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**Autonomic functions and gastric motility in children with functional abdominal pain disorders**

Karunanayake A *et al*. Autonomic functions in functional abdominal pain

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**Abstract**

***background***

Abdominal pain-predominant functional gastrointestinal disorders (AP-FGIDs) are the commonest cause of recurrent abdominal pain in children. Despite the high prevalence, underlying pathophysiology of this condition is poorly understood.

***AIM***

to assess the role of gastric dysmotility and autonomic nervous system dysfunction in the pathophysiology of AP-FGIDs.

***METHODS***

Hundred children, fulfilling Rome III criteria for the AP-FGIDs, and 50 healthy controls, aged 5 to 12 years, were recruited after obtaining parental consent. All patients were investigated for underlying organic disorders. Gastric motility and cardiovascular autonomic functions were assessed using validated non-invasive techniques.

***RESULTS***

Main gastric motility parameters assessed (gastric emptying rate [45.7 *vs* 59.6 in controls], amplitude [48.7 *vs* 58.2] and frequency of antral contractions [8.3 *vs* 9.4], and antral motility index [4.1 *vs* 6.4]) were significantly lower in children with AP-FGIDs (*p* < 0.05). The post-prandial antral dilatation at 1 min after the test meal significantly correlated with the severity of abdominal pain (*p* < 0.05). Assessment of autonomic functions in patients with AP-FGIDs showed neither a significant difference compared to the control group, nor a correlation with gastric motility abnormalities (*p* > 0.05). The duration of pain episodes negatively correlated with the parasympathetic tone (maladaptive parasympathetic tone) (*p* < 0.05).

***CONCLUSION***

Children with AP-FGIDs have abnormal gastric motility, but normal cardiovascular autonomic functions. There is no relationship between abnormal gastric motility and autonomic functions. The pathogenesis of AP-FGIDs is not related to cardiovascular autonomic dysfunction.

**Key words:** Abdominal pain; Functional gastrointestinal disorders; Autonomic function; Gastric motility

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**Core tip:** In this study, we looked at the relationship between cardiovascular autonomic functions and functional abdominal pain disorders (FAPDs) in children. We failed to demonstrate neither a significant difference in autonomic functions, nor significant relationship between gastric motor abnormalities and autonomic functions, in affected children. In this paper, we propose functional extrinsic denervation and maladaptive parasympathetic division as possible contributing factors for impairment of gastric motility and symptom generation in FAPDs, which is demonstrated in the ‘Automatic Stomach’ model.

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**Introduction**

Abdominal pain-predominant functional gastrointestinal disorders (AP-FGIDs) are one of the most recognized groups of gastrointestinal disorders in children across the world. It has an estimated global prevalence of 13.5% in community and school based surveys[[1](#_ENREF_1)]. This group consists of irritable bowel syndrome (IBS), functional abdominal pain (FAP), functional dyspepsia (FD) and abdominal migraine (AM)[[2](#_ENREF_2)]. Although not directly related to mortality, AP-FGIDs have a considerable effect on health related quality of life and healthcare expenditure[[3](#_ENREF_3),[4](#_ENREF_4)]. Even with the highly advanced modern technologies, pathophysiological mechanisms of FGIDs are not yet clearly understood. The recognized pathophysiological mechanisms include visceral hypersensitivity, altered gastrointestinal motility, immunological dysfunction, altered gastrointestinal microbiota, altered intestinal permeability, genetic factors and psychosocial disturbances[[5](#_ENREF_5)].

Abnormalities in the gastrointestinal motor function have been suggested as a potential pathophysiological mechanism in AP-FGIDs. They include, dilated gastric antrum at fasting period[[6](#_ENREF_6),[7](#_ENREF_7)], delayed gastric emptying[[6](#_ENREF_6),[8](#_ENREF_8)-[11](#_ENREF_11)], impaired initial distribution of a meal[[12](#_ENREF_12)], impaired gastric accommodation to a meal[[13](#_ENREF_13)] and antral hypomotility[[8](#_ENREF_8)-[11](#_ENREF_11),[14](#_ENREF_14)].

Autonomic nervous system (ANS) is an integral part of the brain-gut axis that is involved in the regulation of gastrointestinal motility. Some studies have demonstrated dysfunction in both sympathetic and parasympathetic divisions of the ANS in children and adults with functional gastrointestinal disorders (FGIDs)[[15](#_ENREF_15)-[17](#_ENREF_17)]. Elsenbruch and Orr have noted a significant correlation between vagal response and post-prandial abdominal symptoms in patients with diarrhoea-predominant IBS[[18](#_ENREF_18)]. Abnormalities of gastric motility and underlying vagal defects have been demonstrated in adult patients with IBS[[15](#_ENREF_15),[18](#_ENREF_18)]. In addition, autonomic nervous system is thought to play an important role in modulation of visceral sensitivity in FGIDs[[19](#_ENREF_19)]. However, the relationship between autonomic function and gastric motility has not been studied in affected children.

The main objective of this study was to assess the autonomic nervous system functions in paediatric patients with AP-FGIDs and its relationship to gastric motor functions.

**MATERIALS AND METHODS**

***Study design***

This is a comparative, cross sectional study to assess the cardiovascular autonomic functions and gastric motility in children with AP-FGIDs.

***Recruitment of the patients***

All consecutive patients aged 5-12 years, who were eligible according to the inclusion criteria, were recruited from the paediatric out-patient clinics of North Colombo Teaching Hospital, Ragama, Sri Lanka and investigated in the Gastroenterology Research Laboratory, Faculty of Medicine, University of Kelaniya, Sri Lanka. A detailed history was taken from each subject and his or her parents after obtaining written informed consent. Details regarding pain characteristics and autonomic symptoms were obtained using an interviewer administered pre-tested questionnaire. AP-FGIDS were diagnosed using Rome III criteria[[2](#_ENREF_2)].

***Inclusion criteria***

(1) Fulfilment of Rome III criteria for at least one AP-FGIDs AND;

(2) Abdominal pain at least once per week for at least 2 mo prior to diagnosis AND;

(3) Pain severity more than 25 mm on a 100-mm visual analogue scale and severe enough to interrupt the activities of the child (*e.g.*, sleep, play, schooling *etc*.).

All patients were screened for organic diseases using a detailed history, complete physical examination, including growth parameters, stool microscopy, urine microscopy and culture, full blood count, C-reactive protein, liver function tests, renal function tests and ultrasound scan abdomen. Special investigations performed, based on clinical judgment of the consultant paediatrician who assessed the patients, included upper and lower gastrointestinal endoscopy, serum amylase and X-ray kidney-ureter-bladder. Patients were not screened for coeliac disease since it is extremely rare in Sri Lanka[[20](#_ENREF_20)].

***Exclusion criteria***

(1) Clinical or laboratory evidence suggestive of an organic pathology.

(2) Chronic medical or surgical diseases other than AP-FGIDs.

(3) Long-term medication for any illness other than AP-FGIDs.

(4) Previous abdominal surgery.

(5) Subjects who had received prokinetic drugs or any other drugs that can alter gastrointestinal motility during the 30 d prior to the diagnosis being made.

***Recruitment of controls***

Age and sex compatible group of children were recruited from the community of the same geographical area as controls after obtaining written parental consent. None of the controls had acute or chronic disease or symptoms related to the gastrointestinal tract.

***Patients’ preparation for testing***

Autonomic functions and gastric motility were assessed on the same day (gastric motility from 8.30 am to 9.00 am and autonomic function test from 9.30 am to 10.30 am) under thermo-neutral conditions (26 °C). All girls who have attained menarche underwent laboratory investigations during the proliferative phase of their menstrual cycles. All medications with adrenergic and cholinergic properties were discontinued for a period of at least five times the half-life of the specific medication. All subjects were advised to refrain from ingesting beverages containing caffeine, nicotine or alcohol for at least 8 h prior to testing. They were in a fasting state for at least six hours prior to the study. A standard breakfast was given with water after completion of gastric motility assessment. The autonomic function was assessed in all subjects 30 minutes after completion of the breakfast.

***Assessment of gastric motility***

Gastric motility was measured in all children with AP-FGIDs and the controls by a previously reported and validated ultrasound method[[21](#_ENREF_21)] using a high-resolution real-time scanner (Siemens ACUSON X300™) with 1.8MHz to 6.4 MHz curve linear transducer and with facilities to record and playback. All gastric motility parameters were assessed by the same investigator (NMD) who was blind to the diagnosis and results of the autonomic function tests. Main gastric motility parameters assessed were fasting antral area, gastric emptying rate, frequency and amplitude of antral contractions and antral motility index.

***Assessment of cardiovascular autonomic functions***

All subjects underwent autonomic cardiovascular tests according to the test battery described by Ewing *et al.,*[[22](#_ENREF_22)] using the standard procedures described by them. All autonomic functions were assessed by the same investigator (AK) who was blind the gastric motility status. The test battery consisted of four autonomic function tests conducted in the following order and the results were recorded in a data sheet.

(1) Blood pressure response to standing from lying down position.

(2) Heart rate response to standing from lying down position.

(3) Heart rate variation with deep breathing.

(4) Valsalva test.

Before the test, the procedures were explained and mimicked for the benefit of each subject.

After instrumentation, children were subjected to 10 minutes’ mandatory rest period. At the end of the rest period, the ECG recording from lead II was started along with the blood pressure recording. Thereafter, two readings of blood pressure and heart rate were obtained at an interval of 2 minutes between two consecutive recordings. Average of the two readings was recorded as resting heart rate and blood pressure.

**Test 1 - Blood pressure response to standing from lying down position:** Blood pressure (BP) readings were recorded one minute after the unaided standing up, maintaining the arm cuff at the level of the heart. The one-minute systolic BP was compared with the resting systolic BP and postural change in systolic BP was calculated. Automated BP machine (A&D Medical®) with paediatric cuff, which calibrated against a standard mercury sphygmomanometer was used. The blood pressure response to standing is dependent upon sympathetic adrenergic function[[23](#_ENREF_23)].

**Test 2 - Heart rate response to standing from lying down position:** ECG was recorded for a further 60 seconds after standing. The heart rate ratio (30:15 ratio) was calculated as the ratio between the longest R-R interval at around the 30th beat (R-R 30) and the shortest R-R interval at or around the 15th beat after standing (R-R 15). The 30:15 ratio was calculated as R-R 30/R-R 15. An increment in 30:15 ratio was considered as increased parasympathetic response[[24](#_ENREF_24)].

**Test 3 - Heart rate response to deep breathing:** Subjects were instructed to sit quietly and to breathe deeply at six breaths per minute (five seconds in and five seconds out). The investigator guided them through the manoeuvre by counting. Continuous ECG recording (Lead II) was completed for three consecutive artefact free cycles of deep inspiration and expiration. The difference between maximum and minimum heart rates during each cycle was calculated and the mean difference of the three cycles was obtained. Impairment in heart rate variability is a sign of parasympathetic dysfunction[[23](#_ENREF_23)]. Increased parasympathetic response is indicated by widening of the difference[[25](#_ENREF_25)].

**Test 4 - Valsalva test:** Subjects were asked to exhale into a mouthpiece connected to a mercury manometer and to maintain the expiratory pressure at 20 mmHg for 15 s in the sitting position. ECG was recorded during this manoeuvre and for 45 seconds afterwards. Pre-testing the results have shown that most of the children were not able to achieve 40 mmHg expiratory pressure proposed by Ewing's. Therefore, we set the value at 20 mmHg which was achieved by children. The child was allowed to rest for 1 minute before repeating the Valsalva manoeuvre. The Valsalva ratio was calculated by dividing the maximum R-R interval following Valsalva manoeuvre with the minimum R-R interval during the Valsalva procedure. The mean ratio of the two attempts was calculated. A reduced ratio indicates parasympathetic dysfunction[[23](#_ENREF_23)].

***Tools used to assess symptoms***

Autonomic symptoms were assessed by a modified composite autonomic symptom scale (COMPASS) for to assess autonomic symptoms which was translated and validated for local language[[26](#_ENREF_26)].

Gastrointestinal symptoms were assessed using a translated and validated Rome III questionnaire[[27](#_ENREF_27),[28](#_ENREF_28)]. Severity of abdominal symptoms was recorded on a 100-mm visual analogue scale.

***Statistical methods***

We calculated the sample size using on the 30:15 ratio taken from a previous study done on obese children aged 5-10 years in India[[29](#_ENREF_29)]. The similarity with the race and age group was considered for selecting values from the Indian study. At power of 90% and significance level of 95%, the minimum sample required is 26 in a group.

All statistical analyses were completed using PSPP version 0.8.3-g5f9212 statistics software (Free Software Foundation, Inc.http://fsf.org/). Means and standard deviations were calculated for continuous variables and frequencies and percentages were taken for categorical variables. For continuous data, non parametric, Mann Witney *U* test was used. For dichotomous data a chi-square test was used to assess differences between the two groups. A two-tailed level of significance of 0.05 was used for the analysis.

***Ethical approval***

This study protocol was approved by the Ethics Review Committee, Faculty of Medicine, University of Kelaniya, Sri Lanka.

**Results**

***Sample characteristics***

A total of 100 patients with AP-FGIDs [39 (39%)boys, mean age 7.9 years (SD 2.1 years)] and 50 healthy controls [20 (40%) boys, mean age 8.6 years (SD 1.9 years)] were recruited for this study. The AP-FGIDs group was consisted with 54 (54%) children with FAP, 33 (33%) with IBS, 13 (13%) with FD.

***Autonomic symptoms in the study subjects***

The autonomic symptoms related to the gastrointestinal tract were significantly higher among AP-FGIDs group (Table 1). The extra-intestinal symptoms, except the presence of cold feet, were higher among the AP-FGIDs group, but not statistically significant.

***Autonomic parameters in study subjects***

The autonomic parameters were not significantly different between AP-FGIDs and control groups (Table 2). All parasympathetic parameters were lower in the AP-FGIDs group, but these were not statistically significant. Resting heart rate, which is under parasympathetic inhibition, was higher among the AP-FGIDs group but with no statistical significance.

When pain characters of children with AP-FGIDs were correlated with autonomic parameters, the duration of pain episode correlated negatively with the 30:15 ratio (*r* = -0.21, *p* = 0.024, Pearson correlation coefficient). Other characteristics had no such correlation.

***Gastric motility in study subjects***

Gastric emptying rate, frequency of antral contractions, the amplitude of antral contractions and antral motility index were significantly lower in AP-FGIDs group (Table 3). The severity of the pain positively correlated with the antral area at 1min (*r* = 0.2, *p* = 0.02).

***Correlation between autonomic functions and gastric motility***

In healthy controls, gastric emptying rate and frequency of antral contractions correlated positively with the 30:15 ratio. Furthermore, the Valsalva ratio correlated positively with the frequency of antral contractions in healthy controls (Table 4). There was no such correlation between autonomic functions and gastric motility, in patients with AP-FGIDs.

**Discussion**

Current study assessed the cardiovascular autonomic functions and gastric motility in children with AP-FGIDs. Assessment of autonomic functions in patients with AP-FGIDs showed no significant difference when compared with the control group. The gastric motility parameters were significantly impaired in children with AP-FGIDs. None of the autonomic function tests show any significant correlation with any of the gastric motility parameters in the AP-FGIDs group.

The lack of differences in the autonomic parameters in the two groups indicates the possibility of normal autonomic function in children with AP-FGIDs. Since there are no tests that could directly assess the autonomic function of the gastrointestinal system and its interactions with the brain, the cardiovascular autonomic functions are used as a proxy measure to assess autonomic function of the gastrointestinal system[[30](#_ENREF_30)]. Chelimsky *et al*[[16](#_ENREF_16)] noted orthostatic intolerance in six out of eight patients (reflected by excessive increase of the heart rate or reduction in blood pressure) and low Valsalva ratio in 2 patients. Heart rate response to deep breathing which exclusively assesses parasympathetic function was within the normal limits in all eight patients[[16](#_ENREF_16)]. However, this was an observational study with no controls. In addition, the authors do not classify recurrent abdominal pain to definitive functional gastrointestinal disorders using the standard Rome criteria. Several studies have assessed the heart rate variability (HRV) in adult patients with IBS using different methods[[31](#_ENREF_31)] . However, no significant difference in vagal activity and sympatho-vagal balance between children with FAP/IBS and healthy controls have been shown in HRV assessments[[32](#_ENREF_32)]. Furthermore, meta-analysis of studies assessing HRV found that there could be a significant lower vagal influence in patient with IBS when compared to controls[[33](#_ENREF_33)]. The studies included in these meta-analyses have used a different method in assessing autonomic function and therefore, we cannot directly compare our findings with the findings of those meta-analyses.

In addition, the lack of significant difference of extra-intestinal autonomic symptoms between children with AP-FGIDs when compared to controls potentially indicates that children with AP-FGIDs do not have generalized autonomic dysfunction. Similarly, Chelimsky *et al*[[16](#_ENREF_16)] did not find extra-intestinal autonomic symptoms in children with AP-FGIDs.

Similar to our findings some studies have also failed to demonstrate a significant association between autonomic function tests and functional gastrointestinal disorders[[34](#_ENREF_34),[35](#_ENREF_35)]. There are several probable reasons for this discrepancy. The current autonomic tests are only a proxy measure of gastrointestinal autonomic function. Apart from that, contribution of the autonomic input of the local neuronal network at the local level within the stomach has not been taken into account during the testing. These factors may at least partly have contributed to the lack of differences in autonomic function in children with AP-FGIDs and controls. Having said all that, it is essential to understand that with the current knowledge and available tests, this is the closest that we could come to making a reasonable assessment.

Gastric motility abnormalities have been reported in children and adults with FGIDs[[6](#_ENREF_6),[8](#_ENREF_8)-[11](#_ENREF_11),[14](#_ENREF_14),[36](#_ENREF_36)-[38](#_ENREF_38)]. In the current study we also noted a similar pattern of abnormalities in children with AP-FGIDs. In addition, we also found that a positive correlation between abdominal pain and abnormalities in gastric motility similar to a few previous studies[[6](#_ENREF_6),[10](#_ENREF_10),[11](#_ENREF_11),[39](#_ENREF_39)-[41](#_ENREF_41)]. These findings suggest a potential pathophysiological relationship between gastric motility abnormalities and AP-FGIDs.

When we correlated gastric motility with autonomic parameters, we found no clear correlation between them in children with AP-FGIDs. However, the finding of significant correlation in the controls indicates parasympathetic control of the gastrointestinal motor function. None of the other studies in children have assessed the association between autonomic function and gastric motility and therefore we could not make a clear comparison.

Autonomic nervous system (ANS) is a physiological stress system. It is involved in adapting to various stimuli. Available literature has shown that autonomic activity may present as being normal[[38](#_ENREF_38)], hypo-functioning[[42](#_ENREF_42)] or hyper-active[[43](#_ENREF_43)] in functional abdominal pain. Dysfunction of ANS can cause significant gastrointestinal problems[[44](#_ENREF_44)]. At the central level, there is a strong connection between autonomic activation and nociception which is supported by the anatomical and functional overlap of pain processing structures and autonomic regulating structures[[45](#_ENREF_45)]. The interaction between pain and autonomic response become maladaptive in chronic pain[[46](#_ENREF_46)]. In some chronic pain states, sympathetic hyperactivity contributes to increased sensitivity to pain[[47](#_ENREF_47)]. In contrast to that, the pain can result in reduced parasympathetic activity[[48](#_ENREF_48)]. Association of pain and low parasympathetic flow has been reported in women with IBS[[49](#_ENREF_49)].

In the current study, pain duration correlated negatively with 30:15 ratio (parasympathetic) which can be interpreted as increased pain duration when parasympathetic activity is reduced. 30:15 ratio is a sensitive index to detect autonomic abnormalities in children[[50](#_ENREF_50)]. Therefore, we would like to suggest that parasympathetic division may adapt to the initial phase of the disease as shown in Figure 1. However, declining of parameters after 12 month of disease course may be a feature of mal-adapting autonomic flow. Furthermore, progressive autonomic dysfunction over time, has been demonstrated in adults with IBS[[51](#_ENREF_51)]. Therefore, the degree of parasympathetic functional impairment may present as a spectrum extending from normal to severe impairment. In this context, we may not see a similar response from every patient with FGIDs.

All three cardinal findings in this study, such as lack of difference in extra- intestinal autonomic symptoms between AP-FGIDs and controls, lack of differences in autonomic functions between the two groups and lack of correlation between gastric motility and autonomic parameters in those with FGIDs, suggest that the autonomic nervous system does not play a major role in the pathogenesis of AP-FGIDs in children. In this context, abnormalities in the parasympathetic flow are unlikely to be the primary cause for impaired motility in AP-FGIDs. Therefore, the stomach’s unresponsiveness to the extrinsic autonomic signals (functional extrinsic denervation) would be a possible underlying primary pathophysiological mechanism for gastric motility abnormalities seen in AP-FGIDs.

Depending on these observations we have developed a hypothetical model to explain the possible mechanism of pathogenesis of AP-FGIDs, which would be named as ''automatic stomach in AP-FGIDs''. According to the proposed model, functional extrinsic denervation is able to impair motility by three mechanisms (Figure 1). Both impaired motility and maladapted parasympathetic flow have an impact on pain. Possible functional extrinsic denervation demonstrated in the current study would affect gastric motility by increasing dopaminergic inhibition on the stomach, possibly via DAR2 receptors, leading to an “automated stomach” which does not directly respond to the outflow of the autonomic nervous system (Figure 1). Additionally, we have incorporated the modulatory effects of peripheral dopamine receptors on the central dopaminergic system as another possible effect of functional extrinsic denervation[[52](#_ENREF_52)] .

There are several strengths of this study. We have employed well established, non –invasive techniques to assess cardiovascular autonomic functions and gastric motility. The two investigators who assessed gastric motility and autonomic functions were blinded to the diagnosis of the study subjects. In addition, the impact of diurnal variation on motility was minimized by conducting the study from 8.30am to 10.30am. The large sample (100 AP-FGIDs and 50 controls) and detailed evaluation of patients (using history, examination and investigations) to exclude possible underlying organic disorders were the other strengths of the study. Therefore, we believe that our results could be applied to the whole population of children with AP-FGIDs. However, we did not separate children with AP-FGIDs into specific disease entities such as IBS, FD and FAP. In addition, we used cardiovascular autonomic functions to assess the autonomic functions of the gastrointestinal tract which is at best is only a proxy measure.

In conclusion, children with AP-FGIDs showed abnormal gastric motility parameters while their cardiovascular autonomic functions showed no significant abnormalities. There was no correlation between gastric motility parameters and autonomic functions, indicating that abnormalities in the autonomic nervous system does not play a major role in the pathogenesis of AP-FGIDs. However, we believe maladaptive parasympathetic flow and proposed automated stomach model would be able to throw some light upon the pathophysiology of AP-FGIDs in children.

**ARTICLE HIGHLIGHTS**

***Research background***

Abdominal pain-predominant functional gastrointestinal disorders (AP-FGIDs) are a common clinical problem in pediatric practice across the globe, with an estimated prevalence of 13.5%. Although thought to be benign in nature, as a group they are known to associate with poor health related quality of life and high healthcare burden.

***Research motivation***

The pathophysiology of AP-FGIDs is not clearly understood. Previous studies have shown abnormalities in gastroduodenal motility, such as delayed gastric emptying, impaired antral motility, and impaired gastric accommodation as potential pathophysiological mechanisms in children. Studies among adults have found autonomic dysfunction in patients with IBS. However, the association between autonomic dysfunction and gastric motility in children with AP-FGIDs had not been evaluated previously.

***Research objectives***

The main objective of our study was to assess the autonomic functions in children with AP-FGIDs and its relationship to gastric motor functions.

***Research methods***

Hundred children, fulfilling Rome III criteria for the AP-FGIDs, and 50 healthy controls, aged 5 to 12 years, were recruited for the study. All patients were thoroughly investigated to rule out underlying organic disorders. Gastric motility and cardiovascular autonomic functions were assessed using validated, non-invasive techniques.

***Research results***

Gastric emptying rate, amplitude of antral contractions, and antral motility index were significantly lower in children with AP-FGIDs. Autonomic functions, including blood pressure and heart rate responses to standing from lying down position, heart rate response to deep breathing, and Valsalva test, showed no difference between children with AP-FGIDs and controls. These parameters showed no correlation with gastric motor functions as well. However, the duration of pain episodes negatively correlated with the parasympathetic tone.

***Research conclusions***

Although children with AP-FGIDs had abnormal gastric motility parameters, their cardiovascular autonomic functions were normal. In addition, there was no correlation between autonomic functions and gastric motility. Our findings indicate that the autonomic nervous system is not chronically abnormal in patients with AP-FGIDs. Based on evidence available so far, we propose maladaptive parasympathetic flow and automated stomach model as a potential pathophysiological mechanism for AP-FGIDs.

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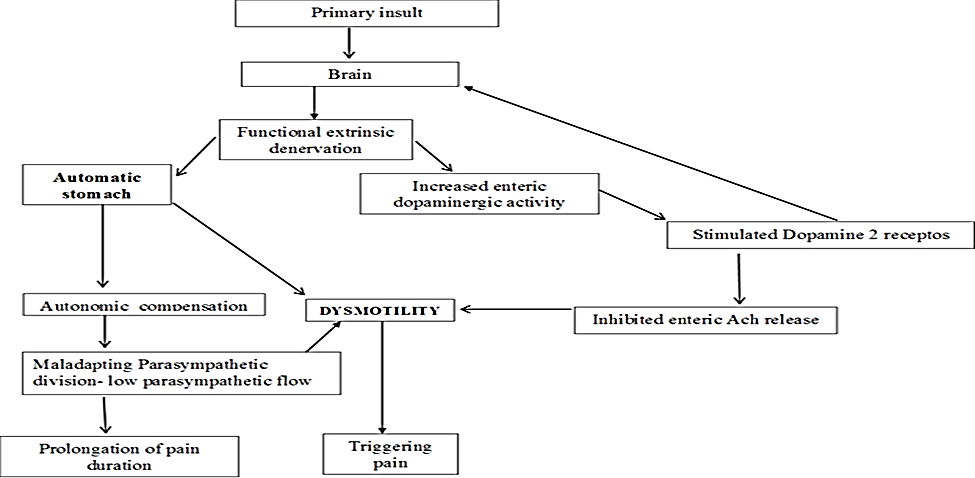
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**Figure 1 Development and consequences of automatic stomach in abdominal pain-predominant functional gastrointestinal disorders according to the proposed model.** Ach: acetylcholine.

**Table 1 Autonomic symptoms among abdominal pain-predominant functional gastrointestinal disorders and controls *n* (%)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Symptoms** | **AP-FGIDs (*n* = 92)** | **Controls *(n* = 50)** | ***p* value** |
| Dizziness/lightheadedness | 14 (15) | 3 (6) | 0.151 |
| Dry mouth or dry eye | 3 (3) | 1 (2) | 1.002 |
| Cold feet | 0 | 0 | - |
| Reduced limb sweating | 6 (7) | 1 (2) | 0.432 |
| Post prandial abdominal pain or discomfort | 55 (60) | 0 | < 0.00011 |
| Constipation or diarrhoea | 32 (35) | 2 (4) | < 0.00011 |

1Chi-square test; 2Fisher's exact test.

**Table 2 Comparison of autonomic parameters between abdominal pain-predominant functional gastrointestinal disorders and controls**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Autonomic test** | **Measurement** | **AP-FGIDs (*n* = 100)**  **Median (range)** | **Controls (*n* = 50)**  **Median (range)** | ***p* value1** |
| Resting heart rate (beats/min) | Resting heart rate (beats/min) | 89.0 (57-110) | 87.0 (63-114) | 0.18 |
| Heart rate response to deep breathing | Maximum-minimum heart rate (beats/min) | 30.8 (10-60) | 32.0 (10-57) | 0.90 |
| Lying to standing heart rate response | 30:15 ratio | 1.2 (0.9-1.6) | 1.2 (0.9-1.8) | 0.67 |
| Valsalva manoeuvre | Valsalva ratio | 1.5 (1-2.1) | 1.5 (1-2.5) | 0.23 |

1Mann-Whitney *U* test.

**Table 3 Comparison of gastric motility parameters between children with abdominal pain-predominant functional gastrointestinal disorders and controls**

|  |  |  |  |
| --- | --- | --- | --- |
| **Gastric motility parameter** | **AP-FGIDs (*n* = 100), median (range)** | **Controls (*n* = 50), median (range)** | ***p* value1** |
| Fasting antral area (cm2) | 1.6 (0.4-5.9) | 1.3 ( 0.4-5.1) | 0.19 |
| Antral area in 1 min (cm2) | 9.8 (3.8-14.6) | 9.8 ( 3.4-19.1) | 0.42 |
| Antral area in 15 min (cm2) | 4.8 (0.9-10.7) | 3.6 (0.6-11.2) | < 0.0001 |
| Gastric emptying rate (%) | 46.3 (16.0-77.9) | 61.6 (10.0-88.5) | < 0.0001 |
| Frequency of antral contraction (/3min) | 8.0 (6-11) | 9.0 (8-11) | < 0.0001 |
| Amplitude of antral contraction (%) | 47.2 (22.8-83.0) | 59.4 (32.6-85.4) | < 0.0001 |
| Antral motility index | 4.0 (1.7-7.5) | 5.7 (2.9-8.1) | < 0.0001 |

1Mann-Whitney *U* test.

**Table 4 Correlation between autonomic parameters and gastric motility parameters among abdominal pain-predominant functional gastrointestinal disorders and controls**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Gastric motility parameter** | **Valsalva ratio** | **Minimum –maximum heart rate** | **30:15 ratio** |
| AP-FGIDs | FAA | -0.01 | 0.04 | -0.09 |
| (*n* = 100) | AA1 | -0.02 | -0.02 | -0.06 |
|  | AA15 | -0.01 | -0.03 | -0.07 |
|  | GER | 0.07 | -0.03 | 0.06 |
|  | FAA | -0.02 | -0.07 | 0.04 |
|  | AAC | 0.07 | -0.06 | 0.13 |
|  | MI | 0.07 | -0.07 | 0.14 |
| Controls | FAA | 0.11 | -0.05 | -0.11 |
| (*n* = 50) | AA1 | 0.03 | 0.01 | -0.01 |
|  | AA15 | 0.07 | 0.05 | 0.17 |
|  | GER | 0.2 | 0.1 | 0.39a |
|  | FAC | 0.7a | -0.09 | 0.14a |
|  | AAC | -0.07 | 0.11 | -0.20 |
|  | MI | 0.05 | 0.17 | 0.07 |

Spearman correlation coefficient, a*p* < 0.05**.** FAA: Fasting antral area; AA1: Antral area in 1 min; AA15: Antral area in 15 min; GER: Gastric emptying rate; FAC: Frequency of antral contraction; AAC: Amplitude of antral contraction; MI: Antral motility index.