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Research Article

DIFFERENTIAL CLINICAL PROFILES AND COMORBIDITIES IN CYCLIC VOMITING SYNDROME AND MIGRAINE: IMPLICATIONS FOR TREATMENT STRATEGIES

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ABSTRACT

This cross-sectional study aimed to explore the association between cyclic vomiting syndrome (CVS) and migraine headaches, comparing them with healthy controls. Using the ODYSA instrument, the probability of various functional and autonomic diagnoses, including CVS and migraine, was assessed in 103 subjects. Among them, 21 had CVS, 45 had migraine, and 36 were healthy controls. The analysis revealed that fibromyalgia, orthostatic intolerance (OI), syncope, and functional dyspepsia did not significantly differ between migraine and CVS groups. However, complex regional pain syndrome (CRPS) was notably more prevalent among CVS patients. This finding suggests potential differences in the pathophysiologies of CVS and migraines, despite their shared comorbidities. Additionally, the study suggests that treatment strategies targeting OI, a common abnormality in both conditions, may also be beneficial for CVS patients.

Key words:-. Cyclic vomiting syndrome (CVS), Migraine, Cross-sectional study, Comorbidities, Fibromyalgia.

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INTRODUCTION

In CVS, severe vomiting and nausea persist for several hours to several days, followed by returns to baseline health between episodes [1]. There is a 2% prevalence of CVS among children and a higher prevalence of CVS among adults [2]. Pallor, increased salivation, listlessness, anorexia, nausea, vomiting, abdominal pain, headache, and photophobia may accompany vomiting episodes that vary in intensity and duration. Autonomic nervous system symptoms also occur in migraine patients [3] and are often caused by the autonomic nervous system. Anecdotal similarities suggest a link between CVS and migraine, including antecedent auras, associated headaches, and photophobia [4].

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One third of CVS patients will develop migraines in one year if they receive migraine therapy [5]. Furthermore, nausea and vomiting are enough of a cornerstone of migraine presentation for the International Headache Society to incorporate them into its criteria [6]. The clinical significance of abdominal pain associated with migraine is unclear [7]. They may suggest a common pathogenesis for migraines and CVS as they both involve the autonomic nervous system. Fibromyalgia, irritable bowel syndrome, and syncope are several of the well-described complications associated with migraine [8, 9]. A comparison of migraine patients and control subjects reveals a spectrum of clinical similarities.

METHODS

Healthy controls or people with CVS or migraines were also included. It is a comprehensive clinical questionnaire intended to assess 12 different autonomic disorders, including orthostatic intolerance, reflex syncope, chronic fatigue syndrome, Raynaud's syndrome, complex regional pain syndrome (CRPS), interstitial cystitis, CVS, chronic fatigue syndrome, functional dyspepsia, functional abdominal pain, migraine headaches, and fibromyalgia. By developing the questionnaire, these disorders were linked. Two urologists, two cardiologists, two neurologists, an adult gastroenterologist, two pediatric gastroenterologists, a rheumatologist, two geneticists, one epidemiologist, one psychologist, and two basic scientists with a special interest in dysautonomia developed the ODYSA instrument over the past 6 years. To determine the diagnosis of each of 12 dysautonomias noninvasively, we designed and validated a clinical instrument. Our goal was to adapt or use validated or published questions-based diagnostic tools for each of the 12 disorders in the following table, as illustrated in Table 1. Because the instrument allows participants to skip entire pages based on the lead question on each page, a typical participant completes the instrument in only 16 minutes. A relevant symptom is assessed in this question.

Instrument

The ODYSA questionnaire incorporates sets of "probability" and "severity" questions within each disorder category, totaling 12 disorders. The purpose of the probability questions is to ascertain the presence of the disorder, while the severity questions gauge the extent of impairment caused by the disorder. Notably, only the probability scores are used to determine inclusion in the disorder group, with scores constrained to either 0 or 1, leaving no room for intermediary values. Meanwhile, severity scores span from 0 to 10. These scores are automatically generated by the Filemaker Pro database upon entry of subject data, obviating the need for observer input. For comorbid disorders, probability scores are tabulated for CVS and migraine headache, as seen in the subject inclusions.

Orthostatic Intolerance: The validation of orthostatic intolerance probability criteria relied on a tilt-table study, revealing positive and negative predictive values of 90.4% and 94.1%, respectively (awaiting publication). Interstitial Cystitis: Two methods were employed. The first, O'Leary-Sant Method, encompasses validated and published questions addressing urinary urgency, frequency, nocturia, and bladder pain or burning. Scoring adheres to the original protocol. The second, NIDDK Method, expands on the NIDDK conference of 2006, targeting key diagnostic historical criteria for PBS. Preliminary data review indicated superior reliability and validity for method 2, which is the current approach.

Fibromyalgia: Probability hinges on pain duration and location. Subjects must experience pain exceeding 3 months, and assign a pain value (0 to 5) to 21 specific body areas, grouped into four quadrants. A probability score of 1 is attained when pain is present in at least one area per quadrant and the total value surpasses 4. This setup is face-valid and supplemented by the McGill Short Form [10]. Reflex Syncope: Syncope probability is determined by frequency and duration of unconsciousness. Validated questions from Sheldon's publications were employed. A score of 1 requires infrequent unconsciousness, lasting less than 5 minutes, with return to baseline awareness within an hour.

Irritable Bowel Syndrome: Criteria are based on inclusion and modular questions from the Rome II book [11]. Sufferers must experience abdominal pain or discomfort for at least 3 months, which alleviates after bowel movement, coupled with changes in bowel movement frequency and quality in tandem with pain onset. Functional Dyspepsia: Like IBS, this disorder's criteria stem from Rome II guidelines and modular questions [12]. Upper abdominal pain or discomfort should lack evidence of organic causation and not alleviate with defecation or accompany changes in stool attributes (which would align with IBS).

Subjects

The study recruited participants from three tertiary care institutions that offer a variety of medical services. The autonomic laboratory housed clinics for adults and children, rheumatology, urology, autonomic, neurology and family medicine.

A variety of medical centers located in Northeast Ohio recruited subjects, including adult and pediatric clinics in gastrointestinal diseases, rheumatology, urology, neurology, autonomic disorders, and family medicine. The survey was administered to each participant's spouse or friend, in order to establish a control group.

According to the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition [13], CVS (Cyclic Vomiting Syndrome) inclusion criteria were adapted. In order to meet this criteria, participants had to experience intense vomiting and nausea at least three times in a six-month period or five times in their lifetime. A peak vomiting frequency of no less than four times per hour was required during these episodes, lasting between one hour and ten days. It was also necessary to show a return to baseline health between attacks and separate the attacks by at least a week. There was also a subgroup with the label "milder CVS," acknowledging that some patients could exhibit less severe symptoms. Only one to three episodes of vomiting per hour constituted the peak vomiting frequency for these individuals.

According to the International Headache Society, migraine inclusion criteria are adapted from its

[14]. It was enough to have at least five migraine attacks over the course of your life, each lasting from 4 to 72 hours (whether you successfully treated them or not). It must be a one-sided attack, exhibit pulsating characteristics, be moderate to severe in pain intensity, and have been aggravated by or causing abstinence from routine physical activity. At least one of the following elements was required during an attack: nausea and/or vomiting, photophobia, or phonophobia. There was no other cause for the headache [15].

Several family or friends of the probands were selected as control subjects, who did not meet the CVS/migraine criteria established by the ODYSA questionnaire. Probands, family members, and control subjects were included in these groups based on ODYSA criteria for migraine or CVS. These three groups were examined for various comorbidities, including orthostatic intolerance, fibromyalgia, irritable bowel syndrome, complex regional pain syndrome, functional dyspepsia, syncope, and interstitial cystitis. According to Table 1, these comorbid disorders were included based on adapted inclusion criteria. Categorical variables and continuous variables were analyzed using chi-square, Fisher exact tests, and student's t-tests.

RESULTS

Twenty-one patients with CVS (3 children), of whom seven were classified as mild CVS, 46 patients with migraine (3 children), and 36 healthy controls were included. Five family members and one friend of a proband made up the CVS group (71%) of 15 subjects. Twelve migraineurs (26% of the group), 27 family members (59%) and seven friends of migraineurs (15%) were in the migraine group. All three groups were dominated by females [CVS (86%), migraines (85%), and healthy controls (64%). For those suffering from CVS, the mean age was 41 + 19.8 (range 6–68) and for those suffering from migraine, 38.6 + 14.1 (range 12–67) (P +0.6). The mean age of healthy controls was 22.6 ± 13.9 (range 8–55). Each group's comorbidities are summarized in Table 2. There was no significant difference between CVS and migraine subjects for the prevalence of fibromyalgia (38% and 22% respectively; P = 0.012) and orthostatic intolerance (47% in CVS and 39% in migraine; P = 0.002). 9.5% of CVS patients and 8.7% of migraine patients reported functional dyspepsia, no difference between the groups. In CVS group, 23.8% of patients reported complex regional pain syndrome compared to 2.2% in migraine group; P 01.

When compared with the controls, the CVS group showed a higher prevalence of autonomic syndromes such as orthostatic intolerance, fibromyalgia, and complex regional pain syndrome. There was no functional dyspepsia among the controls.

Table 1: The criteria for inclusion According to this table, the comorbidities mentioned in the ODYSA questionnaire were prepared with the help of the following sources

Symptoms and causes	Ailment
Bowels and bladders	Symptoms of IBS Idiopathic cystitis Vomiting with cyclic patterns Dyspepsia with Functional Signs Abdomen that functions
Aesthetics	Asthenia orthostatica Syncope due to reflexes
Fatigue and pain	Headache caused by migraines Myalgia fibrosis Complex regional pain syndrome refers to reflex sympathetic dystrophy. Inflammatory Bowel Disease Angioedema raynaudi

Table 2: A comparison of CVS patients and healthy controls with regards to co-morbidities

	The 21st CVS	n = 46 migraines	CVS and migraine P values	Number n multiplied by 36	The P value of CVS compared to controls
Women n (%)	18 (85.3)	39 (5.6)	.920	23 (63.4)	.03
The mean (SD) of age	40.9 ± 19.3	38.6 ± 15.1	.022	22.64 ± 15.6	.033
n (%) of orthostatic intolerance	10 (47.5)	18 (39.2)	.77	2 (8.7)	.212
N (%) of syncopes	2 (8.3)	4 (7.6)	.77	0 (0)	.32
Dyspepsia with functional causes	2 (7.6)	(6.8)	.82	0 (0)	.32

Anxiety n (%)	5 (23.8)	18 (39.1)	.22	5 (13.9)	.34
Amount of migraines (%)	11 (52.4)	46 (100)	—	0 (0)	—
% of people with fibromyalgia	8 (38.1)	10 (11.7)	.12	2 (5.6)	.0015
There are n (%) people with chronic fatigue syndrome	0 (0)	3 (4.5)	.54	2 (5.7)	—
Pain syndromes with complex regional origin n (%)	5 (22.8)	1 (2.3)	.22	0 (1)	—
Inflammation of the cysts	1 (3.4)	0 (0)	Not run	0 (0)	Not run

DISCUSSION

The main findings of our study on CVS in a predominantly adult population can be summarized as follows. The prevalence of adult CVS is clearly associated with various dysautonomies, including orthostatic intolerance, fibromyalgia, and complex regional pain syndromes. It is important to note that this correlation is only observed in certain dysautonomies, not in all. [16] As an example, patients with CVS are not more likely than controls to suffer from irritable bowel syndrome (IBS). In discovering links between disorders that share similar pathophysiological aspects and others that do not, these selective associations may provide valuable insights into the underlying mechanisms of these disorders. CVS might also be influenced by autonomic dysfunction, which may also contribute to orthostatic intolerance, because CVS is closely related to orthostatic intolerance.

Furthermore, even though there are some comorbid disorders that share similarities with CVS and migraine, there are also a number of differences between them. Contrary to prior reports, CVS has a higher prevalence of CRPS than migraine sufferers. CVS and migraines seem to be connected, but their relationship may not be as close as expected, especially among adults, if they were just variants. Thirdly, migraines as well as CVS may be managed with treatments that enhance orthostatic tolerance, due to their significant correlation with orthostatic intolerance. Further research and evaluation are needed to test this hypothesis.

CAMERA studies have previously shown a link between migraine and syncope, with syncope occurring more frequently in migraine sufferers than in controls (46% versus 31%) [17]. In our previous study, CVS had been linked to postural tachycardia syndrome and syncope, but its results were confounded by referral bias because the patients were selected from an autonomic laboratory. Due to the diverse referral sources in the present study, both CVS and migraine groups are less susceptible to referral bias when it comes to the prevalence of orthostatic intolerance. Irritable bowel syndrome and chronic fatigue are all disorders that have an elevated prevalence . Many other disorders within the same group also have elevated prevalences, including fibromyalgia, chronic fatigue, and fibromyalgia. [18] The correlation between orthostatic intolerance and these disorders suggests that their central autonomic functions are altered in a similar manner.

CVS and fibromyalgia are associated for the first time in this report. According to existing knowledge, fibromyalgia is associated with functional gastrointestinal disorders thus correlating fibromyalgia and CVS, both functional gastrointestinal disorders. [19] Apart from orthostatic intolerance, chronic pain syndromes like fibromyalgia and CRPS are the most common associations of CVS. In light of this, CVS could possibly be classified as a chronic pain disorder, with nausea being a variant of pain. As a result of a reclassification, adults might be able to receive treatment similar to chronic pain syndromes which is more aggressive.

The use of tricyclic antidepressants in the treatment of pediatric CVS is currently recommended, but their vasodilatory effects may aggravate orthostatic intolerance. We may be able to provide additional guidance regarding management strategies for orthostatic intolerance based on the high prevalence of the condition observed in our study. [20] The use of treatments that reduce orthostatic intolerance in patients with CVS should be considered and further assessed. These treatments include salt supplementation, fludrocortisone, and beta-adrenergic blockers. Our study mostly involves adults, whereas the recommended treatments were formulated for children.

The study we conducted has several limitations. Instead of clinical assessments or laboratory tests, questionnaires were used to establish diagnoses. There are no clinically validated question sets even though they were based on specific criteria. In addition, only a subset of subjects was tested for autonomic function. A third limitation may be that the control group was slightly younger than CVS and migraine groups, but the results of comorbidity studies should not be significantly affected by this factor. It remains unclear whether adult CVS is equivalent to childhood CVS, and our findings may not directly apply to pediatric populations.

CONCLUSION

In conclusion, our study indicates that while CVS and migraines share certain autonomic comorbidities, such as orthostatic intolerance, there are sufficient distinctions, at least in adults, to challenge the conventional notion that CVS is merely a variant of migraine. Moreover, the strong correlation between CVS and chronic pain disorders like CRPS and fibromyalgia suggests potential shared underlying factors. This raises the question of whether CVS might be better categorized

as a chronic pain disorder, prompting considerations for a more comprehensive therapeutic approach, particularly in adults.

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