

## Case Report

# Panayiotopoulos syndrome: a clinico-electroencephalographic presentation of three cases from Nigeria

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### ABSTRACT

Panayiotopoulos syndrome (PS) is a common benign, childhood, focal, seizure susceptibility syndrome presenting with mainly focal aware or focal impaired awareness autonomic seizures and autonomic status epilepticus that is under diagnosed in our locality. Increased awareness through reporting will aid diagnosis, reduce misdiagnosis and prevent aggressive and deleterious interventions. The classic clinical and electroencephalographic (EEG) features of three cases are described and the literature reviewed. The aim is to underscore the presence in our locality of this remarkably benign epileptic syndrome that must be differentiated from febrile seizures, encephalopathy, migraine or cardiogenic syncope.

**Keywords:** Focal aware autonomic seizures, Ictal vomiting, Panayiotopoulos syndrome

### INTRODUCTION

Panayiotopoulos syndrome (PS) is a common benign epileptic syndrome of early childhood that affects 2-3/1000 children in the general population.<sup>1</sup> In 2006, an expert consensus defined PS 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 EEG [electroencephalogram] that shows shifting and/or multiple foci, often with occipital predominance."<sup>2</sup> After several years of escaping recognition, the International League Against Epilepsy (ILAE) eventually recognized PS as a distinct electro-clinical syndrome called "early onset benign childhood occipital epilepsy (Panayiotopoulos type).<sup>1</sup> PS is an important epileptic syndrome for the fact that it is commonly misdiagnosed as one of common conditions like febrile seizures (or complex febrile seizures), gastroenteritis, motion

sickness, atypical migraine, encephalopathies and cardiogenic syncope.<sup>1,3-5</sup>

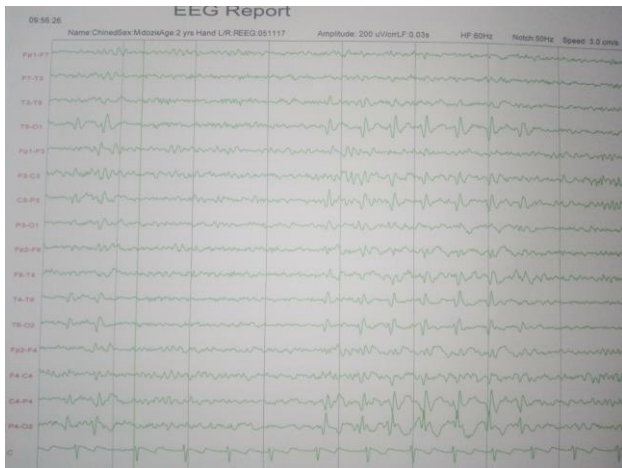
The diagnosis of PS has become easier following the recognition of ictus emeticus, ictal syncope and other autonomic manifestations as seizure events.<sup>2</sup> PS has been confirmed in long-term studies of over 1000 children worldwide.<sup>2</sup> However, this common childhood epileptic syndrome remains under diagnosed in Nigeria as there are no reports or mention of it in studies on epilepsy in Nigeria.<sup>5-8</sup>

The three cases reported here all manifested the unusual constellation of autonomic symptoms in addition to the conventional seizure symptoms. One of the cases had visual hallucinations which are rare in PS while another had adverse natal, perinatal and early postnatal events that suggested a symptomatic aetiology for the autonomic seizures.

## CASE REPORT

### Case 1

Patient C.C, a 2-year 9month-old male was referred to the Child neurology clinic/ EEG unit of Mother Healthcare Diagnostics and Hospital, Owerri, Imo State from another private hospital in Imo State on the 18<sup>th</sup> of October 2017 due to recurrent convulsions and a diagnosis of seizure disorder. Seizure onset was at 2 years of age. In the first episode, he woke up from sleep at about 11pm, vomited and on getting back to bed his eyes rolled up and “he became lifeless with floppy limbs as if he was dead”. This lasted about 10 minutes and there was no accompanying fever. The other two episodes occurred in sleep while at school; he had up rolling eyes, mouth deviation, jerking of the left sided limbs and passage of urine. There was no accompanying fever and ictal events lasted about 10-15 minutes. He had normal pre-natal, natal and early postnatal history. His development is normal and there is a positive family history of seizure disorder. Physical examination was unremarkable and apart from a positive blood film for malaria parasite (MP), initial laboratory investigations (complete blood count, serum electrolytes, urea and creatinine [SEUC] and urinalysis) were normal.



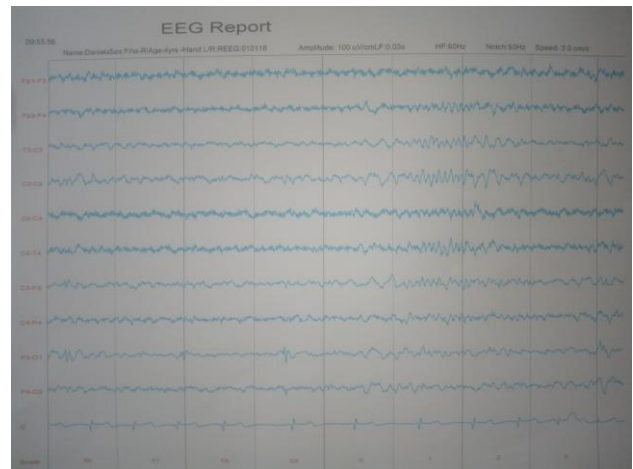
**Figure 1: A sample from inter-ictal sleep-induced EEG in a 2-year 9-month-old male with Panayiotopoulos syndrome (index case 1); background was normal but there were clone-like repetitive multifocal high amplitude sharp-slow waves mostly in the posterior regions.**

Inter-ictal sleep-induced EEG done one week after the third episode of seizure showed age-appropriate background activity and repetitive, clone-like, multifocal high amplitude sharp-slow wave complexes mostly in the posterior regions in stage 2 Non-Rapid Eye Movement sleep (NREM) (Figure 1). A diagnosis of Panayiotopoulos syndrome was made. The patient’s parents were counseled on the diagnosis, management and prognosis and they opted for anti-epileptic drug (AED) therapy. The patient was commenced on tabs

carbamazepine at 10mg/kg/day in two divided doses and after a week increased to a maintenance dose of 20mg/kg/day. Further follow-up visits at three monthly intervals showed that the AED was well tolerated with good compliance. He has remained seizure-free for the past one year and is still being followed up.

### Case 2

Patient D.O, a 4-year 4month- old female was referred for EEG from Federal Medical Centre, Owerri, on the 6<sup>th</sup> of November 2017 due to recurrent convulsions with onset at 1 year and 10 months of age. The first episode occurred at about 4pm; while eating, she was noticed to be “staring into space as if she was seeing things”, then her “colour changed”, fingers became clenched, lower limbs stiffened and crossed and she passed stool. Ictal events lasted 5-10 minutes and were followed by post ictal sleep. The second episode occurred 1 year later and was similar to the first except that she vomited in addition and it lasted less than 5 minutes. The third episode happened about 2 years after the second episode. At about 3pm, she had complained of headache and subsequently had eye deviation to the right side, vomited and became “lifeless with dark lips and palms”. She also had urinary and faecal incontinence but no fever. Ictal events lasted about 30 minutes and were followed by a prolonged post ictal sleep (“virtually slept the whole day”).



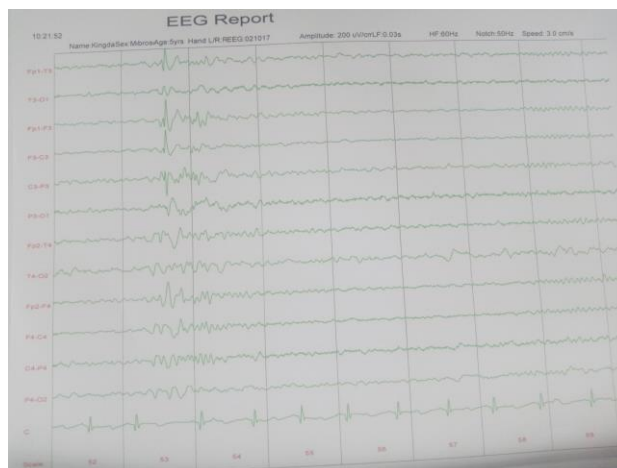
**Figure 2: A sample from inter-ictal EEG in a 4 year 4-month-old female with Panayiotopoulos syndrome (index case 2); background was normal but there were sparse paroxysmal sleep-activated left occipital small spike-slow waves.**

The mother had an emergency section at gestational age GA 29 weeks in a hospital in Johannesburg, South Africa due to severe pre-eclampsia and twin gestation in a primigravida. Her birth weight was 760g and her twin brother weighed 1.5kg. She had prolonged stay in the nursery and was transfused thrice. At discharge, baby was said to be in good condition and that investigations done including those on the brain were normal.

Developmental history is normal. The mother had seizures as a child but there is no history of seizures in the twin brother. She is academically doing better than the twin brother. A sleep-induced inter-ictal EEG done four days after the third episode of seizure showed age-appropriate background activity and infrequent paroxysmal left occipital biphasic spike-slow wave complexes in stage 2 NREM sleep (Figure 2). Neuroimaging of the brain (MRI brain) was requested for but the parents declined due to financial constraints and felt their child's brain was okay because they were told everything was fine before discharge from the hospital in South Africa. A diagnosis of Panayiotopoulos syndrome was made, and parents were counseled. Due to the infrequent seizures, aversion of the parents to AED therapy and good prognosis of the diagnosis, patient was managed without any AED. The patient is being followed up and seen at three monthly intervals. Compliance to clinic appointments is poor but she has had no seizures in the past one year and is still under our care.

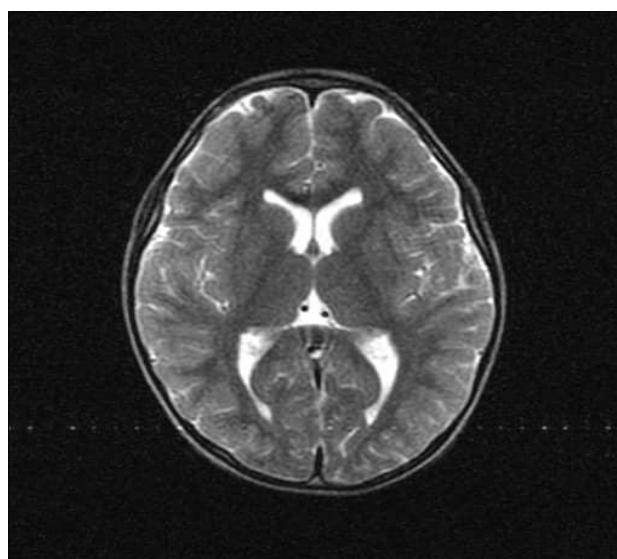
### Case 3

Patient K.A, a 5-year 2month-old male referred to the EEG unit/ Child Neurology clinic of Mother Healthcare Diagnostics and Hospital Owerri for EEG on the 7<sup>th</sup> of October 2017 from Vaden Specialist Hospital, Owerri because of recurrent convulsions with onset at 5 years of age. The first episode happened 2 months prior to presentation; he woke up from sleep in the afternoon, vomited and subsequently lost consciousness. He was rushed to the referral hospital but on getting to the hospital he recovered consciousness and on evaluation fever (Temperature 39° C) was documented. Blood film for malaria parasite done at the referral hospital was positive and other blood and urine tests were said to be normal. He was treated for severe malaria and later discharged after three days on admission. About one month later, while playing in the afternoon, he suddenly had up rolling eyes, loss of consciousness and faecal incontinence. The third episode involved change in behavior and disorientation; he cried and "acted as if he was seeing things" and said that "his younger sister was beating him" which did not actually happen. This lasted about 5 minutes and there was no fever, no up rolling eyes or jerking of the limbs. He had normal prenatal, natal and early post natal history. Developmental history is normal. Both parents had seizures in childhood and seizures were particularly frequent in the father. Academic performance in school is good. An inter-ictal sleep-induced EEG showed normal background and paroxysmal left hemispheric spike-slow wave complexes in drowsiness (Figure 3). A diagnosis of Panayiotopoulos syndrome was made, counseling done but anti-epileptic drug (AED) therapy was withheld and patient was given three months appointment. Patient defaulted on follow-up clinic visits. During this period, he presented to the Paediatric Neurology Clinic of Federal Medical Centre, Owerri due to persisting seizures; though frequency of seizures was same (about twice every three months).



**Figure 3: An inter-ictal EEG sample of a 5-year-old male with Panayiotopoulos syndrome showing normal background and sleep-activated paroxysmal left hemispheric high-amplitude sharp-slow wave complexes.**

However, the seizures no longer manifested vomiting or fever but involved mainly behavioural arrest, staring, impaired awareness and visual hallucinations and illusions lasting 5-10 minutes. An MRI of the brain was done, and patient commenced on tabs carbamazepine 200mg mane and 100mg nocte (10mg/kg/day). MRI brain was normal (Figure 4).



**Figure 4: Magnetic Resonance Imaging (MRI) brain for patient K.A (index case 3) done 6 months after presentation; axial T2w sequence showing age-appropriate intracranial appearances with no evidence of significant intra or extra-axial lesions; no cause for the patient's symptoms identified.**

After six months of AED therapy, the patient came back to the Child Neurology clinic of Mother Healthcare Diagnostics and Hospital Owerri. Parents complained that "the AED was not working" because despite good

compliance, seizures have persisted (but not worsened) and so they wanted a change of drug. On review, clinical features were same. Parents were advised to stop “doctor shopping” and be compliant with clinic visits. They were given information on anti-epileptic drug therapy including adverse effects. They were told that maximum doses of carbamazepine (35mg/kg/day) had not been reached because they defaulted also with follow-up visits at Federal Medical Centre, Owerri but they insisted on having a new drug. Patient was then commenced on tabs levetiracetam 250mg b.d (20mg/kg/day, wt 26kg) to increase to 375mg b.d after a week (almost 30mg/kg/day). Carbamazepine was tapered off over a week. He is yet to visit again before this report.

## DISCUSSION

These are the first reported cases of Panayiotopoulos syndrome from Nigeria. While Rolandic epilepsy is well recognized and appears in studies on epilepsies in Nigeria, PS is underdiagnosed and escaping recognition.<sup>6-9</sup> The three cases reported all had at the onset unusual autonomic (focal, nonmotor) symptoms such as vomiting, ictal syncope (“lifeless and floppy body”), behavior change and cyanosis/ pallor (“colour change”, “dark lips and palms”). These initial symptoms are difficult for the General practitioner or even Paediatricians to recognize as ictal events and failure to do so is a major reason for misdiagnosis of PS. Moreso, in Nigeria, there is limited access to child Neurologists and these index cases were diagnosed because they had presented to paediatricians and could afford EEG. These index cases represent only the tip of an iceberg because in developing countries, there are gaps in diagnosis and treatment of neurological disorders due to poor infrastructure and lack of neurologists.<sup>10,11</sup> Mclane et al reported the unavailability, inaccessibility and low affordability of neurodiagnostic tests such as Magnetic Resonance Imaging (MRI), Computed Tomography (CT) scan, Electromyography (EMG), Electroencephalography (EEG) in low income countries.<sup>11</sup> Poor health knowledge and a high level of stigma associated with neurological disorders are other reasons for the delay in seeking medical attention.<sup>10</sup> The first two index cases had three seizures over a period of nine months and two and a half years respectively before having an EEG done for accurate diagnosis. However, even if these children had presented early to hospitals, misdiagnosis is rife. For instance, the index case 3 in his first episode had documented fever on arrival at the hospital and a positive blood film for malaria parasite and so misdiagnosis as febrile seizure secondary to malaria is excusable in our environment. In PS, fever may be subjectively or objectively documented during seizure or in the immediate post-ictal period.<sup>1</sup> This could be a coincidental finding, a precipitating factor or an ictal abnormality, but fever recorded immediately after seizure onset is most likely an ictal autonomic manifestation.<sup>1</sup> In addition, for index case 3, an initial differential diagnosis of Epilepsy with Febrile Seizure plus (EFS+) is also valid because of the history of febrile seizures beyond age five

years together with afebrile seizures, normal development and a positive family history of seizures.<sup>12</sup> But an EEG becomes very useful in this scenario because the electrographic signatures of both syndromes differ although a normal EEG could occur in both EFS+ and PS.<sup>12</sup> The occurrence of autonomic status epilepticus as seen in the index case 2 may result in a diagnosis of an acute encephalopathy like cerebral malaria in a malaria-endemic zone like ours. Such misdiagnosis of prolonged severe episodes of autonomic seizures of PS result in erroneous treatments, costly hospital admissions and avoidable morbidity and mortality.<sup>1,3-5</sup> Migraine or its variant called cyclical vomiting syndrome becomes the common misdiagnosis when headache occurs with vomiting as seen in index case 2.<sup>1,3-5</sup> The history of “became lifeless with floppy limbs as if dead” and “lifeless with dark lips and palms” obtained in index case 1 and 3 respectively describe ictal syncope or syncopal-like symptoms.<sup>1</sup> Ictal syncope or syncopal-like symptoms occur in one-fifth of seizures with the child becoming “completely unresponsive and flaccid like a ragdoll” and cyanosis occurs often while the child is unresponsive.<sup>1</sup> In our environment, due to our dark skin, cyanosis manifests with darkening of the lips and palms. In PS, cyanosis is less common than pallor and occurs principally during the evolution of the seizures while pallor usually occurs at the onset with ictus emeticus.<sup>1</sup> The clinical feature of ictal syncope or syncopal-like symptoms in PS can mislead the attending physician to diagnose cardiogenic syncope or pseudoseizure.<sup>1,3-5</sup> PS is significantly different from Idiopathic Childhood Occipital Epilepsy-Gastaut type (ICOE-G) but there are some overlapping features as seen in index case 3 that had visual hallucinations. Ictal visual symptoms such as elementary visual hallucinations occur after more typical seizure symptoms of PS and are rare occurring in only 6% of cases of PS.<sup>1,3-5</sup> However, in the rare ICOE-G, frequent and brief purely occipital seizures of predominantly elementary visual hallucinations or blindness occur diurnally in more than 90% of cases.<sup>1,4</sup> The hallmarks of PS are autonomic seizures and autonomic status epilepticus. The ILAE revised classification of seizures in 2017 and defined autonomic seizure as “a distinct alteration of autonomic nervous system function involving cardiovascular, pupillary, gastrointestinal, sudomotor, vasomotor, and thermoregulatory functions”.<sup>13</sup> Our patients had either focal aware nonmotor autonomic seizures or focal impaired awareness autonomic seizures in the episodes described.<sup>13</sup> All in all, our patients had the classic features of PS with the unusual constellation of autonomic symptoms and more conventional seizure symptoms like eye or mouth deviation, limb jerking, urinary and faecal incontinence and impaired awareness. There was a positive family history of seizures in all the cases which agrees with PS being genetically determined like Rolandic epilepsy.<sup>1,3-5</sup> However, about 10-20% of children with autonomic seizures may have structural brain pathology (symptomatic autonomic seizures) and an MRI brain may be indicated.<sup>1,3-5</sup> This informed the request for MRI brain for the index case 2 who had a

history of twin gestation, severe preeclampsia, severe prematurity and extreme low birth weight. Indeed, an MRI brain should have been done for this patient but unfortunately this was not the case here. Nevertheless, the normal development, positive family history, infrequent seizures, good academic performance and an EEG record of normal background with occipital spike-slow waves all suggested a benign childhood seizure susceptibility syndrome-PS. The index case 3 due to quasi-frequent seizures and visual hallucinations and illusions had an MRI brain done and it was normal which further supported a genetic aetiology. The EEG findings in these patients were conspicuously variable and typical of PS as described by Panayiotopoulos.<sup>1,3-5</sup> The multifocal epileptiform potentials in the EEG of index case 1 accords with the documented diffuse and multifocal cortical hyperexcitability in PS.<sup>1,4,5</sup> The multifocal epileptogenicity in PS has been shown by magnetoencephalography (MEG) and dipole analysis to predominate in the posterior areas; mainly along the parieto-occipital, calcarine or central (rolandic) sulci.<sup>1,4,5</sup> Though occipital spikes predominate in PS (60%), as seen in index cases 1 and 2, they may not occur in 30% of patients.<sup>1,4,5</sup> The index case 3 did not have occipital spikes and further ruled out ICOE-G which was a differential diagnosis because of the visual hallucinations. While ICOE-G is purely “occipital epilepsy” with predominantly occipital spikes (in 90%), patients with PS have both occipital and extraoccipital spikes or only extraoccipital spikes.<sup>1,4,5</sup> In index case 2, the occipital spike was infrequent, small amplitude and lateralized and such interictal EEG finding has been documented in PS.<sup>1,4,5</sup> The infrequent seizures suggested a benign childhood epileptic syndrome and the intra-individual seizure variability in PS was evident in all our cases.<sup>1,3-5</sup>

## CONCLUSION

This report has documented the occurrence of PS in Nigerian children, the need for further education of doctors and the invaluable role of EEG in diagnosis.

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