AICARDI SYNDROME: A CASE REPORT

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ABSTRACT

Aicardi Syndrome is an extremely rare genetic disorder characterized by infantile seizures/spasms, agenesis of the corpus callosum, chorioretinal lacunae, and learning disabilities. It is likely caused by a de novo mutation in a gene in the X chromosome. However, the gene that causes this syndrome is still not known. It is diagnosed based on clinical findings. Aicardi syndrome may present as a clinical spectrum, from mild to severe disease. In general, the younger the age at which epilepsy and learning disabilities are diagnosed, the more severe the epilepsy and learning difficulties become later in life. Hence, long-term surveillance and management are warranted. This paper presents a 6-month-old Filipino female who exhibited the classic triad of Aicardi Syndrome: profound seizure episodes; callosal agenesis and interhemispheric cysts; and chorioretinal lacunae. Several anti-epileptic drugs such as Phenobarbital, Clonazepam and Topiramate were given for the seizures. Ophthalmogic examination and retinal camera fluorescein angiogram were advised to be performed regularly as well as consistent neurodevelopmental follow-up.

INTRODUCTION

Dr. Jean Dennis Aicardi, a French Neurologist, studied 8 children with infantile spasms, complete or partial agenesis of the corpus callosum, and a variety of ocular anomalies in 1965 [7]. This constellation of clinical findings, along with learning disabilities, were then termed as a distinct clinical entity known as Aicardi Syndrome. While no gene for Aicardi syndrome has been found, several studies support the theory that Aicardi syndrome is caused by de novo pathogenic variants in an X-chromosome gene that is inactive [11]. There are between 300 and 500 cases of Aicardi syndrome worldwide, according to estimates. Between 2000 and 2005, 5 cases of Aicardi syndrome were recorded in India, ranging in age from 1 to 13 years old, and were diagnosed using the classic triad described above. All the patients had severe psychomotor retardation, necessitating the use of multiple antiepileptic drugs (AEDs) to control their epileptic seizures. Just two of the five cases recorded had 100 percent remission, and both used Vigabatrin as an AED [4]. In Philippine Pediatric Society Registry, 145 out of 4 million cases have been reported with Aicardi Syndrome and only 2 cases have been reported in Philippine Children's Medical Center in a span of 10 years.

Between the ages of four months and four years, involuntary muscle spasms are a common clinical feature of Aicardi syndrome. Intellectual deficiency and developmental delay are present in varying degrees in people with Aicardi syndrome. Many girls have optic nerve developmental defects, and others have microphthalmia (small eyes). In some, skeletal issues such as missing or irregular ribs, as well as

anomalies in the spinal column's vertebrae (including hemivertebrae and butterfly vertebrae), have also been identified. Hence, infants presenting with seizure should undergo neurodiagnostic examination such as cranial ultrasound, cranial CT scan or MRI, and/or EEG to determine the cause of seizure.

Aicardi syndrome is diagnosed clinically based on neurodevelopmental assessment, neuroimaging, and ophthalmologic findings. The inclusion of the classic triad, or two of the classic triad plus at least two other major or supporting features, is one of the updated diagnostic criteria. The prognosis for people with Aicardi syndrome varies depending on how severe their symptoms are. While there is an increased risk of death during childhood and adolescence, survivors reaching adulthood have been recorded. Hence, long-term management by a pediatric neurologist with expertise in the management of infantile spasms is recommended [1].

CASE REPORT

This is the case of a 6-month-old, Filipino female who came in with a chief complaint of seizure, characterized as left versive gaze, tonic extension of right upper extremity and tonic flexion of right lower extremity for four minutes.

She was born to a 33-year-old Gravida 5 Parity 4 (4014) nonsmoker, non-alcoholic beverage drinker mother who was cognizant of pregnancy at the first month age of gestation. Her mother had regular prenatal check-ups at a local hospital. Ultrasonography done at 5 months age of gestation revealed fetal ventriculomegaly. The first congenital anomaly scan done at 6 months age of gestation revealed borderline ventriculomegaly, an intracranial cyst to consider arachnoid cyst measuring 3.5 x 3.3 x 2.3cm with an estimated volume of 13.8mL. A second congenital anomaly scan done at 9 months age of gestation revealed an intracranial cyst measuring 2.4 x 2.8cm, midline supratentorial region in location. Hence, the mother was advised to consult a tertiary hospital for further prenatal management. She had no maternal illness, exposure to viral exanthems or radiation and took multivitamins, ferrous sulfate, folic acid, and calcium regularly.

The patient was born full-term at a local tertiary hospital assisted by an obstetrician via normal spontaneous delivery. There was no premature rupture of membrane, prolonged labor, difficult delivery, cord coil or meconium-stained amniotic fluid. Birth weight was 2.88 kilograms. Apgar scores were 8 and 9. The patient had urine output and bowel movement within 24 hours after birth. Routine newborn care was done. She was given Hepatitis B and BCG vaccines. She was eventually discharged after 72 hours, with good activity and suck. Newborn screening and hearing screening were normal.

The patient in the interim was apparently well, with good cry, suck, and activity, until one month prior to admission when she had an episode of seizure described as left versive gaze, associated with tonic extension of right upper extremity and tonic flexion of right lower extremity

lasting for 15 seconds. There was no fever, gastrointestinal losses, post-ictal drowsiness, or drooling. There was no medication given and no consult was sought.

Three weeks prior to admission, she had seizure recurrence of the same semiology and duration. The seizure occurred twice, six hours apart, with no associated fever, losses, or postictal drowsiness. She was then brought to a tertiary hospital in active seizure, characterized as blank stares with circumoral cyanosis. She was hooked to oxygen at 10 lpm. Capillary blood glucose was 103 mg/dL. She was given diazepam at an unknown dose and Phenytoin was given at a loading dose of 20 mg/kg/dose and was subsequently maintained at 10 mg/kg/day. During her hospital stay, she still had seizure recurrences of the same semiology, occurring 10 times each day, lasting for 5 to 15 seconds per episode. Hence, levetiracetam at a dose of 100mg/kg/day and phenobarbital at 5mg/kg/day were also started. She had good activity and suck in between seizure episodes. She was advised for cranial MRI but was not done due to unavailability. She was then discharged after ten days, with seizure of the same semiology, occurring 3 to 4 times a day, lasting for 5 to 15 seconds. Take home medications were levetiracetam at 100 mg/kg/day and phenobarbital 5 mg/kg/day.

A few hours prior to admission, she had an episode of seizure characterized as left versive gaze, tonic extension of right upper extremity and tonic flexion of right lower extremity for four minutes associated with postictal drowsiness, increased sleeping time and decreased activity. At this time, she was described to be lying in bed throughout the day, in contrast to her usual playful disposition. Due to the associated poor activity and increased sleeping time, a consult was made in our institution.

The patient received only one dose of BCG, Hepatitis B, and Oral Polio. All vaccines were administered at a local health center with no noted adverse reactions post-vaccination. Immunization was not updated due to the illness of the patient. The patient was exclusively breastfed since birth. She has no known allergy to food or medication. The patient exhibited head control and social smile at 1 month old, cooed at 3 months old, rolled over at 4 to 5 months, turned to noise and voice at 4 months old, and transferred objects at 5 months old. At 6 months of age, the patient still cannot sit with support.

COURSE IN THE WARD

On the day of admission, the patient was seen awake, playful with good suck, not in cardiorespiratory distress with stable vital signs. Systemic exam was essentially normal. Neurologic examination revealed 3 mm pupils equally brisk reactive to light, intact extraocular muscles with visual tracking, with dazzle on both eyes and with visual threat, no facial asymmetry, tongue and uvula midline, and with spontaneous and equal movement of all extremities. She had reflexes of +2 on all extremities, positive for Babinski and negative for clonus. Laboratory and imaging results such as phenobarbital assay, ALT, AST, and chest radiograph were all normal. She was given diazepam for frank seizure.

Cranial CT scan done during admission showed a cystic focus intimately related to the 3rd ventricle and right parasagittal area measuring 3.0 x 2.14 x 2.85 cm. Considerations were colloid versus arachnoid cyst. There was also a dilated 3rd ventricle with consequent compressive effect to the adjacent lateral ventricles. A cranial MRI was subsequently done, which showed multiple variably sized CSF-intensity thin-walled cysts seen in the interhemispheric region with the following measurements: 2.26 x 1.91 x 1.76 cm (interhemispheric region); 2.8 x 2.67 x 3.01 (interhemispheric region) 1.64 x 8.78 x 2.13 cm area of the 3rd ventricle, and 1.34 x 1.07 x 1.28cm posterior horn of the right lateral ventricle. Callosal agenesis and interhemispheric cysts were also noted. An electroencephalogram (EEG) was performed, which revealed two clinical events consisted with focal seizures coming independently from the right and left hemispheres. There were generalized as well as multifocal epileptiform discharges coming predominantly from the left mid to posterior temporal and left centrotemporal regions as well as independent discharges coming from the right centrotemporal and right mid to posterior temporal head regions. Background activity is slow for age.

Medications given during her stay in the hospital were phenobarbital 3.5 mg/kg/day and leviteracetam 28 mg/kg/dose. Despite the combination of two anti-epileptic drugs, she still had seizure recurrences occurring 1 to 10 times a day. Hence, phenobarbital was increased to 9.3 mg/kg/day. Moreover, there was poor head control, lateral rectus palsy on the right, no dazzle and visual threat on the right, and no tracking of objects. She was then referred to Ophthalmology service who considered Congenital Ptosis, right, and Toxoplasmosis, Right with Alternating Exotropia. Other ophthalmologic findings include chorioretinal lacunae measuring ½ disc diameter seen below the optic disc and 2-disc diameters seen superior to the optic disc. Due to the consideration of toxoplasmosis, she underwent work-up which was positive for Cytomegalovirus 24 hours post-inoculation, but the mother was negative. The patient was then referred to Pediatric Infectious Disease service for the initiation of Ganciclovir. During her stay in the hospital, the patient developed healthcare-associated pneumonia and was eventually infected with SARS-COV2. In the latter part of her hospital stay, the patient was transferred to COVID ward and treated with Vitamin D3 and Zinc sulfate as a COVID confirmed case.

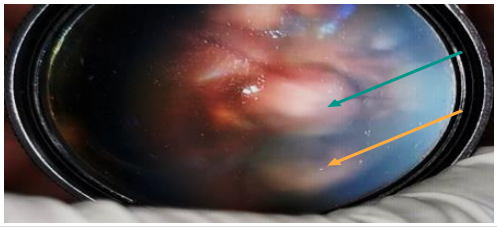
She was discharged last November 4, 2020, with an assessment of Multiple Intracranial Cysts probably secondary to Congenital CMV infection; Focal epilepsy, structural; Ocular toxoplasmosis - bilateral; Congenital ptosis of the right eye; Covid-19 Confirmed (10/7, 10/16, 10/23), ECLIA Non-infectious (10/28). Take home medications were as follows: Phenobarbital (5.2 mg/kg/day), Clonazepam (0.05 mg/kg/day), Topiramate (3.1mg/kg/day), Cotrimoxazole (8 mg/kg/day) and Valganciclovir (33.3 mg/kg/day). Since discharge, the patient would have 1 episode of spasm prior to sleeping increasing to 3 episodes per day with semiology of right versive gaze with clonic spasm. The patient was seen at the Ophthalmology OPD and

was advised to continue Cotrimoxazole. The patient was lost to follow-up with Neurology service.

DISCUSSION

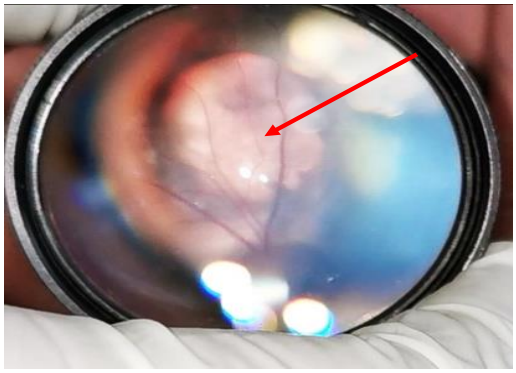
In Aicardi Syndrome, more than 95% present with infantile spasms in the first months of life. Various other seizure types develop over time. The patient presented with mixed focal and generalized seizure as shown in EEG which clinically manifested as infantile spasm. The patient was maintained on multiple anti-epileptic drugs (AEDs) which are Phenobarbital, Clonazepam and Topiramate but still presents with seizure recurrence.

Ophthalmologic exam findings on the patient revealed excavated optic disc with radially oriented retinal vessels, chorioretinal lacunae measuring ½ disc diameter seen below the optic disc, chorioretinal lacunae measuring about 2-disc diameters seen superior to the optic disc, chorioretinal scar seen inferotemporal to the fovea, and multiple cream-colored lesions seen temporal and nasal to the optic disc (Figs 1-2).



Green arrow
Excavated disc (t/c coloboma with radially oriented vessels
Yellow arrow
Chorioretinal lacunae measuring ½ disc diameter seen below the optic disc

Figure 1. Patient's optic disc



Red arrow
chorioretinal lacunae measuring about 2 disc diameters seen superior to the optic disc

Figure 2. Patient's optic disc

Chorioretinal lacunae are considered pathognomonic for Aicardi syndrome. Fundoscopic exam shows thinning of the choroid and sclera with degeneration of the rods and cones appearing as hypopigmented or depigmented regions that are whitish or pink in color. The lacunae are described as having features typical of optic nerve colobomas, but at the edges there are unique convolutions of tubular-like structures lined by pigmented and nonpigmented epithelial cells in close association with the capillaries and photoreceptor folds. The difference between chorioretinal lacunae and coloboma is that the former has defined margins, poorly differentiated or absent choriocapillaris, and a thin but intact Bruch's membrane with attenuated and hypoplastic retinal pigment epithelium [13].

Aicardi syndrome can be diagnosed using neuroimaging. The patient's cranial MRI revealed callosal agenesis and interhemispheric cyst (Fig. 3). Total agenesis (absence), partial agenesis (hypogenesis), thinning (hypoplasia), and thickening (hypoplasia) are all developmental defects or disorders of the

corpus callosum (hyperplasia). The corpus callosum in partial agenesis has a shorter anterior-posterior length due to missing segments such as the splenium and/or the rostrum. Malformations of the corpus callosum are often associated with other cerebral or extra-cerebral anomalies [12]. Agenesis of the corpus callosum (ACC) affects a variety of developmental processes, from midline telencephalic patterning to neuronal specification and commissural axon control. The prevalence has been estimated to be between 1:4000 and 1:5000 live births; however, rates of 2 to 3% have been identified among patients with neurodevelopmental disabilities. The disruption could be caused by genetic, infectious (TORCH infections, Zika virus), vascular, or toxic factors (fetal alcohol syndrome). The most common cause is genetic. In 30 to 45 percent of cases, a "syndromic" diagnosis is made, and in 20 to 35 percent of cases, a monogenic cause is found. People with agenesis of the corpus callosum have a wide presentation of behavioral and cognitive abnormalities – from mild cognitive delays to severe intellectual impairment.

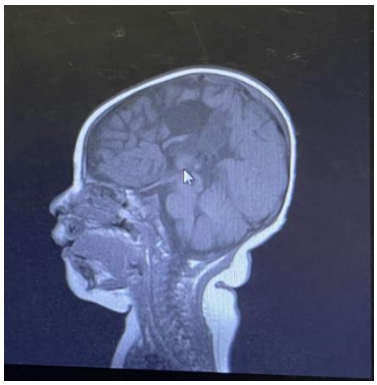


Figure 3. MRI of patient showing Colossal Agenesis

Due to the ophthalmologic findings seen in the patient, one of the differentials was Toxoplasmosis infection. However, the patient's mother tested negative for TORCH infection, and there was also no chorioretinitis or intracranial calcification on subsequent workups.

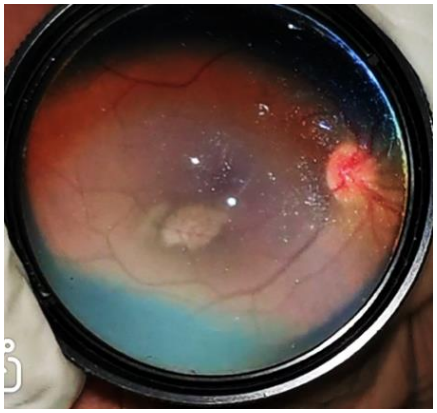


Figure 4. Chorioretinal scar seen inferotemporal to the fovea

As the patient presented with seizures, developmental delay and abnormal ocular findings, congenital cytomegalovirus infection was also considered as another differential diagnosis. On work-up, our patient tested positive for CMV hence, Valganciclovir was started. However, typical ophthalmologic findings of CMV such as retinitis and usual location of lesion did not present in the patient. Thus, Aicardi syndrome is still a strong consideration.

Aicardi syndrome is a neurodevelopmental disorder affecting newborn females. The disease is sporadic, it does not appear to be passed down from parent to child. The mutation that causes Aicardi syndrome has not been identified, but it is thought to be caused by a dominant mutation in an X-linked gene that may be lethal in certain males that appears for the

first time in a family. However, recent evidence suggests that mutations in the TEAD1 gene (chromosome 11) may explain some or all the cases [13]. Hence, genetic counselling is recommended when patient presents with classic features of Aicardi Syndrome.

Medications may be used to suppress the seizure. There is no first line AED identified specific for spasms of Aicardi Syndrome. In a study of Banerjee, 5 children identified with Aicardi Syndrome are treated with multiple AEDs and only 2 children had 100% remission when Vigabatrin was included.

In March 2021, the patient was noted to be playful, with good suck, but still with episodes of seizure and spasm of same semiology occurring for 3 to 4 episodes each day lasting for 15 seconds. However, during these past few months, seizure semiology varied from right versive gaze to blank stares but still with clonic spasm occurring 1 to 2 episodes per day. The patient currently follows up with a neurologist every three months. Valganciclovir and Cotrimoxazole were completed last May 2021. The patient was also seen at PCMC Ophthalmology Department and was advised retinal camera fluorescein angiogram. However, due to financial constraints, her parents were still unable to process the papers for the said procedure. Maintenance medications were revised to as follows: Phenobarbital at 27 mg/kg/day and Topiramate at 2.5 mg/kg/day.

Future plans are to establish regular ophthalmologic examination along with doing a retinal camera fluorescein angiogram. The patient is also yet to be seen by a Neurodevelopmental Pediatrician for evaluation and management.

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