Genetic study of narcoleptic syndrome

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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, or 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.
** Genetic study of narcoleptic syndrome **

### Table 1  Symptoms of narcoleptic syndrome in index patients

<table>
<thead>
<tr>
<th></th>
<th>Narcolepsy</th>
<th>Cataplexy</th>
<th>Sleep paralysis</th>
<th>Hypnagogic hallucinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>50</td>
<td>50</td>
<td>29</td>
<td>26</td>
</tr>
<tr>
<td>Age (y) at onset (mean)</td>
<td>23</td>
<td>25</td>
<td>In frequent to several daily</td>
<td>Unknown</td>
</tr>
<tr>
<td>Attack frequency</td>
<td>3 to 5 daily</td>
<td>Infrequent to several daily</td>
<td>In frequent to several nightly</td>
<td>Weekly to nightly</td>
</tr>
<tr>
<td>Attack duration</td>
<td>15 to 30 min</td>
<td>1 sec to 30 min</td>
<td>Uncertain</td>
<td>Uncertain</td>
</tr>
<tr>
<td>Attack triggers</td>
<td>Monotony</td>
<td>Mainly laughter</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

**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

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Number of Cases</th>
</tr>
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<tbody>
<tr>
<td>Narcolepsy alone</td>
<td>26</td>
</tr>
<tr>
<td>Cataplexy alone</td>
<td>9</td>
</tr>
<tr>
<td>Sleep paralysis alone</td>
<td>2</td>
</tr>
<tr>
<td>Narcolepsy and cataplexy</td>
<td>8</td>
</tr>
<tr>
<td>Narcolepsy and sleep paralysis</td>
<td>5</td>
</tr>
</tbody>
</table>
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; Guillemainault et al., 1974;
Parkes et al., 1975), and narcolepsy appears to be a
fairly common disorder. Many different sleep disor-
ders may mimic narcolepsy and the polygraph has
proved useful in separating these conditions, which
include the sleep-apnoea syndrome, slow-wave sleep
narcolepsy, subwakfulness syndrome, and mixed
hypersomnia (Guillemainault 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 monzygotic
twins, with both concordance (Imah, 1961) and
discordance (Mitchell and Cummins, 1965). Kessler et
al. (1974) studied 50 subjects with narcolepsy and
catatexy, all with early onset REM sleep. Of this
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 electro-
encephalographic 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 con-
sidered 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

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<th>No.</th>
<th>%</th>
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<tr>
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<td>0</td>
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<td>0.00</td>
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<td>13</td>
<td>0.13</td>
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<tr>
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<td>37.6</td>
<td>0.38</td>
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<td>22</td>
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<tr>
<td>21-25</td>
<td>14</td>
<td>84.4</td>
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<td>26-30</td>
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<td>96.1</td>
<td>0.96</td>
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<td>1.00</td>
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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


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

1

2

3

4

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9

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13

Narcoleptic syndrome
Narcolepsy
Sleep paralysis
Cataplexy
Propositus