Pediatric Neurology 158 (2024) 49–56

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Review Article

A Clinical Neurological Approach to the Child With Adenosine Deaminase Deficiency

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ARTICLE INFO

Article history:
Received 23 January 2024
Accepted 28 May 2024
Available online 8 June 2024

Keywords:
Adenosine
Adenosine deaminase
Brain calcifications
Seizures
Cognitive impairment
Sensorineural hearing loss

ABSTRACT

Background: Severe combined immunodeficiency secondary to adenosine deaminase deficiency is rare. The deficiency of this enzyme results in the accumulation of substrates in the tissues, including the brain. Clinical signs of neurological involvement may include seizures, neurodevelopmental disorders, hypotonia, and sensorineural hearing loss. Hematopoietic stem cell transplantation corrects the failure of the immune system but not the neurological involvement.
Objectives: To describe the spectrum of neurological complications identified in a series of children with severe combined immunodeficiency due to adenosine deaminase deficiency. Additionally, we propose a neurological approach including electrophysiological, radiological, and neurocognitive studies to address this group of children in an efficient and timely manner.
Methods: A descriptive, observational, retro-, and prospective analysis of patients with a confirmed immunological diagnosis seen between 1996 and 2021 and referred to the Department of Neurology for neurological evaluation was conducted.
Results: Ten patients met the inclusion criteria. The median age at diagnosis was 4 months (range, 1-36 months). All patients had neurodevelopmental delay with hypotonia in six, language delay in three, sensorineural hearing loss in four, and spastic paraparesis in one patient. Two children developed an epileptic syndrome, consisting of generalized epilepsy in one and focal epilepsy in the other. Neuroimaging showed brain calcifications in the basal ganglia and/or centrum semiovale in four patients and enlarged subarachnoid spaces in two other patients.
Conclusion: In this pediatric series, the rate of neurological involvement associated with abnormalities on neuroimaging was high. Although this involvement could be related to accumulation of adenosine metabolites in the central nervous system, the possibility of associated chronic infections should be ruled out. Given the neurological manifestations, it is important to involve the pediatric neurologist in the multidisciplinary follow-up team.

Introduction

Severe combined immunodeficiency (SCID) is a primary immunodeficiency that is caused by different molecular defects and is characterized by the absence and/or abnormal function of T lymphocytes, and variably of B and natural killer lymphocytes. This disorder is associated with high morbidity and mortality, and patients usually die before one year of life. One of the molecular defects causing SCID is adenosine deaminase (ADA) deficiency. SCID due to adenosine deaminase deficiency (ADA-SCID) is a rare

Data availability: All data generated or analyzed during this study are included in this published article (and its supplementary information files).
Availability of a code: Not applicable.
Ethical approval: Not applicable.
Consent to participate in the study: Not applicable.
Consent to publication: Patients or legal guardians have given written consent for publication.

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https://doi.org/10.1016/j.pediatrneurol.2024.05.022

autosomal recessive disease that accounts for 10% to 20% of all SCID cases.[1,2]

The ADA enzyme, encoded by the *ADA* gene, catalyzes the irreversible deamination of adenosine and deoxyadenosine in the purine catabolic pathway.[2,3] The absene of the enzyme causes an accumulation of toxic substrates (adenosine and deoxyadenosine), leading to deleterious effects on the development and function of the affected cells.[1,2] The ubiquitous expression of ADA explains the additional effects observed outside the immune system, including those on the central nervous system (CNS).[1,4-8]

Enzyme replacement therapy with polyethylene glycol-ADA is used as a bridge to curative therapy of the immune defect. Allogeneic hematopoietic stem cell transplantation (HSCT) and gene therapy have now been shown to be effective curative therapies[9]; however, in Argentina only HSCT is available. Although these patients are at risk of various neurological complications associated with opportunistic infections, greater neurological involvement has been observed in patients with ADA-SCID by different mechanisms.[4,5,7,10] The toxic effect of adenosine accumulated in the CNS at the cellular level may contribute to the development of the neurological conditions seen in this group of children, even after the correction of the immune defect.[6]

The objective of this study was to describe the spectrum of neurological manifestations in a series of patients with this exceptional immunodeficiency diagnosed and followed at a tertiary care hospital. Furthermore, based on the spectrum analyzed, we aimed to propose a plan including electrophysiological, radiological, and neurocognitive studies to address this group of children in an efficient and timely manner.

Materials and Methods

A descriptive, observational, retro-, and prospective analysis was conducted of patients with a confirmed immunologic diagnosis seen between 1996 and 2021 at the Hospital de Pediatría Juan P. Garrahan, in interdisciplinary follow-up at the departments of immunology, bone marrow transplant, and clinical pediatrics and referred to the department of neurology for evaluation of neurological involvement.

The inclusion criteria were (1) patients with a SCID immunologic phenotype as defined by the Primary Immune Deficiency Treatment Consortium 2022 definitions, with a confirmed diagnosis of ADA deficiency by enzymatic activity; (2) presence of signs or symptoms of neurological involvement; (3) detailed and sufficient information available from the medical records (electronic and paper) of the hospital; and (4) availability of complementary laboratory and neuroimaging studies.

The variables that were analyzed included demographic data, clinical characteristics at presentation, outcome characteristics, treatments received and their clinical impact and complications, and complementary studies including neuroimaging, brain evoked potentials, electroencephalography (EEG), and laboratory tests.

Results

Population

Ten patients were included, six of whom were male. All patients had lymphopenia, with T-cell counts below 1000/mm^3. They all met the SCID criteria defined by the Primary Immune Deficiency Treatment Consortium 2022 definitions for SCID.[1] Additional immune phenotyping was performed as necessary, including measurement of naive T cells (CD3/CD4/CD45RA) and lymphocyte proliferation assays to further study T-cell maturation and function (Table 2). Four patients had typical SCID, whereas six had leaky SCID. Additionally, ADA enzyme activity assays confirmed ADA deficiency in all patients, showing very low or absent enzyme activity. Genetic confirmation was achieved in only three patients, one of whom was born to a consanguineous couple, due to technical limitations before widespread genetic testing. Median age at diagnosis was 4 months (range, 1 to 36 months). In nine of 10 patients the diagnosis was made before 12 months and in only one at 36 months of life (Table 1). It is important to consider that universal newborn screening for SCID using an assay to detect T-cell receptor excision circles in dried blood spots is unavailable in Argentina.

Six patients were unable to undergo HSCT, either due to the lack of a donor or due to death before curative treatment, whereas the remaining patients had the opportunity to receive curative gene therapy. Five of these six children died. Patient 5 died at age seven months due to sepsis associated with disseminated bacillus Calmette-Guérin infection caused by methicillin-resistant coagulase-negative staphylococci and influenza A pneumonia, Patient 8 died at age three months due to *Acinetobacter spp.* sepsis/*Pseudomonas* pneumonia, and Patient 9 died at age 1 year and 2 months due to a severe hemolytic crisis. Of note, the bacillus Calmette-Guérin vaccine is given at birth as part of the Argentine immunization schedule in all newborns. In two patients the cause of death was not documented.

Four patients (Patients 1, 2, 9, and 10) received enzyme replacement therapy as a bridge to HSCT, four received HSCT (Patients 1, 2, 3, and 4), and Patient 10 underwent gene therapy in another country. Two of the patients treated with HSCT, including the one who received gene therapy, developed a secondary tumor (abdominal dermatofibrosarcoma). The following infectious complications were observed: one patient was positive for cytomegalovirus pre- and post-transplantation, four patients experienced Epstein-Barr virus reactivation and required early treatment with rituximab, and two patients developed toxoplasmosis (reactivated three to six months post-transplantation).

Neurological involvement

Of the 10 patients included in the analysis, eight showed neurodevelopmental delay of gross motor predominance; in four of them who underwent some form of neuropsychological assessment, abnormal results were found. Patients 1, 2, 3, and 4 had language delay and lower scores on the neurodevelopmental screening tests (Table 3). Patient 2 developed a paraparetic gait.

Four patients (1, 2, 9, and 10) had sensorineural hearing loss with different findings on the hearing tests, and in two other patients (3 and 5) the otoacoustic emissions (OAE) were absent. Three patients did not complete OAE due to their age (two to three months) and clinical severity at the time of evaluation.

Clinical seizures were observed in two patients (1 and 4), associated with abnormal EEG recordings: Patient 1 had generalized seizures with a compatible EEG pattern (Fig 1), and Patient 4 developed right focal seizures with EEG correlates. One patient (3) did not have clinical seizures, but the EEG showed an abnormal interictal pattern. Both patients who had clinical epileptic seizures received treatment with levetiracetam. In one of them, a benzodiazepine had to be added for adequate seizure control, whereas in the other levetiracetam had to be discontinued due to the development of disruptive behavior, switching to valproic acid with a good clinical response. Although in the latter patient the seizures were successfully controlled, the EEG pattern remained severely abnormal (Fig 1). Neuroimaging studies identified calcifications in the basal ganglia and centrum semiovale in four patients (1, 2, 5, and 9) and enlargement of the subarachnoid spaces over the convexity with ventricular asymmetry in three others (3, 4, and 6) (Figs 2-5).

TABLE 1.
Demographic Data, Treatment, and Outcome of Our Series of Patients

Patient	1	2	3	4	5	6	7	8	9	10
Age at diagnosis (months)	1	3	4	36	7	4	2	3	2	4
ADA enzyme activity Reference value: 63 ± 41.4 nmol/h/mg	0.0	0.0	0.0	8	12.4	1.03	0.04	0.15	0.4	0.11
Molecular studies	c.484 C>T homozygous	No	No	c.320 T>C; c.466 C>A	No	No	No	No	c.484 C>T homozygous	No
Enzyme replacement therapy	4 months	8 months	No	No	No	No	No	No	8 months	22 months
HCST	6 months	13 months	8months	3 years	No	No	No	No	No	No
Gene therapy	No	No	No	No	No	No	No	No	No	3 years
Tumors	-	-	Abdominal dermatofibrosarcoma protuberans	-	-	-	-	-	-	Abdominal fibrosarcoma
CMV	Negative	Negative	Negative	Positive pretransplant and 1 month post-transplant	Negative	Negative	No data	No data	Negative	No data
Toxoplasmosis	Reactivation at 3 months post-HSCT	Negative	Positive at 6 months post-HSCT	Negative	Negative	Negative	No data	No data	Negative	No data
HIV	Negative	Negative	Negative	Negative	Negative	Negative	No data	No data	Negative	No data
EBV	Positive at 2 months post-HSCT, treatment with rituximab	Positive at 3 months post-HSCT, treatment with rituximab	Positive at 3 months post-HSCT, treatment with rituximab	Positive at 1 month post-HSCT, treatment with rituximab	No data	Negative	No data	No data	No data	No data
Death	No	No	No	No	Yes	Yes	Yes	Yes	Yes	No

Abbreviations:
ADA = Adenosine deaminase
CMV = Cytomegalovirus
EBV = Epstein-Barr virus
HIV = Human immunodeficiency virus
HSCT = Hematopoietic stem cell transplantation

TABLE 2.
Immunology Data in Our Series of Patients

Patient	1	2	3	4	5	6	7	8	9	10
Cellular immunity										
Total lymphocytes	**1040/mm^3**	**361/mm^3**	**189/mm^3**	**180/mm^3**	**873/mm^3**	**465/mm^3**	**259/mm^3**	**1512/mm^3**	**59/mm^3**	**550/mm^3**
CD3	**2%**	**23%**	**48%**	**71%**	**10%**	**22%**	**0%**	**33%**	**5%**	**67%**
CD4	**1%**	**6%**	**20%**	**6%**	-	**8%**	**0%**	**8%**	-	**39%**
CD8	**0.70%**	**16%**	**28%**	**43%**	-	**13%**	**0%**	**23%**	-	**27%**
Humoral immunity										
CD19	**7%**	**3%**	**5%**	**0,70%**	**4%**	**3%**	**23%**	**58%**	**15%**	**<2%**
IgG	392 mg/dL	577 mg/dL	262 mg/dL	1410 mg/dL (con endovenous gamma globulin)	52 mg/dL	288 mg/dL	1600 mg/dL (con endovenous gamma globulin)	210 mg/dL	255 mg/dL	296 mg/dL
IgA	<6.67 mg/dL	<6.67 mg/dL	24 mg/dL	179 mg/dL	13 mg/dL	15 mg/dL	Not measurable	<7 mg/dL	<6.67 mg/dL	48 mg/dL
IgM	4 mg/dL	6 mg/dL	18 mg/dL	278 mg/dL	30 mg/dL	18 mg/dL	Not measurable	51 mg/dL	<4.17 mg/dL	45 mg/dL
Natural killer immunity										
CD16/56	78%	70%	42%	16.60%	78%	70%	77%	8%	80%	19%

The bold data in table reflect the immunological profile of this group of children.

Discussion

In our setting, the only curative treatment for ADA-SCID is HSCT; however, although HSCT resolves the immunologic impairment, it fails to prevent the development of neurological complications.[4]

The association between primary immunodeficiencies and neurological involvement is not uncommon. Neurological dysfunction has been observed in patients with various immunodeficiencies, including ataxia in ataxia telangiectasia, motor delay and microcephaly in ligase IV deficiency, and spastic paraplegia in purine nucleoside phosphorylase deficiency.[5] Nevertheless, neurological abnormalities are much more prevalent in patients with ADA-SCID. Epilepsy, sensorineural hearing loss, motor involvement, and neurodevelopmental delay have been described as part of the clinical spectrum in patients with this disease.[4-8,10,11]

In our series, all patients had motor developmental delay. In the six nontransplanted patients hypotonia was observed, and in the transplanted patients a delay in the onset of walking or gait disturbances was seen. On audiological evaluation, six of seven patients who underwent OAE measurement or brain stem auditory evoked potentials were found to have sensorineural hearing loss or absent OAE; three of them had undergone HSCT at the time of the screening, two patients did not reach the transplantation, and the remaining one received gene therapy. In a study including 12 patients with ADA deficiency who underwent transplantation, a high rate of sensorineural hearing loss was reported[6,9,11]; however, no exposure to ototoxic treatment and no history of viral infections were identified.[3,8]

Similar to the report by Nofech-Mozes et al., in our series neuroimaging findings were abnormal in seven of 10 patients.[6,7] Calcifications in white matter and basal ganglia were identified in four and increased subarachnoid spaces and ventricular asymmetry in three (Figs 2-5). Similar findings have been described in two series of patients with ADA treated with enzyme replacement therapy or HSCT.[5,6]

Although an infectious etiology should be one of the etiologies to be excluded in an immunocompromised patient with neurological dysfunction and similar findings on neuroimaging studies, none of our patients was admitted because of CNS infections (encephalitis or meningitis), and investigations for neurotropic viruses, toxoplasmosis, and human immunodeficiency virus were negative. Therefore, it is important to emphasize the hypothesis reported in the international literature that high levels of adenosine and deoxyadenosine triphosphate (dATP) generate an effect on the neurons and lead to the neurological clinical spectrum described in this article, which has also been reported previously. A research study on CNS complications in patients with ADA deficiency describes that six of 12 patients who underwent transplantation, one group that received conditioning treatment and one that did not, presented throughout the 12-year follow-up with motor abnormalities, hypoacusis, and cognitive involvement.[7] This finding suggests that these complications are not due to the transplant conditioning treatments. Although the pathophysiologic mechanism is not entirely clear, one possibility is that the accumulation of dATP causes a neurotoxic effect. To confirm this hypothesis it would be useful to analyze the values of deoxyadenosine and dATP levels, but this should be done before and after immunodeficiency correction.

In the literature, high adenosine concentrations are considered to be the cause of the deleterious effect at the neuronal level.[6,12] Adenosine acts as a neuromodulator, and four receptors named Adora—A1, A2A, A2B, and A3—have been identified, which are ubiquitously distributed throughout the body.[13] High expression

TABLE 3.
Neurological Complications in Our Series of Patients

Patient	1	2	3	4	5	6	7	8	9	10
Seizures	Seizures with upper limb hypotonia and flexion of lower limbs Atonic seizures	No	No	Right eye and head deviation left-sided hypertonia	No	No	No	No	No	No
EEG	Short bursts of generalized sharp waves of moderate frequency Paroxysmal voltage attenuations Bilateral temporal sharp wave paroxysms of moderate discharge frequency	EEG without focus of paroxysms	Disorganized diffuse slow waves predominantly in the anterior quadrant	Disorganized, predominantly left centrotemporal diffuse slow waves with brief paroxysmal voltage attenuations	No	No	No	No	No	No
Cranial MRI/CT scan	CT scan: bilateral calcifications in basal ganglia and bifrontal white matter	CT scan: multiple focal, bilateral, asymmetric calcifications in white matter in upper parietal regions	Mild asymmetry of lateral ventricles	Enlarged subarachnoid spaces and predominantly left-sided ventricular asymmetry	Calcifications in right thalamus	Enlarged subarachnoid spaces	No	No	Bilateral calcifications in basal ganglia and centrum semiovale	No
Hearing involvement	Severe bilateral sensorineural hearing loss	Severe bilateral sensorineural hearing loss	Failed acoustic emission testing	Brainstem auditory evoked response: normal	Failed acoustic emission testing	No	No	No	Moderate unilateral hearing loss	Moderate unilateral hearing loss
Motor involvement	No History of delayed gait acquisition	Paretic gait	Independent gait at 2 years	Global developmental delay (motor and language)	Hypotonia	Hypotonia	Hypotonia	Hypotonia	Hypotonia	Hypotonia
Neurodevelopment	CAT-CLAMS (4 years) Cat age equivalent to 18 months Expressive Clams age equivalent: 12 months Receptive Clams age equivalent: 16.5 m. Language delay associated with stereotypies and auto- and heteroaggression (autism)	WPPSI IV (3 years): Verbal comprehension: 62 mild impairment Motor CAT-CLAMS: gross and fine motor: 12 months (DC 60%) Clams language skills: 12 months (DC 70%)	Celf-2 (4 years): age equivalent: 3 years 2 months S.S: 7 S.P.: 85 Sentence structures (Celf-2): age equivalent: 3 years 1 month S.S: 8 S.P.: 90 Equivalent Gardner test: 2 years 8 months AE: 2 years, 10 months	Standford Binet IV: Challenging behavior in task performance. Vocabulary subtest: SS 94 Can name family figures Visual Abstract Reasoning: SS 92 Is able to trace simple geometric designs Graphic production is semicontrolled doodling. Does not achieve grip. Not able to copy horizontal or vertical line or circle	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated

Abbreviations:
AE = Age equivalent
CAT-CLAMS = Clinical adaptive testing/clinical auditory and linguistic milestone scale
Celf = Clinical Evaluation of Lenguaje Fundamentals
CT = Computed tomography
DC = Developmental quotient
EEG = Electroencephalography
MRI = Magnetic resonance imaging
S.P. = Scalar puntuation
SS = Standard score
S.S. = Smile social
WPPSI = Wechsler Intelligence Scale for preschool and elementary school

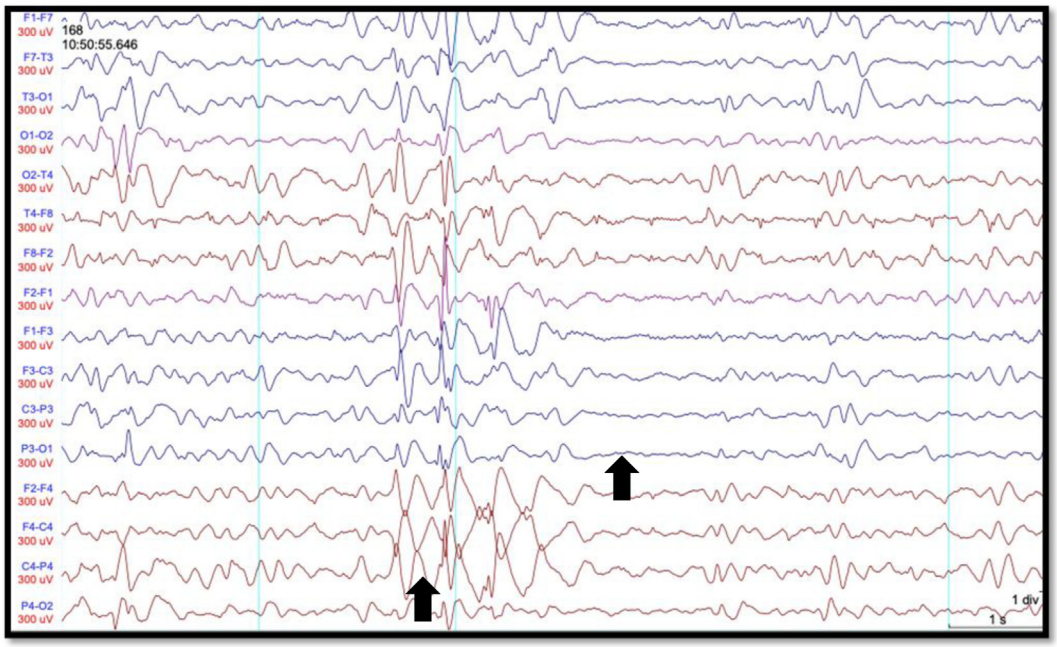

FIGURE 1. The electroencephalographic recording of Patient 1 shows brief bursts of generalized sharp waves of moderate discharge frequency, paroxysmal voltage attenuations, and bilateral temporal sharp wave paroxysms of moderate discharge frequency (black arrows). The color version of this figure is available in the online edition.

levels of the A1 and A2A receptors are found in the brain.[11] It has been hypothesized that overstimulation of the A1 receptor leads to inhibition of axon development with subsequent cell damage and death and that high adenosine levels increase the risk of seizures.[3] The abundance of adenosine receptors in the basal ganglia would justify the reported brain abnormalities.[3,7] In animal models, the

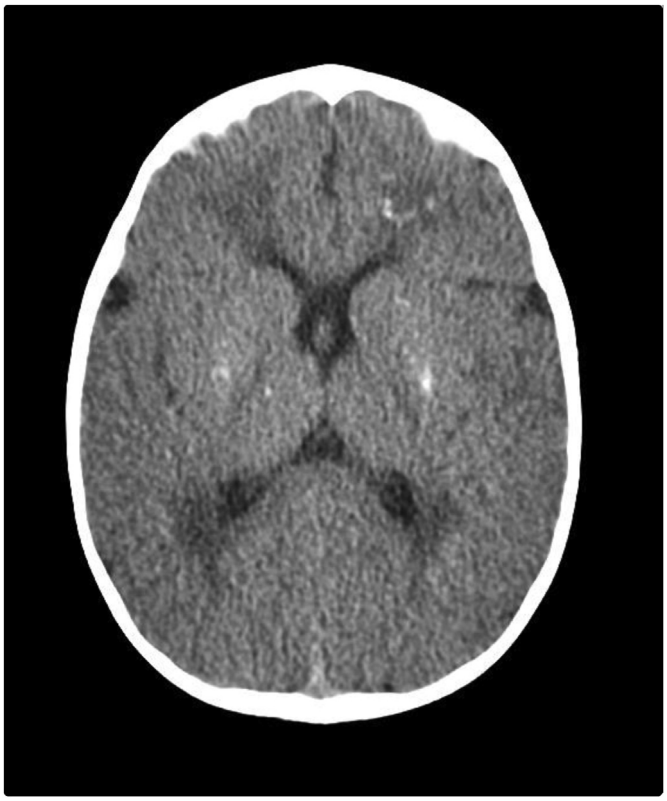

FIGURE 2. Patient 1: Cranial computed tomography shows bilateral basal ganglia and bifrontal calcifications.

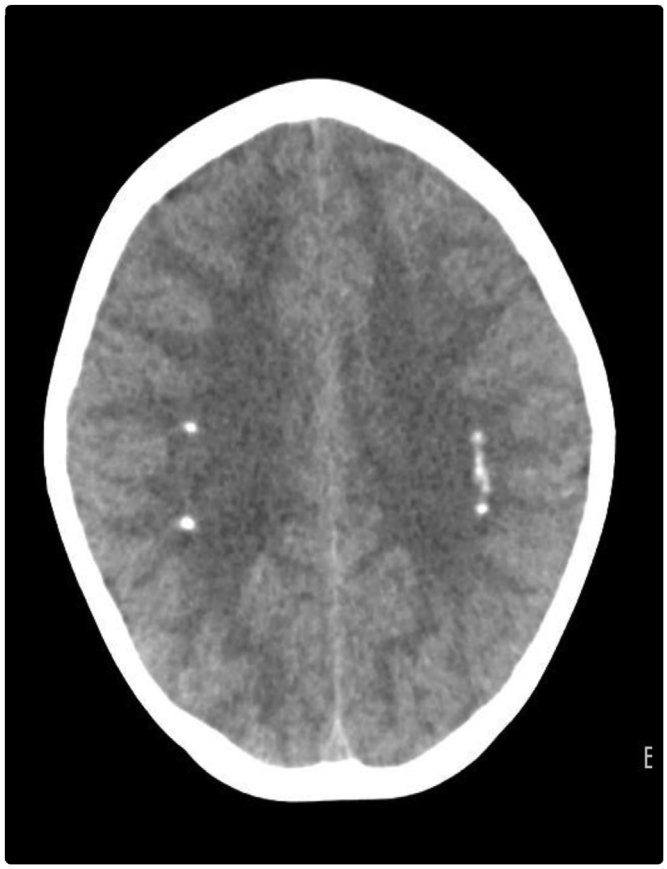

FIGURE 3. Patient 2: Cranial computed tomography scan shows multiple focal, bilateral, and symmetric calcifications in white matter in superior parietal regions.

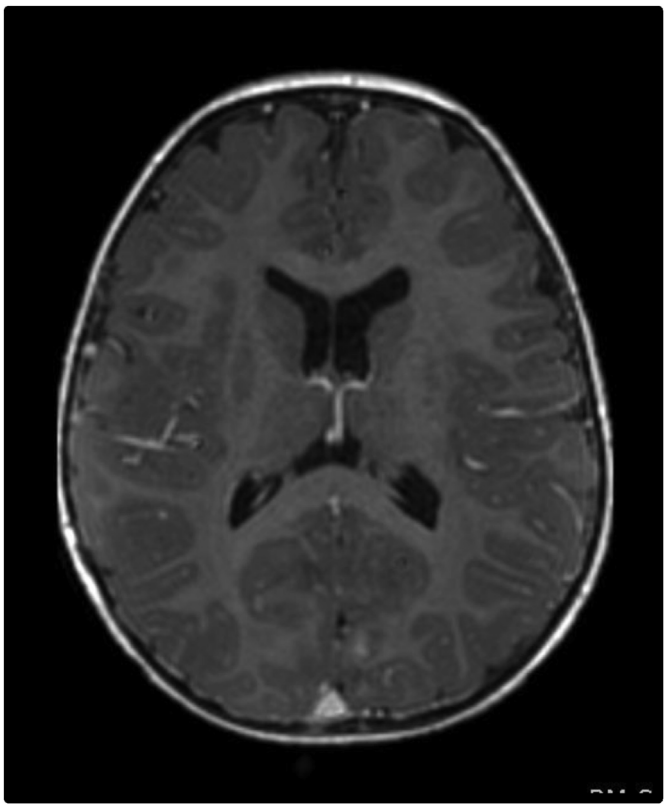

FIGURE 4. Patient 3: T1-weighted axial brain magnetic resonance imagingwith contrast enhancement shows mild asymmetry of the lateral ventricles.

concentration of ADA in brain tissue was measured using Western blotting, and high ADA concentrations were detected in the thalamus, hippocampus, cerebral cortex, and cerebellum, which would imply that the absence of the enzyme produces alterations in these areas due to the effect of its undegraded metabolites.[6]

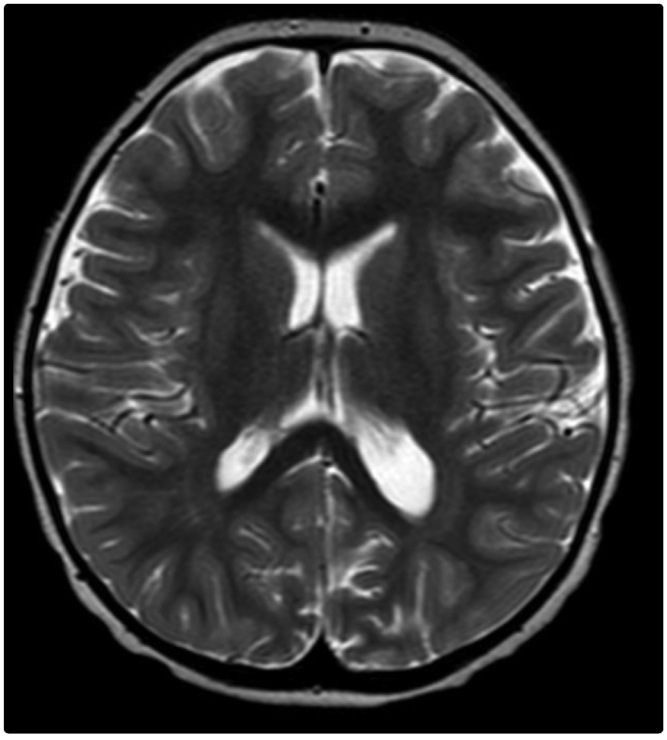

FIGURE 5. Patient 4: T2-weighted axial brain magnetic resonance imaging shows enlarged subarachnoid spaces and left ventricular asymmetry.

In a comparative study of patients with SCID with and without ADA deficiency (post-transplantation), cognitive involvement was evaluated. The authors found that children in whom ADA was absent had lower intelligence quotient scores compared with ADA-positive children; they also identified a negative impact of higher levels of dATP, an adenosine metabolite, on intelligence quotient.[14] In our series, the children who survived and continued in follow-up showed neurodevelopmental disorders, reflected in lower scores on screening studies such as CAT-CLAMS, Binet, and the Wechsler Intelligence Scale for preschool and elementary school (Table 3).

As ADA deficiency is rare, only a few small series on the association with epilepsy have been published in the literature and no characteristic electroclinical pattern was identified.[6,7]

Our results show that in spite of restoration of the immune response after the correction of ADA deficiency, during follow-up our patients developed neurological alterations similar to those reported in the literature. Therefore, we suggest that in the case of a patient with a diagnosis of immunodeficiency and ADA deficiency, a brain magnetic resonance imaging, EEG, and brain stem evoked potentials be performed and repeated annually. Regarding medications, we recommend the use of benzodiazepines and levetiracetam. In some cases, such as our patient's, the use of valproic acid is also suggested, not only for epilepsy but also for managing disruptive behaviors.

Conclusions

In this pediatric series, the rate of neurological involvement associated with neuroimaging abnormalities, hearing loss, and cognitive and motor developmental complications was high.

Although it is important to rule out the possibility of associated chronic infections, this involvement may cause neurological complications related to accumulation of metabolites of adenosine in the CNS.

The high prevalence of neurological complications in patients with ADA-SCID, even after correction of immune failure, leads us to recommend brain magnetic resonance imaging, EEG, neurological evaluation, psychodiagnostic tests, and auditory evoked potentials before transplantation and annually thereafter. Given the neurological manifestations observed, it is important to understand the clinical spectrum of neurological comorbidities and to include the pediatric neurologist in the interdisciplinary follow-up to improve the outcomes and quality of life of these patients.

CRediT authorship contribution statement

Paula Ivarola: Writing – original draft. **Roberto Caraballo:** Supervision. **Silvia Tenembaum:** Supervision.

Declaration of competing interest

The authors declare that there are no competing interests.

Acknowledgments

We would like to thank Ms. Janneke Deurloo for assistance in editing the manuscript.

Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.pediatrneurol.2024.05.022.

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