Italian Journal of Pediatrics

RESEARCH

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Ictal vomiting as the first manifestation of Tuberous Sclerosis Complex: report of two pediatric cases

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Abstract

Background Tuberous sclerosis complex (TSC) is a multisystem genetic disorder caused by pathogenic variants in *TSC1* or *TSC2*, affecting approximately 1 in 6,000 live births. Diagnosis can be established genetically or clinically based on characteristic neurocutaneous, renal, and cardiac findings. Epilepsy occurs in up to 90% of individuals, with a wide spectrum of seizure types, including epileptic spasms and focal seizures, often evolving into Lennox–Gastaut syndrome.

Methods We describe two pediatric cases with genetically confirmed TSC who presented with prolonged, stereotyped episodes of retching and vomiting as the initial clinical manifestation. Brain MRI and long-term video-EEG monitoring were performed to investigate the neurological origin of these symptoms.

Results In one patient, video-EEG recordings demonstrated an ictal pattern temporally correlated with the vomiting episodes, confirming their epileptic nature. In the other, although no episodes were captured during monitoring, the interictal EEG revealed both synchronous and asynchronous epileptiform discharges in the bilateral frontal regions, supporting a possible epileptic basis. To our knowledge, these represent the first reported cases of ictal vomiting as the initial seizure manifestation in TSC.

Conclusions These cases emphasize the need to consider recurrent, stereotyped gastrointestinal symptoms as potential ictal phenomena, particularly in individuals with TSC who are at high risk for epilepsy. Early and prolonged electroencephalographic monitoring may be crucial for timely recognition and appropriate management.

Keywords Tuberous sclerosis, Vomiting, Ictal vomiting, Epilepsy, Diagnosis, Children

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Background

Tuberous sclerosis complex (TSC) is a multisystem genetic disorder caused by inactivating mutations in either the *TSC1* or *TSC2* genes, which encode proteins that regulate the mammalian/mechanistic target of rapamycin (mTOR) pathway [1, 2]. TSC is characterized by age-related histologically benign tumors affecting multiple organs, including the brain, skin, kidneys, heart, and eyes. Prenatal diagnosis of TSC has become increasingly common, as cardiac rhabdomyomas – often present early in fetal development - can be detected during routine fetal ultrasounds [3]. The disorder affects approximately 1 in 6,000 live births [2], with central nervous system involvement observed in almost all cases. Epilepsy develops in up to 80–90% of affected individuals [2], with seizures typically emerging in early childhood [4].

A hallmark of TSC is the presence of cortical malformations, known as cortical tubers, which may serve as epileptogenic foci. Other characteristic brain lesions include subependymal nodules, subependymal giant cell astrocytomas, and radial migration lines [5].

Seizure types associated with TSC are diverse and may include epileptic spasms, focal, tonic, atonic, and tonic-clonic seizures, with some patients developing Lennox-Gastaut syndrome [6, 7]. Early recognition of subtle focal seizures in infants is crucial for timely treatment, which is a key factor in optimizing long-term outcome [8, 9]. However, these seizures can be challenging to identify, as they often present with subtle and highly variable clinical features depending on the epileptogenic focus.

Focal seizures may occasionally present with vomiting as the sole or predominant manifestation. Although rare, ictal vomiting is frequently misdiagnosed as a more common condition, such as gastroesophageal reflux, infectious gastroenteritis, or migraine [10, 11]. This phenomenon has been observed in various types of focal epilepsy, including Panayiotopoulos syndrome, temporal lobe epilepsy, and frontal lobe epilepsy. Ictal vomiting can arise from either cerebral hemisphere but it is more commonly linked to the dominant one [11–13].

Methods

Here, we describe two children with genetically confirmed TSC who experienced numerous episodes of retching and vomiting as their initial ictal manifestation. For both patients, detailed clinical and developmental histories were obtained, and neurological examinations were performed. Brain MRI was conducted to assess for cortical tubers and other structural abnormalities typical of TSC. Long-term video-EEG monitoring was carried out to investigate a possible correlation between vomiting episodes and epileptic activity and to document interictal abnormalities. All investigations were performed as part of routine clinical care, and parents provided informed consent for publication of anonymized data.

Results: case descriptions

Patient 1

The patient is a male born at term via emergency Caesarean Section (CS) due to acute fetal distress (decreased fetal heart rate). He was the first child of healthy, non-consanguineous parents. Early motor and language developmental milestones were achieved within normal timeframes.

At 18 months of age, he began experiencing recurrent episodes lasting approximately one minute, occurring both during wakefulness and sleep. These episodes were characterized by apnea, gasping sounds (distinct from laryngospasm), and subsequent vomiting. A clear reduction in responsiveness during these events was not observed. Initially suspected to be of gastrointestinal origin, the patient was placed on a modified diet and treated with proton pump inhibitors. However, due to persistent symptoms, at 21 months of age a neurological evaluation was performed, followed by video EEG monitoring during both wakefulness and sleep. No episodes were recorded, and the EEG showed interictal normal brain activity. Given the lack of response to gastrointestinal treatment, two months later the patient was hospitalized for further investigations, suspecting whether a metabolic condition or a neurological one. Brain MRI was performed and revealed multiple cortical/subcortical T2/FLAIR hyperintense and T1 hypointense lesions in the frontal and parietal lobes, consistent with cortical/subcortical tubers. Additional findings included radial migration lines and a small subependymal nodule (SEN) along the ependymal profile of the left lateral ventricle (Fig. 1). Based on radiological findings, a definite diagnosis of TSC was made according to established diagnostic criteria [5].

Furthermore, during the same hospitalization, long-term video EEG monitoring was performed, d uring which nine stereotyped episodes were recorded (seven during sleep and two during wakefulness). These episodes began with bilateral facial twitching, repetitive legs movements and ended with vomiting. EEG findings showed hypersynchronous rhythmic 5 Hz fronto-central theta activity, strongly suggestive of opercular epilepsy (Fig. 2). No interictal epileptiform abnormalities have been detected. The patient was started on carbamazepine (CBZ), titrated to 23 mg/kg/day, resulting in a marked reduction in daytime seizures and partial improvement of nocturnal episodes. Clobazam was introduced one year later to achieve better control of persistent nocturnal seizures, but was quickly discontinued due to excessive daytime somnolence. Subsequently, due to the exacerbation of nocturnal episodes (4–5 per night), Everolimus was

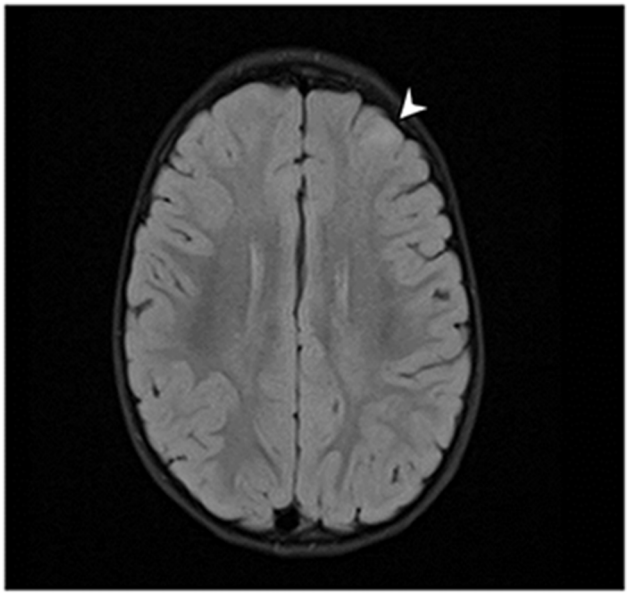

Fig. 1 Axial T2 fluid-attenuated inversion recovery (FLAIR) image showed subcortical frontal tuber (white arrow)

added to CBZ therapy (up to 8.7 mg/m²), with good tolerability and efficacy, leading to the complete disappearance of these episodes.

Following brain MRI, dermatological, cardiological, and genetic evaluations were conducted to assess other organ involvement. Initially, no cutaneous manifestations or renal or cardiac abnormalities were detected. However, at 6 years of age, angiomyolipomas (AMLs) and isolated renal cysts were identified.

Genetic testing, including sequencing of *TSC1* and *TSC2* genes, MLPA, and SNP array analysis did not reveal pathogenic mutations.

A neuropsychological assessment at six years old using the Wechsler Intelligence Scale for Children-IV revealed an IQ score of 126 (above the standard range). Symptomatic and clinical evaluation through ADOS-2 (module 3) and parent-based questionnaires indicated deficits in social communication and occupational abilities without fulfilling criteria for Autism Spectrum Disorder, leading to a diagnosis of Mixed Development Disorder associated with Developmental Coordination Disorder.

Patient 2

The patient is a male, born at term to healthy, non-consanguineous parents. Early motor and language developmental milestones were achieved within normal timeframes, nevertheless the child developed poor vocabulary and unusual speech patterns.

At approximately 2 years of age, he experienced seven nocturnal episodes within one month, characterized by crying, grimacing, vomiting, and waking up. Responsiveness during these episodes was not clearly reduced. Due to the frequency of symptoms, he was hospitalized for further evaluation. Brain MRI revealed numerous subcortical tubers in the bilateral fronto-parietal-temporal regions and small subependymal nodules in the lateral ventricles. The largest nodule, measuring approximately 6 mm, was located near the foramen of Monro (Fig. 3). As for the first patient, a definite diagnosis of TSC was made according to established diagnostic criteria [5].

For a better characterization of the aforementioned episodes, l ong-term video EEG monitoring was

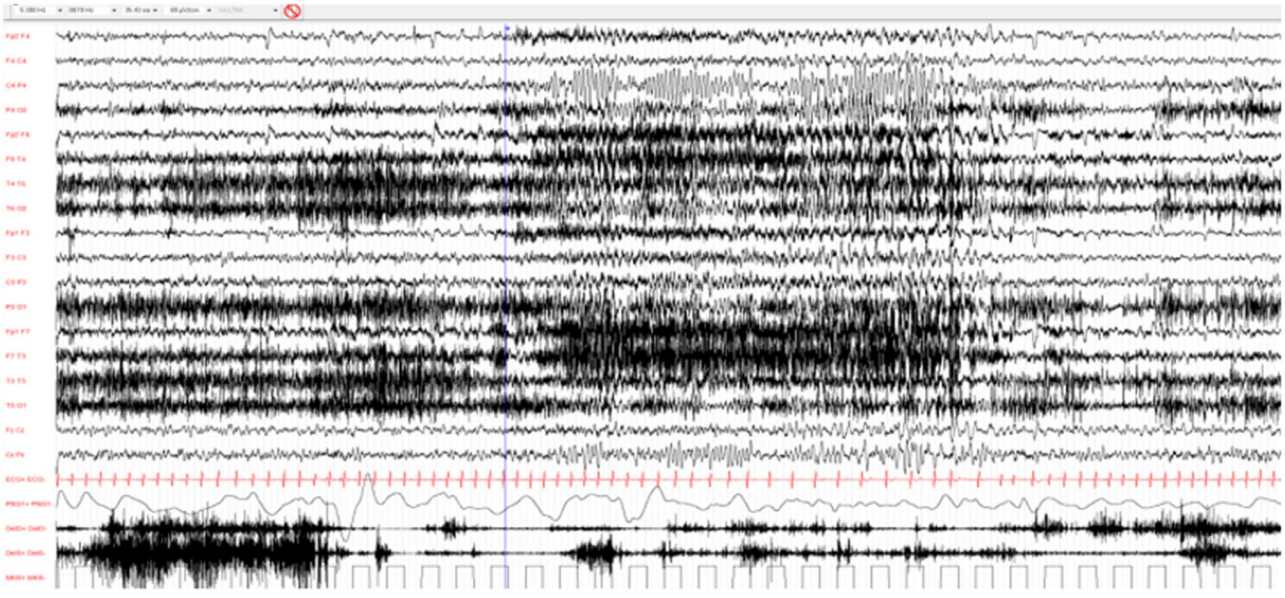

Fig. 2 Registration of bilateral opercular crisis during sleep. Clinically the patient presented repetitive legs movements, facial grimace and retching

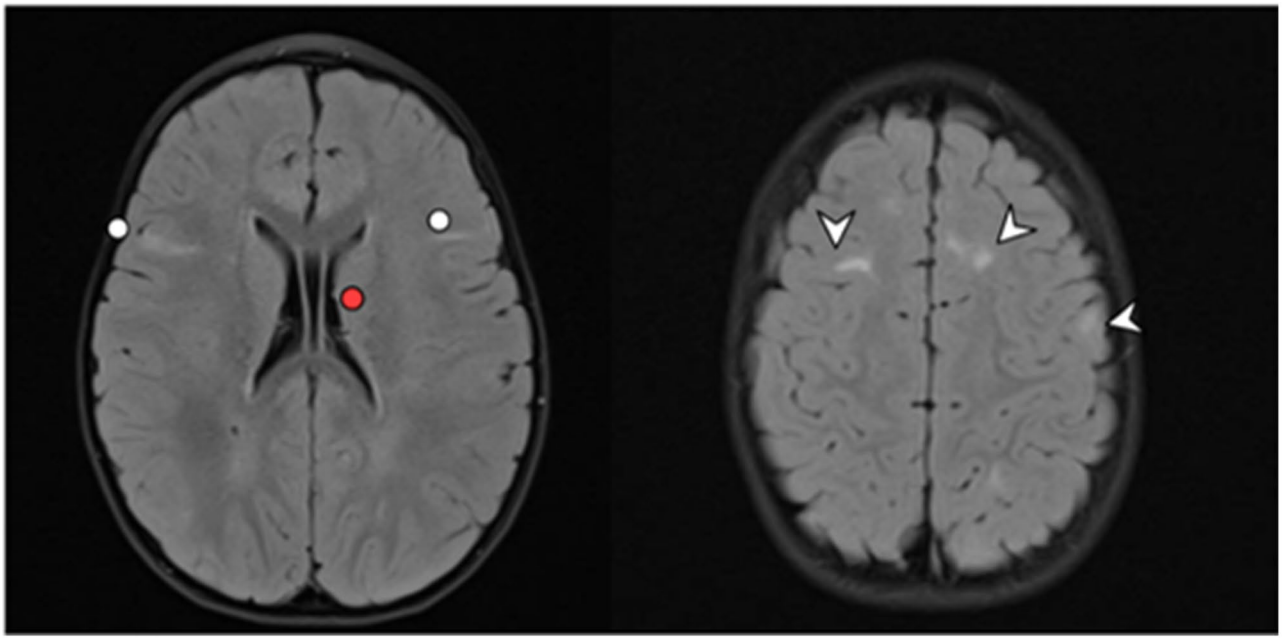

Fig. 3 Axial T2 fluid-attenuated inversion recovery (FLAIR). The image on the left shows linear white matter lesions located bilaterally (white dot) and small subependymal nodules along lateral ventricles (red dot). The image on the right shows cortical and subcortical tubers located bilaterally along the frontal-temporal-parietal lobes (white arrow)

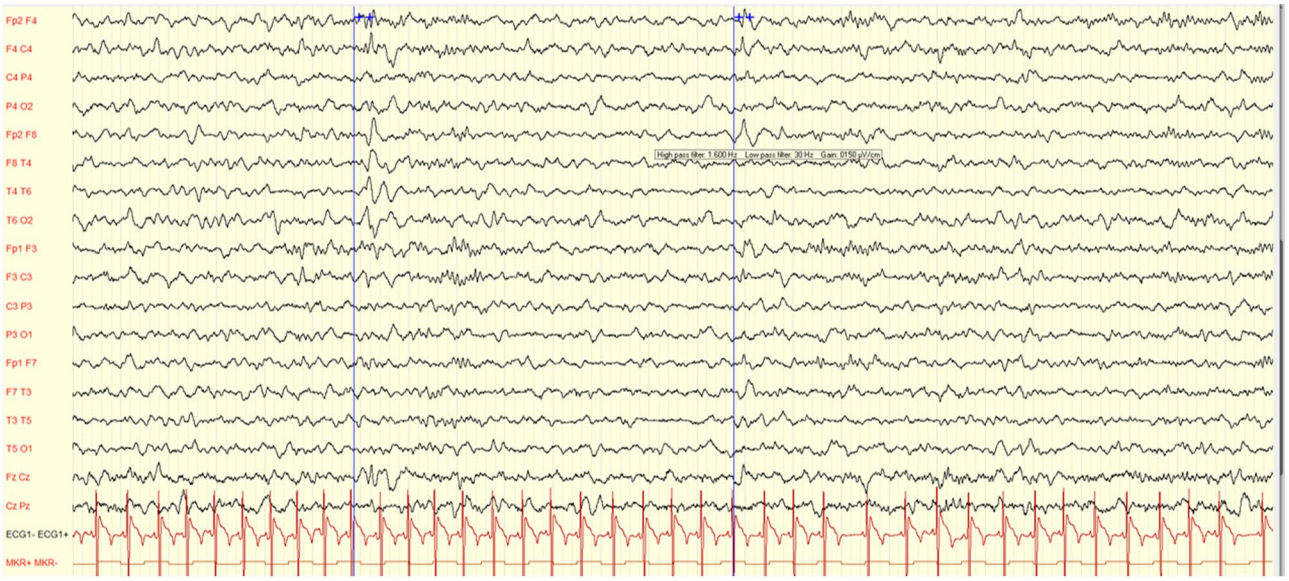

Fig. 4 Epileptiform abnormalities prevalent in the right fronto-temporal region

performed. It did not capture nocturnal vomiting episodes but revealed both synchronous and asynchronous epileptiform discharges in the frontal regions bilaterally (more prominent in the right hemisphere) and at the vertex (Fig. 4).

The child is now 3 years old and, although lateralization cannot be defined with complete precision, he shows a clear preference for using the left arm.

Treatment with CBZ was initiated, reaching a dose of 23 mg/kg/day, which led to seizure freedom that has been maintained at the 1-year follow-up.

Genetic analysis identified a de novo heterozygous variant (c.2263_2266del) in the *TSC1* gene, confirming the diagnosis of TSC.

Comprehensive evaluations, including dermatological, ophthalmological, and radiological assessments, were performed to screen for other TSC-related

manifestations. While no initial skin, renal, or ocular abnormalities were detected, echocardiography revealed a cardiac rhabdomyoma.

A neuropsychological assessment at two years of age using the Griffiths Mental Development Scales-III revealed global developmental delay (developmental age equivalent of 16 months vs. chronological age of 25 months), with particular impairment in the Language and Communication and Personal, Social Emotional Subscales. At 27 months, ADOS-2 (toddler module) identified unusual social interactions, communication patterns, and atypical play behaviors. However, the symptoms did not meet the criteria for ASD, leading to a diagnosis of Mixed Development Disorder.

Discussion

In our first patient, the diagnosis was delayed for several months due to the initial misinterpretation of recurrent retching and vomiting as gastrointestinal disorders such as gastroesophageal reflux or infectious gastroenteritis. This led to the administration of gastrointestinal therapies before the epileptic nature of the symptoms was identified. Only after multiple EEG recordings the ictal origin was demonstrated, making possible a better characterization of the episodes. In contrast, in the second patient, retching and vomiting were promptly considered as possible neurological manifestations. This approach facilitated early brain MRI and long-term video EEG, which confirmed the presence of the characteristic TSC-related cortical tubers and epileptiform discharges, enabling a timely diagnosis and appropriate management.

Recurrent ictal vomiting was first described by Panayiotopoulos, who reported that pediatric patients are the most frequently affected population, particularly in idiopathic cases. In prepubertal children, these seizures predominantly occur at night and are often accompanied by vomiting, eye deviation and impaired consciousness [14]. The underlying mechanism is believed to involve seizure activity originating in the mesial temporal structures (Ammon's horn), with propagation to the medulla via pathways connecting to the chemoreceptor trigger zone and vomiting center [10]. Ictal vomiting has also been associated with structural brain abnormalities, including hippocampal sclerosis, astrocytomas, genetic conditions such as TSC, a nd acquired causes such as head trauma or central nervous system infections [10, 15]. Sometimes a clear diagnosis is difficult, as subtle functional or connectivity abnormalities – not visible on conventional MRI – may underlie ictal episodes [16]. In TSC, such network dysfunctions are well recognized and can extend beyond the macroscopically visible lesions.

To the best of our knowledge, these are the first detailed cases describing ictal vomiting as the presenting epileptic manifestation in patients later diagnosed with TSC, although ictal vomiting has been previously reported in a patient with TSC [15]. In our patients, MRI revealed subcortical tubers in the bilateral fronto-parieto-temporal regions, without clear mesial temporal involvement. EEG showed fronto-central-parietal regions, more pronounced on the right side in the second patient, in whom the right hemisphere appears to be dominant [12].Although MRI and EEG findings did not localize the seizure focus to mesial temporal structures, the clinical features of grimace, retching, and vomiting support involvement of the central autonomic network [16]. Given seizure freedom in both patients, no further invasive investigations were deemed necessary.

Conclusions

These cases highlight the importance of recognizing stereotyped gastrointestinal manifestation as potential ictal phenomena, particularly in patients at high risk for epilepsy.While ictal vomiting is usually accompanied by other epileptic signs, such as eye deviation or impaired consciousness [14], our patient show that it can occasionally occur without clear alteration of consciousness, with only subtle motor or autonomic signs. Recurrent, stereotyped vomiting – especially during sleep – should prompt video-EEG monitoring to confirm the epileptic nature and guide treatment. Early recognition and management are crucial for improving long-term outcomes in TSC.

Abbreviations

TSC	Tuberous sclerosis complex
mTOR	mammalian/mechanistic target of rapamycin
CS	Caesarean Section
EEG	Electroencephalogram
SEN	Subependymal nodule
CBZ	Carbamazepine
AML	Angiomyolipomas

Acknowledgements

Not applicable.

Author contribution

EC and SM wrote the first draft and revised it, reviewed the literature; GS, AV, MPC revised the clinical charts of the patients and identified relevant clinical material; LM and MV supervised the whole work; RM conceptualized the paper, revised the clinical charts of the patients, revised the different versions of the draft. All the Authors approved the final version of the manuscript.

Funding

This work was supported by the Italian Ministry of Health with Current Research funds.

Data availability

No datasets were generated or analyzed during the current study.

Declarations

Ethics approval and consent to participate

We collect informed consent form from the parents if the two children. Publication of this paper was approved by our Hospital IRB.

Consent for publication
The informed consent contained also agreement to publication.

Competing interests
The Authors declare they have no conflict of interest to disclose.

Received: 9 July 2025 / Accepted: 9 December 2025
Published online: 10 January 2026

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