Case report

Two Cases of Ohtahara Syndrome

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Abstract

Background: Ohtahara syndrome (OS) is a rare and severe form of epileptic encephalopathy. It is frequently caused by gene mutations, metabolic disorders, or brain abnormalities. However, there are some cases that have no definite brain pathology. It is a syndrome affecting young infants characterized by epileptic encephalopathy with an encephalographic pattern of suppression-burst.

Aim: This is to present two cases of Ohtahara syndrome in a 1-year-old female infant and a 5-year-old male child.

Case: Two patients were diagnosed with Ohtahara syndrome, both of whom presented with the early onset of epileptic seizures. Both underwent neurodiagnostic tests. The two children had an electroencephalogram (EEG) that showed epileptiform waves. The 5-year-old showed an Aristaless-related homeobox (ARX) mutated gene that is associated with Ohtahara syndrome.

Conclusion: Ohtahara syndrome is characterized by recurrent tonic spasms in early infants. It is associated with a burst-suppression EEG pattern throughout both the awake and sleep periods, as well as severe encephalopathy and treatment-resistant epilepsy. The most common causes are anatomical brain abnormalities and gene mutations. Two cases were reportedly admitted to our institution who were diagnosed with Ohtahara syndrome. Both cases began experiencing seizures at the age of 3 months, and their electroencephalograms revealed a burst-suppression EEG pattern.

Keywords: Ohtahara syndrome , Early Infantile Epileptic Encephalopathy (EIEE), ARX gene, burst-suppression EEG pattern, epileptiform waves.

Introduction

Ohtahara syndrome, also known as Early Infantile Epileptic Encephalopathy (EIEE), comes with a unique EEG finding of burst suppressions. The incidence has been estimated at 1 in 100,000 births in Japan and 1 in 50,000 births in the United Kingdom [1]. At present, there are approximately 100 total cases worldwide. However, this may be an underestimation. The Philippine Pediatric Society Registry of Childhood Diseases recorded 9,102 cases of generalized epilepsy from January 1, 2006, through January 31, 2025 but has not broken them down into specific seizure diagnosis types [2]. Hence, the actual number of cases of Ohtahara syndrome among these cases of generalized epilepsy is unknown.

In Ohtahara syndrome, the onset of the epileptic seizures occurs within the first 2 weeks of life or the first 3 months of age [3]. Infants usually present with tonic spasms that can either be generalized or focal, occur singly or in clusters, and are independent of the sleep cycle. Spasms typically last up to 10 seconds and can occur

hundreds of times per day [2]. Approximately one-third of patients with Ohtahara syndrome will also develop other types of seizures, like generalized tonic-clonic, myoclonic, or clonic seizures [5].

Electroencephalograms in Ohtahara syndrome indicate a suppression burst pattern, comprising bursts of high-amplitude spikes and polyspikes that alternate at a regular rate with periods of electric suppression. The bursts coincide with the tonic spasms. The pattern typically remains unchanged during both wakefulness and sleep [3].

The prognosis is generally poor. Patients with Ohtahara syndrome frequently die during infancy, and the survivors have neurologic sequelae manifesting as psychomotor impairment. The sequelae may occur whether or not the seizures are controlled [3].

In this institution, there have been two cases of Ohtahara syndrome that were admitted.

Objectives

General Objective:
To present two cases of Ohtahara syndrome

Specific Objectives:

1. To present two cases of Ohtahara syndrome in a 1-year-old female infant and a 5-year-old male child
2. To discuss the epidemiology and etiology of Ohtahara syndrome
3. To give possible differential diagnosis of early-onset seizures
4. To determine how to diagnose patients with Ohtahara syndrome
5. To discuss the management and prognosis of Early Infantile Epileptic Encephalopathy (EIEE)

Cases

Case No. 1

The first case is O.A., a 1-year-old female who was born to a 39-year-old primigravida mother with spinal scoliosis. Prenatal and postnatal histories were unremarkable. However, at birth, she was noted to have microcephaly with a head circumference measuring 30.5 cm (Z score -3). She was also noted to have poor feeding and jitteriness in both upper extremities. Magnetic resonance imaging (MRI) done at 6 days old revealed incomplete lissencephaly, with agyria and pachygyria, cerebellar hypoplasia, and cerebral volume loss (Figure 1; see Appendix B). Genetic testing was negative for any epilepsy-related disease. The TORCH panel showed positive immunoglobulin G (IgG) for HSV 1 and 2 and CMV. The patient was treated with antibiotics for 2 weeks for early-onset neonatal sepsis. Hearing screening and newborn screening tests came back negative. The patient was discharged after a month with the final diagnosis of lissencephaly-pachygyria complex.

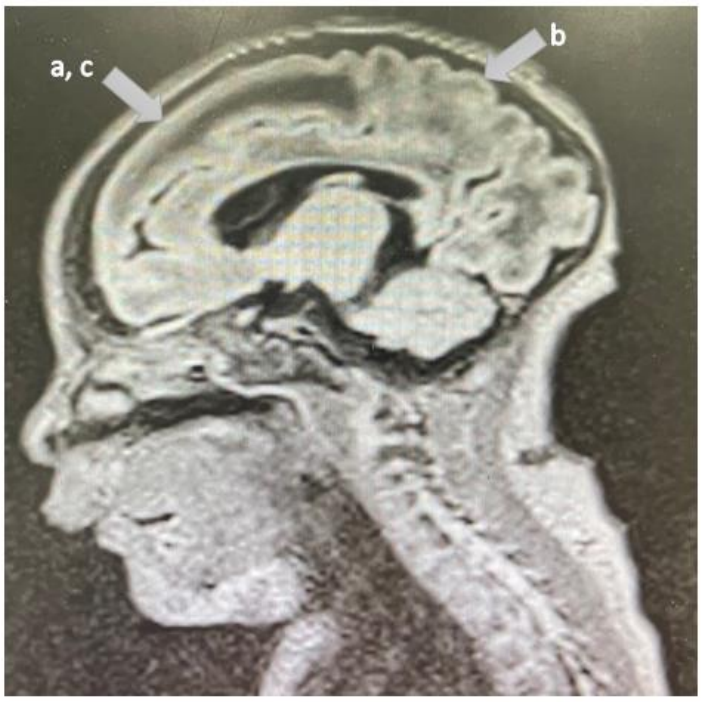


Figure 1. Cranial Magnetic Resonance Imaging of Case Number 1
a) Lissencephaly, b) agyria, and c) pachygyria, associated with cerebellar hypoplasia and cerebral volume loss (arrows to a, b, and c)

At three months old, epileptic seizures are characterized as either tonic or multifocal tonic, occurring at least 2–3 times per day. An electroencephalogram (EEG) revealed epileptiform waves (Figure 2; see Appendix C) thus, antiseizure medications were started. The patient was initially treated with valproic acid and clonazepam. Seizures remained uncontrollable; thus, topiramate, vigabatrin, and perampanel were added.

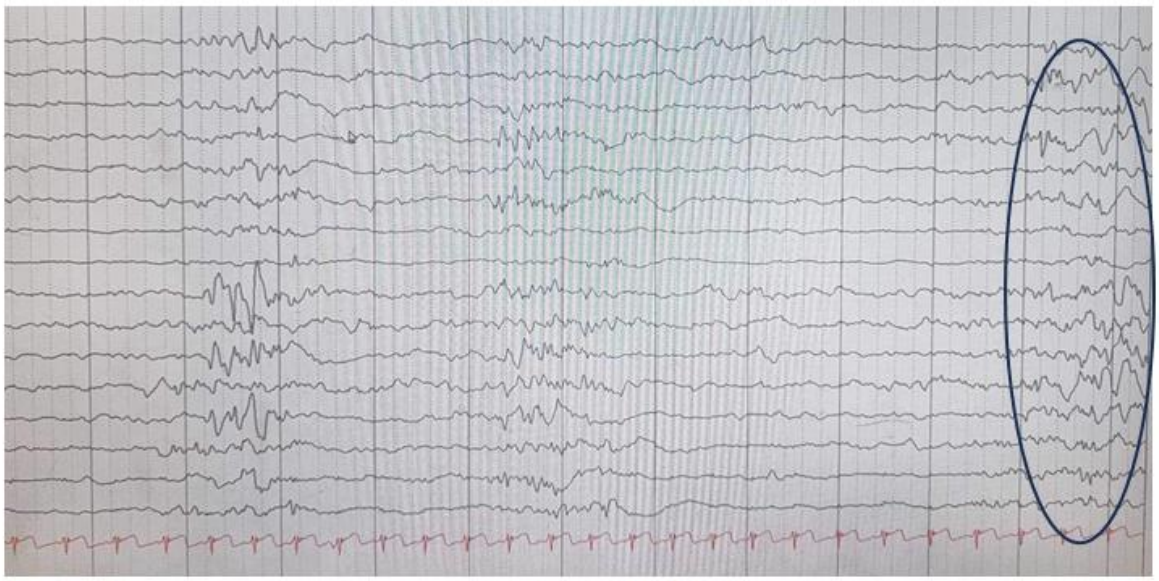


Figure 2. An EEG (electroencephalogram) of Case Number 1 showing a burst suppression pattern

At 1 year and 8 months old, the head circumference was 39.5 cm (Z score -3) (see Appendix A). By this time, developmental milestones were markedly delayed. The patient still had no head control and could not sit up or walk. The patient could only make babbling sounds but did have a visual following. She did not reach out for objects.

The patient had been repeatedly admitted due to respiratory problems and poor seizure control. On her last admission, a percutaneous endoscopic gastrostomy (PEG).

Case No. 2

The second case is E.C., a 5-year-old male child who was born full term to a 32-year-old primigravida mother. The prenatal and postnatal histories were unremarkable. A congenital scan at 20 weeks of age of gestation showed no apparent anomalies. At birth, the pertinent physical examination revealed ambiguous genitalia and bilaterally undescended testes.

At three months of age, the infant developed tonic, clonic, and multifocal seizures. An EEG showed generalized epileptiform waves (Figure 3; see Appendix E); thus, the patient was started on levetiracetam and prednisone. He was initially diagnosed with infantile spasm. However, worsening of seizures in spite of additional antiseizure medications like lacosamide, gabapentin, clonidine, and clonazepam was noted. This prompted a genetic workup, which revealed an ARX gene mutation, a mutation that is consistent with Ohtahara syndrome. An MRI, newborn screening, and hearing screening tests were also done and had unremarkable results.

The patient had repeated bouts of respiratory infections that needed hospitalization. At 5 months of age, a gastrostomy-jejunostomy tube was inserted to facilitate feeding and somehow protect the airway from recurrent bouts of aspiration. He was also previously admitted for a herniotomy and a severe COVID-19 infection.

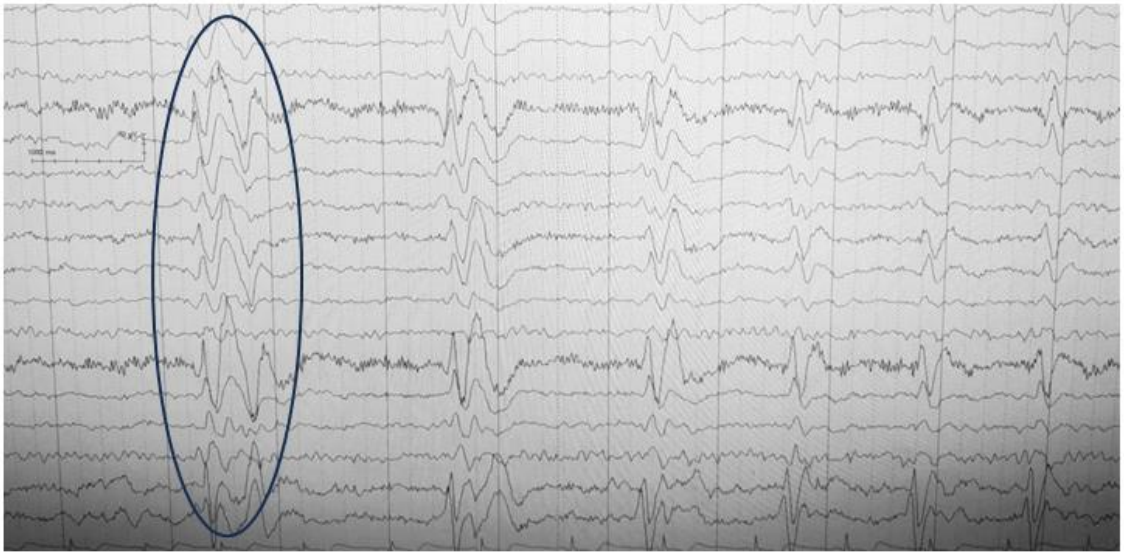


Figure 3. An EEG (electroencephalogram) of Case Number 2 showing burst suppression pattern

The last admission, E.C., had a head circumference of 43 cm (Z score -3) (see Appendix A) with a gastrostomy-jejunostomy tube in place. The antiseizure medications given on this admission were levetiracetam and phenobarbital, which afforded good seizure control. The patient was also placed on a ketogenic diet. Neurodevelopmental milestones were markedly delayed since, at 5 years old, he still had poor head control, could not sit up, stand up, or walk. He could reach out for toys and babble words like "mama" and "papa", but it is questionable that he understood the words. He communicated his needs mainly by crying. However, he would respond when his name was called, and on verbal stimulus, appeared to listen and smile. As of this writing, he is still on continuous physical, occupational, and speech therapy.

These two cases highlighted infants with early-onset seizures that started at around 3 months of age and were difficult to control, coupled with significant developmental delays. The EEG of these 2 patients showed the typical pattern of burst suppressions, which were characteristics of Ohtahara syndrome. These findings, together with structural brain abnormalities in the first case and the presence of the ARX gene mutation in the second case, clinched the diagnosis of Ohtahara syndrome for both cases.

Appendix A: Head Circumference of Cases 1 and 2 showing microcephaly with a Z score of -3

Patient	Age	Head circumference	Z score
O.A.	Newborn	30.5 cm	-3
O.A.	1 year and 8 months	39.5 cm	-3
E.C.	5 years old	43 cm	-3

Discussion

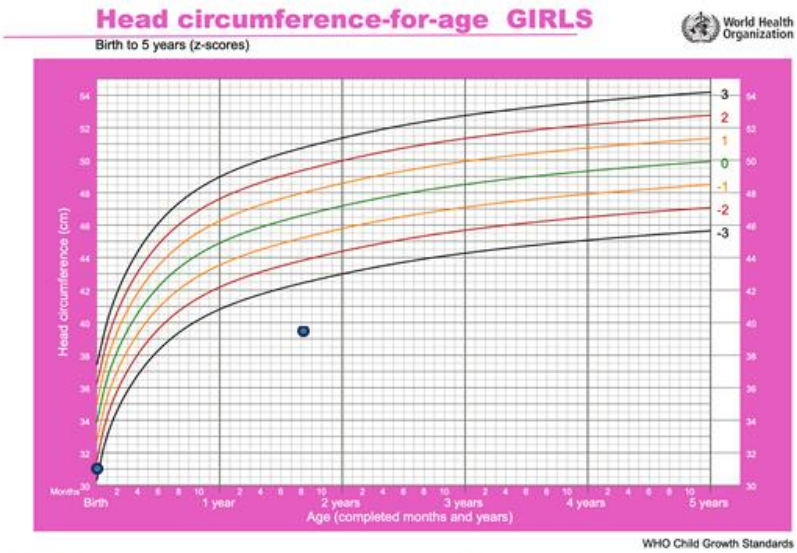
In 1976, Shunsuke Ohtahara et al. described an epilepsy syndrome affecting very young infants with characteristic electroencephalographic changes and termed it "early infantile epileptic encephalopathy" with suppression burst, or EIEE. The term early infantile epileptic encephalopathy (EIEE) has also been used, mostly by genetics experts. There are an increasing number of other genetic epileptic encephalopathies and developmental epileptic encephalopathies that are associated with an increasing number of specific genes with pathogenic mutations [7]. These conditions frequently evolve into West syndrome and Lennox-Gastaut syndrome.

Infantile spasm, also known as West syndrome, presents with infantile seizures and has typical EEG patterns of hypsarrhythmia, high-voltage, a slow, chaotic background, and multifocal spikes (see Appendix F). The two patients presented had infantile seizures but had an EEG pattern of burst suppressions, which are not seen in West syndrome.

Benign familial neonatal epilepsy (BFNE) was considered, but seizures in this syndrome occur early on the second or third day of life. In some cases of BFNE, genetic testing may show KCNQ2 mutations, a gene

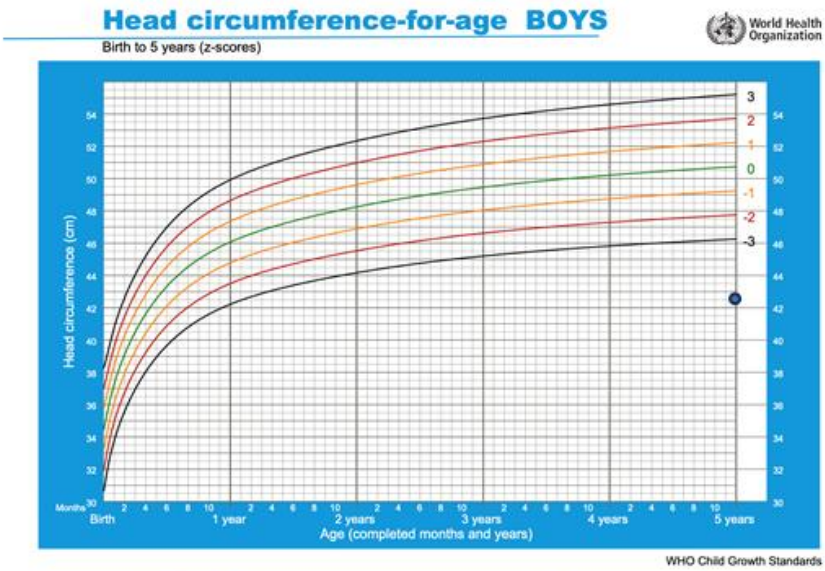
mutation that can also be detected in individuals with Ohtahara syndrome. However, psychomotor deficits in patients with BFNE are almost nonexistent. Despite the presence of seizures, electroencephalograms in BFNE are usually normal. Although O.A., the first case, had jittery movements of the upper extremities in the immediate perinatal period, these movements were not actual seizures but were merely jitteriness. Both cases presented had the onset of their seizures at 3 months of age. The electroencephalograms in these TWO cases were abnormal. Both patients had neurodevelopmental delays. Thus, BFNE was totally ruled out.

A-1: Girls chart: head circumference for age: birth to 5 years (percentile)



The head circumference of patient O.A. at birth and 1 year and 8 months old

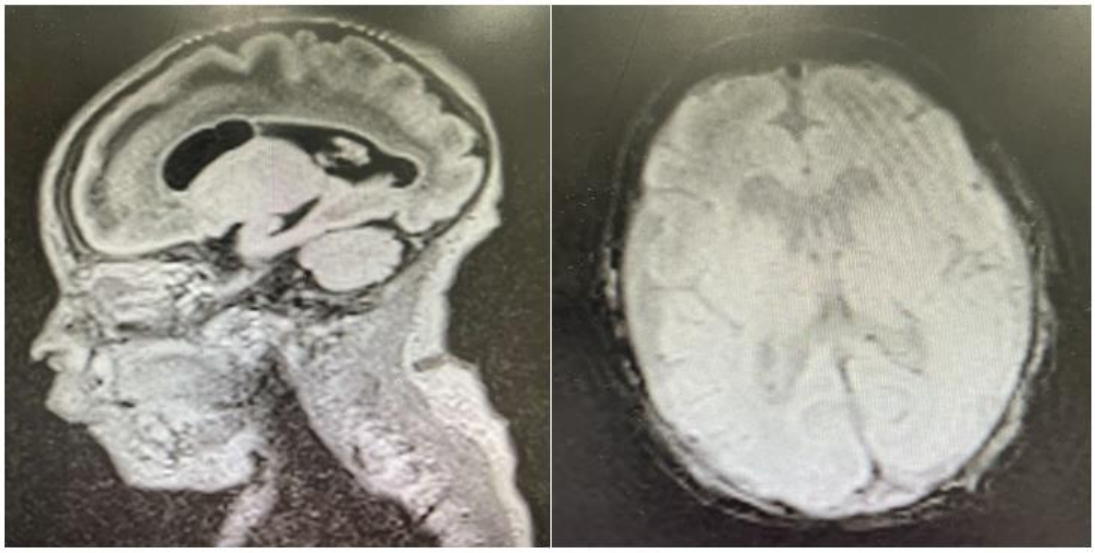
A-2: Boys chart: head circumference for age: birth to 5 years (percentile)



The head circumference of patient E.C. at 5 years old

Early Myoclonic Epilepsy of Infancy (EMEI) should also be taken into consideration because it can start at birth and last up to three months. EMEI similarly exhibits a burst suppression pattern on the EEG, just like Ohtahara syndrome. The EIEE and EMEI are different in that the former typically begins with tonic seizures, while the latter is more frequently associated with myoclonic seizures. While the majority of EMEI cases are linked to metabolic abnormalities, the majority of EIEE cases are linked to structural brain anomalies. The two cases presented did not present any metabolic problems. Patients with EMEI often have a bad prognosis, and some would go into a vegetative condition within the first year of life, as in our two cases. However, EMEI was ruled out in O.A., in the first case, as she had structural abnormalities in the brain on MRI. E.C., the second case, on the other hand, had genetic testing that showed the presence of an ARX-mutated gene, which is consistent with Ohtahara syndrome.

Appendix B: Cranial MRI of Case Number 1 which noted lissencephaly, agyria, and pachygyria, associated with cerebellar hypoplasia and cerebral volume loss.

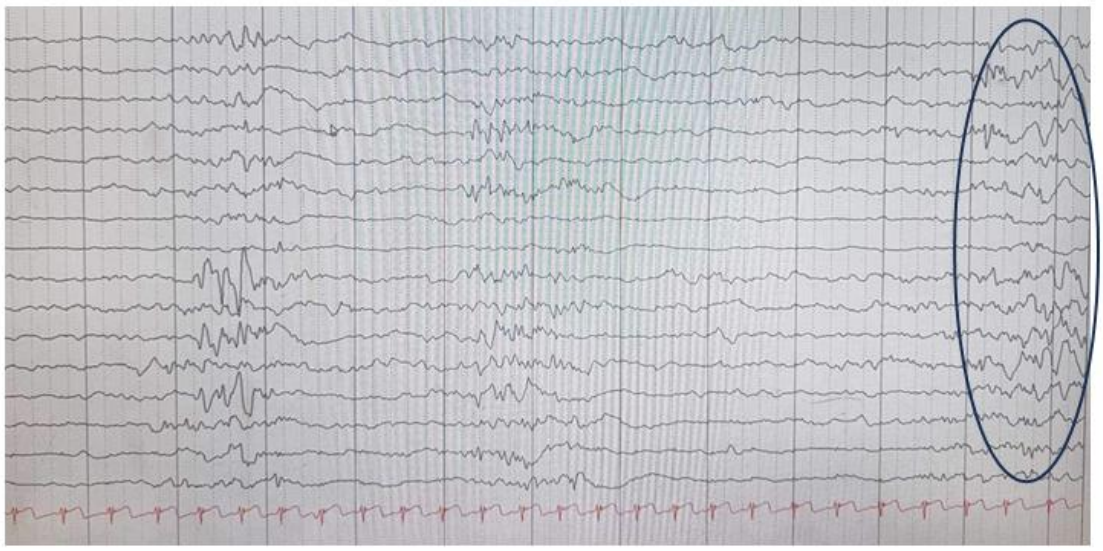


The first signs of Ohtahara syndrome (OS) show up in the first three months. The main seizure type is tonic spasms, and the EEG shows a burst suppression pattern (see Appendix G). There is severe neurodevelopmental impairment and a high death rate. Both patients described here presented with tonic seizures at the age of 3 months and EEG findings of epileptiform waves and neurodevelopmental delay. OS is most often linked to large brain problems like cerebral dysgenesis, porencephaly, hemimegalencephaly, agenesis of the corpus callosum, agenesis of the mamillary bodies, and dentato-olivary dysplasia [3], but up to one-third of cases are caused by genetic factors that don't involve brain problems. The first case had structural defects seen on MRI of the brain in the form of incomplete lissencephaly, with agyria and pachygyria, cerebellar hypoplasia, and cerebral volume loss.

The genes mutated in OS tend to be regulators of cortical development and/or synaptic function [6]. Genetic variants of EIEE have been associated with mutations in certain genes. ARX, KCNQ2, CDKL5, SLC25A22, STXBP1, SPTAN1, ARHGEF9, PCDH19, PNKP, SCN2A, PLCB1, SCN8A, ST3GAL3, TBC1D24, and

BRAT1 are some of the genes that are linked to Ohtahara syndrome. [8]. The genetic abnormalities are thought to lead to EIEE as they result in neuronal dysfunction or brain dysgenesis. The second case had the ARX-mutated gene. Gene changes in ARX, which codes for the Aristaless-related homeobox protein and is involved in brain development and patterning, were first found to be the cause of idiopathic EIEE in newborns or babies who had early-onset seizures but no other brain problems. True enough, in this second case, the MRI of the brain was unremarkable (see Appendix D). However, premature termination mutations and missense mutations within the homeobox of the ARX gene have been linked to lissencephaly and aberrant genitalia. This condition affects males. [6]. Case number 2 is a male who had a mutant ARX gene and who also presented with ambiguous genitalia and undescended testes. Case number 1 is a female who had associated brain malformations (lissencephaly, agyria, and pachygyria, with cerebellar hypoplasia and cerebral volume loss) on the MRI with no genetic mutations.

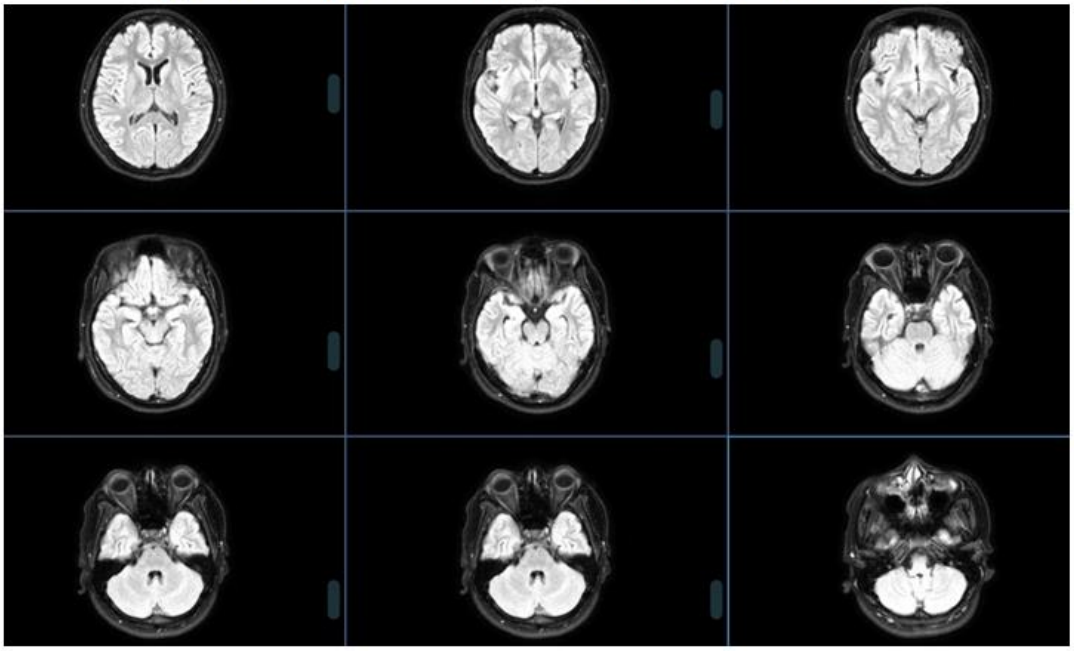
Appendix C: An EEG (electroencephalogram) of Case Number 1 showing burst suppression pattern



In addition to genetic testing, comprehensive epilepsy gene panels are also often used, and whole exome sequencing may be needed in some cases [6]. Case number 2 had genetic testing by whole exome sequencing, which as mentioned, showed the ARX mutated gene.

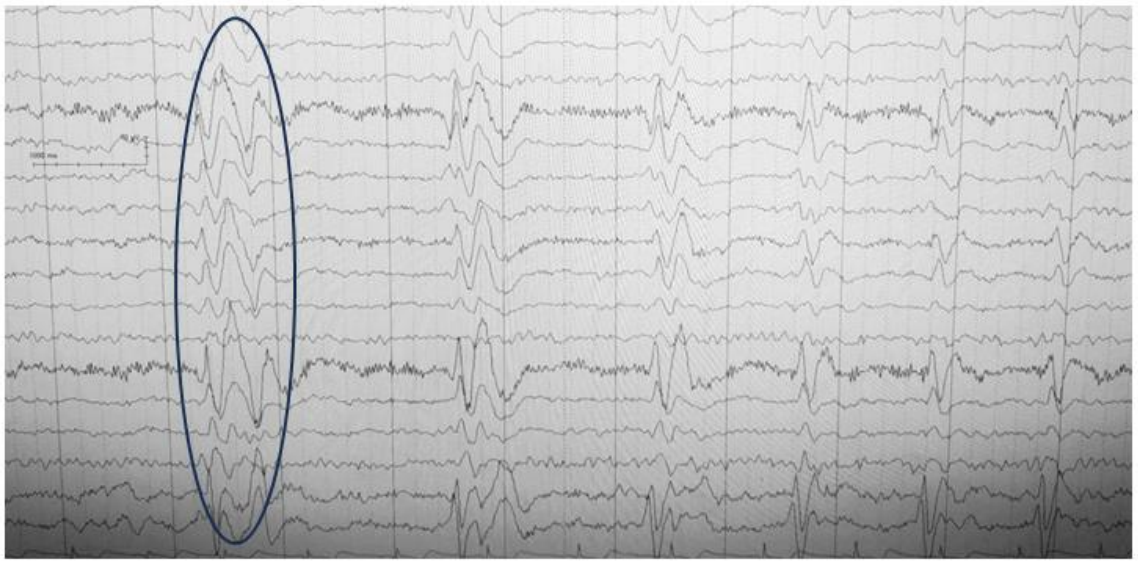
The diagnosis is based on clinical and electroencephalographic findings. The characteristic electroencephalogram (EEG) displays a suppression burst pattern, which appears with the onset of spasms. This is composed of bursts of high-amplitude spikes and polyspikes that alternate with periods of low-voltage basic rhythm (suppression) (see Appendix G). This EEG pattern is continuous and remains unchanged during both waking and sleeping states [5]. Both patients' EEG patterns exhibited epileptiform waves (see Appendices C and G), with a burst suppression pattern characterized by high amplitude spikes followed by little brain activity or flattening of the brain waves. Brain imaging such as cranial MRI typically confirms the presence of an underlying cerebral malformation and structural abnormalities, such as in Case Number 1 (Figure 1; see Appendix B).

Appendix D: MRI of Case Number 2, which showed an unremarkable result



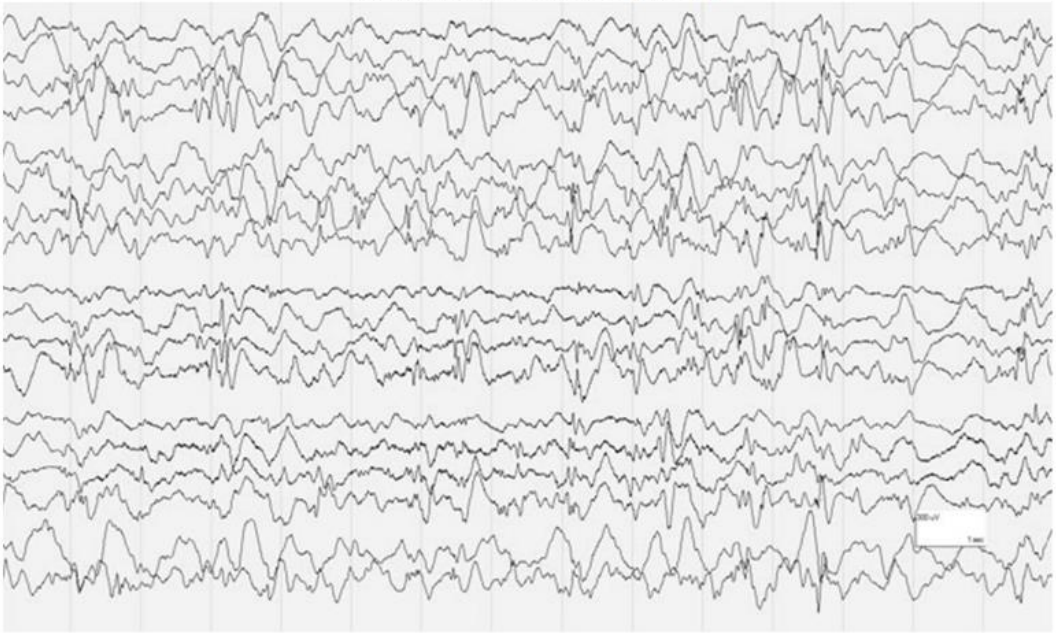
Ohtahara syndrome is also associated with certain metabolic problems that include Glycine encephalopathy (also called nonketotic hyperglycinemia), Cytochrome C oxidase deficiency, Leigh encephalopathy, Pyridoxine and pyridoxal-5-phosphate dependency, Carnitine palmitoyltransferase deficiency, Biotinidase deficiency, and Mitochondrial respiratory chain complex I deficiency. More recently, a patient with biotinidase deficiency and two patients with mitochondrial respiratory chain complex I deficiency were described [3]. There was a reported case of Ohtahara syndrome with cytochrome oxidase deficiency, with a noted impairment of the function of the respiratory chain. Because of these reports, it is also important to have a metabolic workup for patients with Ohtahara syndrome. The expanded newborn screening tests in both cases were normal; however, the further metabolic screening mentioned above was not performed.

Appendix E: An EEG (electroencephalogram) of Case Number 2 shows a burst suppression pattern



Ohtahara syndrome is frequently associated with a high morbidity and mortality rate. Approximately half of the patients die in infancy, while the other half acquire persistent, severe mental and neurologic deficits. Our patients had been repeatedly admitted for respiratory problems. Case number 1 had a tracheostomy and gastrostomy-jejunostomy tube inserted to control the recurrent aspirations and for pulmonary toileting. Case number 2 had only a gastrostomy tube inserted. Both cases have neurodevelopmental delays.

Appendix F: Hypsarrhythmia: This image showed highly disorganized high-voltage irregular slow waves intermixed with multifocal spikes and polyspikes [9]



Patients who survive frequently progress into Lennox-Gastaut syndrome, which has a high death rate and profound psychomotor impairments [6]. Lennox-Gastaut syndrome typically starts between the ages of 2 and 10 years old and consists of a triad of developmental delays and multiple seizure types that, as a rule, include atypical absences and myoclonic, astatic, and tonic seizures, as well as specific EEG abnormalities showing spike and slow waves, polyspike bursts in sleep, and a slow background in wakefulness. Patients commonly have tonic, myoclonic, atonic, and other seizure types that cause falls and are difficult to control. Most are left with long-term cognitive impairment and intractable seizures, despite multiple therapies. Some, but not all, patients start with Ohtahara syndrome, develop West syndrome, and then progress to Lennox-Gastaut syndrome [7].

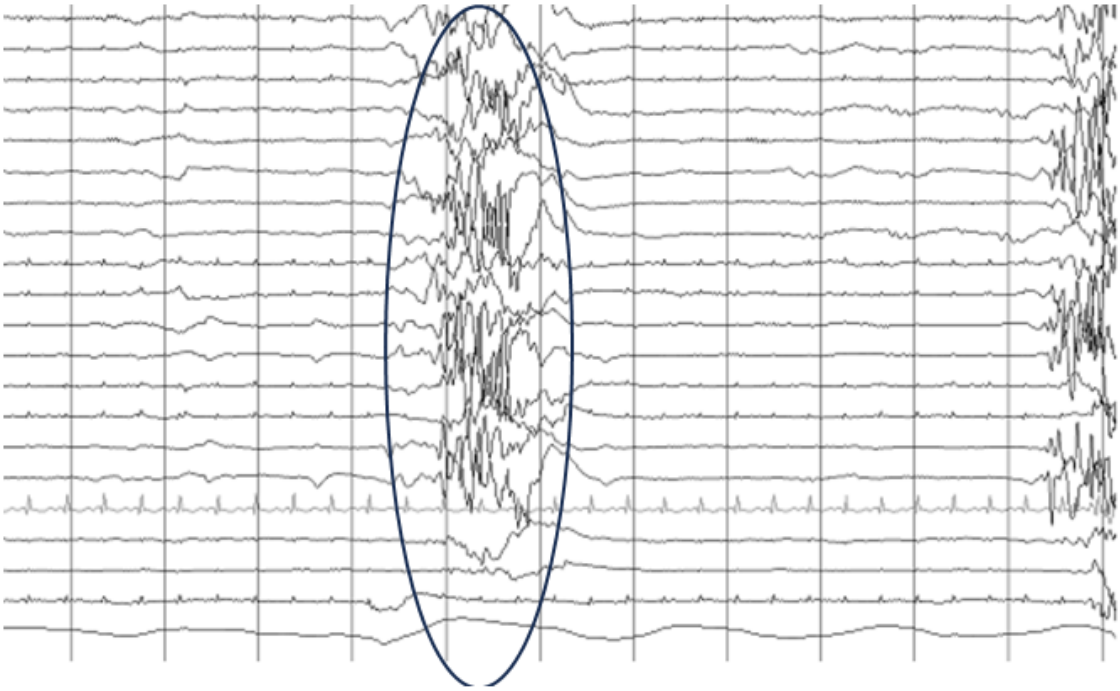
Both cases had experienced recurrent admissions for various medical issues, including pneumonia, respiratory tract infections, and poor seizure control. Case number 1 had evolved into Lennox-Gastaut syndrome, presenting as developmental delay and multiple seizures. In contrast, case number 2 had good seizure control, but tonic seizures still occurred at least once or twice a month.

The treatment of Ohtahara syndrome remains challenging, as it often involves a combination of antiepileptic medications and supportive measures. There is no cure for EIEE, and patients require constant supervision and care. Antiepileptic drugs such as benzodiazepines, valproate, levetiracetam, zonisamide, and phenobarbital have shown limited success in controlling seizures, as has pyridoxine. A ketogenic diet has been reported to show

some success in seizure control and should be considered if seizures are drug-resistant and the child is not a candidate for epilepsy surgery [8]. For those with associated metabolic disorders, once these conditions have been treated, there can be an improvement in the course of EIEE. Similarly, EIEE patients with certain structural abnormalities have benefited from neurosurgical intervention, if unilateral [4]. Both cases presented needed multiple antiseizure medications to control seizures. Case number 2 underwent a gastrostomy-jejunostomy tube insertion at 6 months old and was initiated on a ketogenic diet using a milk formula. Case number 1 was recently admitted for the insertion of a PEG tube and a tracheostomy. These maneuvers reflect the multifaceted approach required in managing these cases.

These two cases underscore the importance of a comprehensive diagnostic workup, including genetic testing, to identify underlying genetic abnormalities associated with Ohtahara syndrome. The management of associated complications such as respiratory infections, growth, and developmental delay requires a multidisciplinary approach involving pediatricians, neurologists, pulmonologists, gastroenterologists, nutritionists, and other specialists.

Appendix G: An EEG (electroencephalogram) in Ohtahara syndrome is very abnormal with a burst suppression pattern (high amplitude spikes followed by little brain activity or flattening of the brain waves) [8]



Summary

Ohtahara syndrome is a rare form of one of the more severe types of epilepsy syndrome that presents both diagnostic and therapeutic challenges to clinicians. These two cases demonstrated the diversity in clinical presentations, genetic abnormalities, the complexities of managing seizures, and other medical issues that arise in

patients with neurological problems. They were both diagnosed with significant neurodysabilities, recurring respiratory problems, seizures that were difficult to control, and nutritional issues.

Further research is needed to fully understand the genetic underpinnings and treatment strategies that are necessary to improve the outcomes of patients with Ohtahara syndrome.

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