Leukoencephalopathy From SDHAF1-Related Mitochondrial Deficiency

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None

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HUMAN AND ANIMAL RIGHTS
All procedures performed in this study involving human participants were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

ABSTRACT

We present exceedingly rare cases of leukoencephalopathy due to SDHAF1-related mitochondrial complex II deficiency in identical twins. These findings contribute to the scarcity of reports present in both the radiology literature and the medical literature describing imaging characteristics associated with this condition. Like other mitochondrial disorders affecting the CNS, this disease typically presents in infants or young children with symptoms of weakness, hypotonia, and developmental regression. However, the imaging findings of SDHAF1-related mitochondrial complex deficiency in this pair of patients are unique and include symmetric white matter diffusion restriction most pronounced in the genu and splenium of the corpus callosum with sparing of the body. We propose that the specific imaging findings described in this report may be considered pathognomonic and may therefore be added to the list of previous neuroimaging findings associated with this entity. Recognition of this distinctive pattern by radiologists would allow for a prospective diagnosis on imaging that can then be confirmed with genomic testing and magnetic resonance spectroscopy analysis.

CASE REPORT

BACKGROUND

SDHAF1-related mitochondrial complex II deficiency is an exceptionally rare cause of infantile leukoencephalopathy, with few imaging descriptions available. This report adds to the limited literature by highlighting a distinctive radiologic pattern, namely symmetric involvement of the genu and splenium of the corpus callosum with sparing of the body, that may be pathognomonic and aid in prospective diagnosis.

CASE REPORT

Twin A is a 15-month-old female presenting to the emergency department with weakness, hypotonia, and regression of psychomotor milestones. She had a history of mild fever and cold symptoms 3 days prior to the onset of motor regression. Twin A underwent an MRI, and axial DWI, ADC, FLAIR and sagittal T1 images revealed symmetrical diffusion restriction and hyperintensity in the genu and splenium of the corpus

callosum, sparing the body (Figures 1a-1d). Additionally, imaging shows diffusion restriction extending to the bilateral frontal and parietal periventricular white matter (Figures 2a-2c), diffusion restriction in bilateral medial thalami (Figure 3a-3c), and hyperintensity in the pons and ventral medulla (Figure 4a-4c). EEG was obtained, which showed encephalopathic background, but epileptiform discharges were not noted. Whole genome sequencing results found a homozygous mutation in the SDHAF1 gene, consistent with a mitochondrial complex II deficiency.

A week later, identical Twin B presented with the same symptoms of regression, and MRI imaging was done. The MRI findings for twin B were identical to twin A (Figure 5-8). Genome sequencing for Twin B also revealed a homozygous mutation in the SDHAF1 gene, consistent with a mitochondrial complex II deficiency.

DISCUSSION

SDHAF1-related mitochondrial complex deficiency is a rare, homozygous, autosomal recessive mitochondrial disease characterized by infantile leukoencephalopathy and decreased succinate dehydrogenase (SDH) activity [1]. Affected patients present in the first two years of life with acute psychomotor regression, cognitive impairment, microcephaly, ataxia, limb spasticity, and dystonia [2,3]. The rarity of this disease presents a complication in diagnosis, as there are few reported cases in the radiology literature and few cases in the medical literature as well. This case offers unique findings that are not illustrated elsewhere and thus enhances the diagnostic capabilities of neuroradiologists and builds upon previous work in the literature.

The differential diagnosis for this case may include other predominantly white matter diseases which can be broadly classified into leukodystrophies and genetic leukoencephalopathies. Among leukodystrophies, metachromatic leukodystrophy may be a consideration as it also presents with symmetric periventricular white matter involvement, however, this does not typically display thalamic or brainstem involvement [4]. Among genetic leukoencephalopathies, Leigh's syndrome is the most common and well-known mitochondrial disorder and is also associated with SDH deficiency and symptoms of neurodevelopmental regression [5]. However, while it may involve the thalami, this predominantly involves symmetric lesions of the basal ganglia, the midbrain, and the medulla oblongata [6].

Radiologic findings for specific subtypes of SDH mitochondrial deficiencies are not exhaustively characterized in the literature to date. Generally, mitochondrial leukodystrophy is associated with white matter rarefaction, well-delineated cysts, T2 hyperintensity of the middle blade of the corpus callosum, and symmetric abnormalities of deep gray matter. Complex II deficiency is associated with T2 hyperintensities of the brain stem, middle cerebellar peduncles, and thalami [7]. SDHA deficiency is associated with cerebral hemispheric white matter abnormalities with sparing of the U fibers, entire corpus callosum involvement with sparing of the outer blades, and involvement of corticospinal tracts, thalami, and spinal cord [8]. SDHB mutation findings include T2 hyperintensities of hemispheric white matter, corpus callosum, and medial and posterior thalami, as well as diffusion restriction in the corpus callosum, white matter, and thalami [9]. Magnetic resonance spectroscopy findings for complex II deficiency include a prominent singlet at 2.40ppm in cerebral and cerebellar white matter, while also arising in cerebrospinal fluid, characteristically due to elevated succinate levels, which may be used to confirm diagnoses made with imaging [10].

These two cases show specific imaging findings that may be considered pathognomonic for SDHAF1-related mitochondrial deficiency. Namely, these findings are symmetric predominant involvement of the corpus callosum confined to the genu and splenium with sparing of the body, symmetric involvement of the periventricular and deep white matter, relatively mild involvement of the medial thalami, and lesser degree of involvement of the ventral pons and medulla. There is sparing of the basal ganglia, unlike Leigh's disease. While there are similar findings of the corpus callosum to what has been reported previously, the lack of involvement of the body is a unique addition to the constellation of findings associated with SDHA mutations. No other entity that we know of causes this specific distribution of findings.

TEACHING POINT

This case emphasizes the inclusion of SDHAF1 mitochondrial leukodystrophy in the differential diagnosis for the radiologic findings described above. The similarities between the radiologic imaging for identical twin patients indicate an underlying pattern that may be pathognomonic for this disease. If radiologists can recognize this pattern prospectively, this diagnosis can be readily made on imaging and subsequently confirmed with both genetic testing and magnetic resonance spectroscopy.

QUESTIONS

Question 1: Which of the following clinical features are commonly associated with mitochondrial complex II deficiency?

1. Psychomotor regression (applies)
2. Poor growth (applies)
3. Hypertension
4. Muscle weakness (applies)
5. Dystonia (applies)

Explanation:

Mitochondrial complex II deficiency has a highly variable phenotype, but common features include psychomotor regression, poor growth, dystonia, progressive leukoencephalopathy, and muscle weakness [Introduction]. Hypertension is not described as part of this condition. Mitochondrial complex II deficiency has a highly variable phenotype, but common features include

psychomotor regression, poor growth, dystonia, progressive leukoencephalopathy, and muscle weakness

Question 2: Which imaging findings described in the identical twins are considered pathognomonic for SDHAF1-related mitochondrial deficiency?

1. Symmetric involvement of genu and splenium of the corpus callosum with sparing of the body (applies)
2. Basal ganglia involvement
3. Symmetric involvement of periventricular and deep white matter (applies)
4. Medial thalamic involvement (applies)
5. Ventral pons and medulla involvement (applies)

Explanation:

The report highlights a distinctive radiologic pattern: symmetric involvement of genu and splenium of the corpus callosum with sparing of the body, symmetric white matter abnormalities, relatively mild medial thalamic changes, and lesser involvement of ventral pons and medulla [Discussion]. Basal ganglia involvement is specifically absent, distinguishing this disease from Leigh's syndrome.

Question 3: Which conditions should be included in the differential diagnosis when evaluating white matter disease on imaging in this clinical context?

1. Metachromatic leukodystrophy (applies)
2. Leigh's syndrome (applies)
3. Multiple sclerosis
4. Adrenoleukodystrophy
5. Genetic leukoencephalopathies (applies)

Explanation:

The manuscript emphasizes that the differential includes leukodystrophies and genetic leukoencephalopathies. Metachromatic leukodystrophy is considered because it also shows symmetric periventricular involvement but lacks thalamic/brainstem findings. Leigh's syndrome is included due to SDH deficiency and regression but primarily involves basal ganglia and brainstem [Discussion]. Multiple sclerosis and adrenoleukodystrophy are not discussed as relevant in this case.

Question 4: Which diagnostic modalities can confirm SDHAF1-related mitochondrial complex II deficiency after recognition of imaging findings?

1. Muscle biopsy
2. EEG
3. Genetic testing (applies)
4. Magnetic resonance spectroscopy (applies)
5. Blood glucose testing

Explanation:

The conclusion stresses that radiologists can prospectively identify the disease based on imaging, which can then be confirmed by genomic testing and magnetic resonance spectroscopy [Abstract, Conclusion]. EEG showed only encephalopathic background without epileptiform discharges, and muscle biopsy or blood glucose testing are not emphasized in this report as confirmatory methods.

Question 5: Which of the following statements correctly describe radiologic features of SDH-related mitochondrial deficiencies more broadly (not only SDHAF1)?

1. T2 hyperintensities in the brainstem, middle cerebellar peduncles, and thalami (applies)
2. Entire corpus callosum involvement with sparing of outer blades (applies)
3. Prominent singlet at 2.40 ppm on MR spectroscopy due to succinate (applies)
4. Symmetric basal ganglia lesions are the hallmark of SDHAF1 mutations
5. T2 hyperintensities of hemispheric white matter, corpus callosum, and medial/posterior thalami (applies)

Explanation:

Different SDH mutations show distinct imaging patterns: complex II deficiency involves brainstem, middle cerebellar peduncles, and thalami [Discussion]; SDHA mutations involve entire corpus callosum sparing outer blades [Discussion]; SDHB mutations affect hemispheric white matter, corpus callosum, and thalami [Discussion]. MR spectroscopy demonstrates a succinate peak at 2.40 ppm [Discussion]. Basal ganglia involvement is typical of Leigh's syndrome, not SDHAF1-related disease.

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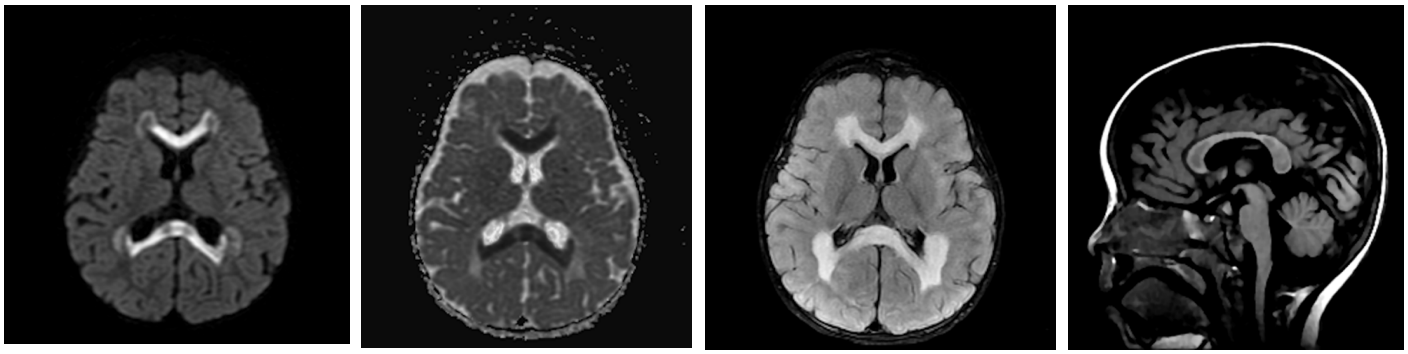
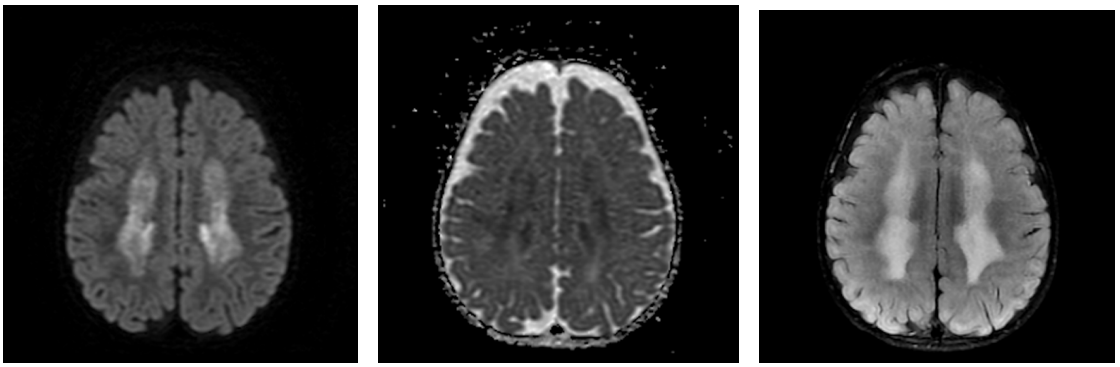
FIGURES



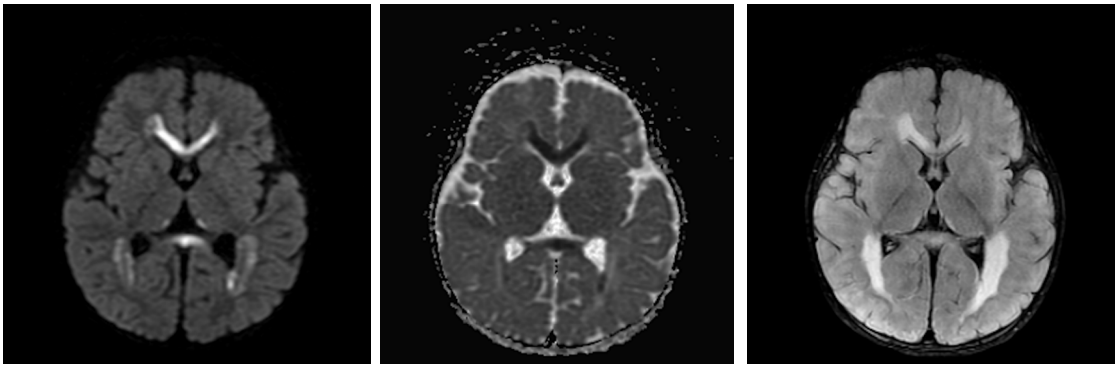
a b c d

FIGURE 1: MRI images of axial DWI (a), ADC (b), FLAIR (c) and sagittal T1 (d) of Twin A show symmetrical diffusion restriction and hyperintensity of the genu and splenium of the corpus callosum, sparing the body.



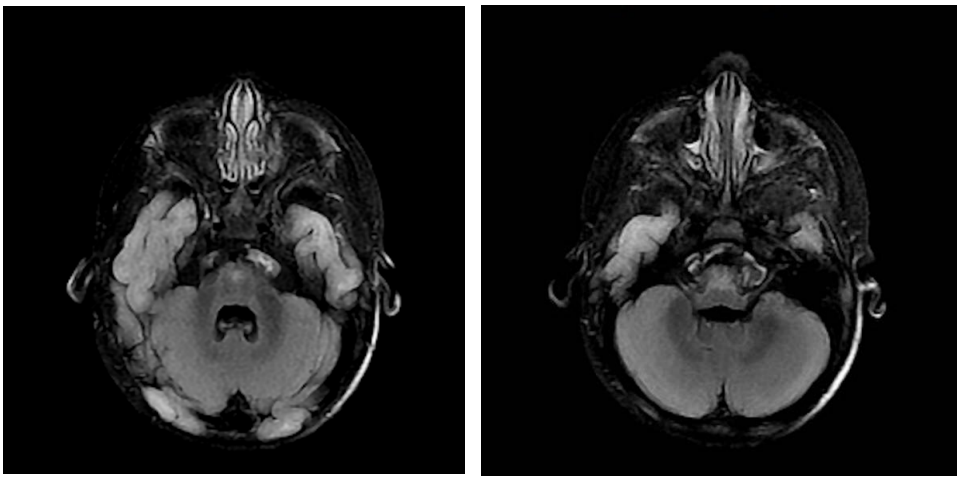
a b c

FIGURE 2: MRI images of axial DWI (a), ADC (b), FLAIR (c) of Twin A show diffusion restriction extending to the bilateral frontal and parietal periventricular white matter.



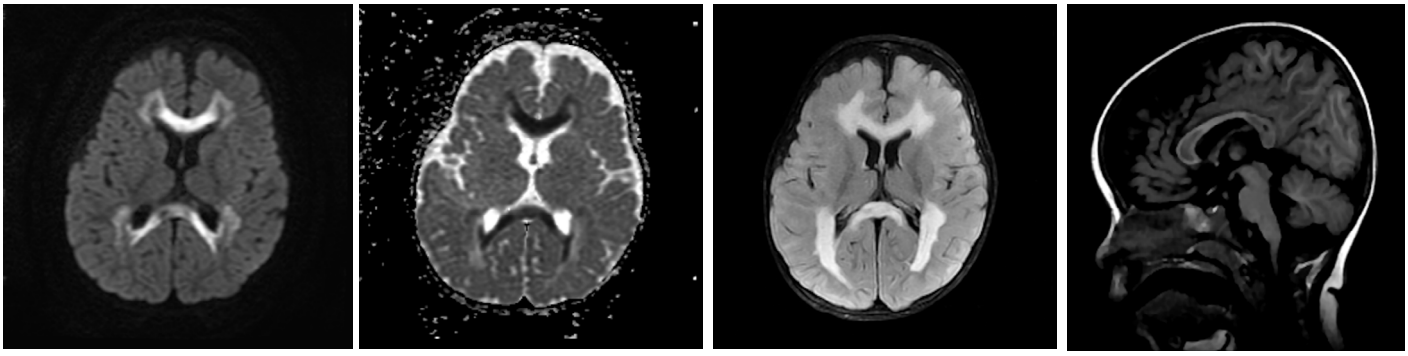
a b c

FIGURE 3: MRI images of axial DWI (a), ADC (b), FLAIR (c) of Twin A show diffusion restriction in bilateral medial thalami.



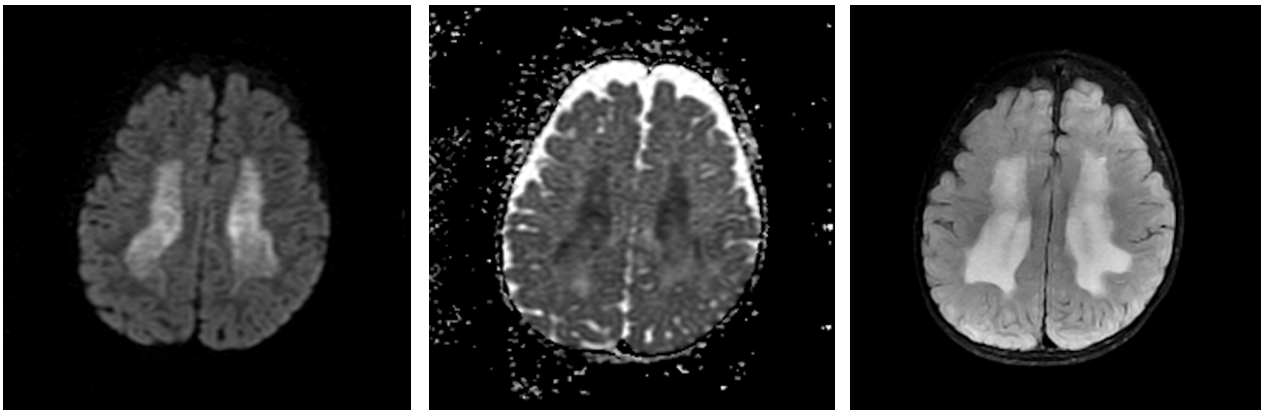
a b

FIGURE 4: MRI images of axial FLAIR of Twin A show hyperintensity in the pons (a) and ventral medulla (b).



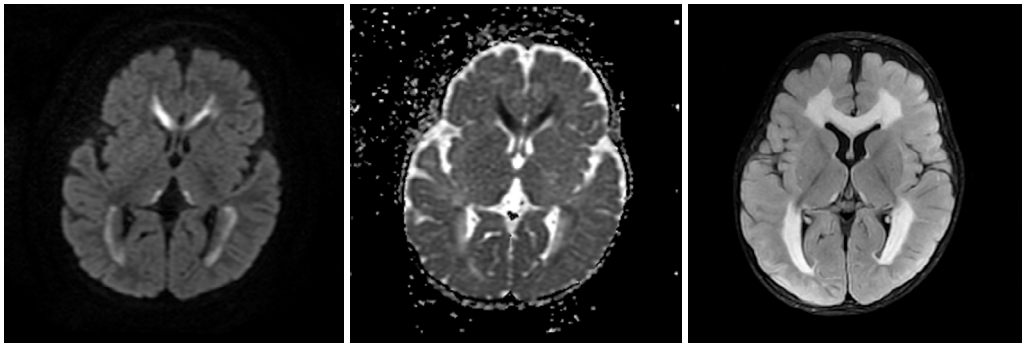
a b c d

FIGURE 5: MRI images of axial DWI (a), ADC (b), FLAIR (c) and sagittal T1 (d) of Twin B show symmetrical diffusion restriction and hyperintensity of the genu and splenium of the corpus callosum, sparing the body.



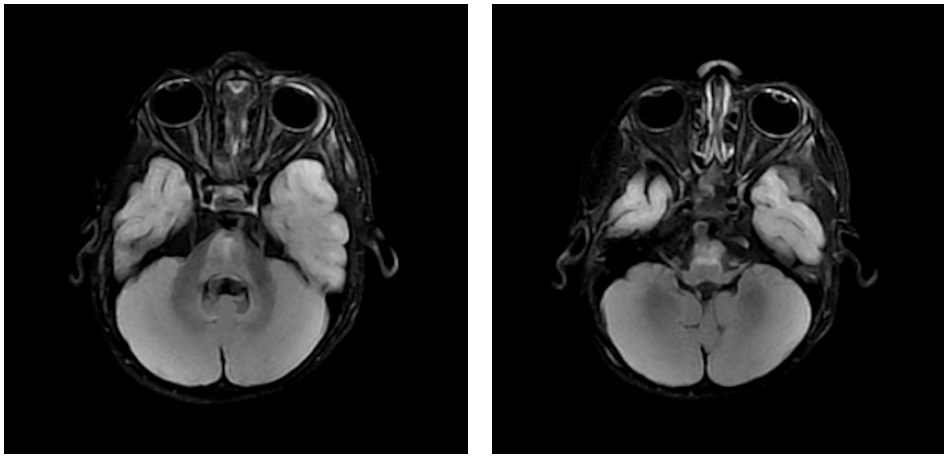
a b c

FIGURE 6: MRI images of axial DWI (a), ADC (b), FLAIR (c) of Twin B show diffusion restriction extending to the bilateral frontal and parietal periventricular white matter.



a b c

FIGURE 7: MRI images of axial DWI (a), ADC (b), FLAIR (c) of Twin B show diffusion restriction in bilateral medial thalami.



a b

FIGURE 8: MRI images of axial FLAIR of Twin B show hyperintensity in the pons (a) and ventral medulla (b).

Category	Summary (key points)
Etiology	Autosomal recessive loss-of-function mutations in SDHAF1, impairing assembly/function of mitochondrial complex II. Leads to succinate accumulation and impaired oxidative phosphorylation.
Incidence	Very rare. Complex II deficiency accounts for ~2% of molecularly diagnosed mitochondrial diseases. Estimated prevalence <<1:100,000 overall; some reviews suggest <1:1,000,000. Exact incidence for SDHAF1-specific disease unknown due to limited case reports.
Gender ratio	No consistent sex predilection. Case reports and series (including identical twins in the manuscript) show no reproducible male:female bias.
Age predilection	Infancy/early childhood. Most present in the first 2 years of life with infantile leukoencephalopathy, psychomotor regression, hypotonia, and global developmental regression [Manuscript].
Risk factors	Autosomal recessive inheritance. Highest risk in individuals with homozygous or compound heterozygous SDHAF1 pathogenic variants. No environmental risk factors established.
Treatment	No curative therapy. Supportive multidisciplinary care (neurology, metabolic, nutrition, physiotherapy, seizure care, respiratory support). Empiric mitochondrial supplements (e.g., coenzyme Q10, vitamins, carnitine) are sometimes used but evidence is limited and not SDHAF1-specific.
Prognosis	Variable but often severe. Many patients experience early progressive neurologic decline; some die in infancy. Prognosis depends on age of onset, severity, and organ involvement. Data limited due to small cohort sizes.
Key imaging findings	Symmetric diffusion restriction and T2/FLAIR hyperintensity in cerebral white matter (periventricular/deep WM). Involvement of corpus callosum (genu and splenium, sparing the body), thalami, pons, medulla. Sparing of basal ganglia (distinguishes from Leigh syndrome). MR spectroscopy: elevated succinate peak (~2.40 ppm) in WM/CSF. Some reports note deep gray involvement, cystic change, and U-fiber sparing.

DIFFERENTIAL DIAGNOSIS

Disease Entity	T1 MRI	T2 MRI	DWI	Other Imaging Modalities	Disease Entity
SDHAF1-related mitochondrial deficiency	Hypointense white matter lesions in genu/splenium of corpus callosum	Hyperintense in genu/splenium of corpus callosum, thalami, pons, medulla	Symmetric diffusion restriction in genu/splenium of corpus callosum, periventricular white matter, and thalami	Magnetic resonance spectroscopy (MRS): succinate peak at 2.4 ppm	SDHAF1-related mitochondrial deficiency
Metachromatic leukodystrophy (MLD)	Symmetric hypointense periventricular white matter	Symmetric hyperintense periventricular white matter with sparing of U-fibers	Restricted diffusion in white matter	-	Metachromatic leukodystrophy (MLD)
Leigh Syndrome	Symmetric hypointense basal ganglia and brainstem lesions	Hyperintense basal ganglia, thalami, midbrain, and medulla	Restricted diffusion in basal ganglia and brainstem	-	Leigh Syndrome

KEYWORDS

SDHAF1-related mitochondrial complex II deficiency; infantile leukoencephalopathy; corpus callosum; white matter; magnetic resonance imaging; diffusion-weighted imaging; thalami; pons; medulla; psychomotor regression

ABBREVIATIONS

ADC = Apparent Diffusion Coefficient
DWI = Diffusion-Weighted Imaging
EEG = Electro Encephalo Gram
FLAIR = Fluid-Attenuated Inversion Recovery
MRI = Magnetic Resonance Imaging
SDH = Succinate Dehydrogenase
SDHAF1 = Succinate Dehydrogenase Assembly Factor 1
WM = White Matter
MRS = Magnetic Resonance Spectroscopy

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