Rare causes of emesis

Stefan L. Popa¹, Giuseppe Chiarioni², Liliana David¹, George I. Golea¹, Dan L. Dumitrascu¹

Abstract
Prompt diagnosis in the emergency department in the case of a patient with emesis may be difficult due to the increasing prevalence of diseases which manifest with emesis. Furthermore, in the case of chronic symptomatology, management and therapy are even more complicated. One episode of emesis rarely causes complications, but severe or repetitive episodes of emesis can cause life-threatening complications. For this reason, the diagnosis of the underlying disease which manifests with emesis is mandatory to be established in a short time in order to choose the correct therapeutic option. In order to systematize the process of diagnosis, this clinical narrative review will discuss only rare causes of emesis.

Keywords: vomiting, Reye’s syndrome, ackee poisoning, systemic mastocytosis, Meniere’s disease, xanthinuria, hydrocephalus

Introduction
Emesis is a complex reflex, frequently preceded by increased salivation, and begins with involuntary retching and allows an animal or person to rid itself of ingested toxins or poisons [1,2]. Constriction of the abdominal muscles with the relaxation of the gastric cardia actively forces gastric contents back up the esophagus.

The medullary vomiting center is responsible for the coordination of the emesis reflex, which is influenced directly by afferent innervation, chemoreceptor trigger zone and other central nervous system centers. The most common causes of emesis are gastrointestinal disorders. Because almost all organs and systems can be involved in the pathogenesis of emesis, the diagnosis of the underlying disease may be difficult in some cases (Figure 1) [2].

An essential step in the management of emesis is to make a distinction between acute versus chronic symptoms. Acute emesis is defined as episodic vomiting that occurs for less than one week and is associated with acute conditions. Chronic emesis is defined as a period of episodic vomiting longer than one week and is frequently associated with chemotherapy, functional gastrointestinal disorders, drugs, neurologic and neuropsychiatric disorders [1].

One episode of emesis rarely causes complications, but severe or repetitive episodes of emesis can cause life-threatening complications including: acid-base imbalance, dehydration and electrolyte depletion or aspiration pneumonia. For this reason, the diagnosis of the underlying disease which manifested with emesis is mandatory to be established in a short time in order to choose the correct therapeutic option [1,2].

If the majority of gastrointestinal disorders manifested with emesis are easy to diagnose using standard techniques (blood tests, abdominal ultrasound, endoscopy or computer scan), several disorders deserve to be described in detail. An essential step in the differential diagnosis of gastrointestinal disorders manifested with emesis is to clarify if the disorder is organic or functional [2].

Functional gastrointestinal disorders (FGID) are a highly prevalent group of disorders characterized by the lack of organic or chemical abnormalities, and the diagnosis is made using Rome IV Criteria, introduced in 2016 [2].

In this narrative review, we do not refer to rare diseases manifested with emesis; we refer to non-gastrointestinal rare causes of emesis (Table I).
Figure 1. Causes of emesis.

Table 1. Rare causes of emesis.

| Disease               | Symptoms and signs                  | Positive diagnosis                                                                 | Treatment and management                                                                                   |
|-----------------------|-------------------------------------|------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|
| Reye’s Syndrome       | Vomiting, Personality changes, Confusion, Seizures, Loss of consciousness      | MRI: symmetric thalamic, basal ganglia and white matter lesions in children with a recent history of salicylates drug intake | Avoiding salicylates, Supportive care to treat: hyperammonemia-sodium benzoate/sodium phenylacetate IV, Hypoglycemia-dextrose 25%, Acidosis-alkalinizing agents, Vomiting-ondansetron, Anticonvulsants- Lorazepam, Increased intracranial pressure-mannitol |
| Ackee poisoning       | Diaphoresis, Tachypnea, Tachycardia, Tonic-clonic convulsions, Seizures          | Patient’s history of eating ackee fruit, Profound hypoglycemia <3 mg/dl                 | Dextrose solution, Active Charcoal, Vomiting-Antiemetics, Seizures-Benzo diazepines                        |
| Systematic Mastocytosis | Anemia and coagulopathy, Abdominal pain, Diarrhea, Nausea, Vomiting, Pruritus and flushing | Anemia, Thrombocytopenia, Leukocytosis, Monocytosis, Increased level of serum tryptase, Bone marrow biopsy: dense infiltrates of mast cells, Liver biopsy | Primarily symptomatic, Management of, Anaphylaxis and related symptoms-epinephrine, H1 and H2 blocker, Corticosteroids, Pruritus and flushing- psoralen ultraviolet A therapy, Intestinal malabsorption |
| Meniere Disease       | Vertigo, Hearing loss, Tinnitus, Vomiting                                     | Audiometry, Electrocochleography, Electronystagmography                               | Symptomatic relief, Vertigo- diazepam, steroids, Vestivulosuppressants and antinausea- meclizine, prochlorperazine |
| Xanthinuria           | Irritability, Vomiting, Hematuria, Pyuria, Renal colic, Joint pain and muscle cramps | Urine xanthine, Hypoxanthine levels, Ratio 4:1, Xanthine plasma levels between 10 and 40 µmol | High fluid intake, Low purine diet, Avoiding dehydration, Treatment of complications                      |
| Hydrocephalus          | Slowing of mental capacity, Headaches, Neck pain, Blurred Vision, Double vision, Vomiting | Head Enlargement, Disjunction of sutures, Dilated scalp Vein, Papilledema              | Decreasing the secretion by the choroid plexus-acetazolamide and furosemide, Increasing the reabsorption of Cerebrospinal Fluid- Isosorbide, Repeated lumbar punctures, Choroid plexectomy, Choroid plexus coagulation, Ventriculoperitoneal shunt |
Methods

We examined articles in PubMed from 1999 to 2019, focused on rare causes of emesis. Keywords of the search were: "Emesis", "Vomiting", "Reye's Syndrome", "Ackee poisoning", "Systemic Mastocytosis", "Meniere's Disease", "Xanthinuria", "Hydrocephalus. Studies written in languages other than English, conference presentations, letters to the editor, editorials, comments, and opinions were also excluded.

Results

Reye’s syndrome

Reye’s syndrome is an acute disorder, potentially fatal, with a usual onset after a viral infection of the upper respiratory tract or gastroenteritis characterized by an acute encephalopathy associated with hepatic dysfunction in pediatric patients with a peak age between 5-14 years [3-5].

The complex pathogenesis of Reye syndrome is still not elucidated. Studies show that mitochondrial injury is directly implicated, resulting in several dysfunctions that disrupt oxidative phosphorylation and fatty-acid beta-oxidation [3-6]. In at least 80% of the cases, the host has usually been exposed to mitochondrial toxins, most frequently salicylates.

Histopathological findings include cytoplasmic fatty vacuolization in hepatocytes, astrocyte edema and loss of neurons in the brain, and edema and fatty degeneration of the proximal lobules in the kidneys. Hepatic mitochondrial dysfunction results in hyperammonemia, which induces astrocyte edema, resulting in cerebral edema and increased intracranial pressure (ICP), which finally leads to severe emesis [3].

The viral infection (Influenza or Varicella are frequently reported) occurs 2 to 3 weeks before the symptomatology of Reye’s Syndrome. The symptomatology is dominated by extended and abundant vomiting, headache, altered mental status (confusion, agitation, delirium), signs of dehydration (xerostomia, oliguria, fluid intolerance), and seizures.

The diagnosis is based on clinical signs in concordance with the laboratory findings, which include elevated glutamic-oxaloacetic transaminase, glutamic pyruvic transaminase, bilirubin, hypoglycemia, increased serum ammonia and decreased serum bicarbonate [3,4].

If a spinal tap is performed, the cerebrospinal fluid contains a decreased level of leucocytes, demonstrating the absence of meningal inflammation [3].

To evaluate cerebral edema, the recommendation is to perform a head computer scan (CT) or magnetic resonance imaging (MRI) in order to exclude other causes of encephalopathy. Frequently reported in MRI findings are the diffuse cerebral edema and symmetric signal modifications of white matter, thalamic and basal ganglia [3].

The management is an emergency because of the rapid progression, but it is still mainly supportive, its primary goals are to maintain hemodynamical stability and the oxygen saturation levels in optimal parameters [3-5].

The treatment consists in correcting the hypoglycemia with dextrose-containing fluids (serum glucose target 100-120 mg/dl), the acidosis with sodium bicarbonate, mannitol of hypertonic saline fluids for cerebral edema, while increased ammonia levels will be treated with phenylacetate-sodium benzoate [4,5]. For severe increased intracranial pressure, mannitol or hypertonic (3%) saline is currently used and hypertonic saline should not be given to patients with elevated levels of sodium [5-7].

Ackee fruit poisoning

Ingestion of Blighia Sapida, known as ackee fruit [8], originally from West Africa and Central America, can lead to metabolic syndrome, generally known as Jamaican vomiting sickness [9]. The unripened fruit may lead to profuse vomiting, convulsions, seizures, hypoglycemia and coma. The main toxin found in the seeds is called hypoglycin B, a hypoglycemic substance.

Recent studies show that a high risk for ackee poisoning is represented by the consumption of unripe ackee fruit or reuse of the water in which an unripe ackee has been cooked or washed.

Since 1976, over 500 poisonings have been linked to ackee fruit in Jamaica and other countries, and more than 100 cases of acute illness and death were reported [9,10].

Toxicity is dose dependent; the first symptoms appear in the 6-48 hours of ingestion and the recovery appears after 7-20 days. In fatal cases, death usually occurs within 48 hours of ingestion and severe hypoglycemia, hepatic injury, and aciduria are responsible for exitus.

Laboratory findings are identical with those from Reye’s syndrome (hypoglycemia, hyperammonemia, metabolic acidosis), but glutaric and ethylmalonic acid levels increase in urine [10]. The treatment is supportive, and its primary goals are to maintain the euglycemia by giving boluses of dextrose to prevent dehydration by giving IV fluids and antiemetics and securing an airway [9,10]. Riboflavin and glycine are in some severe cases useful in therapy as they have been found to antagonize the effects of hypoglycin A intoxication [9].

Neurological symptoms can be treated with benzodiazepines. At the moment, there is no antidote for ackee fruit toxins [9]. Before modern therapies were developed, the mortality rate was more than 80%. With treatment, most patients make a full recovery.

Systemic mastocytosis

Systemic mastocytosis is a subcategory of myeloproliferative neoplasms that consists of an abnormal increase of mastocytes that affects an extracutaneous organ, frequently the bone marrow. There are two types of mastocytosis, the systemic and the cutaneous, which affects only the skin [11]. The clinical presentation has a
Meniere’s disease

Meniere’s disease is a pathology of the inner ear, affecting patients between 40 to 60 years old [15] and consists of spontaneous peripheral vertigo, tinnitus, alternating hearing loss, vomiting, and a fullness sensation in one or both ears [16]. It is considered to be a multifactorial disease with a strong genetic background [17]. This disease can affect one or both ears.

A specific feature frequently reported is the endolymphatic hydrops, which consists of an overflowing accumulation on endolymph in the inner ear, cochlea, and the semicircular channels, damaging the ganglion cells [18-19]. The diagnosis is established by using the patient’s medical history associated with a complex set of test including [19-22]:

I. Audiometry
II. Brainstem auditory evoked potentials
III. Electrocochleography (ECOG)
IV. Otoscopy
V. Caloric testing/electronystagmography (ENG)

Usually, patients with a suspicion of Ménière disease are not submitted imaging studies, but the differential diagnosis with brain cancer or stroke is difficult, therefore magnetic resonance imaging (MRI) or computed tomography (CT) is indicated.

The disease can be classified into several stages of progression. The first stage includes cochlear hydrops, which proceeds to affect the vestibular system. This is the reason why Ménière’s disease is most bothersome in the early stages. As the disease progresses to advanced stages, the hydrops fills the vestibule completely, pressure fluctuation ceases and consequently vertigo disappears [15-18]. The acute attacks are replaced by constant imbalance and progressive hearing loss. Episodes may occur as infrequently as once or twice a year or they may occur everyday. The prognosis of patients varies and some patients have minimal symptoms and others have severe symptomatology [15-20].

The management consists in reducing the symptoms, prevent the recurrence, and also the progression of the disease. For the treatment of the vertigo attacks, there are a few pharmacological possibilities. Antihistaminic agents acting on central receptors have a dual effect, anti-emetics and diminishing the vestibular syndrome [21]. GABA agonist agents, benzodiazepines (lorazepam diazepam) are also an option for the treatment of the acute vertigo attacks.

Surgical treatment is required for 5-10% of patients and consists of endolymphatic sac decompression associated with shunt placement [22-25]. Another treatment option is ablation, consisting of destruction of the labyrinth or the vestibular nerve, which will make the affected ear unresponsive to sense movement anymore, therefore, to stop vertigo [23-25].
Xanthinuria

Xanthinuria is a pathology based on an abnormal purine metabolism, characterized by the insufficiency of xanthine dehydrogenase/oxidase [26]. This rare autosomal recessive disorder characterized by the enzymatic deficiency of xanthine dehydrogenase/oxidase (which is involved in the conversion of the xanthine and hypoxanthine to uric acid) leads to low or even absent levels of uric acid (<1 mg/dL) and increased levels of xanthine levels in blood and urine. Patients can be asymptomatic or can have symptoms due to renal stones, frequently radiolucent, which can lead to kidney failure.

Xanthinuria can be subcategorized in three forms: type I with xanthine dehydrogenase deficiency, type II xanthine dehydrogenase, and aldehyde oxidase deficiencies, type III that includes both type II deficiency and molybdenum cofactor deficiency. To distinguish between Type I and Type 2, allopurinol test is performed. For Type 3, the laboratory findings show an increased urinary excretion of sulfur-containing metabolites [27]. The treatment consists of a restrictive diet with a low intake of purines and low fructose and a high intake of fluids.

Hydrocephalus

Hydrocephalus is a brain condition in pediatric patients that can be either acquired or congenital and consists of the expansion of the cerebral ventricles due to a modification of the cerebral spinal fluid physiology. A large part of children with congenital hydrocephalus has Aqueduct of Sylvius stenosis, holoprosencephaly or other brain malformations [28].

Hydrocephalus can be divided into obstructive and communicating. An intracranial mass (tumor, cyst) or congenital malformations can cause obstruction leading to the obstructive type. The communicating hydrocephalus can have multiple causes such as infections, intraventricular hemorrhage following an acute stroke, sinus thrombosis [28,29].

Acquired hydrocephalus develops due to brain tumors, posttraumatic or impaired venous drainage. The symptomatology depends on the age of the patient and consists in symptoms related to increased intracranial pressure: headache, vomiting without nausea, ataxia. In children with open sutures, the head circumference will expand [28,30].

Clinical signs corroborated with the paraclinical findings (ultrasonography, MRI, computed tomography) or cerebrospinal fluid pressure measurements can lead to the diagnosis of hydrocephalus [29-33].

In pediatric patients, a sign of increased intracranial pressure is represented by the protrusion of the frontal fontanelle. The symptomatology depends on the age of the patient and consists of symptoms associated with an increased intracranial pressure: headache, emesis, diplopia due to VI cranial nerve palsy and ataxia.

Ultrasound in the early stages of fetal development, in 18-20 weeks’ gestation, can identify ventriculomegaly [29]. MRI is preferred over CT to avoid radiation exposure, and it can show the cause and anatomy. The standard treatment is cerebral spinal fluid shunts. A ventriculoperitoneal shunt is frequently used, but other drainage CSF sites are also used: right atrium, pleural cavity. The other treatment solution is Endoscopic Third Ventriculostomy and cauterization of the choroid plexus [30].

The type of treatment is indicated based on the etiology of the hydrocephalus. For secondary hydrocephalus, the shunting or ventriculostomy may not be necessary if the cause is removed [32-34]. The standard treatment is the CSF shunting. The most frequent technique is the ventriculo-peritoneal shunt but other distal sites can be used for drainage (right atrium, pleural cavity) [29-33]. In aqueduct of Sylvius Stenosis, Endoscopic Third Ventriculostomy is recommended or as the solution in shunt failure and Chiari malformation [32-35]. Choroid plexus cauterization can also be associated with this operation.

Conclusions

A thorough understanding of the central and peripheral pathophysiology underlying emesis is essential for the optimal management of this disabling and complex symptom. However, treatments available are not effective in all patients, and the unmet need for a tailored approach would benefit from the development of novel, etiology focused therapies.

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