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Novel *SLC13A3* Variants and Cases of Acute Reversible Leukoencephalopathy and α-Ketoglutarate Accumulation and Literature Review

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Abstract

Objectives

Acute reversible leukoencephalopathy with increased urinary alpha-ketoglutarate (ARLIAK) is a recently described autosomal recessive leukoencephalopathy caused by pathogenic variants in the *SLC13A3* gene. ARLIAK is characterized by acute neurologic involvement, often precipitated by febrile illness, with largely reversible clinical symptoms and imaging findings. Three patients have been reported in the literature to date. Our objective is to report newly identified patients and their genetic variants and phenotypes and review published literature on ARLIAK.

Methods

This report contributes 4 additional patients to the literature; describes novel variants in *SLC13A3*; and reviews genetic, biochemical, clinical, and radiologic features of all published patients with ARLIAK.

Results

We provide additional genetic, imaging, and laboratory insights into ARLIAK, an atypical leukodystrophy with clinical and radiologic findings that can normalize.

Discussion

Our case series highlights the importance of reanalysis of next-generation sequencing in the diagnostic workup.

Introduction

Leukodystrophies are heterogeneous conditions affecting the white matter of the brain, variable in age at onset, severity, progression, and genetic etiology.[1,2] Acute reversible leukoencephalopathy with increased urinary alpha-ketoglutarate (ARLIAK) is characterized by neurologic involvement precipitated by febrile illness. Features include transient leukoencephalopathy, dysarthria, altered mental status, and ataxia and increased urinary excretion of dicarboxylic acids including alpha-ketoglutarate. Patients recover clinically with concomitant amelioration of white matter abnormalities, whereas biochemical abnormalities persist.[3,4]

ARLIAK is autosomal recessive, caused by pathogenic variants in *SLC13A3* encoding the plasma membrane Na+/dicarboxylate cotransporter 3. Three patients are reported to date.[3-5] We report 4 additional patients with novel variants in *SLC13A3* and review features of all published patients.

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Methods

This retrospective review was completed via a University of Utah IRB–approved protocol. Consent to disclose was obtained. We also reviewed published literature. Anonymized data not published within this article will be made available by request from any qualified investigator.

Results

Patients 1 and 2

Patient 1 is a 12-year-old girl with normal development. At age 3 years, she had concern for febrile seizure. Brain MRI was normal (Figure, A); EEG was abnormal with midline central spikes. She started levetiracetam, and after 1 year of seizure freedom, parents discontinued medication.

At age 5 years, she presented with acute onset of fluctuating mental status. She had slurring of speech, partial aphasia, upper extremity weakness, and absent reflexes. Parents noted she had an upper respiratory illness and fevers the week prior. Lumbar puncture was normal. EEG showed slowing. Brain MRI (Figure, B and C) demonstrated extensive confluent abnormalities of bright T2/low T1 signal involving the white matter and accompanying diffusion restriction.

Testing during hospitalization and after discharge was normal including leukocyte lysosomal enzymes, multigene leukodystrophy panel, SNP microarray, mitochondrial genome, and whole-exome sequencing (WES).

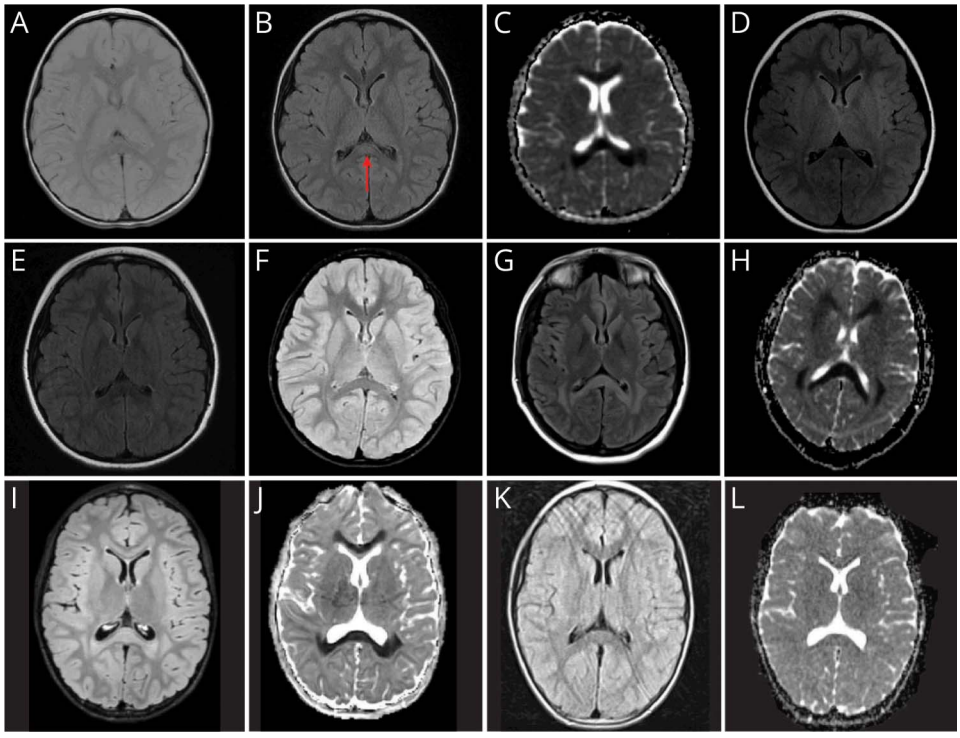
After discharge, she returned to neurologic baseline, though she had school difficulties. Brain MRI (Figure, D) 10 months later showed improved white matter findings with resolution of diffusion restriction abnormalities.

At age 12 years, WES reanalysis detected compound heterozygous variants in SLC13A3 (Table): an intronic variant c.1016+3A>G, previously reported in patients with ARLIAK; and a second variant, c.1167_1169delGTT (p.Leu389del), not previously reported in patients with ARLIAK or population databases. Repeat urine organic acid testing showed persistently elevated alpha-ketoglutarate without other abnormalities.

Patient 2 is patient 1's full sister. She had mild motor delays and failure to thrive with growth at first percentile for height, weight, and head circumference. Testing for Russell Silver Syndrome Panel (H19 methylation and UPD7 analysis) and SNP microarray were normal.

Patient 2 was a comparator for her sister's WES, and the same biallelic variants in *SLC13A3* were found. After her sister's diagnosis, brain MRI completed at 8 years of age was normal (Figure, F). Urine organic acid testing showed elevated alpha-ketoglutarate without other abnormalities. She has had no

Figure MR Images



A–E, Patient 1; F, Patient 2; G–H, Patient 3; I–L, Patient 4. (A) Normal T2 image, age 2.8 years. (B) Age 5 years, T2 FLAIR image, shows hyperintensity in corpus callosum (arrow). (C) ADC map, shows corresponding diffusion restriction. (D) Age 6 years, T2 FLAIR is normal. (E) Age 8 years, T2 FLAIR is normal. (F) T2 FLAIR at age 8 years is normal. (G, H) T2 FLAIR and corresponding ADC map, age 21 years, show diffusion restriction. (I, J) Age 7 years, T2 FLAIR and ADC show hyperintensity in the corpus callosum and corresponding restricted diffusion. (K, L) T2 FLAIR and ADC show normalization.

Table Summary of Clinical, Biochemical, Imaging, and Genetic Features of New and Previously Reported Patients With ARLIAK

Patient	1	2	3	4	5	6	7
Reference	This report	This report	This report	This report	Dewulf et al.[3,5]	Dewulf et al.[3]	Kang et al.[4]
Episode features		N/A					
Febrile	+		+	+/-	+	+	+
Drowsiness	-		-	+	+	+	+
Dysarthria	+		+	-	+	+	-
Ataxia	-		+	+	+	+	+
Altered mental status	+		+	+	-	+	+
Weakness	+		-	+	-	-	-
Abnormal movements	-		+	+	-	+	-
Agitation	-		-	+	-	-	+
Hypotonia	-		-	-	-	+	-
Clinical symptoms reversible	+		+	+	+	+	+
Recurrent	-		+	-	+	+	+
Time between initial episode and recurrence	N/A	N/A	11 y	N/A	12 y	6 y	2 y
Urine α-ketoglutarate mmol/molCr (normal <150)	405	332	174	311	863	592	Elevated
Urine N-acetylaspartate	Normal	N/A	Normal	Increased	Increased	Increased	Normal
Urine succinate	Normal	Normal	Normal	Normal	Increased	Normal	Normal
Urine fumarate	Normal	Normal	Normal	Normal	Increased	Normal	Normal
Treatment							
First episode	Acyclovir	N/A	Unknown	Lorazepam, Levocarnitine	Intravenous glucose and IV fluids	Intravenous acyclovir, ceftriaxone, and methylprednisolone	Acyclovir and intravenous cefotaxime
Additional episode	N/A	N/A	IV fluids	N/A	IV fluids	Intravenous ceftriaxone and acyclovir	Acyclovir and intravenous cefotaxime
Brain MRI findings							
During episode	Confluent restricted diffusion and T2 hyperintensity throughout periventricular and deep frontal and parietal white matter, with involvement of the genu of the corpus callosum	N/A	Confluent, symmetric restricted diffusion in the white matter of the frontal parietal lobes and in corpus callosum	Confluent restricted diffusion and T2 hyperintensity throughout periventricular and deep frontal and parietal white matter, with involvement of genu and splenium of corpus callosum	Bilateral symmetric signal abnormalities of white matter in the periventricular regions, centrum semiovale, and corpus callosum	Bilateral symmetric signal abnormalities of the white matter in periventricular regions, centrum semiovale, and corpus callosum	Bilateral symmetric signal abnormalities of the white matter in periventricular regions, centrum semiovale, and corpus callosum
At follow-up	Almost complete regression of white matter abnormalities	N/A	N/A	Normal	Almost complete regression of white matter abnormalities	Almost complete regression of white matter abnormalities	Almost complete regression of white matter abnormalities
Reversible	+	N/A	Unknown	+	+	+	+
Genetics							
Variant 1	c.1167_1169delGTT p.Leu389del, maternally inherited	c.1167_1169delGTT p.Leu389del, maternally inherited	c.1016+3A>G, maternally inherited	c.1016+3A>G	c.761C>A (p.Ala254Asp)	c.1642G>A (p.Gly548Ser)	c.185C>T (p.T62M)
Variant 2	c.1016+3A>G, paternally inherited	c.1016+3A>G, paternally inherited	c.1033_1035del (p.Val345del), paternally inherited	c.80T>G (p.Leu27Arg)	c.761C>A (p.Ala254Asp)	c.1016+3A>G	c.331C>T (p.R111*)
Other neurologic features/history							
Seizure	+	-	-	+	-	+	+
Developmental delay	-	+, FTT and mild motor delays	-	-	-	-	-
Persistent cerebellar signs	-	-	-	-	-	+	-

Abbreviations: +, presence; -, absence; FTT, failure to thrive; N/A, not applicable.

acute events or neurologic declines to date. Parents had normal urinary alpha-ketoglutarate

Patient 3

Patient 3 is a 22-year old woman referred after hospitalization for acute onset of dysarthria, confusion, and difficulty with ambulation in the setting of COVID-19 with fevers. While hospitalized, she had normal routine laboratory values, drug screening, CT head, CT angiogram, and chest x-ray. Brain MRI revealed confluent restricted diffusion in the white matter of the frontal parietal lobes and corpus callosum (Figure, G and H). After discharge, she returned to neurologic baseline. On further review, patient reported a similar episode at 10 years of age accompanying influenza, with slurred speech and ataxia. Genetic panel testing showed the *SLC13A3* variant c.1016+3A>G; and a second variant, c.1033_1035del (p.Val345del), not previously reported in population databases or patient populations. Urine organic acid testing showed elevated alpha-ketoglutarate without other abnormalities.

Patient 4

Patient 4 is an 11-year-old girl with normal development. She had a single unprovoked tonic-clonic seizure at 3 years of age. At 7 years of age, during a gastrointestinal illness with fever, she became confused, weak, ataxic, and unable to walk. She was hospitalized and admitted to the intensive care unit. On examination, she was somnolent, irritable, and aggressive when aroused, with brisk patellar reflexes. Lumbar puncture and testing for infectious and inflammatory etiologies showed negative results. EEG showed diffuse background slowing. Brain MRI demonstrated extensive confluent restricted diffusion and T2 hyperintensity of the white matter (Figure, I and J).

Patient 4's symptoms resolved approximately 36 hours after admission. She was discharged with no residual neurologic findings. Brain MRI repeated 6 weeks after discharge was normal (Figure, K and L).

Outpatient follow-up included whole-genome sequencing (WGS). Two variants were found in *SLC13A3*: c.1016 + 3A > G and c.80T > G (p.Leu27Arg). Urine organic acids demonstrated elevated alpha-ketoglutarate with no additional abnormalities. To date, she has not had another episode despite several febrile illnesses. She has no neurologic sequelae, but persistently elevated urine alpha-ketoglutarate.

Review of Previous Cases

Clinical, laboratory, and imaging findings of these 4 patients and the other 3 reported patients[3-5] are summarized in the Table. Five patients experienced acute onset of neurologic symptoms in the setting of fever; patient 4 had a fever 2 days prior to her episode. Common neurologic symptoms included drowsiness or altered mental status, dysarthria, and ataxia. Clinical signs and symptoms were reversible in all patients, though one patient was noted to have persistent cerebellar signs following his initial episode. Four patients experienced a second episode. Time between events ranged from 2 to 12 years. All but one patient (who has not yet had any acute events) were reported to have normal development.

All patients showed elevated urine alpha-ketoglutarate, detectable by urine organic acid analysis, both during acute episodes as well as between events when neurologically normal. The 6 patients who experienced acute events had reversible white matter changes compared with initial presentation.

Five of the 7 patients (Table) had the previously reported intronic variant c.1016+3A>G. Patients 1, 2, and 3 had single amino acid deletions. Patient 4 had a novel missense mutation. Compound heterozygous variants were confirmed *in trans* by parental studies.

Discussion

This study reports 4 additional cases to the previously identified patients with ARLIAK and expands our understanding of this condition. All 4 new patients had the previously reported intronic variant in *SLC13A3*, c.1016+3A>G.[3] This variant is present in the gnomAD population database (total allele frequency 0.0008240) with one reported homozygous individual. All other entries in gnomAD are heterozygous. Molecular characterization of this variant demonstrated that it results in 2 aberrant splicing transcripts, one lacking exon 7 and one lacking exons 7 and 8, and which may cause a portion of the transmembrane domain to be deleted.[3] In 3 of our patients, the intronic variant was *in trans* with variants predicted to cause a single amino acid deletion, in exons 8 and 9. Patient 4 had a previously unreported missense variant in exon 1, a highly conserved region of the gene not found in population databases. Together with urine organic acid analysis and similarities in clinical neuroradiologic presentations, these novel variants support a loss-of-function mechanism underlying the pathogenicity of *SLC13A3* variants.

Four patients had seizures, both febrile and afebrile, with onset prior to age 5 years. To date, the seizures appear to have resolved.[3,4] Notably, urinary organic acids in parents of patients 1 and 2 (siblings) were normal, indicating that carriers do not exhibit the biochemical abnormality seen in ARLIAK. Patient 4 had several sets of *qualitative* urine organic acids during and after her episode that did not detect alpha-ketoglutarate, emphasizing the importance of quantitative testing.

Our study also illustrates the value of WES/WGS reanalysis after nondiagnostic testing in cases with objective neurologic and imaging findings[6-8] and may provide important information to improve management of leukodystrophies.

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Adeline L. Vanderver, MD	Department of Neurology, Perelman School of Medicine, University of Pennsylvania; Division of Neurology, Children's Hospital of Philadelphia, Philadelphia, PA	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data
Joshua L. Bonkowsky, MD, PhD	Division of Pediatric Neurology, Department of Pediatrics, University of Utah School of Medicine; Center for Personalized Medicine, Primary Children's Hospital, Salt Lake City, UT	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

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