High Succinate peak in Magnetic Resonance Spectroscopy: A Diagnostic Clue for the Leukoencephalopathy Result from Succinate Dehydrogenase Deficiencies

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Keywords:

Succinate dehydrogenase
Magnetic resonance spectroscopy
Leukoencephalopathy
Complex-II-deficiencies

Received:
11- Jun-2021
Accepted:
01-Sep-2024
Published:
07-Jan-2025

ABSTRACT

The Succinate Dehydrogenase (SDH) enzyme is known as Complex-II in the electron transport chain. This study reports the clinical and molecular investigations of three pediatric patients (two of whom are siblings), with histochemical and biochemical evidence of a severe, isolated complex II deficiency due to SDH gene mutations. The patients presented with severe hypotonia, developmental delay, spasticity, macrocephaly, and megalencephaly. Magnetic Resonance Imaging (MRI) revealed signal changes in the frontal, temporal, parietal, occipital cerebral, and cerebellar white matter, corpus striatum, thalamus, substantia nigra, inferior olivary nucleus, pyramidal tracts at the level of the pons and posterior limb of the internal capsule. Other typical findings involved a high succinate peak at 2.42 ppm and lactate peak at 1.3 ppm in Magnetic Resonance Spectroscopy (MRS). The siblings presented due to compound heterozygous c.143A>T (p. Asp48Val) and c.308T>C (p. Met103Thr) SDHB mutations, while the other patient presented due to compound heterozygous c.1754G>A (p. Arg585Gln) and c.1786G>C (p. Asp596His) SDHA mutation. The demonstration of succinate peak, particularly MRS, is highly diagnostic regarding SDH deficiency. MRS should be a standard part of routine radiological exams when there is a suspicion of a neurometabolic disease, especially mitochondrial disorders. Additionally, employing Next-Generation Sequencing (NGS) is advisable for patients as it allows for accurate diagnosis without requiring invasive procedures like muscle biopsies.

How to cite this article: Koc Ucar H, Orgun LT, Arhan E, Serdaroglu A, Aydin K. High Succinate peak in Magnetic Resonance Spectroscopy: A Diagnostic Clue for the Leukoencephalopathy Result from Succinate Dehydrogenase Deficiencies. Iran J Child Neurol. 2025; 19(1): 97-105. https://doi.org/10.22037/ijcn.v19i1.35156

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Introduction

Mitochondrial respiratory chain diseases are congenital metabolic disorders caused by impaired oxidative phosphorylation. The Succinate Dehydrogenase (SDH) enzyme is known as complex-II in the electron transport chain. Complex II deficiency is a rare cause of mitochondrial respiratory chain defects with a 2-23% prevalence. Complex-II-related deficiencies display a broad clinical spectrum, including isolated myopathy and/or cardiomyopathy and severe multisystem disorders with neurological manifestations (1). In contrast, the majority of the previously reported cases presented fatal respiratory failure with severe hypoglycemia, in addition to neonatal cardiomyopathy, infantile leukoencephalopathy, and Leigh syndrome during the childhood period (2-4).

The clinical diagnosis of metabolic diseases with white matter involvement is problematic. Muscle biopsy remains the most specific method for diagnosis, but it is also invasive. However, identifying a Magnetic Resonance Imaging (MRI) pattern facilitates the diagnosis and shortens the diagnostic process. Therefore, it has been recently suggested that MRI and Magnetic Resonance Spectroscopy (MRS) should be predominantly used in the diagnostic studies of patients with leukoencephalopathy, whose differential diagnoses indicate a high possibility of mitochondrial disease.

In this study, three pediatric cases, two of whom are siblings, who had a leukoencephalopathy phenotype with molecularly confirmed isolated complex-II deficiency demonstrate the importance of the succinate peak in MRS used for the diagnosis. With the addition of MRI and MRS findings, the phenotype and genotype of these cases to the literature will facilitate defining the associated specific neuroradiological features and enable specific molecular diagnosis without invasive procedures such as muscle biopsy.

Materials & Methods

Three pediatric patients (two of whom are siblings) with SDH deficiency-related leukoencephalopathy were reviewed for neuroradiologic, clinical, and genetic findings as part of approved studies by the local bioethics committee.

Case 1-2:

The first two female cases are siblings born to parents of unrelated Turkish origin without significant perinatal history. Their family history did not include any neurological diseases. At four months old, both children exhibited growth retardation, hypotonia, and macrocephaly. They have been under our clinic's care since then. Notably, they have not experienced any seizures, and physical examinations have shown no signs of organomegaly. Neither of the siblings had head control, and they could not sit without support. They had marked axial hypotonia, spasticity in the extremities, increased deep tendon reflexes, and clonus. Complete blood counts, basic blood chemistries, lactate and ammonia levels, lysosomal enzyme levels, and necessary blood and urine metabolic workups were normal. Cardiological and ophthalmologic evaluations were regular. Both cases' brain MRI revealed hyperintensities signal changes in the frontal predominant diffuse white matter, corpus callosum, corpus striatum, thalamus, substantia nigra, cerebellar white matter, middle cerebellar peduncles and brain stem (Figures 1-2). He was suspected of having Alexander disease in the differential diagnosis due to hypotonia, developmental delay, macrocephaly, and megalencephaly and MRI findings. The *GFAP*

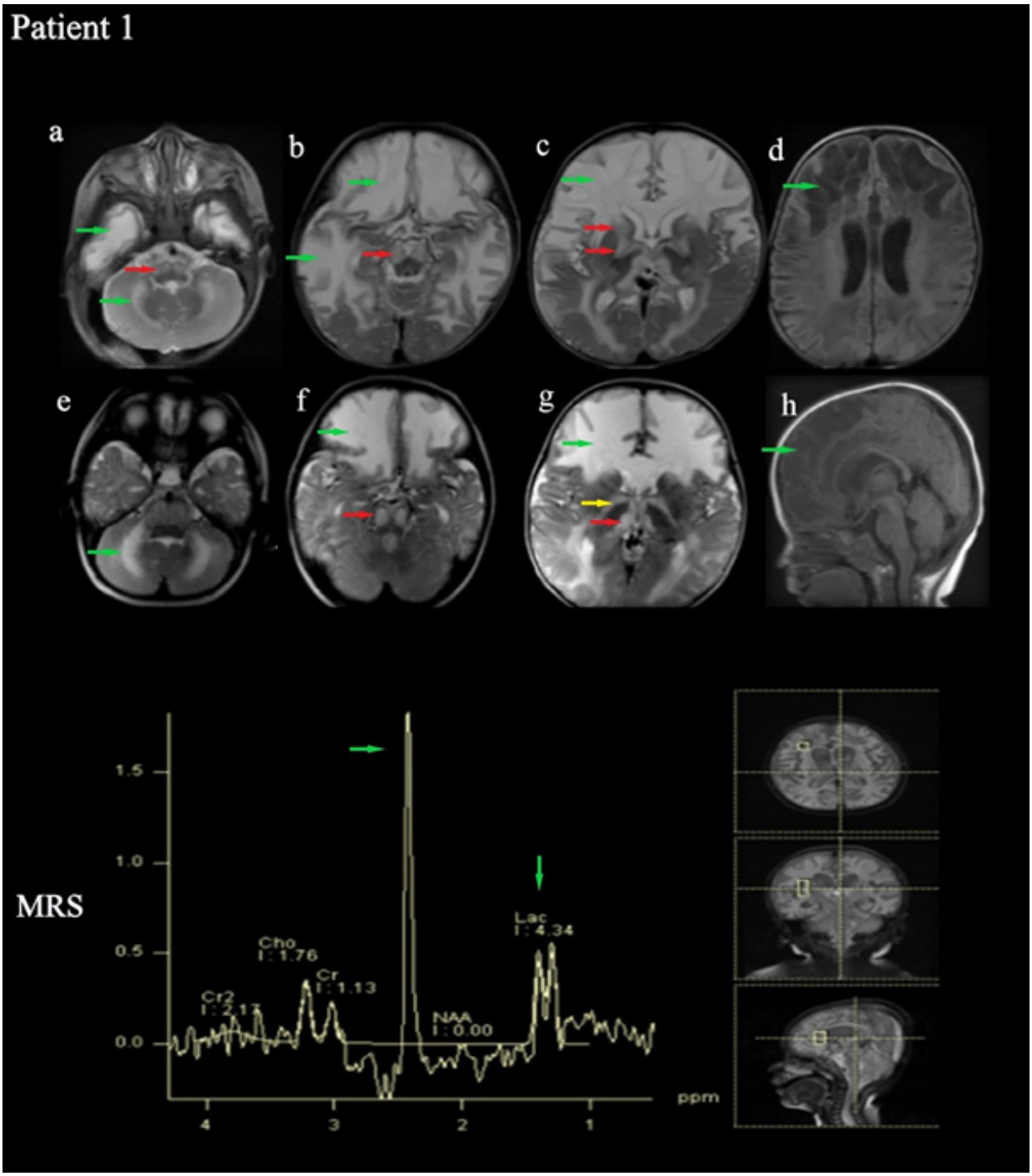

Figure 1. MRI images of Patient 1: Hyperintense T2 signal changes in the frontal, temporal, parietal, occipital cerebral, and cerebellar white matter (green arrows on the a, b, c, e, f, g), corpus striatum (red arrows on the c), thalamus (red arrow on the g), substantia nigra (red arrow on the b), inferior olivary nucleus (red arrow on the a), pyramidal tracts at the level of the pons (red arrow on the f) and posterior limb of the internal capsule (yellow arrow on the g)

gene analysis was normal, and Alexander disease was genetically ruled out. The elder sister, who is now seven years old, had a muscle biopsy at the age of two, which was compatible with mitochondrial disease and fibroblast enzyme activity [Complex-II 55 (control 375-2692) (Father 451, Mother 417)] was found to be consistent with complex-II deficiency. Considering the similar clinical history, suggestive muscle biopsy findings of the sibling, and MRI findings of the younger sister,

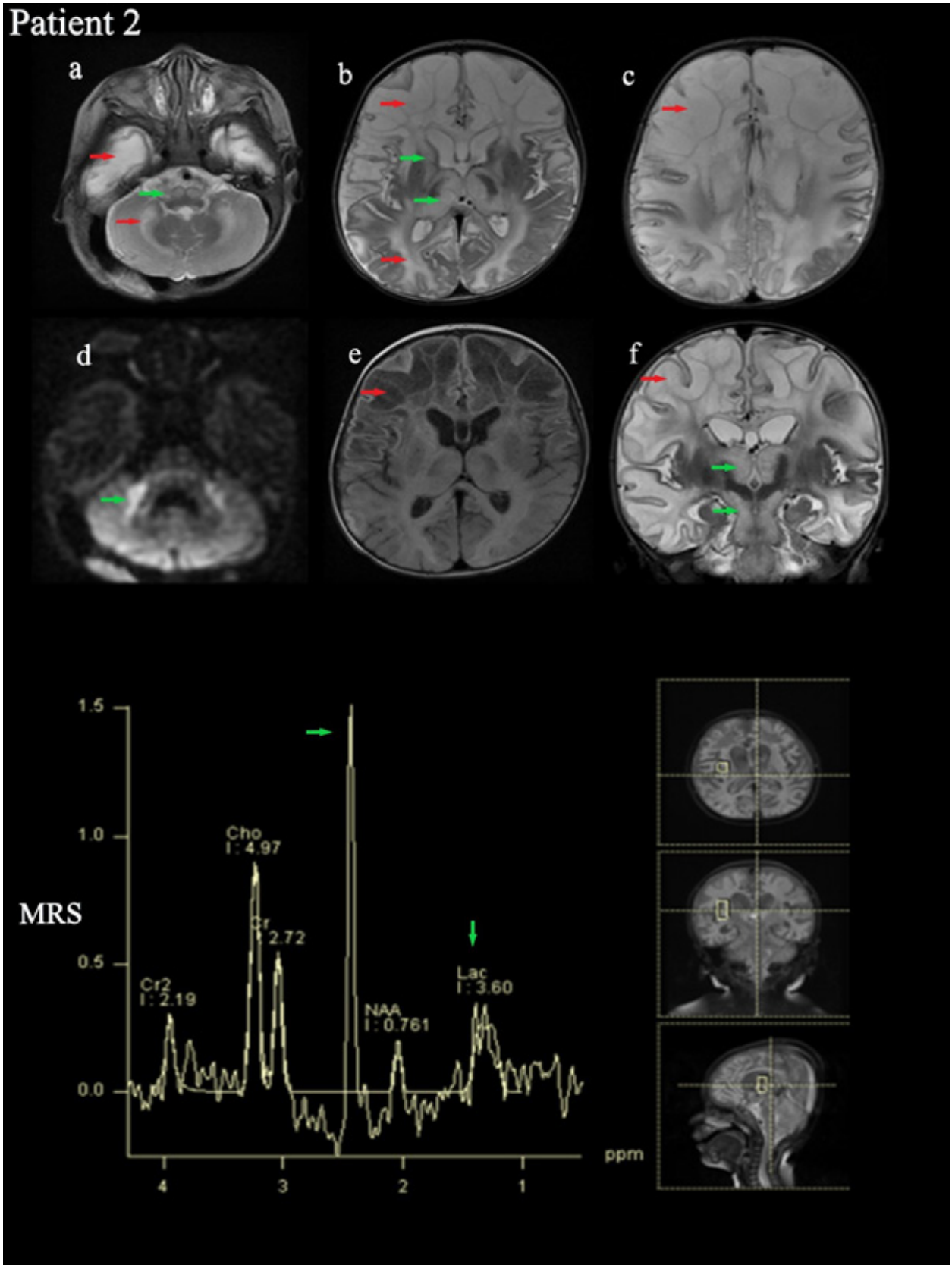

Figure 2. MRI images of Patient 2: Hyperintense T2 signal changes in the frontal, temporal, parietal, occipital cerebral, and cerebellar white matter (red arrows on the a, b, c, f), corpus striatum, thalamus (green arrows on the b,f), inferior olivary nucleus (green arrow on the a), corticospinal tracts at the level of the mesencephalon (green arrow on the f). Hyperintense signal changes in the middle cerebellar peduncle in the diffusion-weighted image (green arrow on the d)

who was 12 months old, MRS was performed and detected succinate and lactate peaks at 2.4 ppm and 1.3 ppm, respectively**.** Thus, an invasive diagnostic approach such as muscle biopsy could be avoided. Molecular analyses detected compound *heterozygous mutation, c.143A>T (p.Asp48Val) and c.308T>C (p.Met103Thr) in the SDHB gene* in both siblings, confirming the diagnosis of complex-II deficiency. The parents of the siblings were heterozygous carriers of these mutations. Oral biotin, thiamine, riboflavin, carnitine, and coenzyme Q10 therapies are started. On clinical follow-up, both cases' recent neurological examinations showed that they began to pay attention to their surroundings, make eye contact, and track objects. However, they still have marked axial hypotonia, spasticity in the extremities, increased deep tendon reflexes, and clonus. Their clinical course was slow-progressive.

Case 3:

The third case was a 14-month-old male born to nonconsanguineous parents of Turkish origin without any perinatal complications. The patient's personal and familial history was unremarkable. He was followed up in other centers due to developmental delay since he was six months old. He was suspected of having Krabbe disease. He was admitted to our clinic when he was 11 months old due to hypotonia and developmental delay. On neurological examination, he did not have eye contact or head control, could not track objects, and had profound axial hypotonia, spasticity in extremities, and increased deep tendon reflexes. Complete blood count, basic blood chemistries, lactate and ammonia levels, lysosomal enzyme studies, and basic blood and urine metabolic workup were normal. Cardiological and ophthalmologic evaluations were normal.

Brain MRI revealed hyperintense signal changes in the frontal predominant diffuse white matter, corpus striatum, thalamus, substantia nigra, and dentate nucleus (Figure 3). Based on these clinical and neuroradiological findings, SDH deficiency was suspected, so MRS was performed. MRS

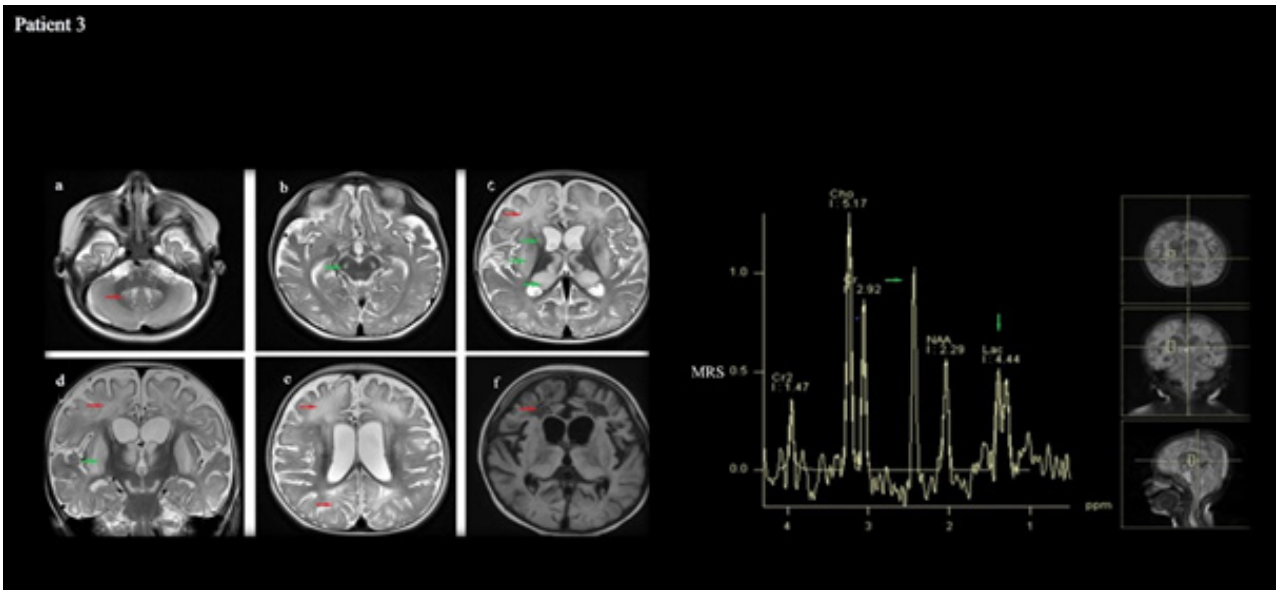

Figure 3. MRI images of Patient 3: Hyperintense T2 signal changes in the frontal, parietal, occipital cerebral white matter (red arrows on the c, d, e, f), corpus striatum, thalamus (green arrows on the c, d), dentate nucleus (red arrow on the a), substantia nigra (green arrow on the b)

revealed a high succinate peak at 2.42 ppm and a lactate peak at 1.3 ppm (Figure 3). The genetic analysis detected *compound heterozygous mutation c.1754G>A (p.Arg585Gln) and c.1786G>C (p.Asp596His) in the SDHA gene*. Both parents were heterozygous carriers of the respective mutations. Regarding diagnostic studies, muscle biopsy, an invasive procedure, was not performed. The patient was started on oral biotin, thiamine, riboflavin, carnitine, and coenzyme Q10 therapies for mitochondrial disease support therapy. On follow-up, the neurological status of the patient was static.

The results of the muscle biopsy and genetic analyses of the cases are summarized in Table 1.

Discussion

Patients with SDH deficiency have variable phenotypes and nonspecific neurological findings expand the differential diagnosis. Muscle biopsy and fibroblast enzyme activities are the most reliable but invasive diagnostic methods when SDH deficiency is suspected. Reportedly, individuals with SDH deficiency may present with leukoencephalopathy, but a specific neuroradiological diagnostic pattern has not yet been identified. SDH deficiency-related leukoencephalopathy is often misidentified due to inadequate diagnostic algorithms in evaluating MRIs and limited information on the MRI phenotype. In the Next-Generation Sequencing (NGS) era, identifying a specific MRI pattern would facilitate diagnosing and evaluating individuals with white matter abnormalities and provide a significant advantage by eliminating the diagnostic delay.

In a recent study, analysis of the MRI of an SDH insufficiency-related leukoencephalopathy case revealed a particular MRI pattern: The involvement of signal abnormalities in the central corticospinal tracts and spinal cord. Other typical findings include effects on at least one of the following areas: the cerebral hemispheric white matter (while sparing the U fibers), the corpus callosum (excluding the outer blades), the basis pontis, the middle cerebellar peduncles, the cerebellar white matter, and the thalamus. The thalamus was involved in most studies with a predilection for the anterior nucleus, pulvinar, and geniculate bodies. The specific MRI patterns observed have strongly indicated a connection to leukoencephalopathy associated with SDH deficiency, highlighting the importance of referring these cases for genetic testing. Furthermore, it was reported that the succinate peak, often observed at 2.4 ppm in MRS, was a specific finding. In most

Table 1. Results of the Biopsies/Genetic Analyses of the Cases

Case-1, 7 years old, Female	❖ Heterozygous 143A>T (p.Asp48Val) and c.308T>C (p.Met103Thr) mutation in the *SDHB* gene ❖ Fibroblast enzyme activity Complex-II 55 (elder sister) (control 375-2692) Father 451 Mother 417
Case-2, 12 months old, Female	
Case-3, 11 months old, Male	❖ Compound heterozygous c.1754G>A (P.Arg585Gln) and c.1786G>C (p.Asp596His) mutation in *SDHA* gene ❖ Biopsy was not performed.

cases, an increased lactate peak accompanied the succinate peak (3,5,6). However, the slightly elevated succinate levels detected in a patient with a splice-site variant in SDHB suggested that these findings may not necessarily be present in all affected patients and that such MRS findings may depend on the stage of the disease and the location of the voxel in the affected tissue (6).

An MRI pattern identification offers a highly effective and non-invasive approach to diagnostic studies of individuals with leukoencephalopathy. An early diagnosis of SDH deficiency-related leukoencephalopathy provides an opportunity to avoid invasive procedures such as muscle biopsy and directly analyze the targeted genes. Thus, these cases will contribute to the identification of disease-specific MRI and MRS patterns for this rare disease. These three cases reported in this study had clinical phenotypes concordant with SDH deficiency due to complex II deficiency. A succinate peak at 2.4 ppm in their MRS and genetically compound heterozygous mutations was observed in SDHA and SDHB genes, respectively.

Previously, three patients who have similar neurological phenotypes with *homozygous p.Asp48Val mutation in SDHB* were reported (7). In contrast, two sisters in this study have *compound heterozygous c.143A> T (p.Asp48Val) and c.308T> C (p.Met103Thr) mutations* in *SDHB genes*. It was clinically observed that both sisters had mitochondrial disease phenotype with infantile leukoencephalopathy. Identifying whether the phenotypes (ranging from leukoencephalopathy to asymptomatic state) are strictly associated with the gene responsible or specific to the mutation is impossible. Thus, newly reported *SDHB-mutated* patients will help identify clinical presentations, genotype/phenotype correlations, and prognostic clues. Each of the recently identified cases will contribute to the literature and lead to further functional studies arising from the need to understand the genetic significance of the newly detected mutations.

Only a few patients with mutations have been reported in the literature since *SDHA* was first identified as a causative gene for complex-II deficiency. *Autosomal recessive SDHA mutations* are the most common cause of complex-II deficiency. Since the *phenotypic overlap of SDHA mutations* causing a mitochondrial disease with tumor formation has been reported, it is recommended to monitor SHDx and assembly factor mutations for possible neoplastic formation in patients and carriers (8,9).

Recently published data revealed that recessive mutations that disrupt complexII can cause infantile mitochondrial disease regardless of the mutated gene. In contrast, germline heterozygous mutations can lead to the formation of inherited paraganglioma or other tumors (5,8,10). Additionally, a second mutation that occurs somatically in the other allele leads to the functional elimination of the active protein and the subsequent induction of the neoplastic transformation. Therefore, in isolated cases of complex-II deficiency in pediatric patients, all genes encoding SDH subunits or assembly factors should be considered (7).

In the context of expanding the use of NGS technologies, it is also useful to identify specific clinical and imaging phenotypes of genetic leukoencephalopathies to allow the interpretation of identified gene variants. Identifying the underlying genetic basis of the isolated complex-II deficiency is vital for providing appropriate genetic counseling for the families. Considering the increased cancer susceptibility, specifically

in association with SDHB defects, routine surveillance allows early diagnosis of tumors and appropriate interventions.

Additionally, Alexander disease's MRI pattern and isolated complex II deficiency show many similarities; testing a cohort of *GFAP-negative*, Alexander patients for complex II deficiency pathogenic variants could give more insight into the true incidence. Accordingly, in patients with this radiologic pattern and clinical phenotype, prior to the genetic exclusion of *GFAP mutations* for Alexander disease, radiological screening with MRS should be considered to search for a complex-II deficiency as the possible genetic cause.

In Conclusion

In summary, identifying a succinate peak through MRS is a significant indicator of SDH deficiency. When a neurometabolic disorder, particularly a mitochondrial condition, is suspected, MRS must be incorporated into the standard radiological assessments. The intentional application of NGS for these patients will facilitate accurate diagnosis while avoiding invasive methods, such as muscle biopsy.

Acknowledgment

The authors thank the patients' families for allowing them to share the current data.

Authors' Contribution

Habibe Koc Ucar conducted the research, performed an extensive literature review, and drafted the initial manuscript. Leman Tekin Orgun, Ebru Arhan, Ayse Serdaroglu, and Kursad Aydin contributed to developing the research protocol. Ayse Serdaroglu and Kursad Aydin played a key role in the data analysis. Leman Tekin Orgun and Ebru Arhan provided supervision during the protocol implementation.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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