

# Succinic Semialdehyde Dehydrogenase Deficiency: Case Reports

## Süksinik Semialdehit Dehidrojenaz Eksikliği: Olgu Sunumu

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#### Abstract

Succinate-semialdehyde dehydrogenase (SSADH) deficiency is a rare neurometabolic disorder of  $\gamma$ -amino butyric acid catabolism with autosomal recessive inheritance. Accumulation of  $\gamma$ -hydroxybutyrate in urine and plasma is biochemically key finding. SSADH deficiency can be demonstrated by measuring level of SSADH enzyme in lymphocytes or leukocytes. In a child with mental retardation and speech disorder the isolated pallidal brain magnetic resonance pattern with absent white-matter changes should raise the suspicion of SSADH deficiency and prompt biochemical analysis of hydroxybutyrate.

Key Words: **Child; Deficiency; Gamma hydroxybutyrate; Succinate-Semialdehyde Dehydrogenase.**

#### Özet

Süksinik semialdehit dehidrojenaz (SSADH) eksikliği,  $\gamma$ -amino butirik asit katabolizma bozukluğu ile karakterize otozomal resesif geçişli nadir nörometabolik bir hastalıktır. Biyokimyasal olarak idrarda ve plazmada  $\gamma$ -hidroksi butirat artması tanıda esastır. Ayrıca lenfositlerde veya lökositlerde SSADH enzim düzeyi ölçülerek tanıda kullanılabilir. Mental retardasyon ve konuşma bozukluğu olan bir çocukta beyin manyetik rezonans görüntülemesinde beyaz cevher değişikliği olmadan sadece globus pallidusda belirgin bir etkilenme varsa, SSADH eksikliği düşünülmeli ve  $\gamma$ -hidroksi butirat düzeyi ölçülmelidir.

Anahtar Kelimeler: **Çocuk; Eksiklik; Gama hidroksibütirat; Süksinat-Semialdehit Dehidrojenaz.**

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### Introduction

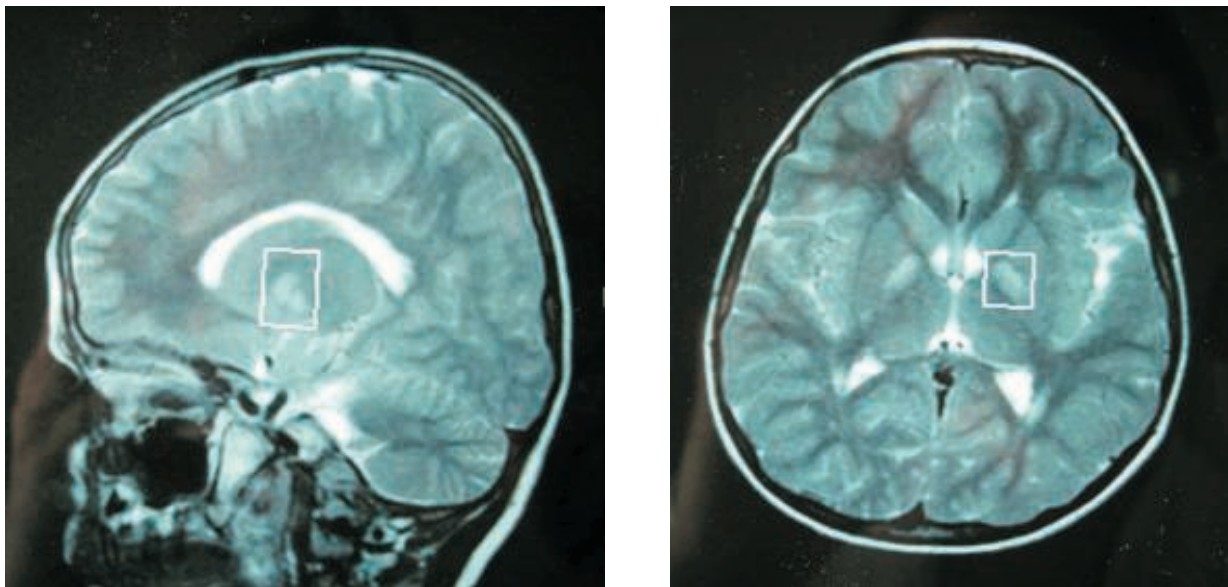
Succinic semialdehyde dehydrogenase (SSADH) deficiency, a rare neurometabolic disease having autosomal recessive inheritance, is characterized by  $\gamma$ -amino butyric acid (GABA) catabolism disorder. Cases are originated frequently from North Europe, North America and Asia (1-3). Up to now more than 350 cases have been reported. Succinic semialdehyde is an intermediate product formed with transamination of GABA. In lack of SSADH, oxidation of succinic semialdehyde is corrupted and succinic acid entering Krebs cyclus is not emanated.

As a result GABA and  $\gamma$ -hydroxybutyrate (GHB or 4 hydroxybutyrate), which is active neurotoxic metabolite of GABA, is accumulated (4). Biochemically, increment of GHB in urine, plasma and cerabrospinal fluid are important. It is possible to use SSADH enzyme level measurement in lymphocyte or leukocyte in diagnosis (5-7).

In this paper a dyslexitic child with SSADH deficiency is presented and discussed with the literature.

### Case Report

A seven-year-old male patient admitted to our clinic with a dyslexia problem. Even though the patient started talking at the age of 2, he had problems of not being able to make meaningful and long sentences and he had also difficulty of learning. The patient did not have any problem in his history but there is an intermarriage history. His speaking and cooperation skills were observed to be less when compared to those of his age period. He had highly arched palate and rethrognathia. Deep tendon reflexes, pupil reflexes and optic fundus examination were normal. Whole blood counting, whole urine examination, liver and kidney functions, troid function tests were within normal limits. WISC-R (Wechsler intelligence scale for children) test performance was indicated medium level retardation. Irregular limited hyper dense areas at bilateral globus pallidus was seen in T2A weight image of cranial magnetic resonance imaging (MRI) (Figure 1). Current findings were interpreted as neurodegenerative or ischemic variation. In single voxel proton MR spectroscopic examination, N-acetyl aspartate (NAA), creatinin and choline peaks were normal. Increased GHB excretion is determined in urine (440 mmol/mol creatinin, normal value 0). Patient was monitored with SSADH deficiency diagnosis.



**Figure 1.** In cranial magnetic resonance monitoring in T2A weighted sagittal and horizontal cross-sections, irregular limited hyper dense areas are seen in bilateral globus pallidus.

## Discussion

In deficiency of SSADH, clinic findings such as psychomotor retardation, delay in speaking, hypotony, ataxia, behavior problems, hyperkinesia, epileptic seizures can be seen. These are nonspecific symptoms of encephalopathy in the childhood. Furthermore, in SSADH deficiency, vomiting, metabolic acidosis, hypoglycemia, hyperammonemia, episodic metabolic balance disorder symptoms, which reminds us the possibility of congenital metabolism diseases, can be also seen (3, 5). Mental-motor-language development deficiency is the most frequently seen symptoms. Ataxia, behavioral problems, epileptic seizures and hypo reflex can be seen in approximately 50% of the patient's. Ataxia increases with aging. Eye symptoms such as strabismus, nystagmus, retinitis, optic disc paleness and oculomotor apraxia may also be detected (4). In 37% of the patients consanguineous marriage has been notified. In the current case report, mental retardation and dyslexia were detected and there was a history of a consanguineous marriage.

The gene responsible for SSADH deficiency is the short arm of the 6<sup>th</sup> chromosome and many mutations have been documented. However, phenotype-genotype relation was not completely understood. Different mutations may cause formation of different enzyme, GHB levels and various clinical symptoms and findings (6). Clinical phenotype is generally heterogeneous and may show difference even in the same family (1). There may be a delay in diagnosing these patients with SSADH deficiency due to inaccurate diagnosis (5).

In spite of high GABA levels, seizures such as tonic-clonic, absence and status epilepticus form can be seen (3, 4). Gibson and his colleagues (8) determined that there was an increase in dopamine and serotonin cycle in patients with SSADH deficiency. 5-hydroxy acidic acid, a serotonin metabolite, and homovalinic acid, a dopamine metabolite, were related with GHB level (8). Disruption of GABA and glutamate cycles between astrocyte and neuron changes glutamate levels and the balance between glutamatergic excitatory activity and GABAergic inhibitory activity. Therefore even though GABA is high, convulsion can occur. Also it is believed that focal metabolic changes cause modifications at receptor level or during carrying of neurotransmitter and causes seizures (4).

In lack of SSADH the most frequently seen brain MRI findings are hyperintensity on T2 weight image in globus pallidus bilaterally and symmetrically and subcortical white substance. Similar MRI symptoms can be seen in

organic acidurias, Canavan disease, cerebrotendinous, infantile rebus disease, Wilson disease, carbon monoxide intoxication and kernicterus (4, 5). However clinic symptoms of these patients are very different from SSADH deficiency. If clinical symptoms such as mental retardation and speaking disorder accompany with isolated globus pallidus and dentate nucleus involvement, SSADH deficiency should be considered. In this case report, in brain MRI, hyperintensity was detected in globus pallidus and NAA, creatinin and colin peaks were normal in spectroscopic examination.

In SSADH deficiency, GHB level can increase up to 2 and 800 times of the normal level. GHB is a volatile metabolite. GBH has the tendency to pass to lactone form and its excretion rate increases with age. For this reason it is especially hard to detect GBH in urine with conventional methods. Especially in perinatal period, more than one urine analysis may be required for the diagnosis (1, 6, 9). Urine can be green, dark green, reddish brown in patients. Apart from GHB, other GABA metabolites can also be excreted with urine. Due to adipic acid, suberic acid and glutaric acid excretion, SSADH deficiency can be interfered mix with di-carboxylic aciduria or acyl-CoA and propionyl-CoA metabolism disorder. However GHB level does not change in those disease (6). 4, 5-dihydroxyhexanoic acid which is not present in mammals under normal conditions, is characteristic for SSADH deficiency. In SSADH deficiency even though there is GHB accumulation in extracellular space of patients, there is no metabolic acidosis (5). GHB excretion was detected in the organic acid scanning of presented case.

There is no optimal treatment in SSADH deficiency.  $\gamma$ -vinyl GABA (Vigabatrin) inhibits GABA transaminase irreversibly and therefore succinic semialdehyde and GHB formation are inhibited. Matern and colleagues (10) reported that administering 25 mg/kg/day dosage of vigabatrin causes healing of cognitive, behavioral problems and lessening of seizures however if given in 75 mg/kg/daily dosage, seizures increased. Clinical efficiency of vigabatrin is restricted and there are no randomized controlled studies. Vigabatrin can cause retinal toxicity (4). For neuropsychiatric symptoms such as anxiety and aggression benzodiazepines can be used (6). Valproic acid is contraindicated as it inhibits residual SSADH activity.

As SSADH deficiency is known for approximately 20 years, information about the disease is mostly limited with solely case presentations. In patients with dyslexia, if there are hyperintensive changes in globus pallidus and dentate nucleus in brain MRI, SSADH deficiency should be considered.

## Kaynaklar

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