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Case Report

Retinoic Embryopathy: A Case Report of Mri Brain Findings.

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Abstract

Retinoic acid embryopathy is a rare but severe condition caused by prenatal exposure to isotretinoin, a potent teratogenic medication. This report describes a neonate who presented with distinct dysmorphic features and significant central nervous system abnormalities identified through magnetic resonance imaging (MRI). Key findings included near-complete absence of the cerebellar vermis, severe cerebellar dysplasia, microcephaly, and thinning of the corpus callosum. This case underscores the profound consequences of isotretinoin exposure during pregnancy and highlights the critical importance of stringent preventive measures, including education, effective contraception, and regular pregnancy monitoring.

Keywords : retinoic acid embryopathy, retinoic acid, isotretinoin, pregnancy.

INTRODUCTION

Isotretinoin is an effective treatment for severe acne and other dermatologic conditions, but its use comes with serious risks, particularly for women of childbearing age (1). It is a potent teratogen capable of causing profound embryonic malformations if taken during pregnancy (1). Retinoic acid embryopathy encompasses a spectrum of anomalies resulting from isotretinoin exposure, including craniofacial abnormalities, central nervous system malformations, and cardiovascular defects (2). These malformations arise due to disruptions in neural crest cell migration and differentiation during critical stages of embryogenesis (2). Despite established safety protocols, such as the iPLEDGE program, which mandates dual contraception and regular pregnancy testing, cases of isotretinoin embryopathy persist (3). Unplanned pregnancies, inconsistent adherence to contraception, and gaps in education contribute to these occurrences (3, 4).

This case report adds to the growing body of literature by detailing the clinical and radiological findings of a neonate with retinoic acid embryopathy, emphasizing the importance of early detection, preventive strategies, and public health awareness.

CLINICAL REPORT

A male neonate was born at 39 weeks of gestation to a 26-year-old mother with a history of isotretinoin use up to the confirmation of pregnancy in the first trimester. The pregnancy was unplanned, but prenatal ultrasounds performed during routine visits showed no abnormalities. The delivery was uncomplicated, and the infant's birth weight, length, and head circumference were within normal ranges. Apgar scores were 8 and 9 at one and five minutes, respectively. Shortly after birth, the neonate was noted to have multiple dysmorphic features. These included microcephaly, hypertelorism, a flat nasal bridge, and low-set, dysplastic ears. Neurological examination revealed generalized hypotonia and delayed primitive reflexes, along with reduced responsiveness to environmental stimuli. The infant's growth parameters were below the third percentile, raising concerns about global developmental delay and the possibility of congenital anomalies.

Given the physical findings and maternal history of isotretinoin use, the clinical team pursued neuroimaging to evaluate potential structural abnormalities. MRI of the brain revealed extensive central nervous system malformations. The cerebellar vermis was nearly absent, with only a small, dysplastic remnant of the superior portion remaining. The

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cerebellum itself was severely disorganized, with abnormal foliation patterns indicative of dysplasia. The midbrain appeared dysplastic, with thickened superior cerebellar peduncles and a narrowed transition zone between the midbrain and pons. Cystic dilation of the fourth ventricle was observed, likely related to the agenesis or hypogenesis of the cerebellar vermis. Additionally, the corpus callosum was thinned, and bilateral subcortical hyperintensities were noted on T1 FLAIR imaging, suggesting potential vascular compromise. Importantly, no evidence of hydrocephalus or holoprosencephaly was present.

Figure 1

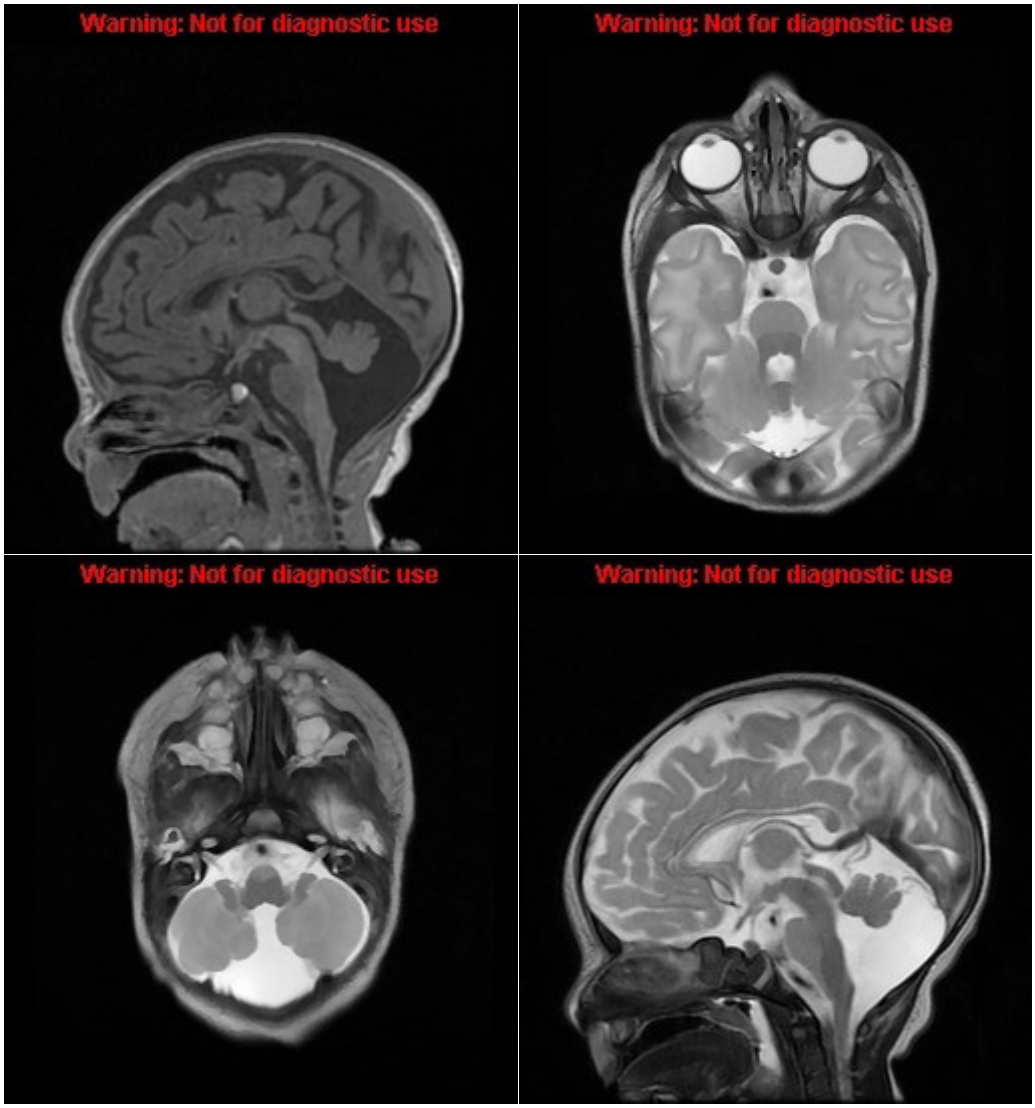
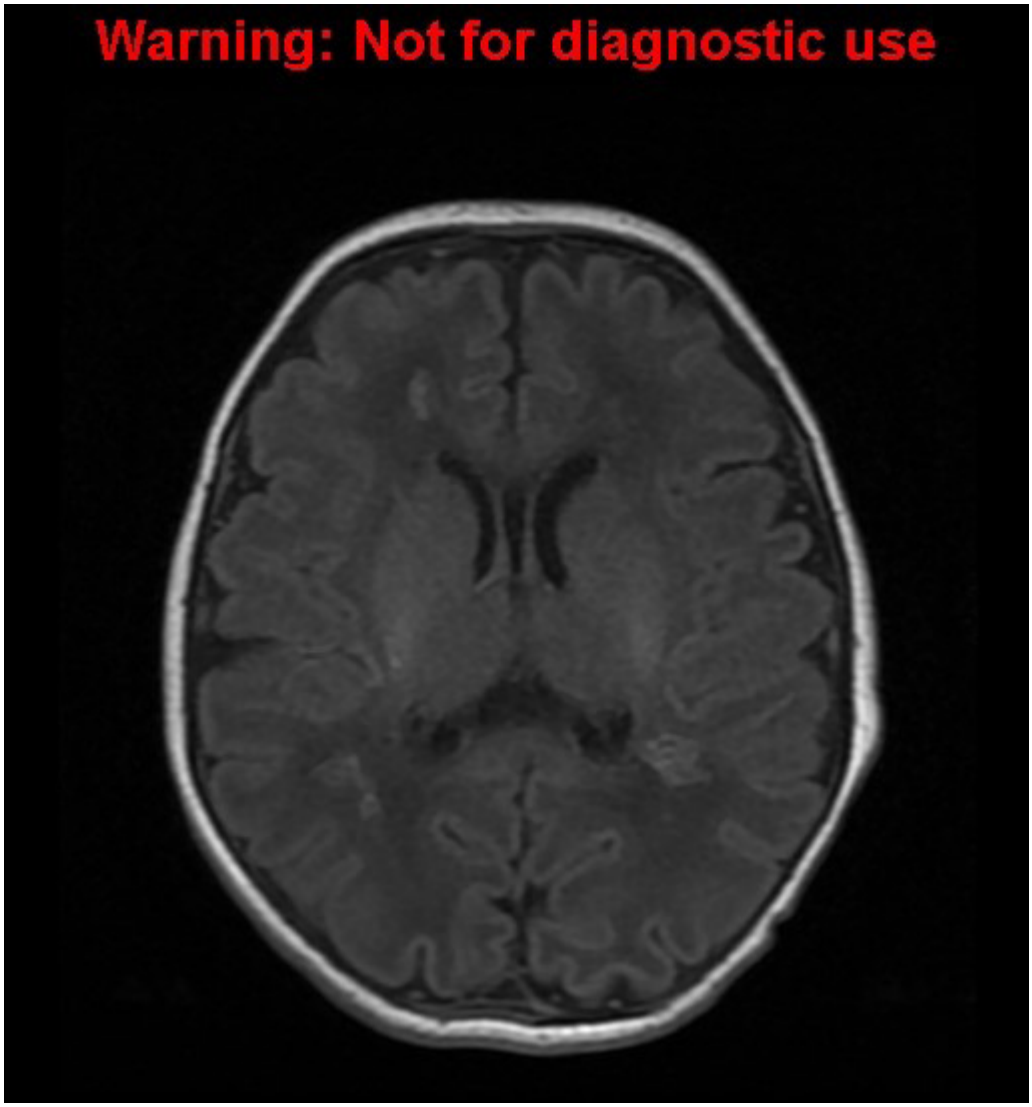


Figure 2



DISCUSSION

Retinoic acid embryopathy is a well-recognized syndrome caused by prenatal exposure to isotretinoin, a medication renowned for its potent teratogenic effects. Isotretinoin interferes with neural crest cell migration, which is critical for the development of various embryonic structures, including the craniofacial region, central nervous system, cardiovascular system, and thymus (1, 5). The clinical and imaging findings in this case align closely with the known spectrum of anomalies associated with this condition, offering a comprehensive view of its impact on fetal development.

The cerebellar vermis is one of the structures most frequently affected in retinoic acid embryopathy. In this neonate, the near-complete absence of the cerebellar vermis, with only a dysplastic remnant of the superior portion, exemplifies the profound disruption isotretinoin can cause during early neural development. The cerebellum itself showed significant dysplasia, with abnormal foliation patterns indicating severe architectural disorganization. This degree of cerebellar involvement is consistent with prior reports that highlight isotretinoin's interference with the early development of the posterior fossa structures (6-8). Similarly, the abnormalities in the midbrain, including its dysplastic configuration and thickened superior cerebellar peduncles, further illustrate the widespread effects of isotretinoin on the central nervous system. These findings suggest that isotretinoin disrupts not only localized regions but also the broader processes of neural differentiation and connectivity. The reduced thickness of the midbrain-pons transition, seen in this neonate, may reflect arrested or incomplete development, a hypothesis supported by studies of isotretinoin's teratogenic mechanisms (9, 10).

Microcephaly, another hallmark feature observed in this case, underscores the systemic impact of isotretinoin on overall brain growth. Microcephaly in retinoic acid embryopathy is thought to result from isotretinoin's inhibition of neurogenesis and

neuronal proliferation. The thinning of the corpus callosum, also noted in this case, is a well-documented consequence of disrupted neural migration and axonal growth (11-13). Together, these findings highlight the profound and multifaceted effects of isotretinoin on the developing brain.

Interestingly, this neonate also exhibited bilateral subcortical hyperintensities on T1 FLAIR imaging, a finding that adds an additional layer of complexity to the clinical picture. While these hyperintensities are less commonly reported in cases of retinoic acid embryopathy, they may reflect secondary vascular insults. Isotretinoin has been shown to disrupt angiogenesis, potentially leading to ischemic damage in vulnerable regions of the developing brain. This hypothesis is supported by animal studies demonstrating isotretinoin's impact on vascular development and integrity (10, 14, 15). The presence of these hyperintensities, in this case, suggests that vascular compromise may be an underappreciated component of retinoic acid embryopathy and warrants further investigation. The absence of hydrocephalus and holoprosencephaly in this neonate, while reassuring, does not diminish the severity of the observed anomalies. These findings suggest variability in the phenotypic expression of retinoic acid embryopathy, which may depend on factors such as the timing, dosage, and duration of isotretinoin exposure. The early stages of organogenesis, particularly during the first trimester, represent a critical window of vulnerability during which exposure to teratogens like isotretinoin can have devastating effects.

Despite the implementation of preventive measures, such as the iPLEDGE program, cases of retinoic acid embryopathy continue to occur. The iPLEDGE program requires women of childbearing age to use two forms of contraception and undergo monthly pregnancy tests while taking isotretinoin (16). However, the persistence of cases highlights several gaps in the system. Unplanned pregnancies remain a significant contributor, often resulting from inconsistent contraceptive use or a lack of awareness about isotretinoin's risks (17, 18). In some instances, healthcare providers may fail to adequately communicate the importance of strict adherence to these preventive measures. Socioeconomic factors, such as limited access to contraception or healthcare services, may further compound the issue (19).

The findings in this case underscore the critical need for enhanced public health efforts to prevent fetal exposure to isotretinoin. Education is a key component of these efforts. Women prescribed isotretinoin must receive comprehensive counseling about its teratogenic risks, the importance of effective contraception, and the necessity of regular pregnancy testing. Healthcare providers play a central role in this process, serving as gatekeepers who can ensure that patients understand and adhere to safety protocols. In addition to education, systemic improvements to the iPLEDGE program may be necessary to address its limitations. Enhanced tracking systems, more frequent follow-ups, and broader access to contraception could reduce the risk of noncompliance. Public health campaigns that raise awareness about isotretinoin's risks and promote safe prescribing practices could further mitigate the incidence of retinoic acid embryopathy.

This case also highlights the need for continued research into the long-term outcomes of children affected by retinoic acid embryopathy. While the structural abnormalities described here provide valuable insight into the condition's immediate impact, the developmental trajectory of these children remains poorly understood. Studies that examine neurodevelopmental, cognitive, and behavioral outcomes over time could inform future interventions and support services for affected families. Finally, this case underscores the broader implications of teratogen exposure in pregnancy. The lessons learned from isotretinoin embryopathy may have relevance for other medications and environmental exposures with teratogenic potential. As science and medicine continue to advance, it is crucial to balance the benefits of therapeutic interventions with their potential risks, particularly for vulnerable populations like pregnant women and their developing fetuses.

CONCLUSION

This case serves as a stark reminder of the devastating consequences of isotretinoin exposure during pregnancy. The neonate's severe structural brain abnormalities and dysmorphic features underscore the teratogen's profound impact on embryonic development. While programs like iPLEDGE have reduced the incidence of retinoic acid embryopathy, this case highlights the need for continued vigilance, education, and innovation in preventive strategies. Healthcare providers play a critical role in minimizing the risk of fetal exposure to isotretinoin. Comprehensive patient education, rigorous monitoring, and improved access to effective contraception are essential components of this effort. Further research is also needed to better understand the long-term developmental trajectories of affected children and to explore new ways of preventing isotretinoin-related teratogenicity.

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