Cognitive impairment and central motor conduction time in chronic alcoholics

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Summary

The non-invasive technique of transcranial magnetic stimulation (TMS) was used in 62 chronic alcoholics to assess the functional status of descending motor pathways. The main aims of this study were: to investigate asymptomatic upper motor neuron dysfunction in alcoholics as well as to assess its relationship with parameters reflecting the intensity of exposure to alcohol; and to evaluate a possible relationship between central motor conduction time (CMCT) prolongation and neuropsychological measures of alcohol-related brain damage. Compared to control subjects, chronic alcoholics exhibited a significant prolongation of CMCT (23 out of 62 subjects). No significant correlation was found between CMCT prolongation and intensity and duration of abuse, presence of peripheral neuropathy, or brain atrophy on CT scans. Prolongation of CMCT from the upper limb correlated significantly with impairment of frontal skills on neuropsychological testing (p<0.01). These findings suggest that TMS may be a sensitive method for the detection in alcoholics of subtle neurological dysfunction, not confined to motor pathways.

**KEY WORDS:** Brain atrophy, central motor conduction time, chronic alcoholics, frontal lobe, magnetic brain stimulation.

Introduction

A wide range of central nervous system (CNS) complications occur in alcoholism, including a progressive cognitive decline that mainly affects frontal lobe functions (1) and is often associated with brain atrophy (2, 3). Although cortical areas 4 and 6 are not spared by the degenerative process, motor disturbances reflecting pyramidal tract involvement are rarely clinically evident: their clinical assessment is indeed difficult in the face of concurrent peripheral neuropathy, a certainly more common neurological complication of alcohol abuse. CNS dysfunctions in alcoholics have been studied using different approaches (neuropsychological testing, event-related potentials, transcranial magnetic stimulation and imaging), often applied in isolation (without the clinical or instrumental correlates) and conducted in non selected groups of patients (4). The aims of the present study were:

1. To detect upper motor neuron dysfunction in alcoholism by means of transcranial magnetic stimulation (TMS) in a homogeneous group of subjects without clinical evidence of pyramidal tract involvement.
2. To assess the relationship between central motor conduction time (CMCT) and those factors which are considered to be major determinants in the development of brain damage, such as vitamin deficiencies and intensity of exposure to alcohol.
3. To explore higher frontal lobe functions in alcoholics and to assess the relationship between neuropsychological scores and both neuroradiological and neurophysiological parameters reflecting CNS dysfunction.

Materials and methods

We studied 62 chronic alcoholics (46 males and 16 females) admitted to our hospital for alcohol detoxification over a period of 1 year. Only patients seeking assistance in terminating their dependence on alcohol and having no signs or symptoms of diseases other than peripheral neuropathy were selected for this study. The inclusion criteria were: age between 25 and 65 years, diagnosis of alcohol dependence according to DSM IV criteria (5), daily alcohol intake >100g. Alcohol intake was calculated on the basis of a questionnaire compiled by the patient and his/her family members. Daily intake denoted the mean amount of ethanol consumed per day over the previous year. We preferred to consider grams of alcohol instead of number of drinks because our subjects often consumed different types of alcoholic drinks.

Through appropriate clinical, laboratory and instrumental investigations, we excluded from the study those patients with one or more of the following conditions known to affect CNS function and assessment: diabetes mellitus, chronic liver cirrhosis, clinically evident cognitive deficits, HIV infection. Cerebrovascular damage and other structural brain lesions, as well as cervical and/or thoracic myelopathy, were excluded by neu-
roradiological imaging. Patients with signs or symptoms of pyramidal tract dysfunction were excluded, as were patients with clinically evident neurological deficits due to conditions other than peripheral neuropathy. On the day following admission, blood samples were taken for measurement of markers of alcohol intake and nutritional status: haemoglobin, total protein, albumin, prealbumin, transferrin; serum folate and vitamin B12, serum aspartate and alanine aminotransferases, gamma-glutamyl transpeptidase, ammonia, red cell count. Brain computerised tomography (CT) was performed in all the patients and brain atrophy was defined as more than 2 mm of subarachnoid space between the cortex and the skull. The degree of cerebral atrophy was not studied.

Neurophysiological assessment

Motor evoked potentials (MEPs). Magnetic stimulation of the motor cortex and spinal cord was performed using an SMN 900 Ates Medica stimulator generating magnetic fields of approximately 2 T, by means of a round coil with an outer diameter of 12 cm. The stimulus intensity was set at the maximum output of the device. Compound muscle action potentials were recorded by conventional electromyography (Medelec Sapphyre 2 M), using surface electrodes attached over the belly and tendon of abductor policis brevis (APB) and extensor digitorum brevis (EDB) muscles, during a mild background voluntary contraction (about 5-10% of the maximum force) for cortical stimulation and during complete relaxation for spinal stimulation. The coil was placed on the subject’s vertex for cortical stimulation and over the spinous processes of C7 and of L5 for spinal stimulation. To guarantee correct latency evaluation, at least 4 reproducible responses were recorded from each stimulation site. Cortical and spinal latencies were determined visually and CMCT was indirectly calculated by subtracting the shortest spinal latency from the shortest cortical latency of MEPs. A calculated CMCT (CMCT-F) was determined using Robinson’s formula (6):

\[ \text{CMCT-F} = \frac{\text{shortest latency of the cortical MEP}}{\text{F+M-1}/2}, \]

in which M is the latency of the muscular response and F the shortest latency of 10 F responses, following stimulation of the median nerve at the wrist or of the tibial nerve at the foot.

Normative TMS data were obtained from a group of 31 healthy, non alcohol-abusing volunteers, matched (1 control subject per 2 patients) for age and height. CMCT and CMCT-F values deviating more than 2.5 SD from the mean control values were considered abnormal.

Electrodiagnostic evaluation of peripheral neuropathy. This consisted of the bilateral study of conduction velocities of the sural and common peroneal nerves and evaluation of amplitude and distal latencies of compound muscle and sensory action potentials. None of the patients or controls were on any medication during the investigations.

Neuropsychological assessment

To explore cognitive impairment in alcoholics by means of neuropsychological testing, we subsequently excluded from the study all patients with one or more of the following conditions known to affect cognitive function assessment: low sociocultural status, major depression or psychosis, history of psychoactive drug dependence or abuse of substances other than alcohol, obstructive chronic respiratory disease, Korsakoff syndrome, previous head trauma. At this stage, 41 patients failed to meet the study criteria and were excluded, while 21 (18 M and 3 F) were left to continue taking part in the study. None of these patients had clinically evident cognitive deficits and they had an average Mini Mental State Examination (MMSE) score of 28.

Cognitive function was explored using i) the Wisconsin Card Sorting Test (WCST), which assesses abstract thinking, cognitive flexibility, concept identification, hypothesis generation and the ability to use response feedback information; and ii) the Trail-Making Test (TMT) parts A and B, which assess spatial planning and psychomotor abilities. These tests were chosen because of their sensitivity to frontal lobe dysfunction (7-9). Cognitive tests were performed on the 10th day of alcohol detoxification in order to avoid interference with withdrawal symptoms. No drugs that might interfere with cognitive function tests were administered during the 48 h prior to the study.

Data from alcoholic patients were compared with those of a control group of 21 healthy volunteers without a history of alcohol abuse, matched for age, sex, height, sociocultural status, and cigarette consumption. All the patients and controls gave their informed consent before the investigation.

Statistical analysis

Models of one-way analysis of variance (ANOVA) and Student’s t test were employed for comparisons of means. Pearson’s correlation test and the Chi Square test were performed to detect the associations between continuous and categorical variables respectively. All variables were expressed as mean values ± SD; a significance level of p<0.05 was used.

Results

None of the control subjects had symptoms of nervous system dysfunction or an abnormal physical examination.

Alcoholic patients had a mean age of 50.7±9.8 years (range 27-65) and a mean height of 167.2±7 cm. Their reported daily ethanol consumption ranged from 100 to 500 g (mean 239±102) over a period of 20.7±10.2 years. Moderate elevation of hepatic enzymes was found in 44 patients, and mild serum folate deficiency in 19 patients; none had laboratory investigation findings indicating protein malnutrition or thiamine deficiency. The mean CMCT and CMCT-F values were significantly prolonged in alcoholics as compared to controls (Table I) (p<0.001). Central motor conduction abnormalities in at least one muscle were observed in 23 patients (37%): CMCT from the arm was prolonged in 15, and from both lower and upper limb in 6. Electrophysiological findings of peripheral neuropathy were given by 43 patients, while mild to modest brain atrophy on CT scan was detected in 41 patients.
The occurrence of CMCT abnormalities was not associated significantly with any of the following variables: age, daily alcohol intake, duration of abuse, MCV, GGT, serum folate and vitamin B12 levels, peroneal and sural nerve conduction velocity or action potential amplitude. No association between CMCT prolongation and brain atrophy was observed.

In addition, within the limits of our measurement technique, we failed to find a significant correlation between cortical brain atrophy and intensity and duration of abuse. The group of alcoholic patients who underwent neuropsychological testing (no. 21) had a mean age of 51.4±9.9 years (range 39-63) and a mean height of 168±6.7 cm. They had been drinking between 185-403 g (mean 294) of ethyl alcohol daily for an average of 19.04±7.9 years. Brain CT showed cortical atrophy in 13 patients, while electrophysiological alterations suggesting peripheral neuropathy were present in 14 patients. Prolongation of CMCT was detected in 3 patients from the arm and in 1 patient from both the upper and lower limbs. Although none of these patients exhibited clinical signs of cognitive impairment, significant differences in both the WCST and the TMT were observed between alcoholics and control subjects (Table II). No relations emerged between neuropsychological and neuroradiological data: the alcoholics with cortical atrophy tended to display lower (non significant) neuropsychological scores than those without. Abnormal performance on the TMT (part A-B) proved to be correlated with upper arm central motor conduction delay (Pearson, r = 0.49, p<0.01; Fig. 1).

Discussion

The existence of specific involvement of the upper motor neuron in well-nourished alcoholics is still debated; motor disturbances reflecting pyramidal tract involvement are rarely clinically evident in alcoholics and often masked by superimposed peripheral neuropathy, certainly a more common neurological complication of chronic alcohol abuse. In addition, alcohol abusers may be affected simultaneously by several disorders (malnutrition, water and electrolyte imbalance, liver cirrhosis and head trauma), making it difficult to identify the cause and extent of CNS dysfunction related to alcohol itself or its metabolites. That said, abnormalities of central afferent pathways have been revealed by evoked potential studies in alcoholics (10), although only two other studies (11,12) have explored spinal efferent pathways, but the results so far remain conflicting. One et al. (11) recently reported prolongation of CMCT only in chronic alcoholics with spasticity, while Oishi et al. (12) reported CMCT prolongation in alcoholics with frontal lobe atrophy, independently of clinical pyramidal signs. Our data show an impairment of CMCT in alcoholics (23/62, 37%) which, less marked than peripheral nervous system impairment (43/62), indicates additional CNS involvement in alcoholism. Since patients with spasticity and patients with muscle weakness had been excluded from this study, we consider an asymptomatic disturbance in the pathway from the frontal cortex to anterior horn cells to be present in chronic alcoholics. CMCT-F abnormalities were characterized by a moderate (up to 4 msec when derived from the upper limb and 6 msec when derived from the lower limb) prolongation, more frequently derived from upper limb muscles.

In the present study we did not observe any relationship between central and peripheral nervous system impairment: CMCT abnormalities also occurred in patients with no clinical or electrophysiological evidence of peripheral neuropathy; this observation seems to suggest that cen-

| Table I - Comparison of CMCT-F values in alcoholics and control group (t test). |
|----------------------------------------|-------------------------------|
| Study group (no. = 62) | Control group (no. = 31) |
| Upper limb | Lower limb |
| 6 (1.4)* | 4.9 (0.9)* |
| 13.6 (3.2) | 11.5 (1.8) |
| All values are presented as mean (SD) |
| * p<0.001 vs controls |

| Table II - Comparison of neuropsychological scores in alcoholics and controls (ANOVA) |
|----------------------------------------|-------------------------------|
| Study group (no. = 21) | Control group (no. = 21) | p |
| TMT, part A | 75.4 (54.7) | 39.3 (11.7) | 0.005 |
| TMT, part B | 235.1 (130.9) | 121.8 (49.7) | 0.001 |
| TMT, part A-B | 159.9 (95.1) | 82.4 (43.4) | 0.002 |
| WCST |
| Categories completed | 2.9 (1.7) | 4.8 (1.0) | 0.0001 |
| Total Errors | 53.8 (19.2) | 24.2 (18.5) | 0.00001 |
| % of Errors | 42.5 (14.0) | 19.9 (13.0) | 0.00001 |
| Persev. responses | 31.9 (23.0) | 15.4 (14.0) | 0.0045 |
| % of persev. responses | 26.0 (17.0) | 20.0 (12.5) | n.s. |

Abbreviations: TMT = Trail Making Test; WCST = Wisconsin Card Sorting Test
Each value is expressed as mean (SD)
longation may result from functional rather than structural damage, i.e., the amount of alcohol intake and the duration of problematic drinking, thus suggesting that evidence of direct toxic effect of alcohol in the pathogenesis of upper motor neuron damage is also poor. The nature of CNS impairment remains unclear: it could be multifactorial or depend on individual susceptibility. Unlike Ono et al. (11), we found a more evident prolongation of CMCT in the upper extremities, in contrast with the typical findings in nutritional myelopathy, thus suggesting that upper motor neuron damage in our patients could be more pronounced at the level of the motor cortex than in the longer tracts directed to anterior horn cells.

To test this latter hypothesis we looked for correlations between CMCT prolongation and brain atrophy; unlike Oishi et al. (12), we failed to find a relationship between CMCT and structural brain lesions: brain atrophy was detected in 41 patients, but only 11 of them showed additional CMCT prolongation. This suggests that CMCT prolongation may result from functional rather than structural changes in motor cortex neurons. Therefore, as consistently demonstrated by previous studies (14, for review), CT atrophy did not even correlate with impaired neuropsychological test performance. We did not evaluate the degree and pattern of brain atrophy, and this may be a limitation of our study. However, the two groups of patients with and without brain atrophy do not differ as regards their performances on neuropsychological and electrophysiological assessment; it is therefore unlikely that the same anatomical condition would influence performance of only some patients on the above tests. The only variable showing a strong positive correlation with CMCT recorded from the upper arm was performance on TMT part A-B, thus suggesting that CMCT prolongation might reflect a more widespread dysfunction of CNS, not confined to motor pathways and mainly affecting frontal lobe functions (7). On the other hand, the TMT score’s dependence on manual skills may have influenced this finding. CMCT may therefore be an aspecific but reliable method for detecting CNS functional damage, whose manifestations, mirroring frontal lobe impairment, are often subtle and therefore not easily detectable during a bedside neurological examination; indeed, the patients enrolled had an MMSE score of over 28. Obviously, generalizations made on the basis of our findings should be considered with caution due to the small size of our study sample; however, it would seem that CMCT evaluation might allow a more accurate functional evaluation of alcohol-related CNS dysfunction and could be used in screening for early cognitive impairment in alcoholics. Further studies are needed to confirm our data and to better analyse the relationship between neuropsychological and neuroimaging findings (including precise computation of morphometric data) and CMCT.

References

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