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ORIGINAL ARTICLE

Tracheostomy with invasive ventilation for ALS patients: Neurologists' roles in the US and Japan

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Abstract

Our objective was to determine whether substantial differences in rates of TIV utilization in the U.S. and Japan are associated with the role of the treating neurologist. Questionnaires in English and Japanese were sent to neurologists who treated ALS patients in both countries. Questions included queries about rates of TIV use in their practices, level of encouragement of TIV use, the role of the neurologist in TIV decision making, management of patient/family requests to discontinue TIV once initiated, and personal choices if neurologists themselves had ALS. Results showed that 84% of American neurologists reported fewer than 10% of their patients had TIV, compared to 32% of Japanese. Americans less often encouraged TIV use (79% of American and 36% of Japanese seldom or never suggested or encouraged TIV). Finally, neurologists were asked whether they would choose TIV for themselves in the hypothetical scenario where they had ALS: over 70% of both groups declined TIV for themselves. In conclusion, consistent with past findings, Japanese neurologists were more likely to recommend TIV and more of their patients received TIV. Both groups believed their recommendations influence patient decisions. While Americans seldom recommended TIV to patients and most would not choose TIV for themselves, Japanese neurologists' recommendations and personal choices diverged.

Key words: TIV, tracheostomy, ALS, end-of-life decisions

Introduction

ALS is a progressive, incurable, irreversible neurodegenerative disease that inexorably progresses to a point where respiratory capacity fails, even with non-invasive ventilatory support. At this point, a choice must be made between tracheostomy with invasive (long-term) mechanical ventilation (TIV or LTMV, we use here TIV), and palliative care with subsequent respiratory failure in the short-term future. With TIV, ALS continues to progress to the point where some patients may reach a 'locked-in' state in which they cannot communicate effectively, but breathing is maintained indefinitely. Survival after TIV varies widely, from months (1) to several years (2).

Substantial disparities in rates of TIV utilization by ALS patients have been noted for some time (3).

Rates vary widely between countries, regions within countries, and even within institutions (3,4). Among American studies, TIV rates of 2% to 6% have been reported (5,6). In European studies, TIV use rates have ranged from 0% to 10.6% (1,7). In contrast, Japanese studies report rates of TIV use ranging from 25% to 46% (8–10).

Several explanations have been offered to account for this variation in TIV use, including different conceptualizations of the physician's role in medical decision-making, attitudinal differences of health care professionals, national variations in health insurance coverage and availability of institutional facilities, varying degrees of commitment to a life-prolonging approach (8), and availability of alternatives such as hospice.

We conducted a survey of American and Japanese neurologists who treat ALS patients in order to determine whether these differences in rate of TIV utilization still persist, and to identify possible contributing factors.

Methods

Sample

In the United States, we (HM) sent e-mails to 324 neurologists who were directors of ALS clinics and adult MDA clinics and their affiliates. Recipients could respond on the internet (using Survey Monkey) or by returning questionnaires as e-mail attachments. In Japan, questionnaires were mailed to 210 neurologists known to see ALS patients (selected by Ogino et al.).

Questionnaire

The questionnaire was written by the New York team (HM, JR with input from colleagues), with 24 fully structured multiple-choice items, several with subscales. Areas covered are shown in Table I. Questions were based on previous findings as well as clinical observations and published suggestions of other investigators (1,8). In order to preserve anonymity, minimal personal information was sought. The instrument was translated into Japanese and then reviewed and edited by MO and the Japanese TIV Study Group members. Questions about withdrawal of tracheostomy were modified to be appropriate in Japan. The protocol was approved by the New York State Psychiatric Institute – Columbia University Department of Psychiatry IRB. Data were collected during 2011.

Table I. Components of TIV questionnaire.

Domain	Number of items
1. Neurologists' experience in general practice, and experience with ALS patients	3
2. Doctor-patient communications: initial diagnosis; discussions of advance directives; assisted suicide	10
3. Beliefs about the doctor's role in TIV decision-making; percentage of patients with TIV in own practice. How often they suggest and encourage TIV	4
4. Attributes of patients and perceived patient preferences that influence their decision-making about TIV; practices regarding TIV discontinuation	9*
5. Personal choices if the neurologist him/herself had ALS (PEG, NIV, TIV)	3

*Includes subscale queries about 16 patient/situational attributes and 12 reasons patients may or may not want TIV.

Statistical analysis

Comparisons of responses of American and Japanese neurologists were first analyzed using χ^2 tests or *t*-tests. Logistic and multiple regression analyses were also performed. For items with skewed response distributions, Mann-Whitney *U*-tests were used. For those with a 1–10 response format with anchors, ranging from 1 = 'almost never' to 10 = 'almost always', responses of 1–3 were classified as 'low' or 'seldom/never'; scores of 4–7 = 'medium' or 'some of the time'; scores of 8–10 as 'high' or 'very often/almost always'. In those analyses regarding neurologists' degree of enthusiasm in recommending TIV to their patients, the 1–10 scale was dichotomized to reflect less (1–5) and more (6–10) enthusiasm. Because of the multiple comparisons examined, trend differences are not reported. Bonferroni corrections were not applied because this is an exploratory study. Alpha = .05, two-tailed.

Results

Samples

One hundred American neurologists in 44 states returned questionnaires, including 258 comments about various issues, a response rate of 31%. In Japan, 120 neurologists (57% response rate) living in all eight provinces, responded to mailed surveys, including 163 written comments. Respondents were highly experienced: over 85% had practiced neurology for > 10 years (87% of U.S. and 90% of Japanese respondents), and over half of each group had practiced neurology 20+ years ($\chi^2 = 0.18$, 1df, $p = .672$). However, Americans were far more specialized regarding ALS treatment: 71% had seen more than 20 new patients in the past year, compared to 10% of Japanese ($\chi^2 = 87.79$, 1df, $p < .0001$). Similarly, 77% of American neurologists were currently treating > 20 patients/year vs. 11% of Japanese neurologists ($\chi^2 = 100.43$, 1df, $p < .0001$).

Question 1. Do diagnostic styles (communication of initial diagnosis, discussion of advance directives, and frequency of requests for assisted suicide) vary by country?

There were more similarities than differences in diagnostic styles and management of advance directives among American and Japanese neurologists. Most said they "tell the diagnosis as clearly as possible", although more Japanese neurologists said they "tell in different words, somewhat vaguely", and 6% of Japanese and no Americans said they defer telling at all (2×3 cross-tabulation analysis, FET = .017). Thus we focus on the data more directly associated with TIV. Regarding when neurologists raise the issue of future preferences, there

were no major differences in timing. However, while advance directives as independent documents are widely used in the U.S., they are not in Japan. Rather, Japanese patients who express preferences have their wishes noted in their charts.

Assisted suicide. Neurologists were asked whether any of their patients raised the issue of physician assisted suicide. Keeping in mind that Americans saw far more ALS patients than Japanese respondents did, and thus were more likely to hear such requests, 51% of their patients vs. 25% of Japanese patients had made such requests ($\chi^2 = 15.25$, 1df, $p < .0001$).

Question 2. Do rates of TIV use in neurologists' practices vary by country? Do they differ in the extent to which they suggest and encourage use of TIV?

Respondents were asked "in your own practice, about what % of patients get TIV?" Response options were "1-2%, 3-9%, 10-25%, 26-49%, 50+%". Eighty-four percent of American neurologists reported fewer than 10% of their patients had TIV, compared to 32% of Japanese. In contrast, 38% of Japanese but only 5% of Americans reported that more than 25% of their patients had TIV ($\chi^2 = 62.08$, 5df, $p < .0001$). Overall, TIV rates continue to show substantial differences between countries.

We then asked "While there are probably always exceptions, in general do you suggest and encourage the use of TIV?" Similarly large differences were seen between samples, with substantially higher rates of encouragement among Japanese neurologists. Classifying the 1-10 rating scale into never/seldom, moderately often, and very often/almost always, 79% of American and 36% of Japanese neurologists seldom or never encouraged and suggested TIV, 20% of American and 58% of Japanese said sometimes, and 1% of U.S. and 6% of Japanese said almost always ($\chi^2 = 39.36$, 2df, $p < .0001$).

Question 3. The role of the neurologist in TIV decision making

Three possible roles for physicians in medical decision-making were offered: 1) It is my responsibility to make decisions for the patient and inform them what will be done; 2) My role is to present treatment options along with my recommendations; 3) I present the options and let them decide.

American neurologists never endorsed the first (doctor decides) and overwhelmingly (70%) chose the second - present options and their recommendations, while Japanese neurologists either agreed that it is their responsibility to make decisions (18%) or present options without a recommendation to let the patient decide (58%). The overall $\chi^2 = 67.19$, 2df, $p < .0001$.

Is there a relationship between size of ALS caseload and level of enthusiasm for TIV? We examined number of patients currently followed and likelihood of recommending TIV. We used a cut-off of 1-10 patients vs. 11+ patients, and dichotomized the 1-10 rating scale, asking "In general do you suggest and encourage use of TIV?" (1-5=less encouragement, 6-10=more encouragement). Among neurologists seeing <10 patients, TIV was not encouraged by 71% of American and 81% of Japanese neurologists ($\chi^2 = 0.21$, 1df, $p = .647$, NS). There was, however, a difference among those who saw 11+ patients: 95% of American neurologists did not recommend TIV compared to 68% of Japanese ($\chi^2 = 15.06$, 1df, $p = .0001$).

Is neurologists' level of encouragement of TIV related to percent of their patients with TIV? Our data show such a relationship. As shown in Table II, patients were more likely to have TIV if their doctors encouraged its use in both Japanese ($\chi^2 = 12.94$, 2df, $p = .002$) and American ($\chi^2 = 18.26$, 2df, $p < .0001$) samples.

Table II. Relationship between neurologist's level of encouragement in recommending TIV¹ and the percent of their patients who receive TIV.

Encouragement for TIV	Patients in practice receiving TIV			
	0-9 %	10 - 25 %	26+%	
U.S.				
Less	75 (87%)	9 (10%)	2 (2%)	$\chi^2 = 18.26$, df= 2, $p < .0001$
More	4 (50%)	1 (13%)	3 (38%)	
Japan				
Less	33 (38%)	28 (33%)	25 (29%)	$\chi^2 = 12.94$, df= 2, $p = .002$
More	3 (12%)	5 (20%)	17 (68%)	

¹Neurologists were asked "In general do you suggest and encourage the use of TIV rather than comfort care?" rated on a 1 (=almost never) to 10 (=almost always) scale which we dichotomized here.

Note: Based upon dichotomizing Encouragement for TIV, only eight of 94 (8.5%) U.S. neurologists were more encouraging of TIV compared to 25 of 111 (22.5%) of the Japanese neurologists. The 2x2 cross-tabulation for samples and the dichotomized encouragement exhibited a significant $\chi^2 = 7.40$, 1 df, $p < .01$.

Question 4. Is neurologists' length of experience with ALS or their perception of patient characteristics related to their encouragement/advice about TIV?

Neurologists' experience and encouragement of TIV. The dependent variable was percent of neurologists' own patients who have TIV. Predictor variables included years practicing neurology, number of new ALS patients seen in past year, and number of ALS patients currently followed. In both samples, only years of practice of neurology was positively associated with higher percent of patients with TIV (U.S.: Beta = .244, $t = 2.44$, $p = .017$; Japanese sample Beta = .234, $t = 2.52$, $p = .013$). Direct experience with ALS patients (new patients seen in past year, number currently followed) was unrelated to percent of own patients with TIV.

Perceived patient attributes that influence neurologists' decision-making about TIV. Neurologists were asked to rate the importance of each of 14 patient attributes in their decision-making and recommendations for TIV, on a 1–10 scale with higher numbers signifying greater importance. Scores on virtually all scales were skewed in the 'important' direction, but there were group differences. We performed a principal component analysis using varimax rotation with Kaiser normalization and identified four factors, as shown in Table III. The samples differed on three of the four factors: Japanese respondents considered Factor 1 (hope for the future) and Factor 3 (younger, young children, believe in cure) as more important than Americans, while U.S. respondents weighed Factor 4, patient functioning, as more important than Japanese respondents did. Regarding the influence of financial considerations on their recommendations, the majority of both American and Japanese neurologists agreed that they were highly important (55% vs. 63%, $\chi^2 = 1.59$, 1df, $p = .451$).

Perceived reasons that patients decide against TIV. Respondents were asked "When patients choose not to have TIV, what are their reasons?" Seven reasons

were listed. As shown in Table IV, responses to five of the seven options differed by country. More American neurologists endorsed the reasons "patient so disabled that he/she is ready to go", "financial burden", and "can't be cared for at home and doesn't want to go to facility". More Japanese neurologists endorsed the items "because it is illegal to discontinue TIV once started", and "patient doesn't want to live any longer".

Perceived reasons that patients decide in favor of TIV. Neurologists were asked "What factors do you think influence the patient's decision to choose TIV?" Five options were listed. Most neurologists (63% and 69%) agreed that "the way the doctor explains TIV" is influential ($\chi^2 = 0.93$, 1df, $p = .335$). Japanese neurologists were far more likely to think that patients are influenced by availability of facilities for ALS patients (72% vs. 36%, $\chi^2 = 24.36$, 1df, $p < .0001$). Questions about frequency of communication with patients who have TIV, and financial factors did not differ by country: about half of all neurologists thought communication with patients who had TIV was an influence ($\chi^2 = .021$, 1df, $p = .647$), and the majority thought financial factors were influential (67% vs. 55%, $\chi^2 = 2.59$, 1df, $p = .108$).

Percent of patients with TIV having emergency intubation. The range of reported rates was zero to 100%. We classified responses as 0–9%, 10–19%, and 20+, based on skew in response distributions. Overall, about one-third of neurologists in both countries reported that more than 20% of their patients received TIV on an emergent basis without an advance directive requesting it ($\chi^2 = 5.71$, 2df, $p = .058$).

TIV discontinuation. Neurologists were queried whether they asked patients starting TIV to specify circumstances in which they would want it discontinued. Seventy-one percent of American and 8% of Japanese neurologists reported such conversations ($\chi^2 = 24.18$, 1df, $p < .0001$). They were asked whether patients or family had requested discontinuation of TIV, and if yes, whether they had done so. Seventy-one percent of American and 49% of Japanese neurologists reported being asked to discontinue TIV ($\chi^2 = 8.39$, 1df, $p = .004$). Of the 63 Americans asked, 78% had agreed to do so, usually after consulting their hospital ethics committee or conferring with their palliative care team. Others referred the family to hospice. Most Japanese told their patients that it is not supported legally to discontinue TIV, while 12% just said it should not be removed. Finally, the proportion of patients who actually had discontinued TIV differed substantially: 39% of Americans reported that more than a quarter of their patients had done so, compared to none in Japan (FET $< .0001$).

Table III. Patient attribute factors that may influence neurologists' decision-making about TIV (1–10 scale: higher = more important).

Factor	U.S. (n = 93)	Japan (n = 120)	t-test, df, p
	Mean (SD)	Mean (SD)	
1. Hope	7.38 (2.00)	8.23 (1.45)	3.42, 161, .001
2. Support	7.74 (1.99)	7.57 (1.71)	0.66, 211, .509
3. Cure/Age	5.29 (1.85)	6.47 (1.97)	4.43, 211, <.001
4. Function	8.12 (2.27)	7.28 (2.16)	2.74, 211, .007

Factor 1: patient characteristics of hope for the future and capacity for enjoyment in the absence of depression and cognitive impairment.

Factor 2: external support (financial and familial).

Factor 3: having young children, being younger, and believing that an ALS cure is imminent.

Factor 4: poor patient functioning and medical comorbidities.

Table IV. Perceived determinants of patients' decisions regarding TIV; number (%) of neurologists who endorse each reason.

	U.S. Yes (%)	Japanese Yes (%)	χ^2	<i>p</i>
Reasons patients do not want TIV				
Patient is so disabled that he/she is ready to go	80 (87%)	45 (38%)	50.62	<.0001
Burden on family	84 (91%)	105 (88%)	0.44	.507
No caregivers	53 (58%)	76 (63%)	0.50	.480
Financial burden	67 (73%)	66 (55%)	6.34	.012
Not able to discontinue TIV once initiated	8 (9%)	58 (48%)	36.34	<.0001
Patient doesn't want to live any longer (including psychological factors)	65 (71%)	103 (86%)	6.40	.012
Cannot be cared for at home and does not want institutional care	70 (76%)	48 (40%)	26.04	<.0001
Influences on patient's decision in favor of TIV				
The way the doctor explains TIV	63 (72%)	83 (69%)	0.14	.706
Communication with patients who already have TIV	44 (50%)	65 (54%)	0.21	.647
Home care availability 24/7	67 (76%)	83 (69%)	0.90	.343
Available facilities for TIV patients	32 (36%)	86 (72%)	24.36	<.0001
Financial factors	59 (67%)	66 (55%)	2.59	.108

Question 5. Would neurologists choose for themselves (in the hypothetical scenario where they have ALS) what they recommend to their patients?

Respondents were asked whether they would choose to have three interventional procedures, if medically indicated, as shown on Table V. In this hypothetical situation, although the majority of both groups did agree to have either percutaneous endoscopy (PEG) or non-invasive ventilation (NIV), Japanese neurologists were less likely to want these procedures than American neurologists ($p = .001$ and $<.0001$, respectively). The groups did not differ with respect to TIV: over 70% of both groups would not choose TIV for themselves, and the remainder was divided between answering affirmatively and saying that they "can't tell now".

We then examined the correspondence between neurologists' choices for themselves and their degree of encouragement of TIV for their patients. If neurologists would not accept TIV for themselves, would they usually recommend it to their patients? Among American neurologists, 80% seldom or never encouraged TIV for their patients and 76% would decline it for themselves. In contrast, only 36% of Japanese neurologists seldom or never encouraged TIV for their patients while 72% declined to have it for themselves (see Table VI). We then examined level of encouragement for TIV for their own patients (using the dichotomous scale "Do you generally encourage

TIV for your patients?") by Japanese neurologists who did not want TIV for themselves compared to those who did want TIV for themselves. We found that 89% of those who did not want TIV for themselves were less likely to recommend it to their patients, compared to only 33% who were less enthusiastic about TIV for their patients among neurologists who did personally want TIV (89% (75/84) vs. 33% (6/18), $\chi^2 = 28.38$, 1 df, $p <.0001$).

Discussion

While Japanese and American neurologists share many beliefs and practices about management of ALS, several consistent differences emerge. These must be considered in view of differences between countries in practice structure, government roles and laws. It is legal to discontinue TIV in the United States. In Japan, the situation is ambiguous. There is no specific law regarding TIV discontinuation, and there are Ministry of Health guidelines for doing so, but discontinuation is rarely considered. Even when a neurologist proposes this, hospital ethics committees and hospital administrators typically refuse, as there is no legal protection from prosecution.

Most American neurologists specialized in treating ALS patients saw them in major clinics with extensive staff. Government insurance (Medicare) is available for all ALS patients. Palliative care is the standard of care for patients approaching death, and

Table V. Neurologists' choices for themselves regarding interventional procedures.

Procedure	PEG Yes (%)	NIV Yes (%)	TIV		
			Yes (%)	No (%)	Cannot tell now (%)
U.S.	80 (94%)	82 (94%)	7 (8%)	68 (76%)	14 (16%)
Japan	85 (76%)	74 (67%)	18 (15%)	84 (72%)	15 (13%)
	$\chi^2 = 10.50$ df = 1 $p = .001$	$\chi^2 = 19.85$ df = 1 $p = <.0001$		$\chi^2 = 2.80$ df = 2 $p = .247$	

Table VI. Relationship between encouraging TIV for patients and personal choice of TIV.

U.S.		
Encourage TIV		
Seldom/Never	Sometimes	Often/Always
69 (80%)	16 (19%)	1 (1%)
Choose TIV for self		
No	Uncertain	Yes
65 (76%)	14 (16%)	7 (8%)
Japan		
Encourage TIV		
Seldom/Never	Sometimes	Often/Always
42 (36%)	68 (58%)	7 (6%)
Choose TIV for self		
No	Uncertain	Yes
84 (72%)	15 (13%)	18 (15%)

Query 1: "In general, do you suggest and encourage the use of TIV rather than comfort care?"

Score on 1-10 scale: 1-3 = seldom/never, 4-7 = sometimes, 8-10 = often/always.

Query 2: "Should you be diagnosed with ALS, and had progressive dyspnea, would you accept TIV?"

Score: choice of yes/probably yes; cannot answer until I find myself in that position (= uncertain); no/probably no.

Note: Within the national samples, there was 65% agreement/consistency among the U.S. neurologists compared to 44% among the Japanese neurologists. The U.S. neurologists exhibited significantly higher agreement for encouraging and self-choosing TIV compared to the Japanese neurologists ($\chi^2 = 9.21$, $df = 1$, $p < .003$).

according to a large database from the 1990s, most ALS patients in the United States receive palliative care, hospice, and die at home (5). Long-term facilities are limited and generally not geared to ALS patients (11).

Japanese neurologists typically have individual practices, are less specialized and personally treat far fewer patients with ALS. They are, however, informed and knowledgeable about the disease and its prognosis. Patients with 'intractable diseases' including ALS receive all necessary medical care including hospitalization without charge, as well as long-term home care visits by personnel including physicians under the Long-term care Insurance Act law (12). A Japanese ALS patient voluntary organization vigorously promotes TIV (13), while American organizations do not take an advocacy position. Consistent with the literature and national policies, in our study Japanese neurologists were more likely to recommend TIV and more of their patients received TIV, while Americans seldom did so and few of their patients received TIV. Most (75%) Americans presented treatment options to patients along with their recommendations. Among Japanese neurologists, 58% said they presented options without recommendations (even though two-thirds said in response to another query that they moderately often encourage/suggest TIV). Both groups believed that their recommendations influence patient decisions, and our data support this. This may be one of the first studies to show a direct correspondence between neurologists' level of enthusiasm for TIV

and the percentage of their patients who actually receive TIV.

In addition, American and Japanese neurologists largely agreed that most of the patient and family characteristics listed in the questionnaire did influence their decision-making, especially familial support and adequacy of financing. There were, however, some differences: Japanese neurologists weighed more heavily the patient's degree of hope for the future, their having young children and believing in an imminent cure, while Americans emphasized current patient functioning including medical comorbidities.

Our finding that two-thirds of Japanese neurologists moderately often encourage TIV for ALS patients is not universally seen among Japanese physicians. Aita et al. (14) queried 27 internists and surgeons about TIV use in older adults with stroke-caused profound impairment and no hope for recovery. Most discouraged TIV use, although artificial nutrition and hydration were considered essential. The difference between Aita's findings and ours may be due to the fact that most ALS patients retain substantial cognitive capacity, an attribute considered 'highly important' in recommending TIV by 87% of the Japanese neurologists we surveyed. Cognitive capacity was the most widely endorsed of the 14 attributes we asked about (listed in Table III). Thus, differences in level of consciousness and cognitive capacity, which are generally present in ALS patients and essentially absent in severely impaired stroke patients, likely account for these disparate attitudes.

An interesting finding concerns the association between what doctors recommend for their patients and what they would choose for themselves, should they have ALS. While Americans were largely consistent in not recommending TIV for patients and not wanting it for themselves, Japanese neurologists were far more likely to recommend TIV to their patients than choose it for themselves. This disparity is consistent with research showing that physicians are more likely to recommend invasive procedures with attendant risks of serious adverse sequelae to their patients than they would choose for themselves, given death as the alternative. For example, Ubel et al. (15) presented to physicians a colon cancer scenario with two options, varying in terms of survival rate with lower survival accompanied by fewer serious adverse events (i.e. length of life versus quality of life). Given two options, 38% of 242 internists chose for themselves the option with better quality of life despite a higher death rate, while only 25% chose this option to recommend to a hypothetical patient. In an invited commentary, Shaban et al. (16) observed that these data suggest physicians more often favor prolongation of life for their patients but place more emphasis on quality of life concerns when making decisions for themselves. Other investigators similarly have observed

contexts that choosing for others differs from choosing for oneself in decision-making (17–19), and this has been widely discussed after a 2012 publication of an article in *The Wall Street Journal* (U.S.) entitled ‘Why doctors die differently’. In our survey, the Japanese neurologists behaved more like participants in these studies than Americans, who seldom recommended TIV either to patients or chose it for themselves. An alternative explanation might be that Japanese neurologists express a general societal option to their patients, that TIV is recommended, which is the message of the influential ALS association in Japan.

We note several limitations. First, although the response rates are equivalent to those expected of e-mail surveys (20) and postal surveys (21) and are regionally distributed, respondents represent only a portion of the population of neurologists treating patients with ALS. Secondly, we collected little information about respondents to protect anonymity, and kept the survey brief to encourage participation. Thirdly, the neurologist’s philosophy and approach regarding TIV for their patients with ALS may be only one component of the story. We are currently surveying patients and caregivers with similar questionnaires. Ultimately, the combined input from neurologists, patients and caregivers is expected to increase our understanding of TIV use in our two countries.

Despite these limitations, to our knowledge this is the first systematic survey concerning neurologists’ roles in TIV decision-making. Responses of 220 neurologists in almost all regions of the two countries do provide a glimpse of our practice philosophy and approach to patients in the terminal stages of this disease, and we are beginning to understand the observed variations in TIV use. A better understanding of the neurologist’s role in this process can improve patient care during this most precarious phase of the disease.

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Declaration of interest: J. Rabkin: Cephalon-Teva currently provides armodafinil for an NIH-funded study, as well as funds and product to

complete an NIH-supported placebo controlled randomized clinical trial of armodafinil in 2010.

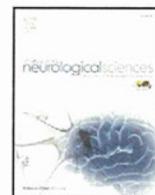
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ZNF512B gene is a prognostic factor in patients with amyotrophic lateral sclerosis

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ABSTRACT

Recently, Iida et al. discovered a new single-nucleotide polymorphism (SNP) in the ZNF512B gene associated with susceptibility to amyotrophic lateral sclerosis (ALS). The ZNF512B gene was found to be a transcription factor promoting the expression of a downstream gene in the signal transduction pathway of the transforming growth factor- β (TGF- β), which is essential for the protection and survival of neurons but the influence of the new SNP (rs2275294) in actual ALS patients remained unknown. The objective of our study was to examine whether the new SNP in the ZNF512B gene might influence the phenotype of ALS. We conducted a retrospective analysis of the ZNF512B gene in 176 patients diagnosed as having ALS at our hospital. Evaluation of the prognosis after the onset using Kaplan–Meier survival curves in patients with versus without the risk allele (C allele: CC and CT genotypes) revealed a significantly lower survival probability in those with the risk allele (log-rank test, $P < 0.01$), independent of the other prognostic factors in ALS. Our study revealed the influence of the new SNP in actual ALS patients. It would be clinically reasonable to suggest that the ZNF512B gene is a new prognostic factor in ALS. This study is the first, as per our knowledge, to indicate that the association between the new susceptibility gene for ALS and its pathway could be identified.

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1. Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease characterized by a loss of both upper and lower motor neurons usually leading to death due to failure of the respiratory muscles. The mean survival time is 3–5 years. Knowledge of disease progression and survival time is very important for clinical care and research. Due to the current lack of an effective disease-modifying therapy, increasing attention has recently been directed towards possible prognostic factors in order to identify additional therapeutic targets but the influence of genetics on the rate of disease progression and survival is scarcely known.

Recently, the study team led by Iida et al. conducted a large-scale genetic association study in 1305 Japanese patients with ALS, discovering a new single-nucleotide polymorphism (SNP) associated with susceptibility to ALS in the ZNF512B gene in chromosome 20q13.33 [1]. In regard to the susceptibility genes for sporadic ALS (sALS), 30 association studies based on the candidate-gene approach have been reported [2,3], and an analysis involving Japanese subjects resulted in the first discovery of the sALS susceptibility gene in East Asians [4]. The ZNF512B gene is a transcription factor with unknown function, and the mechanism underlying the association between the

onset of ALS and this gene was unknown. Iida et al. revealed that the new SNP (rs2275294) located in intron 12 of the ZNF512B gene reduces expression of the gene. Moreover, the ZNF512B gene was found to be a transcription factor promoting the expression of a downstream gene in the signal transduction pathway of transforming growth factor- β (TGF- β) [5], which is essential for the protection and survival of neurons [6–8]. Based on these results, the following mechanism is proposed. In patients with the susceptibility SNP for ALS, ZNF512B gene expression is reduced, resulting in the weakening of the neuronal protection signals.

The objective of the present study was to examine whether the new SNP in the ZNF512B gene might influence the phenotype of ALS. For this purpose, we investigated the disease course and survival data in ALS patients with and without the risk allele (C allele: CC and CT genotypes).

2. Patients and methods

2.1. Patients

We analyzed the ZNF512B gene in 176 patients diagnosed as having definite ALS according to the revised El Escorial criteria [9] between April 1995 and December 2010 at our hospital, and the site of disease onset was determined by experienced neurologists on the basis of the first symptoms. Although ALS patients diagnosed as having probable or definite ALS were included in the original study of Iida et al. [1], probable ALS patients were excluded in our study. The first

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