Incontinentia pigmenti (IP) is a rare X-linked multisystem disease caused because of mutation in the \textit{IKBKG}(inhibitor of kappa-B kinase gamma, previously \textit{NEMO}) gene. Involvement of central nervous system is seen in approximately one-third of these patients. Ischemic strokes, symptomatic seizures, and encephalopathy can be seen during neonatal or early infancy age group. Typically, early bilateral brain involvement is seen with periventricular white matter injury, hemorrhagic infarction, and multifocal cortical injury. We reported a patient who did not have early encephalopathic presentation, but presented with right hemiparesis and intellectual impairment. Magnetic resonance imaging of the brain revealed extensive left cerebral white matter volume loss and encephalomalacia with Wallerian degeneration of the left cortical spinal tract. This case highlights a rare presentation of unilateral cerebral atrophy with no definite episode of acute encephalopathy during infancy to suggest pure intrauterine injury. Microvascular occlusion, inflammatory cerebral vasculopathy, and recurrent silent strokes possibly produced this extensive neurologic manifestation antenatally. We also reviewed the complex pathogenic mechanisms involved in IP.

**Keywords:** Arteriopathy, hemiatrophy, incontinentia pigmenti, NEMO gene, stroke

**BACKGROUND**

Incontinentia pigmenti (IP) is an uncommon X-linked neurocutaneous disorder with pathognomonic skin findings. The molecular defect involves mutations in the kappa-B kinase gamma gene (\textit{IKBKG, NEMO}), located on chromosome Xq28. The \textit{NEMO} protein is an important regulator of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-KB) signaling pathway with critical involvement in the brain development, immune and inflammatory responses, cell adhesion, and also in the protection against apoptosis.\(^1\) The involvement of central nervous system (CNS) is seen in one-third of the patients.\(^1\) Self-limiting monophasic early infantile acute encephalopathy with seizure clusters is the most common neurologic finding. The pathogenesis of CNS lesions is unclear. Several mechanisms have been proposed, including vascular, inflammatory, and excessive apoptosis. Even in mouse models, there is a significant paucity of neuropathological data. We reported a patient with severe neuroradiologic findings without acute encephalopathy during infancy to suggest pure intrauterine injury. We also reviewed the complex pathomechanism responsible for neurologic manifestation in patients with IP.

**CASE REPORT**

A 3-year-old girl with a history of IP was presented to our neurology clinic with a complaint of reduced use of the right upper extremity. She was born after 37 weeks of gestation with a birth weight of 2850 g. There was no family history of IP. Her perinatal history was unremarkable, except the characteristic skin changes seen in IP. She had a normal ophthalmologic examination at that time with no obvious neurologic deficit. She did not have any episode of acute...
encephalopathic state or seizures during infancy, but developed early left-handedness. Later, weakness of her right arm became more obvious. During the clinic visit, her physical examination revealed decreased grip strength of the right hand and a mild right pronator drift. Reflexes were symmetric, and there was no evidence of dysmetria or gait abnormality. She was also noted to have moderate intellectual impairment and speech delay. Characteristic streaking hyperpigmented skin abnormality was seen over both axillae and popliteal fossa with significantly more involvement over the left axilla. Magnetic resonance imaging (MRI) of brain revealed extensive left cerebral white matter volume loss and encephalomalacia with Wallerian degeneration of the left corticospinal tract [Figure 1]. MR angiogram was normal.

**DISCUSSION**

IP is an X-linked dominant skin disorder, which is caused because of a mutation in the kappa-B kinase gamma gene (*IKBKGNEMO*) that is located on chromosome Xq28. This mutation is associated with skewed X-chromosome inactivation with predominant inactivation of one X-chromosome over the other. Early infantile acute encephalopathy in newborns is a classic feature of IP in patients with neurologic manifestation. Clusters of seizures and altered consciousness lasting for few days are typical during the presentation. Subsequently, these patients may develop motor impairment and epilepsy. Classically, diffusion-weighted imaging in brain MRI shows patchy restriction over the subcortical white matter, bilaterally but asymmetrically. Diffusion restriction can also be seen over corpus callosum, basal ganglia, and thalami. Rare involvement of cerebellum and brain stem has also been reported. These changes are likely due to microinfarction or microbleeding. White matter changes subsequently led to cyst or cavity formation because of tissue destruction.

The *NEMO* protein is an important regulator of the NF-KB signaling pathway, which is responsible for the signal transduction including immune regulation. It has been hypothesized that during birth and the first several weeks of life, oxidative stress because of the transition from intrauterine to extraterine life can induce an inflammatory response. Due to a defect in NF-KB activation and subsequent poor immune regulation, large quantities of cytokines are produced with subsequent brain injury. The acute encephalopathic process is usually self-limiting and nonrecurrent. The reason of paucity of recurrence may be due to the elimination of *NEMO*-mutated cells during acute injury with the survival of cells that lack this particular mutation. Normal or mildly abnormal brain MRI is associated with skewed X inactivation, and severe neuroimaging abnormalities are likely in the presence of random X inactivation. Random and late X inactivation and consecutive endothelial damage may produce severe neurologic findings because of the absence of neuroprotective effect of skewing with death and elimination of abnormal cells during early embryogenesis. As our patient did not have acute encephalopathic presentation, it is possible that her neurologic injury occurred prenatally. In utero brain injury has been reported in the past with the demonstration of chronic brain injury in brain MRI at birth, suggesting onset of injury during the latter part of the third trimester. It can be assumed that our patient had occlusive arteriopathy in utero, causing significant injury of middle cerebral artery and anterior cerebral artery distributions in the brain. Subsequently, prominent unilateral atrophy occurred without any recurrence of severe injury after birth. Moreover, it has been suggested that arteriopathic changes of the cerebral vessels can be seen prior to birth because of less stimulated transcription of antiapoptotic genes.
Magnetic resonance angiography was normal at the age of 3 years, as normalization of arteriopathy is seen in patients with IP.\textsuperscript{[4]} Interestingly, unlike moyamoya disease, lack of collateral vessels is noted in this type of patient population.

Hypoplasia of the corpus callosum is a common finding as seen in our patient. It was presumed to be secondary to white matter loss rather than a primary developmental defect. However, developmental defects such as corpus callosum agenesis and posterior encephalocele have been reported in a patient with IP.\textsuperscript{[5]} Moreover, polymicrogyria and cerebral hypoplasia have also been reported to indicate that the cerebral pathology in IP can develop antenatally.\textsuperscript{[8]} Specifically, polymicrogyria is thought to be acquired brain injury because of abnormal perfusion, oxygenation, or infection during the second trimester of pregnancy.

It is well known that brain imaging with angiography should be performed in neonates with IP with clinical symptoms consistent with acute encephalopathic state. However, silent cerebral injury with later manifestations as neurologic deficit and/or epilepsy can occur because of predominant intrauterine injury without an acute encephalopathic presentation during infancy. Further understanding of pathophysiology, random vs. skewed inactivation, and differential role of inflammation, vascular disruption, or apoptosis may help formulate a genotype–phenotype correlation. Given the rarity of the condition, further reports will be needed to understand the prevalence of pure intrauterine injury in this neurocutaneous disease.

**Ethical approval**
All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

**Informed consent**
Informed consent was obtained from all individual participants included in the study.

**Financial support and sponsorship**
Nil.

**Conflicts of interest**
There are no conflicts of interest.

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