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Gastroesophageal reflux disease vs. Panayiotopoulos syndrome: An underestimated misdiagnosis in pediatric age?

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ABSTRACT

Autonomic signs and symptoms could be of epileptic or nonepileptic origin, and the differential diagnosis depends on a number of factors which include the nature of the autonomic manifestations themselves, the occurrence of other nonictal autonomic signs/symptoms, and the age of the patient.

Here, we describe twelve children (aged from ten months to six years at the onset of the symptoms) with Panayiotopoulos syndrome misdiagnosed as gastroesophageal reflux disease.

Gastroesophageal reflux disease and Panayiotopoulos syndrome may represent an underestimated diagnostic challenge. When the signs/symptoms occur mainly during sleep, a sleep EEG or, if available, a polysomnographic evaluation may be the most useful investigation to make a differential diagnosis between autonomic epileptic and nonepileptic disorders. An early detection can reduce both the high morbidity related to mismanagement and the high costs to the national health service related to the incorrect diagnostic and therapeutic approaches.

To decide if antiseizure therapy is required, one should take into account both the frequency and severity of epileptic seizures and the tendency to have potentially lethal autonomic cardiorespiratory involvement.

In conclusion, we would emphasize the need to make a differential diagnosis between gastroesophageal reflux disease and Panayiotopoulos syndrome in patients with "an unusual" late-onset picture of GERD and acid therapy-resistant gastroesophageal reflux, especially if associated with other autonomic symptoms and signs.

1. Introduction

An international consensus [1] defined autonomic epileptic seizures as "an epileptic seizure characterized by altered autonomic function of any type at seizure onset or in which manifestations consistent with altered autonomic function are prominent (qualitatively dominant or clinically important) even if not present at seizure onset".

Autonomic seizures have been best documented in children in the relatively common childhood epilepsy syndrome known as Panayiotopoulos syndrome (PS) [2]. Panayiotopoulos syndrome is a common idiopathic childhood-specific seizure disorder formally recognized by the International League Against Epilepsy and defined as "a benign age related focal seizure disorder occurring in early and mid-childhood. It is characterized by seizures, often prolonged, with predominantly autonomic symptoms, and by an electroencephalogram (EEG) that shows shifting and/or multiple foci, often with occipital predominance" [3,4]. Two-thirds of the seizures start in sleep or daytime naps; the 84% of the seizures occurring soon after the child goes to sleep or in the early hours of the morning. Panayiotopoulos syndrome in the general population affects 2 to 3 in 10,000 children. These figures may be higher if cases with atypical features are included. The estimated prevalence of PS is 13% in children aged 3–6 years with one or more nonfebrile seizures or 6% in the 1–15-year old age group with a peak of onset between 4 and 5 years [5,6].

The predominant features at the start of seizures are emetic symptoms (nausea, retching, and vomiting) that occur in 70–80% of cases and may recur several times during the same ictal event [7,8]. In a typical presentation of PS, the child is fully conscious and aware, is able to speak and respond, and begins to complain of feeling sick [1]. One-quarter of patients have a single seizure only, and half of them have 2 to 5 seizures. The remaining quarter have more than 6 or sometimes very frequent seizures, but the outcome is favorable in most cases. Prognosis is excellent, and remission often occurs within 1 to 2 years after onset. Severe bradycardia or even cardiac arrest has been rarely reported [9,10].

Abbreviations: CAN, central autonomic network; EEG, electroencephalogram; GERD, gastroesophageal reflux disease; PS, Panayiotopoulos syndrome; PSG, polysomnography; SUDEP, sudden unexplained death in epilepsy.

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Other autonomic manifestations include pallor (or, less often, flushing or cyanosis), mydriasis (or, less often, miosis), cardiorespiratory and thermoregulatory alterations, incontinence of urine and/or feces, hypersalivation, and modifications of intestinal motility. Headache or, more often, cephalic auras and behavioral disturbances may occur, particularly at onset.

An EEG is the only investigation with abnormal results. An interictal EEG usually shows a normal background with multiple functional spikes, high-amplitude sharp-slow wave complexes in various brain locations that are accentuated by sleep [11,12].

Nonepileptic conditions misdiagnosed as PS can be dysautonomic disorders that usually have a normal EEG [13]. The most frequent are cardiogenic syncope, atypical migraine, cyclic vomiting syndrome, motion sickness, sleep disorder, or other unrelated medical conditions such as inborn errors of metabolism [14], gastroenteritis, and gastroesophageal reflux disease (GERD) [15].

Gastroesophageal reflux disease is defined as the passage of gastric contents into the esophagus that causes troublesome symptoms and/or complications. The diagnosis of GERD is often made clinically. However, subjective symptom descriptions (such as recurrent regurgitation with/without vomiting, weight loss or poor weight gain, irritability in infants, ruminative behavior, heartburn or chest pain, dysphagia, cough, hoarseness) are unreliable in infants and children younger than 8 to 12 years of age, and many of the purported symptoms of GERD in infants and children are nonspecific.

The diagnosis of GERD is inferred when tests (esophageal pH monitoring, combined multiple intraluminal impedance and pH monitoring, motility studies, endoscopy and biopsy, barium contrast radiography, nuclear scintigraphy, esophageal and gastric ultrasonography, and empiric trial of acid suppression as a diagnostic test) show excessive frequency or duration of reflux events, esophagitis, or a clear association of symptoms and signs with reflux events in the absence of alternative diagnoses [16].

Here, we describe twelve children with Panayiotopoulos syndrome misdiagnosed as GERD for a long time. An early detection due to appropriate investigations can reduce mismanagements and high costs to the national health service.

2. Material and methods

During the last 3 years (January 2011–January 2014), we have recognized 12 children affected by PS misdiagnosed for a long time as GERD (Table 1). These 12 children were referred to pediatric gastroenterological outpatient service (Sapienza University at S. Andrea Hospital in Rome) at the mean age of 6 years (from 4 to 10 years of age) because of drug-resistant and recurrent gastrointestinal emetic symptoms (nausea, retching, and vomiting). The attacks occurred mainly, but not exclusively, during sleep (Table 1); three children (patient numbers 2, 3, and 10) also had episodes of severe headache with clinical characteristics of migraine with visual aura (slowly spreading spots, zigzag lines, colored lights and blobs). None of the children showed clinical signs of seizures except for three (patient numbers 1, 4, and 9). The developmental milestones of all 12 children were normal, and family history was unremarkable except for three of them (patient numbers 1, 2, and 7). Because of a history of a prolonged treatment with antiacid drugs (proton pump inhibitors), associated with antireflux diet and sleep position, without benefits, they were sent to a pediatric neurologist for suspicion of PS. The interictal EEG (awake and asleep) showed brief multifocal and generalized sharp and slow-wave paroxysms in all twelve investigated children; two examples of sleep EEGs are reported in Fig. 1. Brain magnetic resonance was normal in all children.

Everyone underwent sleep EEG recording during the afternoon nap, but only 4 of them agreed to undergo polysomnography (PSG) recording (in our institution, PSG requires hospitalization to be performed).

In patients who underwent PSG, we have not recorded any ictal episodes or severe cardiorespiratory impairment, but in all of them, we found EEG abnormalities (see the example reported in Fig. 2). During the interictal activity, no irregularity in the pulse rate, oxygen saturation, respiratory rate, and apnea/hypopnea events occurred. Despite this, 5 of 12, due to the importance and/or frequency of the seizures,

Table 1
Characteristics of the recognized patients.

Patient no.	Age		History/symptoms	Family history of neurological disease	Anticonvulsant therapy
	Onset of symptoms	Diagnosis of PS at admission			
1	3 years and 7 months	5 years	Nocturnal vomiting (3 episodes/months) unresponsive to PPI. At admission, diagnosis of PS was made. Six months later after AED therapy, the patient showed one episode of right eye deviation followed by TCGS. After adjustment of the drug dose by weight, the patient became seizure-free.	Epilepsy (aunt)	Yes
2	5 years	7 years	Migraine with aura and nocturnal vomiting treated with PPI without benefit	Migraine (mother)	Yes
3	3 years	8 years	Nocturnal vomiting followed by severe headache; diurnal rare episodes of headache without aura	None	Yes
4	4 years and 6 months	5 years and 2 months	Nocturnal retching and vomiting, sometimes followed by generalized hypotonia	None	None
5	2 years and 6 months	6 years and 4 months	Because of the history of nocturnal vomiting at the age of 2 years and 6 months, EGDS was performed and showed GERD and hiatus hernia, which were treated with PPI with little benefit. At the age of 6 years and 4 months, the patient underwent PSG and was diagnosed with PS, which was treated with lamotrigine and PPI that resulted in complete clinical remission.	None	Yes
6	5 years and 8 months	8 years and 5 months	Sporadic nocturnal vomiting, sometimes followed by loss of consciousness	None	None
7	6 years and 8 months	10 years and 5 months	Nocturnal abdominal pain followed by vomiting	Migraine (grandmother)	Yes
8	3 years and 4 months	4 years and 2 months	Nocturnal vomiting treated with PPI without benefit	None	None
9	3 years	4 years	Sporadic episodes of retching and vomiting, once followed by absence of few seconds	None	None
10	3 years and 7 months	4 years and 1 month	Nocturnal vomiting followed by headache	None	None
11	5 years	6 years and 4 months	Nocturnal vomiting	None	None
12	10 months	5 years and 6 months	Nocturnal vomiting treated with PPI without benefit	None	None

AED = antiepileptic drug, EGDS = esophagogastroduodenoscopy, GERD = gastroesophageal reflux disease, TCGS = tonic–clonic generalized seizure, PPI = proton pump inhibitors, and PS = Panayiotopoulos syndrome.