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RESEARCH REPORT

Chronic Diarrhea in L-Amino Acid Decarboxylase (AADC) Deficiency: A Prominent Clinical Finding Among a Series of Ten French Patients

M.A. Spitz · M.A. Nguyen · S. Roche · B. Heron · M. Milh · P. de Lonlay · L. Lion-François · H. Testard · S. Napuri · M. Barth · S. Fournier-Favre · L. Christa · C. Vianey-Saban · C. Corne · A. Roubertie

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Abstract Aromatic L-amino acid decarboxylase (AADC) deficiency is an autosomal recessive inborn error of metabolism, affecting catecholamines and serotonin biosynthesis. Cardinal signs consist in psychomotor delay, hypotonia, oculogyric crises, dystonia, and extraneurological symptoms.

Patients and methods: We present a retrospective descriptive multicentric study concerning ten French children with a biochemical and molecular confirmed diagnosis of AADC deficiency.

Results: Clinical presentation of most of our patients was consistent with the previous descriptions from the literature (hypotonia (nine children), autonomic signs (nine children), sleep disorders (eight children), oculogyric crises (eight children), motor disorders like hypertonia and involuntary movements (seven children)). We described however some phenotypic particularities. Two patients exhibited normal intellectual abilities (patients already described in the literature). We also underlined the importance of digestive symptoms like diarrhea, which occurred in five among the ten patients. We report in particular two children with chronic diarrhea, complicated by severe failure to thrive.

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M.A. Spitz
Département de Pédiatrie, Strasbourg, France

M.A. Nguyen · H. Testard
Département de Pédiatrie, Grenoble, France

S. Roche
Service de Neuropédiatrie et Maladies Métaboliques Hôpital Robert Debré, Paris, France

B. Heron
Département de Pédiatrie Hôpital Jean Verdier, Bondy, France

B. Heron
Service de Neuropédiatrie et Maladies Métaboliques Hôpital Armand Trousseau, Paris, France

B. Heron
Service de Pédiatrie, Hôpital Jean Verdier, Bondy, France

B. Heron
Service de Neurologie Pédiatrique, Hôpital Armand Trousseau, Paris, France

M. Milh
Service de Neuropédiatrie et Maladies Métaboliques Hôpital La Timone, Marseille, France

P. de Lonlay
Service de Neuropédiatrie et Maladies Métaboliques Hôpital Necker Enfants Malades, Paris, France

L. Lion-François
Service de Neuropédiatrie Hôpital Femme Mère Enfant, Lyon, France

H. Testard
Département de Pédiatrie, Annemasse, France

S. Napuri
Département de Pédiatrie, Rennes, France

M. Barth
Service de Génétique et centres de compétence Maladies Métaboliques, Angers, France

S. Fournier-Favre
Service d'Hépato-gastro-entérologie pédiatrique, Montpellier, France

L. Christa
Service de Biochimie Métabolique Hôpital Necker Enfants Malades, Paris, France

C. Vianey-Saban
Service de Biochimie Métabolique Hôpital Femme Mère Enfant, Lyon, France

C. Corne
Service de Biochimie Métabolique, Grenoble, France

A. Roubertie (✉)
Service de Neuropédiatrie Hôpital Gui de Chauliac, Montpellier, France
e-mail: a-roubertie@chu-montpellier.fr

Vanillactic acid (VLA) elevation in urines of one of these two patients led to suspect the diagnosis of AADC deficiency, as in two other patients from our population.

Conclusion: Some symptoms like chronic diarrhea were atypical and have been poorly described in the literature up to now. Diagnosis of the AADC deficiency is sometimes difficult because of the phenotypic heterogeneity of the disease and VLA elevation in urines should suggest the diagnosis.

Introduction

Aromatic L-amino acid decarboxylase (AADC) deficiency is an inborn error of neurotransmitter biosynthesis with an autosomal recessive inheritance. The enzyme AADC is the second enzyme in the catecholamines (dopamine, noradrenaline, and adrenaline) and serotonin biosynthetic pathway (Pons et al. 2004). Currently less than 100 cases are reported in the world (Hyland and Clayton 1990, Hyland et al. 1992; Korenke et al. 1997; Maller et al. 1997; Swoboda et al. 2003; Chang et al. 2004; Pons et al. 2004; Lee et al. 2009; Ito et al. 2008; Brun et al. 2010). This pathology is clinically characterized by oculogyric crises, dystonia and other involuntary movements, hypotonia, global developmental delay and autonomic dysfunctions (Swoboda et al. 2003). The diagnosis relies on the analysis of neurotransmitters in the cerebral spinal fluid (CSF) showing a reduced concentration of homovanillic acid (HVA, main metabolite of dopamine), 5-hydroxyindoleacetic acid (5-HIAA, main metabolite of serotonin), and 3-methoxy-4-hydroxyphenylethyleneglycol (MHPG); an increased concentration of 3-methoxytyrosine (3MT), 3-O-methyldopa (3OMD, main metabolite of L-dopa), L-dopa and 5-hydroxytryptophan (5HTP). Vanillactic acid (VLA) elevation investigated by organic acids profile in urine was also reported in the pathology (Hyland et al. 1992). The confirmative diagnosis is based on enzyme activity in the plasma (Hyland et al. 1992; Verbeek et al. 2007) and DDC gene (coding for the enzyme AADC) analysis (Hyland et al. 1992; Verbeek et al. 2007; Haavik et al. 2008). The therapeutic response is variable (Allen et al. 2009), often disappointing and in only single cases clinical improvement has been observed (Swoboda et al. 2003; Pons et al. 2004; Lee et al. 2009; Allen et al. 2009; Manegold et al. 2009; Brun et al. 2010). Here we report the phenotype of ten patients recruited in France, and we describe particularly two patients with severe chronic diarrhea.

Materials and Methods

Patients

Ten patients with a diagnosis of AADC deficiency (confirmed by enzymatic and/or genetic analysis) established in France were included in this study. Our patients, six boys and four girls, came from nine families with various ethnic background. Two of these patients have already been described in the literature (case 1 and case 5) (Barth et al. 2012; Arnoux et al. 2013) (cf. Table 1).

Detailed data on patients were collected in the medical files. Information on DNA variations was compared with BIOMDB data (http://www.biopku.org) and the literature. Informed consent according to the Declaration of Helsinki was obtained from the parents to collect the data of the patients.

Biochemical and Molecular Investigations

Neurotransmitters in CSF were investigated by high-performance liquid chromatography (HPLC); organic acids profile in urine was investigated by gaseous chromatography with mass spectrometry; enzyme activity was measured in plasma, after adding PLP and L-dopa, reaction products were then quantified by HPLC.

Results

Clinical Findings

Symptoms were present before the age of 1 year in all children except case 5. Oculogyric crises became evident at the median age of 13 months (ranging from 3 to 42 months), and were not documented in two children at the time of investigation. Hypotonia was observed in nine children except case 5; four patients lost head control and four patients never acquired head control. Seven patients presented with a severe encephalopathy although patients 1, 5, and 6 were less severely affected. A good eye contact was however reported in nine children. Two patients had a normal intellectual efficiency: patient 1 composite Intellectual Quotient was 85 (Wechsler Intelligence Scale for Children III) and patient 5 had normal education in elementary school with speech therapy. Limb hypertonia was noticed in seven children, seven children presented with dystonia, four with dyskinesia/chorea, one with non-epileptic myoclonia, one with ballic movements. Autonomic signs were observed in nine children except case

Table 1 Clinical and paraclinical features in our population

Patient/Sex	1/F (Barth et al.)	2/F	3/M	4/M	5/F (Arnoux et al.)	6/M[a]	7/M[a]	8/M	9/F	10/M
Consanguinity	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No
Perinatal history	No	No	No	No	No	No	No	No	No	No
Age at first consultation	3 m	3 m	3 m	1 m	20 m	4 m 1/2	2.5 y	1 y	3 m	2 m
Age at diagnosis (CSF profile)	7 y	3.5 y	8 m	8.5 y	6 y	5 m	NT	5.5 y	3.5 m	3 m
Clinical signs										
Neurologic symptoms										
Severe encephalopathy	–	+	+	+	–	+	+	+	+	+
Ocular contact	+	–	+	+	+	+	+	+	+	+
Acquired microcephaly	–	+	–	–	–	–	+	–	–	–
Axial hypotonia	+	+	+	+	–	+	+	+	+	+
Limb hypertonia	+	+	+	+	–	+	+	+	–	–
Hypokinesia	–	–	–	–	–	–	–	–	–	–
Involuntary movements	+	+	+	+	–	+	+	+	+	+
Functional prehension	+	–	–	–	+	+	–	–	–	–
Tongue thrusting	–	–	–	–	–	–	+	–	–	–
Oculogyric crises	+	–	+	+	–	+	+	+	+	+
Seizures	–	–	–	–	–	+	+	–	–	–
Autonomic signs										
Hyper salivation	+	+	+	+	–	+	+	–	+	+
Excessive sweating	+	+	+	+	–	+	+	–	+	–
Ptosis	+	–	–	–	–	–	–	–	+	–
Nasal obstruction	+	+	+	+	+	+	–	–	+	–
Nonneurological signs										
Sleeping disorders	+	–	+	+	+	+	–	+	+	+
Diarrhea/age at onset	+/3 y	–	–	+/5.5 y	+/3 y	–	–	+/6 y	+/6 m	–
Gastrostomy	–	+	–	+	–	–	–	+	–	+
Hypoglycemia	–	–	–	–	+	–	–	–	+	–
GH deficiency	–	–	–	+	–	–	–	–	–	–
Malaise with cyanosis	–	+	–	–	–	–	–	–	–	–
Stridor	–	–	+	–	–	–	–	–	+	–
Biochemical investigations										
VLA increase in urine	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Enzyme activity pmol/m in/ml (16–130)	4	0	0	0	5	<2	NT	NT	5	0.05

(continued)

Table 1 (continued)

Patient/Sex	1/F (Barth et al.)	2/F	3/M	4/M	5/F (Arnoux et al.)	6/M[a]	7/M[a]	8/M	9/F	10/M
Neurotransmitters CSF values nmol/L normal range)										
HVA	**110** (202–596)	**12** (304–658)	**30** (295–932)	<**10** (202–596)	**248** (304–658)	**27** (310–1,328)	NT	**19** (144–801)	**61** (310–1,100)	**89** (543–1,142)
HIAA	**12** (87–366)	**5** (106–316)	<**5** (114–336)	<**10** (87–366)	**40** (106–316)	**3** (150–1,142)	NT	**20** (88–316)	**19** (150–800)	**74** (383–1,028)
OMD	**520** (5–60)	**740** (3–64)	**NT**	**729** (5–60)	**592** (3–64)	**2,500** (20–162)	NT	**1,048** (3–64)	**NT**	**3,273** (<25)
5–HTTP	**56** (2–16)	55 (4–23)	**74** (<10)	**139** (2–16)	**50** (4–23)	**300** (2–26)	NT	**41** (4–23)	**107** (<10)	**264** (<200)
Mutation analysis										
Mutations DDC gene	c.1040G>A p. R347Q	c. 781+6T>c	c. 1040G>A p. R347Q	c. 106G>A p. G36R	c. 97G>C p. V33L	c. 1040G>A p. R347Q	c. 1040G>A p. R347Q	c. 1040G>A p. R347Q	c. 823G>A p. A275T	c. 1379T>G p. V460G
	c. 478C>T p. R160W	c. 781+6T>	c. l040G>A p. R347Q	c. 1340G>A p. R447H	c. 1385G>C p. R462P	c. 1040G>A p. R347Q	c. 1040G>A p. R347Q	c. 1040G>A p. R347Q	c. 823G>A p. A275T	c. 73G>Ap. E25K

F female, *M* male, *m* months, *y* years, *CSF* cerebrospinal fluid, + present, − absent, *VLA* vanillactic acid, HVA homovanillic acid, *HIAA* 5-hydroxyindoleacetic acid, *OMD* 3-O-methyldopa, *5-HTP* 5-hydroxytryptophan, *DDC* dopa decarboxylase, *NT* not tested

[a] Patients 6 and 7 are brothers, AADC deficiency concerning patient 7 was established after his death according to the diagnosis of his younger affected brother

8 (cf. Table 1) and sleep difficulties in eight children. Seizures occurred in two children, hypoglycemia in two patients, growth hormone (GH) deficiency in one child. Psychiatric symptoms were not reported in our group of patients.

A total of five patients suffered from diarrhea, which was severe in three and in two children diarrhea resulted in severe failure to thrive and malnutrition (a detailed description of these two patients is provided thereafter). Diarrhea was permanent and chronic in three patients (patients 4 and 8 described thereafter and patient 5 described by Arnoux et al.) with an age of onset ranging from 3 to 6 years; diarrhea was transient and/or alternating with constipation in two patients (patient 1 described by Barth et al. and patient 9) (cf. Table 1).

Biochemical Investigations

VLA dosage in urine was performed in all of the patients, and was elevated in 9/10 patients (except patient 7). For three of the patients this elevation suggested the diagnosis of AADC deficiency. CSF analysis was performed in nine children and showed a typical profile in all patients. Enzyme activity was measured in eight patients, and was always very low (maximum 5% of total activity) or not detectable (cf. Table 1).

Molecular analysis

Ten different mutations were detected, five of them had not been described earlier: c.478C>T, c.781+6T>c, c.106G>A, c.1379T>G, c.73G>A (cf. Table 1). New variations were considered as pathogenic according to prediction databases (BIOMDB). The NCBI nucleotide reference sequence used was NM_000790.3 and the protein sequence reference NP_000781.1.

Treatment

The patients benefited from various treatments, with limited benefit in four. Only two patients with a moderate phenotype exhibited significant clinical improvement concerning motor function and oculogyric crises (patient 1) and concerning motor function, diarrhea, and nasal obstruction (patient 5) (cf. Table 2).

Patient 4

This patient was the first child of consanguineous Moroccan parents. He was born full term and had feeding difficulties from birth. Hypotonia was noticed at the age of 1 month. He progressively exhibited limbs hypertonia, dystonia, autonomic signs (excessive sweating, nasal obstruction), sleep disorders. Oculogyric crises appeared at the age of 3.5 years, occurred two times a week, and were associated with dystonic crises. Between the attacks, this patient had a good ocular contact. Due to swallowing difficulties and growth failure, gastrostomy procedure was proposed but the parents finally agreed for gastrostomy feeding when the child was 5 years of age. At this age his neurological examination showed severe axial hypotonia and limb hypertonia, good ocular contact, no language and no prehension. From the age of 5.5 years, this patient suffered from severe chronic diarrhea, which became the most disabling symptom for the family. Diarrheic stools occurred 10–15 times a day; aqueous diarrhea was described, particularly after enteral feeding. This patient also had a GH deficiency, but despite a GH supplementation we noticed only a small positive effect on trophic state. At the age of 8, he weighted 14 kg (below three standard deviations) and his height was 115 cm (below two standard deviations). Biochemical investigations were performed in order to find out the etiology of this chronic diarrhea. Stools infectious investigations (bacteriological, viral, parsitological and mycotic analysis) were normal. There was no ionic, hepatic or pancreatic disorder, no inflammation. Malabsorption (D-Xylose test, steatorrhea, vitamins), celiac disease, CDG syndrome, intolerance to saccharides were excluded. Hormonal tests (TSH, VIP Gastrin, calcitonin) and serotonin dosage in blood were normal. Red Carmin test was concordant with the diagnosis of motor diarrhea. Metabolic investigations were also performed and urine analysis disclosed increased VLA dosage, which suggested AADC deficiency. Typical AADC deficiency profile of CSF neurotransmitters was identified, AADC enzyme activity was not detectable. Levodopa 160 mg/day (10 mg/kg/day), oxitriptan 100 mg/day (6 mg/kg/day), and serotonin were ineffective on diarrhea or other symptoms. Loperamide 2 mg/day (0.15 mg/kg/day) moderately improved diarrhea frequency.

Patient 8

This patient is the third child of nonconsanguineous parents. Pregnancy and delivery were uneventful. Hypotonia was noticed from the age of 3 months. Oculogyric attacks occurred at the age of 1 year; the attacks lasted a few minutes, recurred several times a day. Seizures were suspected; antiepileptic treatment was initiated without any benefit. A gastrostomy was performed at the age of 2 because of swallowing difficulties, which improved with time and gastrostomy was then only occasionally used. The patient was lost of follow-up until the age of 5.5 years, when he was referred for feeding difficulties with hematemesis. Due to these symptoms, a new gastrostomy and a Nissen surgery were performed. At this time, clinical

Table 2 Treatments and clinical evolution with treatments

Patients	Treatments	Evolution with treatment
1	Pyridoxine 250 mg/day Bromocriptine 7.5 mg/day Levodopa 12 mg/day Folinic acid	Positive effects: bromocriptine (transitory effects), levodopa: better balance, fatigue improvement, better intelligibility, better fine motor function, oculogyric crises improvement Side effects: not reported
2	Bromocriptine 3 mg/day (0.3 mg/kg/day) Pyridoxal phosphate 600 mg/day (65 mg/kg/day) Folinic acid L-carnitine 900 mg/day (100 mg/kg/day)	Positive effects: no clinical improvement Side effects: pyridoxal phosphate: vomiting
3	Pyridoxine 50 mg/day (5 mg/kg/day) Folinic acid 5 mg/day (0.5 mg/kg/day) Bromocriptine 7.5 mg/day (0.75 mg/kg/day) Levodopa-carbidopa 150 mg/day (15 mg/kg/day) Serotonin Oxitriptan (Levotonine®) 5 mg/day (7.5 mg/kg/day) Trihexyphenidyl (Artane®) 3 mg/day (0.3 mg/kg/day) Ropinirole (Requip®) Rotigotine patch (Neupro®)	Positive effects: no clinical improvement Side effects: not reported
4	Levodopa 160 mg/day (10 mg/kg/day) Oxitriptan l00 mg/day (6 mg/kg/day) Serotonin	Positive effects: no clinical improvement Side effects: not reported
5	Pyridoxine 600 mg/day (30 mg/kg/day)	Positive effects: diarrhea improvement, nasal obstruction improvement, handwriting improvement Side effects: not reported
6	Pyridoxine 500 mg/day (60 mg/kg/day) Folinic acid 30 mg/day (3.5 mg/kg/day) Bromocriptine 1.25 mg/day (0.15 mg/kg/day) Amitriptyline 4 mg/day (0.5 mg/kg/day) Ropinirole 0.5 mg/day (0.06 mg/kg/day) Rotigotine Patch (Neupro®) Clonazepam Phenobarbital	Positive effects: ropinirole: mild improvement of head control, but persistence of an important axial hypotonia Side effects: not reported
7[a]	Antiepileptic drugs	
8	Pyridoxine 250 mg/day (19 mg/kg/day) Folinic acid l0 mg/day (0.8 mg/kg/day) Ropinirole 0.75 mg/day (0.06 mg/kg/day) L-carnitine l,000 mg/day (75 mg/kg/day) Clobazam 15 mg/day (1. 2 mg/kg/day)	Positive effects: ropinirole: vigilance improvement Side effects: ropinirole: vomiting
9	Pyridoxine 360 mg/day (50 mg/kg/day) Pramipexole 0.56 mg/day (0.08 mg/kg/day) Folinic acid 10 mg/day (1.4 mg/kg/day) Selegiline 4 mg/day (0.6 mg/kg/day) Apomorphine pump 1.8 mg/h (0.25 mg/kg/h) Amitriptyline 8 mg/day (1.l mg/kg/day) Melatonine 6 mg/day (0.9 mg/kg/day)	Positive effects: no clinical improvement Side effects: apomorphine pump: skin rash, vomiting
10	Pyridoxine Selegiline Levodopa	Positive effects: selegiline: sleeping disorders improvement, interaction improvement Side effects: levodopa: vomiting, tremor

[a] As the AADC deficiency diagnosis was established after the death of the patient, patient 7 did not receive treatment specific for AADC defect, data concerning the antiepileptic drugs that were administered are not available

examination showed a severe encephalopathy, with truncal hypotonia with no head control, lower limbs pyramidal tract signs, movement disorders including non-epileptic myoclonia, ballic movements, dyskinesia, dystonia, possible ocular contact but no language; sleep disorders were also reported. The patient exhibited aqueous diarrhea (about 6 per day spontaneously, and after every feeding attempt), associated with severe failure to thrive (weight 12 kg at the age of 6 years, below three standard deviations). Repeated stools infectious investigations were negative. Stools pH was 7, which is concordant with normal oligosaccharides tolerance. There was no ionic or thyroid hormone abnormalities, blood analysis did not disclose inflammation. Hepatic and pancreatic investigations were normal. Malab-

sorption, celiac disease, and cow's milk proteins allergy were excluded. Red Carmin Test was concordant with the diagnosis of motor diarrhea. Loperamide 2 mg/day (0.15 mg/kg/day) did not provide any improvement of diarrhea, lacteol 680 mg/day (50 mg/kg/day) was also ineffective. Further etiological investigations were performed, with exhaustive metabolic analysis including CSF neurotransmitters profile, which was consistent with AADC deficiency. Enteral feeding was rapidly challenged by the severity of the diarrhea, which persisted despite dramatic decrease of the ration and various specific regimens; pharmacological treatments used for AADC deficiency (ropinirole 0.75 mg/day (0.06 mg/kg/day) (dopa agonist), pyridoxine 250 mg/day (19 mg/kg/day), and folinic acid 10 mg/day (0.8 mg/kg/day)) did not provide any improvement. Total parenteral feeding through a central catheter was undertaken, nevertheless the child still exhibited diarrheic stools several times a day. The patient suffered from several nosocomial infections and died at 7 years of age during a severe sepsis, due to central catheter infection.

Discussion

In this paper we describe the phenotype of ten patients with AADC deficiency, and we emphasize the occurrence of motor diarrhea with variable age of onset in half of them. Among these five patients, two children (case 4 and 8) exhibited devastating digestive symptoms, resulting in malnutrition, and requiring surgical procedures whose benefit was very limited (Nissen surgery, gastrostomy, parenteral feeding). Diarrhea occurred in patients with variable severity of neurological involvement, as it was also a main symptom of patient 5 with a milder phenotype characterized by normal motor function and normal learning abilities. Although extraneurological manifestations are common in AADC deficiency, digestive disorders (except swallowing difficulties) are poorly described in the literature. In the largest series of 78 patients reported up to now, Brun described feeding difficulties in 42% of the patients, but diarrhea is not recorded among this series of patients (Brun et al. 2010). Lee et al. reported that four out of their eight patients suffered from diarrhea (Lee et al. 2009), Manegold et al. reported constipation in four patients and diarrhea in two out of nine patients (Manegold et al. 2009); recently, Graziano et al. reported a patient with a complex phenotype including chronic diarrhea (Graziano et al. 2015). Nevertheless, no details are provided concerning the semiology of diarrhea of these patients. The relationship between drug administration and diarrhea in our patients must be discussed. Levodopa, oxitriptan, or L-carnitine might induce diarrhea; in the patients who received these drugs, diarrhea occurred before the introduction of these drugs. The other drugs used in our patients (pyridoxine, ropinirole, selegiline, clobazam) are not known to be responsible for diarrhea, or might rather induce constipation (bromocriptine, pramipexole, apomorphine pump, amitriptyline). Therefore we do not consider that the drugs administered to our patients could be responsible for diarrhea. In our two described patients, aqueous stools are described, and an exhaustive evaluation by gastro pediatricians was concordant with motor diarrhea. Loperamide treatment was ineffective in case 4, and improved moderately the digestive symptoms of case 8. Loperamide, with its antisecretory action and also its action on intestinal motility, is indeed the first line therapy for motor diarrhea (Ooms et al. 1984) but its benefit may vary among patients. Physiopathologic pathway of diarrhea in AADC deficiency might only be hypothesized. The role of serotonin and its metabolites in motor diarrhea has been largely described: serotonin increases intestinal motility, especially by stimulating 5-HT_4 and 5-HT_3 receptors. In AADC deficiency, even though serotonin rate is low, the increased level of the serotonin precursor 5-HTP might be implicated in the occurrence of digestive troubles (Hyland et al. 1992). Autonomic dysfunction is a common cause of diarrhea, and such autonomic dysfunction, which is part of AADC pathophysiology, might also be implicated in chronic diarrhea observed in AADC patients (Swoboda et al. 2003).

Among our group of ten patients, two children (case 1 and case 5) (Barth et al. 2012; Arnoux et al. 2013) are noteworthy because they had normal intellectual efficiency, and they attended a normal school at last follow-up (10 years old for patient 1 and 6 years old for patient 5). Although mental retardation is not reported in all the patients reported in the literature (Brun et al. 2010; Tay et al. 2007), in most cases AADC deficiency causes a severe encephalopathy. However, patients display severe hypotonia and abnormal involuntary movements which dramatically interfere with motricity and communication abilities; therefore, their cognitive level is difficult to evaluate. Other milder phenotypes have been recently described (Helman et al. 2014; Leuzzi et al. 2015), suggesting the heterogeneity and phenotypic widening of the disease.

The diagnosis of AADC deficiency in patient 4 of this series was suggested by increased VLA in the urinary organic acid profile, which was included in an exhaustive metabolic screening for chronic diarrhea. Urine VLA was increased in all but one patient of this series, and actually this elevation is not a constant finding in cases reported in the literature (Brun et al. 2010). This molecule can pass

unnoticed (Braütigam et al. 2000), and it can be necessary to ask specifically for it. Although this peak is not specific for AADC deficiency (Clayton et al. 2003; Mills et al. 2005; Hyland 2007), and is only exhibited by a subgroup of AADC patients, it must be considered as a red flag for AADC deficiency diagnosis, which will be confirmed by CSF neurotransmitters profile analysis. Therefore, organic acid profile in urine (including VLA dosage) is actually an interesting untangling test whatever the phenotype. Recently Atwal et al. reported a novel and less invasive approach to diagnose AADC deficiency using plasma metabolomic profiling (Global MAPS platform) (Atwal et al. 2015). This new technique in case of increased VLA in the urinary organic profile could increase the specificity of urinary organic profile, but is available in a limited number of laboratories up to now.

Molecular analysis identified ten different pathogenic variations including five novel mutations. Four children with a severe clinical phenotype were homozygous for the same mutation. The severity of clinical manifestations might be correlated to the nature of the genetic defect (Tay et al. 2007) and mild phenotypes recognition is important since the treatment might be more efficient (Tay et al. 2007; Allen et al. 2009). All of the patients, except patient 7, were treated according to the recommendations (Allen et al. 2009; Brun et al. 2010). Diarrhea in patient 5 was ameliorated after pyridoxine treatment, which also resulted in a decrease of dysautonomic symptoms like nasal obstruction; pyridoxine is converted to PLP (pyridoxal-5′-phosphate), an AADC cofactor which might result in increased residual enzyme activity. Overall, the various treatments were well tolerated, but therapeutic strategy resulted in poor improvement, and was very disappointing, as previously reported in the literature (Brun et al. 2010). Gene replacement therapy is currently developed and may represent an attractive therapeutic approach for this devastating disorder (Hwu et al. 2012).

Conclusion

Our observations expand the phenotype associated with AADC deficiency as we highlight that diarrhea might be a major symptom of the disease, associated or not with severe encephalopathy; more subtle symptoms suggesting autonomic dysfunction (nasal obstruction, excessive sweating, hypersalivation, ptosis), or sleep disorders might represent minor associated signs that are important to identify, as they might help the clinician to suggest the diagnosis of AADC deficiency and prompt urinary organic acid profile analysis. Diagnosis of the pathology is however difficult because of its clinical heterogeneity and VLA elevation in urine can be useful for the diagnosis.

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Consortium

N Bahi-Buisson (Service de Neuropédiatrie et Maladies Métaboliques Hôpital Necker Enfants Malades, Paris), JF Benoist (Service de Biochimie Métabolique Hôpital Robert Debré, Paris), A Cano (Service de Neuropédiatrie et Maladies Métaboliques Hôpital La Timone, Marseille), B Chabrol (Service de Neuropédiatrie et Maladies Métaboliques Hôpital La Timone, Marseille), L Damaj (Département de Pédiatrie, Rennes), N Garcia (Service de Neuropédiatrie et Maladies Métaboliques Hôpital Robert Debré, Paris), D Gras (Service de Neuropédiatrie et Maladies Métaboliques Hôpital Robert Debré, Paris), A Küster (Département de Pédiatrie, Nantes), F Moussa (Service de Biochimie Métabolique Hôpital Armand Trousseau, Paris), S Nguyen (Service de Neuropédiatrie, Angers), H Ogier (Service de Biochimie Métabolique Hôpital Robert Debré, Paris), C Ottolenghi (Service de Biochimie Métabolique Hôpital Necker Enfants Malades, Paris), L de Pontual (Département de Pédiatrie CHU Jean Verdier, Bondy), F Rivier (Service de Neuropédiatrie Hôpital Gui de Chauliac, Montpellier), E Roze (Service de Neuropédiatrie et Maladies Métaboliques Hôpital Robert Debré, Paris).

Take-Home Message

Diarrhea might be a major symptom of AADC deficiency and subtle associated symptoms (autonomic dysfunction, sleep disorders) are important to identify, as they might help the clinician to suggest the diagnosis of AADC deficiency and prompt urinary organic acid profile analysis.

Compliance with Ethics Guidelines

Disclosure of Conflicts of Interest

MA Spitz, MA NGuyen, S Roche, B Heron, M Milh, P de Lonlay, L Lion-François, H Testard, S Napuri, M Barth, S Fournier-Favre, L Christa, C Vianey-Saban, C Corne, A Roubertie declare that they have no conflict of interest.

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