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Case Report

Diagnostic approach to Aicardi syndrome: A case report☆

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ABSTRACT

Aicardi syndrome is an X-linked-dominant genetic condition that is present almost exclusively in females. To diagnose Aicardi syndrome, the classic triad of agenesis of the corpus callosum, infantile spasms, and chorioretinal lacunae must be present. Here, we described a case of a female newborn baby delivered at 36 weeks of gestation that arrived at the emergency department with stiffening of arms and legs; therefore, an electroencephalogram was performed, showing generalized polypots confirming infantile spasms. Moreover, magnetic resonance was performed, showing complete agenesis of the corpus callosum. The patient was then transferred for an ophthalmoscopic examination, which evidenced multiple hypopigmented chorioretinal lesions corresponding to chorioretinal lacunae. Based on the clinical and radiological findings, the diagnosis of Aicardi syndrome was established, and treatment with anticonvulsive therapy and physiotherapy was initiated. This case report highlights the main characteristics that clinicians should consider to suspect this rare genetic condition, emphasizing the imaging and electroencephalographic findings.

Introduction

Aicardi syndrome (AS) is a rare genetic neurodevelopmental disorder present almost exclusively in females, with an incidence rate of one case per 110.000 life births [1,2]. AS is characterized by a triad of abnormalities that include agenesis of the corpus callosum, infantile spasms, and chorioretinal lacunae [1,3,4]. However, it could also be associated with polymicrogyria, periventricular heterotopia, choroid plexus cysts, cerebellar abnormalities, enlarged cisterna magna, and costovertebral malformations [1,4]. AS is a diagnostic challenge due to its rareness, and it usually requires a multidisciplinary approach based on neuroimaging, ophthalmological examina-

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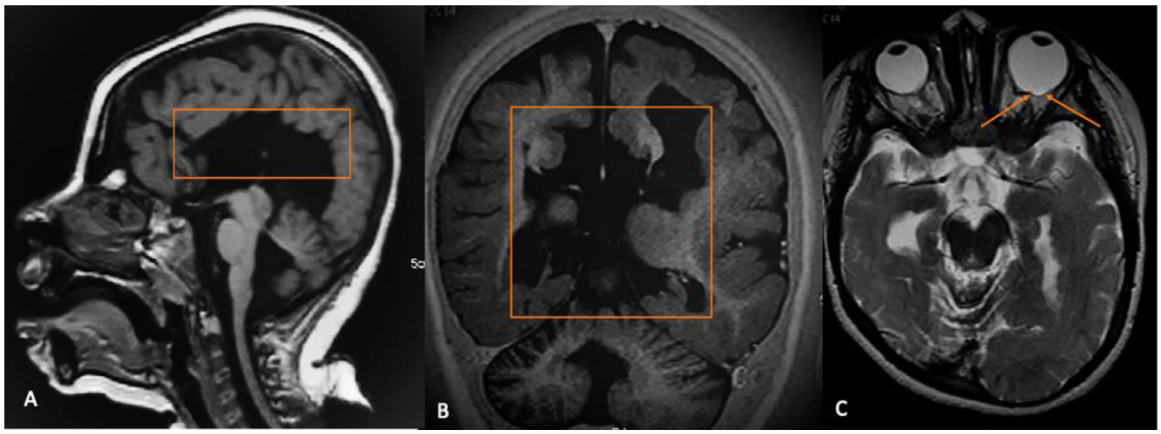

Fig. 1 – Brain MRI. T1-weighted image shows agenesis of corpus callosum (orange box in A) and a multiseptated interhemispheric cyst (orange box in B). T2-weighted image shows a left coloboma cyst located in the posterior portion of the left eyeball (orange arrows in C).

tion, and pediatric neurology assessment [3]. Currently, there is no cure for AS; treatment is based on antiepileptic agents, physiotherapy, and diet [5].

According to Kroner et al., close to 853 cases of AS are reported in the United States and nearly 4000 cases worldwide, representing a disease poorly described in the literature [6]. For that reason, this article aims to report and discuss the neurological and neuroradiological findings of a newborn with AS.

Case description

We present a case of a female baby born by elective cesarean section at 36 weeks of gestation; the mother's age was 42 years old, and during the entire pregnancy, she had several ultrasonographic assessments with an initial diagnostic suspicion of Dandy-Walker syndrome. The baby's birth weight was 2090 g, the height was 42 cm, and the APGAR score was 8/10. No records of congenital diseases in the family were reported during the anamnesis.

At 15 days of life, the first symptoms were observed, including stiffening of the arms and legs, associated with hyperextension of the neck with a periodicity of 12-20 episodes per day. Physical examination revealed an alert patient with adequate newborn reflexes, bilateral iris colobomas resembling a cat's eye, mild scoliosis, and missing ribs 7-9.

Given the clinical picture of infantile spasms and bilateral iris colobomas, magnetic resonance imaging (MRI) was performed, showing agenesis of the corpus callosum, a multiseptated interhemispheric cyst communicating with the ventricular system, and the presence of bilateral coloboma cysts (Fig. 1).

Due to the MRI findings, the patient was transferred to the pediatric neurology department. There, an electroencephalogram (EEG) was requested, revealing frequent paroxysmal activity throughout the entire recording, characterized by generalized polypots (high voltage and slow waves located in the left hemisphere), which confirmed the diagnosis of infantile spasms (Fig. 2).

Due to infantile spasms and agenesis of the corpus callosum, the suspicion of AS was raised; therefore, the patient was transferred to the ophthalmology department, where an ophthalmoscopy was performed, which demonstrated multiple hypopigmented chorioretinal lesions corresponding to chorioretinal lacunae (Fig. 3). Given the presence of corpus callosum agenesis, infantile spasms, and chorioretinal lacunae, the classic triad of AS was completed, and the diagnosis was performed.

Treatment was initiated with lamotrigine, valproic acid, levetiracetam, physiotherapy, and control appointments with pediatric neurology. Currently, the patient persists with infantile spasms, but their frequency has substantially dropped out to 10-12 episodes per day.

Discussion

AS is an X-linked-dominant genetic condition that is present almost exclusively in females [7]. The disease usually affects one of the 2 X chromosomes of the female (XX), which confers a condition compatible with life [8]. However, when the mutation is present in a male (XY), it affects the only X chromosome available and produces a severe disease that results in abortion [8]. Some authors have described the presence of AS in male patients with Klinefelter (XXY); the possible explanation for this is the fact that males with Klinefelter have 2 X chromosomes; therefore, one of them can be affected, and the patient can still survive until birth [9].

AS usually manifests in the first 3 months of life as infantile spasms (characterized by rapid muscle contractions and hyperextension of the upper limbs) presenting several episodes during the day [5]. In this case, our patient presented between 12 and 20 infantile spasms daily, and she continued to have them even after establishing antiseizure therapy.

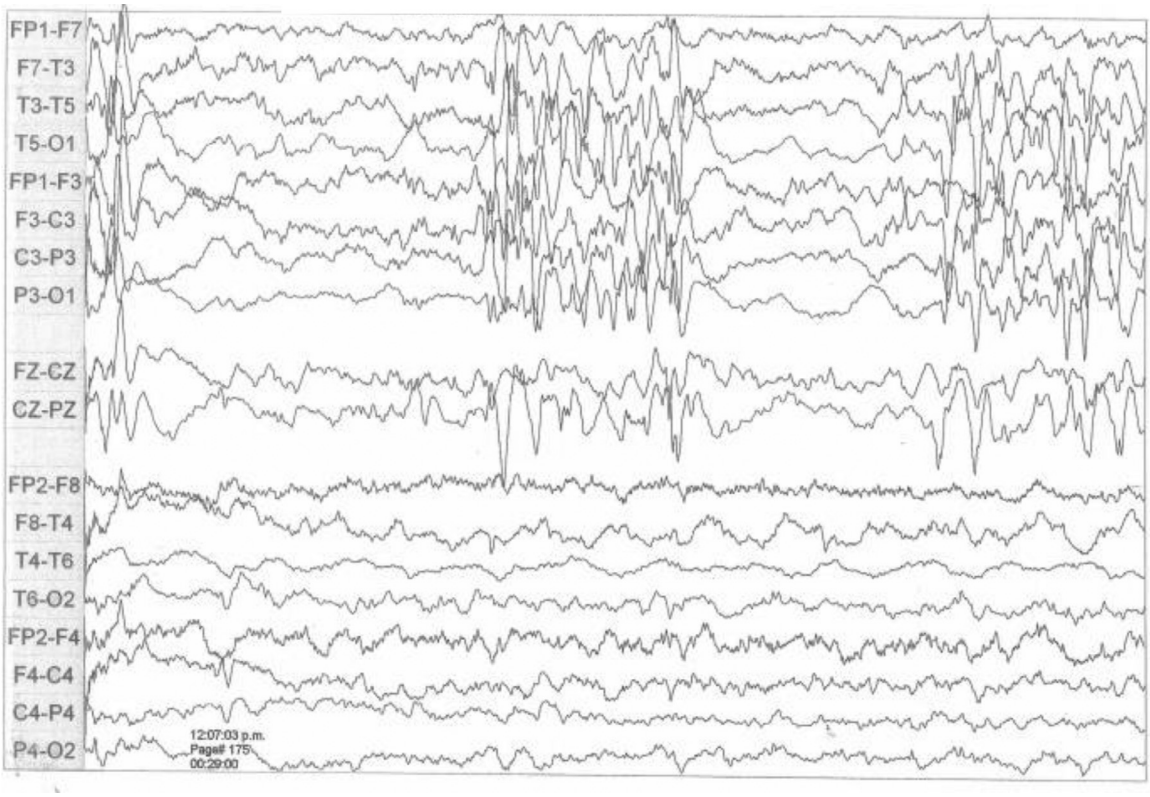

Fig. 2 – Abnormal EEG showing frequent paroxysmal activity throughout the entire recording, characterized by generalized polypots (high voltage and slow waves located in the left hemisphere), which confirmed the diagnosis of infantile spasms.

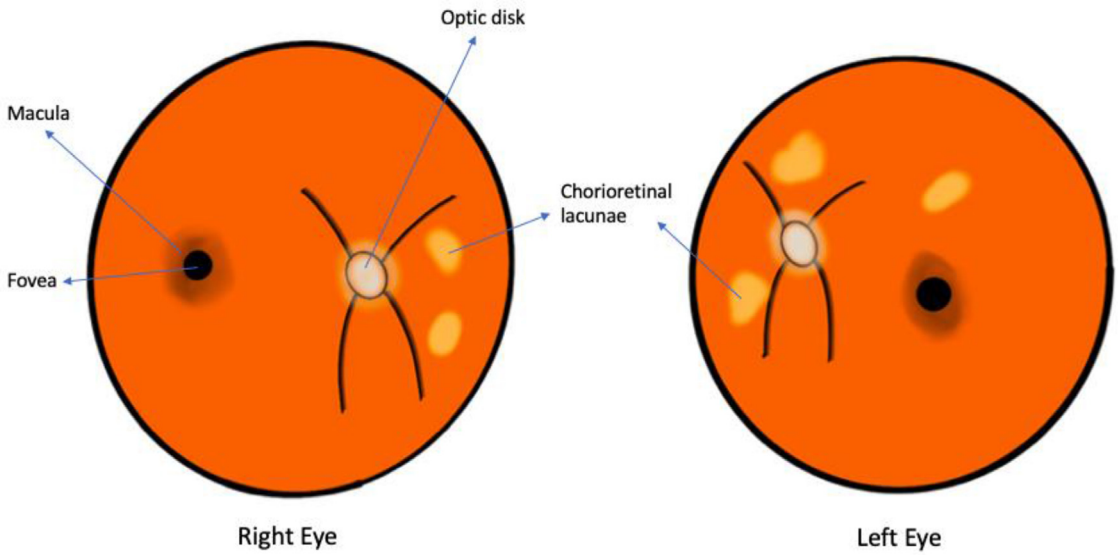

Fig. 3 – Illustration depicting the patient's ophthalmoscopy. Bilateral chorioretinal lacunae are shown.

AS represents a diagnostic challenge due to its rareness, and a multidisciplinary approach is needed to confirm the disease. Some patients with AS can have interhemispheric cysts that could mimic a posterior fossa cyst of Dandy-Walker syndrome, leading to misdiagnosis, especially during the prenatal ultrasonographic assessment, as shown in this case [3]. Another important differential diagnosis of AS is Lennox-Gastaut syndrome, which is an epileptic encephalopathy manifested during infancy and characterized by tonic seizures, which can clinically mimic infantile spasms of AS, leading to misdiagnosis [3].

To accurately diagnose AS and avoid misdiagnosis, the patient must have the classic triad of agenesis of the corpus callosum, infantile spasms, and chorioretinal lacunae; however,

assessing this triad during the prenatal period is not possible; for that reason, physicians must have a clinical suspicion of AS in all patients with brain cysts during the prenatal period [4]. The corpus callosum agenesis in AS can be partial or complete; in this case, our patient presented complete agenesis of the corpus callosum, which has been reported in 72% of cases, while partial agenesis has been reported in 28% of scenarios [10].

The patient described in this paper had the AS triad (infantile spasms, agenesis of the corpus callosum, and chorioretinal lacunae) but also had some associated abnormalities, such as a multiseptated interhemispheric cyst that communicated with the ventricular system. Those interhemispheric cysts usually originate from the choroid plexus and are present in almost 50% of patients with AS. These cysts can vary in size, ranging from a few millimeters to several centimeters in diameter [8]. In rare scenarios, choroid plexus cysts can grow until they compress the aqueduct, leading to hydrocephalus [8].

Hopkins et al. reviewed 23 MRI scans of patients with AS, and they found that 100% of individuals had polymicrogyria (predominantly in the anterior region of the brain) and heterotopias (in periventricular localization); in contrast, 95% of cases showed cerebellar abnormalities, and 78% presented colpocephaly, in this case, none of this findings were manifested [11].

Imaging findings have a crucial role in the diagnosis of AS; according to Aicardi et al., the presence of agenesis of the corpus callosum and choroid plexus cysts are highly suggestive of AS [8]. In this case, AS was initially suspected based on MRI findings, which facilitated the patient's transfer to the pediatric neurology department for further studies to confirm the diagnosis.

Typical EEG findings of AS include disorganization of basal activity and alternative hypsarrhythmia with an independent paroxysm pattern between both hemispheres known as "split-brain," which represents the independent function of each hemisphere caused by the corpus callosum agenesis [12].

AS treatment is based on anticonvulsant medications; nevertheless, therapeutic failure is common, leading to the implementation of adjuvant therapies such as ketogenic diet. In a retrospective study by Sanchez et al., 67% of patients experienced more than a half seizure reduction after 3 months of ketogenic diet therapy; however, the treatment was beneficial for patients who didn't have infantile spasms at the onset of diet [13]. It is essential to highlight that this study had a small sample size, and further research is required.

Patients with AS can often present congenital abnormalities such as hemivertebrae, butterfly vertebrae, severe scoliosis, fusion of ribs, and missing ribs; therefore, physical therapy and orthopedic surveillance are crucial in the treatment [8]. Our patient was under physical therapy due to mild scoliosis, which is expected to progress in the future due to muscle imbalance caused by the absence of ribs [14].

AS has a fatal prognosis, the median age of survival is estimated at 18.5 years, and the most frequent cause of death is related to respiratory complications caused by hypersecretion [5,15]. Yacoub et al. described certain factors associated with a better prognosis; those factors include infantile spasms with a late presentation, partial agenesis of the corpus callosum, and smaller and fewer chorioretinal lacunae [16,17].

Conclusions

The diagnosis of AS requires a multidisciplinary approach with ophthalmology, radiology, and pediatric neurology to accurately identify the classic triad and therefore confirm the disease. The clinical suspicion of AS must be raised in all newborns with stiffening of arms and legs, for which MRI and electroencephalogram are mandatory to establish the diagnosis. Costovertebral anomalies should be sought in all patients with AS.

Patient consent

Verbal and signed consent was obtained from the patient concerned. The study was conducted anonymously.

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