ELSEVIER

Sleep Medicine 5 (2004) 37–41

SLEEP MEDICINE

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Original article

Factors associated with a delay in the diagnosis of narcolepsy

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Received 30 January 2003; received in revised form 10 June 2003; accepted 12 June 2003

Abstract

Background: There can be a long interval from the onset of symptoms before a diagnosis of narcolepsy is made. There are no multivariate analyses reported in the literature of factors that may contribute to this delay. The aims of this study were to describe the delay in diagnosis of people with narcolepsy living in the UK and to identify associated factors.

Methods: The study comprised a postal survey of 500 members of the Narcolepsy Association UK, which included questions regarding age of onset of symptoms, year of diagnosis and subject demographics. Cox's proportional hazards regression was performed.

Results: A total of 313 questionnaires were returned of which 219 had been completed sufficiently for analysis. The interval between symptom onset and diagnosis ranged from within 1 to 61 years with a median of 10.5 years. Multivariate analysis showed that the presence of cataplexy as one of the initial symptoms and a more recent year of symptom onset were the only factors associated with time to diagnosis.

Conclusions: We have confirmed that the diagnosis of narcolepsy can be delayed for many years particularly when cataplexy is absent initially. The delay in diagnosis in the UK appears to be decreasing, probably through greater doctor and patient awareness of the clinical manifestations of narcolepsy.

Keywords: Narcolepsy; Cataplexy; Diagnosis; Symptom onset; Multivariate analysis

1. Introduction

Narcolepsy is classically characterised by a tetrad of symptoms; excessive daytime sleepiness (EDS), cataplexy, sleep paralysis and hypnagogic hallucinations [1], although other symptoms are now recognised [2]. Not all four symptoms are necessary for diagnosis and the majority of people with narcolepsy do not have all of them [1,3–7].

The symptoms of narcolepsy usually, but not necessarily, start in the second or third decades of life [1,3–6,8–13] and new symptoms can develop over many years [3–5,9–11,13].

Delays between the first symptom and diagnosis have been reported to range from 1 to 60 years [13], with a mean delay of between 16 and 22 years [14–16]. Patients with a more recent onset of symptoms have been reported to have a shorter interval before they were diagnosed compared to those whose symptoms started further in the past [15]. A reduction in time to diagnosis has also been shown in people with more recent dates of birth [17]. Factors such as mild- or late-onset cataplexy, concomitant sleep apnoea and socio-economic factors can also contribute to a delay in diagnosis [18].

The aim of this study was to investigate the reported delay between symptom onset and diagnosis in people with narcolepsy living in the United Kingdom. Relationships were sought between the delay in diagnosis and; age at symptom onset, year of symptom onset, presence of cataplexy as an initial symptom, number of initial symptoms, gender and who made the diagnosis.

2. Methods

2.1. Subjects and questionnaire

A questionnaire was sent to 500 members of the Narcolepsy Association UK (UKAN), randomly selected by the UKAN membership secretary from their confidential database. The total membership of UKAN was unknown at the time of the study.

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doi:10.1016/j.sleep.2003.06.002

The questionnaire asked which of the tetrad of narcolepsy symptoms were present, the age at onset of these symptoms, year of diagnosis, who made the diagnosis, and general subject demographics including age at time of questionnaire completion. To be included in the analysis, subjects had to have completed all these questions and to have specified that narcolepsy had been diagnosed by their general practitioner (GP) or a hospital consultant.

2.2. Statistical analysis

Descriptive analysis was performed for: subject age and sex, combination of symptoms at the time of the questionnaire, who made the diagnosis of narcolepsy and in what year, age and calculated year of symptom onset and number of initial symptoms (defined as those that developed in the first year of the condition). Non-parametric tests were used to compare the distributions of age and sex between subjects included in the analysis and those whose questionnaires had missing data.

The interval between symptom onset and diagnosis of narcolepsy was calculated in whole years using relevant data from the questionnaire and adding 0.5 to create an approximate average. Thus people who reported being diagnosed within a year were recorded as being diagnosed after 6 months, people who reported being diagnosed after 1 year but before 2 years were recorded as being diagnosed after 18 months, and so on.

Univariate Cox's proportional hazards regression was carried out to identify any significant associations between time to diagnosis after symptom onset and a number of factors.

Statistical significance was assessed by the likelihood ratio test. In this case the hazard rate is a relative diagnosis rate. Significant factors identified in the univariate analysis were entered into a multivariate model. A backward stepwise procedure was used to identify factors independently associated with the delay in diagnosis.

3. Results

3.1. Subjects

A total of 313 questionnaires (63%) were returned and 219 (70%) of these were complete and were analysed. These 219 subjects had the same gender distribution as the 94 whose questionnaires had missing data ($P = 0.705$), but were significantly younger at the time of the questionnaire ($P = 0.009$).

The majority of subjects were female (59.4%). They were aged between 12 and 83 years (median = 54 years). EDS was reported by 98.2% of subjects, cataplexy (C) by 90%, hypnagogic hallucinations (HH) by 73.1%, and sleep paralysis (SP) by 69.4%. The distribution of the most commonly reported combinations of symptoms can be seen in Fig. 1A and other reported combinations in Fig. 1B.

The earliest diagnosis of narcolepsy was reported as being made in 1927. Seventy-six subjects (34.7%) had been diagnosed before 1981 (when UKAN was founded). Over half of the subjects (55.3%) were diagnosed by neurologists, hospital consultants with other specialities diagnosed 27.4%, and 17.4% had been diagnosed by their GPs.

3.2. Onset of symptoms

The reported age range of symptom onset was 1–68 years with a median of 18 years. Fifty percent of subjects reported having their first symptoms between the ages of 13 and 30 years (Fig. 2).

The year of symptom onset ranged between 1919 and 1995 (median = 1967). The majority (60.3%) had one

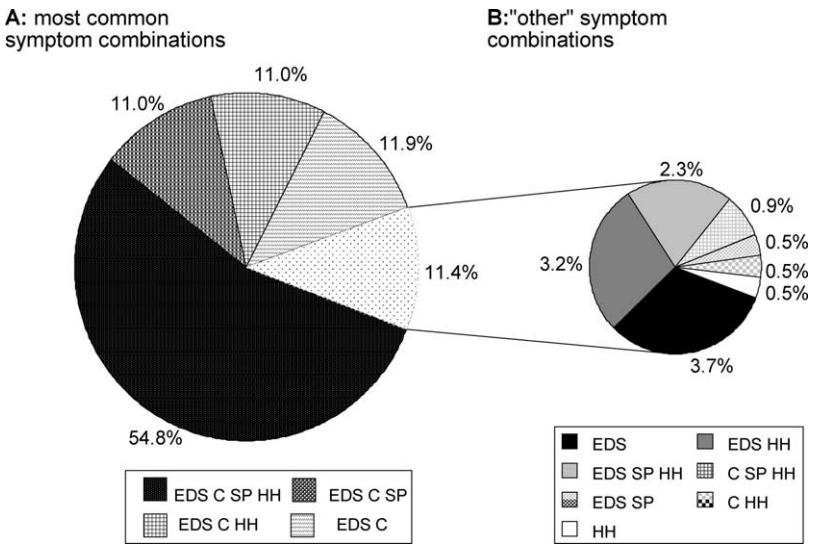

Fig. 1. Reported symptom combinations at the time of the questionnaire.

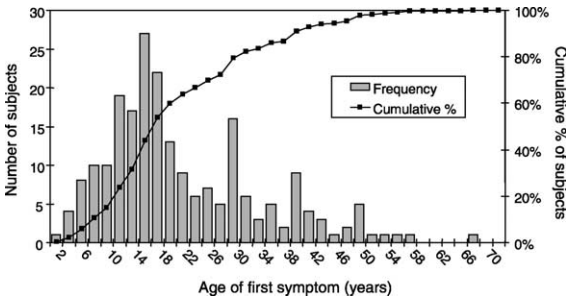

Fig. 2. Age of first symptom of narcolepsy.

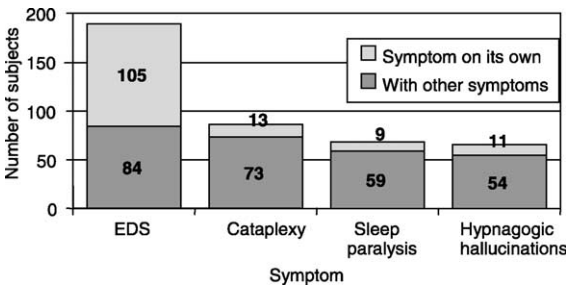

Fig. 3. Initial symptoms of narcolepsy.

symptom initially and only 9.1% had the complete tetrad initially. The most common initial symptom was EDS, which occurred alone in 46.1% of the subjects, and with other symptoms in 32.9%. The prevalence of each symptom developing first is shown in Fig. 3.

3.3. Delay in diagnosis

The interval between first symptom and diagnosis varied from within the same year to within 61 years with a mean length of time of 15 years and median of 10.5 years. Time to diagnosis showed a large spread for each decade of symptom onset (Fig. 4). The mean and median ages at diagnosis were 36 and 35 years, respectively.

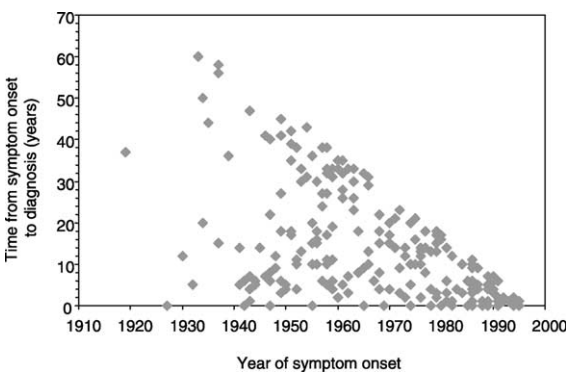

Fig. 4. Time from onset of symptoms to diagnosis by year of symptom onset.

The results of univariate Cox's regressions that showed significant associations, and the results of the multivariate Cox's regression are shown in Table 1. They are expressed as hazard rates with 95% confidence intervals. In the multivariate model the year of symptom onset and whether or not cataplexy was one of the initial symptoms were significant ($P < 0.001$ and $P = 0.002$) and stayed in the final model as shown by the table.

4. Discussion

We have described the symptom evolution and the interval between symptom onset and a diagnosis of narcolepsy being made in a sample taken from the membership of the Narcolepsy Association UK, all of whom specified that their GP or a hospital consultant had diagnosed them with narcolepsy. Excessive daytime sleepiness was reported by 98% of the subjects and a high percentage of subjects reported the additional symptoms of cataplexy, sleep paralysis and hypnagogic hallucinations. The age at onset of symptoms and their pattern of evolution was similar to those previously described for populations with narcolepsy [3–6,8–10,19,20].

As in previous studies [13–16] we found that there was frequently a long delay in diagnosis. The interval between symptom onset and diagnosis is determined by the time taken for a patient to present to their doctor, plus the time for the correct diagnosis to be made. It has been shown that 77 patients diagnosed with narcolepsy at a sleep disorders centre had a total of 715 visits to a doctor in the previous year but only 38% had received a diagnosis of narcolepsy [21].

We examined a number of factors to see if they were associated with a delay in diagnosis and found that in a multivariate model the presence or absence of cataplexy as an initial symptom and year of symptom onset were significantly associated with likelihood of diagnosis. Thus our results are consistent with previous reports that the onset or worsening of cataplexy often prompts patients to seek medical help [18] and that the interval between symptom onset and diagnosis is greater for people whose symptom onset was further in the past [15].

Our results indicate that the likelihood of being diagnosed with narcolepsy at any given time after the onset of symptoms is almost double if they started in the 1960s or 1970s, rather than before 1960, and six times more likely if they started during or after 1980. However, an inherent problem in analysing time from symptom onset to diagnosis in this type of study is that all subjects require a diagnosis to be included. There may be many people with recent onset of narcolepsy symptoms who have yet to be diagnosed. This may explain some of the difference but it seems likely that the decrease in time to diagnosis for recent years of symptom onset is genuine since all the three groups contained a similar number of subjects and the magnitude of

Table 1
Median and interquartile range for time between symptom onset and diagnosis of narcolepsy for associated factors, and results of univariate and multivariate Cox's regression

Factor	*N*	Median (years) (interquartile range)	Univariate analysis		Final multivariate model	
			Hazard rate (95% CI)	*P*-value	Hazard rate (95% CI)	*P*-value
Year of symptom onset						
≤ 1959	85	17.5 (7.0, 37.0)	1		1	
1960–1979	70	14.5 (7.25, 21.75)	1.9 (1.4, 2.7)	<0.001	1.9 (1.3, 2.6)	<0.001
≥ 1980	64	3.5 (1.5, 7.25)	6.5 (4.4, 9.8)		6.0 (4.0, 9.0)	
First symptom(s)						
Excluded cataplexy	142	14.5 (6.5, 29.75)	1	<0.001	1	= 0.002
Included cataplexy	77	5.5 (1.5, 14.0)	1.9 (1.4, 2.5)		1.6 (1.2, 2.1)	
Number of first symptoms						
1	132	14.5 (6.5, 30.0)	1			
2	37	6.5 (2.5, 13.5)	1.8 (1.2, 2.5)	<0.001		
3	30	6.0 (1.5, 15.25)	1.9 (1.3, 2.8)			
4	20	3.5 (0.75, 9.5)	2.3 (1.4, 3.6)			
Age of first symptom (years)						
≤ 14	69	14.5 (6.0, 33.0)	1			
15–29	94	10.5 (4.5, 23.75)	1.4 (1.0, 2.0)	<0.001		
≥ 30	56	6.5 (2.5, 15.25)	2.1 (1.4, 3.0)			

Note: Factors not significantly associated with time to diagnosis in the univariate analysis were gender, symptom combination at the time of the questionnaire and by whom the diagnosis was made.

the difference is great, particularly between the groups whose symptoms started before 1960 or after 1980.

The development of sleep medicine in the UK both in terms of diagnostic services and public awareness may have reduced the time to diagnosis for those with more recent onset of symptoms. There were only four or five major sleep centres available at the time we carried out our survey [22], and even fewer previously.

Unlike reports from France and Canada [15] our sample did not show a linear reduction in time to diagnosis with increasingly recent decades of symptom onset. The difference may be because our study sample was taken from a national narcolepsy association rather than a sleep clinic. UKAN has many members that were diagnosed prior to its inception while a sleep clinic population is likely to comprise patients who are first diagnosed at that clinic.

The age at onset of symptoms might be expected to influence the time to diagnosis. Narcolepsy usually begins during the teens or twenties and could be overlooked in people whose symptoms appear outside this range particularly if clear-cut cataplexy is absent. Children with the disorder may see many doctors before being correctly diagnosed [23] and have often been incorrectly diagnosed with a psychiatric disorder, epilepsy or learning difficulties or their symptoms attributed to temperament [7,23]. In our study, age at first symptom was associated with the delay in diagnosis when considered on its own but was not significant when other factors were taken into account.

A limitation of this study, as with previous studies, is the reliance on subjects correctly recalling when their symptoms started. The onset of EDS may be difficult to remember accurately if it was many years ago [24], especially as it may have a gradual onset [3,4]. The onset of cataplexy appears to be remembered more precisely [3,4,24]. It has been observed that a patient's family members may report a different date of onset of symptoms from the patient [3]. In our study 72% of the questionnaires excluded due to missing data had the age of onset of at least one of the symptoms missing. The subjects with missing data were older than the subjects without missing data when they completed the questionnaire and may have had more difficulty recalling when their symptoms started because it was longer ago.

A further limitation is that we did not confirm the diagnosis of narcolepsy but relied on people's reports that they had received such a diagnosis. However, since 89% of the sample reported having at least EDS and cataplexy from the tetrad of symptoms, and the frequency of reported auxiliary symptoms of sleep paralysis and hypnagogic hallucinations was similar or higher than in other adult samples [1,5,6,8,9,20,24,25], narcolepsy was probably the correct diagnosis in almost all of our subjects.

This is the first study to our knowledge to complete a multivariate analysis to assess the causes of the delay in diagnosing narcolepsy. We have found that even when other variables are taken into account, more recent onset of symptoms appears to be associated with a shorter time to diagnosis although this cannot be proved for certain with this type of study. Diagnosis was also reached sooner if cataplexy was an initial symptom. The age of onset of symptoms does not influence the delay in diagnosis in this multivariate model. There is often still a substantial delay

in diagnosis, but it is encouraging that this seems to have reduced in more recent years.

Acknowledgements

We would like to thank both the administration of the Narcolepsy Association UK for their help in posting the survey to their members and those who completed it. We would also like to thank the Research and Development department at Papworth Hospital for their help, particularly Susan Charman for her assistance with the statistical analysis.

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