PAPER

Chronic alcohol use and first symptomatic epileptic seizures

M Leone, C Tonini, G Bogliun, F Monaco, R Mutani, E Bottacchi, P Gambaro, E Rocci, T Tassinari, C Cavestro, E Beghi, for the ARES (Alcohol Related Seizures) Study Group

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See end of article for authors' affiliations

Correspondence to: Dr M Leone, Clinica Neurologica, Ospedale Maggiore, C. Mazzini 18, 28100 Novara, Italy; leomau@iol.it

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Objective: To establish whether chronic alcoholism and alcohol consumption are risk factors for developing a first symptomatic epileptic seizure.
Methods: Multicentre case-control study of 293 patients (160 men, 133 women) with a first seizure symptomatic (either acute or remote) of head trauma, stroke, or brain tumour, matched to 444 hospital controls for centre, sex, age (±5 years), and underlying pathology.
Results: The risk of first seizure in alcoholics was no higher than in non-alcoholics for men (odds ratio 1.2, 95% confidence interval 0.4 to 3.2) or women (1.5, 0.1 to 54.4). The odds ratio (both sexes) was 1.2 (0.8 to 1.7) for an average intake of absolute alcohol of 1–25 g/day, 0.9 (0.5 to 1.5) for 26–50 g/day, 1.6 (0.8 to 3.0) for 51–100 g/day, and 1.4 (0.5 to 3.5) for >100 g/day.
Conclusions: We found no evidence of an association between alcohol use or alcoholism and a first symptomatic seizure.

Symptomatic epileptic seizures, according to the guidelines for epidemiological studies on epilepsy,[1] are classified as provoked or unprovoked, depending on the time between the insult to the central nervous system (CNS) and the seizure. Provoked is equivalent to acute symptomatic, and unprovoked symptomatic includes seizures with a presumed remote cause, or owing to progressive CNS disorders. Three aetiological factors (stroke, head trauma, and brain tumours) account for half to two thirds of symptomatic seizures in incidence studies in adults.[2 3] Alcohol use was one of the strongest risk factors for a first seizure,[4 5] with a dose-relation for idiopathic/cryptogenic seizures; the risk was also evident for symptomatic seizures, although lower and with a less clear trend. In both these studies, however, the sample for symptomatic seizures was small.

We therefore designed a study to establish whether alcohol consumption is a risk factor for a first symptomatic seizure. Since alcohol use might also have a confounding effect for some "aetiologies",[6 7] we considered confounding in our study design. Secondary objectives were to estimate these risks in different patient subgroups based on sex and type of seizure (acute or remote symptomatic), and in relation to the underlying "cause" (stroke, head trauma, and brain tumour).

PATIENTS AND METHODS

This was a multicentre case-control study in Northern Italy. Eighteen referral neurological and neurosurgical departments in Northern Italy participated.

Cases and controls

Cases

We studied patients consecutively admitted to one of the participating hospitals with either a first ever seizure, or a first medically evaluated seizure. Seizures were classified according to the 1981 proposal for Revised Clinical and Electroencephalographic Classification of Epileptic Seizures.[8] A first seizure was defined as the first seizure (or the first cluster of seizures within a 24 hour period) ever experienced by the patient, excluding febrile seizures; a first medically evaluated seizure was the first seizure ever evaluated by a physician in patients who had had previously unevaluated seizures of any type. Seizures were divided into provoked (occurred in close temporal association with an acute brain insult), unprovoked symptomatic (secondary to conditions resulting in static encephalopathy, or associated with a progressive CNS disorder), and unprovoked of unknown aetiology (including idiopathic and cryptogenic), on the basis of history, clinical examination, electroencephalography (EEG), and computed tomography (CT) results. In this paper we will use the terms *acute symptomatic* and *remote symptomatic* as the equivalent of *provoked* and *unprovoked symptomatic*, and *idiopathic/cryptogenic* as the equivalent of *unprovoked unknown cause*.

No assumptions were made with regard to the effects of alcohol: seizures occurring during alcohol withdrawal and in persons with a history of chronic alcohol abuse were therefore divided into idiopathic/cryptogenic, acute, or remote symptomatic solely on the absence or presence of an insult to the CNS, its type, and its time relation with the seizure. Patients with only CT signs of previous asymptomatic hemispheric stroke were classified as remote symptomatic seizures. A panel of three neurologists (ML, CT, GB) decided on the inclusion or exclusion of cases which could not be easily classified. When a patient presented concurrent remote and acute insults to the CNS, the seizure was classified as acute symptomatic.

Inclusion criteria were: age 15 years or older; having had a seizure in the 48 hours before hospital admission; evaluation by a neurologist; seizure described by eye witnesses (93% of cases); or, for generalised tonic-clonic seizures, at least three of the following criteria: loss of consciousness, urinary or faecal incontinence, laceration of tongue or cheek, and post-ictal confusion or Todd's paralysis.[4]

Between January 1995 and October 1998 we observed 725 first seizures or first medically evaluated seizures, 340 idiopathic/cryptogenic seizures, and 385 symptomatic seizures. Only seizures symptomatic of stroke, head trauma, or brain tumour were included in the study (n = 324). Five cases

Abbreviations: ADAA, average daily intake of absolute alcohol; CNS, central nervous system; CT, computed tomography; EEG, electroencephalography; γ-GT, gamma-glutamyl-transpeptidase; MALT, Münchner Alkoholismustest; MCV, mean corpuscular volume; OR, odds ratio

were excluded because they presented a dual aetiology (for example, stroke and brain tumour). The other aetiologies of symptomatic seizures were: cerebral atrophy (n = 22), multi-infarct dementia (n = 8), CNS infection (n = 8), blood electrolyte disorder (n = 3), perinatal encephalopathy (n = 4), multiple sclerosis (n = 2), and other CNS disorder (n = 9).

Controls

We found two controls for each case from the list of patients admitted to the emergency room, with a negative history of epileptic seizures (excluding febrile seizures). We excluded five possible controls who did not drink alcohol for religious reasons or lifestyle rules (no case was forbidden to drink for these reasons). The first two controls that matched the case were interviewed. Controls were matched to cases according to centre, age (±5 years), sex, and timing and type of the CNS insult. For example, we matched acute symptomatic seizures after stroke and head trauma (that is, occurring within seven days) to controls with stroke or head trauma in the seven days preceding the interview. Remote symptomatic seizures from stroke and head trauma were matched to controls with the same conditions occurring more than seven days before interview. Seizures occurring as the presenting symptom of a brain tumour (acute symptomatic) were matched to controls with a brain tumour diagnosed within one week; other seizures in patients with a brain tumour (remote symptomatic) were matched to controls with a brain tumour diagnosed more than a week before the interview. Controls of patients with remote symptomatic seizures had to have an interval between CNS insult and study entry at least equal to that of the matched case.

Definition of the cause

Stroke was defined according to the WHO criteria,[9] as the acute onset of neurological symptoms of presumed vascular origin and >24 hours duration. Head trauma and brain tumours were accepted when diagnosed by the attending neurologist. Brain tumours included primary and secondary tumours, and arteriovenous malformations.

Design of the questionnaire and data quality

The questionnaire collected information on demographic data (sex, level of education, marital status, residence, place of birth, occupation); family history of seizures; prenatal, perinatal, and postnatal risk factors; and problems related to alcoholism (family history of alcoholism and use of illicit drugs; number of road accidents, jail convictions, dismissals from work, and hospital admissions for alcohol abuse). Specific information on the preparation and validation of the questionnaire and the definitions of the risk factors are reported elsewhere.[5 10]

Subjects were classified according to their current drinking status as: non-drinkers if they drank less than once a year[4]; ex-drinkers if they had abstained from drinking for at least one year and had previously drunk at least once a month[4]; occasional drinkers if they drank at least once a year, but less than once a month; or current drinkers if they did not fit into any of the previous categories. Current drinkers were classified according to their drinking habits during the week (continuous versus binge drinkers) and during the day (at-meal versus between-meals drinkers). Continuous drinkers were persons who drank every day of the week, binge drinkers those who drank only, or considerably more, at the weekend in terms of both quantity and frequency. At-meal drinkers were those who drank only during meals, between-meals drinkers those who drank at meals and between meals. Subjects were asked about the age at starting and, for ex-drinkers, at stopping drinking, and their patterns of drinking.

The average daily intake of absolute alcohol (ADAA) in the six months before inclusion in the study, or before stopping drinking for ex-drinkers, was calculated for each person, asking separately about white and red wine, beer, aperitifs, "bitters", spirits, and laced coffee to obtain the number of servings drunk per occasion, the number of occasions per day, and the number of days per week. We multiplied the number of servings per drinking occasion by the number of occasions per day by the number of days per week to calculate the number of servings per week for each beverage. This number was multiplied by the average alcohol content (grams) of each beverage, and the total of all beverages was divided by seven to calculate the ADAA in grams per day.[10]

Table 1 Cases and controls according to time and type of symptomatic seizure

	No.	%	Ratio
Acute symptomatic controls/cases			
Stroke	193/105	44/36	1.8
Head trauma	13/10	3/3	1.3
Brain tumour	121/102	27/35	1.2
Total	327/217	74/74	1.5
Remote symptomatic controls/cases			
Stroke	86/56	19/19	1.5
Head trauma	18/13	4/4	1.4
Brain tumour	13/7	3/2	1.9
Total	117/76	26/26	1.5

The diagnosis of chronic alcoholism was based on the Münchner Alkoholismustest (MALT).[11] A MALT score under 6 is normal, between 6 and 10 is borderline, and above 10 is diagnostic for alcoholism. Instructions were given on how to standardise use of the MALT.[10] Mean corpuscular volume (MCV) and gamma-glutamyl-transpeptidase (γ-GT) were considered altered when ≥98.0 fl and ≥45 U/l.

Conduct of the study

Cases and controls were interviewed by a neurologist who was blind to the classification of cases. Interviews were done within 48 hours of the seizure (cases) or admission (controls), after informed consent. When the interview was impossible (patient unable to cooperate), the next-of-kin was interviewed (proxy respondent). Proxy respondents were necessary for 67 cases (23%) and 75 controls (17%) ($p < 0.05$). When neither the case nor the proxy was available or able to respond, the case was considered lost. When neither the control nor a proxy was available, the control was replaced.

MCV was not recorded for 14% and γ-GT for 19% of subjects. A CT scan was done in all cases and an EEG in all but 19. Other examinations (for example, magnetic resonance imaging) were scheduled according to the clinical decisions in each centre, but the results were not used to classify patients.

Statistical analysis

The role of the risk factors was estimated by calculating the odds ratios (OR), with 95% confidence intervals (CI) determined according to Cornfield.[12] The χ^2 test and Student's two tailed *t* test were used where appropriate. The percentage of non-responses was less than 2% for quantification of alcohol use, less than 5% for demographic data, and less than 10% for the MALT, problems related to alcoholism, and drinking patterns. The percentages of missing data were similar for cases and controls, except that MCV and γ-GT were missing more frequently among controls, and problems with alcoholism were missing more frequently among cases.

Assuming a prevalence of exposure of 5%, the sample needed to detect a risk of 2.5 with an alpha error of 0.05 and a beta error of 0.20 was 215 cases with two controls per case, and 301 cases with one control per case.[12]

Table 2 Grams of alcohol per day for each beverage used by current drinkers (cases and controls)

	Men		Women	
Beverage*	Cases	Controls	Cases	Controls
White wine	13.4 (17.4)	13.7 (20.1)	6.0 (6.3)	7.2 (10.3)
Red wine	28.1 (25.3)	24.5 (21.5)	17.7 (13.2)	14.1 (10.3)
Beer	7.2 (16.8)	3.5 (12.7)	2.9 (7.1)	5.8 (9.8)
Aperitifs†	1.6 (2.0)	4.6 (9.6)	0.9 (0.3)	4.1 (6.7)
"Bitters"‡	3.2 (4.4)	4.2 (6.9)	1.4 (0.5)	3.6 (7.0)
Spirits§	10.1 (30.0)	6.6 (12.9)	4.4 (5.2)	1.4 (0.0)
"Laced" coffee¶	1.2 (1.4)	1.0 (1.0)	0.9 (0.8)	0.9 (1.7)

*Mean (SD); all comparisons NS.
†Including vermouths and fortified wines (for example, port, sherry, marsala).
‡Liqueurs are included here, such as those commonly drunk at the end of a meal ("digestifs").
§Including "grappa", whisky, gin, vodka, rum, cognac, and other distillates.
¶A local beverage made of coffee, with "grappa" or brandy added.

Table 3 Drinking patterns (current drinkers) of cases and controls

	Cases (%) No. (n=181)	Controls (%) No. (n=253)	p
Drinking 1 beverage	62 (34)	68 (27)	NS
Drinking ≥4 beverages	51 (28)	70 (28)	NS
Between meals drinkers	36 (20)	46 (18)	NS
Binge drinkers	24 (13)	39 (15)	NS
Wine (red or white)	175 (97)	247 (98)	NS
≥3 days/week	153 (87)	220 (89)	NS
≥3 occasions/day	15 (9)	17 (7)	NS
≥3 glasses/occasion	20 (11)	27 (11)	NS
Beer	70 (39)	89 (35)	NS
≥3 days/week	24 (34)	20 (23)	NS
≥2 occasions/day	11 (16)	14 (16)	NS
≥2 cans/occasion	10 (14)	8 (9)	NS
High strength beverages	96 (53)	136 (54)	NS
≥3 days/week	35 (36)	38 (28)	NS
≥2 occasions/day	6 (6)	14 (10)	NS
≥2 glasses/occasion	2 (2)	5 (4)	NS

RESULTS

We included 324 patients, 303 with a first ever seizure and 21 with a first medically evaluated seizure. The two groups were similar with respect to the main demographic characteristics. Thirty one cases (10%) were excluded: four were discharged or transferred to other hospitals before interview, three refused, seven died before the interview, and 17 had no surrogate responders. Thus we ended up with 293 cases (160 men, 133 women). There was no significant difference between included and excluded cases in age, sex, schooling, marital status, occupation, place of birth, MCV, γ-GT, medical part of the MALT, time and type of underlying aetiology, and type of seizure. In the cases, partial seizures with or without secondary generalisation were the predominant pattern (151 patients, 52%) followed by generalised tonic-clonic seizures (95, 32%) and by complex partial seizures with/without secondary generalisation (47, 16%). The leading cause of seizures was stroke (161, 55%), followed by brain tumour (109, 37%) and head trauma (23, 8%). We collected 444 of the 586 expected controls (76%), giving a ratio of 1.5 controls per case, 1.2–1.9 in each aetiological category (table 1).

Cases and controls were similar with respect to mean age, schooling, marital status, residency, place of birth, road accidents, problems with the law, and dismissals from work. Cases were more frequently employed (42% *v* 34%, $p < 0.05$) than controls.

The risk of first seizure in alcoholics (MALT >10) was not significantly higher than for non-alcoholics, for men (OR 1.2, 95% CI 0.4 to 3.2) or women (1.5, 0.1 to 54.1). It was also not higher for men (1.2, 0.5 to 2.8) and women (1.5, 0.2 to 9.2) with borderline values (MALT 6–10). Altered biological markers of alcoholism were similarly distributed in cases and controls (men: MCV 10% *v* 8%, γ-GT 29% *v* 25%; women: MCV 3% *v* 2%, γ-GT 21 *v* 14%; NS).

Current drinkers did not have a higher risk of first seizure than non-drinkers for men (OR 1.0, 95% CI 0.5 to 1.9) or women (1.4, 0.8 to 2.3). The mean age at starting for current drinkers was similar in cases and controls, both for men (17.7 *v* 19.0 years, NS) and women (20.0 *v* 19.0 years, NS). Ex-drinkers had a risk of first seizure lower than 1 for both sexes (men 0.7, 0.3 to 2.0; women 0.7, 0.3 to 2.1).

The mean ADAA was similar for current drinker cases and controls of both sexes: men 39.5 *v* 37.2 g/day; women 19.2 *v* 18.5 g/day; NS). The average amount of each beverage drunk (table 2) was similar for seizure patients and controls, for both sexes. No difference was found in drinking patterns between cases and controls for men and women separately (data not shown) and for both sexes combined (table 3). As the risk was no higher for occasional drinkers than non-drinkers, we pooled the two categories for further analysis. The risk was not significant in all categories of alcohol consumption (table 4).

Considering the timing of seizures (all aetiologies combined), the mean ADAA for current drinkers was no different for cases and controls, either acute (34.2 *v* 32.1 g/day, NS) or remote (27.6 *v* 30.7 g/day, NS). After combining patients with acute and remote symptomatic seizures, the mean ADAA was significantly higher for cases with head trauma (52.1 *v* 25.8 g/day, $p < 0.05$), slightly higher for stroke (34.2 *v* 30.5, NS), and lower for brain tumour (26.1 *v* 36.2, NS). Tables 5 and 6 show the risk of first seizures in relation to seizure timing and aetiology.

Table 4 Average daily intake of absolute alcohol (ADAA) in cases and controls during the six months before seizure (cases) or admission (controls)*

	Men		Women		Both sexes	
ADAA (g/day)	Cases/ controls	OR (95% CI)	Cases/ controls	OR (95% CI)	Cases/ controls	OR (95% CI)
>100	10/11	1.6 (0.5 to 4.7)	0/1	–	10/12	1.4 (0.5 to 3.5)
51–100	23/26	1.5 (0.7 to 3.4)	2/0	–	25/26	1.6 (0.8 to 3.0)
26–50	25/48	0.9 (0.4 to 1.9)	6/9	1.1 (0.3 to 3.4)	31/57	0.9 (0.5 to 1.5)
1–25	62/94	1.2 (0.6 to 2.1)	53/64	1.3 (0.8 to 2.2)	115/158	1.2 (0.8 to 1.7)
Reference category†	27/47	1	65/103	1	92/150	1

*Ex-drinkers (20 cases and 41 controls) are not included.
†Reference category includes non-drinkers and occasional drinkers.

Table 5 Average daily intake of absolute alcohol (ADAA) in cases and controls during the six months before seizure (cases) or admission (controls)*, stratified by timing of seizure

	Acute symptomatic		Remote symptomatic	
ADAA (g/day)	Cases/controls	OR (95% CI)	Cases/controls	OR (95% CI)
>100	9/10	1.6 (0.5 to 4.4)	1/2	0.7 (0.1 to 10.8)
51–100	21/17	2.1 (1.0 to 4.6)	4/9	0.6 (0.2 to 2.6)
1–50	110/164	1.2 (0.8 to 1.7)	36/51	1.0 (0.5 to 2.0)
Reference category†	64/110	1	28/40	1

*Ex-drinkers are not included.
†Reference category includes non-drinkers and occasional drinkers.

Table 6 Average daily intake of absolute alcohol (ADAA) in cases and controls during the six months before seizure (cases) or admission (controls)*, stratified by underlying pathology

	Stroke		Head trauma		Brain tumour	
ADAA (g/day)	Cases/controls	OR (95% CI)	Cases/controls	OR (95% CI)	Cases/controls	OR (95% CI)
>100	6/5	2.5 (0.6 to 10.0)	3/1	3.4 (0.2 to 109.2)	1/6	0.2 (0.1 to 1.8)
51–100	14/19	1.5 (0.7 to 3.5)	2/3	0.8 (0.1 to 8.6)	9/4	2.7 (0.7 to 11.5)
1–50	81/134	1.3 (0.8 to 2.0)	10/18	0.6 (0.1 to 2.7)	55/63	1.1 (0.6 to 1.9)
Reference category†	46/95	1	7/8	1	39/47	1

*Ex-drinkers are not included.
†Reference category includes non-drinkers and occasional drinkers.

DISCUSSION

Seizures are defined as symptomatic when they are considered the consequence of a known or suspected cerebral dysfunction such as head injury, cerebrovascular accident, brain tumour, and others.[1] However, the identification of an epileptogenic lesion in a patient's history does not exclude the role of other factors. For example, why do some patients with vascular lesions in similar brain areas develop seizures while others do not? Does the factor considered as "aetiological" explain the risk of having a seizure, or are other factors needed? From an epidemiological point of view each risk factor should be evaluated as one of several that dictates the higher or lower probability of a first seizure.

Alcohol use is a powerful risk factor for a first seizure for adults of both sexes; its strength is high for idiopathic/cryptogenic seizures with a dose-response effect, while its role in symptomatic seizures is more controversial. Acute symptomatic seizures were only slightly related to alcohol in our previous study,[5] while the New York study[4] showed a two- to ten-fold risk for alcohol users (although significant only above 200 g/day). Furthermore, in our previous study we did not find any relation between alcohol and remote symptomatic seizures.[5] Clinical series have reported a high frequency of symptomatic[13] or partial[14] seizures in alcoholics. These differences may depend on various factors, including different populations, ascertainment methods, levels of exposure, and drinking habits. Confounding could also play a role: as heavy alcohol use is a risk factor for stroke[6] and head trauma,[7] any change in risk could be erroneously attributed to alcohol. To control for confounding we matched our cases to controls having the same underlying pathology, to eliminate its effect on the risk of seizures. Since stroke, head trauma, and brain tumour account for the majority of symptomatic seizures in population studies,[2 3] we limited our sample to these three categories.

The main finding is that alcohol use did not increase the risk of a first symptomatic seizure in both sexes. Current drinkers were similarly represented among patients with seizures and non-epileptic controls, and the mean quantity of alcohol consumed, in total and for each beverage, was similar for cases and controls of both sexes. The risk did not increase significantly, even with ADAA higher than 100 g/day. No dose-response pattern was detected. Ng and colleagues[4] found a high risk for those drinking more than 200 g/day, but we had only one person (a control) who drank this much. Thus, we cannot rule out that there may be an association for very heavy alcohol consumption, as our sample was not large enough to draw conclusions for such high levels.

The mean ages for starting drinking and drinking patterns were similar for cases and controls; biological markers and the alcoholism test were also similarly distributed. All these observations point in the same direction and seem to exclude any association between alcohol use and a first symptomatic seizure. One possible explanation of the difference between this and other studies is that the associations observed were a result of confounding.

No substantial difference was evident between acute and remote symptomatic seizures, although acute seizures had a slightly higher risk in all alcohol consumption categories. Considering each putative cause, we found a minimal (not statistically significant) effect of alcohol for stroke and head trauma patients, but only for high doses in the latter.

Some possible flaws of our study need to be discussed. The identification of alcoholics and the measures of alcohol intake were based on a questionnaire and self reporting; this could lead to under-reporting of an undesirable social behaviour, such as heavy alcohol use. However, self reporting is traditionally considered superior to biochemical markers,[15] and questionnaires have greater sensitivity and positive predictive value than blood chemistry tests in the identification of alcoholics; in addition, there is no reason to think of a different recall between cases and controls. On the other hand, alcohol exposure could have been overestimated in hospital controls, though this seems improbable as the ADAA in controls was similar to that in our other study with different controls,[4] and in a survey on the general population in the same study area.[16]

Some problems arise from the larger proportion of proxies interviewed among cases than controls, and the incompleteness of control recruitment. In a previous reliability analysis,[10]

proxies gave a slightly higher ADAA, which was not statistically significant; for this reason a bias caused by the larger number of proxies would have increased the ADAA of cases, with consequent higher risk estimates. We were able to recruit less than two controls per case, because of the difficulty of matching for the underlying pathology. If the control:case ratio were higher for the aetiology thought to be less frequently associated with alcohol use (brain tumour), this could have lowered the risk estimates; however, this was not the case as brain tumours had the lowest ratio (134:109, that is 1.2). Finally, compared to incidence studies,[2 3] we had a lower percentage of head trauma and a higher percentage of brain tumour, given the type of participating centres (mostly neurology departments).

In conclusion, this study provides no evidence of any association between alcohol use and a first symptomatic seizure, either acute or remote, and gives some clues to explain better the relation between alcohol and seizures. When another powerful aetiological factor, such as stroke, brain tumour, or head trauma is identified, alcohol use no longer has any influence. Furthermore, if alcohol causes a generic lowering of the seizure threshold, its effect should be similar in idiopathic and symptomatic seizures, which is not the case. In fact the effect of alcohol seems specific only for idiopathic/cryptogenic seizures, although its mechanism is not yet understood.

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Authors' affiliations

M Leone, F Monaco, Clinica Neurologica, Università A. Avogadro, Novara
C Tonini, Divisione di Neurologia, Ospedale G. Salvini, Garbagnate Milanese
G Bogliun, E Beghi, Clinica Neurologica, Ospedale S. Gerardo, Monza
R Mutani, Clinica Neurologica II, Università di Torino
E Bottacchi, U.O. di Neurologia e Neurofisiopatologia, Ospedale Regionale, Aosta
P Gambaro, Divisione di Neurologia, Ospedale Sacco, Milano
E Rocci, Divisione di Neurologia, Ospedale di Novi Ligure
T Tassinari, Divisione di Neurologia, Ospedale S. Corona, Pietra Ligure
C Cavestro, Laboratorio di Farmacologia Clinica, Istituto di Ricerche Farmacologiche Mario Negri, Milano

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