SUMMARY

Somatosensory evoked potentials (SEP) were studied in 35 Parkinson's Disease (PD) patients. The amplitude and the peak latency of each component of the potentials were measured. The author examined thirty-three subjects as controls.

The following results were obtained:

1) Marked increases in the amplitude of each component of the SEP were observed in PD, especially in the N2-P2 (N34-P46) and P2-N3 (P46-N69) amplitudes, whereas no significant changes were observed in the peak latency of the primary response and the association response, except for the N3 (N69) component.

2) The threshold of the N2-P2 (N34-P46) amplitude of the SEP in PD showed significant changes on an increase in the stimulus intensity. The N2-P2 (N34-P46) amplitude of the potentials increased much more abruptly in the PD patients than in the normal subjects and rapidly reached a maximum at MT.

3) With L-DOPA administration, the high amplitude of the N2-P2 (N34-P46) and P2-N3 (P46-N69) components of the SEP were normalized, but there was no change in the peak latency of the primary response; P9-P1 (P15-P27) and in the association response; N5-N3 (N34-N69).

4) In the cases of PD, the abnormally high amplitude of the association response is thought to be related to dopamine deficiency caused by the degeneration of the striato-nigral system.

INTRODUCTION

Somatosensory evoked potentials (SEP) from the human scalp have been recently studied in relation to various neurological disorders (Halliday, 1967; Bergamin et al, 1967; Williamson et al, 1970; Desmedt and Noel, 1973; Cracco, 1975 and Halliday, 1975). Most previous studies have associated clinical impairment of vibration-position sensitivity with the appearance of SEP abnormalities (Halliday & Wakefield, 1965; Giblin, 1964; Larson & Sances, 1966 and Noel & Desmedt, 1975). Thus the integrity of both the dorsal column medial lemniscus pathway and primary sensory area has been considered as essential to record a normal SEP (Domino et al, 1965; Stohr & Goldring, 1969 and Celesia, 1979).

However, in the course of these clinical studies, we have frequently encountered another group of patients with abnormal SEP, even though their clinical pictures and pathology are distinct from diseases with the specific sensory impairment. Some of the patients have Parkinson's Disease (PD), a condition generally thought of as the results of involving only motor and not sensory pathways. In this disease at least one neurotransmitter (dopamine) has been shown to be deficient, caused by the degeneration of the striato-nigral system and its replacement is capable of relieving the symptoms.

In an attempt to develop objective measurements that may aid in the assessment of the clinical state and evaluation of the effect of therapy, the author have undertaken a study of the SEP in this disorder. The results suggest the possibility that SEP measurement may be useful in following up the progress of the disease and the effects of the therapy.
akinesia, tremor and rigidity were observed in all patients, for whom L-DOPA therapy was effective.

Patients with Parkinson's syndrome were excluded. Patients were classified according to the Yahr's grade criteria for PD cases (Grade 1; 10, Grade 2; 10, Grade 3; 8, Grade 4; 4, Grade 5; 3). Ten PD patients were given from 200 to 500 mg of L-DOPA intravenously. The test of SEP followed 30 minutes after the L-DOPA administration. Thirty-three healthy volunteers, with ages ranging from 29 to 64 years (average age 50 years), were also examined as the control group.

METHODS

The subject was placed in a supine position with closed eyes in a semi-darkened shielded room.

1) Stimulation: Silver-disc stimulation electrodes were placed on the skin just above the median nerve at the wrist. The intensity of the stimulation was adjusted to approximately 10% above the threshold of the thenar muscle contraction. The pulse duration was 0.2 msec. The intensity ranged from 20 to 125 volts. The bilateral simultaneous stimuli (Cohn, 1970; Misawa et al, 1973; Terao et al, 1976; Yamada, 1978) were delivered at intervals of 1 to 2 secs., and were manually controlled in order to exclude an habituation effect.

2) Recording: For recording evoked potentials, spin-electrodes were applied at points 2 cm posterior and 7 cm lateral to the vertex on each side, with the ipsilateral ear electrode used as reference. The evoked responses from the scalp were recorded by a Medelec MS-6 (Saneiokki). The EEGs were amplified with a time constant of 0.1 sec. and the filter was set at 0.32 Hz. to 32 Hz. Averaging was accomplished by summation of the responses to 128 stimuli within the analysis time of 200 and 800 msecs. At least two trials were performed with the same stimulus setting to confirm the reproducibility of the results.

3) Measurements: The peaks of the evoked response within the first 200 msecs. after stimulation are shown in Fig. 1 (A). The initial small positive response (downward deflection, P0) occurred with a latency of about 15 msecs., followed by alternate negative and positive deflections, which were designated N1, P1, N2, P2, N3, P3, and N4, respectively. The amplitude was measured between each successive trough and peak. The values obtained on the left and right hemispheres, evoked by the bilateral simultaneous median nerve stimulation, were averaged.

RESULTS

SEP models of normal subjects and PD cases are shown in Fig. 1 (B).

Fig. 1(A) Schematic SEP by bilateral simultaneous median nerve stimulation, which represents the average of 33 normal volunteers. In this paper, the upward deflection indicates negative potentials. Po=Pis, Ni=N2i, Pi=P27, N2=N4, P2=P4, N4=N6, Ps=P61, N6=N8, R-PR=right-post-rolandic sensory area. L-PR=left-post-rolandic sensory area. Right: Increased SEP amplitude, especially N2-P2, P3-N3, of a 71-year-old patient.

Fig. 1(B) Left: Normal SEP on bilateral median nerve stimulation at the wrist. N and P indicate the negative and positive peaks, respectively. In this paper, the upward deflection indicates negative potentials. P0=P15, N1=N11, P1=P27, N2=N46, P2=P46, N3=N65, P3=P101, N4=N133. R-PR=right-post-rolandic sensory area. L-PR=left-post-rolandic sensory area. Right: Increased SEP amplitude, especially N2-P2, P3-N3, of a 71-year-old patient.
Table 1

<table>
<thead>
<tr>
<th>Normal control (Range*)</th>
<th>Parkinson’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>P0</td>
<td>15.1±0.82</td>
</tr>
<tr>
<td>N1</td>
<td>20.9±1.5</td>
</tr>
<tr>
<td>P1</td>
<td>26.9±3.2</td>
</tr>
<tr>
<td>N2</td>
<td>33.7±2.3</td>
</tr>
<tr>
<td>P2</td>
<td>46.3±3.6</td>
</tr>
<tr>
<td>N3</td>
<td>68.6±7.5</td>
</tr>
<tr>
<td>P3</td>
<td>100.8±12.5</td>
</tr>
<tr>
<td>N4</td>
<td>133.2±10.1</td>
</tr>
</tbody>
</table>

* ± 2 SD

1) **Comparison of the SEP peak latencies of the control subjects and all of patients with PD.**

Table 1 shows the mean peak latencies of the normal control subjects (on the left) and 85 patients with PD (on the right). Comparing the peak latencies of SEP in PD cases with those in normal subjects, the peak latency in PD cases was remarkably delayed from Ns to N4 component, while the peak latency in the primary response (P0−P1) and in the association response (AR) (N2−N3) appeared to be within the normal limits, except for the N3 component (Fig. 2). The peak latency after N3 up to N4 was significantly prolonged as compared with the normal control (P<0.01).

2) **Comparison of the amplitude of the control group and of patients with PD.**

Table 2 shows the mean amplitudes of the normal control subjects (on the left) and 85 patients with PD (on the right).

Comparing the amplitudes of the SEP in PD cases with those in normal subjects, the SEP in PD cases showed a remarkably high amplitude (Fig. 3). The amplitudes of N2-P2 (N54-P46) and P2-N3 (P46-N60) were especially marked (P<0.01). In fact, in some PD cases, the amplitude was six to ten times as high as that in the normal subjects. The amplitude between P3-N2-P1 also showed some increase but were statistically not significant.

3) **Relation between stimulus intensity and amplitude in the control subjects.**

Figure 4 shows the relation between the stimulus intensity and variations of the amplitude. Motor threshold (MT) indicated by an arrow, represents the threshold at which contraction of thenar muscle occurs. These results show that these responses are roughly classified into three groups. The first one is the amplitudes generated between P0 and P1, which reach a maximum at MT, and then become flat. The amplitudes between N3 and N4 reach a maximum at MT, rapidly decreasing after that. The maximum amplitude between N2 and N3 appears at stimulus intensity 1 (ST-1: at which a
slight electrical stimulation is perceived) and then gradually decreases. On the other hand, the peak latency is constant, regardless of stimulus intensity.

4) Relation between stimulus intensity and the N2-P2 amplitude in PD patients who showed high amplitude of AR.

In normal subjects, the N2-P2 amplitude was noticed at stimulus intensity 1 (ST-1) and reached a maximum between ST-1 and ST-2, and then slowly decreased. In those PD patients (n=7) with high amplitude N2-P2, N2-P2 amplitude was noticed at ST-1, rapidly reached a maximum at MT, then gradually decreased, as shown in Fig. 5.

5) Peak latency and amplitude before and after intravenous injection of L-DOPA.

With L-DOPA administration, the high amplitude of each component of the SEP was markedly suppressed especially both interpeak N2-P2 and P2-N3 amplitude (P<0.01) but there was no change in the peak latency of the early component (P0-N3), as
shown in Fig. 6 and Fig. 7.

As to the relation of N2-P2 amplitude to the handicapped score (Yahr), the SEP recordings of severely handicapped patients showed more remarkable SEP abnormalities in N2-P2 amplitudes than did those of slightly handicapped patients.

The abnormal SEP findings were almost normalized in the PD patients after being given the L-DOPA for several years, as showing improvement of symptoms.

DISCUSSION

On the basis of the reports of Ciganek (1961), Goff et al (1962), Allison (1962), and Kato (1974), each component of the SEP was categorized into three groups: As shown in Fig. 1A, P0, N1 and P1 were regarded as a primary response, N2, P2 and N3 as association response (AR), and the component following AR as late response. The present report is focuses on the association response (AR) of the SEP in PD patients.

From the view point of peak latency, the N1-P1 of the SEP obtained by the method used in this study corresponds to component 1, which was thought to be pre-synaptic in origin by Allison (1962) and Goff et al (1962). However, it is recently reported that the N1-P1 is more likely to be responsible for post-synaptic in origin (Obukawa 1978). The N2-P2 of SEP may correspond to component 3 of Allison (1962), which is considered to be the response of the association area (Amassian, 1954 and Hirsch, 1961) and that the origin of the response may be in some part of the cortical area anterior to the Rolandic sulcus. The N3 component corresponds to component 4, whose amplitude may be easily affected by the level of alertness. However, the neurophysiological definition of the neural source of N3, P2 and N3, which are regarded as an AR has not yet been established.

In general, evoked potentials increase in amplitude with age and show shorter latencies in female subjects. The control subjects were matched for age with the PD patients to minimize the possible effects of these factors.

The amplitude of the SEP becomes smaller on the affected side in cerebral vascular disease, brain tumors and other lesions in the nervous system (Halliday and Wakefield, 1963, Giblin, 1964;
Williamson, 1970; Takahashi et al, 1970; Noel & Desmedt, 1975; Terao et al; 1976, Goya, 1976; Shibasaki; 1977). Increases in amplitude are known only in a few diseases such as myoclonic epilepsy (Dawson, 1947; Halliday, 1970; Halliday & Halliday, 1970; Shibasaki et al, 1980; Kelly et al, 1981), hyperthyroidism (Takahashi & Fujita, 1970) and in some kinds of brain-stem lesions (Halliday & Wakefield, 1963). In PD patients, marked increases in amplitude were observed in each component of the SEP. The amplitude of cerebral evoked responses have considerable individual variability even in normal subjects. However, as shown in Table 2 and Fig. 3, the increases in the amplitude of the SEP in PD patients, especially that of interpeak N2-P2 and P2-N3 in the AR, were significantly greater than in normal controls and also characteristic of this disease.

1) Neurological disorders and AR
De la torre (1977) recently presented cases of movement disorders including PD with their SEP. However details of relation between the disorders and SEP were not mentioned in the report. There is only one report by Koziel et al (1977) on SEP in PD patients. They recently studied the effects of L-DOPA combined with decarboxylase inhibitor on SEP. They performed SEP test on 4 patients with PD and 8 with Parkinson's Syndrome using the bipolar technique. Their findings were rather similar to the results of present report in terms of a tendency that increased amplitude was shown by the waves early III and late VII wave in both hemispheres.

However, there can not be strict comparison between the present results and their data, since Parkinson's Syndrome patients were included and bipolar technique, which is well known to be changeable in wave form, amplitude and peak latency of SEP (Kato 1974), was used in their study.

So, in summary, in the reports on the disease and its lesions, abnormal amplitude in the AR and normal or nearly normal amplitude and peak latency in primary response were the major findings.

1) An abnormally high amplitude in the AR with or without a prolonged peak latency and/or absence of the each component of the AR.

Clinically several lesions seem to result in an abnormal AR. Internal capsular lesion (s), provided with an intact specific sensory pathway and pyramidal tract lesions were observed by Kato (1970), Ogashiwa (1972), Tsumoto et al (1973), and by Tsumoto (1979). In thalamic lesion (s), the N3 component was noticed to have a highly abnormal amplitude, were observed under conditions of hyperpathy with or without the following primary response abnormalities (Tsumoto, 1973; Suzuki, 1978), and in focal thalamic lesion without involving VPL and VPM nuclei similar AR abnormalities were observed by Tsumoto (1979).

These abnormalities were also observed in focal epilepsy with the primary somatic cortex lesion, myoclonic epilepsy (Halliday, 1967; Kato, 1974; Terao et al, 1976; Onuma & Sato, 1973; Kelly et al, 1981), anoxic encephalopathy, cerebrovascular accident, head injury (Takahashi et al, 1974; Kato, 1974), and the cases with focal brain lesions remote from the primary sensory area (Obeso et al, 1980).

2) Relation of high-amplitude of AR to PD
N2-P2 in the AR, is mainly involved in the function of the inter-cortical connective pathway in reaching the primary somatic cortex. This mechanism is more likely to be responsible for the SEP, according to Williamson et al (1970). Tsumoto
et al (1972) proposed that the N1 wave may be related to the position-vibration sense, whereas the N2 wave is attributable to the pain-temperature sense. However, according to Ogashiwa et al (1972), the amplitudes of N2-P2 wave may be influenced by the activity of upper motor neurons and the recovery of N2 wave is thought to be a sign of clinical improvements of cerebral functions for motor performances.

As to the N3 component, the close functional relation between N3 in the AR and non specific diffuse projection system has been suggested by Shagass & Schwartz (1964) and Yamada et al (1978).

On the other hand, the impulses that arise from the specific thalamic nuclei and project to the cortex via the non-specific thalamic nuclei, may also possibly play a part in the organization of the AR. (Goya, 1974; Terao and Nomura, 1979). With regard to the amplitude in AR, a close functional relation between the N2-P2 amplitude and the upper motor neuron system was suggested by Ogashiwa et al (1972). As the result of the high amplitude of the P2 component, disturbance of the inhibitory system was pointed out by Takahashi (1970).

It is well known that PD is caused by degenerative changes in the dopaminergic striato-nigral system (Richardson et al, 1977). Recently, a few reports (Anden, 1976; Fuxe et al, 1976; and Fuxe, 1978) demonstrated that PD patients have abnormalities in the meso-limbic and meso-cortical dopaminergic system. The abnormalities were recognized as a result of a fluorescence-histochemistry study. Fuxe suggested in his reports (1976 and 1978), the disturbance of the motility founded in PD patients might be caused by an imbalance of development, degradation and degeneration of the two systems. The meso-limbic and meso-cortical systems are now being studied histochemically and neurophysiologically to elucidate their relationship with some parts of the cerebrum, especially the frontal cortex (Denian et al, 1980).

According to Takahashi et al (1970 and 1972), P2, a part of the AR component, may reflect the frontal lobe function. And the possible influence of this on the AR cannot be ignored.

In short, abnormal high interpeak N2-P2 amplitude (the amplitude between negative and positive reaction in the association area) and slightly prolonged peak latency possibly occur owing to the disturbance in sensory motor areas and systems such as the frontal lobe cortex, VPL nuclei in thalamus (Domino et al, 1965) and corpus striatum (Demetrescu et al, 1962; Krauthamer et al, 1964 and 1964). It is suggested that such abnormal SEP findings are caused by a metabolic abnormality.

The N5 component was closely related to the non-specific afferent system. The N5 component's abnormally prolonged peak-latency and high amplitude, as found in PD patients, was remarkable. The N3 wave seems to closely reflect the functional state of the reticulo-cortical pathways (Allison et al, 1966; Lukas and Siegel, 1977). There were significant changes in EEG that L-DOPA treatment increased alpha power, which was reported by Yaar (1977). So, the N5 abnormalities seem to be caused by disturbance of alertness due to dopamine deficiency, because those abnormal component changes were normalized by the administration of L-DOPA, as shown in Fig. 7.

Huntington's Chorea shows hypotonic and hyperkinetic symptoms and also manifests an increase of dopamine in the urine which is contrary to the symptoms and results in examination of PD. It is very interesting that the SEP pattern in unon's Chorea is the opposite of that of PD, including the lowering of AR amplitude and the absence of AR components in SEP recordings.

We have to do further study on the neurophysiological basis of the abnormal SEP in PD, because it is not yet certain what systems or parts of the brain are responsible for the abnormal findings in SEP. However, it is clear at least that AR abnormality seems to appear as a result of dopamine deficiency in the striato-nigral systems, because with L-DOPA administration, the high amplitude of the N2-P2 and P2-N3 components of the SEP were normalized. And, as shown in Fig. 5, the changes of the threshold of the N2-P2 amplitude in the PD may be also based on dopamine deficiency. The fact that dopamine deficiency affects various functions of the brain can be postulated not only from the measurements of the SEP, but also from that of the visual evoked potentials (Bodis-Wollner et al, 1978).

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