

Attention Deficit Hyperactivity Disorder Comorbidity in an Adolescent Diagnosed with L-2 Hydroxyglutaric Aciduria and Response to Atomoxetine Treatment: a Case Report

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ABSTRACT

Attention deficit hyperactivity disorder comorbidity in an adolescent diagnosed with L-2 hydroxyglutaric aciduria and response to atomoxetine treatment: a case report

L-2-hydroxyglutaric aciduria (L-2 HGA) is a rare, neurodegenerative, slowly progressing and autosomal recessively inherited metabolic disorder. The disease progresses with mental retardation, behavioral disorder, ataxia, extrapyramidal signs and epileptic seizures. Diagnosis is made by detection of increased levels of L-2-hydroxyglutaric acid in urine, plasma or cerebrospinal fluid. In this report, we presented a 13 year old male patient diagnosed with L-2 HGA and had seizures, intellectual disability, attention deficit hyperactivity disorder (ADHD) symptoms and failure in school performance. Here we discussed this rare disease with ADHD symptoms and the response to atomoxetine treatment.

Keywords: Atomoxetine, attention deficit hyperactivity disorder, L-2-hydroxyglutaric aciduria

ÖZET

L-2-hidroksi glutarik asidüri tanıli bir ergende dikkat eksikliği hiperaktivite bozukluğu eş tanısı ve atomoksetin tedavisine yanıt: Bir olgu sunumu

L-2-hidroksi glutarik asidüri (L-2 HGA) nadir görülen, yavaş ilerleyen ve otozomal resesif kalıtılan nörodejeneratif metabolik bir hastalıktır. Hastalık mental retardasyon, davranış bozukluğu, ataksi, ekstrapiramidal bulgular ve epileptik nöbetlerle seyreder. Tanı; idrar, plazma ya da serebrospinal sıvıda L-2-hidroksiglutarik asid yüksekliği ile konulur. Bu yazıda nöbetler, mental retardasyon, dikkat eksikliği hiperaktivite bozukluğu (DEHB) belirtileri, okul başarısında sorunlarla belirti veren ve L-2 HGA tanısı konulan 13 yaşında bir erkek hastadan bahsedilmiş olup nadir görülen bu hastalığa eşlik eden DEHB semptomlarına atomoksetin tedavi yanıtı tartışılmıştır.

Anahtar kelimeler: Atomoksetin, dikkat eksikliği hiperaktivite bozukluğu, L-2-hidroksi glutarik asidüri



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INTRODUCTION

L-2-hydroxy glutaric aciduria (L-2 HGA) which is a rare, slowly progressing metabolic disease with autosomal recessive inheritance, and was first defined in 1980 by Duran et al. (1). Clinical picture consists of

psychomotor developmental and mental retardation, cerebellar signs, and extrapyramidal signs due to involvement of basal ganglions, and seizures (2). Diagnosis is made by cranial imaging signs, and increased L-2-hydroxy glutaric acid levels in serum, urine or cerebrospinal fluid (CSF) accompanied by

clinical signs (3). Although patients may show clinical signs in neonatal and early adolescent periods, majority of them are diagnosed in late childhood. The main specifically involved areas of brain are basal ganglions (putamen, caudate nucleus, and globus pallidus) and dentate nucleus. Besides, subcortical white matter involvement and cerebellar involvement might be observed (3). Differently from other organic acidurias, acute metabolic attacks are not seen, and brain damage is unrelated to acidosis or electrolyte inequilibrium (4). Clinically, mild psychomotor developmental retardation is observed within first years of life, and then progressive cerebellar ataxia, dysarthria, and retardations in cognitive functions are seen. Additional signs such as pyramidal and extrapyramidal signs, afebrile seizure, macrocephaly, and cessation of development may be added to the picture. Psychiatric pictures such as behavioral changes, hyperactivity, attention and learning problems may be encountered before neurological signs (5,6).

In this article, an adolescent who had first attention and learning problem at preschool age and evaluated by a child-adolescent psychiatrist, and then referred to pediatric neurology clinic where he was diagnosed with L-2 HGA, was presented.

CASE

A 13-year old boy was brought to our outpatient clinic due to his "learning and attention problems". In his history, it was learned that he was being followed up for attention deficit and hyperactivity disorder (ADHD) for 5 years at an external healthcare unit, and he received drug therapy. As it was difficult for the family to attend control visits which were outside the city, and due to easy transportation, he was referred to our outpatient clinic. In his developmental history, he was born as the first child of the family at term without any problems during the pregnancy by normal spontaneous route. His birth weight was 2500g, and walked when he was 1.5 years old; he started to talk approximately at 2 years of age. Until 5 years of age, he had no childhood problems except some occasions when his parents applied to a pediatrician for his

developmental and growth retardation. In his family history, his parents were alive and healthy, there was no consanguinity in the family, and the patient had two healthy brothers.

The patient had afebrile convulsions when he was 5 years of age, and he had seizure episodes six times during that time period, and he was treated and his follow-up was continued by a pediatrician. The patient started preschool day nursery when he was 6 years of age, and his teachers referred him to a rehabilitation research center because of learning and attention problems. The patient was referred to a child and adolescent psychiatrist from the rehabilitation center, where he was diagnosed with "ADHD and mild mental retardation", and treatment was started with risperidone 1mg/day and short acting methylphenidate 20mg/day. As he was observed to have difficulties in language, coarse and fine motor activities, such as walking and talking, holding a pencil, during the first application, he was referred to Pediatric Neurology Unit for further evaluation. The evaluation was reported as normal findings in cranial nerve and sensory examination, moderate loss of strength in lower and upper extremities accompanied by dystonia, his tendon reflexes were normoactive and symmetrical; it was difficult for him to perform heel and step gait; he had a wide-based and ataxic gait; and dysarthric speech, intentional tremor, dysmetria, and dysdiadokinesia were diagnosed in his cerebellar examination. Biochemical parameters and thyroid functions which were tested for differential diagnosis of neurometabolic diseases were all normal. In sleep-awake EEG evaluation, signs which were consistent with diffuse cerebral dysfunction and epileptic activity were determined. Periventricular hypodensity was determined in cranial CT, whereas diffusely increased signaling was determined bilaterally in cerebral deep white matter and subcortical U fibers. In the urine organic acid examination, 10 folds increased 2-OH glutaric acid and 2-OH glutarate lactone excretions were determined. The patient diagnosed with "L-2-hydroxy glutaric aciduria" was given riboflavin, L-carnitine, and Na valproate was started for epileptic seizures. During the follow-up of Pediatric Neurology,

the latest treatment schedule was levetiracetam and lamotrigine, and the patient had no seizure with two antiepileptics for about 5 years. In cranial MRI performed to control the risk of brain tumor, marked involvements were detected in basal ganglion, dentate nucleus, and cerebellum, so riboflavin and L-carnitine treatments have been regularly continued.

In psychiatric evaluation at application to our clinic, it was determined that his cognitive abilities were retarded when compared with his peers; he had dysarthric speech; there was no problem with the thought content; his affect was euthymic, and when it was evaluated according to intelligence level of the patient, he had more than expected and marked attention problems. His history and psychiatric examination were consistent with ADHD and mild mental retardation diagnoses. According to Clinical Global Impressions (CGI) scale, the patient received 5 points, and he received 22 points according to Attention Subtest of Tugay Disruptive Behavior Disorders Symptom Screening Scale. It was diagnosed at the application that the patient did not benefit from methylphenidate 20mg/day and risperidone 1mg/day, so the treatment was tapered down and switched to atomoxetine 18mg/day, and according to the clinical response atomoxetine dose was increased to 40mg/day gradually during the follow-up. Clinically, the patient benefitted markedly from the treatment, and his last evaluation was 3 (mildly diseased) points in CGI, and 13 points in Attention Subtest of Tugay Disruptive Behavior Disorders Symptom Screening Scale. Our patient has gained reading and writing abilities in the last one year, and he is attending at formal education with special training, special subclass of 6th grade.

DISCUSSION

In this article, atomoxetine treatment and treatment response in an adolescent with L-2 HGA, and accompanying ADHD and mild mental retardation were presented. It was decided that the case was noteworthy to present, because L-2 HGA was late diagnosed and encountered rarely; there were concomitant attention and learning problems at disease

initiation; patient did not benefit from former treatment of methylphenidate and risperidone, whereas responded to atomoxetine treatment. Clinical progression and signs of our patient were consistent with diagnosis of L-2 HGA. Our case was definitely diagnosed nearly 2 years after initiation of afebrile seizures, the first symptoms were encountered as learning problems due to cognitive function loss before diagnosis, attention deficit signs, and behavioral changes. In the literature, it was also reported consistently with our case that some psychiatric sign such as behavioral changes, excessive talking, hyperactivity, attention and learning problems before the disease initiation might be observed, and these symptoms might be only noticeable presenting symptoms of the disease (7,2).

In our clinical evaluation, attention problems were more prominent than irritability and behavioral problems in our case. As he responded partially to the treatment and had epileptic seizure risk, the previous treatment methylphenidate and risperidone was switched to atomoxetine, and the dose was increased gradually according to the clinical response. In the evolution performed before and after approximately 1-year's follow-up, it was noted that our patient markedly benefitted from atomoxetine treatment, and it was decided to continue treatment with atomoxetine. Atomoxetine is one of the first line agents used in ADHD treatment, and it is an effective option in patients who do not benefit from methylphenidate sufficiently or who have risky conditions such as seizures (8). In our patient, as methylphenidate response to attention and learning problems was insufficient, treatment was switched to atomoxetine, and marked clinical improvement was observed.

L-2 HGA is a neurometabolic picture which is slowly progressing, so it is lately diagnosed. It presents itself by learning problems, attention problems, and behavioral changes, and as in our case, patients may be sometimes evaluated by a child and adolescent psychiatrist (7). After a normal clinical developmental period, if excessive activity, behavioral changes, learning and attention problems are observed in a patient after a certain age before or concomitantly with

neurological symptoms, such as seen in L-2 HGA, an underlying organic cause should be considered, and these patients should be referred to a pediatric neurologist for detailed investigations for neurological symptoms. Although there is no specific treatment for L-2 HGA after the diagnosis, careful follow-up of neurological symptoms and signs related to involvement of central nervous system (for a possible brain tumor development), and seizure control should be performed. As it has been performed in our case, it is considered significant to determine underlying causes for learning and attention problems in these patients, so that the most appropriate treatment can be

given with the least risk, and both child and the parents are informed correctly which will help them to cope with the disease and increase their adaptation abilities.

| Contribution Categories | Name of Author |
|--------------------------------|----------------|
| Follow up of the case | C.Y. |
| Literature review | C.Y. |
| Manuscript writing | C.Y. |
| Manuscript review and revision | A.T. |

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