
both increased susceptibility and a shorter survival in ALS patients [58]. However this association was not replicated in all studies. In a sample of patients from the Netherlands that SNVs rs10419420>G>A of gene UNCI13A was found exclusively in long survivors (3/25) and rs4808992>G>A exclusively in short survivors [64]. Patients with ALS with expanded repeat sizes of ATXN2 gene ranged from rapidly progressive typical ALS to slowly progressive ALS with reduced sensory nerve action potentials [65]. Some research showed completed interaction. Patients carrying C9orf72 had a median survival of 2.37 years, patients with a co-occurrence of C9orf72 and TARDBP p.A382T had a median survival of 3.1 years, and patients carrying TARDBP p.A382T had a survival of 6.5 years [13]. In a basic research, functional evidence of UNC-13/UNCI13A regulating motor neuron degeneration [66] provided implied the modifier of some genes in ALS survival.

We know that old age and bulbar onset are associated with a severe prognosis. Some genetic mutations are believed to reduce survival and they are also associated with both the age at onset and bulbar onset. The interactions between genetic factors entail different combinations of genes such that they may exert different influences on the risk and survival in patients with ALS [13]. The hypothesis is that some mutant genes may act more as survival modifiers than risk factors. To exclude confounds and find true intrinsic risk factors for disease onset and/or prognosis is important for clarifying Ethnic and individual heterogeneity.

The traditional stratification procedure adopted in clinical trials for ALS to divide patients by age at onset and bulbar onset is no longer sufficient and adequate. Indeed, the respiratory status at the beginning of the study and the disease progression as measured by the ALSFRS-R should be part of the criteria used for stratification. Selecting a homogeneous group based on the genetic background of the patients is another approach that has to be taken into consideration when drafting the inclusion criteria in trial design. However, the effect of PEG and NIPPV on ALS outcome in the treatment section of the protocol should also be noted when we evaluate the effect of one therapy in a clinical trial.

A further issue that needs to be addressed is which factor, or interaction of factors, results in the rapid progression of ALS. Identifying the genetic factors influencing susceptibility, age at onset, and survival of ALS may provide insight into the pathogenic mechanism underlying ALS, motivate the search for new pharmacologic targets, and facilitate clinical trial design for this fatal neurodegenerative disease. Future research should aim to develop an international registry using a standard protocol and central data center to guarantee the quality of studies. The use of the multivariate Cox regression is also important. Among the several prognostic factors identified so far, including factors such as the age at onset, bulbar onset, and genes that increase risk (e.g., C9orf72, TARDBP, FUS, SOD1) or modify survival (e.g., ATXN2, UNCI13A, KIFAP3, CX3CR1), more efforts should be done to determine the factor, or interaction of factors, that affects ALS prognosis. Gaining insight into the complex factors that affect ALS prognosis will both promote the identification of novel therapeutic targets for slowing the progression of the disease and support the development of appropriate clinical trials.

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