ELSEVIER

Neurologic Abnormalities in Patients with Adenosine Deaminase Deficiency

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Defects in adenosine deaminase enzyme cause severe immunodeficiency. Without enzyme replacement or allogeneic bone marrow transplantation, patients often suffer fatal infection in infancy. Adenosine deaminase is expressed ubiquitously; deficiency may affect various organs, including the brain. Neurologic abnormalities occur in some adenosine deaminase-deficient patients, mostly in association with infection or after bone marrow transplantation. Three cases with significant neurologic abnormalities, including hypotonia, head lag, nystagmus, difficulty in focusing gaze, seizure disorder, and moderate-severe developmental delay but with no evidence of infection or transplant-related medication toxicity are presented. Computed tomographic scans and cranial MRI revealed volume loss and abnormalities of basal ganglia and thalamus, which may reflect accelerated nerve cell death or altered stimulation of adenosine receptors. Detailed neurologic and neuroimaging evaluation should be performed for all patients with adenosine deaminase deficiency upon diagnosis, to identify potentially significant brain lesions.

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Introduction

Adenosine deaminase (EC 3.5.4.4) is a ubiquitous enzyme crucial for purine nucleoside metabolism. Adenosine deaminase-deficient patients often present in early infancy with infections that are fatal unless treated by gene or enzyme replacement therapy and allogeneic bone marrow transplantation [1]. In addition, adenosine deaminase-deficient patients suffer from bone, kidney, or liver abnormalities that often are not related to infection and that improve with the removal of toxic purine metabolites, suggesting a direct effect of adenosine deaminase on cells in these organs [1]. Indeed, pharmacologic inhibitors of adenosine deaminase induce apoptosis [1].

Central nervous system abnormalities have been reported in several adenosine deaminase-deficient patients, before and after hematopoietic stem cell transplant [1-4]. In some, concomitant infections or medications may have contributed to the development of neurologic abnormalities. Recently, among 94 patients with severe combined immunodeficiency who received bone marrow transplant, significant neurologic abnormalities were found in 2 of 6 patients (33%) with adenosine deaminase defects, compared with only 4 of 88 (4.5%) among all other patients [5]. Similarly, behavioral problems were described more frequently in adenosine deaminase-deficient patients after bone marrow transplant, compared with patients who received a transplant for other conditions [6].

The objective was to better characterize and understand the effect of adenosine deaminase deficiency in the brain by reviewing the clinical and radiologic features in adenosine deaminase-deficient patients who suffered from significant neurologic abnormalities without evidence for associated infection or recent medication effects.

Materials and Methods

A retrospective analysis was conducted of all patients at the Hospital for Sick Children in Toronto who were diagnosed with adenosine deaminase deficiency and had neurologic abnormalities. Adenosine deaminase deficiency was diagnosed by demonstration of <1-2% enzyme activity, as described previously [5]. Only patients without an identifiable infection, medication, or anatomical cause for the neurologic abnormalities were included in the study.

Upon diagnosis of adenosine deaminase immunodeficiency, patients were treated in reverse isolation, as described previously [5]. Patients with significant neurologic abnormalities underwent extensive infectious and metabolic evaluations of the blood and cerebrospinal fluid, including

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polymerase chain reaction analysis for Epstein-Barr virus, cytomegalovirus, and herpes simplex viruses.

Computed tomographic axial images scans of the brain, at 5 mm, were obtained in patients with significant neurologic abnormalities before and after intravenous contrast-enhancement administration.

Magnetic resonance imaging was performed on a General Electric 1.5T superconducting magnet (Signa EchoSpeed, version 8.2.3 software; GE Medical Systems, Milwaukee, WI). Multiplanar, multisequence imaging included sagittal and axial T_1-weighted (TR/TE = 600/20 ms) and fast spin-echo T_2-weighted (TR/TE = 2000/100 ms) axial and coronal two-dimensional time-of-flight magnetic resonance angiography (33/4.8; flip angle, 30; matrix, 256 × 256; field of view, 14-15 cm). In addition, fluid-attenuated inversion recovery (TR/TE = 9000/100 ms; Time of Inversion, 2200) sequences, diffusion-weighted imaging and intravenous gadopentetate dimeglumine (0.2 mL/kg) enhanced scans were performed.

Results and Discussion

Of 14 patients with adenosine deaminase deficiency who were treated at the Toronto Hospital for Sick Children since 1991, 5 had significant neurologic abnormalities. Two of the five were excluded from the present study: one patient with progressive cytomegalovirus meningoencephalitis and another who suffered from bacterial meningitis prior to diagnosis [7]. The present report concerns the remaining three adenosine deaminase-deficient patients with significant neurologic abnormalities in whom no other etiology could be found (Table 1).

Patient 1 was born after 40 weeks of uncomplicated pregnancy at the 50th percentile for height, weight, and head circumference. He presented at 4 months of age with a 3-week history of bilateral pneumonia, chronic diarrhea, failure to thrive, and severe lymphopenia, typical of severe combined immunodeficiency. At that time, he was noticed to have stopped smiling; vocalizing was reduced, with no babbling. He also had moderate hypotonia of the trunk and extremities with head lag, severe rotatory nystagmus, and inability to make eye contact. Electroencephalography and visual evoked potential findings were normal.

Computed tomography (performed at 4½ months of age) and cranial magnetic resonance imaging (at 5 months) revealed mild to moderate dilatation of the ventricular system and the pericerebral fluid spaces (data not shown). The patient received supportive care, with resolution of his infections and with weight gain. By 9 months of age, however, little neurologic improvement was seen, and he could not roll from back to front or sit by himself. At 9 months of age, the patient received bone marrow transplant from an HLA-matched unrelated donor; 2½ months later, however, he died from respiratory insufficiency and multiorgan failure.

The second patient was well until 6 weeks of age, when he developed respiratory tract infection, oral thrush, and diarrhea and failure to gain weight. His weight and length were at the 50th percentile at birth but were <3rd percentile at 3 months of age, when he was referred to the Toronto Hospital for Sick Children. Profound lymphopenia and absent adenosine deaminase activity confirmed the diagnosis of adenosine deaminase-deficient severe combined immunodeficiency. This patient, too, had moderate hypotonia with head lag. Four weeks later, he received a bone marrow transplant without myeloablative chemotherapy, which was followed by rapid and complete immune reconstitution. One month later, at 5 months of age, he developed generalized seizures. There were no leukocytes or lymphocytes in the cerebrospinal fluid, although both were present in the peripheral blood, and concentrations of glucose and protein were normal, with no evidence of microbial organisms (including herpes group viruses).

Electroencephalographic studies revealed multiple independent spike foci with bilateral temporal-parietal epileptiform activity. Cranial scans with computed tomography (performed at 8 months; Fig 1a) and magnetic resonance imaging (performed at 12 months; Fig 1b) revealed cystic changes, calcification, and volume loss in the caudate nuclei, basal ganglia, and ventral thalami. At 1 year of age, severe psychomotor retardation was noticed. He could not support his head, roll, crawl, or sit without support. When placed on his stomach, he was unable to support himself with his extremities. He turned his head and eyes toward auditory stimulation, but made no attempt to grasp. There was no evidence of monosyllabic babbling. He had hypertonia of all extremities, with the tone in the lower limbs greater than in the upper limbs. In the front position and ventral suspension, truncal hypotonia was noted. When pulled to sitting position, he had complete head lag. Tendon reflexes were brisk, particularly in the lower limbs, without clonus. Visual evoked potentials were normal. At writing, the patient was 6 years old; his seizure disorder was controlled with valproic acid

Table 1. Immune and neurologic abnormalities in adenosine deaminase-deficient patients

Characteristic	Patient 1	Patient 2	Patient 3
Immune evaluation			
Infections prior to transplant	yes	yes	no
Leukocytes, × 10^9/L	8.5	11.2	7.7
Lymphocytes, × 10^9/L	0.085	0.112	0.023
CD3+, % total lymphocytes	1.1	3.8	38.2
CD19+, % total lymphocytes	3.7	38.7	38.2
CD56+, % total lymphocytes	62.1	42.8	14.5
ADA activity in blood, % control	1	2	<1
Immunoglobulin levels			
IgG, g/L	0.6	NA	NA
IgM, g/L	<0.1	<0.1	<0.1
IgA, g/L	<0.2	<0.1	<0.1
Neurologic evaluation			
Age of first neurologic abnormality	4 mo	3 mo	4 mo
Head lag	yes	yes	yes
Truncal hypotonia	yes	yes	yes
Rotary nystagmus	yes	no	no
Developmental delay	yes	yes	yes
Convulsive disorder	no	yes	yes
Sensorineural deafness	NA	NA	yes

Abbreviations:
ADA = Adenosine deaminase
NA = Not available

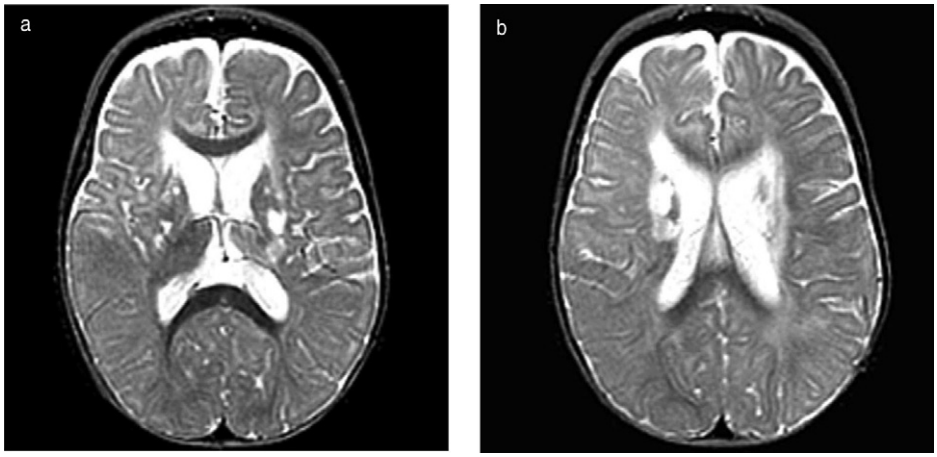

Figure 1. Cranial imaging of Patient 2. (a) Axial computed tomographic scan of the brain performed at 8 months of age, at 5-mm intervals and without enhancement, reveals focal cystic infarctions (white arrows) and volume loss in the caudate heads and basal ganglia and ventral thalami (black arrow). (b) Magnetic resonance imaging performed at 12 months of age. T_2 weighted images show extensive cystic change and volume loss in the basal ganglia, bodies of the caudate nuclei, and white matter of the centrum semiovale bilaterally.

and clobazam, but he did not sit unsupported, had poor swallowing coordination, had not progressed with motor or cognitive skills, and was nonverbal.

Patient 3, the younger sibling of patient 2, was diagnosed shortly after birth as suffering from adenosine deaminase deficiency. He remained free of infections and was growing between the 5th and 10th percentile for his age. At 4 months of age, it was noted that he has moderate hypotonia and head lag. Cranial magnetic resonance imaging (Fig 2a) revealed prominent pericerebral fluid and mild ventriculomegaly, which, together with discordantly large head circumference (43 cm, 75th percentile for age), was suggestive of extraventricular obstructive hydrocephalus. At 5 months of age, after myeloablative conditioning with busulfan and cyclophosphamide, he received CD34+ selected peripheral blood stem cell transplant from his HLA-haploidentical mother. Repeat assessments at 12, 18, 24, 36, and 48 months demonstrated severe sensory-neural deafness and moderate to severe motor and cognitive psychomotor delay.

At 2 years of age, he developed generalized seizures that manifested as apneic spells accompanied by clinical cyanosis and eye rolling, lasting for few minutes with a postictal period of 10-15 minutes. Blood biochemistry profile and metabolic findings were normal. Electroencephalographic and cerebrospinal fluid findings were normal, and no bacterial, viral, parasitic, or fungal organisms were found. Since then, seizures have recurred, with normal electroencephalography. Repeat cranial magnetic resonance imaging (Fig 2b) showed some resolution of pericerebral fluid, but abnormal persistence of ventriculomegaly; head circumference was 49 cm, almost at the 75th percentile for age—in contrast to height and weight, both of which were below the 5th percentile for age.

The three patients described herein suffered from significant neurologic abnormalities but, except for the adenosine deaminase deficiency, no definitive etiology could be found. Neurologic abnormalities in patients with severe immune defects are often secondary to infections that cause meningitis and encephalitis. No infectious etiology

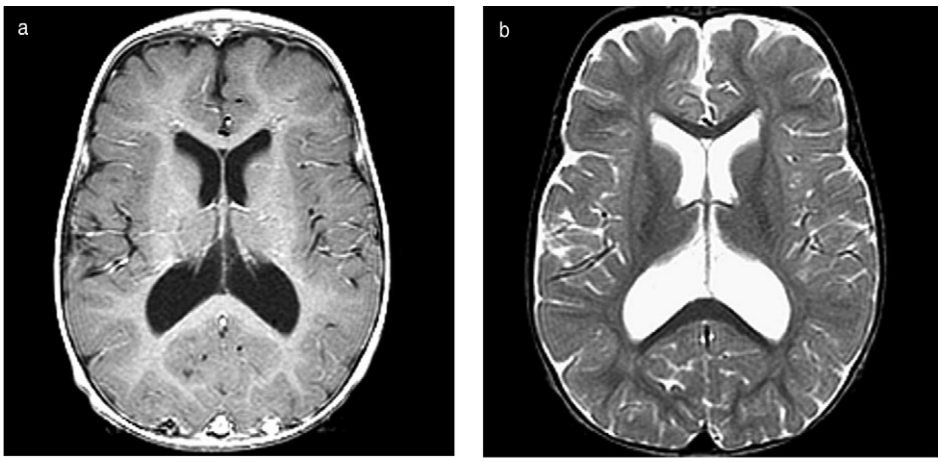

Figure 2. Cranial magnetic resonance imaging of Patient 3. (a) Imaging at 4 months of age. T_1 (left panel) and axial fast spin-echo T_2 (right panel) weighted images demonstrate prominent pericerebral fluid accumulation and mild ventriculomegaly. (b) Imaging at 22 months of age. The T_1-C+ (left panel) and T_2 (right panel) weighted images demonstrate some resolution of pericerebral fluid, but abnormal persistence of ventriculomegaly.

could be documented, despite extensive studies, and the patients had no other signs of infection, such as fever or leukocytosis, which patients with severe immunodeficiency (including adenosine deaminase deficiency) can exhibit. Thus, although infectious agents cannot be conclusively excluded, infections were unlikely causes for neurologic abnormalities in these three patients.

Neurologic abnormalities are more frequently reported in patients with adenosine deaminase deficiency than in patients with most other causes of severe immunodeficiency, although the severity of the immune defect and the frequency of other infections are often not different [8]. Patients 1 and 3 had neurologic abnormalities prior to transplant; patient 2 did not receive any myeloablative conditioning, and so the brain damage was likely unrelated to chemotherapy. These patients were not receiving medications commonly associated with neurologic damage, and none had asphyxia after birth, suggesting that the adenosine deaminase deficiency itself may have caused the neurologic abnormalities. Similar neurologic abnormalities, which improve after enzyme replacement, were described in patients with adenosine deaminase deficiency, which also supports the role of the enzyme deficiency in inducing these abnormalities [1-3].

A few other immunodeficiency diseases have an increased frequency of nervous system damage, unrelated to infections. These include spastic diplegia in patients with purine nucleoside phosphorylase deficiency, microcephaly and developmental delay in patients with ligase IV, and the ataxia in patients with ataxia-telangiectasia [9-10]. Different pathogenic mechanisms probably are involved in the neurologic abnormalities in each immunodeficiency.

The reason for increased frequency of neurologic abnormalities in adenosine deaminase deficiency is not known. Defective adenosine deaminase activity results in accumulation of adenosine and 2′-deoxyadenosine, which are toxic particularly to rapidly dividing cells such as thymocytes [1]. A similar mechanism may induce death of nervous systems cells and explain the brain volume loss documented in some ADA-deficient patients. The present magnetic resonance imaging findings, novel for a group of adenosine deaminase patients, suggest an additional mechanism. In one patient, magnetic resonance imaging also revealed basal ganglia and thalamic abnormalities, which may explain the increased frequency of movement disorders reported in adenosine deaminase-deficient patients [1,11,12] and in mice with low adenosine deaminase activity [13]. The basal ganglia and thalamus are also areas where adenosine receptors are particularly abundant [14]. Thus, the altered adenosine homeostasis in adenosine deaminase deficiency may also lead to abnormal basal ganglia stimulation and consequently abnormal movement and motor function.

In conclusion, patients with adenosine deaminase deficiency suffer frequently from a variety of neurologic abnormalities. Careful neurologic and neuroimaging evaluation can, as in these present cases, identify, significant lesions in the nervous system.

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