
#greatminds
IN OUR WORLD, A STEADY FLOW KEEPS PATIENTS ALIVE.
LET'S TAKE CARE OF IT. TOGETHER.
Driving Excellence in Neurology.
Be part of one of humankind's most ambitious projects to help uncover the workings of the nervous system. EAN connects 45,000 specialists in neurology in 47 countries across Europe. Promoting excellence, cutting-edge science and innovative therapies for a better life for more than 430 million patients in Europe alone. Read more on ean.org
Great Minds.
ean
european academy of neurology

ALS disease onset may occur later in patients with pre-morbid diabetes mellitus

A. Jawaid[a], A. R. Salamone[a], A. M. Strutt[a], S. B. Murthy[a], M. Wheaton[a], E. J. McDowell[a], E. Simpson[b], S. H. Appel[b], M. K. York[a] and P. E. Schulz[a]

[a]*Department of Neurology, Baylor College of Medicine; and* [b]*The Methodist Neurological Institute, The Methodist Hospital, Houston, TX, USA*

Keywords:
amyotrophic lateral sclerosis, cognition, diabetes mellitus, onset, progression, survival

Received 31 August 2009
Accepted 11 November 2009

Background Several metabolic derangements associated with diabetes mellitus type 2 (DM) have been associated with a better outcome in amyotrophic lateral sclerosis (ALS), including hyperlipidemia and obesity. Here, we tested the hypothesis that DM would have a positive effect on the motor and cognitive findings of ALS.

Methods: We compared data from ALS patients with pre-morbid DM (ALS-DM; $n = 175$) versus without DM (ALS; $n = 2196$) with regard to the age of onset, rate of motor progression, survival, and neuropsychological test performance.

Results: The age of onset was later for women, Caucasians and patients with bulbar-onset ALS. However, we also found that after adjusting for gender, ethnicity and site of onset, DM was associated with a 4-year later onset of ALS (ALS = 56.3, ALS-DM = 60.3, $P < 0.05$).

Conclusion: Diabetes mellitus type 2 may delay the onset of motor symptoms in ALS. These findings support other studies suggesting a relationship between the pathophysiology of ALS and metabolic derangements. Further investigations are needed to ascertain whether manipulating metabolic parameters would improve outcomes in ALS.

Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder leading to progressive paralysis and death, often within 2–5 years of symptom onset [1]. More than half of patients with ALS also suffer from some degree of cognitive impairment which in 15% is severe enough to be classified as frontotemporal dementia (FTD) [2].

In order to gain insights into the pathophysiology underlying ALS, factors have been sought that influence the course of ALS. The age at onset, site of onset, gender, ethnicity and apolipoprotein (ApoE) genotype have been proposed to be important in this regard [3–7]. Patients with a younger age at the onset of symptoms (<45), men and patients with limb-onset are known to have a longer survival [3]. A correlation between plasma ApoE levels and survival has also been observed [7]. With regard to age of onset, patients with bulbar-onset and women have been shown to have an early onset [4,5]. It generally appears that factors associated with a later onset are also associated with a shorter survival and *vice versa*. Apart from these factors, ethnicity and ApoE genotype have also been suggested to modify ALS, but the supporting evidence is inconclusive [6,7].

Some metabolic derangements have also been observed in patients with ALS. Two-thirds of patients develop a stable hypermetabolism during the course of the disease [8,9]. Similarly, glucose intolerance and insulin resistance have been linked to ALS [10,11]. Dupuis *et al*. [12] found an association between dyslipidemia and the course of ALS: ALS patients with a high LDL/HDL ratio at the time of diagnosis were noticed to have a median survival 13 months longer than ALS patients with a high HDL/LDL ratio. A potential protective effect of hyperlipidemia in ALS has also been observed in some rodent studies: increasing the lipid content in the diet of ALS animal models offered neuroprotection and extended survival [13,14]. We reasoned that the presence of diabetes mellitus type 2 (DM), which shares risk factors with dyslipidemia and raises the LDL/HDL ratio, could also have a positive effect on the course of ALS.

The goal of this study was to investigate the hypothesis that pre-morbid DM is associated with a protective effect on the motor and cognitive findings of ALS. We investigated this hypothesis by comparing

Correspondence: P. E. Schulz, NB-302, Baylor College of Medicine, 6501 Fannin Street, Houston, TX 77030, USA (tel.: +1 713 798 8986; fax: +1 713 798 8530; e-mail: pschulz@bcm.edu).

motor and cognitive disease variables between ALS patients with and without pre-morbid DM whilst adjusting for the possible confounding effects of factors proposed to be associated with altered disease variables in ALS.

Methods

Study design and participants

The study involved a retrospective review of clinical data. The Baylor College of Medicine (BCM) Vicki M. Appel MDA/ALS clinic evaluated 2650 patients for ALS between 1984 and 2007, which were entered prospectively into an ALS database. Patients were diagnosed with ALS after 1994 using the El Escorial criteria for definite or probable ALS [15]. Patients seen prior to 1994 were diagnosed with ALS based on clinical findings and electromyography studies. The database was searched for patients with sporadic ALS. Patients with ambiguous past medical history, uncertain diagnosis of motor neuron disease, familial ALS or diagnosis of a motor neuron disease other than ALS were not included in this study.

From a total of 2650 patients in our database, 2371 patients were included in the analysis: those with clinically probable or definite sporadic ALS and with symptom onset after the age of 45 years. Exclusion criteria are discussed in the Results section. This study was approved by Baylor College of Medicine's Institutional Review Board.

Information about the disease characteristics [site of onset, age of onset, survival, serial Appel ALS Scale (AALSS) scores, family history and pre-morbid history of DM] as well as demographic details (gender, age, ethnicity and number of years of education) were included for all patients in the final analyzes.

Patients were labeled as having pre-morbid DM (ALS-DM) if one or both of the following criteria were fulfilled:

1) Laboratory investigation records revealed two fasting blood sugar values 126 mg/dl and higher or two random blood sugar values 200 mg/dl and higher at/before the time of ALS diagnosis.

2) Medication records showed use of Insulin and/or Diabetic medications at/before the time of ALS diagnosis.

Procedures

The major outcome variables of the study were age of onset, rate of disease progression and survival.

'Age of onset' was defined as the chronological age of the patient at which he/she first started to notice the motor symptoms of ALS. This data was gathered prospectively and approximated to the nearest year.

'Rate of disease progression' was calculated using serial AALSS scores. The motor findings for all patients with ALS were recorded at the time of diagnosis and at each follow-up visit, and the severity of their symptoms was gauged using the AALSS. The difference between the first and the last available AALSS scores for each individual patient divided by the number of months that separated the two evaluations determined the rate of motor disease progression for each patient with ALS.

'Survival' was defined as the time from the onset of symptoms to death.

Based on the literature and our previous studies, we hypothesized that that 'age of onset' in ALS could be influenced by four potential disease-modifying factors: gender, ethnicity, site of onset and history of DM, whereas 'rate of progression' and 'survival' could be influenced by five potential disease modifying factors: age of onset, gender, ethnicity, site of onset and history of DM. In order to ensure uniformity in the analysis, we elected to exclude patients with symptom onset before the age of 45 years. To ascertain the collective and individual influence of the other potential disease-modifying factors, we decided to study their impact on the major disease variables through both univariate and multivariate analysis.

Neuropsychological evaluation

All patients seen after the year 2000 ($n = 453$) underwent a comprehensive neuropsychological evaluation at the time of ALS diagnosis. Measures administered included a modified (Satz-Mogel) version of the Wechsler Adult Intelligence Scale Revised (WAIS-R); American version of the National Adult Reading Test (AMNART); Stroop Color and Word Test; Verbal Series Attention Test (VSAT); Logical Memory (LM I & II) and Visual Reproduction (VR I & II) subtests from the Wechsler Memory Scale–Revised (WMS-R); Symbol Digit Modalities Test (Oral and Written), Rey Auditory Verbal Learning Test (RAVLT), Rey-Osterrieth Complex Figure Test (Rey-O), lexical (FAS) and semantic (animals) fluency and Trail Making Test, Parts A& B (Trails A; Trails B) [16–25]. Results of only non-verbal and non-timed neuropsychological tests (Rey-O, LM I & II, VR I & II) or tests in which motor control is incorporated into the measure (VSAT-error, Stroop interference, Trails B-A) were considered valid. This was carried out because motor impairment in ALS may falsely exaggerate deficits on neuropsychological tests that involve a motor component (for example writing or speaking) [3].

Statistical methods

The data was entered into SPSS version 16 (SPSS Inc, Chicago, IL, USA) and validated through dual entry prior to being analyzed. Associations between categorical variables were established through *chi* square and Fisher's exact calculations. Mann–Whitney *U* tests were performed to analyze differences in age of onset, rate of disease progression on AALSS and survival across gender, ethnicity (Caucasian versus non-Caucasian), site of onset (bulbar versus limb) and diabetes status (ALS versus ALS-DM). Differences in age of onset, rate of disease progression and survival were further explored through linear regression models to adjust for the contribution of gender, site of onset, ethnicity and history of pre-morbid diabetes. The *Bonferroni correction* was applied to the resulting *P* values to adjust for multiple comparisons. Mann–Whitney *U* tests were performed to investigate whether there were significant differences between neuropsychological performance of ALS–DM and ALS groups. Non-parametric tests were performed wherever possible to ensure that the disparity between the large ALS group and a relatively small ALS–DM group was properly managed in the statistical analyzes.

For the outcome variables of age of onset, rate of disease progression and survival, a small fraction of the data was unavailable. Patients for whom data on more than one major outcome variable was missing were excluded from the analysis. As the neuropsychological testing was not conducted prior to the year 2000, patients diagnosed before then were not included in the analysis of neuropsychological performance.

Results

Demographics

A database of 2650 patients was searched for patients with sporadic ALS. Of them, 2457 of them had sporadic ALS. Those with familial ALS or another etiology for weakness were excluded. Then 37 were excluded because of missing data on more than one major outcome variable. Of the remaining, 49 patients were excluded because their symptom onset was before the age of 45 years. Thus, 2371 patients were enrolled.

ALS-DM and ALS groups did not differ with regard to gender, education, ethnicity, or site of onset (Table 1). The ALS-DM group was found, however, to have significantly lower estimates of pre-morbid verbal IQ (AMNART score). The mean AMNART scores for both groups were classified within the average range.

Age of onset

The age of ALS onset was earlier for men, non-Caucasians and patients with limb-onset ALS (Table 2). Age of onset for patients with ALS-DM was 4 years later than for the ALS group (60.3 vs. 56.3, $P < 0.05$). These associations were further explored through a multiple linear regression model (Table 3). Results

Table 1 Demographics according to the presence or absence of diabetes

	Diabetes mellitus status		
	Non-diabetic ($N = 2196$)	Diabetic ($N = 175$)	Whole sample ($N = 2371$)
Gender			
Female/Male (%)	34.3/65.7	38.3/61.7	38/62
Education (years)			
Mean (SD)	13.9 (3.24)	12.7 (2.95)	13.8 (3.23)
Ethnicity (%)			
Caucasian	89.6	82.3	88.9
Hispanic	3.7	6.3	3.9
African–American	5.2	8.0	5.4
Others	1.5	3.4	1.6
Site of onset			
Bulbar/Limb (%)	26.6/73.4	28.2/71.8	26.4/71.3
AMNART Mean (SD)	111 (10.7)*	104 (8.25)*	110.2 (10.7)

*Significant between group difference ($P < 0.05$) on Mann–Whitney *U* test.

Table 2 Comparison of disease variables between ALS patients with different gender, site of onset, ethnicity and diabetes status

	Gender		Site of onset		Ethnicity		Diabetes Status	
	Male ($n = 1470$)	Female ($n = 901$)	Bulbar ($n = 626$)	Limb ($n = 1745$)	Caucasian ($n = 2108$)	Non-caucasian ($n = 263$)	Diabetic ($n = 175$)	Non-diabetic ($n = 2196$)
Age of onset (years)	55.0 (13.6)*	59.1 (12.4)*	60.7 (12.4)*	55.1 (13.3)*	57.0 (13.2)*	52.9 (13.7)*	60.3 (10.7)*	56.3 (13.4)*
Rate of disease progression (AALSS/Month)	3.46 (3.02)*	2.89 (2.82)*	3.30 (2.63)*	3.01 (2.98)*	3.08 (2.93)	2.80 (2.45)	3.58 (3.53)	3.01 (2.83)
Survival (years)	3.31 (2.34)	3.15 (2.72)	2.73 (1.85)*	3.47 (2.45)*	3.19 (2.23)	3.78 (3.01)	3.60 (2.58)	3.04 (2.29)

*Significant within group difference on Mann–Whitney *U* test. ($P < 0.02$). AALSS, Appel ALS Scale.

Table 3 Multiple Linear Regression Model in patients with amyotrophic lateral sclerosis investigating the independence of gender, site of onset, ethnicity, and diabetic status on the age of onset, rate of disease progression, and length of disease

	Gender			Site of onset			Ethnicity			Diabetes Status		
	Male (n = 1470)	Female (n = 901)	β (95%CI)	Bulbar (n = 626)	Limb (n = 1745)	β (95% CI)	Caucasian (n = 2108)	Non-Caucasian (n = 263)	β (95%CI)	Diabetic (n = 175)	Non-Diabetic (n = 2196)	β (95%CI)
Age of onset (years)	55.0 (13.6)	59.1 (12.4)	−0.12* (−4.43, −2.27)	60.7 (12.4)	55.1 (13.3)	−0.17* (−6.06, −3.81)	57.0 (13.2)	52.9 (13.7)	−0.10* (−5.91, −2.59)	60.3 (10.7)	56.3 (13.4)	0.09* (2.41, 6.40)
Rate of disease progression (AALSS/Month)	3.46 (3.02)	2.89 (2.82)	−0.09 (−1.05, −0.07)	3.30 (2.63)	3.01 (2.98)	−0.04 (−0.79, 0.24)	3.08 (2.93)	2.80 (2.45)	−0.03 (−1.05, 0.50)	3.58 (3.53)	3.01 (2.83)	0.05 (−0.28, 1.43)
Survival (years)	3.31 (2.34)	3.15 (2.72)	0.01 (−0.25, 0.38)	2.73 (1.85)	3.47 (2.45)	0.13 (0.29, 0.02)	3.19 (2.23)	3.78 (3.01)	0.07 (0.06, 1.10)	3.60 (2.58)	3.04 (2.29)	0.00 (−0.53, 0.58)

Multiple Linear Regression Model. Dependent variables = age of onset, rate of disease progression, survival; Independent variables = gender, type of onset, ethnicity, diabetes status; Reference category = male for gender, limb for type of onset, non-Caucasian for ethnicity and diabetic for diabetes status. CI, Confidence Interval; SD, Standard deviation; AALSS, Appel ALS Scale. *P < 0.02.

demonstrated independent associations between these four factors and age at diagnosis.

Rate of progression

We then investigated the question of whether there is a relationship between the four factors and the rate of progression of the motor symptoms of ALS as measured by monthly change on the AALSS (Table 2). The rate of progression was significantly faster in men (3.46 vs. 2.89, $P < 0.05$) and patients with bulbar onset ALS (3.30 vs. 3.01, $P < 0.05$). Ethnicity was not associated with a change in the rate of motor progression. There was a trend toward a difference in the rate of disease progression between patients with ALS and patients with ALS–DM (3.58 vs. 3.01), but it was not statistically significant ($P = 0.09$). In the multiple linear regression model, we found no significant association between the rate of progression and any of the four factors tested, including gender and site of onset (Table 3).

Survival

Survival was significantly shorter in patients with bulbar-onset ALS in the bivariate analysis (2.73 vs. 3.47 years, $P = < 0.05$) (Table 2). However, in the multiple linear regression analysis, we found no independent association between any of the four factors (gender, site of onset, ethnicity, and DM status) and survival (Table 3).

Table 4 Scaled and Z Scores on neuropsychological tests for non-diabetic (n = 429) versus diabetic (n = 24) patients with amyotrophic lateral sclerosis

Neuropsychological test	Non-diabetic mean (SD)	Diabetic mean (SD)	P value
Rey-O	−1.43 (1.56)	−1.71 (1.58)	0.63
VSAT-error	−0.58 (1.44)	−0.99 (1.30)	0.19
Stroop interference	−0.47 (1.16)	−0.78 (1.12)	0.22
FAS	−0.85 (1.02)	−1.24 (1.16)	0.07
Animals	−0.35 (1.18)	−0.90 (0.81)	**0.03**
LM I	0.02 (1.07)	−0.63 (1.03)	**0.01**
LM II	0.12 (1.01)	−0.38 (1.14)	**0.03**
VR I	−0.10 (1.13)	−0.49 (0.91)	0.15
VR II	−0.21 (1.15)	−0.45 (0.97)	0.37
Trails B-A	−0.19 (1.33)	−0.51 (1.35)	**0.05**

Rey-O (Rey-Osterrieth complex figure test).
VSAT-err, Verbal Series Attention Test-error; VSAT-time, Verbal Series Attention Test-Time (VSAT).
Stroop interference (Stroop color and word test).
LM I, Logical Memory I; LM II, Logical Memory II, VR I, Visual Reproduction I; VR II, Visual Reproduction II (WMS-R).
Trails B-A (Trails making test parts A & B).
The bold values signify $P < 0.05$.

Neuropsychological test performance

We compared the neuropsychological test scores of the 429 patients with ALS to 24 patients with ALS–DM. The ALS–DM group performed significantly worse than the ALS group on a number of motor adjusted tests including animal fluency ($P = 0.03$), LM I ($P = 0.01$) and LM II ($P = 0.03$), and Trails B-A ($P = 0.05$). Both groups performed within the average range on LM I and II, although the DM group had lower scores on these measures. In contrast to the average performances of the ALS group, the ALS–DM group performed within the low average range on animal fluency and the borderline impaired range on Trails B (Table 4). Both groups of patients with ALS showed clinically significant impairments on the same neuropsychological tests that we reported previously, such as the Rey-O, FAS and VSAT-error. However, the scores of the patients with ALS and ALS–DM did not differ significantly.

Discussion

We found that there was a 4-year later onset of motor symptoms of ALS in patients with pre-morbid DM after controlling for other ALS disease modifiers, including female gender, Caucasian ethnicity, and a bulbar site of onset. In contrast, the cognitive findings were either similar to non-diabetics or worse in diabetics at the time of diagnosis of ALS.

The relationship between DM and ALS

Diabetes mellitus type 2 was associated with a significantly later onset of ALS. ALS patients with pre-morbid DM also showed a non-significant trend toward a slower rate of motor progression and a slightly longer survival. None of the previously identified modifiers of the clinical features of ALS are 'protective' in the sense that a later onset is still associated with shorter survival, as is typical for ALS. Thus, the later onset for ALS noted here in diabetics, coupled with no increase in the rate of progression and no decrease in survival, is remarkable. To the best of our knowledge, this may be the second disease after hyperlipidemia shown to modify ALS. Finding a relationship between the two disorders is interesting in terms of both understanding the pathophysiology underlying ALS and in terms of therapeutics.

The design of this study does not allow us to distinguish between a cause-and-effect association for DM and ALS. Nonetheless, this study raises several interesting possible relationships between DM and ALS that warrant further investigation.

First, DM may, in fact, delay the onset of the motor findings of ALS. Other related disorders are already known to be associated with an altered course for ALS. For example, Dupuis *et al*. [12] recently showed that dyslipidemia may have a protective role in ALS. Low pre-morbid body weight and caloric restriction have been associated with an increased risk of developing ALS [26,27]. By demonstrating a relationship between DM and ALS, this study reinforces the hypothesis that the pathophysiology underlying ALS includes a change in cellular metabolism that may, in turn, be altered by high serum lipids, body mass index (BMI), and/or DM.

Second, the association between DM and ALS could be mediated by another factor. For example, dyslipidemia and obesity are frequent in DM, whereas a slim body type is uncommon. Dyslipidemia has been shown to have a protective role in ALS [12]. On the other hand, a slim body type and athletic life-style have been suggested as risk factors for ALS [1]. Hence, diabetics could have a less malignant course of ALS because of either the presence of a protective factor (dyslipidemia) or absence of certain risk factors (slim body-type and active life-style).

Third, DM may produce symptoms that make it difficult for the patients to recognize the initial symptoms of ALS. Fatigue and 'lack of vigor' are common symptoms in DM that might lead to overlooking weakness as an initial symptom of ALS.

Fourth, ApoE genotype may independently influence the risk of developing DM and the onset and progression of ALS. In a few small studies, patients with ALS carrying one or more ApoE4 alleles were shown to have an earlier age of onset. A later age of onset in patients carrying the ApoE2 allele has also been observed [7]. Both ApoE2 and ApoE4 have been found to be over expressed in diabetic and hyperlipidemic populations in North America [28]. Consequently, ApoE genotype may affect the probability of contracting DM and independently affect the age of ALS onset.

Another observation that suggests a possible 'protective' effect of DM in ALS was a low prevalence of DM (7.4%) in our ALS cohort. National Institute of Health estimates suggest a DM prevalence of 10.8% in individuals aged 40–59 and 23% in individuals over 60 years in the US [29]. Future prospective trials, which employ matched-control groups, will be required to confirm this observation.

Clearly, further research is necessary to ascertain the relationship between ALS and DM, ApoE genotype, dyslipidemia, caloric restriction, and BMI. Understanding these relationships more fully is important for understanding the pathophysiology underlying ALS. In addition, it could be particularly important from a therapeutic point of view. For example, because DM is

associated with a later age of onset of ALS, one could test whether the exogenous production of hyperglycemia and/or hyperlipidemia slows the progression of ALS.

Cognitive performance in diabetes and ALS

We found that pre-morbid DM was associated with either similar or worse cognitive performance on neuropsychological tests at the time of ALS diagnosis. The patients with ALS–DM performed worse on tests of memory, semantic fluency and executive function. Additional investigation is required to ascertain the relationship between DM and ALS-associated cognitive deficits.

In addition to some current cognitive function being worse, we observed that patients with ALS–DM had slightly lower AMNART scores, which is thought to test for pre-morbid verbal IQ. The AMNART scores of both groups are still within the normal range so that the differences are unlikely to be clinically significant. However, they may indicate that ALS–DM patients have slightly less cognitive reserve before the onset of ALS, which may make them more vulnerable to the cognitive changes that can occur with ALS.

It is unclear why diabetes would have a protective effect on the motor symptoms but not on the cognitive symptoms of ALS. There are precedents for selective vulnerability, and it may be that DM has greater affects on motor neurons than the frontotemporal neurons. Some bench studies have shown that motor neurons require more calories compared to other neurons. This makes them more susceptible to caloric deficits that result from the hypermetabolism associated with ALS [8,14]. One possibility is that patients with greater serum lipids or glucose (HLD and DM), or who consume a higher calorie diet, may counter the effects of caloric restriction. Hence, their motor neurons are damaged to a lesser degree. This could account for a later age of onset and slower progression of the motor symptoms of ALS. But, this hypothesis clearly requires further investigation and is speculative at this time.

There are some caveats to this study. First, some data is missing on the studied variables. Second, this study was performed in a tertiary care clinical setting, and hence our observations regarding ALS and DM may not be applicable to the general ALS population. Third, the presence of pre-morbid DM was established retrospectively at the time of database review. Electronic records of medications and laboratory investigations (as listed in the Methods sections) were used for this purpose. Although this methodology has a high specificity, it has a low sensitivity: patients with borderline DM could be missed.

Fourth, it is possible that DM could have developed after the onset of ALS, but before its diagnosis in some patients. DM would then be *co-morbid* rather than *pre-morbid*. Also, because glucose intolerance has previously been associated with ALS, a subset of such patients might have actually developed glucose intolerance because of ALS. Fifth, we did not investigate the effects of DM on the risk of FTD: we tested for cognitive performance. The recently recommended consensus criterion for diagnosis of frontotemporal syndromes in ALS was not applied at the time of neuropsychological evaluation. Finally, we examined the presence or absence of DM, but lack data regarding glycemic control, medications, BMI and the life-style of the diabetic patients. It would be important to prospectively study the relationship between these variables and the motor and cognitive findings in ALS.

Conclusions

In this study, ALS onset was 4 years later in patients with pre-morbid DM. These findings support the hypothesis that metabolic perturbations may contribute to the clinical course of ALS. Future studies might quantify blood sugar, lipids, cholesterol, and lifestyle to further clarify the relationships between these factors and ALS.

The study design here does not distinguish between an association versus a cause-and-effect relationship for DM and a later age at the time of ALS onset; hence, one cannot yet use this data to recommend an increase in the caloric or carbohydrate intake by patients with ALS. However, the results of this study and several others suggest that it may be appropriate to avoid weight loss, caloric restriction, or agents that lower serum cholesterol and triglycerides in patients with ALS until the relationship between these variables and the rate of progression for ALS is clarified.

Acknowledgements

The authors thank the patients with ALS and physicians of the MDA and ALS Association Clinics at The Methodist Hospital and the Baylor College of Medicine. The authors also thank the Lou DeGeorge Family for its continued, generous support.

References

1. Brooks BR. Natural history of ALS: symptoms, strength, pulmonary function, and disability. *Neurology* 1996; **47:** S71–S81.
2. Ringholz GM, Appel SH, Bradshaw M, *et al*. Prevalence and patterns of cognitive impairment in sporadic ALS. *Neurology* 2005; **65:** 586–590.

3. Strong MJ, Grace GM, Freedman M, *et al*. Consensus criteria for the diagnosis of frontotemporal cognitive and behavioural syndromes in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler* 2009; **10:** 131–146.
4. Qureshi MM, Hayden D, Urbinelli L, *et al*. Analysis of factors that modify susceptibility and rate of progression in amyotrophic lateral sclerosis (ALS). *Amyotroph Lateral Scler* 2006; **7:** 173–182.
5. del Aguila MA, Longstreth WT Jr, McGuire V, Koepsell TD, van Belle G. Prognosis in amyotrophic lateral sclerosis: a population-based study. *Neurology* 2003; **60:** 813–819.
6. Cronin S, Hardiman O, Traynor BJ. Ethnic variation in the incidence of ALS: a systematic review. *Neurology* 2007; **68:** 1002–1007.
7. Lacomblez L, Doppler V, Beucler I, *et al*. APOE: a potential marker of disease progression in ALS. *Neurology* 2002; **58:** 1112–1114.
8. Desport JC, Torny F, Lacoste M, Preux PM, Couratier P. Hypermetabolism in ALS: correlations with clinical and paraclinical parameters. *Neurodegener Dis* 2005; **2:** 202–207.
9. Funalot B, Desport JC, Sturtz F, Camu W, Couratier P. High metabolic level in patients with familial amyotrophic lateral sclerosis. *Amyotroph Lateral Scler* 2008; **10:** 1–5.
10. Pradat PF, Bruneteau G, Gordon PH, *et al*. Impaired glucose tolerance in patients with amyotrophic lateral sclerosis. *Amyotroph Lateral Scler* 2009; **10:** 1–6.
11. Reyes ET, Perurena OH, Festoff BW, Jorgensen R, Moore WV. Insulin resistance in amyotrophic lateral sclerosis. *J Neurol Sci* 1984; **63:** 317–324.
12. Dupuis L, Corcia P, Fergani A, *et al*. Dyslipidemia is a protective factor in amyotrophic lateral sclerosis. *Neurology* 2008; **70:** 1004–1009.
13. Dupuis L, Oudart H, René F, Gonzalez de Aguilar JL, Loeffler JP. Evidence for defective energy homeostasis in amyotrophic lateral sclerosis: benefit of a high-energy diet in a transgenic mouse model. *Proc Natl Acad Sci U S A* 2004; **101:** 11159–11164.
14. Mattson MP, Cutler RG, Camandola S. Energy intake and amyotrophic lateral sclerosis. *Neuromolecular Med* 2007; **9:** 17–20.
15. Brooks BR. El Escorial World Federation of Neurology criteria for the diagnosis of amyotrophic lateral sclerosis. Subcommittee on Motor Neuron Diseases/Amyotrophic Lateral Sclerosis of the World Federation of Neurology Research Group on Neuromuscular Diseases and the El Escorial "Clinical limits of amyotrophic lateral sclerosis" workshop contributors. *J Neurol Sci* 1994; **124:** 96–107.
16. Satz P, Mogel S. An abbreviation of the WAIS for clinical use. *J Clin Psychol* 1962; **18:** 77–79.
17. Grober E, Sliwinski M. Development and validation of a model for estimating premorbid verbal intelligence in the elderly. *J Clin Exp Neuropsychol* 1991; **13:** 933–949.
18. Golden CJ. Identification of brain disorders by the Stroop Color and Word Test. *J Clin Psychol* 1976; **32:** 654–658.
19. Mahurin RC. The verbal series attention test: normal and demented older adults. *Clin Neuropsychol* 1996; **10:** 43–53.
20. Wechsler D, ed. *Wechsler Memory Scale–Revised Manual*. San Antonio, TX: The Psychological Corporation, 1987.
21. Smith A, ed. *Symbol Digit Modalities Test Manual*. Los Angeles: Western Psychological Services, 1973.
22. Mitrushina M, Satz P, Chervinsky A, D'Elia L. Performance of four age groups of normal elderly on the Rey Auditory-Verbal Learning Test. *J Clin Psychol* 1991; **47:** 351–357.
23. King MC. Effects of non-focal brain dysfunction on visual memory. *J Clin Psychol* 1981; **37:** 638–643.
24. Tombaugh TN, Kozak J, Rees L. Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming. *Arch Clin Neuropsychol* 1999; **14:** 167–177.
25. Gordon NG. The Trail Making Test in neuropsychological diagnosis. *J Clin Psychol* 1972; **28:** 167–169.
26. Scarmeas N, Shih T, Stern Y, Ottman R, Rowland LP. Premorbid weight, body mass, and varsity athletics in ALS. *Neurology* 2002; **59:** 773–775.
27. Pedersen WA, Mattson MP. No benefit of dietary restriction on disease onset or progression in amyotrophic lateral sclerosis Cu/Zn-superoxide dismutase mutant mice. *Brain Res* 1999; **833:** 117–120.
28. Eichner JE, Dunn ST, Perveen G, *et al*. Apolipoprotein E polymorphism and cardiovascular disease: a HuGE review. *Am J Epidemiol* 2002; **155:** 487–495.
29. National Institute of Health (NIH). *National Diabetes Information Clearinghouse- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)*. http://www.diabetes.niddk.nih.gov/dm/pubs/statistics (accessed 22/10/2009).

