Natural History of Aromatic L-Amino Acid Decarboxylase Deficiency in Taiwan

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Received: 20 May 2017 / Revised: 30 July 2017 / Accepted: 10 August 2017 / Published online: 31 August 2017
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Abstract Objectives: Aromatic L-amino acid decarboxylase (AADC) deficiency is a rare inherited disorder of monoamine neurotransmitter synthesis; this deficiency leads to psychomotor delay, hypotonia, oculogyric crises, dystonia, and extraneurological symptoms. This study aimed to provide further insight into the clinical course of AADC deficiency in Taiwan.

Patients and Methods: We present a retrospective, descriptive, single-center study of 37 children with a confirmed diagnosis of AADC deficiency. Their medical histories were reviewed for motor milestones, motor development, *DDC* mutation, and body weight. The termination point for each patient in this study was defined as no further follow-up, death, or enrollment in a gene therapy trial.

Results: The median age of the study patients at the end of the study was 4.39 years (1.28–11.30). Of the 37 patients, 36 did not develop full head control, sitting ability, standing ability, or speech at any time point from birth to the termination points. Motor scales were administered to 22 patients. Their Alberta Infant Motor Scale scores were below the fifth percentile, and their Peabody Developmental Motor Scales, Second Edition, scores were below the first percentile. Their body weights were normal in the first few months of life, but severe growth retardation occurred at later ages. The mutation c.714+4A>T (IVS6+4A>T) accounted for 76% of all their *DDC* mutations.

Conclusion: In this chapter, we report the clinical course of AADC deficiency in Taiwan. Our data will help guide the development of treatment strategies for the disease.

Introduction

Aromatic L-amino acid decarboxylase (AADC, EC 4.1.1.28) deficiency (MIM #608643) is a rare inherited disorder of neurotransmitter synthesis. AADC is responsible for the synthesis of dopamine and serotonin; furthermore, dopamine is the precursor of epinephrine and norepinephrine. AADC deficiency was first identified in 1990 by Hyland and Clayton through screening of cerebrospinal fluid (CSF) samples from children with unidentified neurologic disorders for identifying abnormalities in neurotransmitter metabolites (Hyland and Clayton 1990; Hyland et al. 1992). Currently, approximately 130 patients with AADC deficiency have been reported worldwide according to a recent summary from the International Working Group on Neurotransmitter Related Disorders (Wassenberg et al. 2017). The key symptoms include extreme hypotonia, hypokinesia, oculogyric crises (OGCs), and signs of autonomic dysfunction since early life. However, a few patients with mild or atypical manifestations have also been reported (Graziano et al. 2015; Kojima et al. 2016; Opladen et al. 2016; Spitz et al. 2017).

The prevalence of AADC deficiency is higher in the Chinese population because of the presence of the founder mutation c.714+4A>T (IVS6+4A>T) (Tay et al. 2007; Lee et al. 2009). We previously described the developmental milestones in 20 living patients carrying this prevalent mutation; all patients had typical symptoms of AADC deficiency, and all of them failed to achieve any develop-

Communicated by: Saskia Brigitte Wortmann, M.D., Ph.D.

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mental milestone despite receiving therapeutic combinations (Hwu et al. 2012). In this chapter, we provide the updated natural history data of 37 patients with AADC deficiency. Moreover, we provide additional information on genotypes, growth, motor developmental milestones, and motor scales to help guide the treatment of the disease in the future.

Methods

In this retrospective, descriptive, single-center study, we explored the natural history of patients who received a diagnosis of AADC deficiency at National Taiwan University Hospital (NTUH), particularly their growth and motor development. Their medical records were reviewed. All patients were followed up by the authors. The diagnoses of AADC deficiency were made based on the presence of a combination of clinical manifestations plus a characteristic CSF neurotransmitter or the presence of two pathogenic *DDC* mutations. The termination point for each patient in this study was defined as no further follow-up, death, or enrollment in a gene therapy trial. Some patients died at home, and the exact dates of death were not recorded in the medical records. Therefore, the age at death was not known and was excluded from analysis in this study. This study was approved by the Institutional Review Board of NTUH (201303100RIND).

The body weights of patients were retrieved from the medical records for every visit. Moreover, the ages at which the developmental milestones, namely head control, sitting ability, and standing ability, were achieved were obtained from medical histories. The scores in standard motor developmental scales, if performed, were also extracted. The scales used for evaluation included the Alberta Infant Motor Scale (AIMS) and Peabody Developmental Motor Scales, Second Edition (PDMS-2). The AIMS is an observational measure of infant motor performance and can be administered from birth to the age at which independent walking occurs (Darrach et al. 2014). It assesses the sequential development of motor milestones. The PDMS-2 is a skill-based measure of gross and fine motor development for infants and children, and it is administered from 6 months to 6 years of age; it consists of four gross motor and two fine motor subtests. Body weight at each visit was plotted according to age, with respect to the body weight distribution of normal female children (Chen and Chang 2010). The AIMS score was also plotted according to age, in comparison with the fifth percentile of normal children (Darrach et al. 2014).

Results

Demographic Data

Through medical history review, we identified 37 patients who received a diagnosis of AADC deficiency from 2004 to 2016 (Table 1). All patients presented with hypotonia, hypokinesia, and dystonia, and all but patient No. 37 had OGCs. Two *DDC* mutations were identified in 36 patients, and one mutation was identified in patient No. 37. All patients showed decreased CSF homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA) levels or elevated 3-*O*-methyldopa (3-OMD) levels in dried blood spots. The termination point for 15 patients was their latest visit, and the termination point for the remaining 22 patients was the last visit before entering a gene therapy trial. The median age of patients at the end of this study was 4.39 years (range: 1.28–11.30). The median age of patients at their first visit to NTUH was 1.10 years (range: 0–7.31), and the median follow-up period was 2.64 years (range: 0–9.34). Three patients (patient No. 10, 21, and 25) were diagnosed through newborn screening; therefore, they visited NTUH shortly after birth. Other patients were referred to NUTH for undiagnosed neurological conditions or for treatment or a second opinion after the diagnosis of AADC deficiency. All patients were ethnically Chinese, except that the ethnicity of patient No. 8 was found to be one-half Caucasian, one-quarter Chinese, and one-quarter Thai.

Mutations

The sequence status of the *DDC* gene was available for all 37 patients. For all patients, *DDC* mutations were detected using Sanger sequencing. The most common mutation IVS6+4A>T represented 76% of all *DDC* mutations (56 of 74 mutated chromosomes), followed by c.1297dupA (p. I433Nfs*60) (5 of 74 mutated chromosomes or 6.8%) and c.1234C>T (p.R412W) (3 of 74 mutated chromosomes or 4.0%). Other mutations included one small deletion and eight rare mutations. Only one mutation was found in patient No. 37 after Sanger sequencing of all *DDC* exons and exon–intron borders. However, for this patient, the results of biochemical analyses were compatible with the diagnosis of AADC deficiency: decreased CSF HVA level of 54.4 nmol/L (normal range: 97–367), decreased 5-HIAA level of 229.0 nmol/L (normal range: 236–867), and increased 3-OMD level of 809.1 nmol/L (normal level <50) in dried blood spots.

Table 1 Demographic data, mutation, and motor development of patients with AADC deficiency in Taiwan

	Sex	Termination point	First visit	Mutation 1	Mutation 2	AIMS	PDMS-2	Development
1	F	6.17	0.91	C.714+4A>T	C.714+4A>T	1	12	—
2	M	7.58	0.48	C.714+4A>T	C.714+4A>T	2	4	—
3	F	8.42	0.85	C.714+4A>T	C.714+4A>T	1	8	—
4	M	2.42	0.84	C.714+4A>T	c.1058T>C (p.L353P)	1	4	—
5	M	2.58	0.87	C.714+4A>T	C.714+4A>T	1	15	—
6	F	6.42	0.98	C.714+4A>T	c.1297dupA (p. I433Nfs*60)	2	14	—
7	M	2.58	1.98	C.714+4A>T	c.179T>C (p.V60A)	2	10	—
8 ^a	F	2.83	2.72	C.714+4A>T	c.286G>A (p.G96R)	1	6	—
9	M	2.08	0.63	C.714+4A>T	C.714+4A>T	1	10	—
10	F	1.67	0.03	C.714+4A>T	C.714+4A>T	4	12	—
11	F	4.25	0.43	C.714+4A>T	C.714+4A>T	0	3	—
12	M	4.42	1.26	C.714+4A>T	C.714+4A>T	0	8	—
13	F	4.50	1.52	C.714+4A>T	C.714+4A>T	0	6	—
14	F	6.17	1.10	C.714+4A>T	c.1297dupA (p. I433Nfs*60)	0	2	—
15	M	2.00	0.00	C.714+4A>T	C.714+4A>T	3	16	—
16	F	2.67	0.31	C.714+4A>T	C.714+4A>T	1	7	—
17	M	6.58	2.42	C.714+4A>T	C.714+4A>T	4	12	—
18	F	8.25	7.31	C.714+4A>T	C.714+4A>T	5	16	—
19	M	5.79	0.75	C.714+4A>T	c.1234C>T (p.R412W)	2	11	—
20	M	4.13	3.75	C.714+4A>T	c.304G>A (p.G102S)	8	26	—
21	M	1.63	0.00	C.714+4A>T	C.714+4A>T	1	8	—
22	F	3.42	0.78	C.714+4A>T	C.714+4A>T	2	7	—
23	M	1.28	0.80	C.714+4A>T	C.714+4A>T			—
24	M	2.27	0.67	C.714+4A>T	c.1234C>T (p.R412W)			—
25	M	1.51	0.03	C.714+4A>T	C.714+4A>T			—
26	F	6.08	3.41	c.1297dupA (p. I433Nfs*60)	c.1234C>T (p.R412W)			—
27	F	5.63	2.47	C.714+4A>T	C.714+4A>T			—
28	F	4.03	1.26	C.714+4A>T	C.714+4A>T			—
29	M	7.30	1.91	c.1297dupA (p. I433Nfs*60)	c.436G>C (p.G146R)			—
30	M	6.05	0.43	C.714+4A>T	C.714+4A>T			—
31	F	3.58	3.58	C.714+4A>T	c.1297dupA (p. I433Nfs*60)			—
32	M	11.30	1.96	C.714+4A>T	c.236A>G (p.Y79C)			—
33	F	5.50	2.29	C.714+4A>T	c.179T>C (p.V60A)			—
34	F	4.39	4.39	C.714+4A>T	c.848A>C (E283A)			—
35	M	6.22	4.69	C.714+4A>T	c.58_60delTAC (p.Y20del)			—
36	M	10.62	6.71	C.714+4A>T	C.714+4A>T			—
37	M	4.08	1.63	C.714+4A>T	?			H, Sit, St

Reference sequence: NM_000790.3. c.714+4A>T mutation is also called IVS6+4A>T

— did not achieve any milestones, *H* head control, *Sit* sitting without support, *St* standing without support, *W* walking without support^a Ethnicity: one-half Caucasian, one-quarter Chinese, and one-quarter Thai

Growth

The body weights of patients with AADC deficiency were within normal ranges in the first few months of life (Fig. 1). Their growth began to slow down at the end of the first year, and their weight gain was minimal between 1 and 4 years of age, although all of them were treated with a combination of pyridoxine, dopamine agonists, and monoamine oxidase inhibitors. Body weight improved in three patients who survived for more than 4 years, although their weight was still below the 50th percentile. Body weight did not improve in the remaining patients, although some of them received nutrition through a nasogastric tube or gastrostomy feeding. Patient No. 37 was diagnosed at the age of 1.67 years; at that time, the patient could sit and stand but not walk. After treatment with a dopamine agonist (through the rotigotine transdermal system) and pyridoxine, the patient gained weight normally (indicated by the arrow in Fig. 1). At 6.1 years of age, the patient was able to walk freely and spoke slowly but clearly. The patient had one allele carrying the IVS6+4A>T mutation, but a mutation in the second allele was not found. The undetected mutation is likely located in the promoter, regulatory elements, or introns of the allele and is probably less harmful than the

IVS6+4A>T mutation. Patient No. 37 was the only child with AADC deficiency who developed any one of the objective motor milestones of head control, sitting ability, and standing ability.

Motor Development

With the exception of patient No. 37, all patients had profound motor deficits consistent with severe AADC deficiency (Wassenberg et al. 2017). None of these 36 patients had full head control, defined by the ability to hold their head upright in the sitting position, at their termination point in the study. None of them could sit, stand, or speak. None of these patients showed improvements in developmental milestones before their termination point in the study; that is, they did not gain any motor skills at any point during their lives.

AIMS and PDMS-2 scores were available for 22 patients at their termination points when they entered a clinical trial. Their median total raw score for the AIMS was 1 (range: 0–8), and their scores were far below the fifth percentile of normal infants aged 0–18 months (Fig. 2). Their median total raw score for the PDMS-2 was 9 (range: 2–26), and their scores were below the first percentile of normal

Fig. 1 Body weight of 37 patients with AADC deficiency. Body weight at each visit was plotted according to age, in comparison with the body weight distribution of normal Taiwanese female children

(Chen and Chang 2010). Each line represents one patient. One outlier (patient No. 37), who had significantly greater growth than other patients, is indicated by the red arrow

children of the same age. Their AIMS scores were strongly correlated with PDMS-2 scores [correlation coefficient (C.C.) = 0.692, $p < 0.05$, Spearman's rho test]. No correlation was observed between age and raw AIMS or PDMS-2 scores (AIMS: C.C. = 0.035, $p = 0.876$; PDMS-2: C.C. = -0.042 , $p = 0.852$), because these 22 patients had virtually no gross motor development.

Discussion

In the past few years, many patients with AADC deficiency in Taiwan visited NTUH to participate in an ongoing gene therapy trial that started in 2010 (Hwu et al. 2012). A few patients were from other countries, but most of them were, at least in part, ethnically Chinese. This provided a unique opportunity to study the natural history of AADC deficiency in the Chinese population. In this study, we collected the data of a total of 37 patients, a relatively large number in one region in comparison with a global registry of 130 patients described by Wassenberg et al. (2017). In addition to the IVS6+4A>T mutation, which represented 76% of all *DDC* mutations, other recurrent mutations included c.1297dupA and p.R412W, both of which are severe mutations according to the phenotypes of patients. The allele frequency of IVS6+4A>T was found to be 0.34% in Taiwan (Chien et al. 2016). We recently saw two patients from China (who were not included in the present study); one had the genotype of homozygous IVS6+4A>T, and the other had the genotype of IVS6+4A>T/p.R412W. Because most of the Taiwanese population came from southern China, it is likely that the incidence of AADC deficiency is also high in southern China and in the Chinese population

in southeastern Asia who also came from southern China. Because of the high allele frequency of IVS6+4A>T and other severe mutations, most of our patients (36 of 37) had profound motor deficits.

Motor dysfunction is a significant component of AADC deficiency. In the present study, 36 of 37 patients did not develop full head control, sitting ability, standing ability, or speech. None of them showed improvements in these developmental milestones or gained any motor skills at any point during their lives. The study also evaluated AIMS and PDMS-2 scores that were available for 22 patients. These scores provided evidence that confirmed the lack of motor development in these patients. Typically, AIMS and PDMS-2 scores increase with age in normal children. However, the scores did not increase with age in our patients with AADC deficiency (Fig. 2). We also obtained evidence that the disease led to severe growth retardation in these patients. Regardless of disease severity, patients with AADC deficiency appeared normal at birth. However, when symptoms appeared, their growth slowed, and most of these patients ceased to gain weight after 1 year of age (Fig. 1). Motor dysfunction impaired patients' feeding and chest hygiene. Moreover, autonomic dysfunction, gastroesophageal reflux, and laryngomalacia affected the general health of these patients.

It may not be feasible to conduct controlled clinical trials for rare and rapidly fatal diseases because of the small case number and the ethical considerations involved in enrolling a placebo arm. Under such conditions, the outcome from clinical trials for rare diseases may be compared to the natural history of the diseases. Therefore, the data from the present study are critical to guide the development of treatment strategies for the disease.

Fig. 2 AIMS scores of 22 patients with AADC deficiency. Data from patients (blue diamond) are depicted according to the age at the time of measurement. The red diamonds indicate the fifth percentile and the

green diamonds indicate the 50th percentile of normal children (Darrah et al. 2014)

Synopsis

Patients with severe aromatic L-amino acid decarboxylase deficiency, which is more prevalent in Taiwan, present with profound motor dysfunction and failure to gain weight.

Contributions of Individual Authors

Wuh-Liang Hwu: study design, patient care, and writing.

Yin-Hsiu Chien: patient care and writing.

Ni-Chung Lee: patient care.

Mei-Hsin Li: patient care assistant.

Conflict of Interest

Wuh-Liang Hwu received research grants from Agilis Biotherapeutics, USA.

Funding

Research fund for AADC deficiency, National Taiwan University Hospital.

Ethics Approval

This long-term follow-up study for AADC deficiency was approved by the Institutional Review Board of National Taiwan University Hospital (201303100RIND). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients before participation in the study.

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