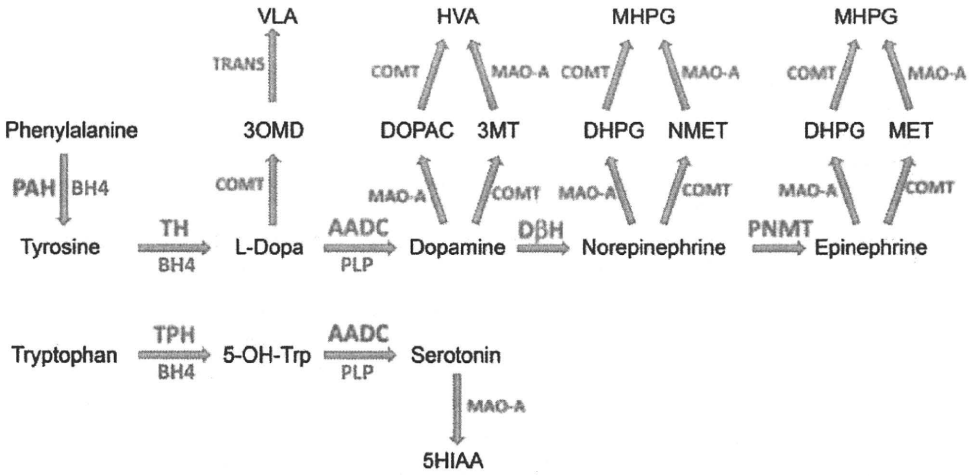
Figure 1 **Biosynthesis and metabolism of catecholamines and serotonin**



Enzymes and abbreviations: AADC = aromatic L-amino acid decarboxylase; COMT = catechol-*O*-methyltransferase; DβH = dopamine-β-hydroxylase; MAO-A = monoamine oxidase A; PAH = phenylalanine-4-hydroxylase; PNMT = phenylethanolamine *N*-methyltransferase; TH = tyrosine-3-hydroxylase; TPH = tryptophan-5-hydroxylase; TRANS = transaminase. Reactions catalyzed by MAO-A are coupled with an additional step catalyzed by either aldehyde or aldose dehydrogenase (catabolism of dopamine and serotonin; not shown) or aldehyde or aldose reductase (catabolism of norepinephrine and epinephrine; not shown). Metabolites and abbreviations: 3MT = 3-methoxytryptamine; 3OMD = 3-*O*-methyldopa; 5-OH-Trp = 5-hydroxytryptophan; 5HIAA = 5-hydroxyindoleacetic acid; DHPG = 3,4-dihydroxyphenylglycol; DOPAC = 3,4-dihydroxyphenylacetic acid; HVA = homovanillic acid; L-dopa = 3,4-dihydroxyphenylalanine; MET = metanephrine; MHPG = 3-methoxy-4-hydroxyphenylglycol; NMET = normetanephrine; VLA = vanillactic acid. Cofactors and abbreviations: BH4 = tetrahydrobiopterin; PLP = pyridoxal phosphate.

of AADC (pyridoxine or PLP), catechol-*O*-methyltransferase inhibitor, precursors of dopamine and serotonin (L-dopa, 5-OH-Trp), folinic acid, and melatonin. Response to treatment varies, but in many cases the therapy shows no or little benefit.[13-22]

In this article, we summarize the biochemical and molecular findings and the course of the disease in 78 patients with AADC deficiency tabulated in the international JAKE database (http://www.biopku.org/BioPKU_Databases JAKE.asp).

METHODS Biochemical investigations. Neurotransmitter metabolites in CSF were investigated by high-performance liquid chromatography with electrochemical detection, with slight modifications in different laboratories, but essentially as described elsewhere.[23] VLA was investigated by a standard method for organic acids profile in urine.[23]

Standard protocol approvals, registrations, and patient consents. Written informed consent was obtained from all patients or their physicians who participated in this study. No approval was required from the regional ethical committees. All biochemical and clinical data were collected within the routine diagnostic procedures.

Case reports. The age at diagnosis ranged from 4 months to 24 years (median 3.9 years) and was available from 60 of 78 patients. Twenty patients were diagnosed at the Children's Hospital in Zürich.

A questionnaire with the following sections was distributed to physicians managing AADC-deficient patients: 1) general patient information, 2) birth information and laboratory tests, 3) clinical information with signs and symptoms and treatment protocols, 4) EEG/CT/MRI data, 5) DNA analysis, and 6) follow-up information. A written consensus was provided for all submitted data by physicians.

A literature search was conducted using MEDLINE (1990–August 2009) for the following key words: aromatic L-amino acid decarboxylase, monoamine decarboxylase, dopa decarboxylase, AADC, and DDC.

Detailed information on AADC-deficient patients is tabulated in the JAKE database (http://www.biopku.org). Clinical information is summarized in table 1, biochemical and molecular data in table e-2 on the *Neurology*® Web site at www.neurology.org, and therapy in table 2. Detailed information on DNA variations is available from the BIOMDB database (http://www.biopku.org). Most important information is included in the case reports (table e-1).

RESULTS Signs and symptoms. All patients showed symptoms typical for deficiency of catecholamines and serotonin. In 96% of them, symptoms became clinically evident during infancy (≤18 months) or during childhood (≤10 years). Only 6 patients were clinically conspicuous at adolescence or adulthood.

Almost all patients (95%) presented with muscular hypotonia. Episodes of oculogyric crises were doc-

Table 1 Most common signs and symptoms in patients with AADC deficiency

Symptoms[a]	%	All patients	Infancy, ≤18 mo	Childhood, ≤10 y	Adolescence, ≥11 y	Adulthood
Characteristic features						
Hypotonia	95	74/78	35/38	33/33	3/4	3/3
Oculogyric crises	86	67/78	33/38	28/33	3/4	3/3
Other neurologic signs						
Sweating	65	51/78	20/38	26/33	2/4	3/3
Developmental retardation	63	49/78	22/38	24/33	1/4	2/3
Dystonia	53	41/78	21/38	16/33	1/4	2/3
Hypertonia	44	35/78	14/38	18/33	1/4	2/3
Feeding/swallowing difficulties	42	33/78	17/38	16/33	0/4	0/3
Dysarthria/speech difficulties	41	32/78	9/38	20/33	1/4	2/3
Hypersalivation	41	32/78	12/38	17/33	1/4	2/3
Ptosis	39	30/78	18/38	10/33	2/4	0/3
Insomnia	37	29/78	11/38	17/33	1/4	0/3
Irritability	35	27/78	12/38	12/33	1/4	2/3
Hypokinesia	32	25/78	8/38	14/33	1/4	2/3
Nasal congestion	31	24/78	10/38	12/33	2/4	0/3
Temperature instability	29	23/78	12/38	9/33	1/4	1/3
Poor head control	28	22/78	10/38	9/33	2/4	1/3
Athetosis	27	20/78	8/38	11/33	0/4	1/3
Poor eye fixation	26	19/78	10/38	9/33	0/4	0/3
Chorea	22	17/78	7/38	9/33	1/4	0/3
Brain imaging						
Abnormal MRI	24	19/78				
Abnormal EEG	13	10/78				
Abnormal CT	6	5/78				

Abbreviation: AADC = aromatic L-amino acid decarboxylase.
[a] For the full list of signs and symptoms and description of radiologic findings, see table e-1 and online information in the JAKE database (http://www.biopku.org).

umented in 86% of patients at the time of investigation. Thus, oculogyric crises and hypotonia can be considered characteristic features of AADC deficiency (table 1). A total of 63% of the patients developed developmental retardation: mental or motor retardation or both. Additional autonomic symptoms such as excessive sweating or temperature instability occurred in 65% and 29% of the patients. Further, most frequent symptoms described were feeding or speech difficulties (42%) and movement disorders like athetosis (27%), chorea (22%), dystonia (53%), or hypokinesia (32%). Poor eye fixation was documented in 19 patients (26%), poor head control in 22 patients (28%), hypersalivation in 32 patients (41%), and hypertonia in 35 patients (44%). A total of 37% of the patients had insomnia and 35% had irritability. In 24 patients (31%), nasal congestion was reported, and in 30 patients (39%), ptosis was evident (table 1).

For more detailed information, see table e-1 or the JAKE database (http://www.biopku.org).

Biochemical investigations. The age at laboratory diagnosis varied from 4 months to 24 years (median 3.9 years). None of the patients was diagnosed in the neonatal period. The results of the CSF, plasma, and urine analyses at the time of diagnosis are shown in table e-2. All patients whose biochemical data are reported showed significantly reduced 5-hydroxyindoleacetic acid (5HIAA), homovanillic acid (HVA), and 3-methoxy-4-hydroxyphenylglycol (MHPG) levels in CSF together with elevations of 5-OH-Trp and 3-*O*-methyldopa (3OMD). In all patients in whom AADC activity in plasma was measured, it was always very low or not detectable. VLA elevation in urine was reported in a few cases and in some elevation was rather mild. L-dopa (3,4-dihydroxyphenylalanine) was, however, normal in 6 out of 78 patients. A typical pattern of CSF metabolites is summarized in figure 2.

Genotypes. We found a wide range of mutations and genotypes (table e-2 and figure e-1), and DNA analysis was available in 49 out of 78 patients. Out of 30 mutations described in the BIOMDB database, 24 different mutations were detected in patients from the JAKE database, of which 8 had not been described earlier (p.L38P, p.Y79C, p.A110Q, p.G123R, p.I42fs, c.876G>A, p.R412W, p.I433fs). In 3 patients (ID#36, ID#37, ID#48), mutations were found on 1 allele only. The substitution mutation in Intron 6, IVS6+4A>T, was by far the most common mutation (allele frequency 45%), followed by p.S250F (allele frequency 10%), p.G102S (allele frequency 8%), and p.R462P (allele frequency 6%). It is conspicuous that all patients with an IVS6+4A>T mutation are of Chinese or Taiwanese origin and 7 patients whose ethnic origin is not known are living in Taiwan. All the other mutations are presented with allele frequency of 1%–3%. The 3 most common genotypes are IVS6+4A>T/IVS6+4A>T (35%), p.S250F/p.S250F (6%), and p.G102S/p.G102S (4%).

Neuroimaging and EEG investigations. A total of 24% of patients showed an abnormal MRI, 13% an abnormal EEG, and 6% an abnormal CT (table 1). The patients with an abnormal EEG mostly showed slow or rapid activity or polyspikes. Patients with abnormal MRI or CT presented with cerebral atrophy, degenerative changes of the white matter, thinning of corpus callosum, prominent ventricular bodies, leukodystrophy-like pattern, or hypomyelination.

Treatment. Although a variety of medications have been used in patients with AADC deficiency, some therapeutic protocols are used more frequently and

Table 2 **Summary of the most frequently used medications in patients with AADC deficiency and recommended treatment modalities**

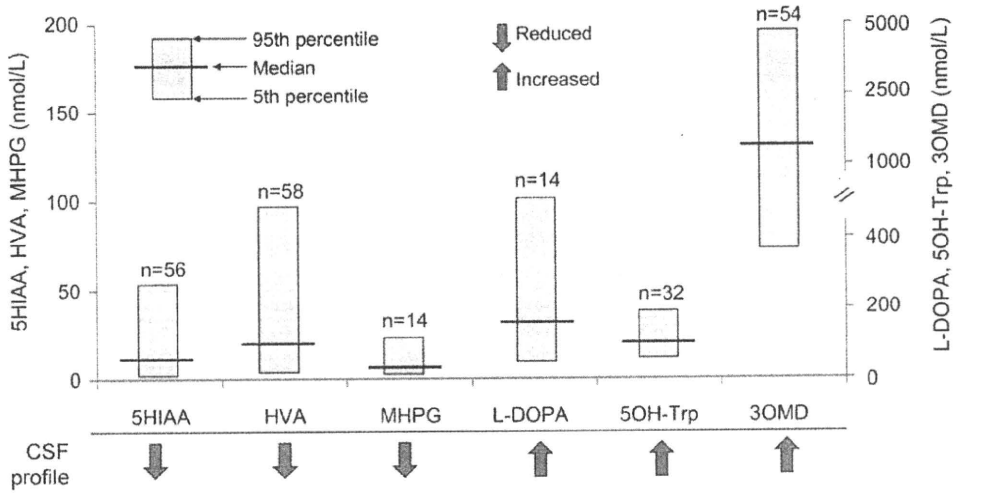
Medication	Dosage reported in JAKE database	No. of patients	%	Starting dosage,[a] mg/kg/d	Dose per day[a]	Maximal dosage,[a] mg/kg/d
Pyridoxine (B6)[b]	40–1,800 mg/d or 4.0–81 mg/kg/d	55/78	71	50	3	200
Bromocriptine[b]	1.0–45.5 mg/d or 0.013–4.0 mg/kg/d	38/78	49	0.25	3	0.5
Pergolide[b]	0.3–1.5 mg/d or 0.006–0.75 mg/kg/d	12/78	15	0.006	2–3	0.05
Selegiline	0.1–6.0 mg/d or 0.03–1.5 mg/kg/d	19/78	24	0.1	2–3	0.3
Tranylcypromide	1.5–54 mg/d or 0.4–0.5 mg/kg/d	22/78	28	0.1	2	0.5
Trihexyphenidyl	0.231–4.62 mg/d or 0.3–0.5 mg/kg/d	15/78	19	0.1	3	0.5
L-Dopa	400–2,250 mg/d or 11.2–54 mg/kg/d	10/78	13	1	3	15

Abbreviation: AADC = aromatic L-amino acid decarboxylase.
[a] Modified according to Hoffmann and Surtees.[30]
[b] Therapy is usually initiated with a combination of the low-dosage pyridoxine and one of the dopamine agonists (bromocriptine or pergolide). In a second step, monoamine oxidase inhibitor is added (e.g., selegiline). All other medications are added only if the initial treatment protocol fails to improve neurologic symptoms.

pyridoxine is the most common drug used (71% of patients). The dosage reported varied between 40 and 1,800 mg/day (4.0–81 mg/kg/day). Bromocriptine was used in 38 out of 78 patients, with a dosage of 1.0–45.5 mg/day (0.013–4.0 mg/kg/day), and tranylcypromide (1.5–54 mg/day or 0.4–0.5 mg/kg/day) and selegiline (0.03–1.5 mg/kg/day) were applied in 28% and 24% of patients. A total of 19% of patients had a therapeutic trial with trihexyphenidyl with dosages of 0.231–4.62 mg/day (0.3–0.5 mg/kg/day), 15% were tried on pergolide (0.3–1.5 mg/day or 0.006–0.75 mg/kg/day), and 13% of patients were treated with L-dopa (400–2,250 mg/day or 11.2–54 mg/kg/day). The majority of cases showed no or poor response despite different protocols and a combination of different drugs. Only 15 patients (nos. 10, 13, 14, 15, 26, 27, 45, 47, 53, 55, 56, 64, 66, 67, and 71) were reported with good or very good clinical benefit (improvement in at least 5 symptoms). Patients 1–3 have been previously described with favorable clinical benefit,[6] and 2 other patients (26 and 27) with an excellent response to MAO inhibitor and dopamine agonist therapy.[20] There was no significant difference between 2 groups (responder and nonresponder) with regard to biochemical and genetic data.

A total of 73 patients (96%) were clinically inconspicuous before the age of 10 years and most of them

Figure 2 **CSF metabolites**



CSF concentrations (median and 5th–95th percentile) of key neurotransmitter metabolites in patients with aromatic L-amino acid decarboxylase deficiency at the time of diagnosis. 3OMD = 3-O-methyldopa; 5HIAA = 5-hydroxyindoleacetic acid; 5OH-Trp = 5-hydroxytryptophan; HVA = homovanillic acid; L-dopa = 3,4-dihydroxyphenylalanine; MHPG = 3-methoxy-4-hydroxyphenylglycol. For reference ranges, see table e-2. These may differ between laboratories.

were started on medication immediately after diagnosis. Many of these patients also developed additional non-neurologic symptoms such as ptosis, excessive sweating, temperature instability, and nasal congestion (table 1).

DISCUSSION In this study, we documented clinical, biochemical, and molecular data of 78 patients with AADC deficiency, tabulated in the JAKE database of pediatric neurotransmitter disorders. A total of 32 cases have not been published previously. The clinical presentation of these new patients is in line with the clinical picture of AADC deficiency described in the literature.[2,5,6,18,24,25] The most frequent neurologic signs and symptoms were muscular hypotonia and oculogyric crises and approximately half of the patients showed movement disorders with hypokinesia, dystonia, athetosis, and chorea. While hypotonia is a rather nonspecific feature, oculogyric crises are typical for AADC-deficient patients and were not present or not reported at the age of investigation in only 11 patients.[14,25,26] Seven previously unreported cases (49, 52, 53, 60, 61, 63, and 74) also did not present with oculogyric crises at the age of investigation (5 months–11.5 years); however, it is possible that some of these patients will develop such episodes in the future, particularly since some of them were not on treatment. A total of 49 patients were reported with mental or motor retardation.

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. Dopamine is synthesized in substantia nigra, ventral tegmentum, and hypothalamus, and its deficiency affects voluntary movements, cognitive function, and emotion, but also hormonal-related functions. Norepinephrine and epinephrine deficiency affects attention, mood, sleep, cognition, and stress hormones, and disturbance in serotonin biosynthesis affects appetite, sleep, memory, learning, body temperature, mood, cardiovascular function, and endocrine functions. Consequently, AADC-deficient patients present with parkinsonism and dystonia, motor activity, and sleep problems (dopamine functions); autonomic dysfunction, temperature instability, and ptosis (norepinephrine and epinephrine function); and sleep disorders, memory and learning disability, and behavioral disturbance (serotonin functions).[27]

Brain imaging and EEG revealed normal findings in most patients. Ten patients had an abnormal EEG, mostly showing slow or rapid activity or polyspikes.[4,14,18,19,28] Five patients with an abnormal brain CT and 19 patients with an abnormal MRI presented with cerebral atrophy, degenerative changes of the white matter, thinning of corpus callosum, prominent ventricular bodies, leukodystrophy-like pattern, hypomyelination, or adult pattern of myelination.[2,14,19,22,25,28,29]

The clinical phenotype, although quite typical in classic patients, will hardly ever be recognized as AADC deficiency due to its rarity, physicians thus being unfamiliar with the disorder. In general, the results of biochemical investigations will point to AADC deficiency as the underlying cause in a child with a complex neurologic disorder. Laboratory protocol for the diagnosis of AADC deficiency includes investigation of metabolites of dopamine and serotonin (HVA, MHPG, L-dopa, 3OMD, 5-OH-Trp, and 5HIAA) in CSF,[8] AADC activity in plasma,[3] and organic acids (VLA) in urine.[19] Although measurement of VLA within the organic acids profile would be the most practical approach in the diagnosis of AADC deficiency, a number of patients who we investigated presented with only mildly elevated concentrations of urinary VLA (data not shown). Measurement of additional metabolites in urine such as vanilpyruvic acid and N-acetyl-vanilalanine, both metabolites of VLA, may increase the sensitivity of this approach.[19] Thus, CSF investigation of neurotransmitter metabolites is essential for the diagnosis. As shown in table e-2 and figure 2, all patients whose biochemical data are known presented with a typical pattern of metabolites in CSF, specifically reduced concentrations of HVA, 5HIAA, and MHPG, and an elevation of 3OMD, L-dopa, and 5-OH-Trp. L-dopa was reported as elevated in 40 out of 78 patients. In 32 patients, it was not measured (nos. 1, 9, 11, 12, 14, 16–20, 26–35, 48, 49, 58–63, 70, and 75–78), and in patients 13, 53, 69, and 71–73, it was normal. Some variability in the biochemical data could, however, relate to diurnal variation. If there is diurnal variation, then any correlation between treatment response and biochemical data could be obscured by this variation.

In 49 patients, mutation analysis of the *DDC* gene was performed. Different point mutations were identified; 8 mutations have not previously been reported in AADC-deficient patients (p.L38P, p.Y79C, p.A110Q, p.G123R, p.I42fs, c.876G>A, p.R412W, p.I433fs). With the exception of patients with Chinese origin with a common splice mutation IVS6+4A>T, most patients harbor private mutations spread out through the entire *DDC* gene (table e-2). There is no indication for a genotype–phenotype correlation.

The therapy is aimed at correcting the neurotransmitter abnormalities, especially those of serotonin and catecholamines. Unfortunately, a substitution therapy with neurotransmitter precursors L-dopa and 5-

hydroxytryptophan is not effective in nearly all AADC-deficient patients, as they cannot be further metabolized and in fact already circulate in enormous amounts. Nevertheless, 3 siblings responded dramatically to L-dopa. They carry a homozygous mutation affecting the binding of the substrate L-dopa to the enzyme.[5] Thus, treatment strategies are aiming either at an augmentation of residual AADC activity with pyridoxine and PLP or the use of MAO-B inhibitors and dopamine agonists are commonly used.

Patients received dopamine receptor agonists, anticholinergics, monoaminoxidase inhibitors, α-adrenergic agonists, selective serotonin reuptake inhibitors, cofactor of AADC (pyridoxine or PLP), catechol-*O*-methyltransferase inhibitors, precursors of dopamine and serotonin (L-dopa, 5-OH-Trp), L-dopa decarboxylase inhibitors, folinic acid, and melatonin. Other medications were used to lesser degree. The overall response to drug therapy was good in 15 patients, with unsatisfactory or no response in the other 63 patients. There may be a difference in response to treatment between male and female patients, as reported by Pons et al.[6] Ten out of the 15 patients with a satisfactory clinical benefit were male. However, more male than female patients were investigated. There were 41 male patients, 31 female patients, and 6 patients with unknown sex who took part in our study. The 15 patients with a good clinical response still have different symptoms that never completely resolved.

First-choice medications appear to be dopamine agonists such as bromocriptine or pergolide in combination with pyridoxine, and MAO inhibitors such as selegiline in the second step (table 2). Bromocriptine is usually given at a starting dosage of 0.25 mg/kg/day divided in 3 doses per day. Another dopamine agonist, pergolide, should be given at a very low starting dosage of 0.006 mg/kg/day twice a day. Beneficial effect of pergolide was described in patients with a severe neurotransmitter deficiency due to tetrahydrobiopterin deficiency. Alternatively to selegiline, tranylcypromine can be given in 1–3 doses a day at a dosage around 8 mg/day. The therapy with trihexyphenidyl should start at a dosage of 1–2 mg/kg 3 times daily. The dosage should then be increased by 1 or 2 mg/day each week until the child shows any improvement, the child develops side effects, or a limit of 10 mg/kg/day is reached. As alternative therapy, L-dopa may be given. L-dopa should be given 3 times a day at a dosage of $\leq$15 mg/kg/day. L-dopa should be increased in steps of not more than 1 mg/kg over days, weeks, or sometimes several months. It should be introduced slowly because of receptor hypersensitivity in early-diagnosed severe cases, and start at very low doses given up to 6 times a day. In late-diagnosed severe cases, patients maximally tolerate a dose of up to 10 mg/kg/day, which should be given for 6 months before deciding whether it is beneficial or not. Additional carbidopa treatment should be avoided, because of a possible deterioration of symptoms. Pyridoxine, precursor of the natural cofactor of AADC, should not be given at doses of >200 mg/kg/day.[30] Pyridoxine is first phosphorylated to pyridoxine 5′-phosphate and subsequently converted to PLP. There is evidence that an optimal level of PLP is important for AADC stability and that PLP may be required for the maintenance of AADC activity.[13]

Folinic acid substitution in AADC-deficient patients is recommended at a dosage of 10–20 mg/day because of possible cerebral folate depletion due to methylation of accumulated L-dopa.

Drug therapy in patients with AADC deficiency is a challenge and unfortunately there are still no good therapeutic strategies available. For many patients, the overall outcome is disappointing.

There is a new hope that AADC-deficient patients may benefit from gene therapy in the future. By delivering the human *DCC* gene into patients' cells,[13] this technique may stabilize expression of a functional AADC protein. Similar attempts are in progress for patients with Parkinson disease.[31] In a phase I safety trial, patients with moderate to advanced Parkinson disease received bilateral infusion of a low dose of the adeno-associated viral hAADC vector into the putamen. This gene therapy approach has been well-tolerated and shows evidence of sustained gene expression.

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Case report

Abnormal glucose metabolism in aromatic L-amino acid decarboxylase deficiency

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Abstract

We report sibling cases of aromatic L-amino acid decarboxylase (AADC) deficiency, which is a very rare congenital metabolic disorder. These patients were born to healthy and non-consanguineous parents, and presented oculogyric crises, paroxysmal dystonic attacks, and severe psychomotor retardation since early infancy. In cerebrospinal fluid the levels of homovanilic acid and 5-hydroxyindoleacetic acid were very low and the level of L-dopa was very high. The diagnosis was confirmed by the lack of AADC activity in plasma, and a point mutation in the *AADC* gene. MRI revealed a slightly small volume of the prefrontal areas and normal myelination in both patients. Positron emission tomography using 2-deoxy-2[^{18}F] fluoro-D-glucose was performed in one patient, which revealed hypometabolism in the prefrontal cortex and bilateral basal ganglia with a little laterality. These findings suggested that the severe dystonic features were caused by abnormal function of bilateral basal ganglia and severe psychomotor retardation could be due to abnormalities in prefrontal cortical activity.

Keywords: AADC deficiency; MRI; PET; Prefrontal cortex; Caudate nucleus

1. Introduction

Aromatic L-amino acid decarboxylase (AADC or dopa decarboxylase; DDC) deficiency (OMIM #608643) is an extremely rare congenital metabolic disorder and one of the infantile movement disorders, which is very intractable to treat [1–4]. Although less than 100 cases have been reported worldwide [1–8], a relatively high occurrence rate was reported in Taiwan [7]. AADC converts L-dopa to dopamine and 5-hydroxy tryptophan to serotonin, and its deficiency results in the depletion of both dopamine and serotonin in the brain. As a consequence, several characteristic symptoms are caused.

We experienced sibling cases of AADC deficiency, confirmed by enzymatic and genetic analysis. We report magnetic resonance imaging (MRI) findings in both cases, and positron emission tomography (PET) using 2-deoxy-2[^{18}F] fluoro-D-glucose (FDG) between dystonic attacks was performed in patient 1.

2. Case reports

2.1. Patient 1

This 3-year-old boy was born to healthy and unrelated parents with mild asphyxia at full term. He cried

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Table 1
The concentration of catecholamine of the CSF.

	L-Dopa	HVA	MHPG	5-HIAA
Patient 1	13.6	5.7	<1.0	<1.0
Patient 2	27.4	12.2	<1.0	<1.0
Normal range	<2.0(ng/ml)	28–200(ng/ml)	6.5–51(ng/ml)	17–116(ng/ml)

HVA, homovanillic acid; MHPG, 3-methoxy-4-hydroxy-phenylglycol; 5HIAA, 5-hydroxyindoleacetic acid.

weakly, was motion-less since birth, and needed tube feeding for 1 week. He first showed oculogyric crisis at 3 months of age, and had similar attacks several times a week. Oculogyric crisis usually lasted about 30 min. He also suffered from generalized dystonic attacks for 30–120 min several times a week. Opisthotonus or bicycle-riding movements were observed during these attacks. He showed visual pursuit at 6 months of age, but had not yet obtained head control or rolling over. He had a severe intellectual and motor developmental delay. He was always nasally congested and his face was frequently running with sweat during wakefulness.

A neurological examination between dystonic attacks revealed general hypotonia, paucity of movement, slightly exaggerated deep tendon reflexes and pathological reflexes. Eye movement was normal. Ordinary blood analyses were normal. An electroencephalogram (EEG) showed no paroxysmal discharges during either dystonic attacks or inter-

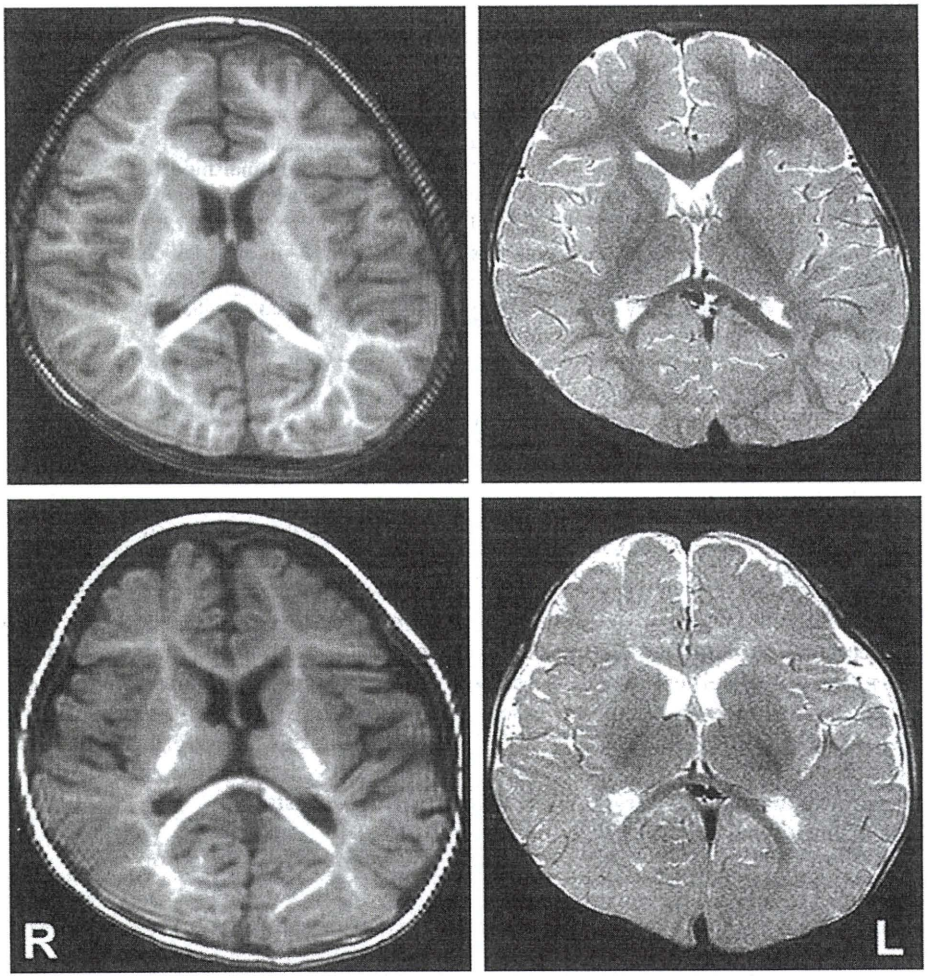

Fig. 1. Axial T1-weighted (left) and T2-weighted (right) MRI at the level of the putamen. Upper row is patient 1 and lower row is patient 2. MRI shows a slightly small volume of the prefrontal areas in both patients. The volumes of basal ganglia and brain cortex are normal, and myelination is also normal. No abnormal intensity areas are seen.

mittent states. A catecholamine analysis of the cerebrospinal fluid (CSF) revealed a very high concentration of L-dopa and a very low concentration of homovanilic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA) (Table 1). These results strongly suggested AADC deficiency.

2.2. Patient 2

This 6-month-old girl was the younger sister of patient 1. She was born healthy with no adverse events. She also showed oculogyric crisis since 1 month of age, and paroxysmal general hypertonia lasting for a few hours since 3 months of age but she was alert during the attack. She had not yet obtained head control or rolling over. She also disclosed general hypotonia and paucity of movement between hypertonic attacks. Her CSF revealed a high concentration of L-dopa and a very low concentration of HVA and 5-HIAA (Table 1).

2.3. AADC activity

AADC activity was measured in the serum to confirm the diagnosis using previously reported methods [9]. Serum AADC activity was very low in both patients (AADC activity: 0.5 pmol/min/ml in patient 1, 0.4 pmol/min/ml in patient 2; normal; 50–100).

2.4. Gene analysis

The *AADC* gene mutation was analyzed after obtaining informed consent from the parents of the patients. Genomic DNA from peripheral blood of the patients was extracted according to standard procedures. Each exon of the *AADC* gene was amplified by PCR using primers designed to amplify the coding and flanking non-coding *AADC* regions. Bidirectional cycle sequencing reactions were performed with the ABI Big Dye Terminator Sequencing Kit (Applied Biosystems: Foster city, CA, USA), and the purified products were subject to an automated capillary array sequencer (ABI 3100, Applied Biosystems). Sequencing results revealed a heterozygous point mutation (g.329C > A). The other mutation was not detected. We confirmed that this point mutation was not present in 50 normal Japanese controls.

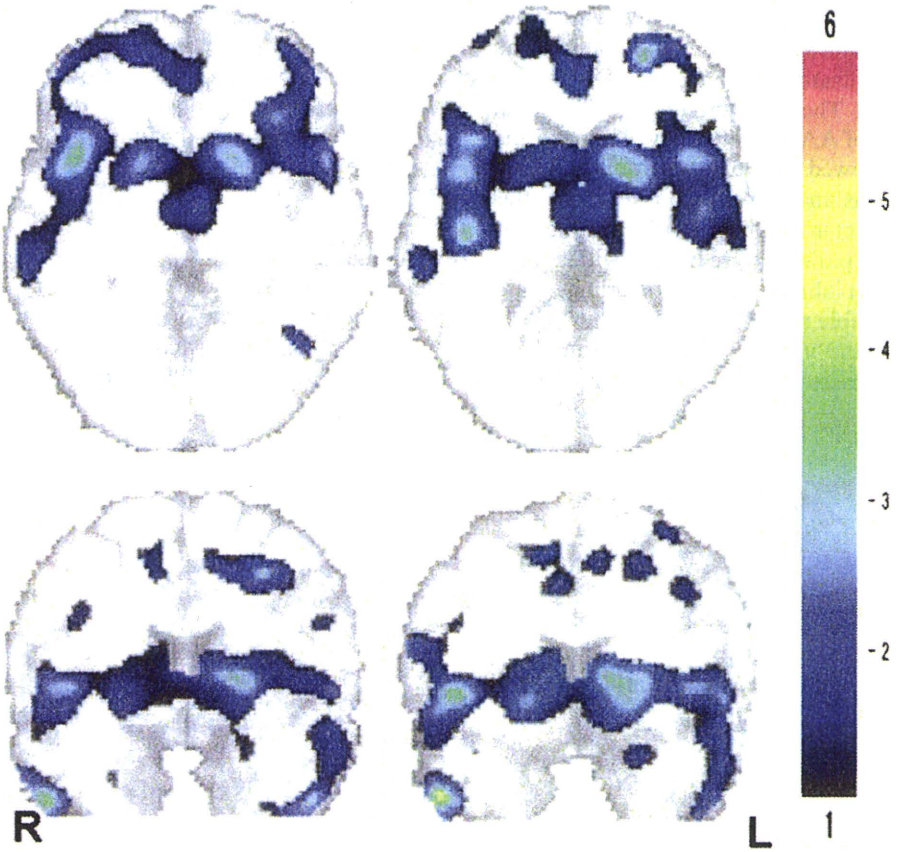

Fig. 2. Easy Z-score imaging (eZIS) analysis of FDG-PET in patient 1. Hypometabolim is observed in bilalateral caudate nuculei to putamina (lower in the left side) and insular cortex with some laterality. Upper; axial section, lower; coronal section.

3. Neuroradiological studies

MRI: Brain MRI in both patients revealed a slightly small volume of the prefrontal areas (Fig. 1) and normal myelination. No abnormal findings in the basal ganglia were observed.

PET: Glucose metabolism was evaluated by FDG-PET in patient 1. We evaluated the results by using an easy Z-score imaging system (eZIS) [10], eZIS revealed hypometabolism in both caudate nuclei and putamina with some laterality (lower in the left side) (Fig. 2) and prefrontal cortex (Fig. 3). The area in which the level of the area was lower than −2SD compared with the standard is colored with purple or blue and the area lower than −3SD is colored with green.

4. Discussion

Patient 1 was at first assumed to have cerebral palsy (CP) because he was born with mild asphyxia. He had been diagnosed with a dystonic type of CP before patient 2 was born. Patient 2, who was born healthy, showed oculogyric crises and dystonic attacks. Since these symptoms were the same as those in patient 1, it was presumed that they both had a basic disorder. Repeated attacks of dystonia reminded us of childhood movement disorders, especially neurotransmitter diseases, and the catecholamine in the CSF indicated an abnormality in the level of neurotransmitters. The low activity of AADC confirmed the diagnosis of AADC deficiency. The gene analysis of the *AADC* showed heterozygous mutation. Since we examined all exons and intron–exon junctions, there must be other mutation in other area. After the diagnosis was established, both patients were treated with a monoamine oxidase (MAO) inhibitor and a dopamine agonist, but showed no favorable response.

In MRI studies, the volume of the prefrontal area was reduced in both cases by visual inspection, although we did not performed volumetric study. The volume of the basal ganglia was normal.

We performed FDG-PET in patient 1 to investigate the brain glucose metabolism. The eZIS analysis revealed hypometabolism in both basal ganglia and prefrontal cortex. To our knowledge, these findings have not yet been reported in other patients with AADC deficiency [3].

In AADC deficiency, both dopamine and serotonin depletion must have occurred in the brain. Dopamine is mostly involved in substantia nigra and basal ganglia circuits. Hypometabolism in caudate nuclei shown in this FDG-PET study probably could be the cause the symptoms of dystonia and muscle tone abnormality.

The mechanism for the slightly small size and hypometabolism in the prefrontal cortex was not identified. Mesencephalic dopaminergic neurons are known to project to the prefrontal cortex and striatum [11]. The dopamine depletion probably causes dysfunction in dopaminergic innervation, and depleted dopaminergic pathways in the prefrontal cortex probably cause the occurrence of prefrontal cortical dysfunction. Similar dysfunction could occur in the serotonergic pathways. Most patients with AADC deficiency have both severe motor developmental and severe intellectual disability, which might be explained by the prefrontal cortical dysfunction.

Both dopamine and serotonin depletion could produce not only basal ganglia dysfunction but also prefrontal cortical dysfunction, especially in the developing brain.

Acknowledgments

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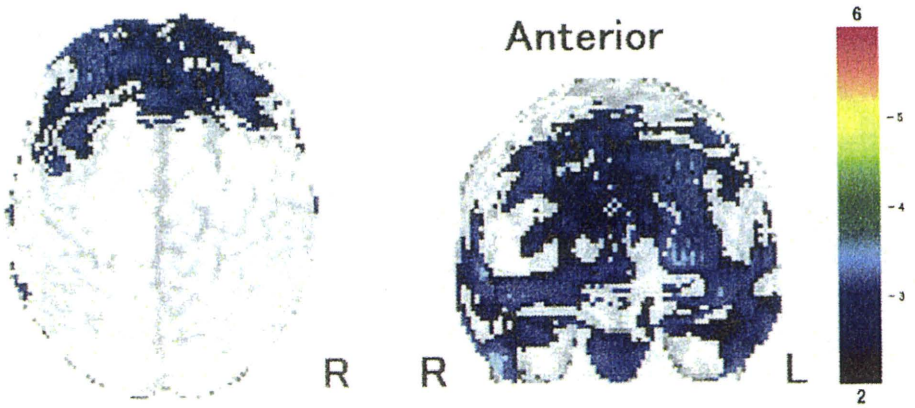

Fig. 3. eZIS analysis of FDG-PET in the projected view show hypometabolism in the prefrontal cortex. Left: from the upper side. Right: from the anterior side.

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FULL-LENGTH ORIGINAL RESEARCH

Interictal cerebral blood flow abnormality in cryptogenic West syndrome

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Summary

Purpose: To elucidate the abnormality of interictal regional cerebral blood flow (rCBF) of West syndrome at the onset.

Methods: Quantitative measurement of rCBF with an autoradiography method using *N*-isopropyl-(^{123}I) p-iodoamphetamine single photon emission computed tomography (SPECT) was performed on 14 infants with cryptogenic West syndrome. Regions of interest (ROIs) for rCBF were placed automatically using an automated ROI analysis software (three-dimensional stereotactic ROI template), and were grouped into 12 segments: callosomarginal, precentral, central, parietal, angular, temporal, posterior cerebral, pericallosal, lenticular nucleus, thalamus, hippocampus, and cerebellum. We compared rCBF between the patients and seven age-matched infants with cryptogenic focal epilepsy as a control group. The patients were divided into two groups according to the duration from onset to SPECT, to compare rCBF.

Results: Quantitative analysis revealed cerebral hypoperfusion in cryptogenic West syndrome with normal SPECT images under visual inspection. In bilateral central, posterior cerebral, pericallosal, lenticular nucleus, and hippocampus, and in the left parietal, temporal, and cerebellum, and in the right angular and thalamus segments there were statistical differences ($p < 0.05$). Compared with the duration from onset to SPECT, there were no significant differences of rCBF in all segments.

Discussion: Broad cerebral hypoperfusion with posterior predominance involving the hippocampus and lenticular nucleus implies that even cryptogenic West syndrome has a widespread cerebral dysfunction at least transiently, which would correspond to clinical manifestations of hypsarrhythmia and epileptic spasms. Hippocampal hypoperfusion suggests the dysfunction of hippocampal circuitry in the brain adrenal axis, and may contribute to subsequent cognitive impairment of cryptogenic West syndrome.

KEY WORDS: ^{123}I-iodoamphetamine, Cerebral metabolism, Development, Hypsarrhythmia, Infantile spasms, Three-dimensional stereotactic ROI template.

West syndrome is severe epileptic encephalopathy of infancy consisting of epileptic spasms and the characteristic electroencephalographic pattern called hypsarrhythmia, and is classified into symptomatic and cryptogenic types. Cryptogenic West syndrome shows normal development before onset, and also displays no brain abnormality according to structural neuroimaging examination. However, even in the patients with the cryptogenic type, almost half demonstrate moderate to severe mental retardation during long-term follow-up (Koo et al., 1993; Ito et al., 2002; Hamano et al., 2003).

Neurofunctional imaging studies have revealed that a subset of patients with West syndrome had focal abnormalities of the cerebral cortex (Chugani et al., 1990, 1992; Maeda et al., 1994; Haginoya et al., 1998, 2000; Munakata et al., 2004; Kakisaka et al., 2009). These studies proposed an important role of those focal abnormalities of the cerebral cortex in the pathophysiology and the development of West syndrome. Focal cortical abnormalities of neurofunctional imaging indicated subtle focal brain lesions, which probably provoke epileptic spasms through cortical–subcortical interaction (Chugani et al., 1990; Haginoya et al., 2000). Some of the localized cerebral dysfunction seems to contribute to mental retardation (Maeda et al., 1994). These authors demonstrated that the localized cortical abnormalities were transient and changed with the clinical symptoms, by visual

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inspections of positron emission tomography (PET), and concluded that these functional abnormalities of the cerebral cortex may be associated with the development of the clinical manifestations of West syndrome.

We previously studied the alteration of the regional cerebral blood flow (rCBF) by adrenocorticotropic hormone (ACTH) therapy using single photon emission computed tomography (SPECT) (Hamano et al., 2007). Our quantitative analysis could not reveal the differences of the rCBF between the patients with cryptogenic West syndrome before ACTH therapy and the controls. Manual determination of regions of interest (ROIs) and unmeasured broad regions outside of ROIs might be disadvantages of the previous study. Therefore, our present study of the rCBF of 14 patients with cryptogenic West syndrome used *N*-isopropyl-(^{123}I) p-iodoamphetamine (IMP)-SPECT and fully automated ROI analysis software instead of manual determination of ROIs to reveal quantitatively the abnormality of rCBF associated with the clinical symptoms of West syndrome and the duration of the appearance of epileptic spasms and hypsarrhythmia.

Methods

The subjects of the present study were 14 infants (eight male and six female) with cryptogenic West syndrome. Cryptogenic West syndrome in this study was defined according to the following criteria: (1) clusters of epileptic spasms with onset <3 years; (2) hypsarrhythmia on electroencephalography (EEG); (3) normal pregnancy, normal development, and no eventful past history, including no other type of seizures before onset of spasms; (4) no focal abnormality on neurologic examinations; (5) normal brain images on computed tomography (CT) and magnetic resonance imaging (MRI); and (6) no focal abnormality and asymmetry of IMP-SPECT images. The mean onset age of the epileptic spasms of the 14 patients was 6.4 ± 2.5 [mean ± standard deviation (SD)] months, ranging from 3.0–10.0 months (information of seizure onset was obtained from the patients' parents). Investigations were performed on every patient to detect the etiologic factors of West syndrome. These included neurologic examinations, ophthalmologic examinations, EEG, brain CT and MRI, biochemical and metabolic tests including urine amino acids and organic acids, and chromosomal analysis.

SPECT examinations were performed before ACTH therapy or antiepileptic medications except pyridoxal phosphate. The age of patients at SPECT study was 9.3 ± 3.3 (mean ± SD), ranging from 3.7–16.5 months, and the duration from the onset to SPECT was 3.0 ± 3.2 (mean ± SD), ranging from 0.4–11.8 months. Quantitative measurement of rCBF was conducted with the autoradiography (ARG) method developed by Iida et al. (Iida et al., 1994). A triple-head gamma camera (Siemens Multispect 3, Siemens Medical Systems Inc., Hoffman Estates, IL, U.S.A.) was equipped with a fan beam collimator, and data were acquired with a 128 × 128 matrix for 120 degrees and 24 min in five-degree steps of 60 s per frame. In data processing, Siemens Icon-P was used for reconstruction of SPECT images, and a Butterworth filter and absorption correction (Chang, $\mu = 0.1$ cm^{-1}) were used to produce scanning images with an OM line and 256 × 256 matrix (1.2 mm/pixel). For all patients ^{123}I-IMP was injected intravenously at a dose of 55.5 megabecquerel (MBq) during their interictal periods ≥30 min after their last seizures. On all patients SPECT scanning was performed during sleep, and triclofos sodium, chloral hydrate, or pentobarbital calcium was used as a sedative. A 24-min scan was performed at 40 and 180 min (early image center time and late image center time, respectively). Approximately 10 min after intravenous injection of ^{123}I-IMP, arterial blood was collected from the opposite side of the ^{123}I-IMP infusion, and whole-blood radioactivity concentration was measured using a well-type scintillation counter. Obtained cross-calibration factors were input to determine quantitative measurements of rCBF. Thyroid block for radioactivity was performed by oral administration of Lugol's solution in a dose of two drops for 4 days, from 2 days before the SPECT examination.

We adopted fully automated ROI analysis software developed by Takeuchi et al., named three-dimensional stereotactic ROI template (3DSRT) (Takeuchi et al., 2003, 2004, 2006). This software is available free on Windows at any facility and is used by many clinicians to investigate rCBF quantitatively for adults and children (Ito et al., 2005; Kobayashi et al., 2008; Tateno et al., 2008; Kimura et al., 2009; Nagasawa et al., 2009). The SPECT images were anatomically standardized using statistical parametric mapping 99 followed by quantification of 318 ROIs unilaterally, grouped into 12 segments: callosomarginal, precentral, central, parietal, angular, temporal, posterior cerebral, pericallosal, lenticular nucleus, thalamus, hippocampus, and cerebellum (Fig. 1).

The SPECT data of seven age-matched epileptic infants with focal seizures were used as a control for comparison with the infants with cryptogenic West syndrome. They had a diagnosis of focal epilepsy; however, their interictal SPECT images were visually symmetric in distribution of CBF, their brain MRIs were normal, they had no focal neurologic deficits, and their development at the age of 3 years was normal. The seven infants comprised four boys and three girls, and their mean age at SPECT study was 10.1 ± 5.6 (mean ± SD), ranging from 3.1–17.7 months. Those variables were not significantly different from the values of the 14 patients with cryptogenic West syndrome. The SPECT procedure was similar to that described earlier.

Furthermore, to reveal the influences on cerebral blood flow by lasting epileptic spasms and hypsarrhythmia, the patients with West syndrome were divided into two groups by the duration from the onset to SPECT examination (<2 or ≥2 months). Demographic variables of the two groups were

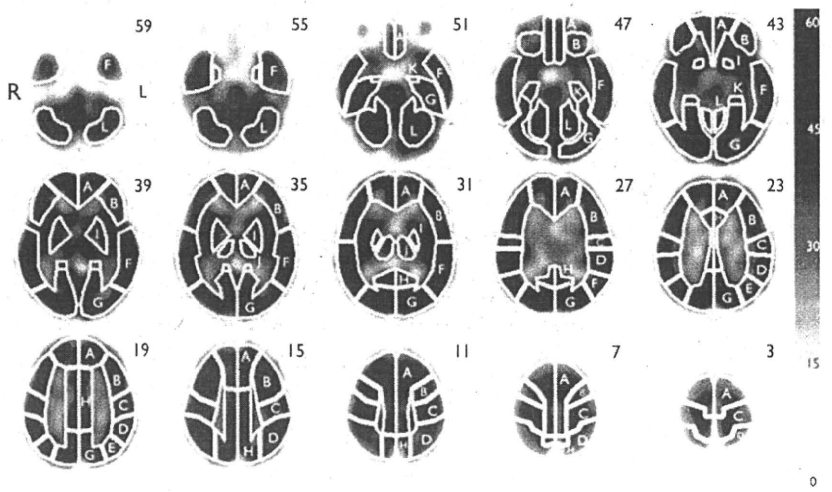

Figure 1.
The delineation of each segment of three-dimensional stereotactic region of interest template on the ^{123}I –iodoamphetamine single photon emission computed tomography (SPECT) image (**A**) callosomarginal segment, (**B**) precentral segment, (**C**) central segment, (**D**) parietal segment, (**E**) angular segment, (**F**) temporal segment, (**G**) posterior cerebral segment, (**H**) pericallosal segment, (**I**) lenticular nucleus segment, (**J**) thalamus segment, (**K**) hippocampus segment, (**L**) cerebellum segment.
Epilepsia © ILAE

not significantly different from each other except with regard to duration from the onset to SPECT (Table 1).

All SPECT examinations were performed in accordance with the policies of the Saitama Children's Medical Center Institutional Steering Committee, and informed consent was obtained from the parents.

The Mann-Whitney *U* test or Fisher's exact probability test was used for statistical analysis. Differences were considered statistically significant with a p-value of 0.05 or less.

Results

The rCBF values of the patients with cryptogenic West syndrome were lower than those of the control group in each corresponding segment (Table 2). In bilateral central, posterior cerebral, pericallosal, lenticular nucleus, and hippocampus segments; in the left parietal, temporal, and cerebellum segments; and in the right angular, and thalamus segments, there were statistically significant differences of the rCBF values ($p < 0.05$). The mean values of rCBF of West syndrome ranged from 35.6 (the right hippocampus segment) to 46.6 (the left thalamus segment) ml/100 g/min, and those of the control group ranged from 41.1 (the left hippocampus segment) to 54.6 (both sides of the lenticular nucleus segments) ml/100 g/min. The rCBF distribution patterns of the cryptogenic West syndrome group were similar to those of the control group, which indicated that the rCBF values in the central, angular, posterior cerebral, lenticular nucleus, and thalamus segments were higher than those in other regions in both groups, which ranged from 40–47 ml/100 g/min (West syndrome) and 48–55 ml/100 g/min (control). There were no statistically significant differences between the right and the left sides in each segment in the patients with West syndrome, and also in the control group.

Table 1. Demographic variables of two groups of the cryptogenic West syndrome divided by the duration from the onset to SPECT (<2 or ≥2 months)

	Duration from onset to SPECT		
	<2 months (n = 7)	≥2 months (n = 7)	p-value
Boy : girl	3:4	5:2	n.s.
Onset age of spasms in months, mean ± SD (range)	6.9 ± 2.9 (3.0–10.4)	5.9 ± 2.2 (3.6–10.0)	n.s.
Age at SPECT in months, mean ± SD (range)	7.7 ± 2.9 (3.7–11.6)	10.9 ± 3.0 (6.9–16.5)	n.s.
Duration from onset to SPECT in months, mean ± SD (range)	0.9 ± 0.5 (0.4–1.97)	5.0 ± 3.4 (2.4–11.8)	**

**p < 0.01.
n.s., not significant statistically between two groups; SPECT, single photon emission computed tomography.

Table 2. Regional cerebral blood flow (rCBF) in 12 segments of cryptogenic West syndrome compared with those of control group

Segment		Side	West syndrome (n = 14) rCBF in ml/100 g/min (mean ± SD)	Control (n = 7) rCBF in ml/100 g/min (mean ± SD)	p-value
A	Callosomarginal	R	36.8 ± 8.2	43.6 ± 8.2	n.s.
		L	36.6 ± 7.9	43.7 ± 9.2	n.s.
B	Precentral	R	39.5 ± 8.3	47.0 ± 9.3	n.s.
		L	38.5 ± 8.5	47.0 ± 8.9	n.s.
C	Central	R	40.4 ± 8.0	48.9 ± 9.2	*
		L	40.2 ± 8.6	49.6 ± 9.8	*
D	Parietal	R	39.6 ± 7.9	48.1 ± 11.3	n.s.
		L	38.6 ± 7.6	47.9 ± 11.9	*
E	Angular	R	40.8 ± 8.6	50.9 ± 11.5	*
		L	40.4 ± 8.5	51.0 ± 11.9	n.s.
F	Temporal	R	37.2 ± 7.2	45.3 ± 9.2	n.s.
		L	35.9 ± 7.8	44.6 ± 9.0	*
G	Posterior cerebral	R	42.3 ± 8.3	52.0 ± 8.9	*
		L	41.9 ± 8.1	51.5 ± 8.7	*
H	Pericallosal	R	40.2 ± 8.1	49.0 ± 8.8	*
		L	39.7 ± 8.0	49.0 ± 9.9	*
I	Lenticular nucleus	R	44.9 ± 8.5	54.6 ± 10.3	*
		L	45.3 ± 8.0	54.6 ± 9.7	*
J	Thalamus	R	44.0 ± 7.6	53.5 ± 11.4	*
		L	46.6 ± 8.8	53.7 ± 8.3	n.s.
K	Hippocampus	R	35.6 ± 6.6	41.7 ± 5.1	*
		L	35.7 ± 7.9	41.1 ± 4.7	*
L	Cerebellum	R	37.1 ± 6.6	43.5 ± 6.9	n.s.
		L	37.3 ± 6.4	44.4 ± 6.9	*

*$p < 0.05$.
n.s., not significant statistically between two groups; R, right; L, left; SD, standard deviation.

To reveal the influences on cerebral blood flow by lasting epileptic spasms and hypsarrhythmia, rCBFs were compared between the two groups of patients with cryptogenic West syndrome divided by the duration from the onset to SPECT examination (<2 or ≥2 months). There were no significant differences of rCBF between the two groups in all segments (Table 3).

Discussion

This quantitative study revealed a decrease of rCBF by 15–20% in the patients with cryptogenic West syndrome, in broad regions from central to occipital regions involving the lenticular nucleus and hippocampus, compared with the patients with cryptogenic focal epilepsy. To the best of our knowledge, this is the first report that has revealed hippocampal hypoperfusion in the early period of West syndrome by quantitative cerebral blood flow analysis using SPECT. Baram and Hatalski (1998) proposed the brain adrenal axis hypothesis concerning the pathophysiology of West syndrome. They suggested that corticotropin releasing hormone (CRH)–expressing γ-aminobutyric acid (GABA)ergic interneurons of the hippocampus might be influenced by stress-evoked excessive release of CRH from the amygdala via the entorhinal cortex. Hippocampal hypoperfusion may indicate hippocampal dysfunction associated with excessive CRH, and will be concordant with the brain adrenal axis hypothesis. Steroids normally exert a negative feedback on the production of CRH in the hypothalamus directly and via the hippocampus. Hippocampal dysfunction can cause an inappropriate negative feedback on CRH and may lead to a vicious spiral. Riikonen and Amnell (1981) demonstrated frequent comorbidity of autism in West syndrome, and they suggested a close association between the limbic system and autism. Hippocampal hypoperfusion in the early period of West syndrome may be associated with autism as a comorbidity of West syndrome.

Electrophysiologic study revealed the important role of pre- and/or postcentral gyri in the pathophysiology of epileptic spasms (Asano et al., 2005). It was found that the pre- and/or postcentral gyri involvement of the fast wave bursts were associated with the severity of limb movement of epileptic spasms (Asano et al., 2005). Hypoperfusion of the bilateral central segments in our study may be a consequence of frequent epileptic spasms, with which the fast wave bursts were associated.

Our study showed significant rCBF decrease in the bilateral occipital regions, and the left temporal and parietal

Table 3. Regional cerebral blood flow (rCBF) of the cryptogenic West syndrome compared by the duration from the onset to SPECT

Segment		Side	Duration from onset to SPECT: <2 months (n = 7) rCBF in ml/100 g/min (mean ± SD)	Duration from onset to SPECT: ≥2 months (n = 7) rCBF in ml/100 g/min (mean ± SD)	p
A	Callosomarginal	R	36.9 ± 10.2	36.6 ± 6.5	n.s.
		L	36.5 ± 9.8	36.7 ± 6.2	n.s.
B	Precentral	R	39.6 ± 10.9	39.4 ± 5.6	n.s.
		L	39.0 ± 11.0	38.1 ± 6.1	n.s.
C	Central	R	40.8 ± 9.5	39.9 ± 6.9	n.s.
		L	40.9 ± 10.8	39.4 ± 6.6	n.s.
D	Parietal	R	39.4 ± 10.0	39.8 ± 5.8	n.s.
		L	38.6 ± 9.9	38.7 ± 5.1	n.s.
E	Angular	R	40.2 ± 10.7	41.5 ± 6.8	n.s.
		L	39.9 ± 11.1	40.9 ± 5.8	n.s.
F	Temporal	R	37.0 ± 8.3	37.3 ± 6.6	n.s.
		L	36.2 ± 9.6	35.5 ± 6.2	n.s.
G	Posterior cerebral	R	41.8 ± 10.2	42.8 ± 6.7	n.s.
		L	41.4 ± 10.3	42.3 ± 5.9	n.s.
H	Pericallosal	R	40.4 ± 10.2	39.9 ± 6.2	n.s.
		L	39.6 ± 10.1	39.7 ± 6.0	n.s.
I	Lenticular nucleus	R	45.7 ± 11.4	44.1 ± 5.0	n.s.
		L	45.7 ± 9.9	44.8 ± 6.3	n.s.
J	Thalamus	R	44.3 ± 10.1	43.7 ± 4.8	n.s.
		L	46.5 ± 11.8	46.7 ± 5.4	n.s.
K	Hippocampus	R	36.1 ± 7.6	35.1 ± 6.1	n.s.
		L	36.4 ± 10.2	34.9 ± 5.6	n.s.
L	Cerebellum	R	36.9 ± 7.5	37.4 ± 6.1	n.s.
		L	36.7 ± 7.4	38.0 ± 5.9	n.s.

n.s., not significant statistically between two groups; R, right; L, left; SD, standard deviation; SPECT, single photon emission computed tomography.

segments in the patients with cryptogenic West syndrome with normal SPECT images under visual inspection. PET studies frequently detected hypometabolism in the parietooccipital-temporal regions, and the dysfunction of those cortical regions is considered to be associated with the development of West syndrome (Chugani et al., 1990; Chiron et al., 1993; Maeda et al., 1994). Electrocorticography showed that the fast wave bursts associated with epileptic spasms involved cortical regions extensively and rapidly, at least in two lobes (Asano et al., 2005). The normal brain development proceeds from the sensorimotor cortex to parietooccipital cortices, and eventually attains frontal cortex (Yakovlev & Lecours, 1967; Chugani et al., 1987; Chiron et al., 1992; Kato & Okuyama, 1993; Yoshinari et al., 2006). The fast wave bursts associated with epileptic spasms may propagate easily to cerebral cortices, which develop earlier during infancy. The hypometabolism and the hypoperfusion in parietooccipital temporal regions may be the consequence of cerebral dysfunction by the propagation of the fast wave bursts, although we should consider an undetectable lesion such as microscopic cortical dysplasia, which shows normal MRI and abnormal findings in PET (Chugani et al., 1990). Transient hypometabolism in posterior cerebral cortices during the early period of West syndrome was not associated with developmental delay (Maeda et al., 1994). However, when patients with intractable epileptic spasms such as candidates for resective surgery showed bitemporal hypometabolism, their outcomes were particularly poor (Chugani et al., 1996). These findings seem to correspond to the concept that the hypometabolism and the hypoperfusion in the posterior regions are the consequence of cerebral dysfunction by the repetitive propagation of fast wave bursts.

Concerning subcortical structures, our study showed hypoperfusion in the bilateral lenticular nucleus and hippocampus also. Hippocampal hypometabolism was detected in the patients with intractable West syndrome and poor developmental outcome (Chugani et al., 1996). Influence to hippocampus by repetitive epileptic spasms may contribute to developmental outcome. However, abnormality of lenticular nucleus is controversial. Hypermetabolism of lenticular nucleus and brainstem in the patients with West syndrome was reported (Chugani et al., 1992, 1996). Although there would be differences in investigation such as cerebral blood flow and cerebral metabolism, there is remarkably close correlation. The opposite results may contribute to the differences of examination timing. SPECT was performed on the patients as soon as possible from their onset before treatment except vitamin B6 in our study; however, PET

was performed for the evaluation of resection surgery at various times in their study, when epileptic spasms had disappeared or changed to partial seizures in some patients. Other fluorodeoxyglucose (FDG)-PET studies, which were performed at the onset of spasms, showed cortical hypometabolism frequently in parietotemporooccipital regions without lenticular hypermetabolism (Maeda et al., 1994; Natsume et al., 1996). These results correspond to the results of our cerebral perfusion study by SPECT. Cerebral perfusion was examined qualitatively using SPECT on 40 patients with West syndrome (Haginoya et al., 2000). Hyperperfusion in the basal ganglia or in the brainstem was observed in only one patient. We consider that lenticular nuclei would be hypoperfused in cryptogenic West syndrome just after the onset at least, and may be hypometabolized similarly.

Prolonged hypsarrhythmia is considered to lead to subsequent cognitive impairment (Koo et al., 1993; Kivity et al., 2004). Some researchers consider hypsarrhythmia to be a kind of nonconvulsive status epilepticus (Lux, 2007). The duration of hypsarrhythmia and spasms probably affects hypometabolism and hypoperfusion. We also analyzed the differences of rCBF by the duration from onset to SPECT examination; however, there were no significant differences in any segments between the two groups divided by the duration, more than 2 months or less. One of the causes associated with absence of differences between the two groups would be due to limitations in performing examinations and in obtaining clinical information concerning onset and severity of symptoms. We were unable to obtain the exact duration of hypsarrhythmia. Electroencephalography could not be performed before the patients visited hospitals. We were able to obtain information about the onset of epileptic spasms from the patients' parents; however, it is difficult to obtain accurate information of spasm frequency and intensity during the first visit from the parents. Aggregate and expanse of electrical propagation in cluster of spasms, which affect seizure frequency and intensity, could change the severity of interictal hypoperfusion. Not only the duration from the onset and continuity of hypsarrhythmia, but also the frequency and intensity of epileptic spasms, may influence interictal rCBF in cryptogenic West syndrome. It would be important to discriminate between the effect by spasms and the effect by hypsarrhythmia, and further study needs to be done on subject patients with infantile spasms without hypsarrhythmia and/or hypsarrhythmia without infantile spasms.

Our study showed that widespread cerebral hypoperfusion with posterior predominance involved the hippocampus and lenticular nucleus in West syndrome. This result implies that even cryptogenic West syndrome would have a broad region of cerebral hypoperfusion, at least transiently, which would reflect widespread cerebral dysfunction. Hypsarrhythmia or epileptic spasms themselves probably contribute to developmental outcomes; however, where in the brain they have effect remains obscure. Hippocampal hypoperfusion suggests the dysfunction of hippocampal circuitry in the brain adrenal axis, and may lead to subsequent cognitive impairment such as autism.

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Disclosure

None of the authors has any conflict of interest to disclose.

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