A Case of Carbonic Anhydrase Type 2 Deficiency Syndrome with Autistic Disorder

Karbonik Anhidraz Tip 2 Eksikliği Sendromu ve Otistik Bozukluk

Birim Günay KILIÇ, Çağatay UĞUR, Nagihan SADAY DUMAN, Melda AKÇAKIN

Department of Child and Adolescent Psychiatry, Ankara University Faculty of Medicine, Ankara, Turkey

ABSTRACT

Carbonic Anhydrase Type II Deficiency Syndrome (CADS) is a disease with an autosomal recessive inheritance that mainly includes characteristics of osteopetrosis, renal tubular acidosis and cerebral calcification. Pathological fractures, poor vision due to cranial nerve pressure, wide forehead, disproportionate mouth and jaw, physical and mental developmental delay are other features. In this paper, we present the case of a patient who was referred to our department with a diagnosis of CADS and diagnosed with autistic disorder after a psychiatric evaluation. We performed a detailed literature search, however, we did not find any report of co-existence of CADS (osteopetrosis intermediate type) and autistic disorder. (*Archives of Neuropsychiatry 2014; 51: 172-174*)

Key words: Carbonic anhydrase type II deficiency syndrome, autism, osteopetrosis

Conflict of Interest: The authors reported no conflict of interest related to this article.

ÖZET

Karbonik Anhidraz Tip II Eksikliği Sendromu (CADS); osteopetrozis, renal tübüler asidoz ve serebral kalsifikasyon temel özelliklerini içeren otozomal resesif (OR) geçişli bir hastalıktır. Bunların dışında patolojik kırıklar, kranial sinir basısına bağlı olarak görme azlığı, geniş alın, ağız ve çene yapısında orantısızlık, fiziksel ve zihinsel gelişme geriliği bulunmaktadır. Bu yazıda CADS tanısı ile kliniğimize yönlendirilen ve yapılan psikiyatrik değerlendirme sonrasında otistik bozukluk tanısı konulan bir olgu sunulmuştur. Yazında yapılan ayrıntılı tarama sonucunda karbonik anhidraz II eksikliği sendromu (osteopetrozis intermediate tip) ve otistik bozukluk birlikteliğine ilişkin herhangi bir bildiriye rastlanmamıştır. (*Archives of Neuropsychiatry 2014; 51: 172-174*)

Anahtar kelimeler: Karbonik anhidraz II eksikliği sendromu, otizm, osteopetrozis

Çıkar Çatışması: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemişlerdir.

Introduction

Carbonic Anhydrase Type II Deficiency Syndrome (CADS) is a disease with an autosomal recessive inheritance that mainly includes characteristics of osteopetrosis, renal tubular acidosis and cerebral calcification (1). It is known as the intermediate form among the forms of osteopetrosis. It has a milder course compared to infantile malignant osteopetrosis and is observed with a lower rate. Generally, severe hematological findings related with osteopetrosis are not observed. Short and underdeveloped body structure, deformations in the mouth and jaw, growth retardation, pathological fractures, findings related with cranial nerve compression and mental retardation are found in CADS (2).

In most patients, proximal and distal renal tubular acidosis combinations are found. Bone marrow transplantation does not reverse metabolic acidosis and renal lesions (3).

Until the present time, about 23 structural gene mutations related with carbonic anhydrase type II enzyme have been found (4). It

has been reported that 65% of the patients reported are of Arabic origin and metabolic acidosis and mental retardation accompany clinically (2,5,6).

As a result of the assessments performed in the patient who had a diagnosis of osteopetrosis and who was referred to our clinic for evaluation in terms of difficulty in comprehension and delay in speech, psychiatric examination findings which could not be explained by cognitive retardation alone were found. As a result of psychiatric evaluations, the patient was diagnosed with "autistic disorder" which is included in the spectrum of "pervasive developmental disorder". Carbonic Anhydrase Type II Deficiency Syndrome has been found in 200 cases worldwide until the present time. Autism has been reported to have a prevalence of 20/10,000. Association of autism with many rare diseases has been demonstrated. Accidental association of these two disorders in one case was found to be notable in terms of etiological gene relation. Association of CA 2 enzyme deficiency syndrome with autistic disorder led to presentation of this case.

Correspondence Address

Dr. Birim Günay Kılıç, Ankara Üniversitesi Tıp Fakültesi, Çocuk ve Ergen Ruh Sağlığı Hastalıkları Anabilim Dalı, Ankara, Türkiye

Gsm: +90 506 619 64 67 E-mail: birimkiliç@yahoo.com Received: 30.04.2012 Accepted: 09.01.2013

©Copyright 2015 by Turkish Association of Neuropsychiatry / ©Telif Hakkı 2014 Türk Nöropsikiyatri Derneği

Case

A 6-year old male patient was referred for consultation to our clinic from the department of neurology with complaints of difficulty in understanding and comprehension, delay in speech and growth and developmental retardation.

The patient was the second of three boys of a 22-year old mother. He was born at term by normal vaginal delivery as the third living child from the fourth pregnancy of the mother. The mother's second pregnancy resulted with a preterm delivery at the 6.5th month and this baby was lost in the second month with an unknown reason. There was no familial history of similar disease. There was third-degree consanguinity between the mother and father.

It was learned that the patient was hospitalized for the objective of diagnosis and treatment for many times. The patient presented to pediatrics clinic at the age of 9 months for the first time because of complaints of inability to sit without support and chronic constipation. It was decided that he should be hospitalized as a result of the detailed investigations and clinical assessments in pediatrics clinic. Primary dysplastic changes were found in the bony structure on cranial magnetic resonance imaging (MRI). Calcifications were not observed on cranial computerized tomography (CT). Electroencephalogram (EEG) and echocardiogram (ECHO) were found to be normal. The blood pyruvate and lactate levels were found to be normal. In the laboratory tests, abnormalities were found in the electrolyte levels and blood acid-base balance. As a result of the investigations performed, a diagnosis of distal renal tubular acidosis was made at the age of 15 months and treatment was initiated.

Visual evoked potential (F-VEP) revealed prolongation in the latencies showing gradual increase and decreased vision in the right eye. Auditory evoked potential (BAER) was found to be normal bilaterally. Although electroneuromyography (ENMG) performed to investigate delay in walking and motor retardation revealed accidental distal myopathy, mitochondrial degenerative disease was not considered. Rectal biopsy which was performed because of chronic constipation revealed neuronal intestinal dysplasia and laxatives were added to treatment. As a result of detailed investigations and clinical evaluations, a diagnosis of Carbonic Anhydrase Type II Deficiency Syndrome was made.

Phenotypic features

On physical examination, flattened nasal bridge, prominent forehead and structural disorders in the teeth and jaw were found in the male patient who had blue eyes and light brown hair and who appeared younger than his age.

Developmental steps

When the gross motor development was evaluated, it was learned that he held his head high at the age of 10 months, sat without support at the age of 14 months and walked with support at the age of 2 years. It was stated that he spoke his first words at the age of one year and two-word sentences at the age of four years. He knew a limited number of words and made a limited number of sentences. He did not gain toilet training yet.

Clinical evaluation

The patient was brought to our clinic at the age of 6 years for the first time with complaints of delay in speech, inability to make sentences and difficulty in understanding. Physiatric evaluation revealed that he did not answer to his name consistently, under-

stood and carried out only simple commands and did not start a conversation spontaneously in addition to retardation in speech. It was found that his social communication and interaction was limited and he could not make contact with his peers. It was found that he did not play imaginative plays, his imitation talent was not developed and he had stereotypical movements including rocking by himself, clapping and whirling around. It was learned that he had much interest for whirling objects including washing machine and toy car wheels and he preferred non-living objects including tape recorder, cell phone and trash cover. It was found that he confused pronouns and sometimes squinted. It was learned that he played routinized plays including filling and depleting and he frequently bit his arm and had crying and temper tantrums.

Developmental assessment was made using Ankara Developmental Screening Inventory (ADSI) for the patient who had difficulty in making sentences and had a limited vocabulary and it was found that he had developmental retardation. The total score for general development was found to be 101 which approximately showed a development level of 20-21 months. His language-cognitive development score was found to be 33 which corresponded to 20-21 months. When his fine motor skills were examined, his score was found to be 18 which corresponded to a development level of 2 years- 2 year and 2 months. His score for gross motor skills was found to be 23 which corresponded to a development level of 3 years-3 year and 2 months. His score for social skills and self-care was found to be 27 which corresponded to a development level of 20-21 months. The Autism Assessment Form which screened the symptoms of "autistic disorder" according to the DSM-IV diagnostic criteria was applied to the patient (7). Besides, the Autism Behavior Checklist (ABC) form was applied and the patient scored 71 in this form which had a cutoff value of 39 (8).

A diagnosis of "autistic disorder" and "severe mental retardation" was made in the patient who was being followed up with a diagnosis of Carbonic Anhydrase Type II Deficiency Syndrome. A special education report was prepared to provide special education support. It was recommended that he should be supported with pre-school education so that he could communicate with his peers and develop self-care skills. Outpatient follow-up visits with certain intervals were planned.

On psychiatric evaluation performed one year later, it was found that his vocabulary expanded and could make a few sentences made up of two words, could look at the object indicated and could occasionally point out with his hand, though inconsistently.

Since gene mutations related with CADS have been reported in the literature and mental retardation is also found in these cases, gene analysis was planned in our case.

Discussion

Carbonic Anhydrase II which is a cytoplasmic enzyme is one of the 14 Carbonic Anhydrase isoenzymes known in humans (9). It is responsible in reversible reaction of carbondioxide, acid-base and fluid-electrolyte balance. In addition, it plays a role in provision of aqueous humor, gastric acidity, pancreatic enzyme secretion and cerebrospinal fluid. It participates in gluconeogenesis,

lipogenesis, urogenesis, bone resorption and calcification reactions in the metabolism (10).

CA II is involved in different biological processes in the central nervous system, but its function is still not known clearly. It is known that it is a glial enzyme and is found in oligodendrocytes (11). It has been reported that this enzyme is active in protection of membrane borders. It provides ionic balance in memory gain and remembering information (12,13). Proteins related with Carbonic Anhydrase enzyme have been found in fetal and adult astrocytes, neuron cell bodies and myelin sheaths (14). Mutations and deficiencies in these enzymes lead to retardation in neuron development and abnormal operation in neuron functions.

The main findings of Carbonic Anhydrase Type II Deficiency Syndrome (CADS) include renal tubular acidosis, cerebral calcification and osteopetrosis. In addition, pathological fractures, reduced vision related with compression on cranial nerve, wide forehead, disproportion in the mouth and jaw and physical and mental developmental retardation are found (15,16).

Autism is a neurodevelopmental disorder characterized with retardation and deviation in social relations, communication, behavioral and cognitive development starting in the early period and continuing for a life time.

Studies have shown that multiple genetic factors play a role among the causes of autism. Interactions between multiple genes lead to "idiopathic autism". No specific prenatal or perinatal cause which may lead to autism has been found.

Unless the genes causing to autism and the effects of these on brain development and physiology are determined, it would not be easy to find an efficient treatment method (17). Since autism is a disorder related with multiple genes, success can be obtained in prevention of transmission or treatment of the disorder with identification of any responsible gene (18).

This patient was diagnosed with autistic disorder because of presence of delayed speech, inconsistent answering to his name, lack of turning to an object pointed out, growth and developmental retardation, retardation in mental development, lack of reciprocity in social communication, stereotypical movements including clapping and whirling around. While our patient was being discussed, the literature was screened in detail, but no association of Carbonic Anhydrase Type II Deficiency Syndrome (CADS) and autistic disorder could be found.

Identified gene mutations have been found in 70% of the cases of osteopetrosis (19). The relation of chromosome 8q21,2 with CADS was found in gene analyses (MIM 259730). Cases in which gene mutations and mental retardation are found in association suggest that these mutations may also lead to retardation in mental development.

Carbonic Anhydrase Type II Deficiency Syndrome has been identified in 200 cases worldwide until the present time. The prevalence of autism has been reported to be 20/10,000. Association of autism with many rare diseases has been demonstrated. Association of these two disorders in one case was found to be notable in terms of etiological gene relation. Addressing many cases with different aspects with a multidisciplinary approach as in our case will make new studies full of hope and excitement gain importance in the future.

We think that genetic analyses in such cases will also elucidate the genetic etiology of autistic spectrum disorders.

References

1. Ohlsson A, Cumming WA, Paul A, Sly WS. Carbonic anhydrase II deficiency syndrome: Recessive osteopetrosis with renal tubular acidosis and cerebral calcification. *Pediatrics* 1986; 77:371-381.
2. Nagai R, Kooh SW, Balfe JW, Fenton T, Halperin ML. Renal tubular acidosis and osteopetrosis with carbonic anhydrase II deficiency: pathogenesis of impaired acidification. *Pediatr Nephrol* 1997; 11:633-636.
3. McMahon C, Will A, Hu P, Shah GN, Sly WS, Owen PS. Bone marrow transplantation corrects osteopetrosis in the carbonic anhydrase II deficiency syndrome. *Blood* 2001; 97:1947-1950.
4. Shah GN, Bonapace G, Hu PY, Strisciuglio P, Sly WS. Carbonic anhydrase II deficiency syndrome (osteopetrosis with renal tubular acidosis and brain calcifications): Novel mutations in CA2 identified by direct sequencing expand the opportunity for genotype-phenotype correlation. *Hum Mutat* 2004; 24:272.
5. Hu PY, Lim EJ, Ciccolella J, Strisciuglio P, Sly WS. Seven novel mutations in carbonic anhydrase II deficiency syndrome identified by SSCP and direct sequencing analysis. *Hum Mutat* 1997; 9:383-387.
6. Awad M, Al-Ashwal AA, Sakati N, Al-Abbad AA, Bin-Abbas BS. Long-term follow up of carbonic anhydrase II deficiency syndrome. *Saudi Med J* 2002; 23:25-29.
7. Akcakin M. Gender differences in autism. *J Child Adolescent Mental Health* 2002; 9:3-15.
8. Irmak YT, Sütçü TS, Aydın A, Sorias O. Autism Behavior Checklist (ABC) Validity and Investigation of Reliability. *J Child Adolescent Mental Health* 2007; 14:13-23.
9. Sly WS, Hewett-Emmett D, Whyte MP, Yu YS, Tashian RE. Carbonic anhydrase II deficiency identified as the primary defect in the autosomal recessive syndrome of osteopetrosis with renal tubular acidosis and cerebral calcification. *Proc Natl Acad Sci U S A* 1983; 80:2752-2756.
10. Pushkin A, Abuladze N, Gross E, Newman D, Tatishchev S, Lee I, Fedotoff O, Bondar G, Azimov R, Ngyuen M, Kurtz I. Molecular mechanism of kNBC1-carbonic anhydrase II interaction in proximal tubule cells. *J Physiol* 2004; 559:55-65.
11. Kumpulainen T, Nystrom SHM. *Brain Res* 1981; 220:220-225.
12. Sapirstein VS, Strocchi P, Gilbert JM. Properties and function of brain carbonic anhydrase. *Ann N Y Acad Sci* 1984; 429:481-493.
13. Sun MK, Alkon DL. Carbonic anhydrase gating of attention: memory therapy and enhancement. *Trends Pharmacol Sci* 2002; 23:83-89.
14. Taniuchi K, Nishimori I, Takeuchi T, Fujikawa-Adachi K, Ohtsuki Y, Onishi S. Developmental expression of carbonic anhydrase-related proteins VIII, X, and XI in the human brain. *Neuroscience* 2002; 112:93-99.
15. Jacquemin C, Mullaney P, Svedberg E. Marble brain syndrome: osteopetrosis, renal acidosis and calcification of the brain. *Neuroradiology* 1998; 40:662-663.
16. Whyte MP. Carbonic anhydrase II deficiency. *Clin Orthop Relat Res* 1993; 294:52-63.
17. Muhle R, Trentacoste SV, Rapin I. The genetics of autism. *Pediatrics* 2004; 113:472-486.
18. Cook EH. Genetics of autism. *Child Adolesc Psychiatr Clin N Am* 2001; 10:333-350.
19. Stark Z, Savarirayan R. Osteopetrosis. *Orphanet J Rare Dis* 2009; 4:5.