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Original Article

Anti-Migraine Approach to Treat Cyclic Vomiting Syndrome: Response to Anti-Migraine Therapy in Adult Patients

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Abstract

Objective: To determine the efficacy of anti-migraine therapy in the treatment of cyclic vomiting syndrome in adult patients.

Methods: A prospective study was conducted at the Abbas Institute of Medical Sciences (AIMS), between March 2021 and February 2024. All adult patients with the diagnosis of Cyclic Vomiting Syndrome (CVS) as per ROME-IV criteria, were included in the study from outpatient departments of neurology and internal medicine. These patients were treated with anti-migraine therapies. The efficacy of individual drugs was assessed, and then the anti-migraine treatment as a composite group was also evaluated.

Results: A total of 21 patient were included in the study, 62% (13) were female and 38% (8) were male patients. The mean age was 31.3 years, with a range of 14 to 51 years. The mean duration of symptoms was 18.7 months and ranged from 12 to 60 months. The mean duration of treatment after diagnosis with anti-migraine therapy was 2.14 months with a minimum of 1 month and a maximum of 4 months (SD ± 0.9). The mean frequency of symptoms was 4 (SD ± 2.4) episodes and varied from 2 to 8 episodes per year. There was a complete response to treatment with resolution of symptoms in 57% (12), 28% (6) had a partial response, and 14% (3) had no response to treatment. The most effective treatment intervention was found to be topiramate, with a complete response and resolution of symptoms in 43% of the study population. Propranolol was effective in 29%, cinnarizine and amitriptyline were effective each in 14% of patients. As a composite group, the efficacy of anti-migraine treatment was statistically significant (p-0.03).

Conclusion: The diagnosis of cyclic vomiting syndrome is clinical, as there are no available specific diagnostic tests or biomarkers. An anti-migraine treatment approach during the inter-episode phase of CVS was effective.

Keywords: Cyclic Vomiting Syndrome, anti-migraine therapy

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Introduction

Cyclic vomiting syndrome and abdominal migraine share overlapping clinical features with migraine but lack the characteristic feature of headache. These characteristic clinical features of these conditions are recurrent episodes of nausea and vomiting associated with abdominal pain. These symptoms last for a few hours and may persist for a few days. Typically, there are symptom free periods and these patients remain well and symptom free between attacks. These conditions are usually present in childhood, however, it now recognized that both of these cyclic syndromes can present for the first time in adulthood.[1]

Vomiting is a common gastrointestinal disorder in adults and patients suffering from this condition are sometimes misdiagnosed and undergo several invasive and un-necessary investigations and consequently mismanaged as well.[2] The emesis is coordinated by the vomiting center in the brain stem. This complex center located in the floor of the fourth ventricle in the medulla, has four different sources of afferent inputs. These sensory inputs include afferent vagal fibers from the gastrointestinal tract, sensory fibers from the vestibular system, inputs form higher central nervous system including the amygdala and chemoreceptor trigger zone. These diverse sensory

inputs are a reflection of the miscellaneous, heterogeneous and varied etiologies of vomiting. There is a long list of causes of vomiting, some of which include mechanical obstruction of the Gut, dysmotility, peritoneal irritation, hepatobiliary and pancreatic disorders, infections, vestibular disorders, increased intracranial pressure, migraine, anti-tumour chemotherapy, drugs and psychogenic. Another, relatively uncommon cause of recurrent vomiting is cyclic vomiting syndrome, defined by ROME – IV diagnostic criteria as;[3]

1. Acute episodes of vomiting of less than one week duration
2. At least three separate episodes of vomiting during the previous year and 2 episodes in the last six months, occurring after an interval of at least one week apart.
3. No vomiting between episodes, few milder symptoms may persist between episodes.

Three months of symptoms fulfill the criteria, onset of symptoms at least 6 months before diagnosis. The aim of preset study is to determine the efficacy of anti-migraine therapy in the treatment of cyclic vomiting syndrome in adult patients.

Methods

his prospective study was conducted at the Abbas Institute of Medical Sciences (AIMS) Muzaffarabad. AIMS is a public sector teaching hospital of the department of health of Azad Jammu & Kashmir government affiliated with AJK-Medical College. The study was conducted between March 2021 and Feb 2024. All adult patients, with the diagnosis of Cyclic Vomiting Syndrome (CVS), were included in the study from outpatient departments of neurology and internal medicine. The institutional ethical review committee of Abbas Institute of Medical Sciences (AIMS) approved the study. The Rome-IV criteria was used to diagnose this syndrome. A standard Performa, designed for the study was used to collect and document the demographic information, detailed medical history and physical examination of patients. The gender, age, education, marital status, nature of job and profession, chief presenting complaints and associated symptoms, smoking and other recreational activities were recorded. The family history of similar conditions and migraines was also documented. A complete general and systemic physical examination was performed and documented. All patients had a basic laboratory biochemical evaluation which included the complete blood examination, blood sugar levels, urea, creatinine and urine examination. Further evaluation was according to the presenting complaints and clinical condition of the patients, which included an upper GI endoscopy, CT scan and/or MRI of the brain. All patients were evaluated and diagnosed by a team of consultants from internal medicine, a neuro-physician and a gastroenterologist before starting the trial medications. All patients were treated with an anti-migraine approach with topiramate, amitriptyline, propranolol and cinnarizine. The follow up and treatment supervisions were done by the neuro-physician.

Inclusion criteria: Adult patients, with the clinical diagnosis of cyclic vomiting syndrome (ROME-IV criteria).[4]

Exclusion criteria: Patients with any other known and diagnosed systemic conditions or causes of vomiting

Statistical analysis: All statistical analyses were performed using SPSS version 23.0 (SPSS Inc., Chicago, IL, USA). For all tests, p values of <0.05 were considered statistically significant. Continuous parametric variables were reported as mean ± standard deviation; nonparametric continuous variables were reported as median and categorical variables were expressed as percentages. The efficacy of individual drugs was determined and then anti-migraine treatment as a composite group was also evaluated.

Results

A total of 21 patient were included in the study, 62 % (13) were female and 38 % (8) were male patients. The mean age was 31.3 years with a range from 14 to 51 years. The mean duration of symptoms was 18.7 months and ranged from 12 to 60 months. All patients had previously used treatments as given in table-1

The mean duration of treatment after diagnosis with anti-migraine therapy was 2.14 months with a minimum of 1 month and a maximum of 4 months (SD ± 0.9). The mean frequency of symptoms was 4 (SD ± 2.4) episodes and varied from 2 to 8 episodes per year. The typical symptoms were sudden onset of vomiting which persisted from few hours to 2-3 days. In between symptoms patients remained symptom free without any epigastric discomfort or loss of appetite. No patient had warning upper gastrointestinal symptoms. In all patients, baseline investigations blood complete examination, blood sugar levels, urea, creatine, Liver function tests were within normal limits. The plan CT-Scan Brain and upper gastrointestinal endoscopy was also normal.

There was a complete response to treatment with

resolution of symptoms in 57% (12), 28% (6) had a partial response and 14% (3) had no response to treatment. The most effective treatment intervention was found to be topiramate, with a complete response and resolution of symptoms in 43% of the study population. Propranolol was effective in 29%, cinnarizine and amitriptyline were effective in 14% of patients. As a composite group, the efficacy of anti-migraine treatment was statistically significant (*p*-0.03). However, statistical analysis for individual treatment agents (propranolol, topiramate, cinnarizine and amitriptyline) was not statistically significant despite the fact that with all these medications there was variable symptomatic improvement in patients (Table-2). There was a relapse of symptoms in 33% (7) patients during follow up and they were treated with the previously prescribed medicines.

Table 1: *Demography and characteristics of patients.*

Characteristics		n	%
Gender	Male	13	62
	Female	8	38
Investigations	CT-Scan Brain Upper GI endoscopy Baseline Hematology and biochemistries	21	100
Past treatment with no improvement in symptoms	PC/NSAID/PPI	11	52.4
	PPI	1	4.8
	H_2R	1	4.8
	Domperidone	2	9.5
	Dimenhydrinate	1	4.8
	H-Pylori eradication	1	4.8
	Meclizine	1	4.8
	Alternate medicines	1	4.8
	No treatment	2	9.5
Prescribed treatment during trial	Propranolol	6	28.6
	Topiramate	9	42.8
	Cinnarizine	3	14.3
	Amitriptyline	3	14.3
Treatment Response	Complete	12	57
	Partial	6	28.6
	Nil	3	14.3
Relapse of symptoms	Nil	14	66.7
	yes	7	33.3
Characteristics	**Mean**	**SD**	**Range**
Age (Years)	31.3	11.4	14-51
Duration of symptoms before diagnosis (months)	18.7	12.5	Dec-60

Discussion

The cyclic vomiting syndrome (CVS) is a relatively uncommon condition to be diagnosed in adult patients. Given that upper gastrointestinal symptoms and vomiting are very common in both emergency and outpatient departments, and that the underlying etiologies are diverse and varied, the diagnosis of CVS is often delayed.[5]

The clinical features of cyclic vomiting syndrome were first described in France (1806) and later in England (1882). Despite two centuries of recognition, the underlying pathophysiology and optimal management of CVS remain disputed. However, significant progress has been made over the last 2–3 decades, marked by the formation of national support groups (USA & UK - 1993), the recognition of CVS in adult patients (2006), the publication of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) Consensus Statement on CVS (2008), and the inclusion of diagnostic criteria for this condition in the Rome IV classification (2016). These milestones have greatly improved the diagnosis and treatment of CVS.[6,7]

In adults, it is critical to rule out other organic causes of vomiting before diagnosing CVS. Consequently, the diagnosis is often delayed by months or even years. In this study, the mean duration of symptoms before diagnosis was more than 18 months, with a range of 12–60 months. Venkatesan et al. reported an average of 15 emergency department visits before diagnosis.[8] The typical delay in diagnosis is 5–6 years, due in part to specialty-oriented, fragmented care in adult patients.[9]

Most of these patients are attended, evaluated, and managed by young residents in emergency departments. Therefore, increasing awareness of CVS among healthcare providers is crucial to prevent unnecessary delays in diagnosis, avoid invasive diagnostic testing, and reduce inappropriate treatments. CVS has four distinct clinical phases: the prodromal, emetic, recovery, and inter-episodic

Table 2: *Efficacy of treatment agents and composit*

		Estimate	Std. Error	Wald	df	Sig.	95% Confidence Interval	
							Lower Bound	Upper Bound
Composite	group	2.25	1.06	4.48	1	0.03	0.16	4.34
Treatment agent	amt	-0.24	1.53	0.025	1	0.87	-3.25	2.76
	cin	0.31	1.44	0.047	1	0.82	-2.52	3.15
	prop	1.41	1.2	1.37	1	0.24	-0.95	3.77
	tmpt	-0.6	1.48	0.167	1	0.68	-3.51	2.3

amt: amitriptyline cin: cinnarizine prop: propranolol tmpt: topiramate

phases. Treatment depends on the clinical phase, but most patients present during the emetic phase and are treated accordingly. Because these patients remain asymptomatic during the inter-episodic phase, preventive strategies are often overlooked during this time. In this study, the mean frequency of symptoms was 4 episodes per year, with a range of 2–6 episodes. Other studies have reported an annual average frequency of 9.6 to 14.4 episodes per year.[10]

CVS is more common in children, and most clinical data are derived from pediatric populations. In this study, the mean age of patients was 31.3 years (SD ± 11.39), with a range of 14–51 years. All patients were evaluated with routine baseline investigations (hematology and biochemistry) and underwent CT scans of the brain and upper GI endoscopy. Only those with normal investigations were diagnosed with CVS. These patients had been treated symptomatically in the past with various pharmacological therapies, including proton pump inhibitors, H2 receptor antagonists, domperidone, H. pylori eradication, meclizine, dimenhydrinate, and local traditional alternative treatments and herbal therapies. During this study, all patients were treated with anti-migraine therapies, including propranolol, topiramate, cinnarizine, and amitriptyline. There was complete or partial clinical response to therapy, with symptomatic improvement in the majority of patients. As a composite group, the efficacy of anti-migraine treatment was statistically significant ($p = 0.03$). However, statistical analysis for individual treatment agents (propranolol, topiramate, cinnarizine, and amitriptyline) was not statistically significant. In this study, patients were treated with general management during the symptomatic phase, and anti-migraine therapy was continued during the inter-episodic phase. A complete response to treatment was observed in 57% of patients, while another 28% had a partial response. The most effective treatment was topiramate during the inter-episodic phase of CVS.

The American Neuro-gastroenterology and Motility Society (ANMS) and the Cyclic Vomiting Syndrome Association (CVSA) had recommendations for tricyclic antidepressants (amitriptyline) and topiramate as the first-line prophylactic treatment of CVS.[11] There are also recommendations for evaluating and managing associated comorbidities, such as anxiety and depressive illness, along with sleep disorders.[12] These patients may need evaluation by other allied clinical specialties for associated diagnosis and management of associated conditions.

In recent years, topiramate has emerged as an effective prophylactic therapy for CVS. In this study 43% of patients responded to topiramate treatment. Badhian et al found topiramate to be an effective prophylactic treatment of CVS in 39% of patients.[13,14] Recent guidelines also recommend topiramate in moderate-to-severe CVS as prophylactic treatment. However, there is acknowledgment of the poor quality of evidence based on small clinical studies in children and adults.[15,16] This condition is more common in the female population as reported in the review article by Frazier.[17] In this study, 62% of patients were female. In adults the minimum workup includes abdominal radiology and upper gastrointestinal endoscopy. During the study period one third of patients (33.3%) had frequent relapses and were managed again with anti-migraine therapy. A study by Haghighat M et al found relapse of symptoms in 10.5% of patients after stopping treatment with propranolol and which were managed by increasing the dose of propranolol or by adding another anti-migraine therapy.[18]

Conclusion

The diagnosis of cyclic vomiting syndrome remains clinical. There are neither specific diagnostic tests nor biomarkers for diagnosis. Awareness of the symptoms and clinical presentations of this

condition, along with cognitive knowledge of its presence and consideration in differential diagnoses, is crucial when evaluating and managing adult patients. An anti-migraine treatment approach during the inter-episodic phase of CVS was effective.

Ethical Approval: The IRB/EC approved this study via letter no. 5476/AIMS/2021 dated February 9, 2021.

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Authors' Contribution

AK: Conception

RR,MA: Design of the work

MH,MB: Data acquisition, analysis, or interpretation

RR,MA,MB: Draft the work

AK,MH: Review critically for important intellectual content

All authors approve the version to be published

All authors agree to be accountable for all aspects of the work

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