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Case report

Aicardi syndrome in a 20-year-old female☆

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ABSTRACT

Purpose: To describe an unusual case of Aicardi Syndrome that both affirms hallmark characteristics of the condition and introduces new observations.

Observations: We report the case of a 20-year-old woman with Aicardi Syndrome who presented in respiratory distress with bradycardia and died soon thereafter. She had a history of severe mental retardation, seizure disorder, advanced scoliosis and numerous contractures in addition to congenital ocular malformations resulting in bilateral blindness. The case is notable for her age and longevity, as most patients with Aicardi Syndrome expire much younger, as well as the presence of intact nuclei under the posterior lens capsule.

Conclusions and importance: Aicardi Syndrome is a rare X-linked cerebro-retinal disorder typified by seizures, agenesis of the corpus callosum, and chorioretinal lacunae. Documenting alterations from and additions to this triad of symptoms is critical to better understanding both the syndrome itself, as well as the full breadth of its clinical impact on the patient.

1. Introduction

Aicardi syndrome is an X-linked *de novo* autosomal recessive condition characterized by a triad of symptoms: spasm in flexion, agenesis of the corpus callosum, and a number of ocular abnormalities.[1,2] These include microphthalmia, atrophic choroiditis, coloboma of the optic nerve, and unusual papillary proliferations of the retinal pigment epithelium (RPE) termed lacunae.[3,4] Other associated symptoms include congenital defects of the ribs and vertebrae, as well as brain abnormalities such as intracranial cysts or tumors, cortical polymicrogyria, periventricular heterotopia, cysts of the choroidal plexus, and asymmetry of the hemispheres.[2] About one-third of Aicardi Syndrome patients have costovertebral defects leading to severe scoliosis.[5] Patients may also have hemivertebrae, butterfly vertebrae, fusions of ribs or vertebrae, and missing ribs. While the exact gene causing Aicardi Syndrome has not yet been identified despite attempts at whole exome sequencing and deletion analysis, the location of the gene is likely in the Xp22 locus.[6–8] As such, Aicardi Syndrome is reported only in females due to the gene's location on the X chromosome. In males, the hemizygous single X chromosome renders it lethal, unless the individual happens to have an XXY genotype.[2] Aicardi Syndrome has been noted to decrease life expectancy, and there appears to be a high risk of death during infancy and between the ages of four and 16, after which point risk of death decreases.[9]

The chorioretinal lacunae are considered pathognomonic to the diagnosis of Aicardi Syndrome.[2,10] Ophthalmoscopically, they are multiple and bilateral with increased pigmentation at the border. They are scattered throughout the fundus although clustered posteriorly. Colobomas are likewise characteristic of the disease, although not diagnostic.[4] No intraocular inflammation is associated with Aicardi syndrome, the RPE may be hypo- or hyperpigmented, and there is an absence of photoreceptors.[2] Total blindness is often rare, but possible.

The purpose of this report is to document an unusual case of Aicardi syndrome with histopathologic examination of the brain and eyes in which nuclei were observed under the posterior lens capsule.

2. Case report

The patient was a 20-year-old woman with a history of Aicardi Syndrome who presented to the Emergency Department (ED) of The Mount Sinai Hospital in acute respiratory distress after recovering from a recent case of the flu. Tracheostomy and gastrostomy tubes were in

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place on arrival. Emergency Medical Services reported that the patient had dyspnea, hypoxia, and severe bleeding from the tracheostomy tube. The patient continued experiencing severe respiratory distress in the ED, followed by bradycardia. She subsequently went into pulseless electrical activity and asystole. Given the patient's "Do Not Resuscitate" status, no cardiopulmonary resuscitation efforts were initiated, and she was declared dead. The patient's family had abandoned her upon learning of her diagnosis, and as a result, she became a ward of New York State under the care of Catholic charities. She had been institutionalized her entire life in several facilities throughout New York City.

The patient had severe mental retardation, a seizure disorder, severe scoliosis and numerous contractures, and was bilaterally blind and mute. She had been examined by the ophthalmologist working at The Cardinal Cooke Center about two months prior to her death. He noted that she sensed no light perception bilaterally. The external examination revealed microphthalmic eyes. The corneas were clear. The anterior chambers were grossly clear. The pupils were miotic and unresponsive to light. Fundus examination revealed bilateral optic nerve colobomas with "degenerative retinal changes."

The postmortem examination revealed findings consistent with her clinical history of Aicardi Syndrome including agenesis of the corpus callosum, microphthalmia, macrotia, and scoliosis. The cause of death was severe acute and chronic pneumonia with interstitial fibrosis and pleural adhesions.

Gross examination of the eyes (Fig. 1) revealed a right eye measuring 17x19x18mm. The globe transilluminated normally. There was a cystic structure on the posterior aspect of the globe adherent to and part of the globe that measured 3x3x3mm. The cornea was opalescent and measured 10x10mm. The globe was opened horizontally. There were many focal pigmentary abnormalities, or lacunae (Fig. 2), throughout the retina, with a coloboma adjacent to the optic nerve that was devoid of pigmentation (Fig. 1). Similar findings were noted in the left eye.

Microscopic evaluation of the right eye revealed a normal medial rectus muscle, and there were focal calcifications noted on Tenon's capsule. There was postmortem diminution in the corneal endothelial cell population. The anterior chamber and anterior chamber angle structures were normal. The iris showed post-mortem vacuolation of the pigment epithelium. The ciliary body displayed abnormal, hypoplastic ciliary processes and pars plana. The vitreous was clear. The lens

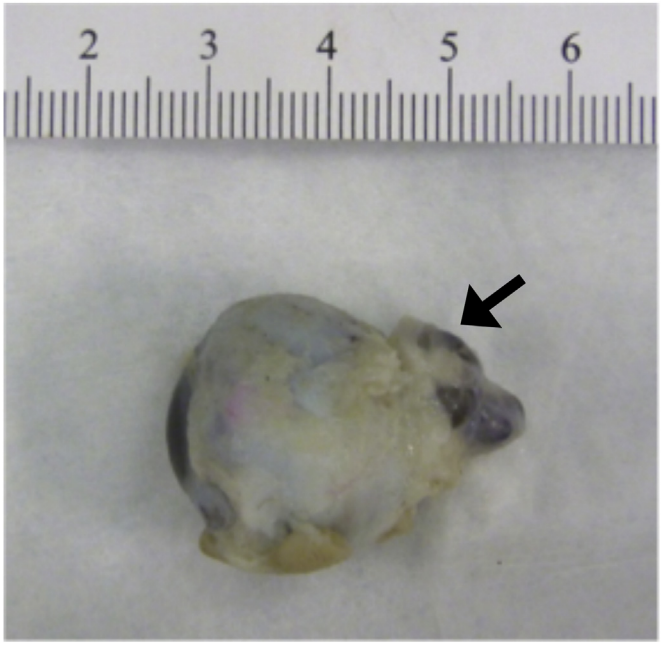

Fig. 1. Gross photograph of left eye. Note coloboma posteriorly.

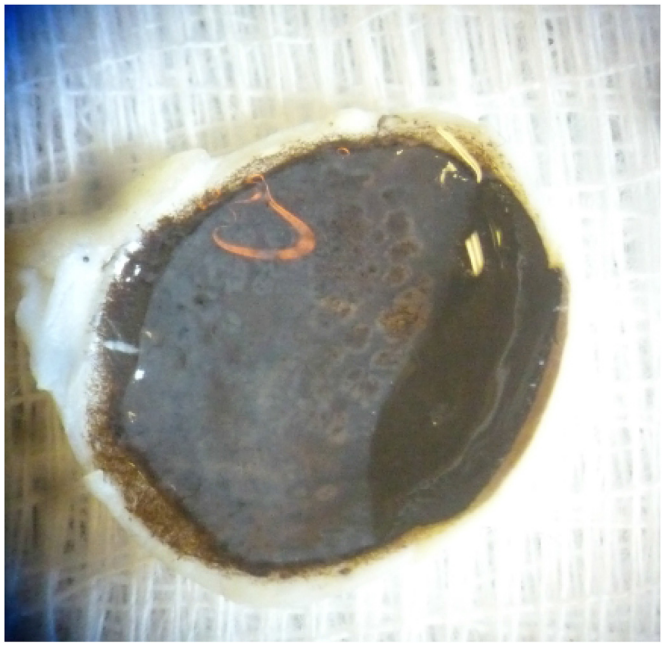

Fig. 2. Gross photograph of a calotte in the right eye. Note the myriad of lacunae, unusual papillary proliferations of the RPE with atrophic centers.

showed 360° of subcapsular epithelium. There was some liquefaction of the cortex. Pigment was present on the posterior lens capsule, which was also notable for the presence of intact nuclei. The choroidal blood vessels were dilated and suffused with mononuclear inflammatory cells. There was an artifactitious retinal detachment. No photoreceptors were present. There were many areas of retinal hypoplasia throughout. In some areas, there were chorioretinal adhesions where the retinal pigment epithelium (RPE) was absent. RPE hyperplasia in the form of characteristic lacunae was found at the edge of these areas (Fig. 3). There were no ganglion cells or nerve fiber layer. At the site of the expected optic nerve, there was a coloboma attached to a cystic structure lined by abortive RPE. The RPE throughout showed misshapen cells and areas of hyperplasia alternating with RPE loss. In some areas where the RPE was lost, there was fibrous metaplasia. There was focal

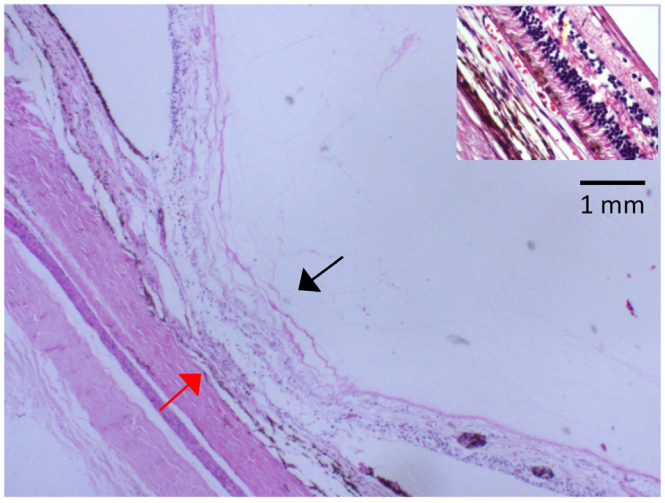

Fig. 3. Photomicrograph of a regional lacuna (black arrow) at the equator using H&E stain at 100x magnitude. Note the atrophic retina with loss of RPE and fibrosis at the base (red arrow). Upper right inset shows a normal retina at the same approximate location at 400x magnification. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

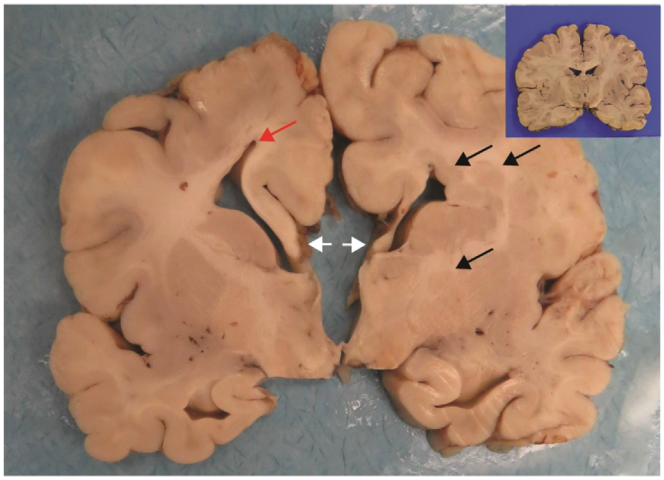

Fig. 4. Cross section of gross brain showing multiple grey matter heterotopias (black arrows), absence of the corpus callosum with Probst bundle formation (white arrows) and abnormal shape of the lateral ventricles (red arrow). Upper right inset shows a normal brain at the same approximate level for comparison. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

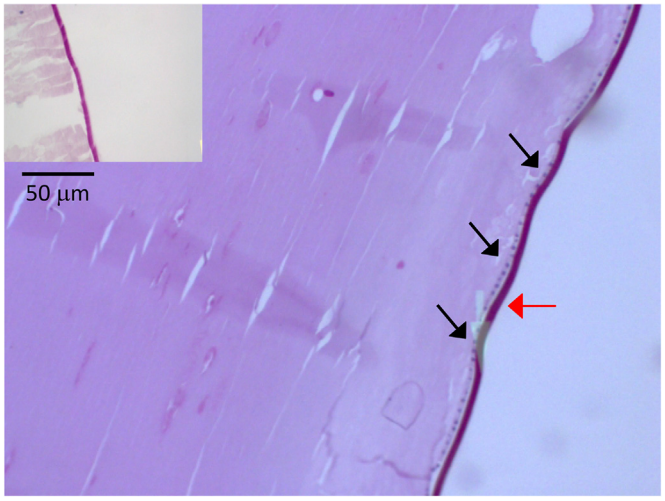

Fig. 5. Photomicrograph of thickened posterior lens capsule (red arrow) using PAS stain at 500x magnification. Note the presence of intact nuclei throughout the lens (black arrows). Upper left inset shows a normal posterior lens capsule at the same approximate location at 400x magnification. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

invasion of the retina by RPE cells. A cross section of the optic nerve failed to demonstrate axons or myelin. The left eye had similar findings.

Neuropathology identified microcephaly (710 g), polymicrogyria, no discernable lateral geniculate bodies, subependymal gray matter heterotopias, and agenesis of the corpus callosum (Fig. 4) with associated Probst bundles and perpendicular radiating medial gyri at the edge of each lateral ventricle replacing the normal architecture of each cingulate gyrus.

3. Discussion

In 1965, Jean Aicardi and colleagues presented a three-paragraph report describing the three characteristic findings of a new syndrome: spasm in flexion, agenesis of the corpus callosum, and ocular abnormalities.[1] The hallmark ocular finding in Aicardi Syndrome is chorioretinal lacunae, which are well-circumscribed full-thickness defects of the RPE and choroid.[3,4] Additional features include microphthalmia, atrophic choroiditis, and coloboma of the optic nerve.[2] The present case of a 20-year-old female demonstrates some of these features that typify the syndrome, but also introduces certain unusual qualities such as the age of the individual and the presence of a thickened posterior lens capsule with intact nuclei.

First, this individual lived until the age of 20 years. She succumbed to pneumonia, the most common cause of death in patients with her disease.[11] While early reports of Aicardi Syndrome suggested a severely poor survival rate of 40% at 15 years,[12] more recent findings suggest a slightly more optimistic outcome, with survival rates up to 60% at 27 years.[9] Regardless, with a median survival of 18 years of age, even with diligent family advocacy and care, Aicardi Syndrome remains a very deadly disease.[13]

Another feature of this case is the existence of a thickened posterior lens capsule with intact nuclei (Fig. 5). Among all the many ophthalmic abnormalities that define and contribute to Aicardi Syndrome, a thickened posterior lens capsule is not one of them.

Finally, we remark on the existence of microphthalmia as a constant feature of Aicardi Syndrome. Jean Aicardi himself estimated that approximately 40 of the 450 cases of Aicardi Syndrome he encountered had accompanying microphthalmia.[2] In a study of 75 eyes with Aicardi Syndrome, Fruhman et al. found that 22.5% of right eyes and 12.5% of left eyes also exhibited microphthalmia.[14] At birth, the normal human eye has an axial length of 17mm, which is roughly the size of the postmortem eyes. As the child grows and develops, the eye undergoes a "myopic shift" and develops an axial length in the emmetropic eye of 25mm. In eyes that do not see as a result of cataract, persistent fetal vasculature (PFV or PHPV), untreated retinopathy of prematurity (ROP), the lack of formed image on the retina is now thought to produce the microphthalmic eye. In fact, the thickened posterior lens in this case could have been the result of an undiagnosed comorbid cataract rather than Aicardi Syndrome itself.[15,16]

4. Conclusions

This case demonstrates the standard characteristics of Aicardi Syndrome while also introducing certain unusual findings that could further diversify the symptoms distinctive of the disease. Additionally, we provide insight into microphthalmia as a consistent feature of Aicardi Syndrome.

Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

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Conflicts of interest

None of the authors have financial disclosures (MAM, AHF, MEF, MMH).

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ajoc.2018.09.004.

References

1. Aicardi J, Lerique-Koechlin A. A new syndrome: spasms in flexion, callosal, agenesis, ocular abnormalities. *Electroencephalogr Clin Neurophysiol.* 1965;19:609–610.
2. Aicardi J. Aicardi syndrome. *Brain Dev.* 2005;27:164–171.
3. Hopkins IJ, Humphrey I, Keith CG, et al. The Aicardi syndrome in a 47, XXY male. *J Paediatr Child Health.* 1979;15:278–280.
4. Carney SH, Brodsky MC, Good WV, et al. Aicardi syndrome: more than meets the eye. *Surv Ophthalmol.* 1993;37:419–424.
5. Grigoriou E, DeSabato JJ, Colo D, Dormans JP. Scoliosis in children with Aicardi syndrome. *J Pediatr Orthop B.* 2015;35:e38–e42.
6. Lund C, Striano P, Sorte HS, et al. Exome sequencing fails to identify the genetic cause of Aicardi syndrome. *Mol Syndromol.* 2016;7:234–238.
7. Wang X, Sutton VR, Eble T, et al. A genome-wide screen for copy number alterations in Aicardi syndrome. *Am J Med Genet A.* 2009;0:2113–2121.
8. Prakash SK, Van den Veyver IB, Franco B, et al. Characterization of a novel chromo domain gene in Xp22.3 with homology to Drosophila msl-3. *Genomics.* 1999;59:77–84.
9. Kroner BL, Preiss LR, Ardini MA, Gaillard WD. New incidence, prevalence and survival of Aicardi Syndrome from 408 cases. *J Child Neurol.* 2008;23:531–535.
10. Font RL, Marines HM, Cartwricht Jr J, Bauserman SC. Aicardi syndrome. *Ophthalmology.* 1991;98:1727–1731.
11. Rosser TL, Acosta MT, Packer RJ. Aicardi syndrome: spectrum of disease and long-term prognosis in 77 females. *Pediatr Neurol.* 2002;27:343–346.
12. Menezes AV, MacGregor DL, Buncic JR. Aicardi syndrome: natural history and possible predictors of severity. *Pediatr Neurol.* 1994;11:313–318.
13. Glasmacher MA, Sutton VR, Hopkins B, et al. Phenotype and management of Aicardi Syndrome: new findings from a survey of 69 children. *J Child Neurol.* 2007;22:176–184.
14. Fruhman G, Eble TN, Gambhir N, et al. Ophthalmologic findings in Aicardi syndrome. *J AAPOS Offcial Publ Am Assoc Pediatr Ophthalmol Strabismus.* 2012;16:238–241.
15. Raj SM, Vasavada AR, Johar SRK, Vasavada VA, Vasavada VA. Post-operative capsular opacification: a review. *Int J Biomed Sci : IJBS.* 2007;3:237–250.
16. Vasavada A, Chauhan H, Shah G. *Incidence of Posterior Capsular Plaque in Cataract Surgery.* 1997; 1997:798–802.