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## THE EFFECT OF BODY TEMPERATURE ON THE “PERIODIC COMPLEXES” OF SUBACUTE SCLEROSING LEUCOENCEPHALITIS (SSLE)<sup>1</sup>

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The periodic complexes seen in the EEG of patients with subacute sclerosing leucoencephalitis (SSLE) are a characteristic if not constant feature of this form of encephalitis (Cobb and Hill 1950; Petsche *et al.* 1961; Cobb 1966). The frequency of the complexes varies somewhat from time to time and from patient to patient but for the most part is unaffected by a wide variety of physiologic stimuli (Fenyő and Hasznos 1964).

The origin of these complexes is not clear. Some authors have speculated that they depend upon a thalamic or mesencephalic reticular source (Petsche *et al.* 1961; Fenyő and Hasznos 1964; Cobb 1966; Lombroso 1968; Petre-Quadens *et al.* 1968), whereas others have proposed that the complex originates within the cerebral cortex itself (Lesse *et al.* 1958; Bogacz *et al.* 1959).

The present study was prompted by a chance observation of the disappearance of the periodic complexes from the EEG in a patient with SSLE during a febrile episode.

We have examined the effects of body temperature on the periodic complexes in patients with SSLE and have attempted to relate these observations to relevant biochemical and electrophysiological parameters to explain the effect of temperature in abolishing the complexes.

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<sup>2</sup> DFF and JMF.

<sup>3</sup> AS.

### MATERIAL AND METHODS

Four patients with documented SSLE were studied. All four patients demonstrated intellectual deterioration and myoclonic jerks. The disease was considered early in one patient (1, C) and moderate to advanced (2, B) in the other three (Freeman 1969). Three of the four patients had the disease confirmed by histological examination of cortical biopsies, and the fourth patient was diagnosed by the elevated measles antibody titer in serum and cerebrospinal fluid, the characteristic EEG and a first zone colloidal gold curve.

EEG recordings were obtained from scalp electrodes placed according to the 10–20 system, and both reference and bipolar montages were used. The patients remained awake during each recording session and were under constant observation. Eight-, 12-, and 16-channel Grass electroencephalographs were used for recording. A recording rectal thermometer was used to monitor temperature continuously.

A total of eleven febrile episodes were studied. The temperature elevation was induced by intravenous administration of typhoid vaccine (20,000–50,000 units) or by a surgical heating blanket. A surgical cooling blanket was used to induce subnormal temperatures. On one occasion recordings were obtained during a spontaneous febrile illness.

Visual evoked responses (VERs) were obtained in two patients at both normal and elevated body temperatures. The pupils were dilated with 1% ophthalmic homatropine. A Grass photic stimulator, placed 18 in. from the closed eyes,

provided the visual stimulus. In one patient flashes were presented at 1/sec during the entire study. In the second patient flashes were presented at various times during or after the initial positive component of the periodic complex. A voltage sensing device was used to define the periodic complex and then to trigger the photic stimulator after a delay. When the patient was febrile and periodic complexes could no longer be detected, flashes were presented at regular 3 sec intervals. The VERs were derived from P<sub>4</sub>-O<sub>2</sub> and recorded on an Ampex FR 1300 tape recorder and subsequently digitized for averaging on a LINC computer. Fifty responses were averaged in the first patient, and in the second patient, 40 responses were averaged.

Nerve conduction studies and H reflex studies (hypothenar and gastrocnemius-soleus) were obtained in a standard manner at normal and elevated body temperatures.

## RESULTS

### *The effect of body temperature on the periodic complexes*

The initial observation of the disappearance of the periodic complexes during a spontaneous febrile illness was made by one of us (JMF). The changes in the EEG to be described were seen on eleven separate occasions in the next three patients admitted with documented SSLE.

At a normal body temperature the EEGs were similar to those described in the literature, showing a disorganized background and high voltage multiphasic complexes lasting 1–2 sec which appeared at fairly regular intervals. The periodicity varied from 5 to approximately 15 sec but was relatively constant for each given subject. At no time could the complexes be initiated or modified by photic stimulation, hand-clapping, name calling or painful stimuli (*i.e.*, pin-pricks). Intravenous Valium (10 mg) and pentobarbital sodium (100 mg) also had no effect on the complexes. The effect of sleep on the complexes was not examined.

An increase in body temperature of 0.5 to 1.0°C was accompanied by a decrease in frequency of the complexes. As the body temperature continued to rise, the periodic complexes decreased in frequency and amplitude until a

body temperature of 38.0–41.0°C was reached, when the complexes could no longer be seen. On one occasion a rise in temperature from 37.5 to 38°C was sufficient to abolish the complexes. The frequency and severity of the myoclonic jerks paralleled the changes in the complexes. On eleven separate occasions the periodic complexes disappeared at an elevated body temperature (Fig. 1 and 2). Epileptiform activity was also attenuated at elevated body temperatures. At normal body temperatures the background activity between the periodic complexes was disorganized, slow (2.5–6 c/sec) and frequently asymmetric. At elevated temperatures the slower activities were attenuated and there was an in-

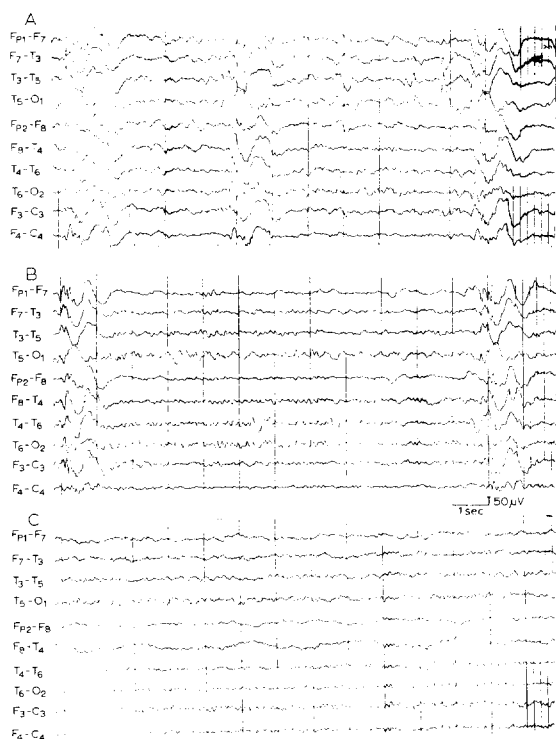


Fig. 1

A: Body temperature, 36.5°C. The complexes are 3–5 sec apart, and the background activity is quite disorganized in general. There is focal delta activity and a focal sharp wave in the left posterior temporal region. B: Body temperature, 37.2°C. The complexes are 10–11 sec apart. Note the background activity is better organized than at the cooler temperature. The left hemisphere continues to be slower than the right. C: Body temperature, 38.8°C. No complexes are seen. There is an increased frequency of the basic rhythms, although the left posterior temporal region continues to demonstrate irregular slow activity in the delta range.

crease in the faster activities (8–12 c/sec). The changes were independent of the method used to produce fever. With a reduction in fever, the characteristic periodic complexes returned as did the slower frequencies.

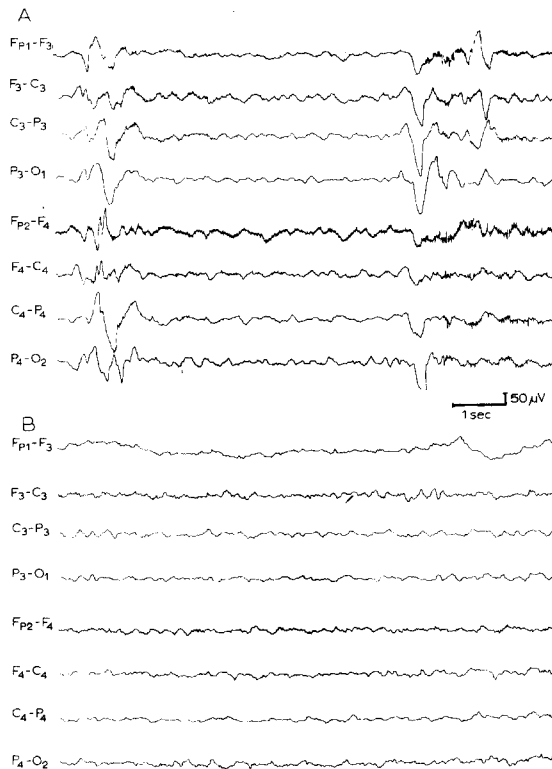


Fig. 2

A: Body temperature, 37.0°C. The complexes are approximately 5 sec apart. The background activity is poorly organized, being primarily in the delta frequency (4 c/sec). B: Body temperature, 39.5°C. No complexes are present. The background activity continues to be disorganized, but is now of smaller amplitude.

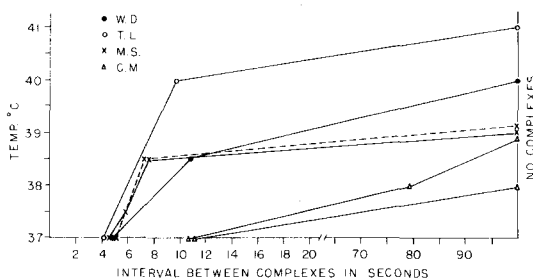


Fig. 3

Effect of temperature on the mean interval between complexes in four patients. Note similarity of response to change in body temperature in two patients, (x, Δ) on separate occasions.

As the body temperature was lowered, the complexes became more frequent (Fig. 1). At 36.5°C they were at approximately twice the frequency seen at a normal temperature. The myoclonic jerks became more prominent and were synchronous with the complexes. The average interval between complexes in each patient at varying temperatures is shown in Fig. 3.

Serum electrolytes, blood gases, cerebrospinal fluid electrolytes and gases showed little change with increasing temperature up to 39.5°C. At this temperature the blood demonstrated a slight respiratory alkalosis (pH 7.44; pCO<sub>2</sub> 30.5), whereas the cerebrospinal fluid became slightly acidotic (pH 7.35; pCO<sub>2</sub> 45.0). To establish whether these slight acid-base changes were contributing to the alterations in the EEG, one patient (CM) was hyperventilated to induce respiratory alkalosis and breathed a mixture of 5% carbon dioxide–95% oxygen to induce respiratory acidosis. The oral administration of ammonium chloride and sodium bicarbonate caused a metabolic acidosis and alkalosis, respectively, greater than those seen with fever, but no alterations in the periodic complexes were noted with any of these manipulations.

#### Visual evoked responses

The VER was obtained in two patients. In the first, only single flashes were presented (Fig. 4) and were not synchronized with the complexes. At 37.2°C the early components of the VERs were of a larger amplitude than those seen at 39.0°C. From this single experiment it appeared that elevation of the body temperature resulted in a moderate depression of the early components

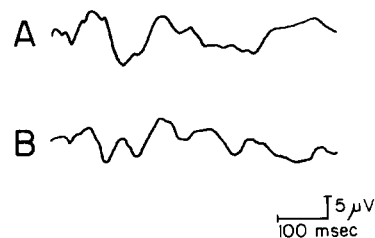


Fig. 4

Patient 1. A: averaged VER at normal body temperature (37.2°C). B: VER averaged at 39.0°C. (See text for further discussion.)

of the VER. However, one could not exclude the possibility that the wave form of the complexes had affected the shape of the VER at a normal temperature by being included in the averaged responses. Thus, in the second patient (Fig. 5), both single and paired flashes were triggered by the complexes and were presented at varying times during and after the occurrence of the complex. The VER could not be detected in the complex (Fig. 5, A) because the large amplitude

of the complex (D, 200  $\mu$ V) served to mask the smaller VER (approximately 10  $\mu$ V).

Both single and paired stimuli, again triggered by the complexes, were then presented between complexes at a normal body temperature. The VER from a single flash showed no abnormalities of either latency or form. When a second flash followed the first by 70–160 msec (Fig. 5 and 6), the second response showed progressively greater facilitation. At 38.8°C no complexes were present in the EEG, and again single and paired flashes were present. The response to the second flash showed more marked facilitation than that seen at normal temperatures with all flash intervals examined.

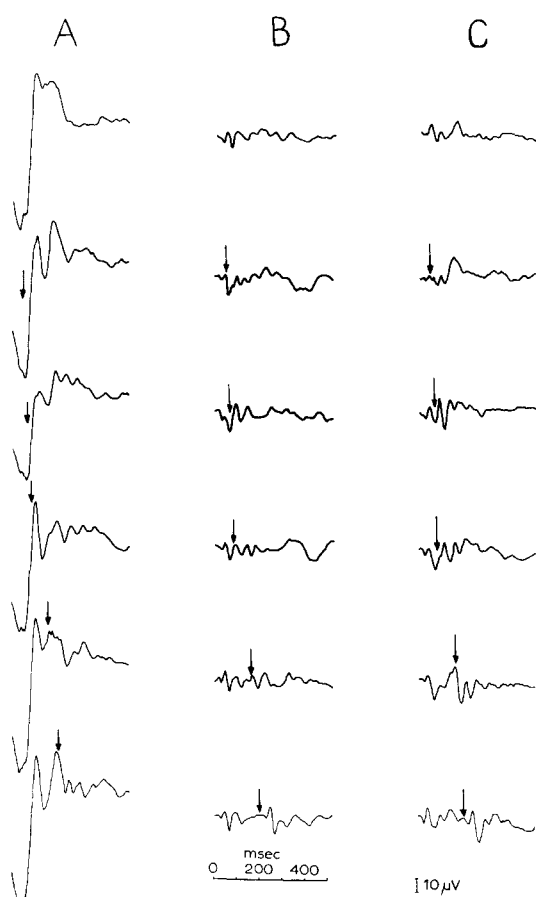


Fig. 5

Patient 2. The first flash at beginning of each tracing is triggered by the initial positive wave of the complex. The latency between the onset of the periodic complex and the first flash is 15 msec. Second flash represented by arrow. A: Averaged VERs from both single and paired flashes during periodic complexes at 37.4°C. The VER is difficult to recognize in the large complex. B: Averaged VERs from single and paired flashes during interval between complexes at 37.4°C. C: Averaged VERs from single and paired flashes at an elevated body temperature (38.8°C). Note the greater facilitation to the second flash than seen at a normal body temperature.

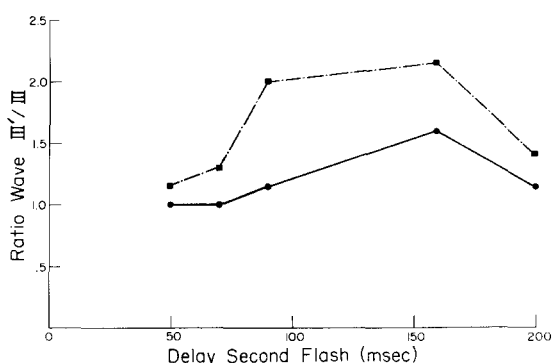


Fig. 6

Recovery cycles from VERs in patient 2. The solid line indicates VERs between complexes at normal temperature (37.4°C). The broken line indicates VERs at elevated body temperature (38.8°C). Throughout all flash intervals there is a marked facilitation to the second flash at elevated body temperature. This suggests an increased population of cells responding to the flash at an elevated body temperature.

Recovery cycles for wave III of the VERs were obtained, using the method of Cigánek (1961), by dividing the amplitude of wave III of the second response (wave III') by the amplitude of wave III of the initial response (Fig. 6). A recovery cycle could not be measured for the VERs obtained during the complex. The recovery cycle obtained during the interval between complexes at a normal body temperature was similar to the normal controls reported by Floris *et al.* (1967). The recovery function obtained at an elevated body temperature showed a marked increase in the ratio of wave III'/III at all intervals.

### *Nerve conduction and H reflex studies*

Peripheral nerve conduction velocities of the ulnar and lateral peroneal nerves remained well within the normal range, and no change was observed with increasing body temperature. H reflexes were obtained from both the ulnar-hypothenar complex and the posterior tibial-gastrocnemius-soleus complex. The ability to obtain the H reflex from the hypothenar muscles following ulnar nerve stimulation in children of this age is considered abnormal (Thomas and Lambert 1960). A series of 30 H reflexes was obtained at both normal and elevated body temperatures. The M wave was maintained at a constant amplitude at all times. At 37.5°C, the H reflex had an amplitude of  $0.489 \pm 0.050$  mV, whereas at 38.8°C, the amplitude was  $0.552 \pm 0.035$  mV (confidence 0.05). Although these findings are not statistically significant, the direction of change is similar to that seen during the VER.

### DISCUSSION

The present study shows that the frequency of the periodic complexes in SSLE has an inverse relationship to body temperature. During febrile episodes the complexes decrease in frequency whereas during periods of subnormal temperature, their frequency increases. Two other factors have been shown to influence the frequency of these complexes. First, frequency increases during sleep (Petre-Quadens *et al.* 1968; Petsche *et al.* 1961), possibly due to the physiologic decrease in body temperature during sleep. Secondly, Fenyő and Hasznos (1964) were able to block the periodic complexes of SSLE pharmacologically with mephensin without altering the jerks, and attributed this effect to the drug's ability to block thalamic outflow (arousal reaction and recruiting response) as demonstrated by Killam and Killam (1958).

Most of the data pertaining to the effect of temperature on the central nervous system relate to the understanding of the pathophysiology of childhood febrile seizures (Swineyard and Toman 1948; Brown 1953; Baird and Garfunkel 1956; Schmidt *et al.* 1956; Millichap 1959) and the effect of temperature on a variety of neurologic

signs and symptoms most frequently seen in patients with multiple sclerosis (Simms 1937; Nelson and McDowell 1959).

The EEG response to fever appears to vary dramatically with age. In adult subjects, Krakau and Nyman (1953) demonstrated that one-half of their patients developed an increase in alpha frequency (0.5 c/sec) at elevated body temperatures, and the remainder showed either no change or slowing of the background rhythms. All showed a decrease in amplitude. Children age 3–10 years, with a history of febrile seizures, on the other hand, were shown by Baird and Garfunkel (1956) to develop high voltage slow waves with occasional spike and wave complexes at increased temperatures. It is clear that fever can alter the EEG, but the mechanism underlying such a change is not clear. From our data and those of others (Baird and Garfunkel 1956), the changes noted in the EEG do not appear to be related to serum or cerebrospinal fluid pH changes.

The EEG picture seen in SSLE is associated with widespread damage to the central nervous system. The cerebral cortex, subcortical nuclei and white matter are involved. Perhaps the combination of involvement of these areas is required to produce the periodic complexes characteristic of this disease (Guazzi 1961; Osetowska 1961). A change in the functional state of any of these anatomic sites would most likely result in the abolition of the periodic complexes.

For instance, the functional activity of the damaged axons passing through areas of demyelination might be further altered by an increase in body temperature resulting in a decrease in the periodic complexes. Davis (1970) has demonstrated that slight elevations in temperature (1°C) block conduction in damaged axons of the lobster. This effect was reversible upon cooling. He felt that this type of functional block might explain the worsening of symptoms seen in patients with multiple sclerosis when heated and the improvement of symptoms upon cooling. Thus, if impaired conduction plays a role in the genesis of the complexes, then an increase in body temperature further blocking conduction might result in an abolition of the complexes.

An alternative hypothesis could be that changes in body temperature directly alter the excit-

ability of the brain by modifying synaptic activity. There is some evidence from the peripheral nervous system that changes in temperature can alter synaptic functioning. Hofmann *et al.* (1966) demonstrated, *in vitro*, the effect of temperature on a phrenic nerve-hemidiaphragm preparation. With decreasing temperature, there was a decrease in the number of spontaneous miniature endplate potentials and fewer quanta of transmitter were released with each nerve impulse. At higher temperatures, an increase in quantal release might therefore result in an altered excitability of the brain. This type of change could alter the cellular substrate necessary for the generation of the periodic complexes. The increase in facilitation seen in the recovery cycles of the VER at higher temperatures, and perhaps the increase of the H reflex at higher temperatures would support this hypothesis.

Although it is impossible to draw firm conclusions from the VER and H reflex studies, the changes encountered would be most compatible with the proposed effects of temperature on alterations in synaptic activity.

#### SUMMARY

The "periodic complex" associated with subacute sclerosing leucoencephalitis is highly responsive to alterations in body temperature. At an elevation in body temperature, the complexes progressively decrease in frequency and amplitude and are eventually abolished. A lowering of the body temperature has the opposite effect. Studies of the VER and H reflex at varying temperatures suggest that the changes in the periodic complexes are mediated by alterations in synaptic activity.

#### RESUME

#### EFFET DE LA TEMPERATURE CORPORELLE SUR LES "COMPLEXES PERIODIQUES" DE LA LEUCOENCEPHALITE SCLEROSANTE SUBAIGUE (SSLE)

Les "complexes périodiques" associés à la SSLE sont très sensibles aux modifications de la température corporelle. Si la température corporelle s'élève, ces complexes diminuent progressivement en fréquence et en amplitude, et

peuvent finalement disparaître. Un abaissement de la température corporelle a l'effet opposé. Les études des réflexes VER et H à différentes températures suggèrent que les modifications des complexes périodiques sont dues à des altérations de l'activité synaptique.

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