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Research paper

Autonomic dysfunction of gastric motility in major depression

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ABSTRACT

Background: Patients suffering from major depressive disorder (MDD) often complain about somatic symptoms. Cardiac complaints have been examined predominantly. However, gastrointestinal complaints are also reported frequently and are associated with worse outcomes. The research concerning changes in gastric motility of these patients is rather sparse. The aim of our study was to determine dysfunction of gastric motility and gastrointestinal symptoms in MDD. The duration and severity of MDD were examined regarding its influence over gastric emptying.

Methods: Gastric emptying was determined by a ^{13}C-acetate breath test in patients with MDD (n = 29) and healthy control subjects (n = 51). Prior to this, depressive illness was operationalized using external and self-assessment scales (HAMD-21, MADRS, BDI, CGI). Whether the severity or duration of MDD influenced the gastric emptying parameters was examined using Spearman's correlation. In addition, autonomic complaints were recorded by means of an ANS score. Each ANS score item was determined using a Mann-Whitney U or Kruskal-Wallis test concerning the gastric emptying parameters.

Results: There was a significant difference in the parameters of the maximum gastric emptying rate (T_{max}) and gastric half emptying time $T_{1/2b}$ between patients with MDD and healthy control subjects (T_{max} 66.21 min vs 53.35 min, $p < 0.006$, $T_{1/2b}$ 207.59 min vs 133.27 min, $p < 0.005$).

There was a significant negative correlation between T_{max} and the severity of MDD determined with the depression rating scales BDI (Spearman's rank − 0.521, p = 0.013) and HAMD-21 (r − 0.384, p = 0.048).

No correlation was found between the duration of MDD and the maximum gastric emptying rate (r − 0.125, p = 0.519) and gastric half emptying time (r − 0.62, p = 0.749).

Conclusion: Gastrointestinal motility is significantly impaired in patients with MDD compared to healthy control subjects. Autonomic complaints were indicated frequently in MDD patients. The duration of MDD had no influence over the time of gastric emptying. There was a significant negative correlation between the severity of MDD and T_{max}, indicating that the T_{max} was reached earlier with the progression of MDD. The slowing of gastric motility in MDD patients is likely a result of a dysfunction of the autonomic nervous system.

1. Introduction

Patients with major depressive disorder (MDD) often complain about somatic symptoms (Bekhuis et al., 2015; Haug et al., 2004; Kroenke et al., 1997; Schmidt et al., 2014). Such complaints may even be the main reason for the initial visit to the primary care physician (Kirmayer et al., 1993; Tylee et al., 2005). Moreover, gastrointestinal symptoms are strongly related to depression and anxiety disorders (Haug et al., 2002).

Somatic complaints are also evaluated in established questionnaires on depressive symptoms, for example, the Hamilton Depression Scale-21 (HAMD-21) (Hamilton, 1960). The etiology of somatic components has not been clarified definitively, despite having been the subject of several studies. Several authors assume that somatic events can be

Abbreviations: AAP, atypical antipsychotics; AD, antidepressant; ANOVA, analysis of variance; ANS-score, Autonomic Nervous Symptom-score; BDI, Beck Depression Inventory; CGI, Clinical Global Impression; DOB, "Delta over Baseline"; EGG, Electrogastrogram; GEC, Gastric Emptying Coefficient; HAMD-21, Hamilton Depression Scale-21; MADRS, Montgomery Asberg Depression Scale; MDD, Major depressive disorder; NDIRS, non-dispersive infrared spectroscopy; NDRI, norepinephrine–dopamine reuptake inhibitor; PD, Parkinson's disease; SSRI, selective serotonin reuptake inhibitor; SNRI, selective noradrenalin reuptake inhibitor; TCA, Tricyclic antidepressants

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attributed to an imbalance within the vegetative nervous system, with an increase in the sympathetic and a decrease in the parasympathetic modulation (Guinjoan et al., 1995; Jangpangi et al., 2016; Yeragani et al., 2002).

Changes in gastrointestinal motility have been less studied in patients with MDD.

Studies evaluating gastric motility during MDD using an electrogastrogram (EGG) showed a change in the myoelectric activity of the stomach (Quick et al., 2010; Ruhland et al., 2008).

In addition, studies investigating the appearance of somatic complaints as a predictive factor within depressive patients have shown that the presence of somatic symptoms is linked to a worse outcome of the depressive illness (Bekhuis et al., 2016; Hung et al., 2010; Novick et al., 2013).

Novick et al. (2013) found indications that somatic complaints are associated with a higher severity of depressive illness.

The aim of the present study was to measure gastric motility using a ^{13}C-acetate breath test in patients with MDD compared to healthy control subjects. Patients with MDD were separated in two groups with and without gastrointestinal complaints to investigate whether changes in gastric motility cause these symptoms. In addition, whether the duration or the severity of MDD has an influence on gastric motility was investigated.

2. Methods

2.1. Study population

A ^{13}C-acetate breath test was performed on 29 patients with MDD and 51 healthy control subjects. All patients were treated in the Department for Affective Disorders in our institution and fulfilled the criteria for MDD as per the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-V) diagnostic code. Patients with additional psychiatric illness or with a severity of MDD that prevented the conduct of the test were not included in the study. Healthy control subjects were hospital employees, medical students and other volunteers, free of psychiatric illness or comorbidities.

Exclusion criteria were the presence of gastrointestinal tract illness or other extra-intestinal illnesses that would influence gastrointestinal motility, for example, diabetes mellitus (Hasler et al., 2007; Soykan et al., 1998), intake of any medication that results in a noticeable change in gastric emptying, for example, erythromycin (Matsumoto et al., 2008; Rozov-Ung et al., 2015; Viramontes et al., 2001), as well as after operations on the gastrointestinal tract (Dirksen et al., 2013; Soykan et al., 1998), except for appendectomy or cholecystectomy.

Pregnant or breastfeeding women were also not included due to proven gastric motility dysfunction (Koch et al., 1990). Individuals suffering from modest or severe extra-intestinal comorbidities were also not included.

Table 1 shows the demographic and clinical characteristics of both groups.

In addition to antidepressants, some patients with MDD took other prescription drugs, including Allopurinol 1/29, Candesartan 1/29, Carbamazepine 1/29, Diclofenac 1/29, Enalapril 2/29, Enoxaparin 1/29, Etoricoxib 1/29, Hydrochlorothiazide 1/29, Ibuprofen 2/29, Loratadine 1/29, Metamizole 2/29, Metoprolol 1/29, Pantoprazole/Omeprazole 4/29,

Phenprocoumon 1/29, Pregabalin 1/29, Simvastatin 1/29, Thiamine 1/29 and Zopiclon 1/29. The study protocol was approved by the ethics committee of the medical faculty of the Ruhr-University Bochum before the experiments (Registration no. 3660-10). Written informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki.

Table 1
Baseline characteristics of patients and controls.

Characteristics	Value patients	Value controls
Number	29	51
Male/Female	19/10	24/27
Mean age, y ± SD	40.3 ± 13.9 (21–69)	34.9 ± 11.8 (20–61)
BMI ± SD	26.9 ± 6.3	24.3 ± 3.2
Smoker	12/17	18/33
Alcohol	10/19	8/43
Illicit Drugs	0/29	0/51
SSRI	9/29 (31)	0/51 (0)
SNRI	10/29 (34)	0/51 (0)
TCA	3/29 (10)	0/51 (0)
AAP	4/29 (13)	0/51 (0)
NDRI	1/29 (3)	0/51 (0)
No AD	8/29 (28)	51/51 (100)
Combination of AD	7/29 (24)	0/51 (0)

Abbreviations: AD = antidepressant; BMI = Body mass index; SSRI = selective serotonin reuptake inhibitor; SNRI = selective noradrenalin reuptake inhibitor; TCA = Tricyclic antidepressants; AAP = atypical antipsychotics: NDRI = norepinephrine–dopamine reuptake inhibitor medication; Data are presented as n (%) or mean ± SD.

2.2. External and self-assessment scales

Self-assessment scales as well as clinician-rated scales were used to evaluate MDD. The self-assessment scale was “Beck Depression Inventory” (BDI) (Beck et al., 1961). The external assessment scales consisted of the HAMD-21 (Hamilton, 1960), Montgomery Asberg Depression Scale (MADRS) (Montgomery et al., 1979) and Clinical Global Impression (CGI) (Guy, 1976).

Furthermore, the Autonomic Nervous Symptom-Score (ANS-score) was used to evaluate autonomic symptoms. Previously, this structured interview was applied to detect ANS symptoms and their severity in schizophrenia (Peupelmann et al., 2009) or depression (Quick et al., 2010; Ruhland et al., 2008). This scale includes questions about abdominal pain, feelings of fullness, heartburn, nausea, vomiting, dry mouth, loss of appetite, constipation, diarrhea, stomach cramps, cardiac arrhythmia, heart palpitations, strong sweating, back pain, muscle pain and headaches, all of which could be listed as mild, medium and severe in terms of severity (Ruhland et al., 2008). These items are similar to the ones of validated scales, such as the Autonomic Symptom Profile (Suarez et al., 1999) and Composite Autonomic Symptom Score 31 (Sletten et al., 2012). Table 2 shows the results of the assessment scales.

In addition, based on the Rome III Consensus criteria for functional dyspepsia abdominal pain, feelings of fullness and heartburn were chosen as criteria to capture the functional symptoms originating in the gastroduodenum (Tack et al., 2006).

2.3. Conduct of the ^{13}C-acetate breath test

One of the mandatory conditions for an examination of gastric function by ^{13}C-acetate breath test was an 11-h period of restriction on the intake of food, fluids, medication and nicotine. The examination started in the morning with the provision of the first breath sample as a “zero value.” After this, the patient was given a test drink (Accu-Check Dextro O.G.-T., 300 ml juice) in which 100 mg ^{13}C-sodium-acetate were dissolved. The drink had to be ingested within 2 min. Thereafter, a total of 12 breath samples were collected over 3 h at 15-min intervals.

The isotope ratio $^{12}CO_2/^{13}CO_2$ in the CO_2 of the breath samples was calculated using isotope-selective non-dispersive infrared spectroscopy (NDIRS).

2.4. Parameters T_{max} and $T_{1/2b}$

The $^{12/13}CO_2$ isotope ratio of each breath sample is presented as a δ-value (Ghoos et al., 1993). The zero value measured prior to the