Aicardi Syndrome, a case report

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Abstract

Aicardi syndrome is a very rare neurological condition caused by an unknown de novo mutation on the X-chromosome. The diagnostic triad is composed of infantile spasms, agenesis of the corpus callosum and chorioretinal lacunae but it can present with more additional neurological and physical manifestations. Epileptic spasms are often the first clinical presentation of a girl with Aicardi syndrome. Due to a wide range of aetiologies in epileptic spasms, identifying a rare cause is not always easy. This case report describes the clinical and imaging characteristics of an uncommon presentation of infantile spasms, Aicardi syndrome.

Case report

A four-month-old girl presented to the emergency department with sudden onset of focal motor seizures. One day before, her mother had noted frequent twitches of the left corner of the mouth and eye deviation to the left. Pregnancy and birth were unremarkable, she had a normal neurological development so far and family history was negative for any neurological disorder. Initial clinical examination was unremarkable, so she was admitted to the hospital for observation. During admission there was an increase in seizure frequency with the occurrence of focal seizures with posturing of the right arm and brief eye deviation to the left. After one day a new seizure type was observed with clusters of brief bilateral arm extensions, consistent with epileptic spasms.

As she developed fever during admission an extensive workup was performed to rule out infection. Blood analysis, urine analysis and lumbar puncture were normal. In addition, a metabolic screening on urine and blood was negative. A short electroencephalogram (EEG) taken the day after admission showed rare isolated centrotemporal spikes on the left side without any evidence of hypsarrhythmia. There were no epileptic seizures during the registration. Magnetic resonance imaging (MRI) of the brain showed an agenesis of the corpus callosum with interhemispheric cysts, grey matter heterotopias, abnormal white matter myelination (figure 1) and a nonspecific cyst in the right cerebellar tonsil. Screening for infection with toxoplasmosis or cytomegalovirus was negative.

Levetiracetam was started and progressively increased because of increasing focal seizure frequency. Unfortunately, there was no clinical improvement and phenobarbital was given once intravenously. As the seizures evolved to flexor spasms, vigabatrin was associated as a third antiepileptic drug.

Given the increasing seizure frequency despite therapy, the patient was referred to a university hospital for further investigation and treatment.

Repeated EEGs showed multifocal spikes with evolution to hypsarrhythmia, and a permanent asymmetry in the background. The left hemisphere showed a burst-suppression pattern and the right hemisphere multifocal epileptic activity maximally posterior temporal with slow onset (figure 2).

Figure 1: A. Agenesis corpus callosum; B. Heterotopia of the grey matter; C. Interhemispheric cysts; D. Abnormal white matter myelination.

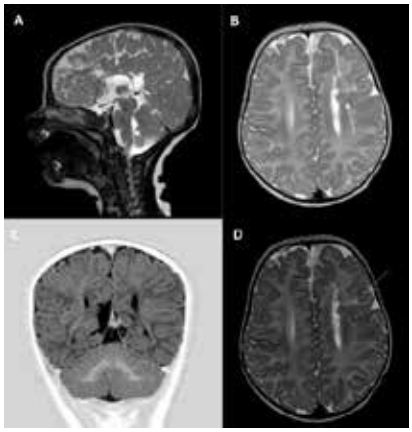
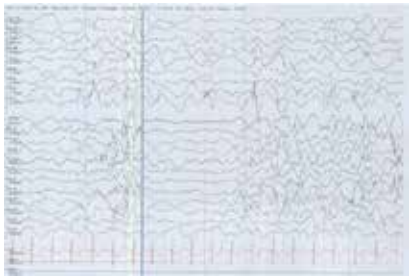
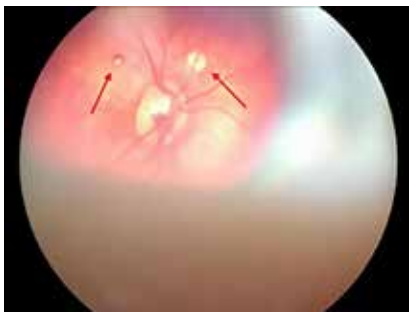


Figure 2: The right hemisphere is represented by the first nine leads, showing rather a multifocal appearance of epileptic activity and slow firing temporally. The left hemisphere is represented by the lower leads, showing rather a burst-suppression pattern (indicated by the vertical line).



There was a high suspicion of Aicardi syndrome, given the female sex, infantile spasms and agenesis of the corpus callosum. In addition, fundoscopy revealed multiple chorioretinal lacunae with peripapillary pigmentation on the right side (figure 3). This pathognomonic sign confirmed the tentative diagnosis of Aicardi syndrome. An X-ray of the dorsal spine was normal.

Figure 3: Fundoscopy of the right eye shows chorioretinal lacunae (arrows).



Consequently, levetiracetam and vigabatrin were increased, and prednisolone was associated. Unfortunately, this was without any improvement and levetiracetam was changed to topiramate for a better seizure control.

Micro-array was negative and a genetic panel for cortical dysplasia showed that the girl was heterozygous for a variant of unknown significance in the *COL18A1* gene, located at chromosome 21. This variant follows an autosomal recessive inheritance pattern. No second variant could be observed in this gene. Consequently, the presence of this variant is probably a coincidental finding.

Discussion

Aicardi syndrome is a rare neurodevelopmental disorder and often presents with epileptic spasms.

It occurs almost exclusively in girls. The presentation is characterised by a typical triad of corpus callosum agenesis, central chorioretinal lacunae and infantile spasms. As more affected individuals have been identified, it has become clear that other neurological and systemic anomalies are also possible. This syndrome occurs in 1 in 100,000 newborns in the US and 1 in 93,000 newborns in the Netherlands. Unfortunately, Belgian numbers are lacking. The prognosis of children with Aicardi is poor and they often have a severe global development delay with refractory epilepsy (1–3).

Children with Aicardi syndrome can present with characteristic facial features such as a prominent premaxilla, tip-tilted nose, small angle of the nose bridge and sparse lateral eyebrows (1,4). Nonetheless, Jean Aicardi stated that dysmorphism was unusual and did not occur in his patients (5).

In the initial phase of the disorder, infantile spasms may pass unnoticed and might be overlooked by parents (4). The average age for presentation in girls with Aicardi Syndrome is 3-4 months. But, as well in this case report, the spasms associated with Aicardi syndrome can be asymmetrical or unilateral, and focal seizures could be seen. Eventually, refractory epilepsy with a variety of seizure types develops over time (1,3,5).

The typical EEG pattern in West syndrome is hypsarrhythmia. But in patient with Aicardi syndrome it is often asymmetrical or absent (5). Another presentation on EEG is a split-brain with a suppression-burst pattern independently arising from the different hemispheres as seen in this case (figure 2). Evolution to a spike-wave pattern and Lennox-Gastaut syndrome is rarely seen due to the lack of certain brain structures for organisation and bilateral spread of paroxysms (1,4–6).

MRI imaging may show an agenesis of the corpus callosum and polymicrogyria as result of the reduced axonal pull on the gyri. It often presents with asymmetry of the cerebral hemispheres and intracranial cysts, of which more than half is located in the choroid plexus. In addition, other brain abnormalities are also possible, such as cortical dysplasia, heterotopia of the grey matter, anomalies of the vermis, and sometimes choroid plexus papillomas. The MRI findings can be wrongly attributed to a toxoplasmosis or cytomegalovirus infection (5,7,8).

Chorioretinal lacunae are a pathognomonic sign for Aicardi syndrome and a fundoscopy is obligatory for diagnosis. The ophthalmic findings associated with Aicardi syndrome are mostly bilateral and do not change with exception of the pigmentation, which is often located in the periphery of the lacunae and may increase with age. Other frequent ophthalmologic findings include microphthalmia and coloboma of the optic disk, also presenting with surrounding pigmentation and resembling the 'morning glory disk'. These features can lead to blindness but barely change over time (2,5). Additionally, girls with Aicardi syndrome have an increased risk of scoliosis, missing ribs and vertebral anomalies and further investigation for co-morbidities is necessary (4,5).

Genetic testing has become increasingly important in the diagnostic evaluation of children with epilepsy. However, the genetic aetiology of Aicardi syndrome is still unknown. It is hypothesised to be caused by a de novo pathogenic mutation on the X-chromosome, lethal to XY males, as most case reports involve females or XXY males (1). Recent case reports have also described male patients (46, XY karyotype) with Aicardi syndrome and one study has shown the possibility of genetic heterogeneity (9). Another recent study described a case of Aicardi syndrome with a duplication event on the X-chromosome (Xp22.33 including SHOX), which could have led to abnormal neural tissue development, but it could also be an incidental finding (10). Other studies have suggested inactivation of the X chromosome because of the variable severity and asymmetry of the phenotype, but the studies are not all consistent (11). Further research is definitely needed to better understand the underlying pathogenic mechanisms in this syndrome.

The diagnosis of Aicardi syndrome is based on the presence of the three classic symptoms. In 2005, Sutton et al. proposed modified criteria for the diagnosis Aicardi syndrome (8). The presence of two symptoms of the classic triad plus at least two other major symptoms (cortical malformations, periventricular and subcortical heterotopia, cysts around third cerebral ventricle and/or choroid plexus, or optic disc/nerve coloboma or hypoplasia) or supporting features (vertebral and rib abnormalities, microphthalmia, "split-brain" EEG, gross cerebral hemispheric asymmetry, vascular malformations or vascular malignancy) is strongly suggestive of the diagnosis of Aicardi syndrome.

Just like the diagnosis, treatment also requires a multidisciplinary management. The survival rate of patients with Aicardi is highly variable and depends on seizure control. The goal of therapy should include resolution or at least modification of hypsarrhythmia as soon as possible. Hormonal therapies and vigabatrin have the most evidence to support their use in infantile spasms. However, epilepsy is difficult to control in Aicardi syndrome and often become refractory. Kroner et al. described a survival rate of 62% at 27 years of age (2). They have often developmental delay with limited language skills and will benefit from physiotherapy with orthopaedic interventions (3,5,8).

In **conclusion**, Aicardi syndrome is a rare genetic disorder that primarily affects newborn girls, due to an unknown de novo mutation on the X-chromosome. It is characterized by the typical triad of infantile spasms, agenesis of the corpus callosum and the pathognomonic

sign of chorioretinal lacunae. Other symptoms may include different seizure types, refractory epilepsy, atypical facial features, skeletal abnormalities, developmental delay and intellectual disability. It requires a multidisciplinary approach to diagnosis and while there is no cure, treatment is focused on managing symptoms and supporting developmental and physical needs. With this case we highlight the awareness of a more infrequent presentation of epileptic spasms, Aicardi syndrome.

Disclosure of potential conflicts of interest

There were no potential conflicts of interest.

Informed consent

Informed consent was given by the mother of this patient.

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