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Restoration of Vagal Tone: A Possible Mechanism for Functional Abdominal Pain

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Abstract Functional abdominal pain (FAP) causes disruption of daily activities/missed school days, over utilization of healthcare, unnecessary surgeries, and anxiety in 10–15% of children. Its etiology is not clearly understood, however the success of several clinical protocols suggests that autonomic dysregulation is a factor. In this study autonomic activity, including heart rate variability (HRV), was compared between children with FAP and a comparison group. Twenty children with FAP and 10 children without FAP between the ages of 5 and 17 years old were compared on autonomic regulation using an ambulatory system at baseline and 8 weeks later. Children with FAP participated in 6 sessions of HRV biofeedback aimed at normalizing autonomic balance. At baseline, children with FAP appear to have more autonomic dysregulation than children without FAP. After completing HRV biofeedback, the FAP group was able to significantly reduce their symptoms in relation to significantly increasing their autonomic balance. In a sample of children with FAP, it appears that HRV biofeedback treatment improved their symptoms and that a change in vagal tone was a potential mediator for this improvement. The present study appears to point to excessive vagal withdrawal as an underlying mechanism of FAP.

Keywords Recurrent abdominal pain · FAP · Vagal tone · Biofeedback

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Introduction

Of the Functional Gastroenterolgical Disorders (FGD) (including Functional Abdominal Pain [FAP], Irritable Bowel Syndrome [IBS], and Functional Dyspepsia [FD]), FAP has been identified as recurrent episodes of abdominal pain severe enough to interfere with a patient's usual activates but not caused by an identifiable organic disease and unrelated to bowel function (Sanders et al. 1994). Minimal criteria for patient inclusion in studies of FAP consist of at least 3 bouts of pain severe enough to affect activities during a period of not less than 3 months, with episodes occurring in the year preceding the examination (Clouse et al. 2006). FAP affects approximately 10–15% of the population (Apley and Naish 1958; Kristjansdottir 1996; Oster 1972; Parcel et al. 1977).

FAP is the cause of disruption of daily activities/missed school days, over-utilization of healthcare (Hyams et al. 1996), unnecessary surgeries, learning difficulties (DiPalma and DiPalma 1997), and anxiety (Jansdottir 1997). Even though FAP has generated these extensive negative outcomes, researchers have yet to clearly identify its etiology.

Investigators have found various combinations of treatments to be effective (Bremner and Sandhu 2009) at reducing symptoms in some patients with FAP. The effective combinations include cognitive-behavioral therapy (Huertas-Ceballos et al. 2008b; Sanders et al. 1989, 1990, 1994), consumption of fiber (Edwards and Bonner 1991; Feldman et al. 1985), hypnotherapy (Vlieger et al. 2007) and temperature and breathing training biofeedback (Humphreys and Gevirtz 2000; Weydert et al. 2003; Bassotti and Whitehead 1994; Gevirtz 2000; Whitehead 1992). Medications have not generally been found to be effective (Huertas-Ceballos et al. 2008a; Saps et al. 2009).

While most of these studies have found these treatments to be efficacious, the etiology of the mechanism of action has not been clarified, and the future direction of research remains uncertain. Hence, further research is needed to identify which children will experience continuous symptoms (Sanders et al. 1989). Several authors have argued for the need to investigate the actual mechanism underlying the symptoms change (Edwards and Bonner 1991; Fritz et al. 1997; Kristjansdottir 1996). More diagnostic schemas and improved outcome studies are required to understand the psychogenic and physiological processes involved in the development and maintenance of FAP.

Several models have been formulated to explain the development and maintenance of FAP. They include psychological stress (Borge and Nordhagen 1995; Garber et al. 1998; Mortimer et al. 1992; Poole 1984; Sanders et al. 1994; Smith and Womack 1987; Whitehead 1996; Wood et al. 1989), physiological or biological (DiPalma and DiPalma 1997; Feldman et al. 1985; Feuerstein et al. 1982; Smith and Womack 1987), and social or behavioral models (Edwards and Bonner 1991; Hyams et al. 1996; Sanders et al. 1994; Schrof 1997; Whitehead 1996). While research evidence over the past 10–15 years suggests that FAP is associated with family illness behavior, increased somatic and emotional distress, and increased anxiety and depression in parents and children (Fritz et al. 1997), the supporting evidence remains inadequate and inconsistent for any particular etiological and persistence model.

Current technology and recent research allows for the formulation of a psychophysiological model to integrate the psychological, physiological, and environmental evidence. It is necessary to jointly consider the value of self-regulation skills, the addition of dietary fiber, and the influence of environmental stimuli. To formulate this model, one can look to irritable bowel syndrome (IBS), a disorder similar to FAP in terms of its population, symptoms, efficacious treatments, and causal models (Walker et al. 1998).

By using psychophysiological monitoring, several researchers have established that dysregulation of the autonomic nervous system is a component of IBS (Aggarwal et al. 1994; Karling et al. 1998; Lee et al. 1998; Smart and Atkinson 1987). Aggarwal et al. (1994) studied physiological variables, including variability in pulse rate, through use of a continuous electrocardiogram (EKG) strip measuring the R–R interval (RRI) to demonstrate that the parasympathetic system is less efficient at achieving homeostasis in IBS suffers. These researchers used the RRI to calculate vagal response, a measure of vagal cholinergic dysfunction. Berger et al. (1986) further analyzed cardiac rhythms by decomposing the total variation into frequency bands and by calculating spectral power. This technique facilitates interpretations of heart rate variability (HRV) (Berntson et al. 1997) and allows researchers to infer the enteric nervous system's sympathetic and parasympathetic activity. Karling et al. (1998) found autonomic dysregulation in IBS suffers by using a spectral analysis of low and high frequency activity. Research into the mechanisms of FAP and IBS continues to support the psychophysiological hypothesis and calls for a re-examination of hypotheses relating deficits in autonomic nervous system recovery to stress and enhanced behavioral and subjective response to pain, using HRV analysis, a larger sample size, and a proven procedure for causing stress or anxiety.

A more comprehensive analysis of the mechanism of FAP can be facilitated using current psychophysiological monitoring equipment. An investigation into the mechanism of FAP examined autonomic dysregulation, specifically whether FAP was due to a combined deficit in autonomic nervous system recovery to stress and an enhanced behavioral and subjective response to pain (Feuerstein et al. 1982). The measure used in this study was not sensitive enough to allow for analysis of activity in specific spectral bands, and the digital blood volume pulse measure provided an indication of the peripheral sympathetic activity to the finger tip, only.

Using current HRV technology, the present study aimed to determine whether autonomic dysregulation (as measured by HRV) is a mechanism of FAP. HRV in children with FAP was compared to HRV in children who did not have FAP, in real-life settings, using ambulatory monitoring technology. In the present study, it was hypothesized that children with FAP would have less HRV than would children without FAP.

The present study also investigated whether children with FAP could increase HRV and decrease pain severity and frequency after completing 6 sessions of biofeedback. The present study advances the current understanding of the mechanism of FAP by demonstrating the potential relationship between the autonomic nervous system and FAP symptoms and the efficacy of biofeedback in treating FAP in children.

Methods

Participants

Participants were 14 male and 16 female children and adolescents. The sample size was based on a power analysis from previous studies investigating the low frequency to high frequency activity ratio (LF/HF) differences between participants with IBS and controls (Adeyemi et al. 1999; Karling et al. 1998; DiPalma and DiPalma 1997; Garber et al. 1998; Huertas-Ceballos et al. 2008a, b; Vlieger et al. 2007). The FAP group included 20 patients and the comparison group included 10 participants recruited during a well-check visit. Male/female balance was matched. The participants without FAP were matched to the patients with FAP by age, gender, and ethnicity (2 Hispanic,4 African American, 2 Asians, 12 Caucasians in FAP group, 2 Hispanics, 2 African Americans and 6 Caucasians in the healthy control group).

There were three patients who dropped out of the comparison group for various reasons. No patients dropped out of the FAP group. No demographic or physiological differences were found between those participants who dropped out of the study and those who stayed in the study.

Inclusion criteria were children between the ages of 5 and 17. Children with FAP were required to have had a clinical examination by the pediatric gastroenterologist to rule out organic causes of pain (Turck 1998) and had to meet the criteria for FAP. Exclusion criteria for the FAP group included (a) the presence of lactose intolerance, urinary tract infections, or recent head trauma (b) the use of prescribed or over the counter medications, which may interfere with the biofeedback data; (c) current medical treatment for FAP; or (d) the receipt of a recent and related surgical procedure. None of the children met exclusion criteria. Comparison children were matched in age to the FAP group. IBS symptoms (bowel changes) were not an exclusionary criterion. IRB approval was obtained from the Alliant International University and Kaiser Permanente review boards.

Materials

Physiological Monitoring Equipment

A VivoMetrics® LifeShirt™ System was used to collect physiological data in real life settings. The VivoMetrics® LifeShirt™ System is an ambulatory, multi-sensor, continuous monitoring system that collects data through various sensors, including RIP bands, which measure pulmonary function (i.e., tidal volume, respiratory rate, etc.), a 3-lead ECG, and a tri-axial accelerometer to measure activity/posture. The LifeShirt™ data used in the analysis consisted of a series of 5 min segments taken sequentially throughout the day. Vivometrics provides a detailed protocol for ambulatory measurement which was closely followed in the present study. This protocol has been used on many other childhood populations, but, to our knowledge, not on children with FAP (Kent et al. 2009).

A J&J Engineering© I-330 C-2 Portable 6-Channel Physiological Monitoring System (C-2) was used with a Toshiba© Tecra Notebook Model to collect physiological data during HRV biofeedback sessions. The C-2 has 2 channels of EMG/EEG for heart rate measurements and 4 channels for temperature, skin conductance, and respiration.

Demographic Questionnaire

The Demographic Questionnaire collected socioeconomic status/personal information such as age, gender, ethnicity, primary language spoken at home, number of parents residing in the same home, parent age, education, and occupation, age, gender, number of siblings residing in the same home, and Body Mass Index (BMI)(from medical records).

Mental Status Verification

A verification of mental status was conducted by the experimenter and gastroenterologist based on ability to give a history, and by asking questions about school, family, etc.

Pain Severity Visual Analogue Scale

A Visual Analogue Scale (VAS) of pain severity was used to assess the progress of patients with FAP. The VAS has been recommended as a valid measure by previous research (Naliboff et al. 1999). The VAS required that the patient indicate on a 10 cm line anchored by 'a little bit' to 'a whole lot', how much pain he or she experienced usually, last week, and at the moment respectively. Distance from the left side was measured in millimeters. This was collected daily for the week prior to treatment and again for the week after treatment concluded.

FAP symptom frequency was derived from a daily diary measure for the period of 5 weeks that listed the typical FAP symptoms (pain, diarrhea, constipation, bloating). A count of symptoms was summed for each week. In the same diary, patients rated severity on a 1–5 scale for each symptom and these were averaged for the week.

Procedures

The investigator verbally solicited participants for the study at well check-up examinations as well as by the distribution of informational flyers. The participants and their parents/guardians were referred to the researcher for more information on how to enroll, at which time the researcher briefly described the purpose of the study and how psychophysiological measurement would be conducted. The researcher gave the participants and parents/guardians a contact phone number to make an appointment or to obtain further information.

All sessions were conducted by the primary investigator or by one of two biofeedback therapists trained by the primary investigator and his supervisor (RG) with a manualized protocol (Lehrer et al. 2000). When participants arrived at their scheduled appointment they completed an informed consent and demographic questionnaire with their parents/guardians. The researcher then conducted the Mental Status

Verification. The researcher briefly explained what was involved in the use of the ambulatory physiological measurement device. The researcher temporarily left the room while the participant put on the LifeShirt™ and attached three electrodes with the help of the parent. The researcher then returned to the room and powered on the LifeShirt™ recorder. The participant was instructed to leave the recorder turned on for at least 4 h each day starting in the morning. They were also instructed on how to remove the LifeShirt™ at the end of the recording sessions. The participants were instructed to return, in 8 weeks from the initial session, to repeat the process. The children tolerated the LifeShirt™ well. A few complained that it felt "tight", but no malfunctions occurred.

Treatment Protocol

The biofeedback intervention consisted of six sessions of resonant frequency training following the manualized procedure describe by Lehrer et al. (2000). It consists of a method of slow diaphragmatic breathing following a designated pace. This intervention has been found to increase baroreceptor sensitivity, cardiopulmonary function, and homeostatic reflexes (Lehrer et al. 2000, 2003). All FAP group participants were instructed to practice this method of diaphragmatic breathing every day for at least 10 min. There was no formal adherence measure, but this breathing technique can only be mastered by frequent practice, making one's progress in treatment dependent on practice frequency. Based on this, all of the FAP group participants were judged by the clinicians to be practicing this technique at home on a regular basis.

Statistical Design

The researcher used the primary comparisons of heart rate activity in children with FAP and children without FAP. This study utilized a 2 × 2 between group repeated measure design. The first independent variable was FAP status with two levels: FAP group and Non-FAP (comparison) group. The second independent variable was time with two levels: time one (baseline) and time two (after 8 weeks). The first dependent variable was autonomic regulation, which was measured by two criteria: (a) activity in the HF and LF bands (heart rate variability), as measured by ECG, and (b) respiration as measured by a pneumograph chest band.

Results

Group Equivalence

The comparison group had an average age of 14.4 (SD = 2.86) years and were evenly divided between boys and girls. The FAP group had an average age of 12.6(SD = 3.03) years with 9 boys and 11 girls.

The groups were compared on age, and body mass index using *t*- tests (Age: $t_{(28)} = 1.65$, n.s.; BMI: $t(28) = 1.16$, n.s.) and chi squares for gender and ethnicity(Gender: $\chi^2_{(1)} = .37$, n.s.; Ethnicity: $\chi^2_{(2)} = .36$, n.s.). No differences approaching significance were found. As a further check, we looked at correlations between starting levels of the continuous measures and treatment gains and found no significant (or even moderate) correlations.

Manipulation Check

Paired samples *t*-tests were conducted to evaluate the difference in the FAP group from time one to time two in percentage value for low frequency, or LF, (%LF) during resonant frequency breathing, which is a slow paced rate that increases LF. Percent LF is a heart rate frequency domain measure used to assess autonomic control. The researcher found a statistically significant increase in %LF from time one ($M = 57.85$, SD = 15.53) to time two, ($M = 73.30$, SD = 9.85), $t_{(19)} = -4.33$, $P = 0.001$). The eta squared statistic (0.50) indicated a very large effect size for the FAP group.

Test of Main Hypotheses

Comparing the Groups on Autonomic Parameters

A mixed between-within ANOVA, with one repeated measure, investigated differences between the groups in Low Frequency/High Frequency (LF/HF) ratio changes from time one (Comparison = 2.34(.16) vs. FAP = 2.50(.13) to time two (Comparison = 2.41(.22) vs. FAP = 2.40(.18)). The interaction was significant ($F_{(1,28)} = 6.83$, $P = 0.014$). Independent samples *t*-tests were conducted to compare whether children with FAP had higher LF/HF ratio than did children without FAP. Within each group, time one and time two were examined. The simple effects analysis showed that the groups differed at time one ($t_{(28)} = 2.95$, $P = 0.006$) but not at time two ($t_{(28)} = -0.21$, $P = 0.838$). The magnitude of the differences between the two groups at time one was large (eta squared = 0.24). Thus, the hypothesis that children with FAP would have higher baseline LF/HF ratio was supported.

Paired sample *t*-tests were conducted to evaluate the differences from time one to time two in LF/HF ratio for both the FAP group and the comparison group. A statistically significant decrease occurred in the FAP group's LF/HF ratio from time one to time two ($t_{(19)} = 2.57$, $P = 0.019$). The eta squared statistic (0.26) indicated a large effect size. There was no significant change in the comparison group's LF/HF ratio (indicating sympathovagal tone) from time one to time two ($t_{(9)} = -1.43$, $P = 0.187$).

A Mixed Between-Within ANOVA with 1 repeated measure investigated differences between the groups in the heart rate time domain measure, NN50, from time one to time two. A significant interaction was found ($F_{(1,28)} = 6.05$, $P = 0.02$). Independent samples *t*-tests were conducted to compare whether the FAP group had higher NN50 than did the comparison group. Within each group, time one and time two were examined. The simple effects analysis showed that the groups were significantly different at time one, ($t_{(28)} = 3.14$, $P = 0.01$). The magnitude of the differences between the 2 groups at time one was large (eta squared = 0.23). The groups did not differ at time two, $P = 0.94$). Similar results were found for pNN50.

A mixed between-within ANOVA with 1 repeated measure investigated differences between the groups in HF changes from time one to time two. The interaction was significant, ($F_{(1,28)} = 5.21$, $P = 0.03$). Independent samples *t*-tests were conducted to assess whether children with FAP(732.57(79.7)had higher HF than did children without FAP(810.44(84.67) at Time 1. Within each group, time one and time two were examined. The simple effects analysis showed that the groups differed at time one, ($t_{(28)} = -2.47$, $P = 0.02$), but not at time two, ($t_{(28)} = 0.41$, $P = 0.69$). The magnitude of the differences between the 2 groups at time one was large (eta squared = 0.18). Time 2 means were FAP = 787.29(111.42) and Comparison group = 770.66(93.39).

Testing Symptom Improvement in the FAP Group

For the FAP group (Figs. 1 and 2), pain measures were compared at time one and at time two after completing HRV biofeedback, using paired samples *t*-tests to evaluate the impact of the treatment on the FAP groups' pain frequency and intensity scores. For pain frequency, there was a statistically significant decrease from time one to time two ($t_{(19)} = 6.16$, $P < 0.001$). The eta squared statistic (0.67) indicated a very large effect size. For pain intensity, there was also a statistically significant decrease from time one to time two ($t_{(19)} = 7.07$, $P < 0.001$. The eta squared statistic (0.73) indicated a very large effect size. Clinically, these results reflect the fact that 75% of the treated FAP patients showed clinically significant reductions (>50%) in self-reported pain and 20% were actually pain free by post test.

Testing Vagal Tone as a Mediator of Symptom Reduction

Pearson correlations were used to investigate whether changes in the FAP group's pain frequency and intensity were related to the change in LF/HF ratio from time one to time two. There was a positive correlation between a decrease in LF/HF ratio and a decrease in pain frequency ($r = 0.54$, $P = 0.018$, $r^2 = 29\%$) from time one to time two. There was also a positive correlation between a decrease in LF/HF ratio and a decrease in pain intensity ($r = 0.62$, $P = 0.004$, $r^2 = 38.4\%$) from time one to time two. This analysis appears to indicate that the changes in vagal tone following treatment mediated the improvement in symptoms.

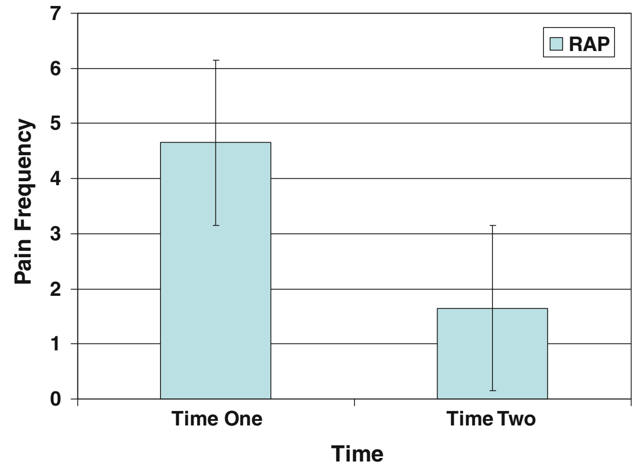

Fig. 1 Mean changes in pain frequency in the recurrent abdominal pain group from time one to time two (8 weeks later), after completion of heart rate variability biofeedback treatment. Pain frequency was measured by number of reported pain episodes per week

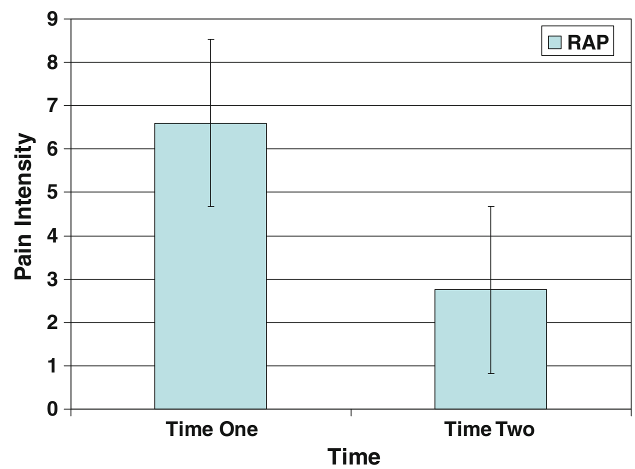

Fig. 2 Mean changes in pain intensity in the recurrent abdominal pain group from time one to time two (8 weeks later), after completion of heart rate variability biofeedback treatment. Pain intensity was measured using a visual analogue scale with a rating scale from one to ten, with one equaling least severe pain and ten equaling most severe pain

Discussion

As expected, results support that children with FAP have a lower vagal tone at baseline, compared to children without FAP. Also as expected, the results appear to support that HRV biofeedback would be efficacious in treating FAP. In the sample of children and adolescents with FAP, it appears that HRV biofeedback treatment improved their symptoms. It also appears that a change in vagal tone was a potential mediator for this improvement, such that, after completion of HRV biofeedback treatment, increased vagal tone in the FAP group correlated with a decrease in pain. The present study appears to point to autonomic dysregulation as an underlying mechanism of FAP. However, changes in pain severity and symptom frequency may have been the result of attention, maturation, or just repeated measurement, so no attribution of cause can be made. Other studies have noted similar gains against various controls (fiber alone) (Humphreys and Gevirtz 2000), however, without a no-treatment control or comparison group, we cannot be sure that the gains were the result of the intervention.

Many previous studies (Aggarwal et al. 1994; Gupta et al. 2002; Karling et al. 1998; Lee et al. 1998; Smart and Atkinson 1987) have established autonomic dysregulation (including low vagal tone) as a component of IBS. The results in the present study appear to support these findings in a pediatric FAP patient population. The present study also shows LF/HF ratio to be significantly higher at baseline in FAP patients compared to healthy patients, which supports the hypothesis that the FAP group would have lower vagal tone at time one. These findings provide evidence for autonomic dysregulation as being a potential causal factor for FAP.

Although the active mechanism underlying HRV biofeedback's success in treating FAP remains unknown, the present study showed that this treatment appeared to be a very effective way to reduce pain. In the present study, 15 of the 20 children with FAP had a significant reduction in pain intensity and frequency, and 4 of these 15 had total elimination of pain. Prior to HRV biofeedback, the average child experienced pain on a fairly severe level (i.e. a rating of 7 on a scale of 1–10, with 10 being most severe) 4–5 times per week. After completion of HRV biofeedback, the composite average child only experienced a mild level of pain (e.g. a rating of 2) 1–2 times per week.

The present study confirmed improvements in self-reported pain with a measurable physiological change in the percentage of low frequency activity during the resonant frequency breathing, thereby reducing the suspicion of any placebo response. While it remains unknown whether or not the present intervention is more effective than other interventions, such as hypnosis or cognitive-behavioral therapy, both patients and parents readily accepted HRV biofeedback treatment. Further, this treatment fit easily into a pediatric medical setting because only a small amount of space was needed to conduct sessions and the equipment used was portable and affordable. The biofeedback sessions were generally 30–45 min in duration. Biofeedback could be a useful tool in a busy pediatric gastroenterologist office.

It is possible that participants might have improved because of factors related to the primary investigator. Although two assistant therapists ran a few participants, the primary investigator ran most of the participants through the procedures. Although this investigator effect cannot be thoroughly ruled out until other researchers conduct several study replications, no evidence for a therapist effect was found in the current study. FAP patients had similar symptom reduction and improvement in sympathovagal tone across all three therapists.

Conclusion

Pending verification from future studies, the results are very promising. While it remains unknown whether or not the present intervention is more effective than other interventions such as hypnosis or cognitive behavioral therapy, the present study has found that both patients and parents readily accepted HRV biofeedback treatment. This treatment also fits easily in a pediatric medical setting in that it is cost effective, portable, and sessions can be conducted in a small work space.

The present study also sheds light on potential criteria for positively diagnosing patients with FAP. Having positive indicators of FAP would be instrumental in eliminating the many invasive and costly procedures, which must now be used in order to arrive at rule out diagnoses. A determination of the factors common to all FAP cases is urgently needed to expand the understanding of FAP and to assist in better treating those afflicted with this disorder.

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