CONTINGENT NEGATIVE VARIATION RESPONSE IN CHRONIC PAIN PATIENTS

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Abstract: The present study assesses central processing of subjective appraisal, expectancy, orientation and reaction time as indexed by Contingent Negative Variation (CNV) response in chronic pain patients. Waves N1, P3 and CNV were recorded during a CNV paradigm in a simple reaction time task with a constant interstimulus interval (ISI) of 1 sec. CNV was measured from CZ x FZ in controls and chronic pain patients suffering from cervical spondylosis and low backache due to sciatica. Duration of pain was 5 to 10 years and intensity varied from moderate to severe as adjudged by Visual Analogue Scale. CNV experiment consisted of 32 trials of S1 and S2 motor response sequence. Each trial consisted of a warning sound click stimulus (S1) followed by the imperative stimulus in the form of flashes (S2). S2 could be terminated by the subject quickly by pressing a response button with the dominant hand. Cursors were hand set to score the latencies for N1 and P3 potentials to S1, maximal CNV amplitude was scored as the largest negative ongoing potential immediately prior to S2 onset. Similarly Reaction Time (RT), Orientation (O) and Expectancy (E) wave amplitudes and latencies were recorded. There was a significant increase in P3 latency, RT in chronic pain patients, indicating that there is a blunting of cognitive functions and increase in reaction time in patients suffering from chronic pain. These patients also take more time to orient to CNV paradigm.

Key words: chronic pain

INTRODUCTION

Pain connotes suffering. The physical basis and the various neurophysiological correlates of pain are still obscure. It is believed that pain has conceptual multidimensional basis consisting of sensory discriminatory, cognitive evaluative and affective motivational components (1). These components interact and produce somatomotor, autonomic and behavioral attributes to pain. The possibility of assessing human pain responses through evoked potentials (EPs) has gained interest in recent years (2, 3), largely motivated by a desire to find an objective measure of human pain experience. Experiments have shown increase in amplitude of EPs that may be related to general arousal and orienting responses which form integrated outcome of the three pain system processes. The recording of long latency event related cerebral EPs has been used as an objective measure of cognitive functions (4, 5), perception (6) and psychological processes such as search, decision making, memorisation, discrimination, expectancy, attention and cognition. Since pain is known to cause psychological aberrations and maladaptive cognition, it was interesting to conduct a study

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to find out whether there are any changes in cognitive functions as reflected by event related EPs (CNV) in chronic pain patients.

METHODS

Subjects

CNV was conducted on 14 patients suffering from chronic pain and attending pain clinic. They were diagnosed and confirmed cases of cervical spondylosis (n=8) and low backache due to sciatica (n=6). Duration of pain was from 5 to 10 years and intensity varied from moderate (n=5) to severe (n=9) as adjudged by Visual Analogue Scale (VAS) (7). Age and sex matched healthy subjects with no present history of neurological and psychiatric impairment were the controls of this study. These subjects were non-smoker and were not on any medication. Both these groups of subjects were given ENT check up and had normal hearing as adjudged by various hearing tests which included Audiometry and Brainstem Auditory EPs.

CNV Principle

The subjects were briefed about the test procedure of CNV. They were asked to lie down and relax on a bed in a standard audiometric, sound proof and air conditioned room. They were given 10 to 15 min for adaptation and practice trials were given in order to ensure that all subjects understand the procedure. CNV was measured from CZ and FZ and it consisted of 32 trials of an S1-S2 motor response sequence. In each trial a warning sound click stimulus (S1) followed by the imperative stimulus in the form of flashes (S2) were delivered through SMP-4100, Auditory/Visual Stimulator. Subject was instructed to press the button to terminate imperative stimulus S2. The EPs were recorded analysed by inbuilt computer of evoked potential recorder and CNV corresponds to high amplitude negative potential prior to S2, in the S1-S2 interstimulus interval. CNV recording procedure was as follows: Each trial consisted of a Warning stimulus (S1) of 70 dB (SPL) intensity, frequency 0.4 Hz and duration of 0.1 msec, followed by 1 sec later by the imperative stimulus (S2). For S2 a standard red LED goggles were used. The MEB evoked potential recorder settings were properly selected and evoked responses were filtered with a band pass 0.5 - 30 Hz (Filter Slope, 12 dB/Octave) and averaged simultaneously for 32 responses. Data so obtained were consequently analysed and averaged by the computer and stored in memory. A manual cursor programme was employed to identify ERPs and maximal CNV amplitude. Cursors were hand set to score the latencies for N1 and P3 to S1 and maximal CNV amplitude was scored as the largest negative ongoing potential immediately prior to S2 onset. Similarly Reaction Time (time between S2 and button press) was also noted for every trial.

RESULTS

Representative CNV potential records of the control and that of pain patient are depicted in Fig. 1 and 2 respectively. Table I shows comparison of N1, P3, maximal CNV, 0 wave (orientation), E wave (Expectancy) and Reaction Time in controls and pain patients. There is
## TABLE I: Showing Mean ± SD values of various components of CNV in controls and chronic pain patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Pain patients</th>
<th>P value (t-test)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age : 28.2 ± 7.1 yrs</td>
<td>Age : 32.55 ± 8.9 yrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N1 Lat.</td>
<td>91.57 ± 31.348</td>
<td>125.36 ± 53.222</td>
<td>0.053</td>
<td>NS</td>
</tr>
<tr>
<td>P3 Lat.</td>
<td>260.79 ± 29.394</td>
<td>333.93 ± 80.148</td>
<td>0.005</td>
<td>Sig</td>
</tr>
<tr>
<td>CNV Lat.</td>
<td>2.31 ± 0.141</td>
<td>2.16 ± 0.284</td>
<td>0.083</td>
<td>NS</td>
</tr>
<tr>
<td>CNV Amp.</td>
<td>17.54 ± 7.853</td>
<td>20.64 ± 7.255</td>
<td>0.287</td>
<td>NS</td>
</tr>
<tr>
<td>RT</td>
<td>102.29 ± 26.424</td>
<td>197.50 ± 126.137</td>
<td>0.015</td>
<td>Sig</td>
</tr>
<tr>
<td>O Lat.</td>
<td>1.50 ± 0.270</td>
<td>1.58 ± 0.253</td>
<td>0.426</td>
<td>NS</td>
</tr>
<tr>
<td>O Amp.</td>
<td>11.02 ± 4.628</td>
<td>12.53 ± 6.407</td>
<td>0.483</td>
<td>NS</td>
</tr>
<tr>
<td>E Lat.</td>
<td>1.11 ± 0.265</td>
<td>1.20 ± 0.236</td>
<td>0.356</td>
<td>NS</td>
</tr>
<tr>
<td>E Amp.</td>
<td>17.54 ± 7.853</td>
<td>20.64 ± 7.255</td>
<td>0.287</td>
<td>NS</td>
</tr>
</tbody>
</table>

significant increase in P3 latency and Reaction Time in chronic pain patients as compared to age and sex matched controls (Table 1). P3 latency in controls was 260.79 ± 29.394 msecs and in chronic pain patients 333.93 ± 80.148 msecs. The Reaction Time was 102.29 ± 26.424 msecs in controls and 197.50 ± 126.37 msecs in chronic pain patients.

### DISCUSSION

Pain is principally perceived like any other sensation in the cerebral cortex. This is the end of the journey that starts at a peripheral nociceptor. Pain may originate at any point on the journey (8). Infact the chronic nociception causes continuous bombardment of limbic system and other associated areas by activity of A delta and C fibres. This results in complex multi-dimensional features of sensory discriminatory, cognitive evaluative and affective motivational dimensions (1). The cognitive process in these patients is also delayed. By the time patient moves into chronic pain stage, his attention is focussed almost exclusively on pain and pain related issues. This restriction of cognition amounts to cognitive-behavioural deterioration (9) and that is why cognitive behavioural treatment helps in these maladaptive cognitive cases (10, 11). The electrophysiological mechanisms involved in these cognitive behavioural changes have not been adequately worked out. The parameter CNV does reflect some of these functions as follows:

The first component of CNV is the O-wave (orientation wave) seems to be associated with a process of orienting to S1, whereas the second component labelled as the E-wave (Expectancy wave) seems to be related to motor preparation prior to S2 (12). O-wave is related to the information delivered by S1 (13). CNV activity is generated in frontal or parietal cortical areas, encompassing the premotor cortex, the supplementary motor area (SMA) for motor...
CNVs and the parietal association cortex for sensory CNVs. In motor CNV paradigms the E-wave reflects activity in neuronal circuits involving not only premotor cortex but also basal ganglia (14). Nevertheless it is still appropriate to conclude that at least part of E-wave encompass a readiness potential in preparation for a motor response to S2.

Present study has shown significant increase in Reaction Time and P3 in response to S1 in chronic pain patients as compared to controls, when CNV paradigm was employed (Table I and Fig. 2). The mechanism of generation of P3 is still being debated. Some reports suggest that cholinergic mediation of mesencephalic reticular formation, resulting in its transient diffuse reduction, helps in generation of P3 event related cerebral evoked potential. There are other reports suggesting that P3 generator lie in limbic structures specially hippocampus (15). Limbic interactions are also cholinergic and are linked with memory mechanism (16). The chronic pain patients not only present with emotional disturbances like depression, anger, frustration, anxiety but they also show memory problems that lead to cognitive blunting (10). Our study thus suggests that increased latency of P3 might be due to interaction of pain with these higher functions emnating from limbic and association areas.

It has further been suggested that chronic pain and depression have similar neurochemical mechanisms (17, 18) i.e. biogenic amines and endogenous opioids. Both opioids and monoaminergic systems, extensively present in hippocampus, are thus involved in generation of P3 (19, 20) that is why the P3 latency shows increase in Parkinson patients and improvement by dopaminergic therapy (21). Whereas in healthy subjects such therapy has no effect on P3. Our previous study has also clearly shown an increase in P3 latency in chronic pain patients (22). Thus our present study also suggests that due to continuous incoming nociceptive stimuli there are changes in neurotransmitters or their interaction, leading on to maladaptive cognition, causing changes in affect and physical deconditioning, which might result in delay in P3 latency.

In our study there is also a significant delay in RT in chronic pain patients as compared to age and sex matched controls (Table I). Since RT reflects the level of arousal of the Central Nervous System and is itself a good measure of vigilance, the delayed RT in chronic pain patients would reflect adverse effect of pain on cerebral functional integrity leading to cognitive blunting. The trend of increase in amplitude and decrease in CNV latency (Table I) in pain patients also hints towards interaction of pain with CNV generators in higher cortical cases. The present study has clearly shown significant increase in P3 latency and RT in CNV paradigm. This would imply that cognitive processes in these patients are delayed leading on to slower motor reactions and thus delayed RT. However, the exact mechanism of interaction of pain with cognitive - behavioural functions of the brain remains to be worked out.

REFERENCES

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