Clinical commentary

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Vomiting and retching as presenting signs of focal epilepsy in children

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ABSTRACT – Ictal vomiting is a rare condition easily misdiagnosed as a common disease. We report two children presenting with retching and vomiting as the main ictal manifestation. Patient 1 was a four-year-old girl with a history of daily nocturnal vomiting for two months, first interpreted as a functional disorder, then as a viral infection. She presented with vomiting accompanied by focal right-sided hemifacial clonic jerking, occurring multiple times per day. Video-EEG demonstrated ictal discharges associated with the retching and vomiting, over a normal background, and occasional interictal focal spikes. MRI was normal. PET demonstrated left-sided opercular hypometabolism. Patient 2 was a girl with a history of focal epilepsy, secondary to a right central dysembryoplastic tumour, first resected with subsequent seizure freedom at the age of three years. At five years of age, she presented with recurrent episodes of retching and vomiting initially diagnosed as migraine. Video-EEG showed ictal discharges, clinically correlating with retching, vomiting and clonic facial jerking, with normal interictal activity. Brain MRI showed a progression of the tumour. A second resection resulted in seizure freedom. Ictal vomiting often goes undiagnosed, especially in children, causing treatment delays. An ictal origin should be considered, particularly when the episodes are recurrent and stereotyped. [*Published with video sequences*].

Key words: ictal vomiting, retching, semiology, autonomic seizure, video-EEG recording

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Recurrent retching and vomiting in children can be caused by a large spectrum of disorders, from a simple infectious gastroenteritis or migraine, to intracranial hypertension, meningoencephalitis, toxic encephalopathies, and brain haemorrhage. However, vomiting can be the sole or main manifestation of a seizure. Ictal vomiting is a rare condition, easily misdiagnosed as a common disease (Shuper and Goldberg-Stern, 2004; Parisi *et al.*, 2014). Ictal vomiting

has been identified in different types of focal epilepsy. It has been reported in the context of Panayiotopoulos syndrome in children with normal development or neurological examination, experiencing rare, often one-time, prolonged seizures with vomiting, dysautonomic signs and other focal features such as eye deviation and impaired consciousness (Panayiotopoulos, 1988). Ictal nausea/retching/vomiting has also been described in adults and children with temporal lobe epilepsy and frontal lobe epilepsy (Kramer *et al*., 1988; Panayiotopoulos, 2004: Tarnutzer *et al*., 2018). Similar to other types of autonomic seizures, ictal vomiting was shown to originate from the anterior part of the temporal lobe, in the amygdala or in the insula. Early studies associated nausea and hypersalivation with insular onset (Penfield and Faulk, 1955; Fiol *et al*., 1988), and those findings have been subsequently confirmed (Russo *et al*., 2019). In ictal vomiting, the epileptic activity can originate from either the left or the right hemisphere, albeit more frequently from the dominant hemisphere (Tarnutzer *et al*., 2018; Sokolov *et al*., 2019).

We present two children who suffered from ictal retching and vomiting for several months before the correct diagnosis was made.

Case studies

A previously healthy, right-handed four-year-old girl presented to the emergency room with a history of refractory vomiting, which had occurred once or twice every night for the past two months, unrelated to meals or specific food intake. Family history was negative for epilepsy, migraine or other paroxysmal manifestations. Her development was normal; she walked and spoke her first words by one year of age. The episodes were first interpreted as functional disorder associated with her sister's birth, then as viral infection. There was no history of fever. Three days before admission, paroxysmal episodes of vomiting became more frequent, occurring up to 10 times a day. Anti-emetic drugs had no effect. Upon admission, it was noticed that the events were stereotyped, characterized by retching and vomiting, often followed by clonic jerks of the right hemiface. Clinical and neurological examination, as well as behaviour, were normal between the events. Fundoscopic examination was normal. Due to the stereotyped nature of the events, ictal vomiting was suspected, and sublingual oral lorazepam was administered, resulting in the disappearance of the hemifacial clonic phase. Nevertheless, the episodes of retching and vomiting persisted and progressively increased in frequency, up to every 10 minutes. The patient developed right-sided central facial paralysis and became disoriented.

Long-term video-EEG showed a normal organization of the brain activity during wakefulness and sleep, as well as rare interictal left fronto-central spikes. In addition, fronto-central bilateral and synchronous fast rhythms with higher amplitude over the left hemisphere were observed during sleep. Ictal EEG was characterized by rhythmic fast spikes with left fronto-central predominance, rapidly propagating to the same regions contralaterally (*figure 1*). Seizures lasted between 40 and 70 seconds with increasing frequency, evolving into focal status epilepticus. Seizures were stereotyped, occurring with the same semiology during wakefulness and sleep (*video sequence 1*). During sleep, seizures were characterized by sudden awakening, followed by retching, vomiting and rapid return to sleep. The onset of clinical manifestations was not always time-locked with the surface EEG ictal discharge, and could precede it by 5 to 15 seconds. The child was unable to talk during the events but was able to interact. Extensive blood and CSF testing was uninformative, and urinary toxic screening was negative. Anti-NMDA and anti-MOG antibodies were negative. 3-T brain MRI was negative. 2-[18F]-fluoro-2-deoxy-D-glucose positron emission tomography (18F-PET) demonstrated left opercular and frontal cortical hypometabolism (*figure 2*).

Intravenous (IV) levetiracetam (LEV) (50 mg/kg loading dose followed by 40 mg/kg/day) reduced seizure frequency, from every 10 minutes to every hour. Oral clobazam (CLB) (0.25 mg/kg) failed due to repetitive vomiting. Two loads of IV phenytoin (PHT) (20 mg/kg followed by 8.5 mg/kg/day) further reduced seizure frequency to one-two per day. Sublingual 0.1 mg/kg lorazepam (LZP) was added with disappearance of vomiting, while episodes of retching persisted. Carbamazepine (CBZ) was introduced at 22 mg/kg/day, leading to seizure freedom within days. The patient was discharged on oral LEV (42 mg/kg/day), PHT (6.3 mg/kg/day), and CBZ (22 mg/kg/day). After eight months of follow-up, the child remained seizure-free on CBZ monotherapy, with normal neurological examination and development.

Patient 2 was a right-handed, five-year-old girl with negative family history. Her development was normal; she started walking at 12 months, and her first words were at 18 months. She first presented at 2.5 years of age with left-sided focal clonic seizures due to a right central dysembryoplastic neuroepithelial tumour (DNET), resected at three years of age. After one year of seizure freedom post-surgery, she presented with recurrent episodes of sudden retching and vomiting, unrelated to meals or specific food intake. While there was no complaint of headache, she was initially diagnosed with migraine. The episodes lasted one to two minutes with increasing frequency, up to several times a day. Home videos showed the presence of retching

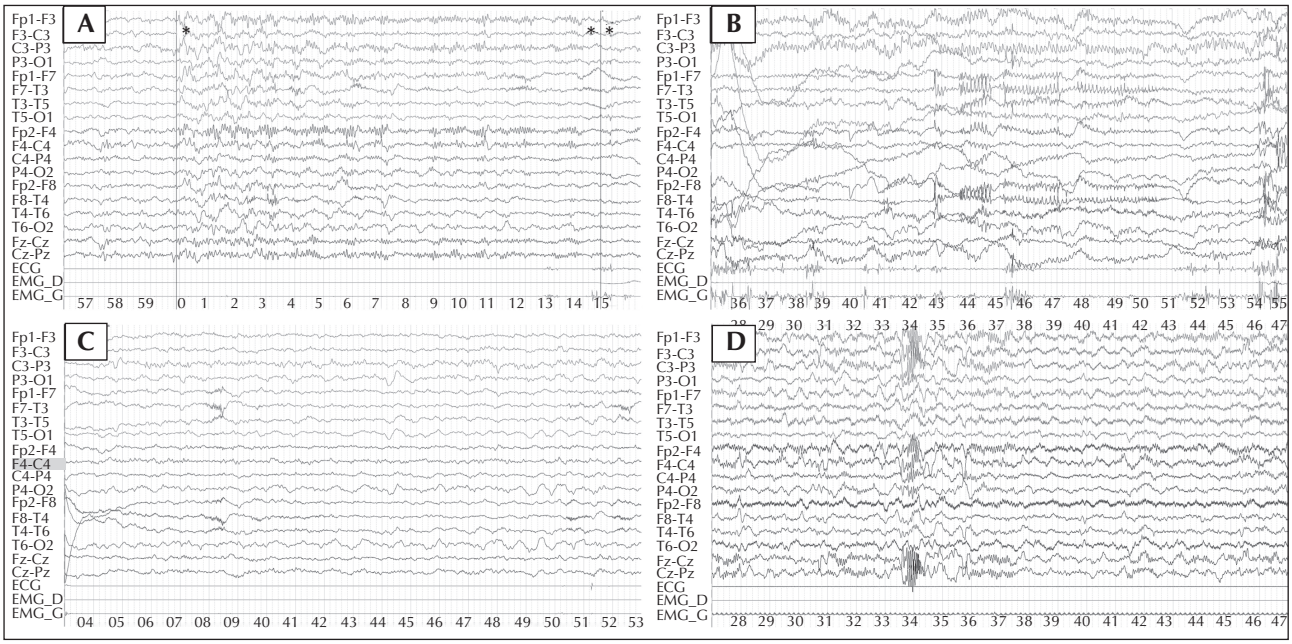

Figure 1. (A-C) Ictal EEG sequence during sleep. Prodromal phase (A) with sudden awakening and chewing showing the occurrence of rhythmic fast activity and polyspikes with left fronto-central predominance, rapidly propagating to the same regions contralaterally (*). Retching starts about 15 seconds later (**) and lasts about 2 minutes with increased frequency and amplitude of ictal discharges on EEG (B). At the end of the seizure, the patient falls back asleep after retching stops, and epileptiform discharges progressively disappear on both hemispheres but persist longer on the left fronto-central region (C). (D) Interictal EEG during sleep showing bilateral and synchronous fronto-central fast rhythms with higher amplitude over the left hemisphere (20 seconds/page; amplitude: 10 μV/mm).

and hypersalivation followed by focal clonic jerking of the right hemiface. Video-EEG demonstrated the epileptic nature of the episodes that recurred with a stereotyped semiology. The ictal discharges consisted of right parietal rhythmic theta arising on the surface EEG with homolateral centro-parietal propagation only 15 seconds after the onset of symptoms, concomitantly with the left hemiface clonic jerks (*video sequence 2*). Interictal EEG was normal. MRI showed a parietal non-enhancing progression of the tumour residue at the edge of the right parietal post-operative cavity, extending to the right thalamus. Tractography demonstrated the involvement of the pyramidal tract. A second surgical resection, including a posterior insulectomy, was performed and led to seizure freedom. Histology confirmed a WHO Grade 1 DNET.

Discussion

Misdiagnosis and costly mismanagement of epileptic disorders, including unnecessary investigations and inappropriate treatments, can be avoided by early recognition. Since vomiting is a common symptom in children, autonomic seizures can be easily interpreted as migraine, gastro-enteritis or gastroesophageal reflux (Parisi *et al*., 2014; Sowell and Youssef, 2016). Furthermore, autonomic status epilepticus can be misdiagnosed and treated as encephalitis (Panayiotopoulos, 2004). In our two patients, despite relatively dramatic symptomatology, seizures remained undiagnosed for months. However, the stereotyped features of the events, which followed the same sequence and the same timing, pointed to an ictal origin. Sudden awakening and rapid return to sleep also suggested an ictal event.

In ictal vomiting/retching, interictal EEG can be normal, and abundant movement artefacts may prevent the recognition of seizure onset (Shuper and Goldberg-Stern, 2004; Sureshbabu *et al*., 2017; Russo *et al*., 2019). In our patients, retching and vomiting were the main ictal manifestations. Interestingly, the hemifacial clonic jerks were initially overlooked, not reported by the family, and disappeared with the administration of benzodiazepines. Therefore, video-EEG recording should be performed as soon as possible, before administration of any anti-seizure drug, in order to obtain accurate seizure characterization.

In both patients, clinical symptoms tended to occur before the onset of EEG discharge, suggesting a deep ictal origin.

Our first patient had a negative MRI. However, 18F-PET revealed left opercular frontal cortical hypometabolism, suggesting an underlying focal

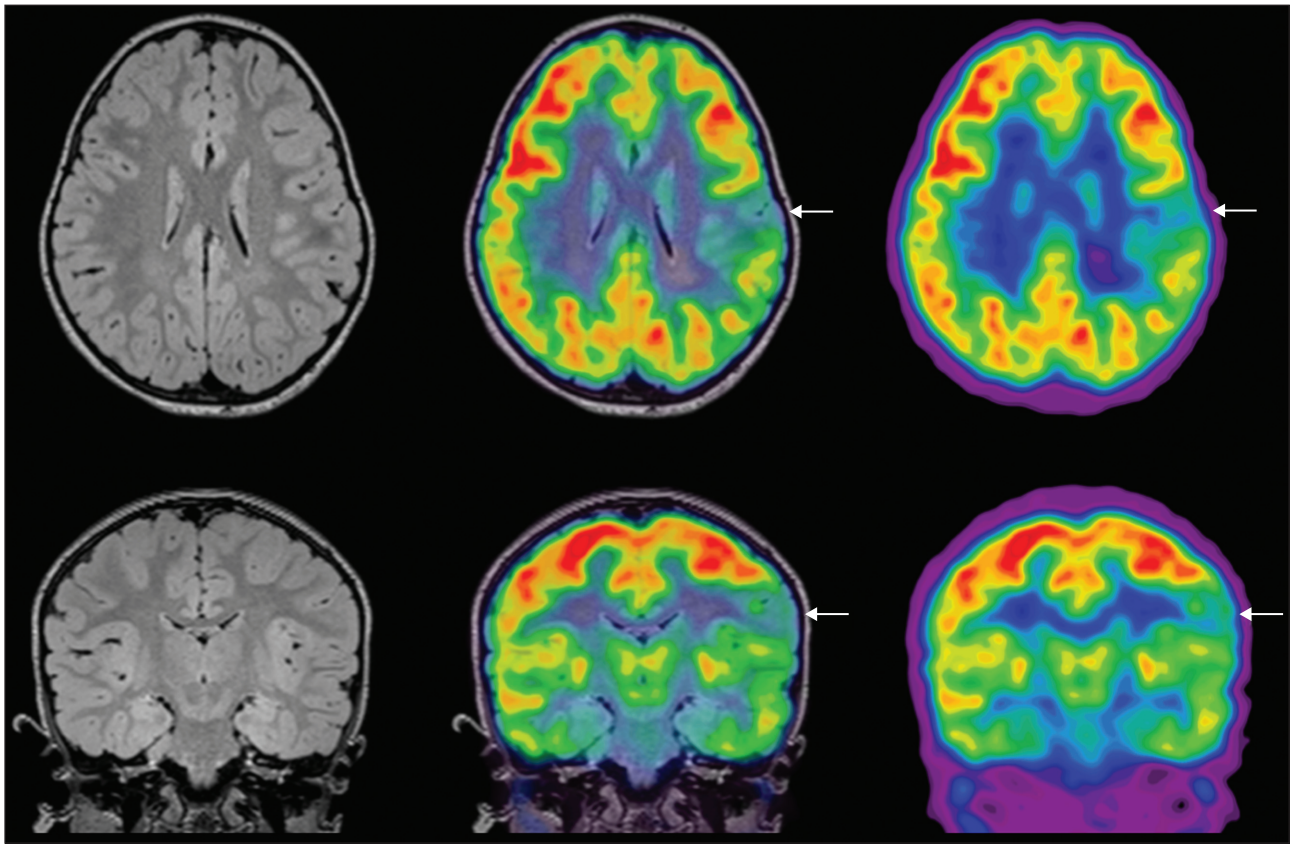

Figure 2. Fused 3D FLAIR MRI sequence with brain F18-FDG PET demonstrates clear interictal pathological cortical hypometabolism at the level of the left supramargical gyrus (white arrows), without any evidence of underlying anatomical architecture remodelling.

cortical dysplasia (FCD). In patients with MRI-negative focal epilepsy, PET and SPECT techniques may detect areas of altered metabolism, which tend to be larger than the seizure onset zone and may represent the functional deficit zone in epilepsy (Goffin *et al.*, 2008). In particular, 18F-PET/MRI co-registration provides add-on value. A recent study showed that the integration of electroclinical data with 18F-PET/MRI contributes to the localization of FCD type 2 in a high percentage of MRI-negative patients (Desarnaud *et al.*, 2018).

Conclusion

While vomiting is a common symptom of various illnesses in children, it may represent an ictal manifestation. Since vomiting can be quite dramatic, associated symptoms, such as myoclonia or transient neurological focal deficit, may be overlooked by the family. Therefore, especially in children, the diagnosis is often delayed or missed, which may result in significant harm. The stereotyped and very similar characteristics, as well as nocturnal awakenings, should prompt prolonged EEG-video recording in order to capture the events and allow diagnosis. □

Legend for video sequences

Video sequence 1.

Patient 1 is sleeping. The EEG abnormalities appear about 10 seconds before retching as rhythmic fast activity and polyspikes, originating from the left frontal and central regions, and rapidly propagating to the same regions contralaterally. The patient experiences sudden awakening and chewing followed by severe retching with preserved alertness.

Video sequence 2.

Patient 2 is awake and conscious. Suddenly, she experiences intense retching followed by tiny palpebral myoclonia and left hemiface clonic jerks. Ictal EEG shows right parietal rhythmic theta discharges with homolateral centro-parietal propagation.

Key words for video research on www.epilepticdisorders.com

Phenomenology: vomiting (ictal), retching (ictal)
Localisation: multifocal
Syndrome: focal, non-idiopathic (localization not specified)
Aetiology: tumour (brain)

Disclosures.
None of the authors have any conflict of interest to declare.

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TEST YOURSELF

(1) What syndrome is associated with ictal vomiting?

(2) What is the value of routine EEG and interictal findings in the diagnosis of ictal vomiting?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".