Diagnosis of Creutzfeldt-Jakob disease by measurement of S100 protein in serum: prospective case-control study

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Abstract

Objective: To analyse serum concentrations of brain specific S100 protein in patients with Creutzfeldt-Jakob disease and in controls.
Design: Prospective case-control study.
Setting: National Creutzfeldt-Jakob disease surveillance unit.
Subjects: 224 patients referred to the surveillance unit with suspected Creutzfeldt-Jakob disease and 35 control patients without dementia.
Main outcome measure: Serum concentration of S100 protein in patients with Creutzfeldt-Jakob disease, in patients with other diseases causing dementia, and in the control group.
Results: Of the 224 patients with suspected Creutzfeldt-Jakob disease, 65 were classed as definitely having the disease after neuropathological verification, an additional 6 were classed as definitely having the disease as a result of a genetic mutation, 43 as probably having the disease, 36 as possibly having the disease, and 74 patients were classed as having other disease. In the 108 patients classed as definitely or probably having Creutzfeldt-Jakob disease the median serum concentration of S100 was 395 pg/ml (SD 387 pg/ml). This was significantly higher than concentrations found in the 74 patients classed as having other diseases (median 109 pg/ml; SD 177 pg/ml; $P = 0.0001$). At a cut off point of 213 pg/ml sensitivity for the diagnosis of the disease was 77.8% (95% confidence interval 68.8% to 85.2%) and specificity was 81.1% (70.3% to 89.3%). There was a significant difference in survival at different concentrations of S100 in Kaplan-Meier curves ($P = 0.023$).
Conclusion: Measurement of serum concentrations of S100 is a valuable tool which can be used more easily than tests on cerebrospinal fluid in the differential diagnosis of Creutzfeldt-Jakob disease. More studies are needed to determine whether serial testing of serum S100 improves diagnostic accuracy.

Introduction

Creutzfeldt-Jakob disease is a progressive and fatal disorder of the central nervous system; it is a transmissible spongiform encephalopathy.[1] The incidence of Creutzfeldt-Jakob disease is 0.5-1 new case per million population.[2] Clinically, Creutzfeldt-Jakob disease is characterised by rapidly progressing dementia and more than 90% mortality within one year of onset.[1] Diagnosis can only be made by neuropathological or immunochemical identification of the pathological isoform of the prion protein in human brain tissue.[3] The pathological isoform has also been identified in tonsillar tissue at necropsy but this identification has not been used to confirm the diagnosis of Creutzfeldt-Jakob disease before death.[4] Diagnosis is usually made clinically[5] and electroencephalographically.[6] Diagnosis can be confirmed by biochemical analysis of cerebrospinal fluid which identifies neuron specific enolase,[7 8] S100 protein,[7 9] tau protein,[10] and 14-3-3 protein.[11–13] However, detection of these proteins in serum has not been useful diagnostically for methodological reasons, such as the detection limits for S100 and 14-3-3 protein and problems with cross reactions with non-brain specific isoforms. Thus biological confirmation of the clinical diagnosis while the patient is still alive has been hampered by the inability to easily and repeatedly identify biological markers.

At our clinic we use an immunoluminometric method to detect brain specific S100b protein in serum (LIA-mat Sangtec100**,** Bromma, Sweden). The detection limit of this assay is 20 pg/ml in serum; earlier assays had detection limits of 0.5 ng/ml.[7 9] S100 is an acidic calcium binding protein which is found as a homodimer or heterodimer of two subunits, α and β, with molecular weights of 10.4 kD and 10.5 kD, respectively. In brain tissue S100 is found mainly in glial cells.[14 15] Raised concentrations of S100 in serum and cerebrospinal fluid have been reported after major[16] and minor head injury.[17] In these cases S100 concentrations decreased rapidly as the protein was eliminated by the kidneys; the estimated biological half life of S100 is 2 hours.[18] S100 was originally thought to be a marker of brain destruction in acute disease, but now it is thought to be a marker of activated astroglia, which is seen at all stages of Creutzfeldt-Jakob disease.[3] We investigated the diagnostic potential of measuring serum concentrations of S100 in the differential diagnosis of Creutzfeldt-Jakob disease.

Subjects and methods

Since June 1993 suspected cases of Creutzfeldt-Jakob disease in Germany have been reported to the

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Creutzfeldt-Jakob disease surveillance unit at the department of neurology at Georg August University in Göttingen. Each patient who is reported to the unit is visited by a research physician and examined using a standardised protocol[19]; a control patient without dementia was examined at the same time. All controls were matched for age and sex with a patient with suspected Creutzfeldt-Jakob disease. Serum samples were obtained from some of the controls.

Between June 1993 and December 1995, 300 patients suspected of having Creutzfeldt-Jakob disease were seen by a member of the research team. Serum samples were obtained from 224 patients; only these patients are included in the present paper. We also analysed serum samples from the first 35 control patients seen.

All suspected cases of Creutzfeldt-Jakob disease were classed as definitely having the disease, probably having the disease, possibly having the disease, or having other disease according to clinical criteria described elsewhere.[5 20] All patients had cranial computed tomography or magnetic resonance imaging of the brain, or both, to exclude ischaemic stroke, haemorrhages, or space occupying lesions as a cause of illness.

Patients were classed as probably having Creutzfeldt-Jakob disease if they had rapidly progressive dementia of less than 2 years' duration and periodic sharp wave complexes on electroencephalography. They also had to have any two of the following symptoms: myoclonus; visual or cerebellar symptoms, or both; pyramidal or extrapyramidal signs, or both; or akinetic mutism. Patients who fulfilled the criteria for probably having the disease but did not have any abnormalities on electroencephalography were classed as possibly having the disease. Patients who did not fulfil the criteria for either possibly or probably having the disease were classed as having other disease. Patients who had an identified pathological isoform of the prion protein in brain tissue on immunohistochemical analysis were classed as definitely having the disease.[3]

Sample collection and analysis

Serum samples were collected by a research physician and stored at – 80°C within 24 hours.

In 6 out of the 116 patients who were tested a mutation was detected in the prion protein gene.[21] Altogether 151 of the 224 patients had died by 1 May 1997. A neuropathological examination was done on 83 patients according to standard protocols.[3]

Serum concentration of S100 protein was measured using the immunoluminometric assay kit already described. This test measures the β subunit of the S100 protein. An intra-assay coefficient of variation of 5.5% and an interassay coefficient of variation of 10.1% were defined at 280 pg/ml. All samples were tested twice and the mean values were used for additional calculations. A coefficient of variation of 10% was accepted. Serum concentrations below 20 pg/ml were reported as 0 pg/ml.

Statistical analysis

Standard measures of test validity including sensitivity, specificity, and predictive values with 95% confidence intervals were calculated.[22] The optimal cut off point for dichotomising serum concentrations of S100 was selected to maximise the Youden index.[23] The receiver operating characteristics curve was calculated to show the variability of sensitivity and specificity for cut off points of different concentrations of S100 protein, which was measured as a continuous variable.[24]

The comparison of the distribution of S100 concentrations between subgroups in the study population was based on non-parametric rank tests (for comparisons between two groups the Wilcoxon signed rank test and Mann-Whitney U test were used; for matched groups the Wilcoxon signed rank test was used; for the three groups described as definitely or probably having the disease, possibly having the disease, and having other disease the Kruskal-Wallis test was used). Additionally, Kaplan-Meier curves were calculated to show the probability of survival for three subgroups of patients classed as definitely or probably having the disease; the subgroups were divided according to serum concentration of S100 (<300 pg/ml, 300-600 pg/ml, >600 pg/ml). Differences between the estimated survival curves were statistically evaluated using the log rank test.

Results

Serum concentrations of S100 protein were determined for 224 patients who were suspected of having Creutzfeldt-Jakob disease and for 35 control patients without dementia. Final diagnoses for the 224 patients included 65 patients neuropathologically classed as definitely having the disease, an additional 6 classed as definitely having the disease as a result of a genetic mutation, 43 classed as probably having the disease, 36 as possibly having the disease, and 74 as having other disease. The most recent clinical information including results of neuropathological examination, if available, was used to divide the patients into groups. The distribution of patients by clinical diagnosis and their final classification is shown in table 1. Final diagnosis for

Table 1 Distribution of 224 patients with suspected Creutzfeldt-Jakob disease by initial diagnosis and final diagnosis. Values are numbers of patients

	Final diagnosis			
Initial diagnosis	Definite CJD	Probable CJD	Possible CJD	Other disease
Probable CJD (n=92)	48*	42	0	2
Possible CJD (n=62)	20†	0	36	6
Other disease (n=70)	3‡	1	0	66

CJD=Creutzfeldt-Jakob disease.
*Includes two patients with a genetic basis to their disease.
†Includes three patients with a genetic basis to their disease.
‡Includes one patient whose disease had a genetic basis.

Table 2 Distribution of 224 patients with suspected Creutzfeldt-Jakob disease and 35 controls without dementia by age and sex

	Sex		Median (range) age (years)
	Male	Female	
Creutzfeldt-Jakob disease:			
Definite	19	46	67 (31-87)
Probable	14	29	65 (31-81)
Possible	16	20	68.5 (51-90)
Other disease	19	55	62.5 (25-84)
Genetic causes	3	3	56 (34-69)
Control group without dementia	11	24	67 (46-81)

Table 3 Clinical and electroencephalographic signs and symptoms of 224 patients with suspected Creutzfeldt-Jakob disease at time of entry into the study. Values are numbers of patients (percentages)

Symptoms	Definite or probable CJD (n=108)	Possible CJD (n=36)	Other disease (n=74)
Rapidly progressive dementia of <2 years' duration	101 (94)	36 (100)	32 (43)
Periodic sharp wave complexes on electroencephalography	89 (82)	0	2 (3)
Myoclonus	93 (86)	26 (72)	26 (35)
Visual or cerebellar symptoms, or both	90 (83)	34 (86)	31 (42)
Pyramidal or extrapyramidal signs, or both	72 (67)	32 (89)	38 (51)
Akinetic mutism	62 (57)	12 (33)	7 (9)

CJD=Creutzfeldt-Jakob disease.

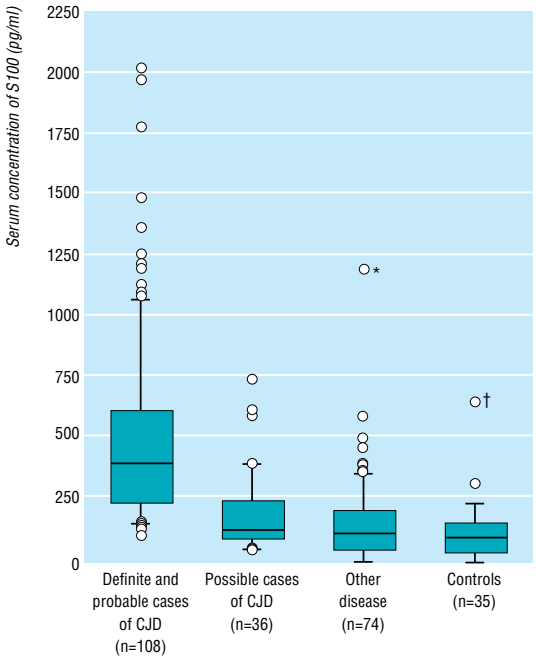

Fig 1 Serum concentrations of S100 protein by final diagnosis. 10th, 25th, 75th, and 90th percentiles are shown. CJD=Creutzfeldt-Jakob disease; *Patient with meningoencephalitis; †Patient with amyotrophic lateral sclerosis

patients classed as having other disease was obtained either at necropsy or by follow up reports from hospitals. The distribution of patients and controls by age and sex is shown in table 2.

Of the cases of Creutzfeldt-Jakob disease with a genetic basis two had fatal familial insomnia with a mutation at D178N, one had Gerstmann-Sträussler-Scheinker disease with a mutation at P102L, two patients had a mutation at V210I, and one had an insert mutation (9*24). The patients with fatal familial insomnia and the patient with Gerstmann-Sträussler-Scheinker had all been classed clinically as possibly having Creutzfeldt-Jakob disease. Initially, the patients with the mutation at V210I had been classed as probably having the disease; the patient with the insert mutation had initially been classed as having other disease.

For further analysis those classed as definitely and those classed as probably having the disease were grouped together since almost all of those classed as probably having the disease became definite cases after necropsy. Patients' clinical symptoms at the time of entry into the study are shown in table 3.

The serum concentrations of S100 protein in the combined group of patients classed as definitely or probably having the disease ranged from 95 pg/ml to 2016 pg/ml (median 395 pg/ml) (fig 1). Among those who definitely had the disease serum concentrations ranged from 120 pg/ml to 2016 pg/ml (median 439 pg/ml); among those who probably had the disease concentrations ranged from 95 pg/ml to 1199 pg/ml (median 347 pg/ml). For those classed as possibly having the disease concentrations ranged from <20 pg/ml to 742 pg/ml (median 118 pg/ml). Among those classed as having other diseases concentrations ranged from <20 pg/ml to 1198 pg/ml (median 109 pg/ml). Concentrations in the control group ranged from <20 pg/ml to 657 pg/ml (median 97 pg/ml). Additional information on serum concentrations of S100 in those classed as having other diseases is given in table 4 with the final diagnoses. Diagnoses and concentrations are given for patients in the control group without dementia in table 5.

Differences between the three groups (the combined group of those with definite or probable disease, those with possible disease, and those with other disease) were significant ($P=0.0001$). There was also a significant difference between matched pairs of the combined group (those with definite or probable disease) and the controls ($n=35$) ($P=0.0001$). There was no significant difference when the group of those classed as possibly having the disease was compared with those classed as having other disease ($P=0.1$).

Table 4 Median serum concentration of S100 protein in patients classed as having other disease (n=74). No of patients whose diseases were verified neuropathologically are given in parentheses

Diagnosis	No of patients	Median (range) (pg/ml)
Alzheimer's disease	16 (5)	100.5 (0-465)
Parkinson's disease	11	91 (24-248)
Multi-infarct dementia	8 (2)	393 (0-393)
Progressive dementia	5	529 (63-592)
Amyotrophic lateral sclerosis	4 (3)	179 (0-179)
Chronic encephalopathy	3	47 (58-105)
Hypoxic brain damage	3 (1)	249 (40-289)
Meningoencephalitis	2 (1)	(504-1198)
Multiple sclerosis	2 (1)	(142-372)
Pick's disease	2	(20-115)
Wernicke's disease	2	(53-360)
Epilepsy	2	(29-36)
Depression	2	(64-112)
Central pontine myelinolysis	1	57
Subdural haematoma	1	84
Psychosis	1	0
Spinocerebellar ataxia	1	28
Post-traumatic brain damage	1	130
Cerebral amyloid angiopathy	1	106
Hyperparathyroidism	1	142
Intoxication	1	209
Huntington's disease	1	59
B cell lymphoma	1	207
Hashimoto's disease	1	0
Paraneoplastic syndrome	1	167

Table 5 Serum concentrations of S100 protein and final diagnosis in controls without dementia (n=35)

Diagnosis	No of patients	Median (range) (pg/ml)
Transient ischaemic attack	6	96.5 (0-188)
Lower back pain	6	24.5 (0-318)
Depression	4	72 (0-178)
Brain tumour	4	170.5 (73-240)
Polyneuropathy	4	47.5 (0-108)
Unknown	2	(0-124)
Borreliosis	1	58
Parkinson's disease	1	125
Intracranial bleeding	1	101
Lung oedema	1	146
Psychosis	1	78
Amyotrophic lateral sclerosis	1	657
Guillain-Barré syndrome	1	187
Colon cancer	1	155
Fracture of the spine	1	316

There was a significant difference when the combined group (those with definite or probable disease) was compared with those classed as having other disease (P = 0.0001). There were no significant differences between those classed as definitely having the disease and those classed as probably having the disease (P = 0.1). No differences that were related to the sex of the patient were found.

The best results for sensitivity and specificity were obtained at the cut off point of 213 pg/ml (Youden Index 0.59). The receiver operating characteristics curve is shown in figure 2. The combined group and the group of those classed as having other diseases were used to calculate sensitivity and specificity. Sensitivity at 213 pg/ml was 77.8% (95% confidence interval 68.8% to 85.2%). Specificity at this value was 81.1% (70.3% to 89.3%). The positive predictive value was 85.7% (77.2% to 92%) and the negative predictive value was 71.4% (60.5% to 80.8%). Applying the same cut off point to the control group gave a specificity of 85.9% (69.0% to 94.6%).

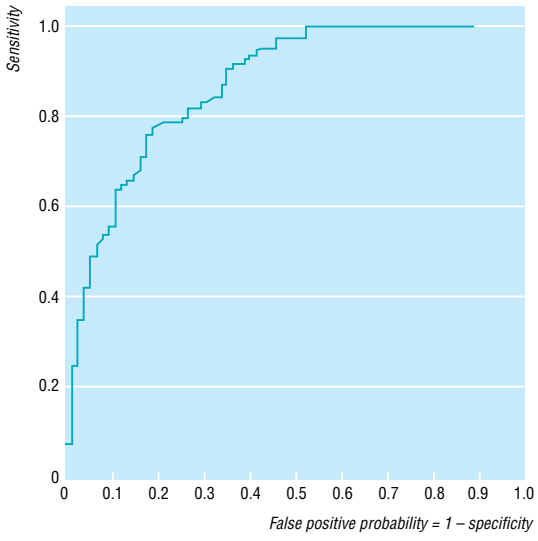

Fig 2 Curve of receiver operating characteristics at different cut off points of serum concentration of S100 protein

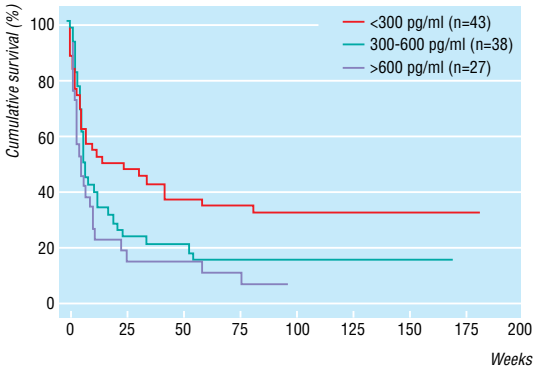

Fig 3 Kaplan-Meier survival curves at different serum concentrations of S100 protein (P=0.023)

Fourteen of the 17 patients who were initially classed as possibly having the disease and whose disease was later confirmed neuropathologically had concentrations of S100 protein >213 pg/ml. Another two patients who were initially classed as having other disease and later reclassified as probably or definitely having the disease had concentrations >213 pg/ml. There were significant differences in the Kaplan-Meier survival curves plotted for different serum concentrations of S100 (fig 3) (P = 0.023). Patients with fatal familial insomnia had concentrations of <20 pg/ml and 22 pg/ml. The serum concentration of S100 in the patient with an insert mutation was 178 pg/ml. The patient with Gerstmann-Sträussler-Scheinker disease had a serum concentration of 1434 pg/ml. The two patients with mutations at V210I had serum concentrations of 296 pg/ml and 757 pg/ml.

Discussion

We have identified raised concentrations of a biochemical marker, S100 protein, in the serum of patients with Creutzfeldt-Jakob disease. Previously, diagnosis of the disease had been difficult because no biochemical marker had been identified in serum. We have obtained sensitivity of 77.8% and specificity of 81.1% at a cut off point of 213 pg/ml. Serum concentrations of S100 in the group of patients classed as definitely or probably having the disease were significantly different from concentrations in the other patients.

The primary use of this test will be in the differential diagnosis of diseases which cause dementia. Raised serum concentrations of S100 protein are found in acute and subacute neurological diseases such as stroke, subarachnoid haemorrhage, and hypoxia causing brain damage[16 17]; however, these diseases are usually excluded by cerebral computed tomography or magnetic resonance imaging. We found high concentrations of S100 in a patient with multiple sclerosis and in two patients with subacute meningoencephalitis (table 4). These diseases can be differentiated from the diagnosis of Creutzfeldt-Jakob disease by magnetic resonance imaging or lumbar puncture. Raised concentrations of S100 were also found in 14 out of 17 patients initially classed as possibly having Creutzfeldt-Jakob disease but reclassified as definite cases after

neuropathological examination. Two out of three patients initially classed as having other disease also had raised concentrations of S100 and were later reclassified as definitely or probably having the disease. Measuring concentrations of S100 protein in serum may aid early diagnosis of Creutzfeldt-Jakob disease, at least until more specific tests are available. Specificity was acceptable when the cut off point of 213 pg/ml was applied to the control group of patients without dementia. However, this test must be evaluated on a larger group of patients who do not have dementia.

The serum test for S100 does not have the same sensitivity and specificity for the diagnosis of Creutzfeldt-Jakob disease as tests on cerebrospinal fluid.[8 9 11] In a smaller study of patients with Creutzfeldt-Jakob disease an immunoblot assay for 14-3-3 protein in cerebrospinal fluid had 98% sensitivity and 99% specificity.[25] However, other studies using this assay reported more false negatives.[13 26] A single measurement of serum concentrations of S100 will not replace a single measurement of proteins in cerebrospinal fluid, but repeated measurement of S100 over intervals of several days may improve diagnostic accuracy. It remains to be seen whether an analysis which combines results from tests on cerebrospinal fluid with results from serum tests would be more useful.

There are significant differences in survival associated with the serum concentration of S100; these differences are shown by the Kaplan-Meier curves. The differences support the hypothesis that serum concentrations of S100 increase during the course of the disease and the quantitative value may provide information about disease progression. Data from serial tests may provide verification of this; there could be alternative explanations for our findings such as that the disease may progress faster in patients with raised concentrations of S100.

A serum test for Creutzfeldt-Jakob disease is preferable to analysis of cerebrospinal fluid. Because of the short biological half life of S100 (2 hours)[18] raised serum concentrations will decrease rapidly in cases of subarachnoid haemorrhage[16] and circulatory arrest during heart surgery,[27] but concentrations of S100 will not fall during the course of Creutzfeldt-Jakob disease because of activation of the astroglia. Thus, acute diseases in which serum S100 concentrations rise can easily be excluded from the differential diagnosis by the transience of the rise. Additionally, because of the high homology between human and bovine S100[28] the serum test may also be used to diagnose bovine spongiform encephalopathy when there are no clinical signs of the disease.

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Key messages

- Creutzfeldt-Jakob disease is a rare, fatal neurodegenerative disease. Diagnosis is made clinically and neuropathologically
- There is no serum test which allows the diagnosis to be made while the patient is alive
- In this study raised serum concentrations of S100 protein were found in patients with Creutzfeldt-Jakob disease
- Serum concentrations of S100 could be used with a sensitivity of 77.8% and a specificity of 81.1% to confirm Creutzfeldt-Jakob disease in the differential diagnosis of diseases that cause dementia
- Serial measurement of S100 concentrations will enhance diagnostic accuracy

Contributors: MO and JW had the original idea for measuring S100. MO, JW, and MU worked together to try to develop the ultrasensitive assay; this was later finalised using a different method with contributions from ES. IZ and AO participated in collecting data and were particularly involved in ensuring the correct documentation of clinical neurological data. Calculations and statistical interpretations were done by OG, AP, and MO. Neuropathological data was provided by AG, and HAK. TW worked in the same line of research and initiated the collection of samples from patients with SP and Professor Felgenhauer. Core ideas were discussed with and research supervised by SP. MO, JW, and SP are guarantors for the paper.

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Conflict of interest: None.

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Slater revisited: 6 year follow up study of patients with medically unexplained motor symptoms

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See editorial by O'Brien

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Abstract

Objective: To investigate psychiatric and neurological morbidity, diagnostic stability, and indicators of prognosis in patients previously identified as having medically unexplained motor symptoms.
Design: Follow up study.
Setting: National Hospital for Neurology and Neurosurgery, London—a secondary and tertiary referral hospital for neurological disorders.
Subjects: 73 patients with medically unexplained motor symptoms admitted consecutively in 1989-91. 35 (48%) patients had absence of motor function (for example, hemiplegia) and 38 (52%) had abnormal motor activity (for example, tremor, dystonia, or ataxia).
Main outcome measures: Neurological clinical diagnosis at face to face reassessment by a neurologist and a psychiatric diagnosis after a standardised assessment interview—the schedule for affective disorders and schizophrenia—conducted by a psychiatrist.
Results: Good follow up data were available for 64 subjects (88%). Only three subjects had new organic neurological disorders at follow up that fully or partly explained their previous symptoms. 44/59 (75%) subjects had had psychiatric disorders; in 33 (75%) patients, the psychiatric diagnosis coincided with their unexplained motor symptoms. 31/59 (45%) patients had a personality disorder. Three subjects had developed new psychiatric illnesses at follow up, but in only one did the diagnosis account for the previous motor symptoms. Resolution of physical symptoms was associated with short length of symptoms, comorbid psychiatric disorder, and a change in marital status during follow up.
Conclusions: Unlike Slater's study of 1965, a low incidence of physical or psychiatric diagnoses which explained these patients' symptoms or disability was found. However, a high level of psychiatric comorbidity existed.

Introduction

In 1965 Elliott Slater published a highly influential study in the *British Medical Journal* that described a 10 year follow up study of patients admitted to the National Hospital for Nervous Diseases with a diagnosis of "hysteria."[1 2] He found that over half of the patients developed clear cut neurological or psychiatric conditions during follow up. Since the 1960s several studies investigating the subsequent incidence of neurological disorder in patients with a diagnosis of "hysteria" or "conversion disorder" have been published, and rates of up to 25% have been reported.[3–8] The proportion of patients whose symptoms are not adequately explained in physical terms and who are being cared for by British neurologists ranges from 20% to 40%.[9 10] Both neurologists and psychiatrists are therefore cautious about making a firm diagnosis in this group of patients.[11]

Thirty years after Slater's work, we carried out a follow up study on a similar population of patients. We attempted to avoid some of the methodological problems of previous studies. Our subjects were a consecutive series with unexplained motor symptoms, admitted between 1989 and 1991 to the National Hospital for Neurology and Neurosurgery, London (formerly the National Hospital for Nervous Diseases). All the patients had been thoroughly investigated with modern diagnostic techniques and all were eligible for inclusion, not only those who had been referred to a psychiatrist. Outcome was assessed on the basis of face to face neurological and psychiatric examination and scrutiny of all available medical records. Standardised instruments were used to ascertain the presence of psychiatric disorder.

Methods

Hospital discharge summaries of all patients aged 18-70 years who had been admitted between 1989 and 1991 were reviewed. We identified 73 consecutive sub-

jects who had presented with motor symptoms that were medically unexplained despite full investigation. The index motor symptom at presentation was categorised as either absence of motor function—for example, hemiplegia or paraplegia—or presence of abnormal motor activity, such as tremor, dystonia, or ataxia. Although motor disorders could be continuous or intermittent, we excluded those patients with apparent unconsciousness (that is, pseudoepileptic seizures) or whose impaired motor function was caused predominantly by pain or fatigue. The presence of a coexistent neurological disorder that did not account for the current symptom was not an exclusion criterion.

General practitioners, neurologists, and psychiatrists were asked if they objected to us contacting their patients. Patients who agreed to participate in the study were seen at the hospital or visited at home. Ethical approval was obtained for the study.

Follow up assessment

At follow up during 1996, subjects underwent a semistructured interview designed to assess the evolution of the index symptom, the occurrence of other somatic or psychological symptoms, the subjects' utilisation of medical and psychiatric services, and details of any state financial benefits received. The schedule for affective disorders and schizophrenia was completed for each subject, and this was supplemented by all available hospital and general practitioner records.[12] Current and lifetime diagnoses according to the 10th revision of the international classification of diseases were obtained.[13] Subjects were reassessed physically by a neurologist.

"Organicity" rating

To validate the selection of subjects, initial ratings of "organicity" were undertaken by a psychiatrist and a neurologist blinded to the outcome. Ratings were based on the medical history taken at the index admission to hospital, the clinical findings at the time of admission, examination of the subjects' physical and mental state, results of investigations, and progress while in hospital. With a scale of 0-3, an organicity rating of 0 was given if the index symptom had no organic basis, and a rating of 3 was given if the index symptom was fully explained by organic factors. The mean of the ratings given by the psychiatrist and neurologist formed the initial organicity rating. A final organicity rating was undertaken by a neurologist and psychiatrist at follow up, based on assessment at that time and including further information gathered to date.

Statistical analysis

Factors associated with good outcome were determined by multiple backward stepwise regression analysis using SPSS software. Subjects with a subsequent new diagnosis and those for whom follow up information was inadequate were excluded from the analysis.

Results

Good follow up data were available for 64 of the 73 subjects (88%). Of these, 55 underwent full interview and examination, four cooperated fully with access to records and a telephone interview but declined to be examined, and five had died (full medical notes and cause of death were obtained). Follow up data were incomplete in the remaining nine subjects (12%). One patient could not be traced (she had given false personal details), and general practitioners asked us not to contact five subjects, although their notes and correspondence were made available to us. In a further three cases the subjects declined to cooperate and refused access to their notes. Because the results include all patients on whom information was available, denominators may differ.

Table 1 Symptoms in 63 patients with additional unexplained neurological symptoms*

Additional unexplained symptoms	No (%) of patients
Paraesthesia	47 (65)
Bladder or bowel symptoms	18 (25)
Pseudoepileptic seizures	17 (23)
Memory impairment	15 (20)
Visual disturbance	10 (14)
Dysphonia or dysarthria	4 (5)
Dysphasia	3 (4)
Disturbed hearing	1 (1)

*31 patients had >1 additional unexplained neurological symptom.

Characteristics of subjects

The mean (SD) age of the 38 (52%) men was not significantly different from that of the 35 (48%) women (38 (13.2) *v* 35 (12.4) years). Seventy subjects (96%) were white, and 21 (29%) were of social class I or II. There were no differences between the nine subjects who did not respond and the remainder in terms of age, sex, social class, or marital status. At the time of the index admission, only 8 (11%) subjects were still working, but 56 (77%) had been in paid employment before the onset of their symptoms. Twenty nine subjects (40%) were on sick leave and 22 (30%) had already retired on the grounds of ill health. Sixteen (22%) subjects had worked in medical or paramedical areas.

Neurological symptoms and signs

In the initial organicity ratings undertaken to validate the selection of subjects, 67 subjects (92%) had a rating less than 1 and six subjects (8%) had ratings between 1 and 2. No subject had a rating of 2 or more. Thirty five subjects (48%) had absence of motor function (weakness) as the index symptom, and 38 (52%) had abnormal motor activity—tremor (12 subjects (16%)), dystonia (13 subjects (18%)), and ataxia (13 subjects (18%)). The duration of index symptoms at admission to hospital ranged from less than 1 month to 140 months (median 18 (26.6) months). Index symptoms were predominantly right sided in 20 subjects (27%), left sided in 21 subjects (29%), and bilateral in the remainder. Most subjects also had other unexplained neurological symptoms or signs (table 1). Subjects with weakness were more likely to be male than female (23 (32%) *v* 12 (16%); $P=0.02$, χ^2 test); of these 35, 20 (57%) had unilateral weakness (hemiplegia), 9 (26%) had weakness in both legs (paraplegia), and 6 (17%) had weakness in both arms and legs. One of the 10 subjects with left hemiplegia and three of the 10 subjects with right hemiplegia were left handed.

Table 2 Range of disorders in the 31 subjects with history of organic neurological disorder

	No of patients
Organic brain disease:	15
Migraine	6
Epilepsy	2
Mild mental handicap	2
Arrested hydrocephalus	1
Cerebellar haemangioma	1
Cerebrovascular accident	1
Arnold-Chiari malformation	1
Parkinson's disease	1
Neurological disorder (no brain disease):	16
Previous disc surgery	9
Peripheral nerve palsy	3
Diabetic neuropathy	1
Myasthenia gravis	1
Steroid myopathy	1
Urinary dyssynergia	1

Thirty one subjects (42%) had a history of organic neurological disorder, although only 15 of these (21%) had disorders affecting the brain (table 2). The current unexplained symptoms were similar to those related to the previous neurological disorder in only 11 subjects (15%). In addition, 32 subjects (44%) had had previous episodes of unexplained neurological symptoms; in 26 (81%) these symptoms were dissimilar to the index symptom. Thirty four subjects (47%) had had non-neurological medically unexplained symptoms, and 14 (20%) fulfilled the ICD-10 criteria for somatisation disorder.

Psychiatric disorder

Of the 59 subjects for whom this information was available, 44 (75%) had had a psychiatric disorder as determined by the scale of affective disorder and schizophrenia (SADS). The most common diagnoses were depressive disorder (24 subjects (41%)) and anxiety or phobic disorders (9 subjects (15%)). Psychotic symptoms were uncommon; only four subjects (7%) had these. No significant differences in the prevalence of psychiatric diagnoses existed in relation to age, sex, or social class. The psychiatric disorder had coexisted with the unexplained motor symptoms in 33 subjects (56%). Of these 59 subjects, 31 (53%) fulfilled criteria for a personality disorder. The most common subtypes were "dependent" (7 subjects), "emotionally unstable" (7 subjects), and "anxious" (6 subjects). Histrionic personality disorder was present in only four subjects (6%). Six subjects (8%) had a concurrent history of substance misuse (mostly associated with alcohol).

Neurological diagnoses at follow up

The organicity rating was the same at follow up in 47/69 subjects (68%) and had fallen in 17 (25%), suggesting a greater degree of certainty at that time. The rating had increased at follow up in the remaining five subjects (7%). In two of the five, the organic component was still insufficient to explain the symptom; in the other three, an organic neurological diagnosis was considered retrospectively to have explained the presenting symptom. The first of the three, a 25 year old woman who had presented with falls and abnormal gait and was of low intelligence, was diagnosed as having genetically confirmed myotonic dystrophy 4 years later. At follow up, the clinical picture had worsened and she had considerable difficulty with walking, swallowing, and breathing. A 49 year old man, first seen with a gait disorder, had been diagnosed as having spinocerebellar degeneration 3 years after his admission to hospital. Communication was difficult because English was not his first language. At follow up his gait, posture, speech, and swallowing had deteriorated appreciably. The diagnosis of a gait disorder in a 68 year old man was changed to one of paroxysmal hemidystonia at follow up.

Five subjects (7%) had died by the time of follow up. The causes of death are detailed in table 3. In no case was there evidence of a new diagnosis related to the original symptom.

Psychiatric diagnoses at follow up

At follow up, 23/64 subjects had a current psychiatric diagnosis. This was more often the case in those with abnormal motor activity rather than weakness ($P = 0.04$, χ^2 test). Most current disorders represented either a continuation or a relapse of a previous psychiatric disorder. However, three subjects had developed a new psychiatric disorder. A 48 year old woman with a head tremor now had florid psychotic symptoms and the head tremor was considered retrospectively to be part of a schizophrenic syndrome. A 49 year old man with unsteady gait and a 40 year old man with hemiplegia had developed major depressive disorders. The motor disorder had resolved only in the third subject.

Outcome

When the 64 subjects whose organicity rating had not increased at follow up were considered, only 21 (33%) were in full time employment; 30 (47%) were now retired on the grounds of ill health and two (3%) remained on sick pay from their job. The index symptom had completely resolved in 18 of these subjects

Table 3 Details of five patients who died before follow up

Age	Sex	Non-organic index symptom	Psychiatric diagnoses	Cause of death	Other somatisation	State of index symptom at death
36	M	Paraplegia	Borderline personality disorder	? Overdose	Pseudoseizures, abdominal pain	Unchanged
22	F	Quadriplegia	Dependent personality disorder, depressive disorder	Pneumonia secondary to immobility	Abdominal pain, joint pains, unexplained urinary problems, pseudoseizures	Worse
51	M	Right hemiplegia	Somatisation disorder, cognitive impairment, anxiety and panic attacks	Congestive cardiac failure	Abdominal pain, headaches, backache, non-cardiac chest pain, hyperventilation	Unchanged
50	M	Left hemiparesis	Somatisation disorder	Carcinoma of the bowel	Pseudoseizures, aphasia, atypical chest pain, hyperventilation, irritable bowel syndrome	Unchanged
62	M	Unsteady gait	None	Myeloproliferative disorder	None	Unchanged

Table 4 Factors predicting outcome in 64 subjects whose organicity rating was not increased at follow up

Factors	Symptom better (n=31)	Symptom not better (n=33)	Logistic regression analysis (unadjusted)		Logistic regression analysis (adjusted)	
			P value	Odds ratio (95% CI)	P value	Odds ratio (95% CI)
Demographic:						
Age >35years	22	22	0.71	1.22 (0.42 to 3.53)	0.72	0.73 (5.72 to 4.15)
Female sex	18	14	0.21	1.88 (0.69 to 2.72)	0.99	1.01 (0.15 to 6.60)
Social class <3	16	20	0.47	0.69 (0.14 to 3.52)	0.86	1.18 (0.12 to 8.41)
Receiving benefit at time of admission	16	26	0.025	0.29 (0.10 to 0.86)	0.03	0.15 (0.027 to 0.84)
Index admission:						
Duration of symptom <1 year	27	16	0.013	0.24 (0.08 to 0.74)	0.018	0.11 (0.02 to 0.67)
Litigation pending at time of admission	4	11	0.062	0.30 (0.08 to 1.05)	0.066	0.09 (0.01 to 1.18)
Comorbid SADS-L psychiatric disorder at time of motor symptoms	22	11	0.0034	4.89 (1.70 to 14.13)	0.025	7.34 (1.29 to 42.28)
Previous illness:						
Personality disorder	10	19	0.044	0.35 (0.13 to 0.97)	0.10	0.24 (0.04 to 1.34)
Further psychiatric treatment	16	17	0.99	1.0 (0.38 to 2.67)	0.72	1.39 (0.22 to 8.61)
History of somatisation	10	21	0.33	0.61 (0.22 to 1.68)	0.56	0.64 (0.14 to 3.00)
Family experience:						
Change in marital status since admission	10	2	0.015	7.38 (1.48 to 36.86)	0.008	33.66 (2.52 to 444.61)
Family history of chronic illness	14	18	0.45	0.69 (0.25 to 1.92)	0.43	0.53 (0.11 to 2.51)

SADS-L=schedule for affective disorders and schizophrenia.

(28%) and had improved in 13 (20%). The presenting symptom was unchanged in nine subjects (14%), while in 24 (38%) it had worsened. For the purposes of multiple logistic regression analysis, these subjects were grouped into the 31 who had improved, and the 33 who had not improved. The factors entered in the analysis are shown in table 4. Factors associated with a good outcome were: symptoms present for less than 1 year at admission to hospital ($P=0.018$), a psychiatric diagnosis indicated by the schedule for affective disorders and schizophrenia that coincided with the unexplained motor symptoms ($P=0.025$), and a change in marital status during the follow up period ($P=0.0075$). Receipt of financial benefits at the time of admission to hospital indicated a poor prognosis ($P=0.03$), as did pending litigation ($P=0.066$).

Discussion

The incidence of subsequent neurological disorder in our study—indicative of initial misdiagnosis—was low. There was also little evidence that symptoms reflected new presentations of an undiagnosed psychiatric disorder. Mitigating factors explain misdiagnosis. In one subject, the diagnosis may have been missed because paroxysmal dystonias have only recently been recognised as a neurological entity.[14] In two others, communication problems may have played a part. It is impossible to assert that the symptoms of the other subjects will never be explained by neurological diagnoses, but after 6 years of follow up this is increasingly unlikely. The high diagnostic accuracy probably reflects improved diagnostic skills as well as better non-invasive investigative techniques.

The equal sex ratio in our cohort, different from the female preponderance of previous studies, remains unexplained. However, the high incidence of affective, anxiety, somatisation, and personality disorders is similar to that previously reported.[15–17] Although five subjects had died by the time of follow up, their deaths did not reflect missed neurological diagnoses. It is important to remember that conversion disorder does not protect patients from developing serious physical illness. The presence of somatisation in other systems may have lead to delay in the diagnosis of severe non-neurological illnesses in two subjects. In a further two subjects who died at a young age, death may have been related to the sequelae of underlying psychiatric disorder.

Few studies have looked at indicators of prognosis. Our results support previous work which found that a short duration of symptoms was associated with a good outcome.[7 8 19] Pending litigation—as is often suggested anecdotally—also emerged as an indicator of poor prognosis. Changed marital status (in either direction) seemed to predict a good outcome, presumably reflecting a favourable change in personal circumstances. The association between comorbid psychiatric disorder and good outcome underlines the importance of screening for affective and anxiety disorders in these patients. These disorders may make some people vulnerable to developing conversion symptoms, which if managed inappropriately may lead to enduring disability. The findings suggest that treatments may need to be targeted specifically. Treating depression and anxiety aggressively and exploring relevant personal circumstances may reduce disability in some patients, while for those with several physical symptoms and personality disorder, prevention of iatrogenic damage and cost effective management strategies aimed at damage limitation may be more appropriate.

This study has several limitations. Follow up studies are always subject to attrition, although we managed to obtain data on 88% of subjects. The setting for the study, a secondary and tertiary neurological teaching hospital, limits the generalisability of our findings. Although inclusion of subjects selected was validated, cases may have been overlooked in the initial selection and milder cases may be underrepresented as they were not perceived to require referral to a neurological centre. Referral bias may explain the high social class, older age, and chronicity of our cohort compared with other studies.[6 19] Similarly, the extent to which organic disorders were excluded by special investigation may not be typical of that in other centres. Another

limitation is the lack of a comparison group. Hence, we were unable to calculate the relative risk of psychiatric disorder in patients with unexplained motor symptoms compared with patients with clear cut neurological syndromes. However, the main purpose of the study was to look at changes within this group and at associated psychological and physical morbidity.

In summary, the stability of the diagnosis in patients with medically unexplained motor symptoms who have been investigated thoroughly is high. Neurologists should be encouraged to make a positive diagnosis early to avoid uncertainty in the minds of the patients, and other health care professionals, thus reducing the risks and costs of further unnecessary investigations. The opportunity to seek psychiatric disorder and treat it appropriately should not be missed.

Contributors: HLC interviewed patients and examined them psychiatrically, collected and analysed data, and wrote the various versions of the manuscript. KB examined the patients neurologically and was involved in the writing of the manuscript. HC and MAR were blind raters of patient documentation. AD, HC, CDM, and MAR had the original idea for the study, discussed core findings, and participated in the writing of the paper. MAR is the guarantor of the paper.

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Conflict of interest: None.

Key messages

- Motor symptoms that remain unexplained medically despite thorough investigation are a common clinical problem, but the emergence of a subsequent organic explanation for these symptoms is rare
- The prevalence of coexistent affective and anxiety disorders is high and many patients also have a personality disorder
- Patients with a shorter duration of symptoms and coexistent anxiety or depression are likely to do better at follow up
- Reinvestigation of these patients is both expensive and potentially dangerous and should be avoided where no clear clinical indication exists

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A memorable patient

An ad hoc blood bank

On a wet afternoon in 1953 a truck drew up at the foot of the steps of the hospital. Four Indian men carried a young boy inside. They operated a saw mill in the bush, they said. That morning the boy had fallen across the blade, which cut his leg off above the knee and then turned him around and went up his thigh and into the hip joint. He seemed to be dead so they covered him with a sack and carried on sawing.

Later, someone thought that they could see that he was breathing so they brought him to the hospital. The only sign of life was indeed a shallow respiration. Our blood bank was, so to speak, on the hoof. Donors were summoned, if they could be located, and were bled into the evacuated bottles supplied by the Canadian Red Cross. A time consuming business, which my partner and I at once instituted and, in the meantime, as both of us were O positive, we took a generous pint from each other and, after a quick major cross match, pumped the still warm blood into the patient.

Sister Superior came to say that the Indians had returned with the leg, still wearing a boot, and left it on the bottom step of the hospital. She also told us that, by chance, an official from the Ministry of Health, who was conducting a province wide survey of hospitals, had arrived. It seemed that he was utterly fascinated to learn what was going on in our quite small hospital, admirably run by the Sisters of Saint Anne. He had asked if it might be possible for him to observe our resuscitative efforts through a small window in the door of the operating theatre. I asked her to inquire if he knew his blood group. It was group O. Yes, I said, he could watch if he would agree to part with some of his blood. He said he would and I took a pint and a half.

I disarticulated what was left of the femur and the boy recovered. I met the ministry man over the years from time to time. He was always very friendly. I noted, however, that he never came back to our town.

Kenneth Macrae Leighton, *retired professor of anaesthesia, Smithers, British Columbia, Canada*

We welcome articles up to 600 words on topics such as *A memorable patient, a paper that changed my practice, My most unfortunate mistake,* or any other piece conveying instruction, pathos, or humour. If possible the article should be supplied on a disk. Permission is needed from the patient or a relative if an identifiable patient is referred to. We also welcome contributions for "Endpieces," consisting of quotations of up to 80 words (but most are considerably shorter), from any source, ancient or modern, which have appealed to the reader.

Effect of temazepam on oxygen saturation and sleep quality at high altitude: randomised placebo controlled crossover trial

Gerald Dubowitz

Abstract

Objective: To determine the effects of temazepam on the quality of sleep and on oxygen saturation during sleep in subjects at high altitude.
Design: Randomised, blinded, crossover, placebo controlled trial.
Setting: Base camp at Mount Everest (altitude 5300 m).
Subjects: 11 members of British Mount Everest Medical Expedition recently arrived at base camp.
Intervention: Participants were randomly allocated to receive either temazepam 10 mg or placebo on their first night at base camp and the other treatment on the second night.
Main outcome measures: Quality of sleep (assessed subjectively), mean arterial oxygen saturation value, and changes in saturation values (as measure of periodic breathing) while participants taking temazepam or placebo.
Results: All participants noted subjective improvements in sleep. Mean saturation value remained unchanged when temazepam was compared with placebo (74.65% *v* 75.70%, P = 0.5437). There were fewer changes in oxygen saturation when participants took temazepam and when measured as decreases >4% below the mean value of saturation each hour (P = 0.0036, paired Student's *t* test (two tailed)).
Conclusions: Participants taking temazepam at 5300 m showed no significant drop in mean oxygen saturation values during sleep. Both the number and severity of changes in saturation during sleep decreased and the quality of sleep improved. This may be a result of a reduction in the number of awakenings and might lead to greater respiratory stability and fewer episodes of periodic breathing. This has the effect of improving the quality of sleep and reducing the number of periods of desaturation during sleep

Introduction

Sleep is impaired in people who have recently arrived at high altitude.[1 2] Impairment is caused by a combination of factors, which include being in a new environment, the low temperature, general discomfort, and development of acute mountain sickness. A feature of sleep at high altitude is periods of awakening or arousal that are associated with pronounced oxygen desaturation and periodic breathing.[3–7] These episodes of periodic breathing may cause more unconsolidated sleep, which may lead to further episodes of periodic breathing.[8] Consequently, daytime symptoms of drowsiness and reduced performance may occur.[9] The use of benzodiazepine hypnotics may lessen the effects of periodic breathing and desaturation.[7 8]

This study compared the effects of a comparatively low dose (10 mg) of the short acting benzodiazepine temazepam with placebo on the sleep patterns of subjects recently arrived at high altitude.

Subjects and methods

Shortly after arrival at 5300 m on Mount Everest nine men and two women (age range 26-46) were randomly selected from the 78 members of the British Mount Everest Medical Expedition. All participants gave informed consent. The study was approved by the Oxford regional ethics committee. A coin was tossed to randomly allocate participants to either temazepam (Norton Pharmaceuticals, Essex) or placebo (Advisory Services, London) on the first night followed by the other treatment on the second night. Participants were unaware which treatment they were given. However, the investigator was aware of participants' allocation at the time treatment was given because of the different sizes of tablets, but was not aware when data were analysed. Arterial oxygen saturation was measured continuously during the night (every 5 s) with a pulse oximeter and finger probe (Minolta Pulseox 7, De Vilbiss, Middlesex). Each morning quality of sleep was appraised subjectively by direct questioning.

The data on saturation and pulse rate were downloaded to a computer and analysed to find the mean saturation values and variation in saturation (the number of times saturation dropped >4% below mean value). Values were analysed with a paired, two tailed Student's *t* test (Statview SE and Graphics, version 1.04, Abacus Concepts, Berkeley, CA). $P < 0.05$ was considered significant.

Results

Six participants took temazepam on the first night and placebo on the second and five took placebo on the first and temazepam on the second. The mean duration of recordings made during sleep was 408 minutes (SD 35 min). Length of recording was limited by sleep duration or oximeter battery life (whichever was shorter).

Mean arterial oxygen saturation—Temazepam had no significant effect on mean oxygen saturation during sleep when compared with placebo (table). The difference of 1.05% was not significant using a paired *t* test (P = 0.54, df = 10, 95% confidence interval −4.73 to 2.65). However, when participants took temazepam there was a significant decrease in the number of times that saturation fell >4% below the mean (P = 0.0036); there were 25.81 fewer falls per hour that were >4% below the mean when participants took temazepam when compared with placebo (df = 10, 10.7 falls per hour on temazepam *v* 40.9 falls per hour on placebo).The effect was more pronounced in the early hours of sleep. These effects were found regardless of

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Mean arterial oxygen saturation in 11 participants at high altitude who took placebo or temazepam

	Placebo	Temazepam	Difference	P value (two tailed)
Mean % (SE) oxygen saturation	75.70	74.65 (1.55)	−1.05 (1.66)	0.54
No of times per hour (SE) saturation fell >4% below mean value	100.79	74.98 (12.25)	25.81 (6.78)	0.0036

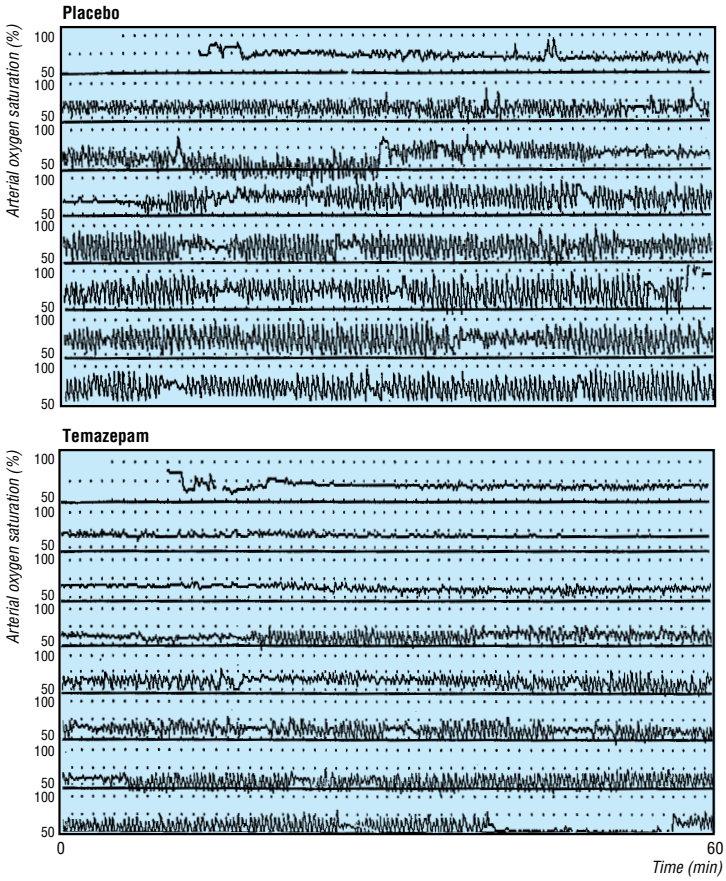
SE=standard error.

whether participants were assigned to take temazepam or placebo first (figure).

Subjective changes in sleep—All participants reported an improvement in sleep when taking temazepam. Improvements noted included a quicker onset of sleep, better quality of sleep, fewer awakenings and less awareness of periodic breathing, and feeling more rested the next day. No participants complained of drowsiness the day after taking temazepam.

Discussion

In this study the use of temazepam during sleep at high altitude improved the subjective quality of sleep without reducing arterial oxygen saturation. The use of various benzodiazepines at high altitude has been considered in several previous studies.[10–14] Many of these have used high doses and long acting preparations which led to heavy sedation and marked desaturation.[11 14] There is, however, evidence that small doses of benzodiazepines may be beneficial in reducing central sleep apnoeas in susceptible patients.[8]



Arterial oxygen saturation during 8 hours of sleep in one participant while taking placebo or temazepam. Each horizontal bar represents 1 hour of sleep

Key messages

- Poor sleep at high altitude is common and may be due to a combination of physiological and physical factors
- Frequent arousals, periodic breathing, and episodes of oxygen desaturation lead to poor sleep and daytime symptoms of drowsiness and reduced performance
- In this study 10 mg temazepam improved subjective reports of the quality of sleep and reduced episodes of arterial desaturation, with no significant effect on mean oxygen saturation during sleep

The reduction in the number of episodes of desaturation is in part due to the sedative effects of temazepam; these effects produce longer periods of consolidated sleep and lead to fewer of the arousals that are usually associated with sleep apnoea.[8] By stabilising sleep and reducing the number of arousals, episodes of periodic breathing are similarly reduced. This leads to an improvement in the quality of sleep and a reduction in both the number of times desaturation occurs during sleep and the amount of desaturation that occurs. In this study the reduction in desaturation was more pronounced in the earlier hours of sleep when temazepam has its strongest effect. By the end of sleep its effect has weakened and saturation values become similar to those found in participants taking placebo.

Though this study suggests an important role for temazepam in reducing periods of desaturation during sleep at altitude it does not elucidate the mechanism by which this occurs. The dose required to produce an effect on desaturation is lower than that needed to produce adequate sedation for sleep at sea level. Although the sedative role of temazepam is important, temazepam is probably affecting desaturation by another pharmacological action. It may act directly by suppressing respiratory receptors or indirectly by affecting cerebral pH. This is analogous to the improvements in saturation found using carbonic anhydrase inhibitors such as acetazolamide.[13]

Conclusion

Until recently, medical advice has been to avoid using hypnotic drugs at altitude. This advice has been based on the assumption that because they have depressant effects on the respiratory system they may cause desaturation of arterial oxygen and might provoke acute altitude sickness, pulmonary oedema, or cerebral oedema. The longer acting benzodiazepines and barbiturates might have these effects.[13] However, this study supports the conclusions of other studies which found that small doses of short acting benzodiazepines actually improve the subjective quality of sleep and reduce changes in saturation without changing mean oxygen saturation.[10 12]

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Case-control study of risk of cerebral sinus thrombosis in oral contraceptive users who are carriers of hereditary prothrombotic conditions

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Abstract

Objective: To investigate whether users of oral contraceptives who are carriers of a hereditary prothrombotic condition (factor V Leiden mutation, protein C, S, or antithrombin deficiency) have an increased risk of cerebral sinus thrombosis.
Design: Comparison of a prospective series of cases of cerebral sinus thrombosis with population data.
Setting: Neurological teaching hospitals from different regions in the Netherlands (cases) and a representative sample of the non-institutionalised Dutch population (controls).
Subjects: 40 women aged 18-54 years with cerebral sinus thrombosis (cases) and 2248 women aged 18-49 years (controls).
Main outcome measure: Current use of oral contraceptives at the time of the thrombosis (cases) or at the time of the questionnaire (controls). Prevalences of a hereditary prothrombotic condition in patients and in the population with odds ratios.
Results: 34 of 40 (85%) women with cerebral sinus thrombosis used oral contraceptives, versus 1007 of 2248 (45%) of the control women; the age adjusted odds ratio was 13 (95% confidence interval 5 to 37). Seven of 36 patients (19%) had a prothrombotic deficiency, versus 7% expected in the population; this corresponds to a threefold to fourfold increase in risk. In women who used oral contraceptives and also carried a prothrombotic defect, the odds ratio for cerebral sinus thrombosis was about 30 relative to women who had neither risk factor.
Conclusion: The use of oral contraceptives and being a carrier of a hereditary prothrombotic condition increase the risk of and interact in a multiplicative way in the development of cerebral sinus thrombosis.

Introduction

Epidemiological studies have shown that oral contraceptives carry a small but increased risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism).[1] Furthermore, women who use oral contraceptives and carry the factor V Leiden mutation have a higher risk of venous thromboembolism than expected from the mere addition of these risks.[2] Although the association between oral contraceptives and venous thromboembolism is generally accepted, there remains discussion about possible sources of bias that might influence the magnitude of the risk.

Cerebral venous sinus thrombosis is a relatively rare disease, often with cerebral infarcts, which may lead to seizures, other neurological symptoms, or death. Patients with sinus thrombosis, however, may recover completely.[3] Oral contraceptives and hereditary prothrombotic conditions, such as protein C, S, and antithrombin deficiency and factor V Leiden mutation, have been reported as possible causes of cerebral sinus thrombosis.[4]

We compared a series of patients with cerebral venous sinus thrombosis from a prospective treatment trial with population data from the Netherlands to investigate the risk of oral contraceptive use and prothrombotic conditions for cerebral sinus thrombosis.

Patients and methods

Cases

Cases were patients with cerebral sinus thrombosis (newly diagnosed) who participated in a treatment trial from July 1992 to November 1996 that compared low molecular weight heparin in a therapeutic dose with placebo in a randomised double blind design. Patients

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younger than 18 years and pregnant women were excluded. The trial was conducted in neurological teaching hospitals in different regions in the Netherlands and the United Kingdom. Cerebral sinus thrombosis was confirmed by conventional angiography or magnetic resonance imaging and angiography. For the present analysis we selected all women aged 18-54 from the Dutch part of the trial population who were not in the puerperium (within 30 days post partum).

Information on use of oral contraceptives at the time of the initial symptoms of sinus thrombosis was obtained from the patient or nearest relative and supplemented with hospital discharge letters.

Blood samples were collected and analysed in the participating hospitals. Antithrombin activity and protein C activity were measured with chromogenic assays.[5] Protein C antigen, and total and free protein S were determined by enzyme linked immunosorbent assay (ELISA) as described elsewhere.[6 7] Values were defined as abnormal if they were below the 5th centiles of the values determined in a group of healthy subjects. Resistance to activated protein C was assessed by the activated protein C dependent prolongation of the activated partial thromboplastin time.[8] An activated protein C ratio below 2.0 or a normalised ratio lower than 0.80 was considered abnormal. The mutation at position Arg 506 in factor V was determined with polymerase chain reaction techniques as described previously.[9]

Controls

The controls comprised a random sample of 2248 women aged 18-49 years from different regions in the Netherlands who were interviewed in 1994 about their current use of contraceptives (continuous health interview survey of the Central Department of Statistics of the Netherlands[10]; the methodology of the questionnaire has been described previously[11]).

Statistics

We calculated odds ratios as approximations of relative risks on the basis of the crude numbers or the percentage distribution; confidence intervals, when appropriate, were calculated by the methods of Woolf or Robins.[12] When observed odds were compared with estimated population frequencies we omitted the calculation of the confidence intervals.

Use of oral contraceptives and prothrombotic disorders in cases (women with cerebral venous sinus thrombosis aged 18-54 years, puerperium excluded) and use of oral contraceptives in controls

	Cases			
Age (years)	Proportion (%) taking contraceptives	No with factor V Leiden	No with C, S, or antithrombin deficiency	Proportion (%) of controls taking contraceptives
18-19	3/3 (100)	1	0	60/107 (56)
20-24	7/7 (100)	0	0	271/336 (81)
25-29	4/4 (100)	1	1	255/400 (64)
30-34	7/7 (100)	2	0	176/392 (45)
35-39	5/6 (83)	0	1	105/342 (31)
40-44	3/5 (60)	0	0	79/336 (24)
45-49	4/5 (80)	0	0	61/335 (18)
50-54	1/3 (33)	1	0	No data
Total	34/40 (85)	5*	2†	1007/2248 (45)

*Data missing for four women. †Data missing for three women.

Results

Forty women with cerebral sinus thrombosis who met the inclusion criteria were studied. The age related use of oral contraceptives in cases and controls and the prevalence of hereditary coagulation abnormalities in the cases are given in the table.

Use of oral contraceptives

Of the 40 cases, 34 (85%) were using oral contraceptives at the time of the sinus thrombosis. In the control group 1007 of 2248 women (45%) aged 18-49 years were using oral contraceptives. The age adjusted odds ratio for all ages (with the control data for the age group 45-49 also covering ages 50-54) was 13 (95% confidence interval 5 to 37). The age adjusted odds ratio restricted to the ages 18-49 was 18 (5 to 59).

Coagulation abnormalities

In 34 of the 40 women factor V Leiden mutation status was determined by DNA analysis and was present in four (12%). Activated protein C resistance was measured in two women in whom no DNA was obtained, indicating the presence of the factor V Leiden mutation in one. Thus five of 36 women had factor V Leiden mutation (14%; 5% to 30%). In the population the prevalence of factor V Leiden mutation is estimated to be 4-5%.[13] Protein C, S, and antithrombin activity were assessed in 37 women; two (5%) were deficient for protein C.

Hence, a prothrombotic disorder was present in seven out of 36 patients with cerebral sinus thrombosis (19%; 8% to 36%). The estimated prevalence of protein C or S deficiency, or antithrombin deficiency, or of both, in the general population is 2-3%.[14 15] Thus, the prevalence of any hereditary prothrombotic disorder, including factor V Leiden, in the population is approximately 7% (6-8%). In carriers of hereditary prothrombotic conditions the odds ratio for developing sinus thrombosis is therefore 3.2.

Interaction between oral contraceptives and hereditary prothrombotic conditions—In the population the use of oral contraceptives and being a carrier of a hitherto unknown hereditary prothrombotic condition are probably independent, at least in women who have never had venous thrombosis. If the prevalence of hereditary prothrombotic conditions is 7% and 45% of women aged 15-49 in the population use oral contraceptives we may expect that 3% of women in the population both use contraceptives and carry a prothrombotic abnormality, 42% use contraceptives only, 4% carry the prothrombotic abnormality only, and 51% have neither risk factor. In the 36 patients for whom we had complete data these percentages were 17%, 72%, 3%, and 8%, respectively. There is a clear excess of women with both risk factors in the patient series (17% *v* 3%). If the estimated population percentages are used as reference the odds ratio for development of sinus thrombosis in women with both risk factors versus women with neither would be 34. The odds ratios we found for the use of oral contraceptives (about 10) and for hereditary prothrombotic disorders (three to four) imply that oral contraceptives and being a carrier of a hereditary prothrombotic condition interact multiplicatively in their association with sinus thrombosis.

Outcome of sinus thrombosis—Most patients recovered from their sinus thrombosis, but six (15%) had a poor outcome after 3 months' follow up (four died, two were handicapped). Use of contraceptives was not associated with a worse outcome. Four of the 34 women (12%) who used contraceptives had a poor outcome after 3 months (three died and one was disabled by a severe paralysis of her right arm and cognitive impairment) compared with two out of six women (33%) not taking contraceptives.

Discussion

We have found an increased risk of cerebral venous sinus thrombosis in women who use oral contraceptives and are carriers of a hereditary prothrombotic disorder. In addition, we found that the use of contraceptives multiplies the risk of hereditary prothrombotic conditions.

Sources of bias

Before evaluating the clinical significance of our findings we must consider potential sources of bias. Because the cases were obtained in a treatment trial and the controls were a representative sample of the population, can the cases really be regarded as originating from the general population base? As all major neurological centres in the Netherlands, to which patients with sinus thrombosis are referred, participated in the trial the patients in the trial are representative of all patients with sinus thrombosis in the Netherlands. As there was no selection as to use of oral contraceptives or any other characteristic that might be related to use of contraception, the use of contraceptives in these patients can be validly compared with population data.

Pregnant women were excluded from the trial, and women in the puerperium or with a recent miscarriage were excluded from the analysis but not from the controls. Therefore oral contraceptive use in the controls might be slightly underestimated. The estimated percentage of premenopausal women who were pregnant or in the puerperium in the Netherlands was 5% in 1994,[10] which is too small to affect our results.

As sinus thrombosis is a rare condition the chance that women with this disease were present in the control group is fairly small. According to the British registrar general the average mortality during the period 1952-61 from sinus thrombosis was $0.4/10^6$/year.[16] If we assume a mortality of 10%, the incidence would be $4/10^6$/year.

Diagnostic suspicion and referral bias might occur if doctors were more likely to diagnose sinus thrombosis in women taking oral contraceptives. Women taking contraceptives might be under better medical supervision, and contraceptive use is known to increase the risk of venous thromboembolism. This type of bias has been suggested for deep vein thrombosis.[17] For sinus thrombosis this bias seems unlikely. Sinus thrombosis is a rare and alarming disease, often with severe neurological symptoms.[3] It seems reasonable to assume that all patients with sinus thrombosis are referred to a hospital, irrespective of oral contraceptive use. Misdiagnosis in our patients is unlikely because conventional angiography or magnetic resonance imaging, which are regarded as reliable diagnostic procedures for sinus thrombosis,[18] were used in all cases.

Known risk factors

In various case series oral contraceptive use alone[19] or superimposed on a hereditary prothrombotic disorder has been suggested as an aetiological factor for sinus thrombosis. A recent Italian case-control study in patients with sinus thrombosis found an odds ratio for oral contraceptive use of 4.2, after exclusion of pregnant and puerperal women. The presence of the factor V Leiden mutation in itself increased the risk for sinus thrombosis about ninefold.[20 21]

Other probable risk factors for sinus thrombosis are pregnancy and puerperium.[3] In our treatment trial seven women in the puerperium were included. Many other risk factors for sinus thrombosis have been reported in retrospective series, including the known risk factors for deep vein thrombosis, but a significant association with sinus thrombosis has not been demonstrated. The influence of smoking—if any—is unknown.

There is ample evidence that oral contraception predisposes to venous thromboembolism,[1 17] especially when the factor V Leiden mutation is present.[2] The risk of leg vein thrombosis in women with the mutation who use oral contraceptives compared with women without the mutation who do not, increases more than 30-fold.[2] The tentative analysis of the interaction between oral contraceptive use and hereditary prothrombotic conditions in our study points in the same direction.

Recently, a biological explanation of the increased risk for venous thrombosis in oral contraceptives users was reported.[22] In this study the effects of activated protein C on thrombin generation in the plasma of women using oral contraceptives were compared with the response in women not using oral contraceptives and in women heterozygotic or homozygotic for the factor V Leiden mutation. Oral contraceptives induced a degree of activated protein C resistance comparable with the resistance caused by a factor V Leiden mutation. In women heterozygotic for factor V Leiden mutation who used contraceptives the activated protein C resistance was as high as that among women homozygotic for the mutation.[22] These results fit with the epidemiological data, including those from our series of patients with cerebral venous thrombosis, and are an additional argument against objections that the epidemiological findings are merely explained by prescription bias or other sources of confounding.

That sinus thrombosis is predominantly a disease of women was already clear from recent retrospective series.[23] A comparison with sex distribution in larger series in the past, which showed no or a much less marked predominance of women in sinus thrombosis,[24] suggests a shift in the epidemiology and aetiology of the disease in recent years. Possibly the widespread use of oral contraceptives has caused this increasing relative number of women with sinus thrombosis.

Conclusion

We conclude that the major risk factors for deep vein thrombosis and cerebral venous sinus thrombosis in women are the same. As the absolute risk for sinus thrombosis in premenopausal women is low, with an

Key messages

- The use of oral contraceptives is associated with an increased risk of cerebral venous sinus thrombosis
- This risk of cerebral venous sinus thrombosis in women who use oral contraceptives is larger if there is an additional hereditary prothombotic factor (protein C, S, or antithrombin deficiency, factor V Leiden mutation)
- The association between oral contraceptives, thrombophilia, and deep vein thrombosis is also valid for cerebral sinus thrombosis
- Women do not need to stop using oral contraceptives as the absolute risk of cerebral sinus thrombosis is very small

estimated incidence of $4/10^6$/year, our findings should not be used to advise against oral contraceptive use in all women. In women who have a history of venous thrombotic disease, including sinus thrombosis, however, advice against use of oral contraceptives should be considered, especially in women with a hereditary prothrombotic disorder.

The Cerebral Venous Sinus Thrombosis Study Group comprised S F T M de Bruijn, J Stam, A W A Lensing, J G P Tijssen, P M Bossuyt, L J Kappelle, J Van Gijn, D W J Dippel, P J Koudstaal, J J Van Hilten, R A C Roos, J L A Eekhof, J J Van der Sande, H L Hamburger, J Lodder, C C Tijssen, F W Bertelsman, J C Koetsier, P Sandercock, P Humphrey, G N Mallo, P Verlooy, H K Van Walbeek, J W Snoek, and C L Franke.

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Contributors: SFTMdeB, JS, and JPV formulated the research hypothesis, designed the study, analysed the data, and wrote the paper. MMWK analysed the data on prothrombotic disorders and helped to write the paper. SFTMdeB collected and checked all data on use of contraceptives and prothombotic disorders, assisted by M Budde. SFTMdeB, JS, and JPV are guarantors for the paper.

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Fifty years ago

The new NHS: The press and the profession

Speaking at the opening of the East Glamorgan County Hospital on Saturday, Mr. Aneurin Bevan, the Minister of Health, gave this advice to doctors: "Do not allow your minds to be inflamed or your judgment to be distorted by slogans which are addressed to your emotions and not to your intelligence." This sound piece of advice is perhaps hardly necessary for members of a profession used to making a differential diagnosis. The doctor uses the methods of science, and the politician the technique of the hustings. At this moment the medical profession is being subjected to abuse, misrepresentation, and malicious innuendo from the highly emotional press which supports Mr. Bevan. This campaign was started by the *Tribune*, of which Mr. Bevan was a director and editor until he took office in the present Government in 1945. The *Tribune* suggested that "the BMA may still try to fight the battle of the Tory Party against the development of a socialist service," and it went on to state: "Politically, the Minister's firmness has been most important. If he had been weak in face of this reactionary profession . . . it would have increased doubts as to the intention to carry out a socialist programme."
(*Editorial*, 24 January 1948, p 155. See also editorial by Gordon Macpherson, 3 January 1998, p 6.)

Single photon emission computed tomography in the identification of new variant Creutzfeldt-Jakob disease: case reports

Rajith de Silva, James Patterson, Donald Hadley, Aline Russell, Martin Turner, Martin Zeidler

New variant Creutzfeldt-Jakob disease may be associated with exposure to the causative agent of bovine spongiform encephalopathy.[1] Currently, a reliable diagnosis is possible only after neuropathological examination of the brain, which is risky for patients and diagnosticians.[2] The sensitivity and specificity of recently developed techniques are not known for new variant Creutzfeldt-Jakob disease, and they are available only in highly specialised centres.[3 4]

Single photon emission computed tomography is a readily available neuroimaging technique that uses intravenously administered radioactive ligands to map different aspects of brain function.

We report the findings on this technique using the cerebral perfusion tracer hexamethylpropyleneamine-oxime (HMPAO) in two patients with neuropathologically confirmed new variant Creutzfeldt-Jakob disease.

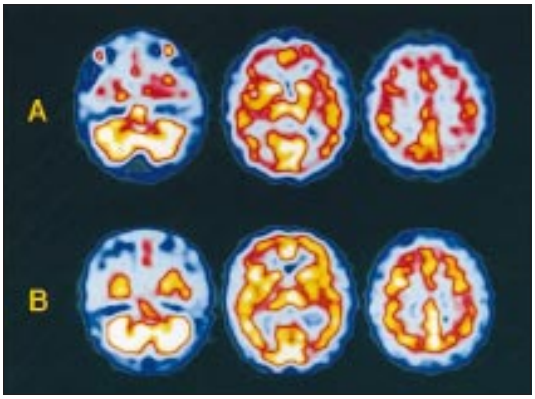
Patients, methods, and results

Case 1—A 28 year old woman developed paraesthesia of her right arm, then right leg, and later both left arm and leg. Six months later she complained of weight loss and fatigue, and had mild ataxia. After 1 year, speech, memory, and behavioural abnormalities were identified, her ataxia had worsened, and choreiform movements were noted. Six months later she developed myoclonus, primitive responses, pyramidal signs, and severe limb and truncal ataxia. Finally, she became rigid and mute; she died 23 months after the onset of her symptoms. An electroencephalogram taken 11 months after initial presentation showed no abnormalities. A repeat tracing 3 months later showed no abnormalities either, and at that time, results from magnetic resonance imaging of the brain were reported as normal apart from showing mild atrophy. Simultaneous single photon emission computed tomography showed hypoperfusion, most marked in the left temporoparietal region. The diagnosis of new variant Creutzfeldt-Jakob disease was established histopathologically.

Case 2—A woman aged 34 was admitted to a psychiatric unit with a 9 month history of presumed agitated depression. Neurological examination gave normal results, and antidepressant treatment was started. Over the next 2 months she developed delusional thoughts and became unsteady. An electroencephalogram showed diffuse slowing, and magnetic resonance imaging of the brain was reported to be normal. She continued to deteriorate with worsening psychiatric symptoms, progressive ataxia, bulbar palsy, and incontinence. Single photon emission computed tomography (two weeks after the magnetic resonance study) showed widespread reduction in cortical perfusion (figure). Over the ensuing months she became more withdrawn, ataxic, and rigid. Finally, she had rest and stimulus sensitive myoclonus, and was mute. She died 14 months after the onset of her illness. The histopathological findings were characteristic of new variant Creutzfeldt-Jakob disease. Serial electroencephalographic recordings (the last was performed 10 days before her death) showed progressive slowing of background rhythms but no typical periodic complexes.

Comment

The two patients presented consecutively at this institute, and necropsy confirmed that they had died of new variant Creutzfeldt-Jakob disease. As with other cases of the disease identified to date, early diagnosis was hampered by the absence or subtlety of neurological features, and by comparatively normal results in investigations. The clinically important abnormalities of cerebral perfusion on single photon emission computed tomography, when findings on electroencephalography or cerebral magnetic resonance imaging were normal, raised or supported the diagnosis of an organic encephalopathy in both cases. Similar abnormalities shown in single photon emission computed tomography have been reported in sporadic Creutzfeldt-Jakob disease, and a patient who died 7 weeks after onset had a unilateral perfusion deficit corresponding to the clinical, electroencephalographic, and pathological abnormality.[5] Although the perfusion abnormalities seen here are non-specific and cannot be claimed to be diagnostic of new variant Creutzfeldt-Jakob disease, they are more marked and widespread than those associated with depression. Consequently, the technique may prove useful in raising the possibility of the disease in young patients presenting with unusual psychiatric or neurological syndromes, with normal or unhelpful results in routine investigations.



Axial sections on single photon emission computed tomography through cerebellum, basal ganglia, and parietal region in case 2 (A) showing widespread reduction in cortical perfusion, and in age matched, healthy subject (B) for comparison

See editorial by Pocchiari and p 577

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Contributors: RdeS, JP, and DH raised the possibility of using single photon emission computed tomography as a diagnostic "pointer" in new variant Creutzfeldt-Jakob disease, and RdeS wrote the paper. AR, MT, and MZ discussed the core concept and suggested amendments to the early drafts. JP and DH reviewed the final manuscript. MT contributed psychiatric data in case 2, and AR interpreted the electrophysiological data. JP and DH interpreted the single photon emission computed tomograms. DH interpreted the other radiological studies and collated these with the single photon emission computed tomography scans. MZ was involved in establishing the final diagnoses.

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Social alcohol consumption and low Lp(a) lipoprotein concentrations in middle aged Finnish men: population based study

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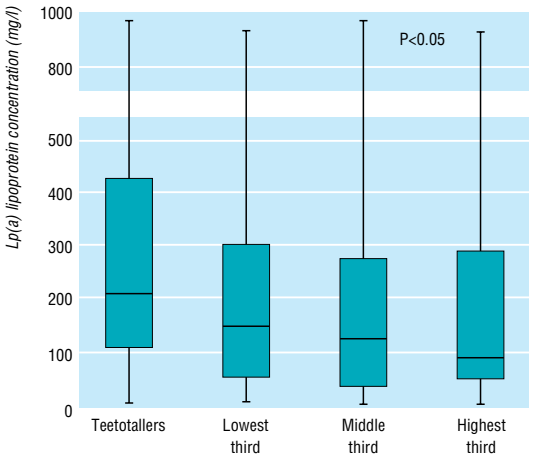
Light or moderate alcohol consumption decreases the risk of coronary heart disease.[1] Beneficial changes in high density lipoprotein cholesterol concentrations are, however, observed at quite high levels of alcohol consumption—that is, ≥20 units per week, 1 unit being 10-12 g.[2] Therefore, other factors may be responsible for decreasing the risk of coronary heart disease when alcohol is consumed in social amounts. We studied the relation between light and moderate alcohol intake and Lp(a) lipoprotein concentrations. Lp(a) lipoprotein is an independent risk factor for coronary heart disease[3] and is affected by alcohol misuse.[4]

Subjects, methods, and results

We performed a population based cross sectional study of 300 men aged 40-60 years selected randomly by age stratification; 259 (86%) participated in the study. Subjects were divided into four groups by alcohol consumption: abstainers (mostly lifetime teetotallers; 37 men) and three groups of drinkers. Drinkers in the lowest third consumed <39 g alcohol/week (74 men), those in the middle third 39-132 g/week (75), and those in the highest third >132 g/week (73). Alcohol intake was ascertained from a questionnaire on the amount and quality of alcoholic beverages consumed during the previous two weeks. Plasma Lp(a) lipoprotein concentrations were determined by a two site immunoradiometric assay that showed a close correlation with two different enzyme linked immunoassays ($r \geq 0.96$). Liver function was assessed by measuring lipid and enzyme concentrations in fasting blood samples using standard techniques. Statistical analysis was carried out with the SAS software package. The groups were similar for age and smoking habits. The body mass index, waist to hip ratio, systolic and diastolic blood pressure, and alanine aminotransferase values were highest in subjects in the third drinking >132 g/week compared with those in the two lower thirds and with non-drinkers ($P<0.001$ for each parameter, analysis of variance). The mean concentrations of serum γ-glutamyltransferase increased with increasing alcohol intake—that is, 34, 33, 49, and 64 U/l respectively for teetotallers, and the lowest, middle, and highest third of drinkers ($P<0.001$). Blood glucose and serum insulin values did not differ between the groups. Lp(a) lipoprotein concentrations were higher (median, 206 mg/l) in the teetotallers than in the drinkers. Lp(a) lipoprotein concentrations for the lowest, middle, and highest alcohol thirds were 137, 109, and 94 mg/l ($P<0.05$, Kruskal-Wallis test) (figure). As noted in other white populations, we observed a highly skewed distribution of Lp(a) lipoprotein concentrations and a wide range within the population. The ranges were similar in the study groups (figure). Lp(a) lipoprotein concentrations showed a weak but significant correlation with body mass index, waist to hip ratio, and insulin concentrations (Pearson's correlation coefficients −0.15, −0.14, and −0.15 respectively, $P<0.025$ for each correlation). There were no significant differences in high density lipoprotein (means for the teetotallers, and the lowest, middle, and highest thirds of alcohol consumption 1.19, 1.19, 1.23, and 1.27 mmol/l respectively) or low density lipoprotein cholesterol concentrations between the groups.

Comment

Our report shows that social drinking—that is, <39 g alcohol/week or 1-4 units/week—is associated with low Lp(a) lipoprotein concentrations in middle aged men. No changes were observed in high density lipoprotein cholesterol or low density lipoprotein cholesterol concentrations, blood pressure, or liver enzyme concentrations.



Plasma Lp(a) lipoprotein concentrations in four study groups. Boxes represent median and middle quarters of Lp(a) lipoprotein concentration and whiskers represent lowest and highest quarters

Other studies of alcohol consumption and Lp(a) lipoprotein cholesterol concentrations have dealt with differences between men and women, analysed alcohol intake qualitatively,[5] and compared heterogeneous groups—that is, non-drinkers together with those who drink regularly on three or less days a week. To our knowledge, ours is the first study to show a relation between moderate alcohol consumption and Lp(a) lipoprotein concentrations. We conclude that low Lp(a) lipoprotein concentrations may be one factor explaining low mortality and retarded progression of coronary artery disease in social drinkers.

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Contributors: MP participated in data analysis, writing the paper, and a discussion of the core ideas. KK discussed the study hypothesis and core ideas, and participated in data analysis and writing the paper. AOR participated in the study design, patient investigations, and data collection. MJS discussed the study hypothesis and core ideas, and participated in writing the paper. ML participated in the study design, data collection, and writing the paper. AR participated in the study design, statistical analysis, and writing the paper. YAK was the principal investigator; he initiated and coordinated the formulation of the primary study hypothesis, designed the protocol, discussed core ideas, and participated in data interpretation and writing the paper. YAK will act as guarantor of the study.

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Drug points

Postural hypotension induced by paroxetine

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Antidepressant prescribing in elderly people is influenced by side effects and the patient's physical state.[1] The high rate of falls and fractures in this age group may relate to antidepressant induced postural hypotension.[2] Tricyclic antidepressants and monoamine oxidase inhibitors may produce postural hypotension,[3] so treatment with selective serotonin reuptake inhibitors is often preferred in older patients. We report a case of postural hypotension induced by paroxetine.

A 75 year old woman who had had coronary artery bypass grafting six months previously was prescribed paroxetine for depression. The starting dose of 10 mg was increased to 20 mg after 14 days, but her other treatment (quinine bisulphate, fluvastatin, and temazepam) was unchanged. She continued to take paroxetine for 6 days, when she became dizzy and developed marked postural hypotension (blood pressure 170/90 mm Hg while lying and 90/60 mm Hg while standing). Physical examination and investigations, including a short tetracosactrin test, gave normal results. Paroxetine treatment was discontinued and her postural hypotension resolved. She agreed to a rechallenge test with paroxetine at a reduced dose of 10 mg. Again, she developed dizziness and postural hypotension (blood pressure 140/90 mm Hg while lying and 110/60 mm Hg while standing), which resolved on withdrawal of the drug.

To our knowledge, the only published report of postural hypotension associated with paroxetine relates to its increasing trimipramine concentrations when prescribed with trimipramine.[4] At the time of writing, 43 cases of postural hypotension associated with paroxetine had been reported to the Committee on Safety of Medicines (personal communication). Other selective serotonin reuptake inhibitors have been reported to exacerbate syncope.[5] Dizziness is cited on the datasheet for paroxetine, though not in relation to postural hypotension.

We suggest that postural hypotension should be considered if dizziness develops. The size of the postural fall in blood pressure seems to be dose related, and the dose should be reduced or drug treatment discontinued.

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