The fact that patients with Parkinson’s disease (PD), suffer frequently from a variety of gastrointestinal (GI) symptoms initiated studies of GI motility utilizing various methods applied to different parts of the alimentary tract.

Indeed, in the last few years it was shown that in addition to slow gastric emptying and decreased gastric motility, there is impaired gastrointestinal motility in Parkinson’s disease may affect absorption of levodopa and contribute to the disabling response fluctuations (RF). In this study gastric myoelectric activity was recorded with electrogastrography in patients with PD and correlated with the duration, severity and the presence of RF. Method: Electrogastrography (EGG) was performed in 36 patients with PD of which 22 were men. The mean age was 67 years (48-81), mean duration of disease was 7.07 years (1-20), and mean duration of treatment with levodopa was 5.07 years (1-20). Gastric dysrhythmia was diagnosed when either preprandial or postprandial dysrhythmia for more than 30% of the recording period was detected. Results: The EGG was abnormal in 24 of 36 patients. Significant association was found between preprandial dysrhythmia and duration of disease (P=0.002); duration of levodopa treatment (P=0.003), severity of 86RF (P=0.001), but not with age (P=0.076). Out of 18 patients with RF, 17 had at least one pattern of dysrhythmia. In 11 out of the 18 patients without RF, the EGG was normal while the remaining seven had at least one pattern of dysrhythmia. Conclusion: Abnormal EGG was quite common in this group of patients with PD, particularly in those with RF. The most common pattern of abnormality was preprandial dysrhythmia, which was positively associated with disease duration and length of levodopa treatment. Although frequently asymptomatic, preprandial dysrhythmia leading to impaired gastric emptying may contribute to irregular absorption of levodopa from the small intestine and contribute to disabling response fluctuations.

RÉSUMÉ: L’électrogastrographie chez les patients atteints de la maladie de Parkinson. Introduction: Une altération de la motilité gastro-intestinale dans la maladie de Parkinson (MP) peut perturber l’absorption de la lévodopa et contribuer aux fluctuations motrices (FM) observées. Dans cette étude, l’activité myoelectrique gastrique a été enregistrée au moyen de l’électrogastrographie (ÉGG) chez des patients atteints de MP et les données recueillies ont été corréllées à la durée, à la sévérité et à la présence de FM. Méthode: Trente-six patients, 22 hommes et 14 femmes, atteints de MP ont subi une ÉGG. L’âge moyen des patients était de 67 ans (48 à 81 ans), la durée moyenne de la maladie était de 7,07 ans (1 à 20 ans) et la durée moyenne du traitement par la lévodopa était de 5,07 ans (1 à 20 ans). On posait un diagnostic de dysrhythmie gastrique quand l’enregistrement démontrait une dysrhythmie pendant 30% ou plus de la période d’enregistrement, soit en période préprandiale ou postprandiale. Résultats: L’ÉGG était anormal chez 24 des 36 patients. Une association significative a été observée entre la dysrhythmie préprandiale et la durée de la maladie (p = 0,002), la durée du traitement par la lévodopa (p = 0,014), la sévérité de la FM (p = 0,047). Aucune association avec l’âge n’a été observée (p = 0,1). Parmi les 18 patients ayant des FM, 17 avaient des signes de dysrhythmie. Chez 11 des 18 patients sans FM, l’ÉGG était normal alors que les 7 autres avaient des signes de dysrhythmie. Conclusion: Un enregistrement ÉGG anormal était fréquemment observé dans ce groupe de patients atteints de la MP, particulièrement chez ceux qui ont des FM. Le tableau le plus fréquent était une dysrhythmie préprandiale associée de façon positive à la durée de la maladie et du traitement par la lévodopa. Bien qu’elle soit fréquemment asymptomatique, la dysrhythmie préprandiale entraînant une altération de la vidange gastrique peut contribuer à une absorption irrégulière de la lévodopa au niveau de l’intestin grêle et contribuer aux FM invalidantes.
also decreased motility of the colon. This abnormal intestinal motility in PD may be caused by the fact that neuronal Lewy bodies are present in the myenteric plexus throughout the GI tract. This may imply that neurodegeneration affects not only nigral neurons but also myenteric plexus neurons. Although some investigators claim that many GI symptoms are caused by drugs used for PD, it was clearly shown that except for disordered defecation there is no correlation between GI symptoms and drug treatment. However, GI symptoms could be correlated with disease severity.

The study of gastric emptying in PD is of special interest since levodopa is absorbed from the proximal small intestine but not from the stomach. Nevertheless, gastric emptying controls the delivery of levodopa to its absorption site. Irregular slow emptying will result in erratic levodopa absorption, leading to fluctuations in levodopa plasma levels, which are believed to contribute to response fluctuations (RF) in PD.

Gastric motility can be evaluated by several methods. Ultrasound is a tedious test, requires dedicated examiners and is very time consuming. The barostat technique requires the insertion, into the stomach, of a balloon which is maintained at a constant pressure. When the stomach contracts the changes in the balloon’s volume, which are concomitant with gastric movements, are recorded. This method is invasive and not widely used. The “gold standard” for measuring gastric emptying is gastric scintigraphy. The patient is given a meal containing a radioactive isotope and the rate of decline of gastric radioactivity, as the stomach empties, is measured with a gamma camera. However, if gastric emptying is found to be delayed, it is impossible to determine with this method whether the patient suffers from gastroparesis or gastric outlet obstruction. Electrogastrography (EGG), on the other hand, can provide some insight into the mechanism underlying gastric dysmotility. This technique measures gastric electrical activity with abdominal wall surface electrodes.

Similar to the small intestine and the colon, the stomach has its own pacemaker. The gastric pacemaker, which is essential for rhythmic gastric contractions, discharges at a rate of three pulses per minute and is easily distinguishable from the intestinal pacemaker, which fires at a rate of 12 pulses per minute. The pacemaker cells are the interstitial cells of Cajal, which lie in an intermediate position between the gastric muscles and the neuronal plexus. The validity of EGG for recording gastric pacemaker activity was demonstrated by Hamilton, who simultaneously recorded from serosal and abdominal electrodes in dogs. The signals recorded from the skin were coupled with those recorded directly from the gastric serosa. It was also shown that the activity recorded from the abdominal wall muscles was easily distinguishable from gastric signals and could be efficiently filtered. Similarly, recordings from human volunteers with electrodes placed simultaneously over the skin and within the stomach disclosed that the signals recorded from the skin were identical to the gastric electrical activity.

Abnormal gastric myoelectrical activity, in the form of bradygastria, tachygastria or both, has a strong positive correlation with delayed gastric emptying as shown by scintigraphy. Both bradygastria and tachygastria seem to evoke the same disturbance in motility, and the same symptoms.

The aim of this work was to record the gastric myoelectrical activity with EGG in a group of patients with PD and to correlate the findings with duration of disease, duration of levodopa treatment and the presence of RF.

Materials and Methods

Subjects

Fourteen healthy subjects older than 60 years, without a history of abdominal surgery or usage of drugs affecting gastrointestinal motility were recruited from the “Friends of Meir Hospital Voluntary Association” and served as controls. There were 11 women and three men with a mean age of 71±8 years.

Thirty-six consecutive patients with idiopathic PD from the PD outpatient clinic agreed to participate in the study. None of the patients had conditions known to influence gastric motility (diabetes mellitus, hypo- or hyperthyroidism, previous gastric surgery etc.). None took cholinergic drugs or drugs known to influence gastric motility. The mean age was 67 years (48-81), the mean duration of disease was 7.07 years (1-20 years). The mean duration of levodopa therapy was 5.07 years (1-20 years). Thirty-four patients received standard carbidopa/levodopa therapy (Dopica®, 25/250 MSD). The mean dose of levodopa per patient was 455 mg (187.5-1000). Two of the patients did not receive drug treatment. The Schwab and England ADL scale (SES), and the Hoehn and Yahr staging scale (H&Y) were evaluated in the clinic within one week of performing the EGG. All patients gave their informed consent and the institutional review board approved the study.

Electrogastrographic recording

All patients were off medications during the morning of the recording which was performed according to Levanon et al. Briefly, three silver chloride electrodes were placed over the abdominal wall to record the EGG. One was positioned along the midsclavicular line below the left rib margin, one equidistant between the xiphoid process and the umbilicus. It is from these two electrodes that data were obtained. The reference electrode was positioned at the right upper quadrant along the line formed by the other two electrodes. All patients had their last meal and drug intake during the evening prior to the recording which was performed during the morning hours. Sixty minutes of recording in the fasting state with an EGG digitrapper (Synectic medical Inc, Denmark), was followed by a test meal of two slices of bread, 50 gr white cheese and a cup of tea with sugar (250 Kcal). Then a second recording was obtained for additional 60 minutes. All recordings were taken at sampling frequencies of 4Hz. The recorded data were digitized and fed into a personal computer. Data were then reviewed manually by one of the investigators (T.N.), and motion artifacts were excluded. A normal recording with some motion artifacts is shown in Figure 1. A running spectral analysis of the dominant frequency was performed with a commercially available software program (Electrogastrogram Version 6.30, Gastrosoft Inc. Synectics Medical, Denmark).

The following parameters were analyzed according to Levanon et al.: 1. Dominant frequency (DF) in cycles per minute (cpm). This was expressed as the percentage of DF in the defined normal frequency of 2.4-3.6 cpm. Each recording was divided into...
two minute epochs and the DF was calculated for each epoch separately.
2. Bradygastria was defined as a DF slower than 2.4 cpm.
3. Tachygastria was defined when DF was 3.7-10 cpm.
4. Pre- and postprandial dominant frequencies were analyzed separately. A dominant frequency faster than 10 cpm was separated from tachygastria, because such high frequencies are believed to arise outside the stomach. The presence of either bradygastria or tachygastria was defined as gastric dysrrythmia.

An abnormal EGG was defined when the percentage of 2-4 cpm slow waves was less than 70% during either preprandial or postprandial period.18

**Statistical analysis**

Two tailed student t test was used for the analysis of the difference between patients with normal and pathological EGG. The test was also applied for the analysis of the differences between patients with and without RF with regard to disease duration, age, duration of treatment with levodopa, daily levodopa dose and the SES, and the H&Y. The association between RF and EGG results was calculated using Fishers exact test.

**Table 1:** Clinical characteristics of fluctuating and nonfluctuating patients. P values were obtained for the subgroups.

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Fluctuating</th>
<th>Non fluctuating</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>67 ±1.7 (48-81)</td>
<td>68.4 ±2.3 (49-80)</td>
<td>67.17 ±2.7 (48-81)</td>
<td>0.752</td>
</tr>
<tr>
<td>Duration of disease (y)</td>
<td>7.07 (1-20)</td>
<td>10.1 ±1.1 (5-20)</td>
<td>4.03±0.48 (2-8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Duration of treatment (y)</td>
<td>5.07±7.3 (1-20)</td>
<td>7.6±1.1 (1.5-20)</td>
<td>2.5 (0-5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean daily levodopa (mg)</td>
<td>455 (187.5-1000)</td>
<td>585 (350-1000)</td>
<td>325 (187.5-500)</td>
<td>NS</td>
</tr>
<tr>
<td>H&amp;Y</td>
<td>2.4 ±0.9</td>
<td>On: 2.95; Off: 4.05</td>
<td>1.97±0.8 (1-3)</td>
<td>NS</td>
</tr>
<tr>
<td>SES (%)</td>
<td>69.4±3 (30-100)</td>
<td>56±3.1 (30-70)</td>
<td>82.7±2.7 (60-100)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

(NS: non significant)

**Table 2:** EGG characteristics from patients with and without response fluctuations

<table>
<thead>
<tr>
<th>EGG features</th>
<th>Without fluctuations</th>
<th>With fluctuations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=18</td>
<td>N=18</td>
</tr>
<tr>
<td>Normal</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Abnormal</td>
<td>7</td>
<td>17</td>
</tr>
<tr>
<td>Preprandial dysrhythmia</td>
<td>3 (bradygastria)</td>
<td>4 (bradygastria, tachygastria)</td>
</tr>
<tr>
<td>Postprandial dysrhythmia</td>
<td>3 (bradygastria, tachygastria)</td>
<td>2 (bradygastria)</td>
</tr>
<tr>
<td>Both pre- and postprandial dysrhythmia</td>
<td>1 (pre- &amp; postprandial bradygastria)</td>
<td>11 (bradygastria, 2 tachygastria)</td>
</tr>
</tbody>
</table>
test. Differences were considered significant when P value was less than 0.05.

RESULTS

Of the 36 patients, 22 were men and 14 women. The mean H&Y score was 2.4 and the mean SES score was 69.4%. Half of the patients had RF. The even number of fluctuating and nonfluctuating patients was coincidental and not due to pre-selection. The pattern of fluctuations documented by the patient was “delayed on” (6), “no-on” (6), “end of dose” (12), and random “on-off” (8). The majority of patients reported more than one form of fluctuations and seven patients experienced frequent transient sudden freezing. The complexity of the different patterns of motor fluctuations made it impossible to further analyze EGG results according to different patterns of motor fluctuation. There were significant differences between the patients with and without RF. The fluctuating patients had a significantly longer disease duration, longer duration of levodopa treatment and worse daily functional impairment, as measured by the SES. However, severity as expressed by the H&Y score was greater in the patients with fluctuations only during the “off” period. The clinical characteristics of the whole group as well as those of the two subgroups (with and without RF) are shown in Table 1.

Significant dysrrythmia (DR) lasting more than 30% of the recording was present in 24 (66.6%) patients. Patients with DR had longer duration of disease (P=0.004) longer duration of treatment with levodopa (P=0.003) and more severe response fluctuation (P=0.001). No association was found between the presence of DR and age (P=0.7), or severity of disease as measured by the H&Y (P=0.3) and SES score (P=0.07). Pre- and postprandial DR were separately analyzed. Preprandial DR (PRD) was present in 18 of the 24 patients with abnormal EGG (75%). Two-tail t test for equality of means showed no significant association between PRD and age (p=0.076), but patients with PRD had longer duration of disease (p=0.002), more years of levodopa treatment (p=0.003), more severe response fluctuation (P=0.001) and more severe disease as measured by the SES (p=0.016). There was no association with disease severity as expressed by H&Y score (P=0.33).

Postprandial DR (POD) was present in 17 of the 24 patients with an abnormal recording (70.8%). It was not associated with age (P=0.79), duration of disease (P=0.42), duration of treatment with levodopa (P=0.35) or disease severity as measured by the H&Y or SES scores (P=0.36 and 0.07, respectively).

Of the 18 patients with RF, 17 (94%) had gastric DR. Four had only PRD, two had only POD and 11 had both. Of the 18 patients without RF, 11 had a completely normal EGG, three had PRD, three had POD and one had both (Table 2). Fisher’s exact test showed a strong association between pathological EGG and RF (P=0.001).

Despite the frequent EGG abnormalities, most patients had no gastrointestinal complaints that could be attributed to gastric dysrrythmia. The most frequent complaint was constipation (15 patients) which was followed by early satiety and abdominal swelling (five with PRD and two with normal EGG). Fourteen patients had no gastrointestinal symptoms.

All controls had a normal EGG as judged from the presence of normal 2.4-3.6 cpm slow waves during 86±10% of the preprandial and 88±9% of the postprandial recording time.

A normal and abnormal EGG is shown in Figure 2.

DISCUSSION

In this study a significant number of patients with PD had abnormal gastric pacemaker activity. Almost all patients with RF had an abnormal EGG in contrast to those without fluctuations. We used the SES and H&Y staging to measure disease severity. The H&Y staging concentrates on gait and motor ability, and may not reflect the full extent of the functional disability of a particular patient. The SES measures overall patient’s function and seems to be a more accurate measurement for the magnitude of the neurological functional impairment. Indeed, the SES scores were significantly associated with EGG abnormalities, whereas the association of the H&Y scores to EGG abnormalities did not reach statistical significance.

The statistical association between EGG proven gastric dysrhythmia, disease severity and duration, and especially the presence of RF may indicate that both striatongiral neurons and myenteric plexus ganglion cells are affected by the same neurodegenerative process responsible for PD.

It was frequently assumed that RF in PD is caused by fluctuations in serum levodopa as a result of impaired intestinal

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Figure 2: left: Normal EGG: preprandial and postprandial period. The dominant frequency is 3 cycles per minute. Right: pathological EGG, with predominant bradygastria
absorption. Although levodopa is rapidly absorbed from the small intestine, irregular gastric emptying due to abnormal activity of the gastric pacemaker may cause irregular delivery of levodopa to its site of absorption. This can result in irregular plasma levels of levodopa and thus explain in part the phenomena of RF. Indeed, by bypassing the stomach either with parenteral administration, or duodenal infusions of levodopa, it was possible to “smoothen” the RF.

Previous studies of gastric emptying in patients with RF lacked uniformity as to the state of motor performance (either “on” or “off”). Djaldetti et al. found slow gastric emptying during the “off” state. Hardoff et al. reported recently that gastric emptying was faster during the “on” state while in non-fluctuating patients it was slower than in controls.

Considering the findings of the present study and the relative simplicity of EGG recording it might be of interest and possible clinical benefits to tailor the timing of levodopa administration according to the EGG pattern in patients with RF.

ACKNOWLEDGEMENT

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REFERENCES