Aromatic L-amino acid decarboxylase deficiency: A new case from Turkey with a novel mutation

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Abstract

Aromatic L-amino acid decarboxylase (AADC), a vitamin B6-requiring enzyme that converts L-dopa to dopamine and 5-hydroxytryptophan to serotonin. Deficiency of this enzyme results in developmental delay, muscular hypotonia, dystonia, involuntary movements, autonomic dysfunction, and oculogyric crises. We now report a 2-year-old Turkish boy with AADC deficiency confirmed by greatly reduced AADC activity in the plasma and by genetic studies. Mutation analysis revealed a homozygous mutation c.208C > T (p. His70Tyr) in exon 3 of the AADC gene which has not been described to date.

Keywords: Aromatic L-amino acid decarboxylase deficiency, case report, novel mutation

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Introduction

Aromatic L-amino acid decarboxylase (AADC) is a vitamin B6-requiring enzyme that converts L-dopa to dopamine and 5-hydroxytryptophan to serotonin. Deficiency of this enzyme results in developmental delay, muscular hypotonia, dystonia, involuntary movements, autonomic dysfunction, and oculogyric crises. We now report a 2-year-old Turkish boy with AADC deficiency confirmed by greatly reduced AADC activity in the plasma and by genetic studies.

Case Report

A 2-year-old male was born as the second child of healthy nonconsanguineous Turkish parents at term after an uncomplicated pregnancy and delivery. From the age of 4 months truncal muscular hypotonia, limb hypertonia, and irritability were noted by his caregivers. Physical examination showed weight loss (7.3 kg, below the third centile), length 65 cm (below the third centile), and head circumference 43 cm (below third percentile). A neurological examination revealed general hypotonia, exaggerated deep tendon reflexes with normal cranial nerve examination. He was not able to sit without assistance and did not grasp objects because of impaired eye-hand coordination. He also presented distinct extraneurological features such as hypersalivation, constipation, hyperhidrosis, and sleep disturbances. He had swallowing difficulty, recurrent vomiting and eventually evaluated for gastroesophageal reflux disease. Cranial magnetic resonance imaging, which performed because of involuntary non-epileptic dystonic movements resembling epileptic spasms, was normal. The patient had admitted several times with the complaints of dystonic movements which were interpreted as tonic epileptic movements and were given antiepileptic medications despite the existing multiple normal electroencephalography (EEG) recordings. After a careful history and reevaluation of the patient with the interpretation of the video recordings of so-called epileptic movements; patient's tonic seizure like movements were diagnosed as dystonic movements with the lateral deviation of eyes. Routine clinical investigations for inborn errors of metabolism were negative. The diagnosis of AADC deficiency was established at the age of 11 months, by screening of the cerebrospinal fluid (CSF) for neurotransmitter metabolites. Examination of a CSF sample showed a strikingly abnormal pattern of biogenic amine metabolites indicating AADC deficiency. The relevant biochemical findings were elevated concentrations of L-dopa, 3-O-methyldopa (3-OMD), and 5-hydroxytryptophan together with decreased CSF concentrations of homovanillic acid (HVA), 5-hydroxyindolicacetic acid (5-HIAA), and normal levels of 5-methyltetrahydrofolate (5MTHF) and pterins [Table 1]. Diagnosis was confirmed by measurement of AADC activity...
in plasma and found to be severely decreased as expected (AADC activity: <5 pmol/min/ml
and normal value: 33-79). The AADC gene mutation was analyzed and sequencing results
revealed a novel mutation in exon 3 of the AADC gene homozygous change c.208C > T (p.
His70Tyr) which renders the patient clinical phenotype resistant to therapies. Treatment with
a combination of the AADC cofactor pyridoxine and bromocriptine was started during the 1st
year of life and showed only a moderate clinical improvement as decreasing the severity and
duration of the dystonic episodes, but had no effect on the muscle tone and development. We
added monoamine oxidase (MAO) inhibitor, melatonin, and folic acid to drug regimes; but
showed no favorable response. He had not yet obtained head control or rolling over. He did
not suffer from hypoglycemia, hyperprolactinemia, and growth hormone deficiency.

Table 1: The laboratory findings of the patient

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Discussion

Aromatic L-AADC deficiency is a rare autosomal recessive congenital metabolic disorder of
neurotransmitter biosynthesis which is very intractable to treat. In general, most of the
signs and symptoms with AADC deficiency can be assigned to deficiencies of dopamine,
norepinephrine, epinephrine, and serotonin. In 1990, Hyland et al., diagnosed the first case of
AADC deficiency by screening CSF samples in patients with psychomotor retardation. Main clinical features are muscular hypotonia, dystonia, oculogyric crises, developmental
delay, and additional extraneurological symptoms. Onset of symptoms is typically in the first
months of life. Although almost all patients reported so far presented oculogyric crises,
current patient had not upward but lateral gaze deviation. It was difficult to discriminate
seizures from nonepileptic spasms. Brain imaging and EEG revealed normal findings in most
patients that are not helpful in diagnosing AADC deficiency. MRI findings that could be seen
in this disorder were atrophy, reduced myelination, and white matter changes. The
first step in reaching the diagnosis is the investigation of neurotransmitters in CSF. In addition
to typical pattern with a distinct reduction of HVA, 5-HIAA, and 3-OMD as well as an
elevation of levo-dopa and 5-hydroxytryptophan; endocrinological findings could be found,
for example, elevated prolactin, hypoglycemia, and growth hormone deficiency. In general,
most of the signs and symptoms described in patients with AADC deficiency can be assigned
to deficiencies of dopamine, norepinephrine, epinephrine, and serotonin. Drug therapy
aims at correcting the central and peripheral deficiency of serotonin and catecholamines.
Medical treatment is challenging and first choice medications appear to be dopamine agonists
in combination with pyridoxine and MAO inhibitors, anticholinergics, melatonin, and others
are thought in the second step. While some children have demonstrated some benefit, the
overall outcome is unsatisfactory. He was started on pyridoxine, pyridoxal phosphate, folic
acid, MAO inhibitor, and trihexyphenidyl; but without any clinical improvement. He was
extremely hypotonic, with no head control and never achieved verbal output and any
developmental milestones. As far as we now, the mutation that was found in this patient has
not been described earlier and unfortunately, the response to treatment was very poor.
Cerebrospinal fluid neurotransmitter metabolite profile remains a critical tool in identifying
patients with suspected neurotransmitter deficiency state. Treatment options are limited, in
many cases not beneficial, and prognosis is uncertain. In the literature, the majority of cases
showed no or poor response despite different protocols and a combination of different drugs.
From the clinical point of view in order to diagnose those patients as early and correctly as possible, a thorough evaluation in terms of medical history and physical and neurological examination should be done in order to rule out epileptic disorders. For now, we expect the development of new strategies and more effective treatments.

References


[Table 1]