The course of the terminal phase in patients with amyotrophic lateral sclerosis

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Abstract

The fear of "choking to death" is on the mind of most patients suffering from amyotrophic lateral sclerosis (ALS). So far, how- ever, there have been no systematic surveys concerning the dying phase in a general ALS population. We therefore performed a structured telephone interview with the relatives of 121 patients who died from ALS and were followed by the Motor Neuron Outpatient Clinic of the Department of Neurology, University of Munich, Germany. These data are compared with those obtained by a retrospective analysis of medical records of 50 ALS patients who were followed by the Wisdom Hospice, Rochester, UK.

The data show that most ALS patients (Germany 88%, UK 98%) died peacefully, and no patient "choked to death". The symptoms most frequently reported for the last 24 hours were dyspnoea, coughing, anxiety and restlessness. Around half (G 55%, UK 52%) of the patients died at home. The main palliative measures in place during the terminal phase were: home mechanical ventilation (G 21%, UK 0%), percutaneous endoscopic gastrostomy (G 27 %, UK 14%), morphine (G 27%, UK 82%) and benzodiazepines (G 32%, UK 64%). The use of these palliative measures was judged to be beneficial by almost all relatives. These data support the hypothesis of a peaceful death process in ALS and should be communicated to patients and their relatives, at the latest after the onset

of dyspnoea, to relieve unwarranted fears.

Introduction

How people die remains in the memories of those who live on.

Dame Cicely Saunders

Nearly all patients suffering from amyotrophic lateral sclerosis (ALS) develop symptoms of respiratory insufficiency during the course of their disorder [2]. Often from the time of diagnosis and certainly in the later stages, ALS patients, when questioned, express fears of "choking to death". Clinical experience suggests that the natural course of the dying phase in ALS is a peaceful one. At present, however, only few data are available concerning the terminal phase of ALS patients, and they are restricted to ALS patients dying under the care of specialist palliative care services [16,17]. We therefore performed a retrospective study on the natural history of the terminal phase in ALS in two different countries and clinical settings.

Subjects and methods

A review of the database of the Motor Neuron Outpatient Clinic of the Department of Neurology, University of Munich, yielded 179 patients who had been diagnosed with probable or definite ALS according to the El Escorial criteria [7], and had died between January 1995 and March 1999. In 121 cases (68 %) we were able to perform a structured telephone interview (standardised list of questions) with the care- giver who was present at the moment of death and for all or most of the 24 hours preceding it (119 relatives, 2 nurses). In addition, we obtained the reports of eight nurses and three physicians who were present at the moment of death and confirmed the relatives' information. The questions focused on the symptoms and the degree of suffering in the terminal phase (as perceived by the caregiver), the state of consciousness during the terminal phase, the place of death and the palliative care administered in the terminal phase (medication, especially opioids and benzodiazepines, nutritional aids and ventilatory support). For 88 of these patients, detailed medical records on the terminal phase were available to complement and confirm the care- givers' reports.

Similar retrospective data were available for 50 ALS patients who died between 1991–1999 and had been followed by the Wisdom Hospice, Rochester, UK. This group comprises virtually all ALS patients in the Rochester area during the study period. The data were obtained from the patients' charts, which included caregivers' accounts as well as medical information recorded by hospice nurses and doctors. Statistical analyses were performed with SPSS 10.0, using the coefficients of correlation by Spearman and Pearson and the Mann-Whitney U- test where appropriate.

Results and Discussion

All 121 German caregivers we reached agreed to be interviewed. Fifty-eight caregivers could not be reached; 9 had died in the meantime, 15 had moved and the address was unknown, and in 34 cases no telephone contact could be established. The demographics (Table 1) show the typical sex, age and site of onset distributions of ALS patient populations [13,21]. There were no significant differences in the demographic data between the German and the UK patient populations. The caregivers' distribution shows a statistically significant preponderance of female caregivers, irrespective of the sex of the patient (Germany: $r = -0.62$, $p < 0.001$; UK: $r = -0.8$, $p < 0.001$). We believe this to be due to socio-cultural influences, since taking care of the sick is usually considered a "female task" in Western Europe.

The causes of death are shown in Table 2 and, as expected, by far the most common cause of death was respiratory failure [8]. Interestingly, 10 sudden deaths (G 8, UK 2) were attributed to cardiac failure without further corroborating evidence. Autonomic function is known to be subclinically affected in a subset of ALS patients [9,20]; whether these patients are more prone to this kind of "sudden" death, is a matter for future investigation.

A crucial question concerned the degree of suffering in the terminal phase as perceived by the caregiver. Wilkes [25] investigated the terminal phase and death of 262 patients with several different diagnoses. In his study the relatives detected pain and dyspnoea of the patients significantly more often than the hospital nurse or the general practitioner. Correspondingly, we assumed that interviewing the relatives could be a sensitive way to assess the

degree of the patients' suffering in the terminal phase. The other important question was the definition of the term "peaceful death". We follow Weismann [24] who defined a good or peaceful death as the type of death one would choose if there were a choice.

The most important result, confirming clinical experience, is that the vast majority of ALS patients (G 88%, UK 98 %; p=0.11) died peacefully and no patient "choked to death" (Table 3). This result corresponds closely with the survey from O'Brien et al. [16], in which all patients were followed by and 91% died in a hospice institution. In the German patient population, only 15 patients (12%) were followed by, and only 11 (9%) died in, a hospice institution. The mechanism most often hypothesised for the dying phase in ALS is that of hypercapnic coma arising from slowly progressing respiratory weakness and leading to a peaceful death in sleep [11]. However, it should also be noted that eight patients (G 7, UK 1) experienced moderate to severe suffering in the terminal phase. The symptoms reported for the last 24 hours are shown in Table 4. Symptoms which were not relieved satisfactorily in the terminal phase included cough attacks due to mucous airway congestion (n=4), restlessness and anxiety (n=3), and painful cramps (n=1).

Six German patients died after a resuscitation attempt, initiated by the relatives. All six relatives considered this in retrospect to have been a grave mistake. This group emphasises the necessity of an early discussion of advance directives with ALS patients and their relatives [3,5,6]. The suicide rate was below 1%, reinforcing the clinical experience that, although suicidal thoughts are common, suicidal acts are rare in ALS.

Consideration of the state of consciousness at the time of death showed that 33 patients (27%) were awake (i.e. had been alert and communicating 5 min or less be- fore death), 75 patients (62%) were asleep and 13 patients (11%) were comatose, incl. the six who died after a resuscitation attempt (these data were not available for the UK patients). As shown in Fig. 1, a high proportion of patients (G 72%, UK 48%) deteriorated rapidly and died within 24 hours.

Around half of the patients (G 55%, UK 52%) died at home. In Germany, 22% died in hospital ($p < 0.001$ compared with UK 0%), while 48% of UK patients died in hospice ($p<0.001$ compared with G 9%; Fig. 2). These differences are most likely due to the fact that all UK patients were followed by a specialist palliative care team. Traditionally, a large proportion of ALS patients in the UK are followed by a hospice team in the late stages of the disease. In a recent survey, 96% of responding British hospices reported being involved in the care of ALS patients [19], while only 40% of German palliative care units accept neurological patients [12]. In addition, the availability of hospice assistance is significantly lower in Germany (around 6.4 hospice beds/million in- habitants, vs. around 54/million in the UK [12]).

Nine of the German patients were intubated shortly before death due to respiratory insufficiency ($p=0.048$ compared with UK 0%). Eight of them died on an intensive care unit; six of them were extubated prior to death at their or their relatives' explicit request. The average duration of intubation was 6.3 days (range 2–8). These data point again to the urgent necessity of early discussion and institution of advance directives in ALS patients to prevent unwarranted medical interventions in the terminal phase [15].

An overview of the most important palliative measures administered during the terminal phase is given in Table 5. Twenty-seven percent of the German patients (UK 14%) had a percutaneous endoscopic gastrostomy (PEG) at time of death, which was considered to be a beneficial palliative measure by 93% of caregivers. Similarly, 95% of the caregivers of patients on noninvasive home mechanical ventilation reported a high benefit of the procedure (but only two out of four using invasive ventilation). This is in agreement with previous data showing a high acceptance of noninvasive ventilation for ALS patients, but a higher burden of care for care- givers of tracheostomised patients [1, 15, 22]. Thick mucous secretions reduced the benefit of ventilation in the terminal phase for three patients (two invasive, one non-invasive). All ventilated patients were in Germany, totalling 21% of the Munich patient group ($p=0.001$ compared with UK). This reflects previously described differences in the availability of this treatment option between countries and centres [4].

The data show that a significant proportion of patients required morphine and/or benzodiazepines in the terminal phase. The indications for morphine were dyspnoea (G 21 %, UK 40 %) and pain (G 7 %, UK 42 %). The indications for benzodiazepines were anxiety due to dyspnoea (G 23%, UK 48%), sleep disorders (G 5%, UK 14%), and restlessness (G 4%, UK 2%). These drugs were significantly more likely to be administered if the patient died on a palliative care unit (morphine: $r=0.45$, $p < 0.001$; benzodiazepines: $r=0.39$, $p < 0.001$) or was a UK patient (morphine: $r=0.49$, $p <$

0.001; benzodiazepines: r=0.29, p < 0.001). These discrepancies reflect, in our opinion, the higher general knowledge on palliative treatment in the UK and correspond with published data indicating a chronic under-consumption of morphine in Germany [26]. Other studies have also shown that morphine can be used safely in patients with ALS [18]. Owing to the small number of non-peaceful deaths in our study, it is not possible to assess statistically whether the likelihood of a peaceful death is indeed influenced by the administration of these drugs. The care- givers' perception of benefit was uniformly positive for both treatments.

This study has several possible shortcomings. First, a selection bias cannot be excluded, since almost one third of the German caregivers could not be contacted. How- ever, our patient sample fully matches published epidemiological data for ALS with regard to age, sex, dis- ease onset and duration. Secondly, proxy assessment may be biased, especially if retrospective. Thirdly, com- paring data from two countries may be inappropriate if the patient groups are different. In our case, the lack of statistical differences between the two groups in terms of demographics argues in favour of the comparability of the data.

The results of our survey support the hypothesis that the natural course of the terminal phase in ALS is generally, albeit not uniformly, a peaceful one. These data require confirmation in a prospective study. Combined, multidisciplinary efforts by palliative care teams and motor neuron disease clinics can allow a high proportion of the patients to die at home. Where this is not possible, inpatient hospices or palliative care units provide a safe and comfortable environment to ease the physical and psychological burden of patients and relatives during the terminal phase [16]. Whether palliative care measures are necessary to ensure a peaceful death can- not be decided on the basis of our data. PEG, noninvasive ventilation, morphine and benzodiazepines, when administered, were regarded as beneficial by almost all caregivers, suggesting a positive effect of these measures on the quality of life of patients and caregivers prior to the patients' death.

The proportion of peaceful deaths observed in our series compares favourably with other published data in non-ALS populations. The rates of peaceful deaths re- ported ranged from 47.5 % (cancer patients without sedatives [23]), to 78.7% (geriatric patients [10]), up to 91,5% (hospice patients [14]). Thus, the chances of ALS patients for a peaceful death appear to be above, rather than below, average. ALS patients are often anxious about the dying process from soon after the time of diagnosis and should be informed proactively, at the latest at onset of respiratory symptoms, about the natural course of the terminal phase and the good efficacy of palliative measures. This could help to dispel unwarranted fears of "choking to death" and thus increase the quality of life of patients and families. The verification of this hypothesis will be the subject of a prospective study.

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Table 1 Demographics

	Germany (n=121)	UK (n=50)
Patients		
sex	71 male (59 %)	28 male (56 %)
mean age	62.7 years (27–86)	66.0 years (36–92)
	37 (31 %) bulbar (17 m, 20 f)	18 (36 %) bulbar (9 m, 9 f)
		32 (64 %) limb (19 m, 13 f)
Caregivers		
spouses/partners	83 (69 %) (58 f, 27 m)	41 (82 %) (25 f, 16 m)
children	25 (21 %) (16 f, 9 m)	2 (4 %) (2 f)
other relatives		
nurses	0	2 (4 %)

Table 2 Causes of death

	Germany	UK
respiratory failure	99	48
heart failure		
pneumonia	8	
suicide		
	8	

Table 3 Suffering in the terminal phase

Germany	UK	
107 (88 %)	49 (98 %)	died peacefully
6 (5 %)	0 (0 %)	died in moderate suffering
1 (1 %)	1 (2 %)	died in severe suffering
6 (5 %)	0 (0 %)	died after a resuscitation attempt
1 (1 %)	0 (0 %)	committed suicide

Table 4 Symptoms in the last 24 hours

	Germany	UK
Dyspnoea	24 (20 %)	15 (30 %)
Restlessness and anxiety	10 (8 %)	3 (6 %)
Choking on saliva or mucus	9 (7 %)	0 (0 %)
Coughing	5 (4 %)	10 (20 %)
Diffuse pain	2 (2 %)	1 (2 %)

Table 5 Palliative effect of nutritional aids, ventilator support and medication in the terminal phase

	PEG		Ventilation		Morphine[a]		Benzodiazepines	
	Germany	UK	Germany	UK	Germany	UK	Germany	UK
Patients	33 (27 %)	7 (14 %)	25 (21 %) (21 noninvasive, 4 invasive)	0	33 (27 %)	41 (82 %)	39 (32 %)	32 (64 %)
Mean dosage (range)	–	–	–	–	90 mg/d (10–360)	115 mg/d (8–570)	n. a.	n. a.
Mean duration (range)	198 d (6–1008)	179 d (18–810)	297 d (2–1695)		6 d (1–52)	n. a.	120 d (1–1400)	n. a.
Beneficial according to caregivers	30 (91 %)	n. a.	20/21 noninvasive (95 %) 2/4 invasive (50 %)		30 (91 %)	n. a.	33 (85 %)	n. a.
Reduced or no benefit	3 (9 %)	n. a.	1/21 noninvasive (5 %) 2/4 invasive (50 %)		3 (9 %)	n. a.	6 (15 %)	n. a.
Comments	2 PEG removals due to infection		Thick mucous secretions limited effectiveness in 3 pts				Neg. side effects in 6 pts: drowsiness, addiction	

Figure 1 Place of death. ICU, intensive care unit * p = less than 0.001 compared to UK

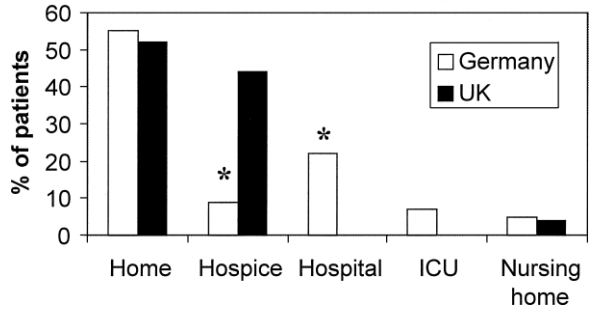

Figure 2 Time between acute deterioration and death