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IN ABSTINENT CHRONIC ALCOHOLICS: ONE YEAR FOLLOW-UP

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Reversibility of brain-stem evoked potential abnormalities in abstinent chronic alcoholics: One year follow-up

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Abstract

Brain-stem auditory evoked potentials (BAEPs) were studied in 34 chronic alcoholics who had been abstinent for 1 year, and in age- and sex-matched control subjects. The patients were examined 3 times, at 1 month, 5 months and 1 year after the start of the abstinence treatment. At 1 month of abstinence the alcoholics showed differences with respect to controls in the peak V latency ($P < 0.01$), and in the III–V ($p < 0.01$) and I–V ($p < 0.01$) intervals. After 1 year of abstinence a significant improvement in the V ($p < 0.01$), III–V ($p < 0.01$) and I–V ($p < 0.01$) parameters was recorded. The most notable development was in the 5–12 month period, with shortening i latency ($p < 0.01$) and in the I–V interval ($p < 0.01$); in the first 5 months there was only shortening in the III–V interval ($p < 0.01$). This improvement was also indicated by a decrease in the number of patients with BAEP parameter abnormalities. The recovery of the functions impaired by chronic alcohol consumption after 1 year of abstinence was incomplete, although the tendency was towards normalization.

Keywords

Alcoholism; Reversibility; Brain-stem auditory evoked potentials

Numerous biomedical studies have reported alter-ations in the central nervous system (CNS) structures and functions in alcoholics (Porjesz and Begleiter 1979; Ron et al. 1982). Although long-term studies of former chronic alcoholics must be interpreted with caution because of the typically high rates of drop-out from the sample (Mackenzie et al. 1978), there are currently a number of studies of the evolution of abnormalities produced by chronic consumption of alcohol during continued abstinence. These studies have mainly used neuro-radiological techniques (Carien et al. 1978; Carien 1979) which offer structural macroscopic data on the evolution of alterations in different areas of the brain (cortex, midbrain). The evolution of these alterations during abstinence has also been studied from the neuropsychological point of view. These techniques have shown a partial recovery from the behavioural perspective (Brandt et al. 1983; Yohman et al. 1985; Goldman and Goldman 1988).

Nonetheless there are few studies which offer more specific data concerning the functional evolution of subsystems in CNS of alcoholic patients which have become affected. Brain-stem auditory evoked potentials allow evaluation of the functional integrity of the auditory pathway, from the auditory nerve to the thalamic nuclei

(Hashimoto 1989). Their recording in alcoholic patients consistently show alterations in short-term abstinent patients (Begleiter et al. 1981; Chu et al. 1982; Chan et al. 1985; Chu 1985).

Using this technique in our laboratory we carried out a 1 year follow-up study on the reversibility of abnormalities caused by chronic alcohol consumption in patients who had remained abstinent for a long time. The study involved examinations 1 month, 5 months and 12 months after starting the abstinence in a group of alcoholics without serious neurological alterations, in order to study the possibility of short- and long-term reversibility. This kind of follow-up study, as well as offering data concerning the evolution of the alterations observed in the nervous systems of these long-term abstinent patients, may provide information about the nature of the underlying pathology.

Material and methods

Thirty-four chronic alcoholics initially participated in this study, all males, diagnosed and treated by the Alcoholic Unit of the *Hospital Clínic i Provincial* (Barcelona). They all met the DSM-III criteria for alcoholism and were aged between 23 and 56 years (mean 40.4 ± 8.9). All the subjects had histories of alcoholism of 8 years or more. In the selection process the following patients were excluded: (1) those with serious psychiatric disorders; (2) those with cardiovascular, hepatic or respiratory disease; (3) those with neurological disorders; (4) those with histories of head trauma, coma or anoxia-ischaemia; (5) those who were found to fulfil DSM-III criteria for drug abuse other than alcoholism, except smoking.

All patients underwent an initial neurophysiological examination between 25 and 45 days after giving up drinking. The treatment programme run by the Alcoholism Unit includes administration of standard medication (calcium carbomide, an alcohol-abuse deterrent), and clomethiazole (a low-toxicity sedative) in the first week of treatment. No patient had received medication in the previous 72 h.

Abstinence was monitored by the Alcoholic Service team; alcohol levels were measured before each examination. Patients who were present at all the medical tests and group therapy sessions, and whose alcohol level results were negative, were included in the abstinent group. Twelve of the 34 subjects in the initial group remained abstinent for the full year. The members of this subgroup were aged between 23 and 55, with an average age of 41.00 ± 6.8 . The remaining 22 subjects were excluded from the sample. Note that mean BAEP parameter values for the 1-year-abstinent subgroup as determined in the first examination were not significantly different from the corresponding mean values determined at the same time for the whole initial 34-subject group.

The control group were 34 male subjects matched subject-to-subject with the alcoholics by sex and age (mean 36.1 ± 8.3 years). They met the additional selection criteria for the patient group and were abstinent or sporadic drinkers (under 20 g alcohol/ day).

EP recording

BAEP recording was performed using pure tin electrodes positioned in an elastic cap (Electrocap, Inc.). Stimulation and amplification, filtering, averaging and graphical

analysis of the signal) were carried out using a SICAN neurophysiological recording apparatus. Contaminated trials were eliminated from further analysis by an automatic artifact rejection. Impedance re-mained under 5 k Ω at all times during sessions.

The EP signals were obtained simultaneously, ipsilaterally and contralaterally, by using reference electrodes located on both mastoids and an active electrode at the vertex. We report only ipsilateral records in this study. The ground electrode was placed on the forehead. Potentials were evoked by monaural auditory stimuli consisting of clicks of alternate polarity with a duration of 100 μ sec, an intensity of 110 dB SPL, and a stimulation frequency of 10 Hz. The EP signal was amplified 100,000 times and filtered with a bandpass of 200-3000 Hz (12 dB/ octave). Each potential was obtained from the average of 2000 responses for a 10 msec period.

Procedure

To perform the neurophysiological tests, subjects were seated in a comfortable armchair in a sound-proofed dimly lit and electrically protected room. The hearing of patient and control groups was assessed audiologically with the same clicks as used for BAEPs. Subjects whose audiological threshold was above 40 dB SPL were not accepted for BAEP studies.

All recording sessions took place between 11.30 and 14.30 h to avoid the possibility of circadian variations. The components studied were the latencies of peaks I, III and V, and the interpeak intervals I-III, III-V and I-V for both ears. These parameters were identified by the computer program without regard to subject diagnosis.

Statistical analysis

Statistical analyses were performed using the SPSS software package. Data for BAEP parameters underwent 2-way ANOVA for each group (alcoholics and controls) X ear (left or right) to evaluate the differences between the alcoholic and control groups. BAEP parameters were unaffected by ear; consequently, in further calculations an average value was taken for both ears of the subject examined, in order to simplify the analysis and interpretation of the results. Linear regression analysis was used to investigate the possible effects of (a) the 25-45 days of abstinence preceding the first examination, and (b) age, on BAEP parameter values in the alcoholic group at first examination and over the evolution with sustained abstinence. Neither number of days of abstinence before the first examination nor age were significant sources of variance in BAEP parameter values. Thus, these factors did not affect our results.

The intrasubject study of the BAEP parameters over the 3 examinations was carried out using repeated measures ANOVA. In all cases the Bonferroni-Holm procedure was used to correct the significance level for the F values.

To study the evolution of the experimental group with respect to the control group during the first year of abstinence, a confidence interval was established at 97.5% of the values for each of the BAEP parameters of the control population. The mean value of the alcoholic group was later compared in each of the 3 examinations, with the control population confidence interval.

Finally, we calculated the number of alcoholic patients that showed clinically abnormal records. A BAEP record was considered to be abnormal if the value of any of its parameters was 2.5 S.D. greater than the control group mean.

Results

Evolution of BAEP parameter values with abstinence

After 1 month of abstinence, the alcoholics showed latencies of peak V ($p < 0.01$) and interpeak intervals of III-V ($p < 0.01$) and I-V ($p < 0.01$) which were significantly longer than control group scores.

On studying the evolution of each parameter in the subsequent examinations using repeated measures ANOVA, we noted a significant reduction in the latency of parameters V ($p < 0.01$), III-V ($p < 0.01$) and I-V ($p < 0.01$) after 12 months of abstinence. The evolution was most notable between 5 and 12 months with shortening of peak V latency ($p < 0.01$) and the interval I-V ($p < 0.01$), compared with the first 5 months, in which there was only shortening of the interval III-V ($p < 0.01$) (see Table 1).

Table I. F values given by 1-way ANOVA of repeated measures of BAEPs of abstinent chronic alcoholics. Results obtained from the comparisons between 1 month and 5 months, between 5 and 12 months, and between 1 month and 12 months of abstinence.

Group		I	III	V	I-III	III-V	I-V
Alcoholics (1 m vs. 5 m)	F	0.92	0.47	3.55	0.03	12.18	3.26
	p	N.S.	N.S.	N.S.	N.S.	0.00*	N.S.
Alcoholics (5 m vs. 12 m)	F	0.00	3.82	21.05	3.41	2.22	11.88
	p	N.S.	N.S.	0.00	N.S.	N.S.	0.01*
Alcoholics (1 m vs. 12 m)	F	1.11	0.95	15.18	2.25	14.10	13.07
	p	N.S.	N.S.	0.01*	N.S.	0.00*	0.01*

* $p < 0.01$ as corrected by the Bonferroni-Holm procedure.

For the study of the evolution of the results of the alcoholic group with respect to the control group, we calculated the interval of confidence (97.5% of the control group values) for each parameter in the control population (I: 1.46-1.56; III: 3.535-3.785; V: 5.29-5.54; I-III: 2.00-2.30; III-V: 1.66-1.87; I-V: 3.76-4.06). Bearing in mind the mean values of the alcoholic group shown in Table I, we see that at 1 and 5 months of abstinence the alcoholics showed values which are higher than the controls and beyond the upper limits of the previous V, III-V and I-V intervals of confidence. After 1 year of abstinence, peak V latency was greater than the upper limit of the interval, peak III-V was at the highest point but within this limit, and I-V showed normal values (see Table II and Fig. 1).

Individual impairment

The calculation of the number of individual impairments is shown in Table III; we see a progressive fall over the first year of abstinence in the number of patients with abnormalities in the parameters V, III-V and I-V (in accordance with the criterion considered). After 1 month of abstinence, 5 patients of the 12 that followed the treatment for 1 year showed impairment in at least one BAEP parameter, 3 alcoholics showed abnormalities after 5 months, and after 1 year only 2 patients still had impaired parameters. During the year of abstinence there was improvement in all the subjects

who presented anomalies in BAEPs, both among patients whose parameters had become normal and among those whose parameters were still abnormal.

Table II. Means (m) and standard deviations (S.D.) of BAEPs of abstinent chronic alcoholics obtained after 1 month, after 5 months, and after 1 year of abstinence, and their control between 1 month and 12 months of abstinence.

Group		I	III	V	I-III	III-V	I-V
Alcoholics (1 m)	m	1.50	3.75	5.78	2.25	2.03	4.28*
	S.D.	0.08	0.15	0.20	0.16	0.20	0.22
Alcoholics (5 m)	m	1.53	3.77	5.71*	2.24	1.94	4.18*
	S.D.	0.11	0.17	0.21	0.16	0.17	0.22
Alcoholics (12 m)	m	1.53	3.71	5.59*	2.18	1.88	4.06
	S.D.	0.11	0.14	0.21	0.18	0.20	0.21
Controls	m	1.51	3.66	5.42	2.15	1.76	3.91
	S.D.	0.08	0.18	0.16	0.21	0.16	0.20

*Variables exceeding the upper limit of the confidence intervals.

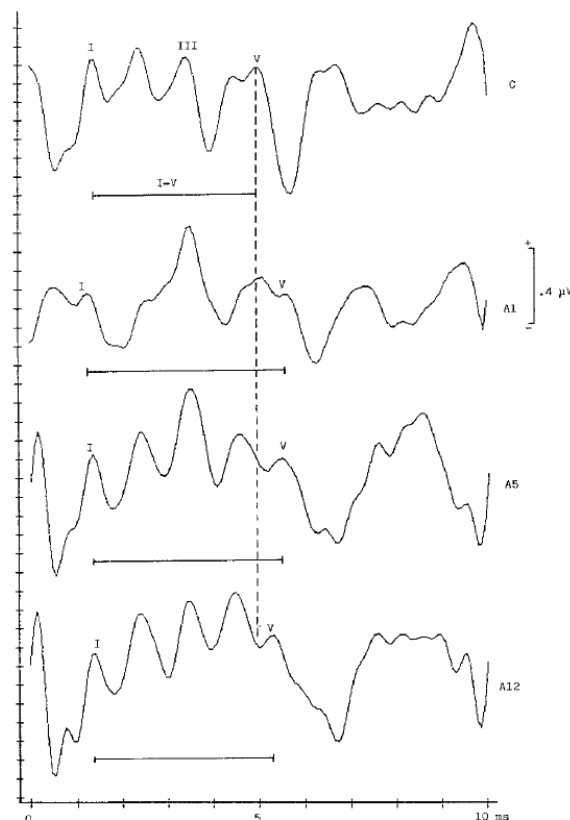


Fig. 1. BAEPs of (i) a typical alcoholic-group subject (A) at the 3 examinations (after 1, 5 and 12 months of abstinence) and (ii) the corresponding control subject (C). Note the initially long peak V latency and I-V interval in A, and the decreasing trend of these parameters over the study period.

Discussion

Effects of chronic alcohol abuse

As described in previous works from our and other laboratories (Porjesz and Begleiter 1979; Cadaveira 1988; Cadaveira et al. 1991) the existence of neurological abnormalities in the brain-stem of chronic alcoholics after 1 month is confirmed: lengthening of the peak V latency ($p < 0.01$) and the interpeak intervals III-V ($p < 0.01$) and I-V ($p < 0.01$).

Table III. Number (N) of alcoholics with abnormal parameters after 1 month, 5 months and 1 year of abstinence (values 2.5 S.D. higher than control group mean).

Parameter	N (1 m)	N (5 m)	N (12 m)
I	0	0	0
III	0	0	0
V	5	3	2
I-III	0	0	0
III-V	3	1	1
I-V	4	2	0
Abnorm. in some parameters	5	3	2

Evolution with abstinence

During the 5 first months of abstinence there was improvement in the alcoholic group and decrease in the mean values of the abnormal BAEP peaks, even though the decrease was only significant in the III-V interval ($p < 0.01$). From the clinical point of view, we observed a fall in the number of patients with abnormal BAEPs. These results coincide partially with those of Chan et al. (1985), who found a significant shortening of the I-III ($p < 0.01$) and I-V ($p < 0.01$) intervals. The differences in terms of impairment and evolution of the I-III interval may be due to the characteristics of their patients. Chan studied patients with Wernicke-Korsakoff syndrome who received vitamin treatment and a suitable diet during their time in hospital. The differences in the components affected and rapid recovery are characteristic of this type of patient. In accordance with these results, Porjesz and Begleiter, in their review of 1985, referring to unpublished data, reported an improvement in latencies and central transmission time in a group of hospitalized chronic alcoholics after 4 months of abstinence, even though there were still differences with respect to the control group.

After 1 year of abstinence our results show significant shortening in the V latency ($p < 0.01$) and in the III-V ($p < 0.01$) and I-V ($p < 0.01$) interpeak intervals. We note that the recovery rate is higher between 5 and 12 months than in the first period. However, recovery is not complete since the mean of the I-V interval is above the upper limit established for the control group. These results correlate with those of the neuroradiological studies. The CT scans show abnormalities in the alcoholic group with evidence of ventricular dilatation and enlargement of the cortical sulci. The morphological aberrations of alcoholics are partially reversible during the first year of abstinence (Carlen et al. 1978; Carlen 1979; Ron et al. 1982; Cala et al. 1983; Carlen et al. 1986) but the recovery is not complete as compared with the prevalence of atrophy in the sample of the general population. Some authors (Lynch 1960; Muuronen et al. 1989) detect anomalies in areas of the mid-brain in evaluations 5 years after cessation of drinking. According to these studies, there are abnormalities that persist after long periods of abstinence.

The progressive evolution of the values of the parameters, studied in the sample of alcoholic patients during the first year of abstinence, suggests that the evolution

towards normality may take place later in those patients who have not shown a complete recovery during the first year. However, a long-term longitudinal follow-up study would be necessary to determine whether this evolutionary tendency continues, or whether some anomalies are permanent. Porjesz and Begleiter (1985), again referring to unpublished data, found no abnormalities in brain-stem potentials, in a sample of non-hospitalized alcoholic patients who had remained abstinent for a period of between 3 and 10 years; nonetheless, these patients had not been examined at the start of abstinence, so we do not know whether they showed brain-stem potential abnormalities.

In our sample of alcoholic patients the abnormalities caused by the chronic consumption of alcohol evolve favourably with continued abstinence. Nonetheless, the scale of this evolution is still to be determined, as is the question of whether the degree of functional improvement is independent of the severity of the initial impairment. With regard to the latter question it would be important to determine whether there is a level of impairment beyond which recovery is impossible, or beyond which there is some deterioration. This information would be of great use in establishing a hypothesis about the pathophysiological mechanisms of these impairments.

The characteristic abnormalities in the later BAEP peaks of alcoholics have generally been interpreted as being due to a drop in the speed of signal transmission in the auditory pathway (specifically the central and posterior pontine). This may be due to any of various factors including demyelination, probably as a result of electrolytic disturbances (Kleinschmidt-DeMasters and Norenberg 1981, 1982), changes in membrane properties, changes in gross or fine neuronal structure. The classic study of Victor et al. (1959) showed that, in alcoholic patients, loss of neurones occurs in the inferior olives, the vestibular nuclei and other brain-stem nuclei. More recently, Chu (1985) reported that in abstinent former alcoholics there is a correlation between the BAEP abnormalities and the presence of structural brain-stem damage (enlarged brain cisterns and atrophy of the brain-stem); these structural abnormalities appear to be more severe in alcoholics with Wernicke-Korsakoff syndrome, in whom lesions, including demyelination and, less frequently, neurone loss, are characteristically observed in the grey matter of the diencephalon and in brain-stem. Secondary effects associated with anoxia-ischaemia or malnutrition, and changes in neurotransmitter metabolism must also be considered in the origin of BAEP abnormalities.

Changes in the BAEPs of alcoholics after a period of abstinence may be attributable to complete or partial reversal of one or more of the above types of effect. Our results indicate that most of the relevant BAEP parameters re-attain normal values within 1 year of abstinence, whilst a few of the relevant parameters remain abnormal beyond this time. One possible explanation for this pattern is that the observed recovery over 1 year of abstinence is due to regeneration of neuronal fine structure (damage of axonic terminations, loss of dendritic connections ...), and those parameters which remain abnormal beyond this time are the result of persistent damage to the CNS at the gross structural level (with neuronal loss or persistent functional disablement). Thus, our results provide support for the hypothesis that the normalization of BAEPs after a long period of abstinence is due to structural recovery rather than to more immediate biochemical changes that occur in the first period of abstinence.

Individual impairment

The results for each patient indicate that individual differences exist in terms of the time necessary for the re-establishment of functional normality. Further studies with larger samples enabling us to study the possible correlation between the degree of recovery and other factors, such as the age of the patients, are necessary. Our data are not only along the same lines as results obtained using other methodologies but support the earlier affirmation that there are great differences in terms of individual susceptibility to alcohol (Cadaveira et al. 1992). In the same way, not all the patients with brain-stem abnormalities show an equally favourable evolution during long-term abstinence.

In sum, during the first year of continued abstinence there is a progressive evolution towards normality in the functional abnormalities detected in the brain-stem of chronic alcoholic patients. This evolution is more marked between 5 and 12 months, although after 1 year of abstinence there are still significant differences compared with the control group. Consequently, although abnormalities in brain-stem potentials caused by chronic alcohol consumption are only partially re-versible during this first year, the tendency is towards normalization.

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