Evaluation of autonomic nervous system function with spectral analysis of heart rate variability in a case of tetanus

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Abstract

The autonomic nervous system is affected in a wide variety of neurological disorders. Its dysfunction may play an important role in the clinical course and may result in serious complications, such as cardiac arrest. We report a case of tetanus who presented with severe autonomic nervous system dysfunction which was detected by spectral analysis of heart rate variability monitored over 24 h. This is a semi-quantitative method for evaluation of the status of the autonomic nervous system. In the present case, the analysis revealed profoundly decreased activity of both sympathetic and parasympathetic nervous system modulation of cardiac rhythm. The parasympathetic nervous system activity was more severely impaired than that of the sympathetic nervous system. The relative predominance of the sympathetic nervous system in the present case may have resulted in unopposed sympathetic nervous system hyperactivity manifested in this patient by tachycardia and excessive sweating. We further infer that the documented diminished buffering capacity of the autonomic nervous system may have lead to a sudden cardiac arrest in our case. Thus, spectral analysis of heart rate variability is a non-invasive and sensitive method for evaluating the status of the autonomic nervous system of critically ill patients in the hospital setting. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Tetanus; Autonomic complications; Spectral analysis; Heart rate variability

1. Introduction

Tetanus is caused by the tetanus toxin secreted from the bacterium, Clostridium tetani. The toxin is a zinc endoprotease that cleaves vesicle-associated membrane protein (VAMP; or synaptobrevin). VAMP is one of the specific integral proteins of the synaptic vesicles (v-SNARES) and binds to target receptor proteins (t-SNARES) in the presynaptic terminal membrane [1]. Thus, the cleavage of the VAMP by the tetanus toxin blocks the synaptic transmissions and leads to characteristic symptoms, such as tetanic contraction of muscle groups or ‘trismus’ and generalized convulsions. The incidence and mortality of tetanus have declined dramatically with the advent of toxoid vaccination and effective antibiotics.

The clinical manifestations of tetanus, like those of a variety of other neurological disorders, may be dominated by manifestations of autonomic nervous systems (ANS) dysfunction, i.e. hypertension (or hypotension in some cases) with unstable blood pressure, tachycardia, and excessive sweating [2]. Such ANS complications in tetanus have been thought to result from hyperactivity of the sympathetic nervous systems (SNS) [3]. However, the absolute activities of SNS and parasympathetic nervous systems (PNS) have not been well investigated.

Spectral analysis of heart rate variability (HRV) has been widely used for ANS evaluation. It has been widely used in adults in cases of myocardial infarction to evaluate the function of the cardiac autonomic nerves [4]. In the field of pediatrics, insulin-dependent diabetes mellitus [5–7], Guillain–Barré syndrome [8] and Duchenne congenital muscular dystrophy [9,10] are among a variety of disorders in which the status of the ANS has been investigated by this method.

Here, we report a case of tetanus with severe ANS complications. Spectral analysis of HRV determined that there was decreased activity of both the SNS and PNS and that the impairment of the PNS was the more severe. Serum
catecholamine levels were normal. We conclude that the SNS symptoms in the present case are attributable to a relative predominance but not to the absolute hyperactivity of the SNS.

2. Materials and methods

2.1. Clinical profile of the patient

The patient, an 11-year-old male, was the product of an uneventful pregnancy and delivery, with subsequent normal development. There were no major past illnesses, although he had experienced what was considered to be a simple febrile convulsion in the past. For this reason, upon the advice of his local medical doctor, he had not received the diphtheria, tetanus, and pertussis (DTP) vaccine.

His presenting illness had been preceded by cough and rhinorrhea, and within 3 days, he started complaining of pain below his ears and noted difficulty in opening his mouth and swallowing solid foods. A local medical doctor diagnosed a common cold and prescribed cefaclor. However, the cough and difficulty in opening his mouth became progressively worse over the following few days and he was admitted to the local hospital. There, on the following day, he developed opisthotonic posturing, aggravated by sensory stimuli such as the sound of footsteps. The opisthotonic posturing on occasion was followed by generalized convulsions. Magnetic resonance imaging, electroencephalogram (EEG) and cerebrospinal fluid were all negative.

He was diagnosed as having tetanus with the diagnosis based upon the clinical presentation, i.e. signs/symptoms and remarkable past history of not having the DTP vaccination. There was no history of recent injury. Moreover, the examination disclosed no evidence of a prior physical injury which would have resulted in tetanus infection. It has been reported that 7–23% of cases with tetanus did not show any apparent source to account for tetanus infection [11].

Anti-tetanus toxoid immunoglobulin was immediately given (1000 IU, i.m.). The titer of anti-tetanus antibody before anti-toxoid immunoglobulin was below the sensitivity of detection. Cultures of blood for C. tetani and other bacteria were negative. The patient was transferred to the Pediatric Service of Keio University Hospital for intensive care. Initially, he was administered pancuronium bromide, vecuronium bromide and morphine, but without achieving the desired level of muscle relaxation and sedation. Generalized convulsions and trismus were ultimately controlled by thiopental sodium given intravenously, and he was sustained with mechanical ventilation. Antibiotics (ampicillin, cefotaxime sodium) were started.

Tachycardia (150/min) and excessive sweating were conspicuous despite normal body temperature. On the 5th day in the hospital, he also developed hypertension (systolic 150–170 mmHg/diastolic 90–100 mmHg) without circadian variation. Calcium channel blockers (nifedipine, nicardipine hydrochloride), a β-blocker (propranolol hydrochloride), dantrolene sodium, anesthetics (thiopental sodium, midazolam), and opiates (fentanyl citrate, morphine hydrochloride) were relatively ineffective in controlling these SNS manifestations. An electrocardiogram (ECG) on the 3rd day in the hospital showed prolonged QT intervals (0.50 ms, corrected for heart rate), which suggested that there might be a SNS/PNS imbalance early in the course of the present case.

On the 73rd day in the hospital, he suddenly had a cardiac arrest, thought at the time to be consequent to obstruction of his airway by secretions. Cardiopulmonary resuscitation was successful; the heart rate recovered within 10 min and cerebral anoxia was thought to be minimal. An EEG showed occasional spikes at the occipital lobe and a small dose of phenobarbital sodium was started. An echocardiogram after the cardiac arrest revealed normal ventricular contraction. After this event, he was no longer hypertensive, but tachycardia and excessive sweating persisted. Cardiac Holter monitoring for the spectral analysis of HRV was undertaken over 24 h on the 122nd day in the hospital.

2.2. Evaluation of autonomic nervous activities by spectral analysis of heart rate variability

The nomenclature of terms and standardized method of measurement for spectral analysis of HRV have been described in detail elsewhere [12–14] and, thus, will be only briefly summarized here. The heart rate oscillates continuously under the influence of ANS activity. Thus, oscillation of the heart rate is considered to be a reliable index of the balance of SNS and PNS activities. The frequency domain of the heart rate tachogram in the HRV spectrum obtained by fast Fourier transformation has three main components. These are high frequency (HF), low frequency (LF), and very low frequency (VLF) components. It has been established that the oscillation of HF corresponds to PNS activity, that of LF to both SNS and PNS activities, and the LF/HF ratio to SNS activity. A biological significance of VLF remains to be determined.

A 24 h ECG recording was obtained with a Holter ECG recorder (GE Marquette 8500) and analyzed by GE Marquette Laser SXP. The frequency-domain indices, HF power (0.15–0.40 Hz, ms²) and LF power (0.04–0.15 Hz, ms²), were computed with fast Fourier transformation on each 2 min segment of the recording.

3. Results

The results of the spectral analyses of HRV are shown in Fig. 1. Fig. 1A shows a normal circadian rhythm in activities of SNS and PNS observed in an age-matched boy. It is obvious that the activities of both the SNS and PNS were diminished in the present case (Fig. 1B), with the reduction in PNS activity being more profound than that in SNS activ-
ity (Fig. 1C). Serum catecholamines (adrenaline, noradrenaline, dopamine) on the 121st day in the hospital (the day before HRV analysis) were normal (Table 1).

4. Discussion

The tetanic state of muscle contraction and generalized convulsions associated with *C. tetani* infection typically respond to aggressive administration of muscular relaxants and mechanical ventilations in the acute hospital setting with intensive care support. Underlying dysfunction of the ANS may not be suspected or assessed, however, and potentially life-threatening dysfunction of the ANS may not receive satisfactory management.

Hyperactivity of the SNS may be a critical component of the *C. tetani* infection and may underlie such typically prominent manifestations as hypertension, tachycardia and excessive sweating. Corroborating evidence has included elevation in catecholamine concentrations [15–18]. Experiments in guinea pigs or rats showed that the C-fragment of the tetanus toxin injected into the medial gastrocnemius muscle is concentrated within the terminal varicosities of the pre- and paravertebral sympathetic ganglia at thoracolumbar levels [19]. These observations that the tetanus changes the concentrations of catecholamines or that the tetanus toxin is involved in ANS suggest that the toxin may accelerate catecholamine release resulting in the SNS hyperactivity observed in tetanus.

The prolonged QT interval observed early in the clinical course of the present case is suggestive of dysfunction of the ANS, which may have been consequent to *C. tetani* infection itself. On the other hand, the normal serum levels of catecholamines observed later in the course require that some other mechanisms must be invoked to account for the apparent SNS hyperactivity in this and presumably other cases of tetanus.

The findings with spectral analysis of HRV suggest a candidate mechanism which could have induced SNS symptoms despite normal levels of serum catecholamines. That is, spectral analysis of HRV identified a SNS to PNS relative imbalance. Whereas the levels of activity of both systems, in so far as they modulate cardiac rhythm, were decreased, that of the PNS was relatively reduced in comparison with that of the SNS (Fig. 2, right). In other words, it is not the absolute level of activity of the ANS which must be considered, but rather the relative balance of activity of SNS and PNS in order to establish optimum therapy in the face of ANS dysfunction (Fig. 2). HRV analysis was conducted on day 122 which was 49 days after the cardiac arrest. Therefore, the apparent impairment in the status of the ANS in the present case may or may not be a direct consequence of tetanus infection. For example, protracted illness and/or cardiac arrest may have contributed to the abnormal ANS status. Be that as it may, HRV was proven to be a powerful tool to elucidate an atypical pattern of ANS abnormality in the present case.

The SNS and PNS imbalance may have contributed in a variety of ways to the cardiac arrest which occurred in the present case. These include the possibility that it lead to an increase in the viscosity of the airway secretions, or that it induced bronchial spasms, which in turn lead to respiratory tract obstruction. It may have provoked instability of blood pressure and/or cardiac arrhythmia resulting from prolonged QT intervals, recorded early in the clinical course by ECG. In this regard, the HRV analysis should have been

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**Table 1**

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<th>Adrenaline</th>
<th>Noradrenaline</th>
<th>Dopamine</th>
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<tr>
<td>Present case</td>
<td>0.03</td>
<td>0.28</td>
<td>&lt;0.02</td>
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<tr>
<td>Normal values</td>
<td>&lt;0.17</td>
<td>0.15–0.57</td>
<td>&lt;0.03</td>
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* Measured in ng/ml.
performed early in the course, which could have given an indication of severe cardiovascular complications in the present case.

Although successful control of ANS symptoms with morphine or fentanyl has been reported in cases of tetanus [17,20,21], ANS symptoms of the present case were relatively resistant to these medicines. Thus, apparently, the effectiveness of these treatments is variable among cases with tetanus. We infer that the unresponsiveness of ANS symptoms to treatment in our case was partly due to the fact that both SNS and PNS activities were declined.

It is plausible that the risk of serious cardiovascular complications in neurological diseases is high under such conditions where the overall activity of the ANS is reduced and the system is not fully operable to maintain homeostasis. Thus, an easy-to-perform, reliable and semi-quantitative method for the evaluation of the ANS function is vital for management of systemic neurological disorders, especially in the prediction of unexpected serious complications. Further, a separate but simultaneous evaluation of the SNS and PNS function is desirable for the reasons described in the foregoing paragraph.

5. Conclusions

We have reported a case of tetanus with severe ANS complications. The results of the spectral analysis of HRV suggest that: (1) both SNS and PNS activities were suppressed; and (2) SNS symptoms (tachycardia and excessive sweating) in our case are attributable to the relative predominance of SNS activities. It is inferred that resistance of ANS symptoms to treatment was partly due to the diminished activities of both SNS and PNS. Spectral analysis of HRV is an easy, real-time tool for a reliable evaluation of the ANS status.

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