Serial Fetal MRI for the Diagnosis of Aicardi Syndrome

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SUMMARY – *Aicardi syndrome (AS) is defined by the triad of corpus callosum agenesis, chorioretinal “lacunae” and infantile spasms. Additional neuroimaging findings including migrational abnormalities are common. We report on serial neuroimaging findings of a female fetus with ventriculomegaly, corpus callosum agenesis and focal migrational abnormalities, suggestive of AS. Postnatal neuroimaging follow-up as well as ophthalmological evaluation and occurrence of infantile spasms confirmed the prenatally suspected diagnosis of AS. This case points out the key role of serial fetal magnetic resonance imaging (MRI) in detecting the full spectrum of pathologies associated with fetal ventriculomegaly. The associated neuroimaging findings may go undetected on prenatal ultrasound, but are important in terms of diagnosis and counseling of the parents. Additionally, this case emphasizes the importance of serial fetal MRI studies to more accurately delineate the progression of findings during brain development.*

Introduction

Aicardi syndrome (AS, OMIM 304050) is a rare, sporadic neurogenetic disorder defined by the triad of partial or total agenesis of the corpus callosum, chorioretinal ‘lacunae’ and infantile spasms¹. AS is believed to be inherited with an X-linked dominant pattern and affects nearly exclusively female subjects. The outcome in AS is usually poor with considerable morbidity including severe intellectual disability and therapy-resistant seizures, and high early mortality². Additional neuroimaging findings include ventriculomegaly with colpocephaly, polymicrogyria, periventricular and subcortical heterotopias, intracranial cysts and cerebellar abnormalities³.

We report on serial prenatal magnetic resonance imaging (MRI) studies in a female fetus with AS. We emphasize 1) the ability of fetal MRI to differentiate between isolated and syndromal ventriculomegaly and 2) the role of serial fetal MRI studies to better characterize the progression of findings.

Case Report

Routine 18-week fetal anatomy screening in a 29-year-old pregnant (G1P0) woman raised the concern for ventriculomegaly. A follow-up ultrasound at 20 weeks confirmed fetal ventriculomegaly. The pregnant woman was referred for a fetal MRI to search for associated brain abnormalities. The MRI study performed at 22 weeks of gestation confirmed a mild ventriculomegaly and demonstrated complete agenesis of the corpus callosum. Additionally, the anterior horn of the right lateral ventricle appeared to be mildly widened and had a malformed shape suggesting an adjacent cortical migration anomaly (Figure 1). Chest, abdomen and extremities were unremarkable. A follow-up MRI was performed at 33 weeks of gestation and confirmed mild ventriculomegaly with colpocephaly and complete agenesis of the corpus callosum. The progressing brain development allowed a more detailed evaluation of the suspected right frontal lobe malformation. The anterior horn of the right lateral ventricle was

Figure 1 Midsagittal (A), coronal (B) and axial (C,D) T2-weighted fetal MR images at 22 weeks of gestation show complete agenesis of the corpus callosum (A), mild ventriculomegaly with colpocephaly (C,D) and widening and abnormal shape of the frontal horn of the right lateral ventricle suggesting adjacent migrational abnormality (arrows in B-D). Midsagittal (E), coronal (F) and axial (G,H) T2-weighted fetal MR follow-up images at 33 weeks of gestation confirm complete agenesis of the corpus callosum (E), colpocephaly (G,H) and abnormal shape of the frontal horn of the right lateral ventricle (arrows in F,H). In addition, the cerebral cortex adjacent to the malformed frontal horn of the right lateral ventricle appears to be thickened (G). Agenesis of the corpus callosum and migrational abnormality in a female fetus are suggestive of Aicardi syndrome (AS).

Figure 2 Midsagittal T1-weighted (A), coronal (B,C) and axial (D,E) T2-weighted MR images at 3 months of age show absence of the corpus callosum and septum pellucidum (A,B), mild ventriculomegaly with colpocephaly and “Texas longhorn” configuration of the lateral ventricles (B), bilateral hippocampal malrotation (B) and asymmetric dilatation and deformity of the anterior horn of the right lateral ventricle with subependymal, nodular heterotopia (short arrows in C,D) and polymicrogyria of the overlying cortex (long arrows in C-E). The findings confirm the suspected diagnosis of AS. Midsagittal T1-weighted (F), coronal (G,H) and axial (I,J) T2-weighted MR images at 2 years of age confirm complete agenesis of the corpus callosum (A), mild ventriculomegaly with colpocephaly and “Texas longhorn” configuration of the lateral ventricles (H), bilateral hippocampal malrotation (H) and asymmetric dilatation and deformity of the anterior horn of the right lateral ventricle with subependymal, nodular heterotopia (short arrows in G,I,J) and polymicrogyria of the overlying cortex (long white arrows in G,I,J). Additionally, polymicrogyria with a T2-hyperintense signal of the adjacent subcortical white matter (long black arrow in G) and Probst bundles (G,H) are seen.

again mildly widened and had an abnormal squared shape. The overlying cortical gyri were abnormally thickened compatible with an area of polymicro- and/or pachygyria. The concomitant right anterior horn deformity raised the suspicion of a closed lip schizencephaly with focal polymicrogyria (Figure 1). In a female fetus, this constellation of neuroimaging findings was believed to be most consistent with a diagnosis of AS.

A baby girl was born at 39 weeks of gestation by an uneventful vaginal delivery. The birth weight was 3060 grams (25th percentile), head circumference 33 cm (10th percentile). The neonatal neurological examination was unremarkable and no dysmorphic features were appreciated. At three months of age, she developed infantile spasms. Electroencephalography showed right-sided hemi-hypsarrythmia. Ophthalmological examination revealed multiple hypopigmented chorioretinal lacunae bilaterally as well as optic nerve colobomas. The prenatal diagnosis of AS was confirmed. A postnatal MRI follow-up confirmed a mild ventriculomegaly with colpocephaly, complete agenesis of the corpus callosum and right frontal polymicrogyria. Additionally, bilateral hippocampal malrotation, hypoplastic optic nerves and periventricular nodular heterotopias along the anterior horn of the right lateral ventricle were seen (Figure 2). Despite antiepileptic treatment including multiple drugs (vigabatrin, topiramate, levetiracetam and valproic acid), epileptic seizures became intractable. Only the introduction of a ketogenic diet brought a temporary drop in seizure frequency. Global developmental delay was noted. At 21 months of age, she was able to babble but did not use words to refer to people. She was able to sit unassisted, but occasionally fell over and was not able to stand up. This corresponds to a developmental age of about nine to ten months representing a moderate developmental delay (EQ 42). At this age, an additional follow-up brain MRI confirmed the previous findings (Figure 2). Additionally, a left frontal polymicrogyria with signal changes of the adjacent subcortical white matter was seen (not appreciable on the previous studies).

Discussion

Fetal MRI is a safe, important and well-established diagnostic tool in the clinical evaluation of fetuses with suspected cerebral anomalies.

While prenatal ultrasonography remains the main technique for screening intracranial abnormalities in utero, fetal MRI plays a key role in the exact evaluation of the complex fetal brain anatomy⁸⁻¹⁰.

Ventriculomegaly is one of the most frequent indications for fetal MRI¹¹ and occurs in about 1% of all pregnancies¹². It is defined as the atrium of the lateral ventricle being wider than 10 mm on coronal imaging¹³. The etiology of fetal ventriculomegaly has proven to be highly variable ranging from isolated ventriculomegaly to complex malformative syndromes or as a secondary complication of prenatal disruptive entities (e.g. intraventricular hemorrhage)^{14,15}. Fetal ventriculomegaly is often the leading imaging finding identified by fetal ultrasonography, but it may be “the tip of the iceberg”. An accurate identification of associated pathologies is essential for a correct and specific diagnosis, planning treatment options, prognosis and accurate counseling of parents for the current and possible future pregnancies.

Isolated ventriculomegaly refers to non-syndromal disorders in which no definite etiology for the ventriculomegaly is identified. Stenosis of the Sylvian aqueduct is a common finding in isolated moderate to severe supratentorial ventriculomegaly associated with a small fourth ventricle, while no additional pathologies are found. In isolated ventriculomegaly the outcome is favorable in up to 80-90% of children¹⁶. On the other hand, ventriculomegaly with associated anomalies or in cases of syndromal ventriculomegaly, outcome is favorable in only 50-60% of children¹⁷. The etiology of associated ventriculomegaly is broad and includes disruptions and malformations^{14,15}. Ventriculomegaly is a well known complication of prenatal intraventricular hemorrhages. Blood products within the Sylvian aqueduct may cause a focal adhesion/stenosis with resultant obstructive, supratentorial hydrocephalus. In addition, acquired ventriculomegaly is also a common finding in congenital cytomegalovirus (CMV) infection¹⁸. Other neuroimaging findings in congenital CMV infection include different types of migrational abnormalities ranging from lissencephaly to polymicrogyria, cerebellar hypoplasia, abnormal white matter signal hyperintensity, intracranial calcifications and cysts in the anterior portion of the temporal lobes¹⁸.

Fetal ventriculomegaly may also be the presenting finding in a variety of brain malformations and syndromes including holoprosencephaly, schizencephaly, Chiari II malformation,

meningoencephalocele, Dandy-Walker malformation, rhombencephalosynapsis and corpus callosum agenesis^{14,15,19}. In these malformations and syndromes, the exact diagnosis requires high-resolution imaging of the complete fetal brain to detect the characteristic additional lesions. For AS, the detection of migrational abnormalities in addition to a complete or partial corpus callosum agenesis is essential.

Cortical malformations are identified on fetal MRI by detecting abnormalities of the normal fetal sulcation pattern for a particular gestational age²⁰⁻²². They can be identified as “too many” sulci for gestational age (e.g. polymicrogyria), “too few” sulci (e.g. lissencephaly) or abnormally deep or malformed sulci (e.g. schizencephaly). Sulcation is a dynamic process during brain development. The cerebral sulci appear in a programmed, sequential pattern with increasing development of primary followed by secondary and tertiary sulci with increasing gestational age. Therefore, knowledge of the gestational age and familiarity with the normal appearance of brain sulci for the different gestational ages is crucial for correct and sensitive identification of malformations of cortical development^{23,24}.

MRI studies performed early in gestation may miss or underestimate disorders of cortical development because the sulcation pattern is still shallow and differences between normal and abnormal cerebral cortex may be very subtle. At follow-up studies later in pregnancy, differences between normal and abnormal sulcation pattern typically become more obvious and the detection rate of disorders of cortical development increase. In our patient, the first fetal MRI at 22 weeks of gestation showed only a mild difference in size and shape of the anterior horns of the lateral ventricles. This subtle finding initiated a follow-up study later in pregnancy. The associated migrational abnor-

malicity affecting the adjacent right frontal lobe became obvious only on the follow-up images at 33 weeks of gestation which assisted narrowing the differential diagnosis to AS.

Callosal agenesis is complete in about 70% and partial in 30% of AS patients³. The outcome seems to be more favorable in AS patients with partial compared to those with complete corpus callosum agenesis²⁵. The additional findings in AS may show a wide variability including polymicrogyria and heterotopias, intracranial cysts, posterior fossa abnormalities such as hypoplasia and/or dysplasia of the cerebellar hemispheres, heterotopias, cerebellar cysts and tectal enlargement and sometimes choroid plexus papillomas^{2,3}. Consequently, the prognosis differs significantly. Correct identification of the full spectrum of malformation is essential for predicting outcome and prognosis. High quality fetal MRI and especially follow-up fetal MRI may be necessary to identify the complete malformation.

In conclusion, we report on serial MRI images in a female fetus revealing callosal agenesis, ventriculomegaly and focal migrational abnormalities. These findings were highly suggestive of AS, that was confirmed postnatally. This case points out the key role of fetal MRI in detecting the full spectrum of pathologies associated with fetal ventriculomegaly. These lesions are important in terms of diagnosis and counseling of the parents. Additionally, this case emphasizes the importance of serial fetal MRI studies to more accurately delineate associated findings that may go undetected on early fetal MRI.

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