

# Genetic study of narcoleptic syndrome

M. BARAITSER<sup>1</sup> AND J. D. PARKES

*From the MRC Clinical Genetics Unit, Institute of Child Health, London; The University Department of Neurology, The Maudsley Hospital; and King's College Hospital*

**SUMMARY** In this family study of the narcoleptic syndrome, 52% of the probands had an affected first degree relative, 41.9% of the sibs of those probands with an affected parent were similarly affected, 33.3% of the parents of 2 affected sibs and 41.2% of the children (after a correction for age) had narcolepsy, cataplexy, or both.

Narcolepsy, alone or combined with other features of the narcoleptic syndrome, often occurs in several members of a family. Westphal (1877) described a patient with narcolepsy and sleep paralysis whose mother had narcolepsy. It is generally accepted that familial cases are common, but the exact genetic mechanism is uncertain. This uncertainty is largely the result of the difficulty of separating physiological symptoms in the normal population from pathological symptoms in narcolepsy, and of difficulties in the clinical diagnosis of other disorders of excessive sleep. The 4 characteristic symptoms of the narcoleptic syndrome, narcolepsy, cataplexy, sleep paralysis, and hypnagogic hallucinations, may all occur in otherwise normal people. Until strict clinical criteria for the diagnosis of narcolepsy were established by Yoss and Daly (1957), narcolepsy was often confused with other disorders causing somnolence, such as head injury, alcoholism, endocrine disorders, cerebral tumours, encephalitis, and many different neuropsychiatric conditions. Narcolepsy and other disorders of excessive sleep have been defined by electroencephalographic abnormalities (Rechtschaffen *et al.*, 1963), but it is still not known at what age early onset rapid-eye-movement (REM) sleep first occurs in patients with narcolepsy. One symptom of the narcoleptic syndrome may precede others by up to 20 years, and the initial diagnosis of the type of sleep disorder may eventually prove incorrect.

Krabbe and Magnussen (1942) described a family in which 4 of 12 sibs had a sleep disorder, and reviewing other reports found 54 narcoleptics belonging to 19 families, with a simple dominant mode of inheritance. The diagnosis of the narcoleptic syndrome was uncertain in some of these patients. Yoss and Daly (1957) using more exact diagnostic criteria

found that 30% of subjects with the narcoleptic syndrome had an affected relative. Daly and Yoss (1959) described a family in which 12 members with narcolepsy occurred in 4 generations, but only 3 of these subjects had cataplexy, while Gelardi and Brown (1967) described a family in which 15 members had cataplexy, 3 had sleep paralysis, and 3 may have had narcolepsy, over 3 generations. Imlah (1961) described identical twins who both developed narcolepsy and cataplexy in late adolescence. More recently, in a detailed study, Kessler *et al.* (1974) found that the overall rate of the narcoleptic syndrome and other disorders of excessive sleep among the parents, children, and sibs of patients with the narcoleptic syndrome was a little under 10%. From these data, a recessive or simple dominant mode of transmission seems unlikely. Yoss and Daly (1960) suggested that narcolepsy was at one extreme of the normal distribution of vigilance and was polygenically determined.

To study the familial distribution of narcolepsy, we interviewed subjects with a definite history of narcolepsy and cataplexy, and personally saw as many of their parents, children, and sibs as possible.

## Patients and methods

### CLINICAL DIAGNOSTIC CRITERIA (MODIFIED FROM YOSS AND DALY, 1957)

**Narcolepsy:** periodic day-sleep episodes occurring in unusual circumstances, such as while eating, talking, and standing. All treated subjects had at least one such episode daily.

**Cataplexy:** partial or complete paralysis of voluntary movement and loss of muscle tone after sudden sensory or emotional stimuli. In most patients this was a frequent occurrence.

<sup>1</sup>M. Baraitser is supported by a grant from the Brain Research Trust.  
Received for publication 18 January 1978

Table 1 Symptoms of narcoleptic syndrome in index patients

	Narcolepsy	Cataplexy	Sleep paralysis	Hypnagogic hallucinations
Number of patients	50	50	29	26
Age (y) at onset (mean)	23	25	27	Unknown
Attack frequency	3 to 5 daily	Infrequent to several daily	Infrequent to several nightly	Weekly to nightly
Attack duration	15 to 30 min	1 sec to 30 min	Uncertain	Uncertain
Attack triggers	Monotony	Mainly laughter	—	—

**Sleep paralysis:** paralysis of voluntary movement between sleep and waking.

**Hypnagogic hallucinations:** dreams occurring at the beginning of sleep. Dreams occurring at any other time were not considered as evidence for this symptom.

#### SUBJECTS WITH NARCOLEPTIC SYNDROME

Fifty subjects with a diagnosis of the narcoleptic syndrome, seen consecutively at King's College and the Maudsley Hospitals, were interviewed. There were 24 males and 26 females, aged 28 to 61 years (mean 39). All had narcolepsy as well as cataplexy; 29 had sleep paralysis and 26 hypnagogic hallucinations. Narcolepsy was of 1 to 50 years' duration (mean 19) and, in untreated patients, attacks occurred from 1 to 10 times daily (mean 3.5). These lasted from a few seconds to 3 hours, in most cases 15 to 30 minutes. Night sleep lasted 6 to 12 hours (mean 8.2) and every patient woke at least once nightly. Cataplexy occurred at least once daily in 30 patients. Cataplexy caused partial loss of muscle tone in 32 patients and complete collapse in 18. Patients had experienced cataplexy for periods of 1 to 50 years. In 30 patients, the onset of narcolepsy preceded or accompanied that of cataplexy, while cataplexy preceded narcolepsy by up to 10 years in the others. Attacks of sleep paralysis were uncommon in most patients, though they occurred several times nightly in 3. The age of onset of sleep paralysis was described as from 10 to 50 years.

Dreams at the onset of sleep occurred at least once weekly in 26 patients. The age at onset of this dream-timing could not be established. Details are summarised in Table 1.

Of the relatives of the 50 probands, 126 were personally interviewed. This sample comprised all the children, 66% of the sibs, and 50% of the parents.

#### SYMPTOM EVALUATION

Day sleep attacks, occurring while talking, eating, or standing up, were taken as definite evidence of narcolepsy, while day sleep during monotonous occupations was not given diagnostic significance. Complete or partial paralysis of voluntary movement and lapse of posture, facial twitching, or double vision triggered by laughter, or other sensory or emotional stimuli were considered as evidence for cataplexy, though this may have resulted in an overestimate of

the prevalence of this symptom. Sleep paralysis was always considered abnormal. Hypnagogic hallucinations were established in the probands by a clear history of dreaming (irrespective of the nature of dream) before falling asleep, but the dream-timing of relatives could not be assessed accurately, and no diagnostic significance was therefore given to this symptom.

#### Results

Of 50 subjects with narcolepsy and cataplexy, 26 had another member of the family with one or more symptoms of the narcoleptic syndrome. Of the index patients, 14 had 1 affected first-degree relative, 3 had 2 affected, 6 had 3 affected, and 3 had 4 affected. In one of these 26 families consanguinity was present, the proband's mother who had narcolepsy being the offspring of a first cousin marriage. All the index patients had narcolepsy and cataplexy but, in contrast, of the 50 affected relatives, 37 had a single symptom (26 narcolepsy, 9 cataplexy, and 2 sleep paralysis), and 13 had 2 or more symptoms (Table 2).

The age at onset of symptoms in relatives could not be established with accuracy in all subjects, though in families in which 2 generations were affected the onset of narcolepsy and cataplexy was at approximately the same age in subsequent generations.

Before the proportion of the affected relatives of the index patients eventually likely to develop one or more symptoms of the narcoleptic syndrome could be calculated, it was necessary to correct the risk according to the age of those at risk. The cumulative risks of developing one or more symptoms of the narcoleptic syndrome in a child or sib reached unity after the age of 35 (Table 3). In this way, the relatives at risk were weighted according to their age. Using this correction, the proportion of children of the index patients likely to be affected was 16 in 34 (41.2%) (Table 4). The proportion of parents and sibs affected

Table 2 Symptoms in 50 relatives (from 26 families) of 50 probands with the narcoleptic syndrome

Narcolepsy alone	26
Cataplexy alone	9
Sleep paralysis alone	2
Narcolepsy and cataplexy	8
Narcolepsy and sleep paralysis	5

Table 3 Cumulative risk using ages in both first and second degree relatives

Age period	No.	%	Cumulative risk
0-5	0	0	0.00
6-10	9	13	0.13
11-15	20	37.6	0.38
16-20	22	66.2	0.66
21-25	14	84.4	0.84
26-30	9	96.1	0.96
31-35	3	100	1.00

Table 4 Percentage of affected first degree relatives after correction for age effect

	Affected	Total	%
All the children	16	34.84	41.2
All the sibs	18	126	14.2
Sibs of 1 affected parent	13	31	41.9
All the parents	16	100	16
Parents of 2 affected children	8	24	33.3

would be expected to be less than 50% if some of the index patients had been affected by fresh mutations. This possibility was excluded by taking only parents of index patients with another sib affected, and the sibs where one parent was affected. After the above correction, the proportion of sibs and parents affected was 41.9% and 33.3%, respectively.

## Discussion

The frequency of narcolepsy in the general population is not known with certainty and recent estimations of 100 000 narcoleptics in the USA, and perhaps 20 000 in the UK, are based on comparatively small samples. However, many large case series have been described (Yoss and Daly, 1957; Guilleminault *et al.*, 1974; Parkes *et al.*, 1975), and narcolepsy appears to be a fairly common disorder. Many different sleep disorders may mimic narcolepsy and the polygraph has proved useful in separating these conditions, which include the sleep-apnoea syndrome, slow-wave sleep narcolepsy, subwakefulness syndrome, and mixed hypersomnia (Guilleminault and Dement, 1974). The combination of narcolepsy and cataplexy is, however, thought to be a specific clinical syndrome, with a clearly defined electroencephalographic abnormality in most studies, and with night sleep beginning with a period of REM sleep (Rechtschaffen *et al.*, 1963). The time of onset and prevalence of REM sleep might, however, be altered by many drugs including amphetamines.

The occurrence of familial cases of narcolepsy is now well documented. Krabbe and Magnussen (1942) found that 54 of 300 narcoleptics belonged to 19 families, with 2 to 8 affected members in each family. Nevsimal and Roth (1958) and Daly and Yoss (1959) provided evidence for the occurrence of

narcolepsy in some families as an autosomal dominant trait. Narcolepsy has been reported in monozygous twins, with both concordance (Imlah, 1961) and discordance (Mitchell and Cummins, 1965). Kessler *et al.* (1974) studied 50 subjects with narcolepsy and cataplexy, all with early onset REM sleep. Of the sample, 52% had an affected relative, either with the narcoleptic syndrome or with narcolepsy alone. Of 50 probands, 9 (18%) showed a family history of narcolepsy and cataplexy, 7 in a first degree relative, 1 in a second degree relative, and 1 in a first cousin. In another 17 probands, there was a family history of disorders of excessive sleep.

The 50 patients we studied had the clinical features of the narcoleptic syndrome, though only 7 of 42 had early onset REM sleep on a single daytime electroencephalographic recording. Of the probands, 52% had an affected first degree relative, and of these index patients 41% of their children, 42% of their sibs, and 16% of their parents had narcolepsy, cataplexy, or both. If these different manifestations are considered as part of a single syndrome, the pattern of inheritance is suggestive of a dominant mode of inheritance with, in 4 families, 3 generations affected. However, whereas the probands all had the narcoleptic syndrome, their relative often had only one symptom of this. A number of children interviewed, who had only a single symptom of the narcoleptic syndrome, nevertheless remain at risk for eventually developing other symptoms. The higher number of affected first degree relatives with a sleep disorder revealed in the present study as compared with Kessler *et al.* (1974) may result from the personal interview technique used. Questionnaires were found to be of limited value in obtaining an adequate family history, and denial or failure to recognise pathological symptoms was not uncommon. It is possible that the proportion of affected sibs and parents is higher than revealed by this study.

Of the 50 patients, 16 had 1 parent affected. This indicates a mutation rate higher than might be expected in a condition where the fertility of the index patient is only a little less than that of the general population (1961 census figure). This apparently high mutation rate might in part be explained by the fact that only half of the parents could be interviewed and examined; other parents may have been affected. Genetic heterogeneity could also account for the finding that just less than half of the families were without another affected member. Clinically, there was no difference between the two groups. Kessler *et al.* (1974) considered that neither a recessive nor a simple dominant mode of inheritance could explain their findings, and they suggest that if narcolepsy and disorders of excessive sleep were taken together, a single continuous distribution of liability with one or

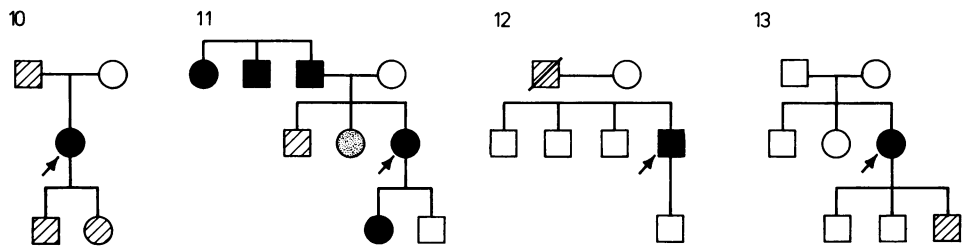
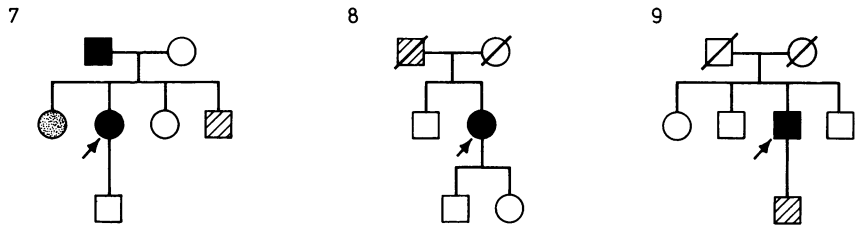
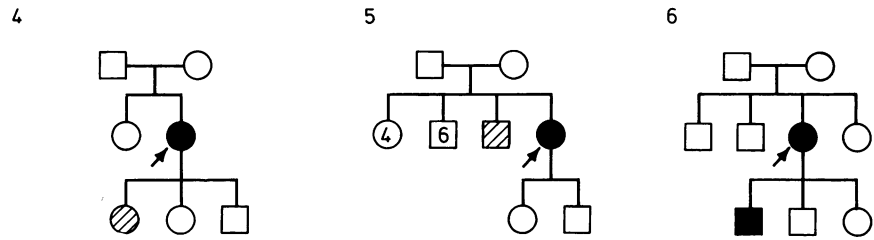
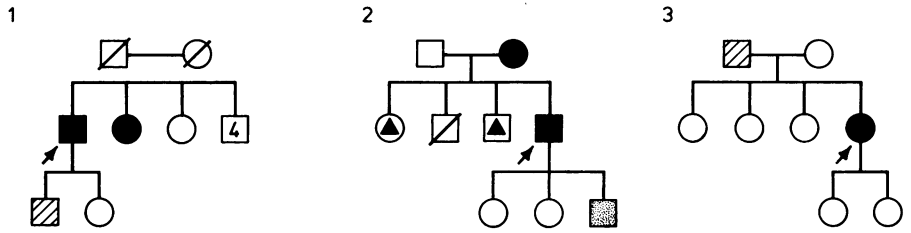
more thresholds may be operative, thus favouring multifactorial inheritance. Kessler *et al.* (1974) did intimate that the number ascertained might be an underestimate, as almost 73% of the children of the probands had not as yet passed through the major period of risk. In the present study, though we cannot exclude polygenic inheritance, the high ratio of affected children suggests a single dominant gene.

#### References

- Daly, D. D., and Yoss, R. E. (1959). A family with narcolepsy. *Proceedings of the Staff Meetings of the Mayo Clinic*, **34**, 313-319.
- Gelardi, J. A. M., and Brown, J. W. (1967). Hereditary cataplexy. *Journal of Neurology, Neurosurgery, and Psychiatry*, **30**, 455-457.
- Guilleminault, C., Carskadon, M., and Dement, W. C. (1974). On the treatment of rapid eye movement narcolepsy. *Archives of Neurology*, **30**, 90-93.
- Guilleminault, C., and Dement, W. C. (1974). Pathologies of 'excessive sleep'. In *Advances in Sleep Research*, Vol. 1, pp. 345-390. Ed. by E. Weitzman. Spectrum, New York.
- Imlah, N. W. (1961). Narcolepsy in identical twins. *Journal of Neurology, Neurosurgery, and Psychiatry*, **24**, 158-160.
- Kessler, S., Guilleminault, C., and Dement, W. C. (1974). A family study of 50 REM narcoleptics. *Acta Neurologica Scandinavica*, **50**, 503-512.
- Krabbe, F., and Magnussen, G. (1942). Familial narcolepsy. *Acta Psychiatrica et Neurologica*, **17**, 149-173.
- Mitchell, S., and Cummins, L. (1965). Idiopathic narcolepsy in one of monozygotic twins. Presented at APSS meeting, Washington DC.
- Nevsimal, O., and Roth, B. (1958). A case of familial incidence of narcolepsy. *Ceskoslovenska Neurologie*, **21**, 54-58.
- Parkes, J. D., Baraitser, M., Marsden, C. D., and Asselman, P. (1975). Natural history, symptoms and treatment of the narcoleptic syndrome. *Acta Neurologica Scandinavica*, **52**, 337-353.
- Rechtschaffen, A., Wolpert, E. A., Dement, W. C., Mitchell, S. A., and Fisher, C. (1963). Nocturnal sleep of narcoleptics. *Electroencephalography and Clinical Neurophysiology*, **15**, 599-609.
- Westphal, C. (1877). Eigentümliche mit einschlafen verbundene anfälle. *Archiv für Psychiatrie und Nervenkrankheiten*, **7**, 631-635.
- Yoss, R. E., and Daly, D. D. (1957). Criteria for the diagnosis of the narcoleptic syndrome. *Proceedings of the Staff Meetings of the Mayo Clinic*, **32**, 320-328.
- Yoss, R. E., and Daly, D. D. (1960). Hereditary aspects of narcolepsy. *Transactions of the American Neurological Association*, **85**, 239-240.

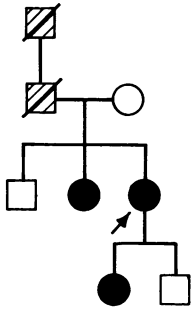
Requests for reprints to Dr M. Baraitser, Kennedy-Galton Centre for Clinical Genetics, Harperbury Hospital, Harper Lane, Shenley, Radlett, Herts WD7 9HQ.

Appendix Pedigrees of those families with more than one affected member

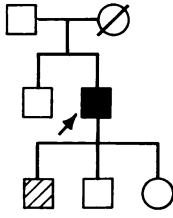


Narcoleptic syndrome	●	■	Sleep paralysis	⊙	⊙	Propositus ↗
Narcolepsy	⊙	⊙	Cataplexy	⊙	⊙	

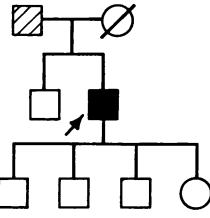
14



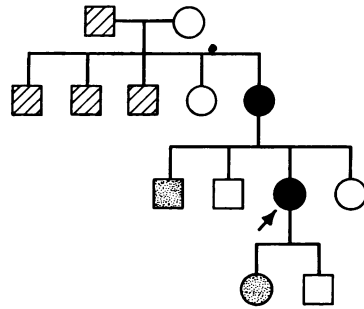
15



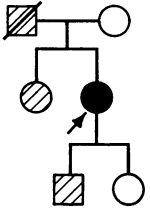
16



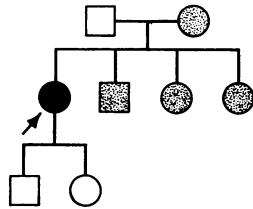
17



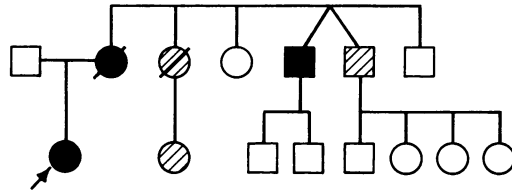
18



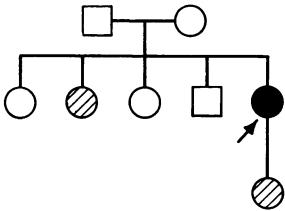
19



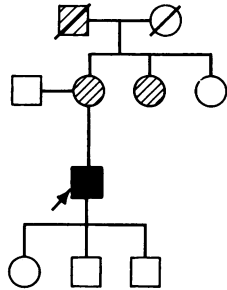
20



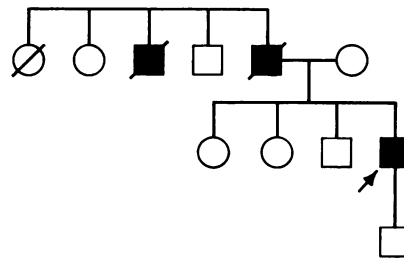
21



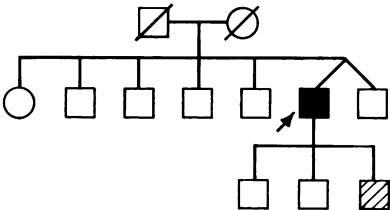
22



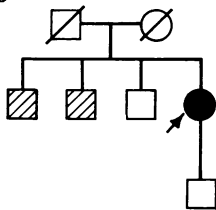
23



24



25



26

