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## Cerebral Arteriopathy in a Newborn with Incontinentia Pigmenti

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### Abstract

**Background**—Incontinentia pigmenti is a rare X-linked neurocutaneous disorder that can present in the neonatal period with seizures and encephalopathy. Brain magnetic resonance imaging and magnetic resonance angiography may reveal cerebral infarction and arteriopathy.

**Patient Description**—We report a detailed neonatal presentation with brain magnetic resonance imaging findings in a newborn presenting with seizures and the typical rash of incontinentia pigmenti.

**Results**—Brain magnetic resonance imaging, magnetic resonance angiogram, and magnetic resonance spectroscopy at one week of age revealed chronic and acute brain injury, arteriopathy of the small and medium size cerebral vessels, and elevation of a lactate metabolite peak. At six months of age there was normalization of the magnetic resonance angiogram. At 2 ½ years of age the infant has well controlled complex partial seizures, global developmental delays, and residual hemiplegia.

**Conclusion**—Despite extensive cerebral arteriopathy in association with incontinentia pigmenti, the infant had a relatively stable early clinical course, steady developmental progress over time, and seizures have been well-controlled. Later brain imaging revealed resolution of the arteriopathy.

### Keywords

incontinentia pigmenti; neonatal seizures; stroke; arteriopathy; newborn

### Introduction

Incontinentia pigmenti is a rare X-linked neurocutaneous disorder with pathognomonic skin findings. Central nervous system involvement is noted in 30-50% of patients.<sup>1-3</sup> The typical skin rash is present during the neonatal period and in some infants this coincides with the

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timing of central nervous system disease. The exact mechanism triggering central nervous system involvement is not clearly understood, as it does not occur in every infant, but oxidative stress may play a role.<sup>4</sup> Encephalopathy may also be present in the first week of life manifesting as seizures and change in level of consciousness.<sup>4-11</sup> Brain magnetic resonance imaging (MRI) in these infants with early central nervous system involvement reveals periventricular white matter injury, hemorrhagic infarction, and scattered cortical injuries that do not have a clear vascular distribution.<sup>5,8,10-13</sup>

We describe a newborn with seizures and clearly documented early MRI and MR angiogram (MRA) abnormalities. Outcome, including imaging findings, development, seizure control, and neurologic examination are discussed.

## Patient Description

A term girl was born following an uneventful pregnancy and delivery. At birth, the typical skin rash and markings associated with incontinentia pigmenti were recognized. The family history was positive for incontinentia pigmenti in her mom and sister. The infant fed well and was discharged home on the second day of life.

On the fifth day of life, the infant had events concerning for seizures and was taken to the hospital. Seizures were treated with levetiracetam and the infant was admitted to the neonatal intensive care unit. A computed tomography scan revealed possible cerebral infarction. The infant was then transported to a tertiary care pediatric hospital for further consultation, imaging, and treatment.

On the sixth day of life, she arrived to Arkansas Children's Hospital and was observed to have eye twitching and tonic body stiffening with arm extension. She was given an additional bolus of levetiracetam, 20mg/kg. Video electroencephalogram monitoring was begun and over 14 hours showed background discontinuity for age, excessive multi-focal sharp waves, but no electrographic seizures.

Brain MRI was performed on a 1.5T Phillips scanner and revealed multiple punctate areas of restricted diffusion involving both cerebral hemispheres, worse on the right, that were randomly distributed and not involving specific arterial territories (Figure 1 A, B). There were scattered punctate areas of signal loss on the susceptibility weighted sequence suggestive of petechial hemorrhage and hemosiderin deposition in the areas of injury vs. venous congestion (Figure 1 C). In addition, there were multiple focal areas of encephalomalacia in the periventricular white matter, which correspond to the low density areas that had been seen on the computed tomography scan (Figure 1 A). These areas represented old ischemic injury. The brainstem and cerebellum showed relative sparing from this injury.

Brain MRI, MRA, and spectroscopy was performed the next day to better characterize the injury likely resulting from microvascular angiopathy. The areas of acute injury were stable. The MRA showed moderate attenuation of bilateral M1, A1, and A2 segments and severe attenuation of distal middle cerebral artery (MCA) and anterior cerebral artery (ACA) branches (Figure 2 A, B). There was reduced visualization and number of the distal terminal

branching in both the ACA and MCA distribution. There was mild attenuation of the posterior cerebral arteries with relative sparing of the vertebral and basilar arteries. These findings were due to arteriopathy affecting both the small and medium size cerebral vessels. The attenuation may also be the result of vasospasm secondary to edema and inflammation of the vascular wall with reduced blood flow. Spectroscopy showed elevation in the lactate metabolite peak at the sites of acute infarction and also some smaller elevation of lactate in areas without restricted diffusion (Figure 1 D).

Meanwhile, the infant remained clinically stable without recurrent seizures. Brain MRI and MRA were repeated one week later and showed an evolution of prior changes to the cerebral vessels and encephalomalacia in areas of prior restricted diffusion with a few new areas of focal restricted diffusion suggestive of progressive repeated episodes of ischemic insult (Figure 3). Genetic testing was positive for a common IKBKG gene deletion that is associated with incontinentia pigmenti. The infant was feeding well and discharged home on levetiracetam, 30 mg/kg/day, at fifteen days of age.

At one month of age, she was seen in the neurology clinic. She was without recurrent seizures and was alert on exam. Brain MRI and MRA at almost 2 months of age showed no new areas of infarction, evolving cystic encephalomalacia in areas of previous injury, and stable findings of decreased cerebral artery branching. At six months of age, brain MRI and MRA revealed that the MCA and ACA and their distal branches were normalized compared to the previous studies. There were no new areas of injury (Figure 2 C, D). She remained seizure free and levetiracetam was weaned.

The infant followed regularly in the neurology clinic and made steady developmental progress, though residual hemiplegia and global delays were noted. Initially, she received physical, occupational, and developmental therapy. At 12 months of age she was rolling over well, able to sit without support, could self-feed using her right hand, and was able to say several words. At 19 months of age, during the course of a febrile illness, she developed complex partial seizures that were controlled by levetiracetam. Brain MRI at this time revealed extensive encephalomalacia and gliosis in the cerebral hemispheres and Wallerian degeneration in the right brainstem with marked thinning of the corpus callosum. There was also restricted diffusivity in the right hippocampus suggestive of acute hippocampal injury following prolonged seizure before the MRI study (Figure 4). Motor development continued to progress with crawling at 21 months of age, standing and cruising at 26 months of age, and walking by age 2 ½ years. Speech therapy was started at age 2 ½ years as her expressive language abilities were showing delay.

At 3 years of age, an EEG revealed frequent focal epileptiform discharges with broad projection to the opposite hemisphere during sleep. MRI showed stable encephalomalacia, gliosis of the right cerebral hemisphere and thalamus, and subtle right hippocampal sclerosis with normalization of the restricted diffusion. Levetiracetam and all therapies were continued. Overall, she is a very active girl with mild language and motor delays. Hemiplegia, with greatest involvement of the left upper extremity, persists. Botox has been discussed as an adjunct to ongoing therapy.

## Discussion

This case provides clear evidence of both small and medium size cerebral arteriopathy on MRA in a newborn with incontinentia pigmenti in the first week of life. The initial brain MRI showed both areas of encephalomalacia, representing chronic brain injury, and areas of acute injury with restricted diffusion. The infant therefore, had onset of brain injury in utero, likely during the latter part of the third trimester and recurrent injury closer to the time of birth. The infant was born with the typical skin rash of incontinentia pigmenti, so the onset and development of the arteriopathy likely coincided with the skin changes prior to birth.

Incontinentia pigmenti results from a mutation at Xq28 encoding the IKBKG (inhibitor of kappa-B kinase gamma, previously NEMO) gene.<sup>14</sup> The IKBKG gene has vital roles in cell inflammation, immune responses, and cellular apoptosis.<sup>14,15</sup> The pathogenesis of central nervous system involvement is not completely understood.<sup>14</sup> Cytokines, tumor necrosis factor-alpha and interleukin-6, in one female infant with incontinentia pigmenti were found to be elevated through the first year of life and then declined when there was a reduction in the skin changes after infancy.<sup>16</sup> This finding demonstrates altered cytokine levels from the time of birth and may provide evidence for the role of inflammation in the development of cerebral arteriopathy. Another study found that the IKBKG mutation activates an eosinophil-selective chemokine called eotaxin which may lead to occlusive arteriopathy due to eosinophilic accumulation as it is found to do in the skin.<sup>17</sup> Given the findings supporting inflammation as part of the pathophysiology of the cerebral vasculopathy in incontinentia pigmenti, corticosteroids may be a potential treatment. There is one recently reported case of a newborn with incontinentia pigmenti and multi-focal areas of restricted diffusion on brain MRI, but with normal MRA, that was treated with dexamethasone at a few days of age and had a favorable clinical response.<sup>18</sup>

The brain involvement in incontinentia pigmenti is more often bilateral, but asymmetric, and as in our reported case usually shows greater involvement of the MCA and ACA distributions compared to the PCA.<sup>19</sup> The arteriopathy of incontinentia pigmenti can be well seen on MRA.<sup>7,20</sup> In our case, the initial MRA at 7 days of age showed occlusive arteriopathy and the absence of collateral vessel formation (Figure 2 A, B). In other conditions of chronic arteriopathy, such as moyamoya, the development of collateral vessels can occur during early infancy and may even begin in utero.<sup>21</sup> At one month of age, MRA in our infant, did not show improvement in the arteriopathy or the development of collateral vessels. Arteriopathy in incontinentia pigmenti does not seem to result in collateralization, but a normalization of the cerebral arteries that occurs over several months. Perhaps, the severity of the arteriopathy and the underlying pathophysiology of the brain involvement in incontinentia pigmenti with ongoing inflammation and cellular apoptosis prevents the formation of collateral vessels during this early time period.

Brain imaging was fairly stable in our patient, so despite the diffuse cerebral involvement we did not consider antithrombotic therapy as it is not well established for this condition. There are reported cases in the literature in which anticoagulation was used, however anticoagulation or antiplatelet therapy did not reduce stroke recurrence.<sup>10</sup> In addition, our infant's brain MRI showed evidence of hemorrhage on susceptibility weighted imaging, so

there would be potential risk for further hemorrhagic infarction if anticoagulation or antiplatelet therapy were used.

Despite the severity of the brain injury the infant showed steady developmental progress. Unfortunately she did develop epilepsy after the neonatal period requiring maintenance anti-epileptic medication and was found to have hippocampal sclerosis on follow-up MRI at 3 years of age. She also has global developmental delays and residual hemiplegia. In cases of incontinentia pigmenti presenting in the neonatal period, brain imaging with angiography should be performed early to assess the extent of cerebral arteriopathy. Further understanding of the pathophysiology leading to central nervous system involvement in incontinentia pigmenti may support specific treatments. Given the infrequent occurrence of this condition, further case reports will be needed to understand the long-term neurologic implications of this condition.

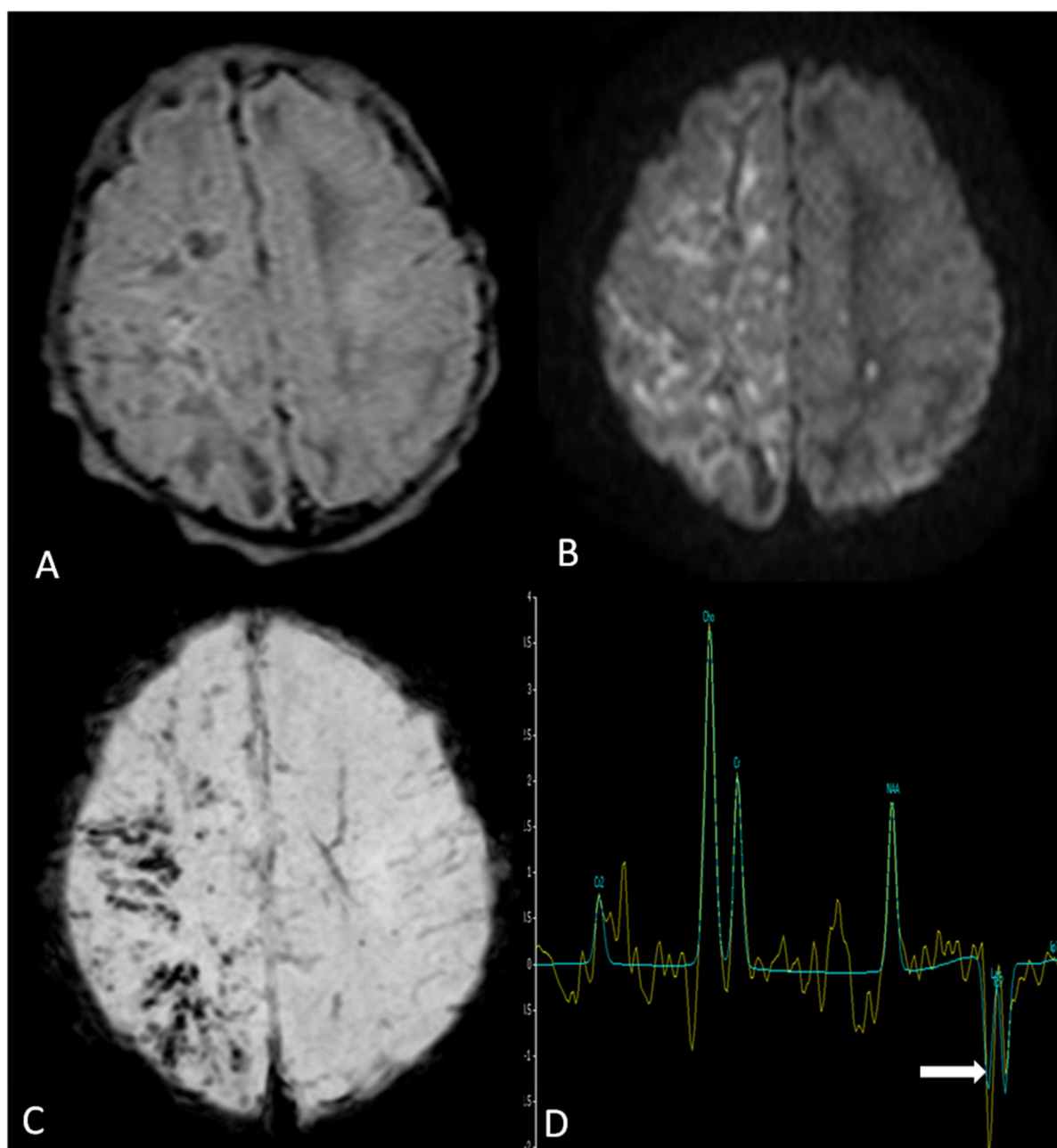
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Axial FLAIR image (A) at the level of centrum semiovale shows patchy areas of hyperintensity with central areas of signal suppression suggesting areas of encephalomalacia related to old injury predominantly in the right frontal and parietal lobes. Note that there is involvement of both cortex and white matter (subcortical and deep white matter). The axial diffusion weighted image (B) at the same level shows areas of subcortical linear restricted diffusivity in addition to areas of prior insult and encephalomalacia seen on the FLAIR image. Susceptibility weighted image (C) show areas of petechial non-acute blood products as signal loss in areas of prior injury in the right hemisphere. The single voxel MR



spectroscopy (D) in the region of the acute injury shows elevated lactate metabolite peak at 1.3 ppm (inverted doublet: white arrow).

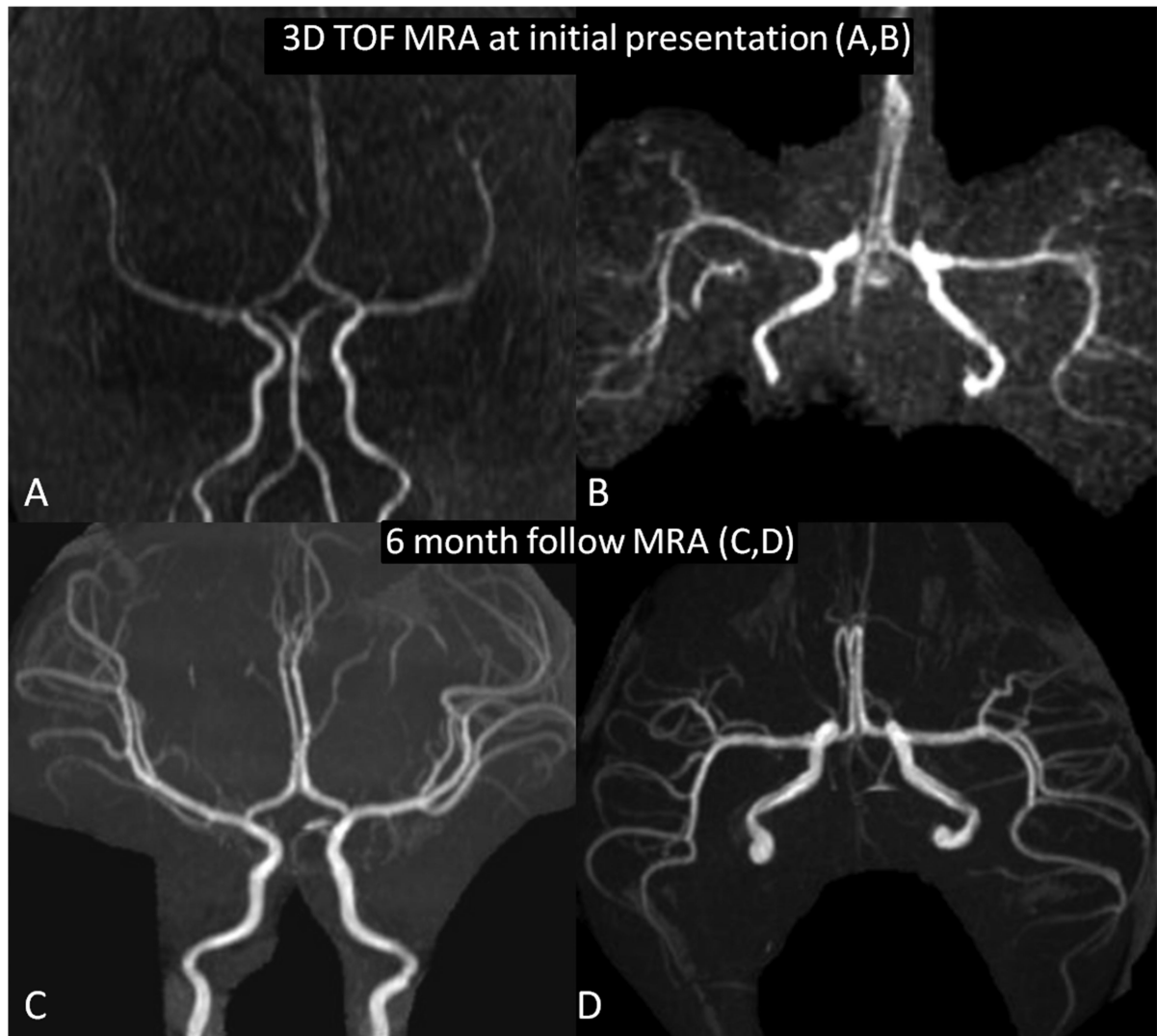
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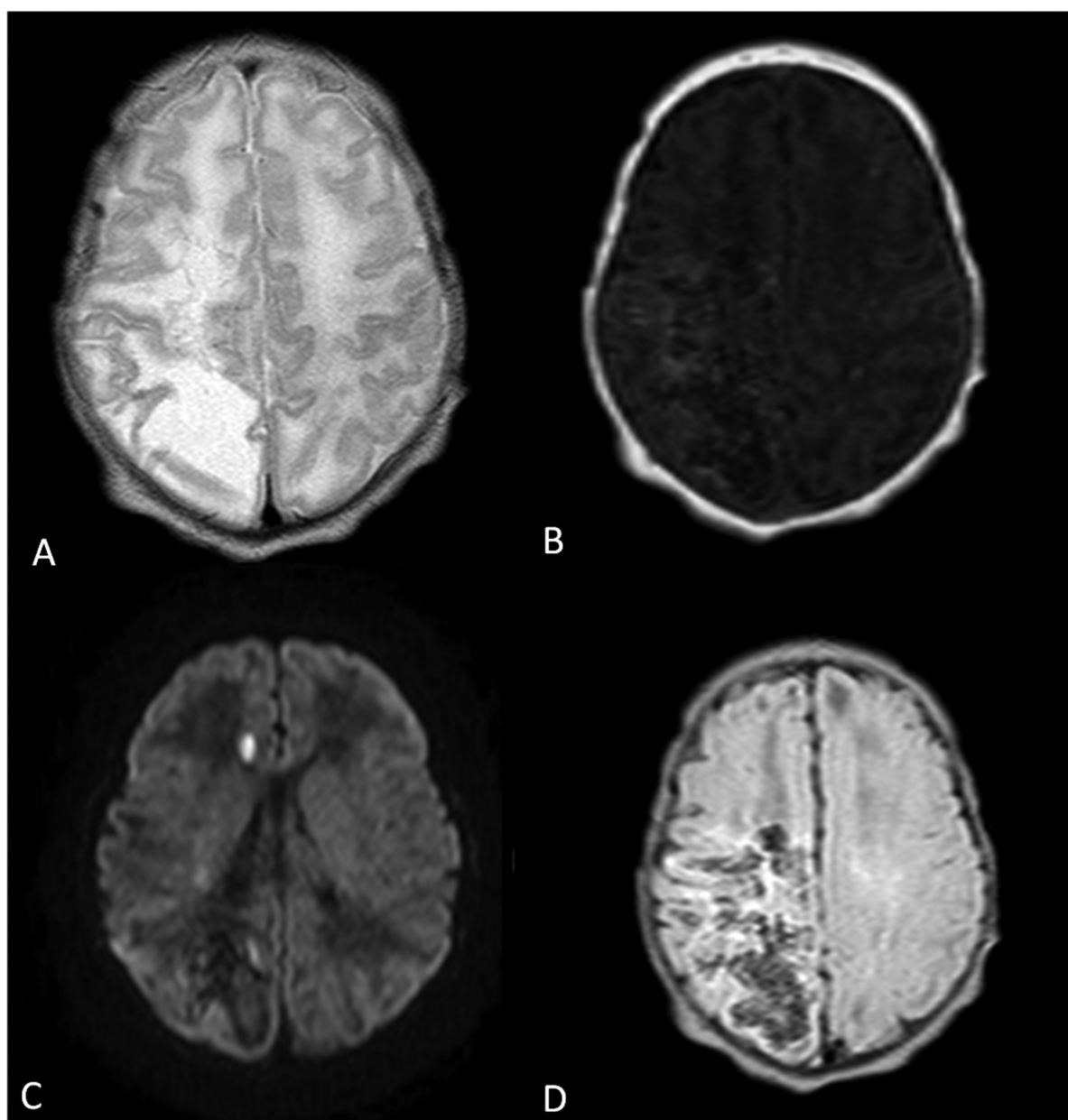
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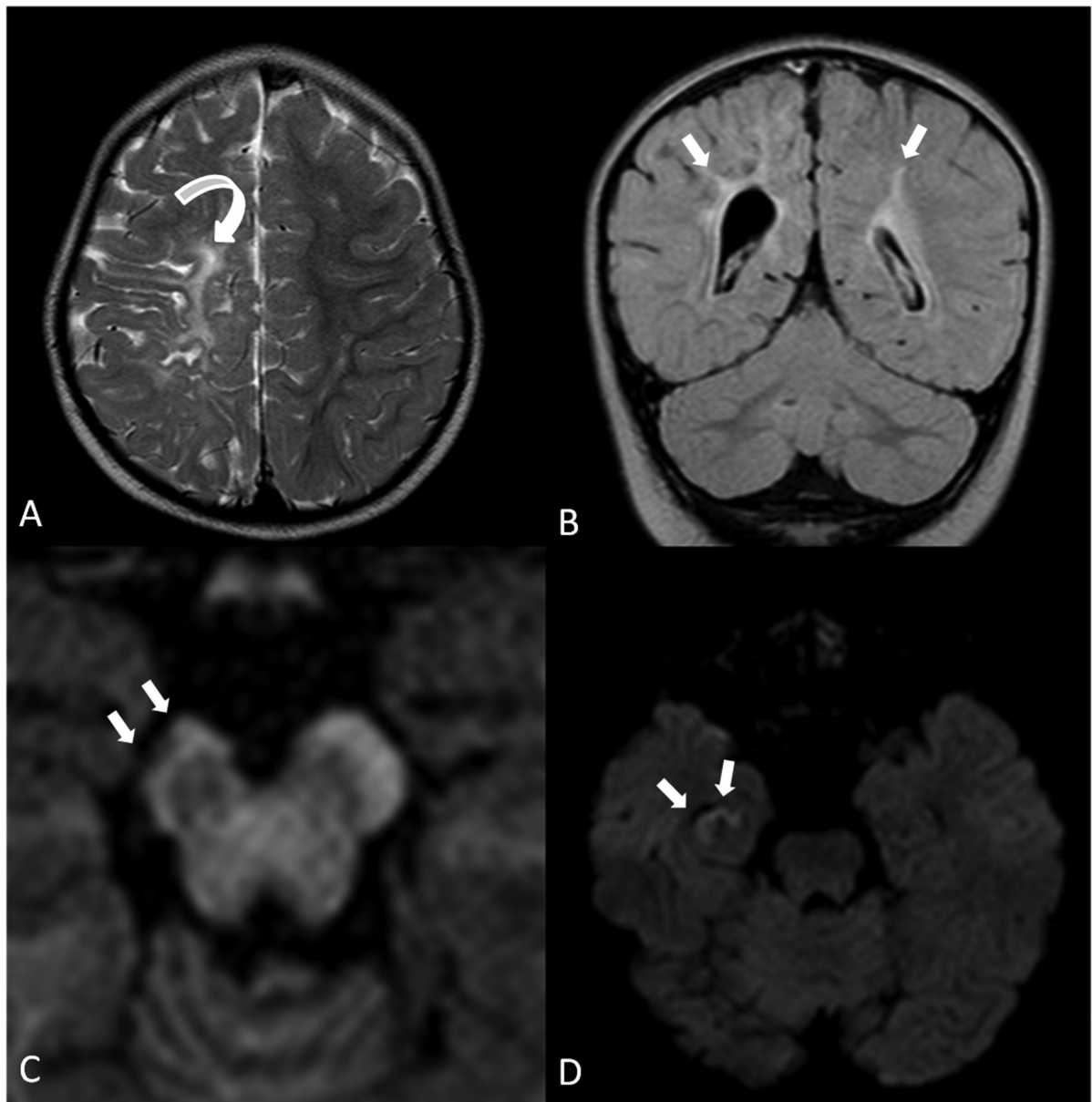


**Figure 2.**

MIP images of initial 3D TOF MRA of brain in axial (A) and coronal planes (B) demonstrating moderate attenuation of bilateral M1, A1, and A2 segments and severe attenuation of distal MCA and ACA branches. There was mild attenuation of the posterior cerebral arteries on the initial MRA (not shown). Notice the reduced visualization and number of the distal branching in both the ACA and MCA distribution. The 6 month follow-up MRA (C, D) showed significantly improved caliber and visualization of bilateral MCA and ACA branching. All scans were done on the same 1.5T Phillips scanner and similar MRA protocol.



**Figure 3.** One week follow-up MRI in patient with incontinentia pigmenti. Axial T2 weighted image (A), inversion recovery image (B), and FLAIR image (D) show areas of evolving progressive encephalomalacia. The axial diffusion weighted image (C) shows normalization of the previously seen areas of restricted diffusivity with new areas of focal diffusion restriction suggestive of progressive repeated episodes of ischemic insult.



**Figure 4.**

Late follow-up MRI study at 19 months of age showing delayed sequelae. Axial T2 weighted image (A) and coronal FLAIR image (B) showing periventricular leukomalacia; worse in the right frontoparietal region (arrows). Cropped axial T1 weighted image at the level of midbrain (C) shows Wallerian degeneration of the right corticospinal tract and thinning of the right cerebral peduncle. Axial diffusion weighted image (D) shows restricted diffusivity in the right hippocampus suggestive of acute hippocampal injury following prolonged seizure before the MRI study.