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Aicardi Syndrome: MR Assessment of Brain Structure and Myelination

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Aicardi syndrome is characterized by the combination, in girls, of agenesis of the corpus callosum, epilepsy, and typical choroidal lacunae. Other associated brain abnormalities that have been described include gross asymmetry of the cerebral hemispheres, irregular ventricular contours caused by subependymal heterotopic nodules, cysts in the hemispheres and the posterior fossa, cerebellar hypoplasia, papillomas of the choroid plexus, holoprosencephaly, microphthalmia, and neuronal migrational abnormalities [1–5]. Detailed neuropathologic reports have not previously described abnormal myelination as a feature of this syndrome [1–3]. We report three cases in which MR Imaging provided detailed information on brain structure and myelination pattern.

Case Reports

Three patients with Aicardi syndrome were studied. An EEG was obtained in all patients. MR imaging was performed on a 1.5-T scanner, and T1-weighted 500/15/4 (TR/TE/excitations) and T2-weighted 2000/90/1 spin-echo (SE) sequences and a short tau inversion recovery (STIR) sequence 3000/150/30/1 were obtained.

Case 1

A baby girl was delivered at 33 weeks gestation following a normal pregnancy. She was growth-retarded with a birth weight of 2.2 kg but was otherwise well. Typical infantile spasms began at 4 months. These consisted of sudden flexion of the head and trunk associated with extension of the arms, lasting only a few seconds and frequently repeated.

When examined at 5 months her head circumference was less than the third percentile (39.3 cm), while her weight was in the 25th percentile. She was visually alert and followed objects in a horizontal plane. Fundoscopic examination showed a small lacuna in the left retina and a large coloboma involving the retina of the right eye, both lesions being consistent with Aicardi syndrome. There were no cranial nerve abnormalities and head control was appropriate for age. Limb tone was increased with brisk tendon reflexes in the legs and extensor plantar responses. The infantile spasms responded well to ACTH therapy.

An EEG performed after starting ACTH therapy showed high-amplitude slow waves over both hemispheres with frequent sharp waves. An intermittent burst suppression pattern was clinically associated with flexor spasms. MR performed at 6 months showed that the body of the corpus callosum was small and the genu and splenium were absent (Fig. 1A). A midline cyst was shown lying posterior to the corpus callosum, extending behind and above the third ventricle, of signal intensity higher than CSF on both T1- and T2-weighted SE images. The origin of the cyst was unknown, and was possibly hamartomatous (Figs. 1A and 1B). Myelination was appropriate for age, being symmetrically present in the middle cerebellar peduncles, the posterior limb of the internal capsule, and the cerebellar white matter (Figs. 1C–1E). The attenuated body of the corpus callosum was best appreciated in the sagittal plane and myelination was best shown on the inversion recovery sequence in the coronal plane (compare Figs. 1D and 1E).

Case 2

A baby girl was delivered at 38 weeks gestation as the second of dizygotic twins. Her birth weight was 2.8 kg, while her twin brother's weight was 2.9 kg. She required resuscitation on delivery and was noted to have microphthalmia of the left eye. Seizures began within the first day and were difficult to control. At 6 weeks of age the seizures became more typical of infantile spasms. There had been no apparent developmental progress with no visual following responses, although she did react to loud noises.

When reviewed at 3 months of age she had facial asymmetry with hemiatrophy of the face on the side of the microphthalmia. The head circumference was below the third percentile. Generalized hypotonia was present with occasional flexor spasms and brisk tendon reflexes. Fundoscopy of the right eye showed an abnormal disk with lacunae of the retina. The left eye was rudimentary.

The EEG showed lateralized discharges consistent with a cerebral malformation. No distinct cortical or retinal responses could be obtained to flash stimulation. The MR image obtained at 3 months showed complete agenesis of the corpus callosum (Fig. 2A), left-sided microphthalmia, posterolateral orbital cysts presumably of developmental origin (Fig. 2B), left-sided hemiatrophy, and focally retarded myelination. Both middle cerebellar peduncles and the posterior limb of the right internal capsule were myelinated. No correspond-

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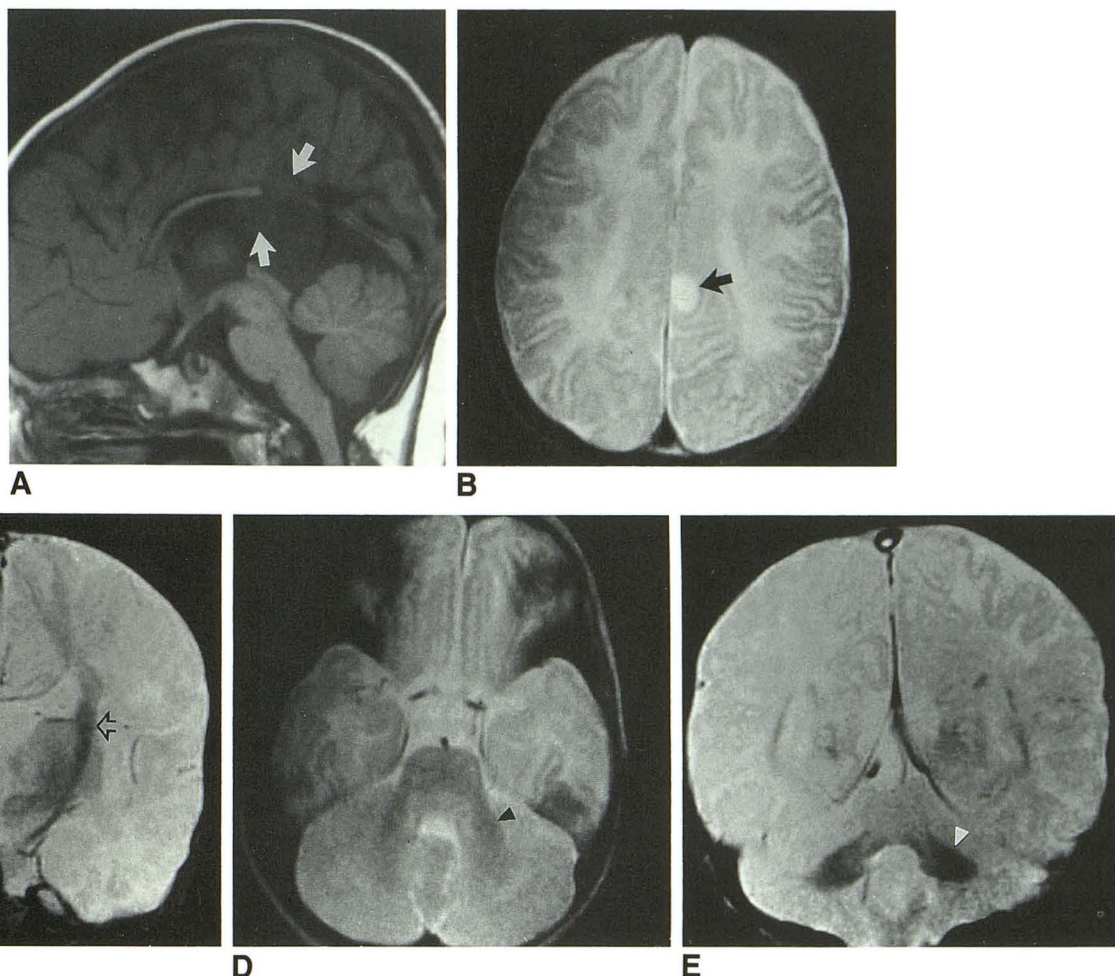


Fig. 1.—Case 1.

A and B, Sagittal SE 500/15 (A) and transverse SE 2000/90 (B) MR images. Corpus callosum is attenuated with deficiency of genu and splenium. A cyst (arrows) of signal intensity higher than CSF appears on both T1- and T2-weighted sequences, lying posterior to the corpus callosum and extending above and into the third ventricle. Cyst is of uncertain origin, possibly hamartomatous.

C-E, Coronal STIR (C), transverse SE 2000/90 (D), and coronal STIR (E) MR images. Myelin, which was present in posterior limb of internal capsule (open arrows) and in middle cerebellar peduncles (arrowheads), was judged normal for age. The gray/white matter contrast is higher with STIR than with SE 2000/90, allowing easier visualization of myelinated tracts (compare D and E).

ing myelination was seen in the posterior limb of the left internal capsule (Figs. 2C–2G). Myelination was more clearly demonstrated on the STIR images than by the SE 2000/90 sequence (compare Fig. 2C with 2D, and Fig. 2F with 2E).

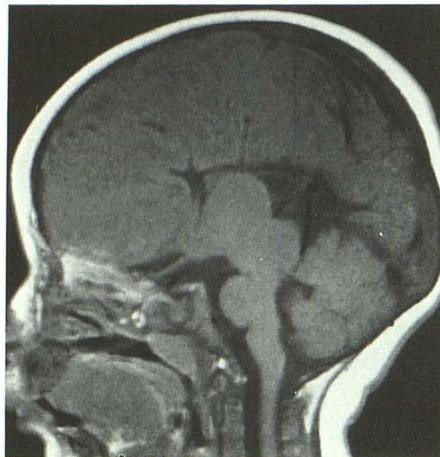
Case 3

A baby girl was delivered at term following a normal pregnancy. Her birth weight was 4 kg and there were no problems in the neonatal period. Typical infantile spasms began at 3 months and occurred as many as six times a day.

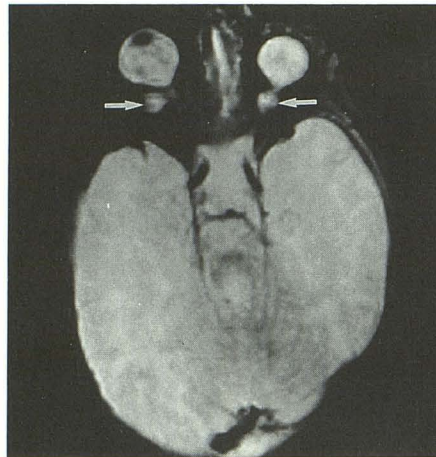
When seen at 7 months the patient's head circumference was in the 95th percentile and there was no obvious visual impairment. Fundoscopy revealed a dysplastic left optic disk with surrounding lacunae, which were typical of Aicardi syndrome. There was no retinitis and the right eye was normal. Although the child was able to sit unsupported for short periods, a right hemiparesis was evident

with increased tone and hyperreflexia on the right side. The rest of a complete neurologic examination was normal.

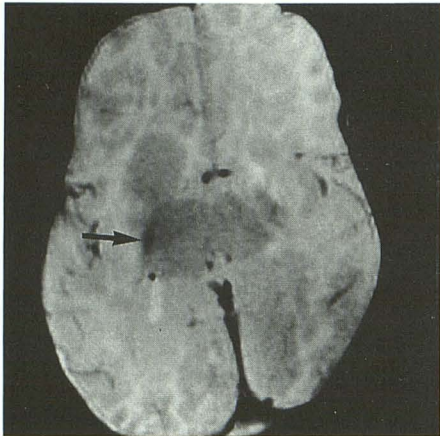
An EEG was performed while the patient was on clonazepam and phenobarbitone medication. High-amplitude slow waves with frequent multifocal discharges were present, most prominently over the left side. Several episodes of low-amplitude fast activity were seen unassociated with clinical seizures. A visual evoked response to flash stimulation for both eyes was normal. The MR performed at 7 months showed total collosal agenesis (Fig. 3A). A cyst was seen related to the anterior end of a high velum interpositum and protruding down into the anterior third of the third ventricle, suggesting the possibility of a paraphyseal origin (Fig. 3A). Colpocephaly was present (Figs. 3C and 3D), more markedly on the left side, and irregularity of the ventricular walls was probably due to heterotopia (Fig. 3B). Myelination was appropriate for age, being present in the cerebellar peduncles, cerebellar white matter, and anterior and posterior limbs of the internal capsule, but was asymmetric. In the right hemisphere, myelination was more apparent and extended more peripherally (Figs. 3C and 3D).



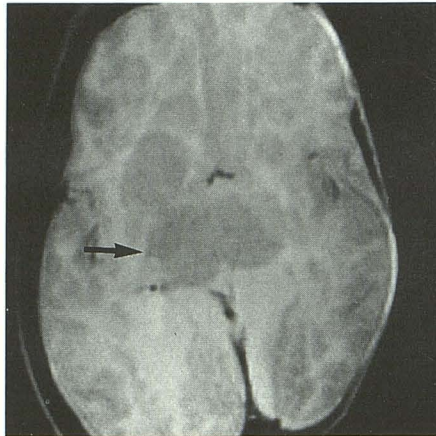
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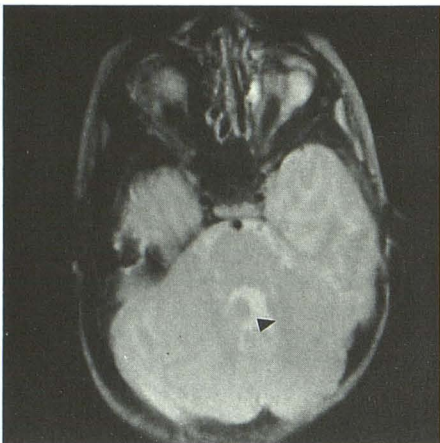
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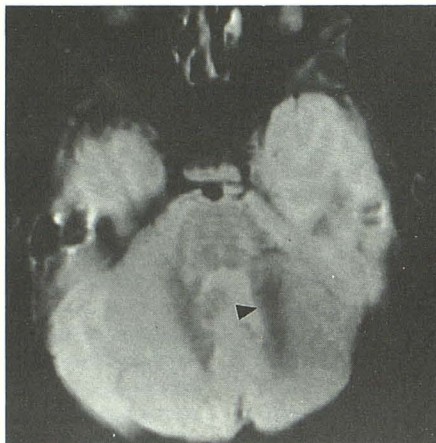
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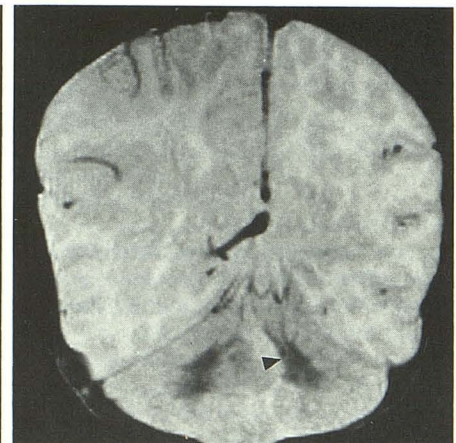
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E



F



G

Fig. 2.—Case 2.

A, Sagittal SE 500/15 MR image shows complete absence of corpus callosum.

B, Transverse STIR MR image shows left-sided microphthalmia. Bilateral cysts are present in posterolateral aspect of orbit (arrows), possibly developmental in origin.

C–G, Transverse STIR (C), transverse SE 2000/90 (D and E), transverse STIR (F), and coronal STIR (G) MR images. Left-sided hemiatrophy is present, and myelin can be seen in posterior portion of posterior limb of internal capsule on the right (arrows in C and D). No corresponding myelination is seen on the left. This is seen more clearly and with greater confidence with STIR than with SE 2000/90. Middle cerebellar peduncles are myelinated and symmetric (arrowheads in E, F, and G). Myelin in middle cerebellar peduncles is more clearly seen on transverse STIR image (F) than on transverse SE 2000/90 image (E); but it is most clearly demonstrated by STIR image in the coronal plane (G).

Discussion

Aicardi syndrome occurs only in females or in rare genetic disorders associated with two X chromosomes, as in Klinefelter syndrome [6]. It is believed to arise as a de novo dominant mutation on the X chromosome. The developmental

disorders that evolve from this mutation probably occur between the fourth and eighth weeks of gestation [1].

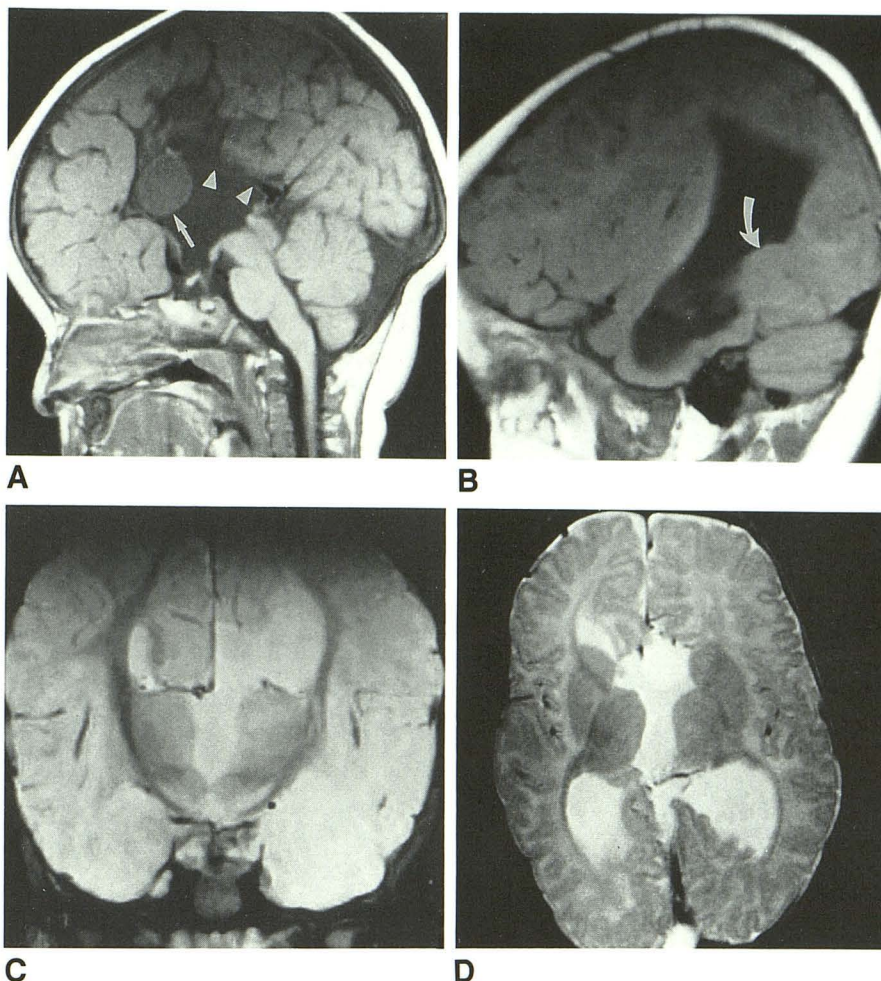
MR imaging is the only technique that can image the pattern of myelination in vivo [7, 8], and it readily demonstrates associated morphologic abnormalities of the brain [8]. MR has now been established as a sensitive means of assessing

Fig. 3.—Case 3.

A, Sagittal SE 500/15 MR image. Corpus callosum is completely absent. A cyst (arrow) of higher signal intensity than CSF is related to the anterior end of a high velum interpositum (arrow-heads) and the roof of the third ventricle, possibly of parafyseal origin.

B, Sagittal SE 500/15 MR image shows irregularity of the wall of the temporal horns of lateral ventricles (curved arrow). No white matter is seen interposed between gray and white matter. These features suggest heterotopia.

C and D, Coronal STIR (C) and transverse SE 2000/90 MR images indicate colpocephaly. Myelin is present in the anterior and posterior limbs of internal capsule and in central cerebral white matter. There is asymmetry in the extent and signal intensity of myelination; myelinated tracts in the right hemisphere are broader and extend more peripherally than those in the left hemisphere (compare left and right sides of C and D).



the corpus callosum [9, 10]. The normal pattern of myelination on T2-weighted SE sequences progresses from the middle cerebellar peduncles and posterior portion of the posterior limb of the internal capsule (birth to 3 months) to the cerebellar white matter (3–5 months), to the anterior part of the posterior limb of the internal capsule (4–7 months), and to the corpus callosum (4–8 months). Myelination of the central and then peripheral cerebral white matter occurs between 9 and 18 months, with occipital white matter myelinating before frontal white matter [7].

To date, the MR appearance of Aicardi syndrome has been described in four cases [9, 11, 12]; however, in none of these cases was comment made as to the degree of myelination. In our case 1, the distribution of myelin was correct for age. In case 2, myelination was delayed in the atrophic hemisphere but had progressed normally in the opposite hemisphere. Although this patient was only 3 months old, the asymmetry between the degree of myelination in each hemisphere suggested that this abnormality was associated with the disorder of neuronal development and with the hemiatrophy, and was not an unrelated event. In case 3, asymmetric myelination

was associated with an asymmetric degree of colpocephaly. Delayed myelination can be related to early local insults [13], and the asymmetry in these two cases may be related to superimposed, asymmetric local factors.

In two detailed neuropathologic reports on Aicardi syndrome, myelination has been shown to be normal. De Jong et al. [2] described a patient with cerebral hemisphere asymmetry, lissencephaly of one hemisphere, and polygyria with microgyria of the other hemisphere, in which the degree of myelination was normal for age. Another autopsy report [3] described a patient with polymicrogyria in whom myelination had occurred but with a reduced volume of cerebral white matter. We believe that ours is the first report of delayed and asymmetric myelination in Aicardi syndrome, and it has been demonstrated in vivo.

In all patients examined in this study T2-weighted SE and STIR sequences were performed. The inversion recovery sequence was more sensitive than the 2000/90 SE sequence in highlighting myelin. In case 2, a minimal degree of myelination, seen in the middle cerebellar peduncles on the transverse 2000/90 SE sequence, was better seen on the trans-

verse STIR sequence and was most clearly identified on the coronal STIR images (compare Figs. 2E, 2F, and 2G). In cases 1 and 3, 2000/90 SE images were obtained in the transverse plane, and STIR images in the coronal plane, precluding direct comparison. However, the coronal STIR sequence showed more extensive myelination than was apparent on the transverse 2000/90 SE sequence. Theoretical considerations support the suggestion that STIR is a sensitive sequence for assessing myelination. During maturation of the white matter, T1 shortening occurs as a result of deposition of myelin, followed by a reduction in water content with a concomitant reduction in proton density and T2 shortening [7]. Inversion recovery images provide the maximum T1-based contrast. With short inversion times, signal intensity on amplitude inversion recovery images decreases with decreasing T1, T2, and proton density. Hence, all the processes of white matter maturation will be accompanied by signal drop-out and increased gray-white matter contrast.

Cerebral hemisphere asymmetry is very common in Aicardi syndrome [2] and microphthalmia is a well recognized association [5]. In all patients described above, the associated structural abnormalities were clearly demonstrated on the MR scan. In conclusion, in this first report of abnormal myelination associated with Aicardi syndrome demonstrated by an imaging method, we found that MR was able to define clearly the nature of the structural brain abnormalities in these patients and that the STIR sequence was able to demonstrate myelination patterns precisely.

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