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2 **Gastric myoelectrical activities in elderly severe tetanus:**  
3 **useful marker to increase volume and calorie of**  
4 **nasogastric tube feeding**  
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19 Short title: EGG data and feeding in tetanus  
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21 **Abbreviations**

22 NTF: nasogastric tube feeding; EGG: electrogastrogram; cpm: cycles/minute  
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**26 Abstract**

27 Background & Aims: Early high nasogastric tube feeding (NTF) is effective for  
28 improving the nutritional status of critical illness. However, potential complications of  
29 NTF in tetanus include aspiration pneumonia because of dysphagia and gastrointestinal  
30 dysfunction induced by over-activity of autonomic nervous system. Methods: We  
31 serially evaluated gastric myoelectrical activities using electrogastrogram (EGG)  
32 recorder in 4 elderly severe tetanus patients, and assess its potential as a marker to  
33 increase volume and calorie of NTF. Results: Although dominant frequencies of EGG  
34 in all patients ( $1.8 \pm 0.6$  cycle/min (cpm)) were lower than those in healthy volunteers  
35 ( $2.9 \pm 0.2$  cpm) at least until 12th hospital day, it tended to improve from 14-24th  
36 hospital day and reached the same levels in healthy volunteers at least until 28th  
37 hospital day. We transferred total NTF along their metabolic costs when the timing of  
38 dominant frequency tended to improve in each patient (17-24th hospital day). No  
39 aspiration pneumonia occurred, and they could be also prevented malnutrition in their  
40 hospital days. Conclusion: EGG data may be a useful marker to know the level of  
41 over-activity of autonomic nervous system and to guess the best timing to increase  
42 volume and calorie of NTF especially in elderly severe tetanus.

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**44 Key words**

45 tetanus; nasogastric tube feeding (NTF); electrogastrogram (EGG); gastric  
46 myoelectrical abnormalities; autonomic nervous activities

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## 54 **Introduction**

55           Early high nasogastric tube feeding (NTF) initiation is well tolerated, and  
56 effective for improving the nutritional status of critical illness <sup>1,2</sup>. However, it is very  
57 difficult to guess the best timing to increase the volume and calorie of the feeding in  
58 patients with tetanus. Tetanus is now a rare disease in developed world. However, it  
59 remains an important cause of death worldwide and is associated with a high case  
60 fatality, particularly in the developing world <sup>3</sup>. Mortality from tetanus is as high as  
61 45% <sup>4</sup>. Especially, a total of 75% of deaths occur within the first week because of  
62 aspiration or pulmonary infection in these patients. In addition, the oral sensorimotor  
63 function for feeding in tetanus is severely compromised <sup>5</sup>. Moreover, it is well known  
64 that gastrointestinal dysfunction induced by over-activity of the autonomic nervous  
65 system, such as abdominal bloating and constipation with the development of paralytic  
66 ileus, affects the prognosis of the patients <sup>6</sup>. These symptoms often disturb the  
67 successful enteral feeding. Thus, physicians need to be aware of special needs  
68 concerning the feeding in patients with tetanus.

69           Recently, electrogastrogram (EGG) has received attention as a useful  
70 non-invasive tool for gastric functional testing <sup>7</sup>. Numerous EGG studies have been  
71 performed in several gastric disorders, such as functional dyspepsia, achalasia,  
72 Parkinson's disease, multiple system atrophy, familial amyloidotic polyneuropathy and  
73 diabetic gastropathy <sup>8-12</sup>. However, EGG study in tetanus has not been performed yet.

74           In this study, we evaluated gastric myoelectrical activities quantitatively in  
75 severe tetanus using cutaneous EGG during the course of illness, and assess its potential  
76 as a marker to increase the volume and calorie of NTF in these patients.

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## 81 **Subjects and methods**

### 82 **(1) Subjects**

#### 83 **1) Patients**

84 Four elderly severe tetanus patients (2 men and 2 women, mean age  $83 \pm 8.3$   
85 years old) who had been investigated at Arao City Hospital and Kumamoto University  
86 Hospital, Japan from April 2003 to November 2009 were available for the study (Table  
87 1). Although blood cultures were negative for *Clostridium tetani* in these patients, we  
88 diagnosed from the clinical manifestations, such as difficulty in opening mouth,  
89 opisthotonic posturing followed by generalized convulsion, tachycardia, and severe  
90 hypertension. Anti-tetanus toxoid immunoglobulin, antibiotics, mechanical  
91 ventilation, anesthetics, muscle relaxants, and antihypertensive drugs were used in all  
92 patients during the course of illness. However, all patients did not receive a  
93 percutaneous endoscopic gastrostomy for enteral nutrition because of their severe  
94 gastrointestinal dysfunction induced by over-activity of the autonomic nervous system.

#### 95 **2) Controls**

96 As control group, we recruited 4 healthy subjects (2 men and 2 women, mean  
97 age  $74 \pm 7$  years old) who had no medication and no symptoms of cardiovascular or  
98 autonomic disorders.

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### 100 **(2) Initial feeding**

101 We initiated 1,640 kcal/day of parenteral nutrition and 400-800 ml (0.4  
102 kcal/ml) of NTF immunonutrition in each patient from their 1st hospital day.

103

### 104 **(3) Data collection**

#### 105 **1) EGG measurements**

106 We serially evaluated gastric myoelectrical activity using a portable  
107 four-channel EGG recorder (Nipro EG; Nipro, Japan) from 1st to 28th day after

108 hospitalization for all patients. Five surface electrodes (Vitrode J; Nihon Kohden,  
109 Japan) were placed on the abdominal skin surface. The EGG data were analyzed using  
110 EGS2 Ver.1.31 software (Gram, Japan). Two-hour segments from 9:00 to 11:00 were  
111 assessed, and we compared with the gastric slow wave between tetanus patients and  
112 healthy controls. All subjects were studied after more than 6 hours fast. In addition,  
113 we performed power spectral analysis for each patient's EGG segment using a fast  
114 Fourier transform with an analysis range 1.0 to 6.0 cycle/min (cpm). The frequency at  
115 which the overall power spectrum displayed peak power in the range 2.0 to 4.0 cpm was  
116 defined as the dominant frequency. The frequency ranges were classified into low  
117 (1.0–2.0 cpm), normal (2.0–4.0 cpm), and high (4.0–6.0 cpm) frequency ranges. We  
118 calculated the ratios of low frequency range, normal frequency range, and high  
119 frequency range components as percentages of total power. As movement artifacts  
120 and noises from various sources can result in abdominal frequency spectra with  
121 significant power in the low-frequency and high-frequency range in EGG<sup>13,14</sup>, our  
122 patients were placed in dark, soundproofed rooms after diagnosing tetanus. In addition,  
123 mechanical ventilation was initiated with a muscle relaxant and anesthetics to avoid  
124 opisthotonic posturing in these patients.

## 125 **2) Nutritional status**

126 Percent change in body weight and serum albumin level for each patient  
127 compared with 1st to 28th day after hospitalization were used to evaluate their  
128 nutritional status.

## 129 **3) Complications and managements**

130 Complications, such as dysphagia, vomiting, abdominal bloating, paralytic  
131 ileus, and aspiration pneumonia, were recorded according to the timing of its occurrence.  
132 Duration of mechanical ventilation and changes of feeding were also recorded.

133

## 134 **(4) Statistical methods**

135 All data are expressed as mean  $\pm$  SD. Differences between groups were  
136 analyzed by Mann-Whitney U test. Statistical significance was considered when  
137  $p < 0.05$ .  
138

## 139 **Results**

### 140 **1. EGG measurements**

141 All 4 tetanus patients showed irregular gastric slow wave, and their dominant  
142 frequencies of EGG in all tetanus patients ( $1.8 \pm 0.6$  cpm) were lower than those in  
143 healthy volunteers ( $2.9 \pm 0.2$  cpm) at least until 12th hospital day (Figure 1). At that  
144 time, the ratio of low frequency range in all patients was significantly higher than those  
145 in healthy controls ( $p < 0.01$ , Figure 2A), and the ratio of high frequency range in all  
146 patients was significantly lower than those in healthy controls ( $p < 0.05$ , Figure 2C).  
147 However, the dominant frequency tended to improve from 17th hospital day, and  
148 reached the same levels in healthy controls at least until 28th hospital day in all patients  
149 (Figure 1).

150

### 151 **2. Feeding and nutritional status**

152 We transferred total NTF when the timing of dominant frequencies tended to  
153 improve (more than 2.6 cpm) in each patient (17-24th hospital day). At least until 28th  
154 hospital day, 2,250-2,450 ml (0.8 kcal/ml) of NTF nutrition was administered in all  
155 patients. Moreover, all 4 patients could prevent the decrease of body weight during 28  
156 hospital days, and their serum albumin levels of 28th hospital day were not also  
157 decrease compared with those of 1st hospital day (Table 2).

158

### 159 **3. Complications and prognosis**

160 Although abdominal bloating and/or constipation with the development of  
161 paralytic ileus were shown at least until 10th hospital day in all 4 patients, no vomiting  
162 and aspiration pneumonia occurred during the course of illness except for Case 2, who  
163 already contacted aspiration pneumonia before admission (Table 2). Mechanical  
164 ventilation could be weaned smoothly in all patients, and they were all discharged from  
165 our hospital to start dysphagia rehabilitation at least by 45th hospital day.

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## 167 **Discussion**

168           This is the first report to demonstrate the changes in gastric myoelectrical  
169 activities in patients with severe tetanus throughout the course of illness.

170           In elderly tetanus, at least 80% of cases are the generalized form <sup>15</sup>. The  
171 prognosis of these patients mainly depends on how effectively the spasm can be  
172 managed and lethal complications, such as aspiration pneumonia and malnutrition,  
173 prevented <sup>16</sup>. Beale, et al. reported that early tube feed pharmaconutrition and  
174 immunonutrition, results in significantly faster recovery of organ function in patients  
175 with severe infectious diseases, compared with disease control patients <sup>1</sup>. But on the  
176 other hand, Emilia, et al. reported that mortality after NTF initiation was high, mainly  
177 due to infectious complications and refeeding syndrome <sup>17</sup>. Moreover, Charvát et al.  
178 reported that 18% of the patients admitted to intensive care unit with life threatening  
179 disease and indication for enteral nutrition had to be replaced for parenteral one due to  
180 complications <sup>2</sup>. In this study, we lead successful outcomes of NTF in all patients.  
181 We could prevent the complications, such as vomiting, aspiration pneumonia,  
182 malnutrition, and refeeding syndrome, using EGG data to guess the best timing to  
183 increase volume and calorie of the feeding. Moreover, mechanical ventilation could be  
184 weaned at the best time to avoid ventilation complications and started physical  
185 rehabilitation as fast as possible in these patients, because the changes in EGG data  
186 constantly preceded the variations in clinical manifestations. These results suggest  
187 that the knowledge regarding this technique may facilitate the next step for considering  
188 a suitable treatment throughout the course of illness.

189           Many factors influence gastric electroactivity and motility, such as  
190 medications, gastric emptying, aging, activity of the autonomic nervous system,  
191 particularly the parasympathetic vagus nerve, and enteric peptides <sup>18-22</sup>. All our  
192 patients were administrated anti-hypertensive drugs, anesthetics for mechanical  
193 ventilation, and muscle relaxants for opisthotonic posturing throughout the course of



194 illness. However, gastric myoelectrical abnormalities appeared in these patients not  
195 only after but also before starting these drugs. Thus, the effects of medications may be  
196 limited. As we initiated 400-800 ml (0.4 kcal/ml) of NTF immunonutrition in each  
197 patient from their 1st hospital day, all patients did not show gastric emptiness  
198 throughout the course of illness. These findings suggest that aging and over-activity of  
199 the autonomic nervous system caused by tetanus are more closely related to  
200 abnormalities of gastric myoelectrical activities in those patients. Thus, EGG may also  
201 be a helpful tool to diagnose tetanus in a very early stage and to quantify the  
202 progression and disease severity.

203 EGG technique, measuring electrical waves in the stomach muscle wall, is  
204 theoretically usable in combination with other examination, such as gastric reflux  
205 monitoring or measurement of residual gastric volume <sup>7</sup>. However, as these methods  
206 are invasive, we could not try the tests in our severe patients. On the other hand, EGG  
207 is a non-invasive tool. Thus, we only evaluated gastric myoelectrical activities using  
208 cutaneous EGG during the course of illness in this study.

209 In conclusion, EGG data may be a useful marker to know the level of  
210 over-activity of the autonomic nervous system and to guess the best timing to increase  
211 volume of NTF especially in elderly severe tetanus.

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### 213 **Conflict of interest statement**

214 All authors of the manuscript have no conflict of interest.

215

### 216 **Statement of authorship**

217 Obayashi K was responsible for data collection, data interpretation and  
218 manuscript writing and reviewing.

219 Ueda M, Yamashita T, Misumi Y, Hirahara T, Tasaki M, and Ohshima T  
220 were responsible for patients' evaluation and data collection.

221           Uchino M and Ando Y were responsible for manuscript writing and  
222 reviewing.

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309 **Figure Legends**

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311 Figure 1 Changes in dominant frequencies of EGG during the course of illness

312 A: Case 1, B: Case 2, C: Case 3 and D: Case 4

313 Open circle: The data of healthy controls (n = 4, mean  $\pm$  SD)

314 Figure 2 Comparison with two-hour segments averages for dominant frequency

315 between 4 tetanus patients in 12<sup>th</sup> hospital day and 4 healthy controls

316 A: Ratio of low frequency range components as percentages of total power

317 B: Ratio of normal frequency range components as percentages of total power

318 C: Ratio of low frequency range components as percentages of total power

319 The data were collected from 9:00-11:00. All subjects were studied after more than 6

320 hours fast.

321 \* P < 0.05, \*\* P < 0.01