Pediatric Neurology 66 (2017) 59–62

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Original Article

RMND1-Related Leukoencephalopathy With Temporal Lobe Cysts and Hearing Loss—Another Mendelian Mimicker of Congenital Cytomegalovirus Infection

Nicole Ulrick BA [a], Amy Goldstein MD [b], Cas Simons PhD [c], Ryan J. Taft PhD [c,d,e], Guy Helman BS [a], Amy Pizzino MS, CGC [a], Miriam Bloom MD [a], Julie Vogt MBBS, MRCP [f], Karen Pysden MD [g], Daria Diodato MD [h], Diego Martinelli MD [i], Ahmad Monavari MD [j], Daniela Buhas MD [k,l], Clara D.M. van Karnebeek MD, PhD [m], Imen Dorboz PhD [n], Odile Boespflug-Tanguy MD, PhD [n,o], Diana Rodriguez MD, PhD [n,p,q], Martine Tétreault PhD [l,r], Jacek Majewski PhD [l,r], Genevieve Bernard MD, MSc [k,s,t,u], Yi Shiau Ng MRCP [v], Care4Rare Canada Consortium, Robert McFarland MD [v], Adeline Vanderver MD [a,w,x,*]

[a] *Department of Neurology, Children's National Medical Center, Washington, DC*
[b] *Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania*
[c] *Institute for Molecular Bioscience, University of Queensland, St. Lucia, Queensland, Australia*
[d] *Illumina Inc, San Diego, California*
[e] *School of Medicine and Health Sciences, The George Washington University, Washington, DC*
[f] *West Midlands Regional Genetics Service, Birmingham Women's NHS Foundation Trust, Birmingham, UK*
[g] *Paediatric Neurology, Leeds Teaching Hospitals NHS Trust, Leeds, UK*
[h] *Muscular and Neurodegenerative Disorders Unit, Ospedale Pediatrico Bambino Gesu, Rome, Italy*
[i] *Division of Metabolism, Bambino Gesu' Children's Hospital, IRCCS, Rome, Italy*
[j] *Temple Street Children's University Hospital, Dublin, Ireland*
[k] *Department of Medical Genetics, Montreal Children's Hospital, McGill University Health Center, Montreal, Quebec, Canada*
[l] *Department of Human Genetics, McGill University, Montreal, Quebec, Canada*
[m] *Department of Pediatrics, Centre for Molecular Medicine and Therapeutics, Child and Family Research Institute, University of British Columbia, Vancouver, Canada*
[n] *INSERM UMR 1141, DHU PROTECT, Paris Diderot University, Sorbonne Paris Cité, France*
[o] *AP-HP, Department of Neuropediatrics and Metabolic Diseases, National Reference Center for Leukodystrophies, Robert Debré Hospital, Paris, France*
[p] *APHP, Department of Neuropediatrics, National Reference Center for Neurogenetic Disorders, Hôpital Armand-Trousseau, GHUEP, Paris, France*
[q] *GRC ConCer-LD, Sorbonne Universités, UPMC Université Paris 06, Paris, France*
[r] *McGill University and Genome Quebec Innovation Center, Montreal, Quebec, Canada*
[s] *Department of Neurology and Neurosurgery, McGill University, Montreal, Quebec, Canada*
[t] *Department of Pediatrics McGill University, Montreal, Quebec, Canada*
[u] *Child Health and Human Development Program, Research Institute of the McGill University Health Center, Montreal, Quebec, Canada*
[v] *Wellcome Trust Centre for Mitochondrial Research, Newcastle University, UK*
[w] *Department of Integrated Systems Biology, George Washington University, Washington, DC*
[x] *Department of Pediatrics, George Washington University, Washington, DC*

Conflicts of Interest: A.V. is supported by Illumina Inc, Gilead, Shire, and Eli Lilly. R.J.T. is an employee of Illumina Inc. G.B. is supported by Actelion Pharmaceuticals, Shire, Bluebird Bio, Allergan, and Genzyme. The rest of the authors report no conflicts of interest.

Article History:
Received August 4, 2016; Accepted in final form September 6, 2016

* Communications should be addressed to: Dr. Vanderver; Department of Neurology; Children's National Medical Center; 111 Michigan Avenue, NW; Washington, DC 20010-2970.
E-mail address: avanderv@childrensnational.org

0887-8994/$ – see front matter
http://dx.doi.org/10.1016/j.pediatrneurol.2016.09.003

ABSTRACT

BACKGROUND: Leukoencephalopathy with temporal lobe cysts may be associated with monogenetic conditions such as Aicardi–Goutières syndrome or *RNASET2* mutations and with congenital infections such as cytomegalovirus. In view of the fact that congenital cytomegalovirus is difficult to confirm outside the neonatal period, excluding a Mendelian disorder is extremely relevant, changing family planning and medical management in affected families. We performed diagnostic testing in individuals with leukoencephalopathy with temporal lobe cysts without a definitive diagnosis of congenital cytomegalovirus infection. **METHODS:** We reviewed a large-scale biorepository of patients with unsolved leukodystrophies and identified two individuals with required for meiotic nuclear division 1 (*RMND1*) mutations and similar magnetic resonance imaging (MRI) features, including temporal lobe cysts. Ten additional subjects with confirmed *RMND1* mutations were identified as part of a separate disease specific cohort. Brain MRIs from all 12 individuals were reviewed for common neuroradiological features. **RESULTS:** MRI features in *RMND1* mutations included temporal lobe swelling, with rarefaction and cystic evolution, enlarged tips of the temporal lobes, and multifocal subcortical white matter changes with confluent periatrial T2 signal hyperintensity. A combination of these features was present in ten of the 12 individuals reviewed. **CONCLUSIONS:** Despite the small number of reported individuals with *RMND1* mutations, a clinically recognizable phenotype of leukoencephalopathy with temporal lobe swelling, rarefaction, and cystic changes has emerged in a subset of individuals. Careful clinical phenotyping, including for lactic acidosis, deafness, and severe muscle involvement seen in *RMND1* mutation positive individuals, and MRI pattern recognition will be important in differentiating these patients from children with congenital infections like cytomegalovirus.

Keywords: genetics, cytomegalovirus, *RMND1*, leukoencephalopathy, MRI pattern recognition

Pediatr Neurol 2017; 66: 59-62

Introduction

Although mitochondrial disorders account for a large portion of inherited disease, this continues to be a diagnostic challenge because of the vast number of genes that can cause mitochondrial dysfunction. Even with the advent of next-generation sequencing, establishing a clinically recognizable phenotype and pathognomonic magnetic resonance imaging (MRI) pattern that can facilitate a diagnosis remains important. We identified a small cohort of patients with the previously described combined oxidative phosphorylation deficiency 11 or required for meiotic nuclear division 1 (*RMND1*)-associated encephalopathy (MIM #614922). These patients have distinct MRI features that may facilitate the diagnosis of this condition.

RMND1 encodes an essential membrane protein that is necessary for the normal assembly and conservation of mitochondrial ribosomes used in the formation of oxidative phosphorylation complexes.[1] In these individuals, lactic acidosis, myopathy, and renal abnormalities may be attributable to respiratory chain enzyme defects associated with *RMND1* mutations.[2] More often these individuals may present initially with less specific features of severe developmental delay, sensorineural hearing loss, seizures, and hypotonia. In these children, clinical and MRI features may overlap with those of acquired conditions of the central nervous system, such as congenital infections including cytomegalovirus.[3]

To alert clinicians to the specific MRI features seen in a subset of individuals with *RMND1*-associated encephalopathy and to expand the list of monogenetic disorders that may mimic acquired perinatal infections, we review the MRI and clinical features of 12 individuals with *RMND1* mutation-confirmed mitochondrial encephalopathy.

Methods

A cohort of mutation positive individuals was ascertained from the Myelin Disorders Bioregistry Project, an institutional review board–approved bioregistry at Children's National, which combines clinical, molecular, and radiological data from individuals with unsolved leukoencephalopathy (Patients 1, 2, 9, and 10). After characterization of clinical and MRI features in the initial cohort, a second cohort of mutation-proven individuals from outside centers was identified for validation of the findings. Clinical features of Patients 1 to 4, 7 to 10, and 12 were published before or during this period of characterization.[4,5] Patients 5, 6, and 11 are newly reported (Table 1).

MRIs were scored according to a standard protocol for extent and localization of white matter abnormalities as well as cystic changes in the temporal lobe or elsewhere.[6] Descriptive analysis of clinical and MRI features was performed because of the small size of these cohorts.

Results

In the Myelin Disorders Bioregistry Project, two individuals with temporal lobe cysts and leukoencephalopathy from the same family underwent next-generation sequencing approaches (Table 1). *RMND1* mutations were isolated in these individuals using whole exome sequencing.[7] We obtained eight additional *RMND1* mutation positive individuals (Table 1) from published and unpublished reports. Ten of the 12 individuals demonstrated shared neuroradiological features (Figure) including temporal lobe swelling with cystic evolution (Table 2). Of note, in six of these 12 individuals, temporal lobe findings were asymmetric, affecting only one temporal lobe. In six of the seven individuals aged more than one year and in whom myelination could be more reliably assessed, we also identified multifocal subcortical white matter changes with confluent periatrial T2 signal hyperintensity. A subset of patients also exhibited dilatation of the temporal horns (4 of 12) and thinning of the corpus callosum (8 of 12).

Clinical findings (Table 2) from individuals within our cohort mimic those previously identified in published cases of individuals with *RMND1* mutations, including cognitive developmental delay (12 of 12), hypotonia (12 of 12), sensorineural hearing loss (12 of 12), and seizures (6 of 12). In addition, most individuals exhibit renal

TABLE 1.
Clinical Manifestations

Patient Number	Age at Symptom Onset	Developmental Delay	Autistic Spectrum Disorder	Sensorineural Hearing Loss	Seizures	Hypotonia	Lactic Acidosis	Renal Abnormalities	Age at Death	Variants (NM_017909.3)
1[†]	2 y	+	+	+	*+	+	+	–	NA	Homozygous c.713A>G p.(Asn238Ser)
2[†]	N	+	+	+	*+	+	–	–	NA	Homozygous c.713A>G p.(Asn238Ser)
3[†]	N	+	–	+	–	+	+	+	5 y 9 mo	Homozygous c.1349G>C p.(*450Serext*31)
4[†]	N	+	–	+	–	+	+	+	6 mo	Homozygous c.1349G>C p.(*450Serext*31)
5	N	+	–	+	–	+	+	+	NA	c.533C>T p.(Thr178Met) and c.713A>G p.(Asn238Ser)
6	2 mo	+	–	+	–	+	+	+	NA	c.533C>T p.(Thr178Met) and c.713A>G p.(Asn238Ser)
7[†]	6 mo	+	UNK	+	–	+	+	+	1 y 4 mo	Homozygous c.1349G>C p.(*450Serext*31)
8[‡]	P	+	–	+	+	+	+	+	4 y 2 mo	c.613G>T p.(Asp205Tyr) and c.713A>G p.(Asn238Ser)
9[†]	4 mo	+	+	+	+	+	+	+	NA	Homozygous c.713A>G p.(Asn238Ser)
10[†]	N	+	–	+	–	+	+	+	NA	c.713A>G p.(Asn238Ser) and c.1317+1G>T
11	P	+	–	+	+	+	+	+	21 mo	c.713A>G p.(Asn238Ser) and c.485del p.(Pro162Glnfs*5)
12[†]	2 mo	+	–	+	+	+	+	+	NA	c.713A>G p.(Asn238Ser) and c.1303C>T p.(Leu435Phe)

Abbreviations:
N = Neonatal period
NA = Not applicable
P = Prenatal period
UNK = Unknown
Key: + = symptoms present; – = symptoms absent; *+ = febrile seizure; variant positions relative to transcript NM_017909.3.
[†] Ng et al., 2016.[5]
[‡] Janer et al., 2015.[4]

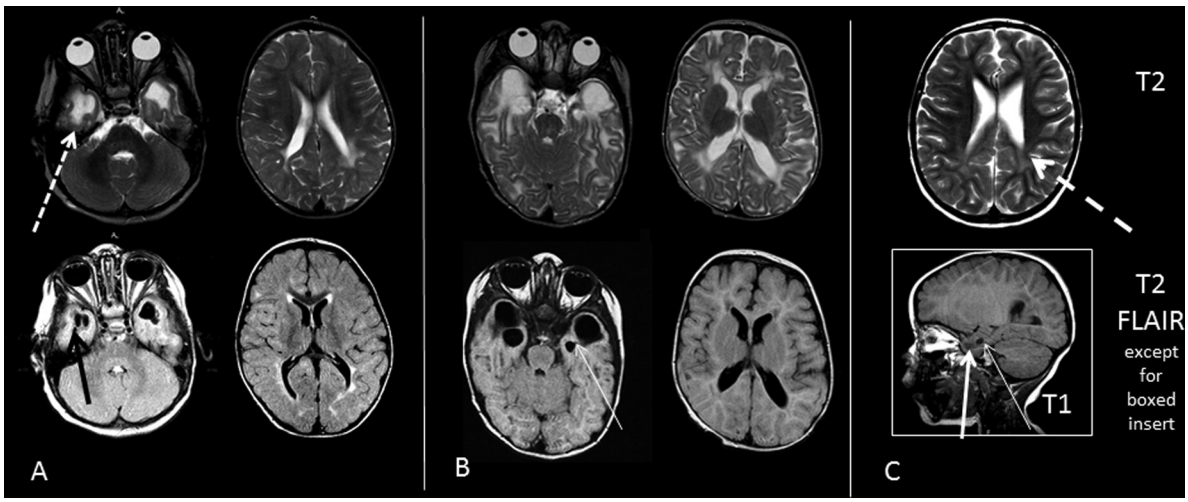

FIGURE.
T2 and T2-FLAIR–weighted imaging in Patient 1 (A, at 8 months), Patient 2 (B and bottom insert in C, at 8 months), and Patient 5 (C, at 8 years) demonstrating temporal lobe swelling (on axial view dotted white arrow, A, and on sagittal view thick white arrow, insert C) with cystic rarefaction (black arrow A). Also notable is dilatation of the tip of the temporal ventricle (on axial views, white arrow B and thin white arrow in insert of C) and thinning of the corpus callosum. Patients additionally may have multifocal white matter changes (A and dotted white arrow C).

TABLE 2.
Neuroradiological Features

Patient Number	Age	Temporal Predominance of White Matter Abnormalities	Multifocal Subcortical or Diffuse White Matter Involvement	Periatrial T2 Hyperintensity	Temporal Lobe Swelling	Temporal Horn Dilatation	Temporal Cystic Changes	Thinning of the Posterior CC
1	2 y	+	+	+	+	+	+	+
2	7 mo	+	NQ	+	+	+	+	+
3	1 y 4 mo	−	−	+	−	−	−	−
4	6 mo	+	NQ	NQ	−	−	+*	−
5	8 y 2 mo	+	+	+	+*	−	+*	+
6	1 y 8 mo	+	+	+	+	+	+	+
7	1 y	−	NQ	+	−	−	−	−
8	1 y 11 mo	+	+	+	−	−	+*	+
9	2 y 1 mo	+	+	+	+	−	+*	+
10	9 mo	+	NQ	−	−	−	+*	−
11	1 y 5 mo	+	+	+	+	−	+	+
12	1 y	+	NQ	NQ	+	+	+*	+

Abbreviations:
CC = Corpus callosum
NQ = Not quantifiable as immature myelination in a child <1 year
Key: + = symptoms present; − = symptoms absent; * = unilateral.

abnormalities (10 of 12) and lactic acidosis (11 of 12), although this was in some instances recognized only after *RMND1* mutations were identified.

Discussion

MRI pattern recognition is invaluable when differentiating between individual leukoencephalopathies.[3] Features of leukoencephalopathy with temporal lobe cysts have been associated with a number of congenital infections, including most notably congenital cytomegalovirus, but have also been seen in early onset genetic leukoencephalopathies including Aicardi–Goutières syndrome and *RNASET2* deficiency.[3,8,9] Differential diagnosis is further complicated because most individuals with leukoencephalopathy with temporal lobe cysts are identified in the postnatal setting, when a diagnosis of a congenital infection is difficult to establish. Thus it is imperative to establish Mendelian mimickers of neurological injury from congenital infection.

A diagnosis of *RMND1*-related encephalopathy has implications for medical management, including risks for sensorineural hearing loss, renal disease, and lactic acidosis. These features were present in the patients within our cohort and in other patients currently identified in the literature.[1,2,4] Although patients may present with these features and a mitochondrial cytopathy may be suggested, they may also present with more subtle features of developmental delay and hypotonia.

In this cohort, most individuals had findings of temporal lobe involvement, with cystic changes, along with a multifocal subcortical leukoencephalopathy. These imaging features may be seen in both acquired and genetic etiologies, and *RMND1*-related encephalopathy should be considered in the differential diagnosis of this radiological presentation.

N.U., G.H., A.P., and A.V. are supported by the Myelin Disorders Bioregistry Project. N.U. and G.H. were supported by the Delman Fund for Pediatric Neurology Education. This publication was supported by Award Number UL1TR000075 from the National Institute of Health (NIH) National Center for Advancing Translational Sciences. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Center for Advancing Translational Sciences or the National Institutes of Health. G.B. was supported by the National Health and Medical Research Council (NHMRC). Patient 11 was identified under the Care4Rare Canada Consortium (OGI-064) funded by Genome Canada, the Canadian Institutes of Health Research, the Ontario Genomics Institute, Ontario Research Fund, Genome Quebec, Children's Hospital of Eastern Ontario Foundation, and "Fondation Leuco dystrophie". G.B. has received a Research Scholar Junior 1 award from the Fonds de Recherche du Québec en Santé (FRQS, 2012-2016) and a New Investigator Salary Award from the Canadian Institutes of Health Research (CIHR, 2017-2022). M.T. is supported by a postdoctoral fellowship from the Canadian Institute of Health Research. D.R. and I.D. are supported by the European Leukodystrophy Association (ELA) foundation (ELA 2009-00714AV2). D.M. is supported by the Association "La Vita e'un dono" ONLUS. Patients 5 and 6 were supported by FP7 Health project RD Connect. R.M. is funded by the Wellcome Trust, MRC (UK), Lily Foundation, and the Ryan Standford Appeal.
Author Contributions: N.U. and A.V. coordinated the project. N.U. and A.V. wrote the manuscript. A.V. performed MRI review and analyzed the clinical and imaging data. L.C., C.S., R.B., and R.J.T. provided bioinformatics analysis. A.G., A.P., M.B., J.V., K.P., D.D., D.M., A.M., D.B., M.T., J.M., G.B, C.V.K., I.D., O.B.T., D.R., Y.N., R.M., and A.V. referred individuals and provided clinical and imaging data, provided clinical care for patients, and also reviewed the manuscript.

References

1. Janer A, Antonicka H, Lalonde E, et al. An RMND1 Mutation causes encephalopathy associated with multiple oxidative phosphorylation complex deficiencies and a mitochondrial translation defect. *Am J Hum Genet*. 2012;91:737-743.
2. Garcia-Diaz B, Barros MH, Sanna-Cherchi S, et al. Infantile encephaloneuromyopathy and defective mitochondrial translation are due to a homozygous RMND1 mutation. *Am J Hum Genet*. 2012;91:729-736.
3. Van Der Knaap MS, Vermeulen G, Barkhof F, et al. Pattern of white matter abnormalities at MR imaging: use of polymerase chain reaction testing of Guthrie cards to link pattern with congenital cytomegalovirus infection. *Radiology*. 2004;230:529-536.
4. Janer A, Van Karnebeek CD, Sasarman F, et al. RMND1 deficiency associated with neonatal lactic acidosis, infantile onset renal failure, deafness, and multiorgan involvement. *Eur J Hum Genet*. 2015;23:1301-1307.
5. Ng YS, Alston CL, Diodato D, et al. The clinical, biochemical and genetic features associated with RMND1-related mitochondrial disease. *J Med Genet*; 2016; http://dx.doi.org/10.1136/jmedgenet-2016-103910.
6. Van Der Knaap MS, Breiter SN, Naidu S, et al. Defining and categorizing leukoencephalopathies of unknown origin: MR imaging approach. *Radiology*. 1999;213:121-133.
7. Vanderver A, Simons C, Helman G, et al. Whole exome sequencing in patients with white matter abnormalities. *Ann Neurol*. 2016;79:1031-1037.
8. Henneke M, Diekmann S, Ohlenbusch A, et al. RNASET2-deficient cystic leukoencephalopathy resembles congenital cytomegalovirus brain infection. *Nat Genet*. 2009;41:773-775.
9. Vanderver A, Prust M, Kadom N, et al. Early-onset Aicardi-Goutieres syndrome: magnetic resonance imaging (MRI) pattern recognition. *J Child Neurol*. 2015;30:1343-1348.