SHORT REPORT

Circadian rhythms in the body temperatures of intensive care patients with brain lesions

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Abstract

The body core temperatures of 31 patients suffering from severe cerebral lesions were measured. Evidence for the existence or nonexistence of circadian rhythms in these patients was found to be associated with diagnosis (acute versus chronic lesions), with the level of consciousness, and with neurological findings (such as best motor response and pupillary reaction), but not with heart rate, corneal reflex, initial Glasgow coma score (GCS), or outcome. This evidence came to light only after multiphasic mathematical transformations of the raw data.

Although most theories concerning the genesis of human circadian rhythms suggest the existence of an internal clock somewhere in the central nervous system, the influences of acute brain lesions on these periodic variations have seldom been systematically studied. Human correlates to animal experiments, in which localised lesions can be produced stereotactically, are impossible and the difficulties in extrapolating the results of animal experiments to the human are well known. Thus, in investigating the anatomical substrate of such rhythmicities in humans, it is only possible to observe the effects of the relatively crude and undesired lesions in patients being treated on neurosurgical intensive care units.

Reasons for the paucity of investigations on humans are obvious: patients with such brain lesions are in a life-threatening situation and subject to a multitude of environmental influences which probably affect their biorhythms in a nearly uncontrollable manner—continuously or intermittently, regularly or irregularly—so that the traditional methods of rhythms research, which are tried and tested under well defined circumstances, are inappropriate.

According to contemporary models, certain cerebral-diencephalic^{2,12} or mesencephalic⁵-structures seem to play a major role in the regulation of circadian rhythms—at least in the rat, and possibly in humans as well.⁶ For humans suffering from cerebral diseases or injuries, the methodological problems mentioned above are formidable, and there is only limited information concerning such circadian rhythms.^{1,7-9,11} We have considered therefore whether in patients suffering from severe cerebral lesions in their appropriate

environment, namely in a neurosurgical intensive care unit, something like a 24 hour rhythm might be detectable despite all the masking effects, disturbances and uncontrollable periodic environmental stimuli in such a situation. As a first attempt we chose body core temperature as a parameter which can be measured simply and inexpensively.

Patients and methods

Body core temperature was measured every three hours by a rectal probe for at least 10 days on 31 patients from a neurosurgical intensive care unit (16 men, 15 women, age 17 to 85 years) with severe cerebral lesions (12 brain injuries, 16 spontaneous intracranial haemorrhages, three chronic subdural haematomas). Mean duration of intensive care treatment was 31.2 days. Thirty patients were intubated and, at times, mechanically ventilated. Twenty patients were sedated, eight received muscle relaxants. Seventeen suffered from intercurrent infections, mainly pneumonia, which were additional to their brain injuries. Fifteen patients died, five from cerebral pathology and ten from other causes. Antipyrexial drugs and physical cooling were given only when body core temperature exceeded 39.5°C. No attempt was made to eliminate the influence of this treatment on the course of body temperature. On 966 patient days, eight daily temperature measurements were performed on each patient. This amounted to a total of 7 728 measurements.

Temperature course was recorded graphically and inspected visually. It was then analysed in two ways: first, the temperature readings of each day were transformed into rank numbers. The time of day in which the lowest temperature of the day was measured was labelled rank 1, the time of day with the second lowest temperature attained rank 2 and so on up to rank 8. In this way the temperature course of each day was represented by a sequence of eight numbers ranging between 1 and 8, and graphically represented as a curve. No consideration was given to the absolute position of the measured temperatures nor to the range of oscillation (RoO) of the day. Second, a sliding-four-day-averaging of the rank numbers of each of the eight measurement points was plotted. The resulting discontinuous curves of mean rank numbers were checked for circadian rhythmicity by two criteria: the first of them was the RoO: the distance between the lowest and

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Figure 1 Transformation from centigrade readings to rank numbers (A) and 4-day-averaging (B) lead to a broken-line curve with sinusoidal shape and a large range of oscillation (RoO): it is labelled "circadian rhythmic".

the highest point of the curve. The second criterion was the degree of similarity of the plotted curve to a sinusoidal curve. The threshold for the first criterion was established by computer simulation, for the second criterion by empirical measures.

Further tests for each patient included: diagnosis, initial Glasgow Coma Scale (GCS),⁴ and outcome according to the Glasgow Outcome Scale.³ Daily registrations were made for the degree of disturbance of consciousness, form of breathing (spontaneous or artificially), spontaneous movement, motor reaction, pupillary reaction to light, corneal reflex, mean daily heart rate, mean daily body temperature and urine production. These parameters were then related to the degree of circadian rhythmicity (Chi-square test).

Results

Inspection of the graphical representation of the measured temperatures in their temporal course does not reveal clear visible circadian rhythmic elements. The mean of all 7728 temperature measurements was 37.64 centigrade.

When transforming centigrade readings into rank numbers and averaging across four days each, a total of 873 curves were obtained for further analysis. Computer stimulation with random numbers showed that in those curves which had an RoO of more than 4.46, the probability of their generation by chance was less than 5%. Of the 873 curves resulting from patient measurement, 249 (=28.5%) showed an RoO of more than 4.46. Of those, 179 (=20.5%) showed a sinusoidal shape. These were called "circadian rhythmic intervals" (CRI) (fig 1). Seventy (=8.0%) had no sinusoidal shape despite an RoO of over 4.46 (fig 2). This proportion roughly equals the value of 5%, which was expected, according to

Figure 2 RoO is large, but the shape is not sinusoidal. This interval does not show circadian rhythm.

the computer stimulation. In 627 four day intervals the RoO was lower than 4.46 (fig 3). Thus, in these curves no circadian rhythms could be detected.

The CRI were not evenly distributed: their proportion in patients with chronic subdural haematomas was 31/90 = 34%, in patients with acute brain injury 106/501 = 21% and in patients with spontaneous intracranial haemorrhages 42/282 = 15%. With the neurological findings, a significant reduction of CRI could be seen in patients who moved their arms and legs spontaneously but indirectly (19/144 = 13.2%, $p = 0.008$), in patients who showed no reaction to painful stimuli (40/276 = 14.5%, $p = 0.0001$) or reacted by flexor or extensor posturing (24/149 = 16.1%, $p = 0.006$), in patients who exhibited no pupillary reaction to light (22/155 = 14.5%, $p = 0.035$) or in febrile patients (mean daily temperature above 38°C, 39/259 = 15.1%, $p = 0.01$). In comatose patients, the proportion of CRI was reduced to 14.5% (18/127). During stupor, somnolence or in a vegetative state, this proportion was between 21% and 22%. There was no correlation with the mode of respiration, with the mean daily heart rate, with a pathological corneal reflex, with the initial GCS or with outcome score. None of the patients manifested diabetes insipidus. In CRI, the median time of day showing the lowest temperature was nine am.

Only three patients exhibited no CRI, but under clinical aspects they did not seem to form a distinct subgroup. In the other patients CRI-intervals were evenly distributed between early and late portions of intensive care treatment.

Discussion

Faced with the multitude of uncontrollable factors influencing very sick patients on an

Figure 3 RoO is small. This interval does not show circadian rhythm.

intensive care unit it is, as expected, impossible to detect circadian rhythms by direct inspection of the temperature curves. Nevertheless, circadian rhythms can be detected when certain formal abstractions of the temperature curves are performed. Thus we conclude that rhythm research in intensive care patients is difficult, but possible.

Whether circadian temperature rhythms are or are not present in a patient is clearly related to certain clinical parameters:

1) The proportion of detectable rhythms is lower in acute lesions (spontaneous intracranial haemorrhage, brain injury) than in chronic ones (chronic subdural haematoma). This observation corresponds with the results of Braunsdorf¹ who found that disturbances in endocrine and electrophysiological rhythmicity of 14 patients suffering from cerebral lesions near the skull base were more severe when the lesions were acute than when they were chronic.

2) Circadian rhythms were significantly reduced in comatose patients with bilateral fixed pupils and in patients whose motor reaction took the form of flexion or extension posturing. These symptoms indicate a predominantly midbrain lesion.¹⁰ With the issue of localisation, we deliberately relied on clinical syndromes and did not consider the results of radiological investigations (CT, MR) which usually showed a polytopic distribution of lesions in our patients.

The significance of midbrain structures for circadian regulation is indicated by considering the nine patients in vegetative syndromes.^{7,11} These lesions are, in a functional sense, something like transverse dissections at the midbrain level. In these patients, circadian rhythms for the secretion of prolactin, cortisol, catecholamines and human growth hormone were mostly eliminated even when the acute incident took place several months before. In these investigations as well as in our own, a multitude of periodic environmental stimuli influenced the temperature course so that the differentiation between endogenous and exogenous elements was not possible. The

present study suggests that, in the human, as in laboratory animals, midbrain structures are involved in the generation of circadian rhythms. It also suggests that, as yet, undiscovered facets of biorhythmicity may be refinable from the large amount of raw data that accumulates from patients on intensive care units.

The physician on the intensive care unit should be aware of the existence of circadian rhythmicity in his patients when interpreting temperature readings and, to an extent that has yet to be investigated, of rhythmicity in other vegetative parameters as well. Even chronopharmacology may find its way into the intensive care unit.

Dedicated to our teacher, Professor B L Bauer, on the occasion of his 60th birthday.

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