Familial intracranial arachnoid cysts with a missense mutation (c.2576C>T) in RERE
A case report

Yubo Wang, MDa, Jiayue Cui, PhDb, Xiaowei Qin, BSb, Xinyu Hong, MDb,∗

Abstract
Rationale: Arachnoid cysts are relatively common intracranial space-occupying lesions; nevertheless, familial intracranial arachnoid cysts are extremely rare, with only a few cases having been reported.

Patient concerns: The proband was a 7-year-old girl who had experienced generalized tonic-clonic seizures 5 times in the 8 days prior to admission. Nine months later, her 6-year-old younger female cousin presented to us with a 3-day history of headache.

Diagnoses: Brain magnetic resonance imaging (MRI) confirmed the diagnosis of arachnoid cyst for both of the girls.

Interventions: A cyst-peritoneal shunting and cyst fenestration were performed for the 7-year-old girl and her cousin separately. Sanger sequencing revealed a heterozygous missense mutation (c.2576C>T) in the Arginine-Glutamic Acid Dipeptide Repeats gene (RERE).

Outcomes: The outcome was favorable and the follow-up was uneventful.

Lessons: We hypothesize that the mutation in RERE may be associated with the pathogenesis of familial intracranial arachnoid cysts.

Abbreviations: CT = computed tomography, MRI = magnetic resonance imaging, RERE = arginine-glutamic acid dipeptide repeats gene.

Keywords: arginine-Glutamic acid dipeptide repeats gene, familial arachnoid cyst, gene, mutation

1. Introduction
Intracranial arachnoid cysts are congenital malformations that are characterized by abnormal cerebrospinal fluid collections within the arachnoidal membrane and subarachnoid space of the cisterns and major cerebral fissures.[1] Intracranial arachnoid cysts are relatively common entities accounting for approximately 1% of all intracranial space-occupying lesions.[2] However, familial intracranial arachnoid cysts are extremely rare, with only a few cases having been reported; the pathogenesis and clinical manifestations of familial intracranial arachnoid cysts are yet to be well elucidated.

Herein, we report a family with familial intracranial arachnoid cysts, and review the relevant published literature.

2. Case report
The proband was a 7-year-old girl who had experienced generalized tonic-clonic seizures 5 times in the 8 days prior to admission. The neurological examination showed no abnormalities, and the previous medical history was unremarkable. Brain magnetic resonance imaging (MRI) revealed an arachnoid cyst in the left anterior and middle cranial fossa (Fig. 1A and B). A cyst-peritoneal shunting was performed, and oral sodium valproate was administrated for 6 months postoperatively. During the follow-up period of 8 months, she was free of seizures; follow up computed tomography (CT) imaging demonstrated that the cyst was significantly reduced in size (Fig. 1C).

Nine months after the presentation of the proband, her 6-year-old younger female cousin presented to us with a 3-day history of headache. The physical examination was normal, and the previous medical history was unremarkable. Brain CT and MRI showed an arachnoid cyst in the right anterior and middle cranial fossa (Fig. 2A and B). A craniotomy with cyst fenestration was performed. The postoperative course was uneventful and the headache was completely relieved. When discharged, repeated CT imaging showed that the cyst was significantly reduced in size (Fig. 2C).

Both of the patients are the only child in their families; brain CT imaging was performed on their parents and no abnormalities were observed.

Editor: N/A.
Yubo Wang and Jiayue Cui contributed equally to this work.

Patient consent: The patients have provided informed consent for publication of the case.

The authors have no conflicts of interest to disclose.

a Department of Neurosurgery, First Hospital of Jilin University, b Department of Histology and Embryology, College of Basic Medical Sciences, Jilin University, Changchun, Jilin, PR China.

Correspondence: Xinyu Hong, Department of Neurosurgery, First Hospital of Jilin University, No. 71 Xinmin Street, Changchun 130021, Jilin, PR China. (e-mail: drhongxinyu@163.com).

Copyright © 2018 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC), where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

Medicine (2018) 97:50(e13665)
Received: 28 August 2018 / Accepted: 21 November 2018
http://dx.doi.org/10.1097/MD.0000000000013665
Sanger sequencing revealed a heterozygous missense mutation (c.2576C>T) in the Arginine-Glutamic Acid Dipeptide Repeats gene (RERE) in both of the patients and their fathers.

3. Discussion

Arachnoid cysts were originally described by Bright et al in 1829, where it was proposed that the formation of arachnoid cysts may be due to the splitting of the arachnoid. In the past hundred years, arachnoid cysts have been considered to be the most common intracranial space-occupying entity in the general population. Arachnoid cysts are congenital and benign, and the majority of these cysts are asymptomatic and require no special attention. However, these gene mutations show great heterogeneity with no repetition. In the current case, we found a RERE mutation in both of the affected patients. RERE, located in the proximal 1p36 critical region, is a widely-expressed nuclear receptor coregulator that positively regulates retinoic acid signaling. Animal experiments indicate that a RERE mutation might be associated with many structural and developmental birth defects. Fregeau et al found that mutations in RERE can cause a genetic syndrome, which was subsequently described as a neurodevelopmental disorder with or without anomalies of the brain, eye, or heart. Jordan et al also reported 9 unrelated individuals with this syndrome that were caused by RERE mutations. Notably, we found that 1 patient in Fregeau report had an arachnoid cyst in the posterior fossa, and 1 patient in Jordan report had mildly prominent cerebrospinal fluid space.

Figure 1. Radiological examination of the proband. Preoperative T1-weighted (A) and T2-weighted (B) MRI show an arachnoid cyst in the left anterior and middle cranial fossa. Follow-up CT 8 months postoperatively shows that the size of the cyst was significantly reduced (C). CT = computed tomography, MRI = magnetic resonance imaging.

Figure 2. Radiological examination of the proband’s cousin. Preoperative CT (A) and T1-weighted MRI (B) show an arachnoid cyst in the right anterior and middle cranial fossa. When discharged, a repeated CT shows that the size of the cyst was significantly reduced (C). CT = computed tomography, MRI = magnetic resonance imaging.
We speculate that RERE may be associated with intracranial arachnoid cysts and intracranial arachnoid cysts may be a part of the RERE-related genetic syndrome. Although human evidence supporting the role of RERE in neurodevelopmental disorders has been lacking, the association between RERE mutations and familial arachnoid cysts should be highlighted.

Author contributions
Conceptualization: Xinyu Hong.
Data curation: Yubo Wang, Jiayue Cui, and Xiaowei Qin.
Writing – original draft: Yubo Wang and Jiayue Cui.
Writing – review & editing: Yubo Wang, Jiayue Cui, and Xinyu Hong.

References
[1] Pradilla G, Jallo G. Arachnoid cysts: case series and review of the literature. Neurosurg Focus 2007;22:E7.
[2] Vernooij MW, Ikram MA, Tanghe HL, et al. Incidental findings on brain MRI in the general population. N Engl J Med 2007;357:1821–8.
[3] Wester K. Arachnoid Cysts—Historical Perspectives and Controversial Aspects. Arachnoid Cysts. 2018; Academic Press, Salt Lake City:3–16.
[4] Wester K. Arachnoid Cysts—Intracranial Locations, Gender, and Sidedness. Arachnoid Cysts. 2018; Academic Press, Salt Lake City:19–26.
[5] Al-Holou WN, Terman S, Kilburg C, et al. Prevalence and natural history of arachnoid cysts in adults. J Neurosurg 2013;118:222–31.
[6] Helland CA, Lund-Johansen M, Wester K. Location, sidedness, and sex distribution of intracranial arachnoid cysts in a population-based sample. J Neurosurg 2010;113:934–9.
[7] Furey CG, Timberlake AT, Nelson-Williams C, et al. Xp22.2 chromosomal duplication in familial intracranial arachnoid cyst. JAMA Neurol 2017;74:1503–4.
[8] Kurt S, Cevik B, Alksoy D, et al. Atypical features in a large turkish family affected with friedreich Ataxia. Case Rep Neurol Med 2016;2016: 4515938.
[9] Degerliyurt A, Ceylaner G, Kocak H, et al. A new family with autosomal dominant porencephaly with a novel Col4A1 mutation. Are arachnoid cysts related to Col4A1 mutations? Genet Couns (Geneva, Switzerland) 2012;23:185–93.
[10] Bayrakli F, Oktarali A, Kartal U, et al. Intracranial arachnoid cyst family with autosomal recessive trait mapped to chromosome 6q22.31–23.2. Acta Neurochir 2012;154:1287–92.
[11] Bilguvar K, Ozurtuk AK, Bayrakli F, et al. The syndrome of pachygyria, mental retardation, and arachnoid cysts maps to 11p13. Am J Med Genet A 2009;149a:2569–72.
[12] Arriola G, de Castro P, Verdu A. Familial arachnoid cysts. Pediatr Neurol 2005;33:146–8.
[13] Orlacchio A, Gaudiello F, Totaro A, et al. A new SPG4 mutation in a variant form of spastic paraplegia with congenital arachnoid cysts. Neurology 2004;62:1873–8.
[14] Guzel A, Tatli M, Bilguvar K, et al. Apparently novel genetic syndrome of pachygyria, mental retardation, seizure, and arachnoid cysts. Am J Med Genet A 2007;143a:672–7.
[15] Alehan FK, Gurakan B, Agildere M. Familial arachnoid cysts in association with autosomal dominant polycystic kidney disease. Pediatrics 110D 2002:e13.
[16] Fregeau B, Kim BJ, Hernandez-Garcia A, et al. De novo mutations of RERE cause a genetic syndrome with features that overlap those associated with proximal 1p36 deletions. Am J Hum Genet 2016;98:963–70.
[17] Jordan VK, Fregeau B, Ge X, et al. Genotype-phenotype correlations in individuals with pathogenic RERE variants. Hum Mutat 2018;39:666–75.