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Neonatal Aneurysm Rupture in a Child with a De Novo Variant to ANKRD17

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Abstract

Ankyrin repeat domain 17 (ANKRD17) is postulated to play a role in the integrity of blood vessels and has been reported to be associated with developmental delays, epilepsy, and growth restriction. Whereas ANKRD17-deficient mice have been demonstrated to experience catastrophic hemorrhages, vascular malformations have not been reported in human patients with pathogenic variants to ANKRD17. We report a term male neonate with a heterozygous de novo variant to ANKRD17 (ANKRD17; c6988 C > G, P.[P2330a]) who experienced subarachnoid hemorrhage from a ruptured aneurysm involving the left middle cerebral artery. He experienced acute symptomatic seizures and required clipping of his aneurysm at 35 days of life, later progressing to developing multifocal drug-resistant epilepsy. To our knowledge, this case represents the first report of a cerebrovascular malformation from a patient with ANKRD17. Further work is needed to investigate whether pathogenic variants to ANKRD17 can lead to cerebral aneurysms or other cerebrovascular malformations in children.

Keywords

ANKRD17, aneurysm, neonate, epilepsy, cerebrovascular malformation

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Background

Ankyrin repeat domain 17 (ANKRD17) is an ankyrin repeat-containing protein which is theorized to be important for the formation and/or maintenance of blood vessels.[1] Mutations of this protein are known to cause a spectrum of neurodevelopmental disorders including developmental delay, dysmorphic facial features, epilepsy, growth restriction, recurrent infections, skeletal anomalies, and ophthalmological abnormalities.[2] In ANKRD17-deficient mice studies, severe embryonic developmental impairments and serious hemorrhages were detected which cause lethality in most cases. However, no studies to date report vascular malformations in human patients with pathogenic variants to ANKRD17. Here, we report a case of neonatal aneurysm rupture and resultant subarachnoid hemorrhagic in a patient with an ANKRD17 de novo variant.

Case

A term male neonate was born without postnatal complications. At 29 days of life, he experienced progressive encephalopathy secondary to subarachnoid hemorrhage from a ruptured aneurysm located between the inferior branch of the M2 division of the left middle cerebral artery as well as the M3 division coursing along the frontal operculum along the sylvian fissure, as demonstrated on brain magnetic resonance imaging (Figure 1). His hospital course was complicated by acute symptomatic seizures and a 5 mm midline shift requiring a decompressive craniotomy. He had evidence of commotio retinae observed during his initial ophthalmologic evaluation, however no evidence of trauma was observed. At 35 days of life, he underwent clipping of his left inferior middle cerebral artery aneurysm. He was discharged on levetiracetam monotherapy and remained seizure free for one year, after which

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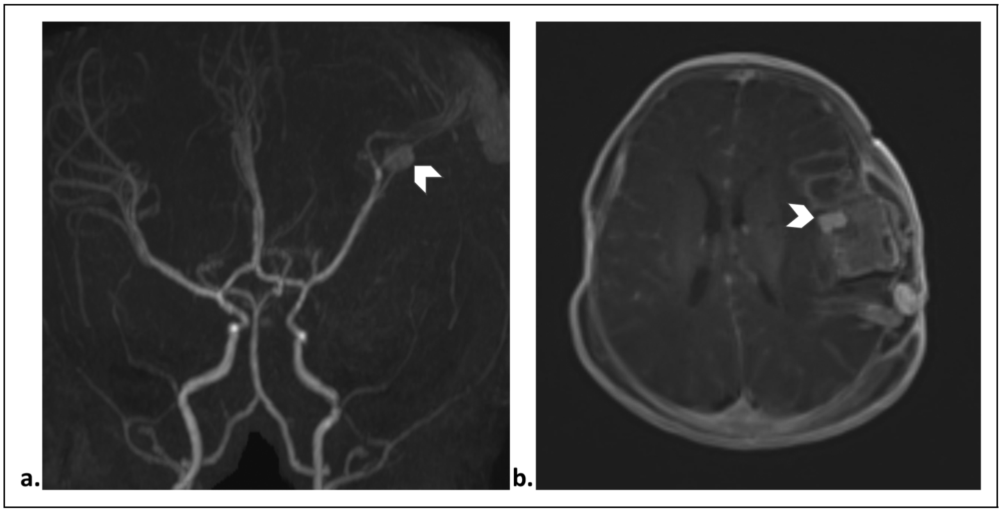

Figure 1. In the neonatal period, three-dimensional reconstruction of time-of-flight magnetic resonance angiography of the head demonstrates a large, ruptured aneurysm involving the inferior division of the M2 and M3 segments of the left middle cerebral artery (a) and contrast-enhanced T1 axial brain magnetic resonance imaging (b) demonstrates the aneurysm with surrounding subarachnoid hemorrhage.

Figure 2. Coarse facial features demonstrated in our case of a male patient with a variant to ANKRD-17.

levetiracetam was discontinued. At 2 years of life, he developed unprovoked focal asymmetric tonic seizures and underwent subsequent electroencephalographic recordings demonstrating multifocal independent epileptiform discharges and generalized slowing worsened over the left hemisphere. Serological whole exome sequencing (GeneDx®) demonstrated a heterozygous de novo variant to the ankyrin repeat-containing protein (ANKRD17; c6988 C > G, P.[P2330a]). Repeat cerebral angiography at 2 years of age demonstrated no further intracerebral aneurysms, and brain magnetic resonance imaging at that time demonstrated extensive left cerebral cystic encephalomalacia, in addition to less pronounced areas of encephalomalacia in the right frontal, parietal and temporal lobes. At 4 years of age, the patient has clinical characteristics of nonverbal intellectual disability, coarse facial features, ride sided hemiplegia, dysphagia, right sided hemianopsia, and drug-resistant multifocal epilepsy (Figure 2). His epilepsy is managed with levetiracetam, clobazam, zonisamide and vagal nerve stimulation. His pediatric performance category score[3] is 3 and functional status scale score[3] is 11 with deficits observed in sensory and motor function and communication.

Discussion/Conclusions

In this report, we provide clinical, radiographic, and genetic characterization of a previously unreported heterozygous ANKRD17 de novo variant in a child with a ruptured cerebrovascular aneurysm occurring during the neonatal period. To our knowledge, this is the first report of a vascular malformation associated with an AKRD17 variant in a human patient.

Clinical studies of ANKRD17 have demonstrated that pathogenic variants cause a neurodevelopmental disorder that manifests with a constellation of intellectual disability, multifocal epilepsy, growth restriction, recurrent infections, skeletal anomalies, dysmorphic facial features and ophthalmological abnormalities.[2] Our patient demonstrated clinical characteristics consistent with that reported in ANKRD17-affected patients, including dysmorphic facial features, speech delays, and multifocal epilepsy. Whereas vascular malformations have not been reported to date in human studies, homozygous ANKRD17-deficient mice have been demonstrated to die from severe hemorrhages in the head, pericardial cavities, and ventral trunk, arising because of defects in vascular smooth muscle development.[1] These hemorrhages emerged as the primary factor for embryonic lethality in homozygous ANKRD17 embryos. ANKRD17 is inherited in an autosomal dominant pattern, and may participate in the regulation, formation, and maintenance of blood vessels. The vascular system is the first functional organ system developed in vertebrae embryogenesis, and disruptions in the genes involved in smooth muscle cell development result in abnormal vessel morphology, leakage of the vasculature, and lethality in early embryos.[4,5] ANKRD17 has been postulated to play an important role in regulatory pathways of the differentiation of vascular smooth muscle precursor cells.[1,6,7] This report demonstrates a novel finding and raises questions as to whether ANKRD17 pathogenic variants in humans can lead to cerebrovascular malformations and hemorrhages only previously seen in mouse studies. It remains unclear why this patient developed commotio retinae. Intraocular hemorrhage has been demonstrated after aneurysmal subarachnoid hemorrhage as part of a condition known as Terson's syndrome.[8] We speculate as to whether contributions of birth trauma, aneurysmal subarachnoid hemorrhage, and underlying vascular instability from ANKRD17 pathogenicity may play a role in the development of commotio retinae. This patient demonstrated encephalomalacia in the cerebral hemisphere contralateral to the site of aneurysm rupture, and we speculate this may have been the result of delayed cerebral ischemia arising from cerebrovascular vasospasms after aneurysmal subarachnoid hemorrhage.[9] Further contributions of genotype-phenotype descriptions from additional patients are needed to complete the spectrum of findings that may be associated with pathogenic variants to ANKRD17.

Authors Contribution

All authors have participated in a meaningful way to this manuscript in its conception and drafting of the manuscript.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: The materials described in this paper are the work of the authors listed, and this work is not simultaneously under consideration by any other journal. All authors have agreed to the content of the manuscript and have seen and approved the submitted version of this paper. No undisclosed group or persons have had a primary role in manuscript preparation. This study was not funded. Dr. Silverstein and Dr. Kuwabara have no relevant conflicts of interest to disclose. The Institutional Review Board (IRB #22-064) at Phoenix Children's Hospital reviewed this work and deemed it to represent a case report study. The mother of the child presented in this case report has agreed to have their child's photograph taken for medical publication purposes, and her written informed consent is provided with this submission.

Ethical Approval

The work described is consistent with the Journal's guidelines for ethical publication.

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