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Review

Misdiagnosis and pitfalls in Panayiotopoulos syndrome

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ABSTRACT

Panayiotopoulos syndrome (PS) is a frequent (6% among children of 1–15 years) and benign epileptic syndrome, characterized by predominantly autonomic symptoms (emesis, pallor, flushing, cyanosis, mydriasis/miosis, cardiorespiratory and thermoregulatory alterations, incontinence of urine and/or feces, hypersalivation, and modifications of intestinal motility) associated with simple motor focal seizures, which can be followed by secondary generalization. Panayiotopoulos syndrome can be extremely insidious, because it can mimic several condition, such as gastroenteritis, gastroesophageal reflux disease, encephalitis, syncope, migraine, sleep disorders, or even metabolic diseases. This peculiar pleiotropism should be kept in mind by child neurologists and pediatricians and general practitioners, because a wrong diagnosis may lead to inappropriate interventions. The consequences are high morbidity, costly mismanagement, and stress for children and their parents.
The availability of electroencephalography (EEG) recording in pediatric Emergency Departments might be useful for a prompt and not-cost-consuming diagnosis. On the other hand, it is important to be aware of the possible, multifaceted, clinical presentations of PS and its clinical, radiological, and neurophysiological features in order to improve both recognition and management.

1. Introduction

Panayiotopoulos syndrome (PS) is an early childhood benign epilepsy, characterized by seizures and autonomic ictal signs and symptoms. It was described for the first time by Chrysostomos Panayiotopoulos in 1988 [1].

The prevalence of PS is 13% among early-onset epilepsies and 6% in children between 1 and 15 years [2,3]; there is no gender prevalence [4]. It was reported an incidence of 2–3/10,000 children in general population [5], and it was recognized recently by the International League Against Epilepsy as a benign epilepsy of childhood [5,6]. Panayiotopoulos syndrome has a good prognosis, with remission of seizures within 1–2 years without significant alterations of neurocognitive development [7]; in fact, most authors do not recommend an antiepileptic prophylaxis therapy [3,4].

2. Etiopathogenesis

Etiopathogenesis of PS still remains unclear. The evidence of familiar aggregation suggests a genetic origin, but the exact genes involved have not been identified so far [8]. Conversely, it has been reported that mutation in SCN1A gene may contribute to the regulation of the disease's severity [8,9]. It has been described an association between PS and febrile seizures; in addition, the fever has been demonstrated as a common precipitant factor for seizures in some reports [10].

A further point of debate is the correlation between neuroanatomical structures that are responsible for epileptogenesis and neurophysiology findings. In fact, even if electroencephalography (EEG) in PS shows frequently occipital spikes, on the other side, wide, bilateral occipital, frontal, central, parietal, and, less often, temporal areas are involved (Fig. 1 a, b, c, d). The most accepted view postulates that ictal autonomic semiology does not come from a "specific" epileptogenic cortical area, but from early activation of low-threshold areas of the deep limbic structures of the brain that are connected to the autonomic nervous system and then spread to multiple areas in the cerebral cortex (Fig. 1 a, b, c, d). It has been proposed that a hyperactivation of the autonomic nervous system through the central autonomic network (CAN) may be elicited. The CAN is an extended circuit that includes the insular cortex, amygdala, hypothalamus, periaqueductal gray

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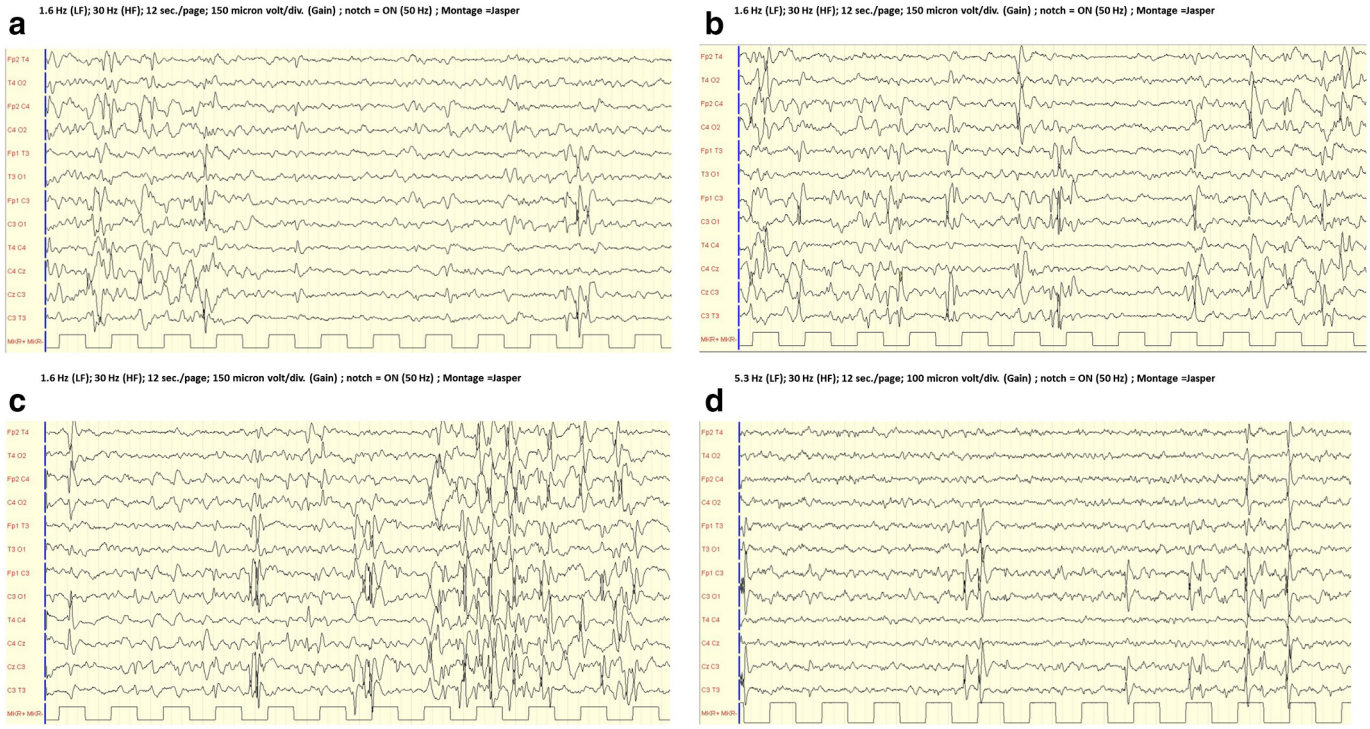

Fig. 1. (a, b, c, d). In Panayiotopoulos syndrome, there are no topographic correlations between autonomic signs/symptoms and EEG anomalies. Central, temporal, occipital, frontal, and diffuse sharps and spikes can be associated with the same autonomic signs/symptoms.

matter, parabrachial complex, nucleus of the tractus solitarius, and ventrolateral medulla [7,11,12]. It controls visceromotor, neuroendocrine, pain, and behavioral responses, and it is supposed to be immature in children. According to this hypothesis, the threshold of activation of autonomic symptomatology may be lower in CAN than in the motor or sensorial areas. This lower threshold could explain the reason why an epileptic discharge activates the autonomic networks, causing autonomic symptoms, without the recruitment of neighboring cortical areas, which control motor or sensory ictal manifestations. Therefore, seizures seem to be the product of a direct excitation or inhibition of the neocortex and limbic cortical areas and the subsequent propagation to the structures of CAN [12,13].

3. Clinical presentation

Panayiotopoulos syndrome usually occurs between 1 and 14 years, but it peaks in early childhood (between 3 and 6 years) with no apparent sex or race predilection [5,7].

Autonomic seizures and autonomic status epilepticus (ASE) are the hallmarks of the disease [13]. The ASE consists of a prolonged isolated or prevailing subdominant autonomic seizures, lasting more than 30 min or shorter epileptic seizures, without complete recovery between the seizures (lasting more than 30 min), characterized by manifestations of the autonomic nervous system associated with loss of consciousness [2,5]. Fever is often a seizure trigger in PS [10].

The autonomic seizures and ASE are more frequent in pediatric age. In childhood, ictal vomiting occurs when the consciousness is intact, without prior focal symptoms, and it can also be the sole ictal symptom. It probably has no localization or lateralization, and it does not show topographical correlations with any specific area [12].

In adulthood, ictal vomiting is rare and reported as late ictal semiological finding. It occurs along the seizures, associated with reduced consciousness, and it is usually presented in seizures arising from the temporal lobe, especially with the involvement of the nondominant temporal mesial region.

Autonomic seizures commonly manifest with the full triad of nausea, retching, and vomiting that occurs in around 80% of patients. Other autonomic features include color changes, particularly pallor (less frequent flushing or cyanosis), pupillary changes (especially mydriasis), cephalgic auras, hypersalivation, incontinence of urine and feces, and other gastrointestinal, cardiorespiratory, and thermoregulatory abnormalities [4,14]. Syncopal-like attacks represent nearly 20% of all seizures in PS; the child appears "completely unresponsive and flaccid like a rag doll" usually before or in the absence of other autonomic symptoms [15]. Potentially life-threatening cardiorespiratory arrest has been rarely described [16].

Almost two-thirds of seizures occur in nocturnal sleep and daytime naps; the child may be found vomiting or may wake up complaining of nausea. If the seizure occurs when the child is awake, he is initially fully conscious but gradually begins to complain of nausea and confusion or unresponsiveness overcome [17]. Almost half of autonomic seizures last for more than 30 min to a couple of hours (approximately 2 h), constituting an ASE. The remainders last on average of 9 min. Autonomic seizures often progress to other more conventional epilepsy manifestations and particularly staring, eye deviation, impairment of consciousness, speech arrest, visual hallucinations, hemifacial spasms, oro-pharyngo-laryngeal movements, hemiconvulsions, and general seizures [2,3,5,17]. A migraine-like headache may commonly appear after a seizure [5]. Most patients with PS have between two and five seizures, and only a minority of patients have a single or more than 10 seizures. Panayiotopoulos syndrome usually remits within 1–2 years from the onset. The risk of progressive epilepsy in adulthood is the same as the general population [7].

Management of PS involves seizure control in order to decrease the risk of sudden unexplained death in epilepsy (SUDEP). The pathogenesis of SUDEP is not clear yet. However, cardiac, respiratory, and neurological alterations of autonomic system are supposed to promote SUDEP. It should be helpful to remove the triggers of seizures: drugs, alcohol, and sleep deprivation. It is necessary for families to have good education about SUDEP, as possible lethal complication of epileptic seizures may arise, to improve the compliance and medical therapy, if indicated [12].

4. Diagnosis

4.1. Genetic tests

Genetic testing can be useful in PS. In fact, prominent autonomic features are seen in epilepsies associated with specific genetic mutations [13].

On the other hand, it was hypothesized that PS could be a genetically determined condition [18], but no specific gene has been identified yet. In some cases, an association was hypothesized with familial febrile seizures [10]. Mutations in SCN1A were reported in a few patients with PS and febrile precipitants, but the association has not been confirmed [8]. Moreover, genetic testing can also help establishing the prognosis, as mutations in the RYR2-encoded cardiac ryanodine receptor/calcium release channel [19] and in the SCN5A-encoded cardiac Nav1.5 sodium channel [20] have been documented in SUDEP. Further studies are needed in order to characterize genetics of PS.

4.2. EEG studies

Electroencephalogram studies describe predominant abnormalities in the posterior regions [15,21–23]. Two-thirds of patients have at least one EEG recording showing occipital epileptiform discharges [2].

Ictal EEGs are rarely described, and a few data come from sleep recordings. The more common abnormalities consisted of rhythmic theta activity intermixed with spike and fast rhythms, spreading on both hemispheres as high-amplitude spike-and-wave activity [24–26].

The EEG background activity is usually normal, even if localized slow-wave abnormalities can appear postictally [2].

Interictal spikes in PS are reported in more than 70% of patients, and more than 90% have at least one abnormal interictal EEG [26]. There is a great electroencephalographic variability of focal spikes at different electrode locations. Bilateral and synchronous occipital spikes are the most common abnormalities described in PS [15,21–23,27–29], often associated with concurrent extraoccipital spikes (>60%) (Fig. 1 a, b, c, d). However, one-third of patients never show occipital spikes but have normal EEG or, in a minority of cases (about 5%), extraoccipital (temporal, parietal, central, and frontal) spikes [26,30]. Studies with adequate follow-up describe a diffusion from occipital to centrotemporal or frontal areas and from frontal to occipital areas in serial EEG recordings [31].

Sometimes, generalized discharges, consisting of diffuse spike-and-wave complexes of short duration, can occur in association with interictal spikes.

Occipital spikes are accentuated by sleep and hyperventilation, but they are blocked by eye opening [30]. Intermittent photic stimulation is usually normal, but a photoparoxysmal response can be observed in a small percentage of patients consisting of generalized spike or spike-and-wave complexes with high amplitude over the occipital regions [26].

Based on the assumption that EEG abnormalities are more likely during sleep studies, if a routine EEG is normal, a sleep-EEG recording should be always performed.

The origin of the autonomic seizures in PS is more elusive, and the exact pathophysiology of interictal EEG findings is still not understood [12]. Some authors argue that the epileptogenic zone in PS is wide and often bilateral with alterations in several cortical areas. This multifocal nature of PS was recently investigated, confirming the great diversity of the spatial distribution of the cerebral areas able to produce and propagate independently interictal spikes [31] (Fig. 1 a, b, c, d). According to the most accepted hypothesis [12], ictal discharges may activate the autonomic network, which is constituted of lower-threshold cortex (insula, medial prefrontal cortices, the hippocampus, and amygdala); this early activation may be responsible for pronounced dysautonomic features. After a brief latency, epileptic focus spreads to higher-level cortical regions (sensory-motor, parietal, occipital cortex), which display a relatively higher threshold, thus generating focal symptoms. This hypothesis may explain the pronounced autonomic features of the condition, as well as the variability of interictal discharges on EEG [12].

4.3. Autonomic testing

There are a few reports exploring ictal and interictal autonomic functions of patients with PS. To date, normal ictal and interictal findings were reported [12,32].

4.4. Neuroimaging

Neuroimaging studies, performed with computed tomography (CT) scan or magnetic resonance imaging (MRI) do not show significant alterations in PS [26,30]. However, neuroimaging studies, specifically MRI, could be useful for differential diagnosis. The indications include patients with unexplained neurocognitive and motor symptoms, impaired neurological examination, and focal epileptic seizures, with or without secondary generalization. Other indications are EEG alterations not consistent with benign seizures, idiopathic generalized seizures and age under one year [2].

5. Evaluation and treatment

There are no neurological deficits in ASE.

A correct diagnosis of ASE in emergency room avoids many invasive procedures (i.e., oral-intubation) and other inappropriate and aggressive approaches that may cause cardiorespiratory depression [13]. Given that PS has a good prognosis, an antiepileptic prophylaxis is not recommended, but parents of children affected by PS should know how to administer rectal benzodiazepines at home during a seizure [4]. However, there is no consensus about treatment for PS. Some authors suggest to use a monotherapy (i.e., carbamazepine or valproic acid) after the second seizure depending on the duration of the seizures and the presence of associated neurologic anomalies [3,33,34]. There are no evidences that preventive antiepileptic drugs (AEDs) can eliminate EEG abnormalities or enhance neurobehavioral state. In general, overall duration of AEDs treatment should last 2–3 years [3,35].

6. Differential diagnosis of PS

6.1. Epilepsy syndromes

Autonomic status epilepticus in PS is often misdiagnosed, because seizures are not recognized as epileptic events, due to atypical symptoms, such as nausea and vomiting [13]; an epileptic basis is suspected only when the seizure ends in motor ictal manifestations.

Even when an epileptic basis is recognized, it may be difficult to distinguish among most common epileptic syndromes. In fact, children with several disease can show prominent autonomic symptoms, such as Dravet syndrome, Lennox–Gastaut syndrome or cerebral palsies [36]; however, anamnesis, age of onset (neonatal), seizure characteristics, and frequency allow an easy differential diagnosis with PS. On the other hand, it is more complex a clinical and EEG differentiation among most common causes of infant epilepsies.

Benign Rolandic epilepsy (BRE or benign epilepsy with centrotemporal spikes) is the most common child epilepsy syndrome, characterized by focal EEG discharges in the lower Rolandic areas; the peak frequency is 3–6 years, not so far from PS [36]. Focal seizures with involvement of face, upper limb, and mouth movements with hypersalivation are the most common symptoms. As for PS, seizures have a low frequency and are often nocturnal contributing to delay in diagnosis. The matter of confusion between BRE is that Rolandic spikes occur in some children affected by PS [37].

Panayiotopoulos syndrome is considered the “early-onset” variant of “childhood idiopathic occipital epilepsy” [38]; according to this definition, PS should be differentiated from benign occipital epilepsy (BOE),

which presents a mean age at onset of 6 years [29]. Patients affected by BOE experience visual symptoms such as visual hallucinations or transient amaurosis at the seizure onset, followed by focal signs and unresponsiveness. However, even if visual symptoms are really uncommon in PS, in a minority of patients with BOE, postictal headache and nausea or vomiting are reported, mimicking a PS seizure. During EEG recordings, intermittent photic stimulation does not facilitate the occurrence of seizures and visual fixation suppresses the discharges.

6.2. Genetic epilepsies

Because of the clinical autonomic presentation and common nocturnal seizures, differential diagnosis is needed among genetic epilepsies: Dravet syndrome, Rett syndrome, 18p- deletion syndrome, and 18q-deletion syndrome. Dravet syndrome is a severe epileptic encephalopathy, with onset during the first two years of age, characterized in most cases by SCN1A gene mutation. Rett syndrome is a genetic encephalopathy with development regression and decreased head circumference. The 18 deletion syndromes are chromosome 18 alterations, characterized by epilepsy, which responses to carbamazepine and valproic acid; the diagnosis is genetic [12,39].

The autonomic dysfunction can be also the principal symptom (orthostatic intolerance, gastrointestinal disturbances, cardiac alterations, autonomic neuropathy) in genetic mitochondrial disorders (e.g., MELAS) [40].

6.3. Acute nonepileptic disorders

Panayiotopoulos syndrome may mimic many nonepileptic conditions ranging from gastrointestinal disorders like cyclic vomiting syndrome and gastroenteritis, to gastroesophageal reflux disease (GERD) [6], because emetic symptoms are the predominant clinical features at the onset of the seizures [41]. Cyclic vomiting syndrome is a disease of unknown etiology, characterized by repeated episodes of nausea and vomiting that can last for days, followed by asymptomatic healthy intervals. It is considered a migraine equivalent (or periodic syndromes) due to the immaturity of the CAN. Consciousness is unaltered in the absence of localizing or lateralizing symptoms like eyes deviation. Electroencephalography analysis shows only focal slowing during the attacks, and it is required to prove a definite diagnosis [12,42]. Sometimes PS is misdiagnosed as GERD [6], whose diagnosis needs a time relation to feeds and specific diagnostic tests pointing out excessive recurrence or duration of reflux events, esophagitis, or an evident relation of symptoms with reflux episodes. In a child with an atypical late onset of GERD, a negative workup and unresponsiveness to therapy make it necessary to perform an EEG or a polysomnography to obtain the correct diagnosis [6,43]. Other systemic diseases that may be differentiated from PS are bowel obstruction, pancreatitis, infections, or calculus involving kidney [12].

In infancy, prominent autonomic seizures can be attributed improperly to inborn errors of metabolism. Nowadays, newborn screening by mass spectrometry is carried out in most countries, and it allows an early diagnosis of these conditions. This kind of epilepsy usually appears during a stress because of illnesses or metabolic alterations and presents very rarely in an otherwise healthy child. These patients generally show dysmorphic features, changes in physical appearance, systemic visceromegaly, developmental delay or regression, and intellectual and behavioral disability [44,45].

From ten to 20% of children with autonomic seizures of similar presentation as in PS suffer from cerebral pathology of different etiology, such as encephalitis, intoxication, or other serious cerebral diseases. These patients usually have altered level of consciousness followed by prolonged and severe convulsions, other neurologic signs, and abnormal brain imaging [2,7,13].

Similarly, ictal syncope may be misdiagnosed as vasovagal or neurocardiogenic syncope [46]. Syncope occurs frequently in adolescence and can be differentiated from a seizure by several prodromal symptoms, such as dizziness, blurred vision, epigastric discomfort, and pallor. In addition, protracted standing, changes in posture, dehydration, hunger, or exposure to warmth are often triggers. In pediatric emergency room, ictal syncope occurs commonly in the absence of premonitory symptoms and without relation with body position; moreover, it does not cease in horizontal position, and it is followed by a rapid recovery. Cardiac evaluation to identify underlying cardiac diseases (arrhythmias, prolonged QT syndrome, cardiomyopathy and valvular diseases) is indicated. If cardiac evaluation is negative, patients should be referred for autonomic testing [44,46].

Paroxysmal headache syndromes, like migraine, and sleep disorders, such as somnambulism or other parasomnias, are further frequent misdiagnosis of PS; they can generally be distinguished by a careful history of the event and EEG or sleep studies [7,44,46]. Behavioral nonepileptic manifestations, such as breath-holding spells and panic attacks or "psychogenic" seizures, can be more problematic to diagnose, due to the difficulty in recognizing the "ictal" event, so that a multidisciplinary approach may be required for the diagnosis. Benign paroxysmal vertigo (BPV) can be confused with epilepsy, because of its paroxysmal and repetitive nature and because it frequently occurs with autonomic symptoms. Consciousness is intact, and there is no postictal period; however, EEG analysis may be required [7,44,47].

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