Case Report

Succinic Semialdehyde Dehydrogenase Deficiency: Three Sibling in A Family (Case Report)

Cengiz DAYAN, Mustafa ÜLKER, Yasemin Hoşver AKGÜN, Sefer GÜNAYDIN, Turan ATAY, Baki ARPACI

Abstract

Succinic semialdehyde dehydrogenase enzyme (SSADH) deficiency is a rare autosomal disorder involving the catabolism of the neurotransmitter γ-amino butyric acid (GABA). In the absence of SSADH, GABA is converted to 4-hydroxybutyrate. 4-hydroxybutyrate, which is regarded as a biochemical hallmark, accumulating in serum, urine and cerebrospinal fluid. We reported three brothers whose parents were second degree relatives. Patients psychomotor development were slow and they had severe language and intellectual retardation. All were detected to have 4-hydroxy butyric aciduria. All revealed bilateral hyperintensities globus pallidus on Cranial Magnetic Imaging (MRI). Besides two of them had hyperintensities on dentate nuclei on T2 weighted images. The patient were started on low dose vigabatrin treatment. We concluded that urinary organic acid analysis is necessary for the diagnosis of patients with unexplained psicomotor and language retardation.

Keywords: Succinic semialdehyde dehydrogenase deficiency, language development retardation, globus pallidus and dentate nucleus hyperintensity

Süksininik Semialdehit Dehidrogenaz Eksikliği: Üç Kardeş Olgu (Olgu Sunumu)

Özet

Süksinik semialdehit dehidrogenaz enzimi (SSADH) eksikliği, inhibitör bir nörotransmitter olan [gamma]-amino bıtırık asit (GABA) katobolizmasıyla ilgili nadir otozomal bir hastalıktır. SSADH eksikliğinde GABA; 4-hidroksi bıtırıkata dönüştür. Hastalığın biyokimyasal belirteci olarak kabul edilen 4-hidroksi bıtırıkat serum, idrar ve beyin omurilik sıvısında birikir. Biz bu çalışmada ailesi 2. dereceden akraba olan 3 erkek kardeşi sunduk.


Anahtar Kelimeler: Süksinik semialdehit dehidrogenaz eksikliği, dil gelişim geriliği, globus pallidus ve dentat nükleus hiperintensitesi
INTRODUCTION

Succinic semialdehyde dehydrogenase enzyme (SSADH) has a role in the catabolism of GABA, an inhibitory neurotransmitter. In the deficiency of this inhibitory enzyme, succinic semialdehyde does not oxide to succinate and therefore can not enter the Krebs cycle for metabolisation. Semialdehyde is reduced to 4-hydroxybutyrate (γ-hydroxybutyric acid, GHB) which accumulates in the CSF, serum and urine. In SSADH deficiency, GHB accumulation is accepted as a biochemical marker that is also responsive of the clinical presentation.(1)

Clinical signs of SSADH deficiency are nonspecific and variable. In most of the patients, mild to moderate psychomotor and language development along with hypotonia and/or ataxia are seen. Oculomotor apraxia, hyperkinesia, choreoathetosis, convulsion, aggressive behavior and somnolence are less common. Most of these signs can be observed in congenital metabolic disorders. This disease can not be diagnosed unless 4-hydroxybutric acid levels are measured. The symmetrical and/or asymmetrical globus pallidus involvement is the most common MRI finding. Improvements with vigabatrin treatment have been reported, which inhibits GABA transaminase irreversibly.(1)

In this study, we present three brothers with SSADH deficiency whose parents were second degree relatives.

The parents gave written informed consent to participate in the study.

CASE PRESENTATION

Case 1: 11 year-old male patient. He learned to crawl at the age of two, walked with three, and was able to make meaningful sounds at five. At the age of 11, there was no development in his speech, he could not construct a full sentence but could use single and limited number of words to express his needs.

Case 2: 9 year-old male patient. He walked at the age of three, made meaningful sounds at 4-5, but he could not construct a full sentence and could only express himself with single words.

Case 3: 8 year-old male patient. He walked at the age of two, made meaningful sounds at 3-4; but at present he can express himself better than his brothers.

The pregnancy, delivery and neonatal periods of all three brothers were uneventful. There was no history of kernicterus, carbonmonoxide intoxication, or any convulsion. The parents were consanguine, second degree relatives. However no similar history in their relatives were retained. Of the eight siblings ( 4 boys and 4 girls ), the other five were alive and healthy.

The patients physical examinations revealed no abnormality. Their consciousness and understanding were adequate. Speech quantity was limited, they were only able to understand a few words and could only express their needs with limited vocabulary. They could not construct complete sentences. Due to severe language defective motor and mental development tests could not be applied. Their neurological examinations were normal except for hypoactive deep tendon reflexes.

Laboratory findings (complete blood count, routine biochemical examination, urine analysis, thyroid function tests, and routine metabolic screen of urine) were within normal limits. EMG and auditory evoked potential studies were found to be normal. Their EEG's demonstrated mild bioelectrical slowing characterized by a delta activity predominating in the posterior regions of both hemispheres. All revealed bilateral hyperintensity on globus pallidus. Beside there was increased signal intensity on dentate nucleus on T2W MR images (1.5 Tesla) in the first two cases . (Figure 1,2,3)
Figure 1: Bilateral hyperintensity on globus pallidus and dentate nucleus on T2W MR images

Figure 2: Bilateral hyperintensity on globus pallidus and dentate nucleus on T2W MR images

Figure 3: Bilateral hyperintensity on globus pallidus on T2W MR images
4-hydroxybutric acid was detected by gas chromatography mass spectrometry test in the urine. Low dose Vigabatrin was started, however no clinical improvement was observed after one-year follow up.

DISCUSSION
GABA is the inhibitory transmitter of central and peripheral nervous systems. It is synthesized from glutamate by glutamic acid dehydrogenase at the GABA-ergic nerve terminals. During the degrading process, GABA is converted to succinic semialdehyde by GABA transaminase. SSADH enzyme provides the oxidative metabolism of GABA by Krebs cycle.(1)

Congenital GABA metabolism disorders are: seizures due to pyridoxine (glutamic acid decarboxylase deficiency), GABA transaminase deficiency, SSADH deficiency, and homocarnosinosis. The enzymatic diagnosis can only be made in two of these four disorders: GABA transaminase deficiency and SSADH deficiency. (1)

SSADH deficiency is a rare autosomal recessive disease of the late infantile and early childhood periods, and can be described as a slowly progressive or static encephalopathy.(2) The major clinical findings are motor and mental retardation and hypotonia. SSADH deficiency was first reported by Jakob et al. in 1981. Approximately 350 (predominantly children) cases and only eight adults with SSADH deficiency have been reported until today.(3) The initial signs of examination are distinct and usually neurologic. Ataxia, hypotonia, speech disorders hyporeflexia, seizures and variable degree of mental retardation may be seen in most of the patients. (4,5,6) Nearly all reported patients have learning disabilities of various degrees.(7) Seizures are observed clinically in half of patients, but hallucinations are regarded as unusual in infants or children and hallucinations rarely appear before adolescence. Hallucinations psychosis and sleep disturbances could be predominantly in adult cases. (3,8,9) Common signs and symptoms of metabolic disorders such as hyperammonemia, metabolic acidosis, hypoglycemia, growth retardation, vomiting and lethargy are not observed in SSADH cases. The non-specific nature of the symptoms and the difficulties of reaching an accurate diagnosis explain why this condition is probably underdiagnosed. Some of the cases have had a misdiagnosis of cerebral palsy or fragile-X syndrome. (3,7)

Gibson et al. studied the clinical characteristics of 62 patients. They observed retardation in language development in 81%, developmental retardation and hypotonia in 71%, mental retardation in 76%, ataxia and behavioral disturbance in 45%, seizures in 44%, and hyporeflexia in 42%. (2) Our cases presented with motor and mental retardation, failure in normal language development and hyporeflexia, while clinical findings like ataxia, seizures, oculomotor apraxia, hyperkinesias and choreoathetosis were not detected.

EEG abnormalities such as generalized or focal epileptiform discharges, photosensitivity and slowing of the background activity are reported. EEG examinations in less than half of the subjects are reported as normal. (2,5,6,9,10) In all of our cases mild bioelectrical slowing characterized by delta activity on posterior regions of both hemispheres were seen on EEG. Although GHB is known to induce absence-like seizures and absence seizures, but the etiology of seizures in the patients with SSADH deficiency is unknown. (6) It has been suggested that some alterations in the metabolism of neurotransmitters and their binding to receptor sites or any defect in their transport may be responsible for seizure occurrences in these patients. (2)

The symmetric and/or asymmetric globus pallidus involvement is the most common finding on cranial MRI. Lesions in the thalamus, brain stem and white matter were also reported in the literature. Ethofer et al. was found elevated GABA levels and traces of GHB in both the white and the gray matter of the brain in Proton MR spectroscopy. (11) All of our cases had bilateral hyperintense lesions at globus pallidus and two of them had
increased signal intensity at dentate nucleus in T2 weighted cranial MR images.\(^{2,7,12}\) Cases with normal MRI were also reported. It has been considered that there is no significant correlation between neuroradiological and clinical findings.\(^{4,6,12}\)

The gene of SSADH enzyme is mapped to the chromosome 6p\(^{22}\). The molecular genetics of SSADH deficiency is still being explored. However limited number of patients makes it difficult to mention about sporadic or variant forms.\(^{13}\) As seen in our subjects, the percentage of relativity is higher.\(^{7}\)

The 4-hydroxybutyric aciduria is known to be the simplest way in diagnosing SSADH deficiency.\(^{7}\) Whereas, the organic acid analysis is not always enough in detection of 4-hydroxybutyric acid excretions. The diagnosis can be confirmed by measurement of enzyme activity in leucocytes or blood. The prenatal diagnosis can be performed by measurement of 4-hydroxybutyric acid concentrations via isotope dilutional gas chromatography mass spectrometry technique in the amniotic fluid or by the measurement of SSADH activity in cultured amniocytes or chorionic villus biopsy specimens.\(^{14}\)

Since Jeaken et al. in 1989 introduced vigabatrin (\(\gamma\)-vinyl-GABA, irreversible inhibitory of GABA transaminase) treatment in SSADH deficiency, most investigators reported some improvement of ataxia and EEG abnormalities. Doses lower than its antiepileptic use are recommended (25mg/kg/day), while higher doses are found to worsen the clinical findings.\(^{1,2,7,10}\)

In recent studies, it was noted that vigabatrin was only effective in one third of the subjects. It is thought that the 4-hydroxybutyric acid forming at the periphery and passing the blood brain barrier is responsible in inconsistent results. Vigabatrin has limited inhibitory capacity in the peripheric organs while it can inhibit GABA transaminase effectively in the brain. It is also hypothesized that the genetic or enzymatic heterogeneity has a role in the unresponsiveness. As a specific inhibitor of SSADH enzyme, Valproate is contraindicated in therapy.\(^{2}\)

In a conclusion, SSADH should be considered in cases that have two or more of motor, language and mental developmental retardation associated with hypotonia. Therefore, quantitative organic acid analysis in the urine should be done in every patient who has a delay in one or more developmental steps and no other explanation for the state of the patient can be detected.

ACKNOWLEDGMENT
The authors thank Cengiz Yalçınkaya for the great aids in diagnosis and measurement of GHB acid in urine.

REFERENCES


Correspondence to
Cengiz Dayan
E-mail: cedayan2000@yahoo.com

Recieved by: Jun 30 2005
Revised by: Sept 07 2005
Accepted : Feb 03 2006

The Online Journal of Neurological Sciences (Turkish) 1984-2005
This e-journal is run by Ege University Faculty of Medicine, Dept. of Neurological Surgery, Bornova, Izmir-35100TR as part of the Ege Neurological Surgery World Wide Web service.
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URL: http://www.jns.dergisi.org
Journal of Neurological Sciences (Turkish)
ISSN 1302-1664