

Clinical Note

Migraine as a Cause of Persistent Nausea or Vomiting in Palliative Care: A Case Series

Becky Hirst, MA, MBChB, MRCP, and Bill Noble, MBChB, MRCP, MD
Academic Unit of Supportive Care, University of Sheffield, Sheffield, United Kingdom

Abstract

Migraine is common, underdiagnosed, and frequently inadequately treated in the general population. Nausea and vomiting are common reasons for patients to be referred for symptom control. Nausea can be the most prominent feature of migraine; the International Classification of Headache Disorders (ICHD) recognizes cyclical vomiting syndrome as a migraine variant in children, and there is increasing evidence for a similar entity in adults. We present three patients with troublesome nausea uncontrolled by conventional antiemetic therapy. On questioning, all three had other symptoms suggestive of migraine, and two had a family history. Their symptoms settled with the use of various antimigraine therapies. Amitriptyline appears to be particularly useful. A therapeutic trial of prophylaxis may be indicated for patients whose nausea and vomiting may be attributed to migraine. J Pain Symptom Manage 2009;37:918–922. © 2009 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.

Key Words

Migraine, nausea, vomiting, cyclical vomiting syndrome, palliative care, amitriptyline

Introduction

Nausea and vomiting are symptoms commonly seen by palliative care teams, with up to 60% of patients with advanced cancer being affected.¹ Cyclical vomiting is a recognized migraine variant in children.² It is becoming increasingly acknowledged that the same symptoms in adults also may represent migraine, without headache being prominent.³ We present three patients who were referred to the palliative care team with nausea and vomiting resistant to antiemetics and whose diagnosis of migraine was key to understanding

the origin of their symptoms. These symptoms subsequently resolved with antimigraine therapy.

Case 1

A 55-year-old man underwent curative resection for esophageal cancer. The immediate postoperative period was complicated by nausea and vomiting resistant to ondansetron, metoclopramide, haloperidol, prochlorperazine, and levomepromazine. An endoscopy showed a narrow pylorus, which was treated by balloon dilatation, and a water soluble swallow showed delayed gastric emptying. His symptoms settled three months after the original surgery, but recurred, and he subsequently required two further admissions for persistent abdominal pain, nausea, and vomiting. The second of these admissions was to the Sheffield Macmillan Unit

Address correspondence to: Becky Hirst, MA, MBChB, MRCP, Northern General Hospital, Herries Road, Sheffield, South Yorkshire S5 7AU, United Kingdom. E-mail: rebeccahirst@nhs.net

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for Palliative Care to achieve symptom control. He was complaining of right upper quadrant pain and constant nausea, associated with retching. He also had episodic dizziness associated with a headache and excessive belching. At that time, his medications included various analgesics and antiemetics. Of these, gabapentin, lidocaine patch, levomepromazine, and methylphenidate were stopped; mirtazepine and fentanyl doses were reduced. He then had an episode of headache associated with nystagmus, dizziness, and temporal tenderness. An erythrocyte sedimentation rate (ESR) was normal, as was a computed tomography (CT) scan of his head.

Although he had never acquired a formal diagnosis of migraine, further questioning revealed a past history of episodic, right-sided headache precipitated by noise. This was associated with dizziness but not nausea and vomiting. Before surgery, he had been started on atenolol for hypertension with instant resolution of his headaches, but symptoms returned when the atenolol had been changed to ramipril. There was no family history of migraine or associated syndromes.

He was commenced on propranolol, which was titrated up to 40 mg three times daily, with complete resolution of nausea, vomiting, headache, and vestibular symptoms. His nausea and vomiting recurred, and he required a further admission. Amitriptyline was added and titrated up to a current dose of 125 mg at night, again with complete resolution of his symptoms. There is no evidence of recurrence of esophageal cancer.

Case 2

A 48-year-old woman had suffered severe, intractable nausea of three months duration. Symptoms began after a meal on an airplane three months previously, and necessitated admission to hospital for intravenous fluids while abroad on holiday. On return to Britain, she had a series of investigations, including gastroscopy, head and abdominal CT scans, and small bowel barium studies, all of which were normal. The nausea had not responded to antiemetics, including prochlorperazine, domperidone, metoclopramide, and ondansetron (which had caused agitation). She had no teichopsia, scotoma, paresis, or conjunctival

injection. The attack was coincident with the onset of menses after having missed a couple of menstrual periods.

She reported five episodes of severe nausea in 25 years, mostly at times of stress. They lasted about a week on each occasion. She also had occasional episodes of severe hunger and right-sided frontal and retro-orbital headache precipitated by exercise. The headache and nausea never occurred simultaneously and were not previously attributed to migraine. Her father has migraine without aura for which he takes amitriptyline, and also has a history of vomiting after meals.

Although her presentation was not typical of migraine, the history of a first degree relative with the condition prompted a trial of antimigraine therapy. The nausea was completely relieved by two subcutaneous 6 mg doses of sumatriptan. She was commenced on pizotifen for prophylaxis. She had a further episode of nausea, vomiting, and headache associated with another delayed menstrual period three months later. She was switched to amitriptyline and experienced no further symptoms on 50 mg daily. Her periods remain unpredictable and less frequent.

Case 3

A 20-year-old woman was referred to the palliative care team having been diagnosed with a left ovarian germ cell tumor four years previously, requiring left oophorectomy followed by chemotherapy. There was no evidence of tumor recurrence. She complained of persistent nausea ever since regaining consciousness after surgery. No antiemetics had been particularly helpful. She also was troubled by headache, tinnitus, teichopsia, and excessive belching. She was overwhelmed by tiredness, which she associated with the headache, and had acquired a diagnosis of chronic fatigue syndrome. She was taking the combined oral contraceptive pill (COC) for decreased ovarian function after the chemotherapy, and noticed that the headache and associated symptoms were worse in the week off the contraceptive pill. Her mother suffers from migraine with aura.

Trials of sumatriptan and pizotifen were unsuccessful. Amitriptyline was commenced and titrated up to a dose of 140 mg. She had no

further severe episodes of headache or nausea, and the tinnitus was also greatly improved. Some further episodes were precipitated by cheese consumption. She is currently taking propranolol 40 mg three times daily and amitriptyline with no recurrence of symptoms.

Discussion

Migraine is common. Epidemiological studies estimate that around 30 million Americans are affected, of whom only a minority are able to function normally during attacks. Around half will get a diagnosis of migraine, and of these, a significant proportion will not receive optimal treatment.⁴ Given how common it is for patients not to receive a diagnosis, it is unsurprising that none of the three cases had previously had their symptoms correctly attributed to migraine. A genetic component to migraine is well known. Some types are inherited in a simple Mendelian way—for instance, familial hemiplegic migraine involves a mutation on chromosome 19—but most show multifactorial inheritance and interplay with environmental factors; hence, there will not always be a family history of the condition.⁵ An absence of family history for Case 1, therefore, does not preclude the diagnosis of migraine. However, all three cases reported here had either a family or a past history of migraine.

Cyclical vomiting syndrome in children is documented in the International Classification of Headache Disorders (ICHD) as a variant of migraine.² Although an adult correlate is not recognized in the ICHD, there is increasing evidence that such an entity might exist. Case series, such as that by Prakash et al., of 39 patients aged between 1.8 and 75 years, show a similar symptom picture in adults as in children, although episodes of vomiting tended to be more protracted in adults.³ Another case series showed that patients subsequently diagnosed and managed as cyclical vomiting syndrome had frequently been seen by two or more physicians and had a myriad of investigations, and even surgery, including partial gastrectomy, pyloroplasty, or fundoplication, with no improvement in symptoms.⁶ Cases 1 and 2 had both been extensively investigated before receiving our input, and all three had multiple attempts at control of symptoms with antiemetics. Recognized precipitants of

cyclical vomiting include stress (which may be emotional, physical, or psychological), infections, foods, and menses in females.³ There is no doubt that Cases 1 and 3 had undergone significantly stressful events; having been previously entirely fit and well, they were then given a diagnosis of cancer and underwent major surgery, albeit with curative intent. Case 3's susceptibility to migraine may relate to lower levels of estrogen because of surgery and chemotherapy, but may also be compounded by estrogen withdrawal in her week off the COC.⁷ Case 2 clearly associated stressful events with previous spells of vomiting, but it seemed that becoming perimenopausal had precipitated the current episode, with the pattern of a couple of missed menstrual periods followed by an attack associated with the onset of menses. Again, this is likely to be because of lower estrogen levels in a susceptible individual. Menopause is known to change migraine patterns, although it may improve or worsen. Up to 13% may develop migraine for the first time with the climacteric, and there is some evidence that those undergoing a surgical menopause have worse symptoms than those undergoing a natural one.⁸

There is evidence that migraineurs have an increased tendency to nausea and vomiting. They are more likely to suffer nausea and vomiting after surgery than patients without a diagnosis of migraine.⁹ This may explain why nausea and vomiting became problematic for Case 1 when previously it had not been a prominent symptom of his migraines. There also appears to be a link between motion sickness and migraine. One study found that around half of migraineurs suffered from motion sickness, compared with only 20% of a group with tension-type headache, and around 5% of a population with other neurological complaints.¹⁰ It seems that less vestibular stimulation is required to trigger motion sickness in migraine sufferers and symptoms tend to be more severe for the same amount of vestibular stimulation. It is possible that an underlying susceptibility precipitates nausea more quickly and causes it to increase more rapidly to a greater severity than in individuals without migraine. A history of motion sickness per se is a strong predictor of postoperative nausea and vomiting.^{11,12}

No one treatment has been shown to be effective in cyclical vomiting syndrome in

children or its corollary in adults. Prokinetics and conventional antiemetics provide some benefit, but this is not sustained.⁶ The fact that the former is not particularly helpful is surprising, as gastric stasis has long been thought to be the underlying cause of nausea in migraine. However, a study by Aurora et al. showed that migraineurs have impaired gastric emptying at all times, not just during an attack, implying impaired autonomic function. Furthermore, nausea is often alleviated by triptans, which, as 5HT_{1B/1D} antagonists, should worsen stasis.¹³ There is anecdotal evidence for the use of propranolol and pizotifen, as well as triptans, but there is little substantial evidence for efficacy. One case series found that about 75% of patients had their nausea fully or partially relieved by amitriptyline.⁶ There is quality evidence (Level A) for the use of a tricyclic antidepressant, particularly amitriptyline, or β -blockers as first-line migraine prophylaxis.^{14,15} Tricyclics may act on afferent pathways involved in the central regulation of vomiting. Commonly accepted indications for migraine prophylaxis include: disability for three or more days a month, attack duration longer than 48 hours or severe disability, and patient preference for preventative treatment.¹⁵ Although it was not always easy to identify discrete attacks in two of our patients, there was no doubt they were profoundly disabled by their symptoms and all three have benefited from prophylaxis.

Given the prevalence of migraine in the general population and that of nausea and vomiting in those referred to palliative care, it behooves us to consider migraine as a possible cause for these symptoms. Although cyclical vomiting syndrome is not yet a formally recognized migraine variant in adults, this case series adds credence to the accumulating evidence that there may be a relationship. Migraine is rarely discussed in palliative medicine texts, with the exception of the *Oxford Textbook of Palliative Medicine*, where it is considered in relation to the use of amitriptyline as an adjuvant analgesic.¹⁶ For the most part, treatment need not be considered differently in the palliative care population than the general population. However, it is worth remembering the high incidence of depression in this cohort and the popularity of selective serotonin reuptake inhibitors (SSRIs) for

treatment of this condition. Side effects of SSRIs include headache and nausea, and there is some evidence from case reports that they may exacerbate migraine.^{17,18} Using a triptan concurrently with an SSRI increases the risk of central nervous system (CNS) toxicity,¹⁹ which is another compelling reason to avoid this class of drugs when treating depression in migraineurs in general.

Physicians should avoid making a diagnosis of migraine as a cause of nausea or vomiting when there is neither a past history nor a family history, but migraine may emerge as a possibility with careful questioning about these factors and associated symptoms. A therapeutic trial of migraine treatment or prophylaxis may then be indicated.²⁰

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