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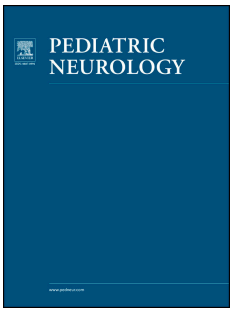

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RMND1 related Leukoencephalopathy with temporal lobe cysts and hearing loss – another Mendelian mimicker of congenital CMV infection

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Abstract:

Background: Leukoencephalopathy with temporal lobe cysts may be associated with monogenetic conditions such as Aicardi Goutières Syndrome or *RNASET2* mutations, as well as with congenital infections such as cytomegalovirus (CMV). In view of the fact that congenital CMV 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 CMV infection.

Methods: We reviewed a large-scale biorepository of patients with unsolved leukodystrophies and identified 2 individuals with *RMND1* mutations and similar 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 neuroradiologic 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 were present in 10 of the 12 individuals reviewed.

Conclusions: Despite the small number of reported cases 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 CMV.

Introduction:

Although mitochondrial disorders account for a large portion of inherited disease, these continue to be a diagnostic challenge due to the vast number of genes that can cause mitochondrial dysfunction. Even with the advent of Next Generation Sequencing (NGS), establishing a clinically recognizable phenotype and pathognomonic 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 *RMND1* (Required for Meiotic Nuclear Division 1) 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 (OXPHOS) complexes (Janer et al., 2012). In these patients, lactic acidosis, myopathy, and renal abnormalities may be attributable to respiratory chain enzyme defects associated with *RMND1* mutations (Garcia et al., 2012). 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 acquired conditions of the central nervous system, such as congenital infections including cytomegalovirus (CMV) (van der Knaap et al., 2004).

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 (MDBP), an IRB approved bioregistry at Children's National, which combines clinical, molecular and radiological data in cases of 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 1-4, 7-10, and 12 were published before or during this period of characterization (Janer et al., 2015, Ng et al., 2016). 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 (van der Knaap et al., 1999). Descriptive analysis of clinical and MRI features was performed due to the small size of these cohorts.

Results:

In the MDBP, 2 individuals with temporal lobe cysts and leukoencephalopathy from the same family underwent NGS approaches (Table 1). *RMND1* mutations were isolated in these individuals using Whole Exome Sequencing (WES) (Vanderver et al., 2016). We obtained 8 additional *RMND1* mutation positive individuals (Table 1) from published and unpublished reports. Ten of the 12 individuals demonstrated shared neuroradiologic features (Figure 1) including temporal lobe swelling with cystic evolution (Table 2). Of note, in 6 of these 12 individuals, temporal lobe findings were asymmetric, affecting only one temporal lobe. In 6 of the 7 individuals over 1 year of age 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 (4/12) also had dilation of the temporal horns, and thinning of the corpus callosum (8/12).

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 (12/12), hypotonia (12/12), sensorineural hearing loss (12/12) and seizures (6/12). Additionally, most individuals exhibit renal abnormalities (10/12) and lactic acidosis (11/12), though this was in some cases recognized only after *RMND1* mutations were identified.

Table 1: Clinical Manifestations

Case Number	Age at Symptom Onset	Develop-mental Delay	Autistic Spectrum Disorder	Sensori-neural Hearing Loss	Seizures	Hypotonia	Lactic Acidosis	Renal Abnormalities	Age at Death	Variants (NM_017909.3)
1*	2y	+	+	+	*+	+	+	-	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 mos	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)

KEY: + = Symptoms Present; - = Symptoms Absent; *+ = Febrile Seizure; mo = months; y = years; UNK = UNKNOWN; NA = Not Applicable; N = Neonatal Period; P = Prenatal Period. Variant positions relative to transcript NM_017909.3.

***(Ng et al., 2016)**

****(Janer et al., 2015)**

Table 2: Neuroradiologic Features

Case Number	Age	Temporal predominance of white matter abnormalities	Multifocal subcortical or diffuse white matter involvement	Periatrial T2 hyperintensity	Temporal lobe swelling	Temporal horn dilation	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	+	+	+*	+

KEY: + = Symptoms Present; - = Symptoms Absent; mo = months; y = years; * = unilateral; CC = Corpus Callosum; NQ = not quantifiable as immature myelination in a child <1 year

Discussion:

MRI pattern recognition is invaluable when differentiating between individual leukoencephalopathies (van der Knaap et al., 2004). Features of leukoencephalopathy with temporal lobe cysts have been associated with a number of congenital infections, including most notably congenital CMV, but have also been seen in early onset genetic leukoencephalopathies including Aicardi-Goutières Syndrome and *RNASET2* deficiency(van der Knaap et al., 2004, Henneke et al., 2009, Vanderver et al., 2015). Differential diagnosis is further complicated because most individuals with leukoencephalopathy with temporal lobe cysts are identified in the post-natal setting, when a diagnosis of a congenital infection is difficult to establish. Thus, it is imperative to establish Mendelian mimickers of neurologic 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, as well as other patients currently identified in the literature(Garcia-Diaz et al., 2012, Janer et al., 2012, Janer et al., 2015). 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, a majority of 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 radiologic presentation.

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Authorship Contributions:

NU and AV coordinated the project. NU and AV wrote the manuscript. AV performed MRI review and analyzed the clinical and imaging data. LC, CS, RB, and RJT provided bioinformatics analysis. AG, AP, MB, JV, KP, DD, DM, AM, DB, MT, JM, GB, CvK, ID, OBT, DR, YN, RM, and AV referred individuals, and provided clinical and imaging data, provided clinical care for patients, and also reviewed the manuscript.

Conflicts of Interest:

AV is supported by Illumina Inc., Gilead, Shire and Eli Lilly. RJT is an employee of Illumina Inc. GB is supported by Actelion Pharmaceuticals, Shire, Bluebird Bio, Allergan, and Genzyme. The remainder of the authors report no conflicts of interest.

Figure Legend

Figure 1. 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).

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