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SHORT RESEARCH ARTICLE

Adjunctive acetazolamide for drug-resistant seizures in SLC6A1-related neurodevelopmental disorder: An exploratory case series

Gia Melikishvili[1] | Olivier Dulac[2] | Otar Koniashvili[1,3] | Giorgi Mamardashvili[1,4] | Tamar Gachechiladze[1] | Nazhi Tabatadze[1] | Mariam Melikishvili[1] | Rimma Gamirova[5] | Tatyana Tomenko[6] | Igor Bakhtin[7] | Amber Freed[8] | Elena Bossi[9,10] | Bruria Ben-Zeev[11,12] | Gerhard Kluger[13,14] | Antonio Falace[15] | Antonella Riva[16] | Kai Kaila[17] | Pasquale Striano[15,16]

Correspondence
Gia Melikishvili, MediClubGeorgia Medical Center, 22 A, Tashkenti St, Tbilisi 0160, Georgia.
Email: g.melikishvili@mcg.ge

Abstract

Pathogenic variants in *SLC6A1* cause a neurodevelopmental disorder characterized by developmental delay with behavioral disturbances, seizures, often pharmacoresistant, and a spectrum of movement disorders such as ataxia. A similar triad is observed in other monogenic conditions, such as *SLC2A1*, *CHD2*, and *CACNA1A*-related disorders, where acetazolamide (ACZ) has shown beneficial effects. We assessed the efficacy of ACZ as an adjunctive treatment in patients with SLC6A1-related neurodevelopmental disorder (SLC6A1-NDD) and drug-resistant seizures. We recruited patients with genetically confirmed pathogenic *SLC6A1* variants and drug-resistant seizures treated with add-on ACZ. The medical records were reviewed to evaluate changes in seizure frequency and severity, and to document adverse events. Improvements in ataxia and social interaction were determined by clinical judgment together with caregiver reports. Six patients with a mean age of 7 years were included. The mean dose of ACZ was 16.2 mg/kg/day, and the mean treatment duration was 30 months. Three (50%) patients achieved full seizure remission, and the remaining three patients had a reduction in seizure frequency ranging from 50 to 90%. Except for weight loss in one patient, no serious adverse effects were reported. Three out of four patients with baseline ataxia showed improvement. Caregivers noted improvement in social interaction and school engagement in five out of six patients. ACZ may offer a promising therapeutic option for drug-resistant *SLC6A1*-related seizures. Prospective studies with larger cohorts and standardized outcome measures are necessary to confirm the efficacy and long-term safety of ACZ in this population.

For affiliations refer to page 8.

Plain Language Summary: Pathogenic *SLC6A1* variants in children cause developmental delay with behavioral issues, seizures, and often ataxia. In six children with drug-resistant seizures, adjunctive acetazolamide (ACZ) led to seizure freedom in three and a 50–90% reduction in the others. Improvement in ataxia and behavior, with better social and school performances, was reported. One child had mild weight loss. These early findings suggest ACZ may be a safe, effective, and affordable option for SLC6A1-related neurodevelopmental disorder when standard treatments fail, warranting further study.

KEYWORDS

acetazolamide, ataxia, autism, developmental delay, episodic ataxia, GABA, photosensitivity

1 | INTRODUCTION

SLC6A1 encodes the main GABA uptake transporter GAT-1, which regulates synaptic (phasic) and extrasynaptic (tonic) inhibitory neurotransmission.[1] Pathogenic variants in *SLC6A1* cause a neurodevelopmental disorder characterized by intellectual disability, behavioral problems, including autism, and neurological problems, including ataxia and epilepsy.[2–4] Despite the apparent heterogeneity of this phenotype among the affected individuals, the combination of epilepsy, ataxia, and developmental disorder is quite remarkable, and this is also reported in patients with *CACNA1A, SLC2A1* (GLUT1 deficiency), and *CHD2* mutations.[5–7]

Furthermore, the epilepsy phenotype itself is quite peculiar, starting in early childhood and including myoclonic and atonic seizures with generalized spike-waves, a pattern reminiscent of epilepsy with myoclonic–atonic seizures, also called Doose syndrome.[8–10] One-third of patients with SLC6A1-related neurodevelopmental disorder (SLC6A1-NDD) develop epilepsy that is pharmacoresistant to conventional anti-seizure medications (ASMs), with rates exceeding 50% in the adult population.[11] Thus, the epilepsy phenotype in SLC6A1-NDD resembles that reported with *CACNA1A*, *SLC2A1*, and *CHD2* mutations, highlighting a converging clinical pattern despite genetic diversity.[5–7]

Even more striking is the beneficial effect reported with acetazolamide (ACZ) on these three conditions. ACZ, a carbonic anhydrase inhibitor, is known to suppress neuronal network excitability by inducing an acidification within and outside brain cells.[12–15] Here, we investigated the potential of ACZ as an add-on treatment in patients with drug-resistant SLC6A1-related epilepsy.

Key points

- SLC6A1-related epilepsy commonly presents with myoclonic–atonic, myoclonic, and absence seizures and is often pharmacoresistant.
- To date, there is no precision medicine for SLC6A1-related NDD.
- Adjunctive acetazolamide was effective in all six patients with drug-resistant seizures in SLC6A1-related NDD.
- With adjunct acetazolamide, ataxia improved in 3/4 and photosensitivity resolved in 2/2; school/social engagement improved in 5/6.
- Larger controlled studies are needed to confirm the reproducibility of these findings.

2 | METHODS

Patients with pharmacoresistant epilepsy due to a pathogenic or likely pathogenic variant in the *SLC6A1* gene, who had been treated with ACZ at epilepsy centers in Eastern Europe and Israel, were eligible for inclusion. All consecutive eligible cases from participating centers were enrolled, and no patients were excluded. All participating centers have clinical experience using ACZ in developmental and epileptic encephalopathies, particularly in patients with generalized (myoclonic) seizures and co-occurring ataxia, as part of routine practice. Pharmacoresistance was defined as the failure to achieve sustained seizure control despite trials of at least two standard ASMs.[16]

Genetic testing was performed using trio-exome sequencing, achieving ≥20× coverage depth for ~99.10% of targeted bases. Variant interpretation was performed using the guidelines of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology.[17,18] ACZ was administered as an adjunctive therapy according to the usual clinical practice in the corresponding centers.

TABLE 1A Clinical features of our cohort and previous treatments.

Patient number/ current age/sex	SLC6A1 gene alteration	Age at seizure onset (years)	Seizure types since the onset	Seizure types prior to ACZ initiation	Photosensitivity (Hz)	Cognitive development	Ataxia/ paroxysmal movement disorders	ASMs used
1/7 years/F	c.913G>A/p. Ala305Thr likely pathogenic missense	6	Myoclonic–atonic seizures	Myoclonic–atonic seizures	No	Mild delay	Ataxia/ Episodic ataxia	OXC, CLZ, VPA, LTG
2/4 years/F	c.1070C>T/p. Ala357Val pathogenic missense	1.5	Eyelid myoclonus, atypical absences	Eyelid myoclonus	Yes	Moderate delay	Ataxia	VPA, ESM, TPM, LTG, LEV, CLB
3/8 years/F	c.1622C>T/p. Ala541Val likely pathogenic missense	1.5	Atypical absences, Myoclonic–atonic seizures	Atypical absences	Yes	Mild delay	No	LEV, VPA, ESM, LTG
4/21 years/F	c.863C>T/p. Ala288Val pathogenic missense	2.5	Atypical absences, Myoclonic–atonic seizures	Atypical absences, Myoclonic–atonic seizures	No	Borderline	No	VPA, LEV, CLZ, LTG
5/17 years/F	c.223G>A/p.Gly75Arg pathogenic missense	1	Eyelid myoclonus, Atypical absences, Myoclonic–atonic seizures	Eyelid myoclonus with/without absences, Myoclonic–atonic seizures	No	Moderate delay	Ataxia	VPA, TPM, LEV, CLB, ESM
6/2 years/F	c.1342A>T/p. Lys448Ter pathogenic nonsense	2	Atypical absences	Atypical absences	No	Moderate delay	Ataxia	VPA, TPM

Abbreviations: ACZ, acetazolamide; ASM, anti-seizure medication; CLB, clobazam; CLZ, clonazepam; d, daily; ESM, ethosuximide; F, female (Age is given in years); LEV, levetiracetam; LTG, lamotrigine; mo, month(s); OXC, oxcarbazepine; TPM, topiramate; VPA, valproate.

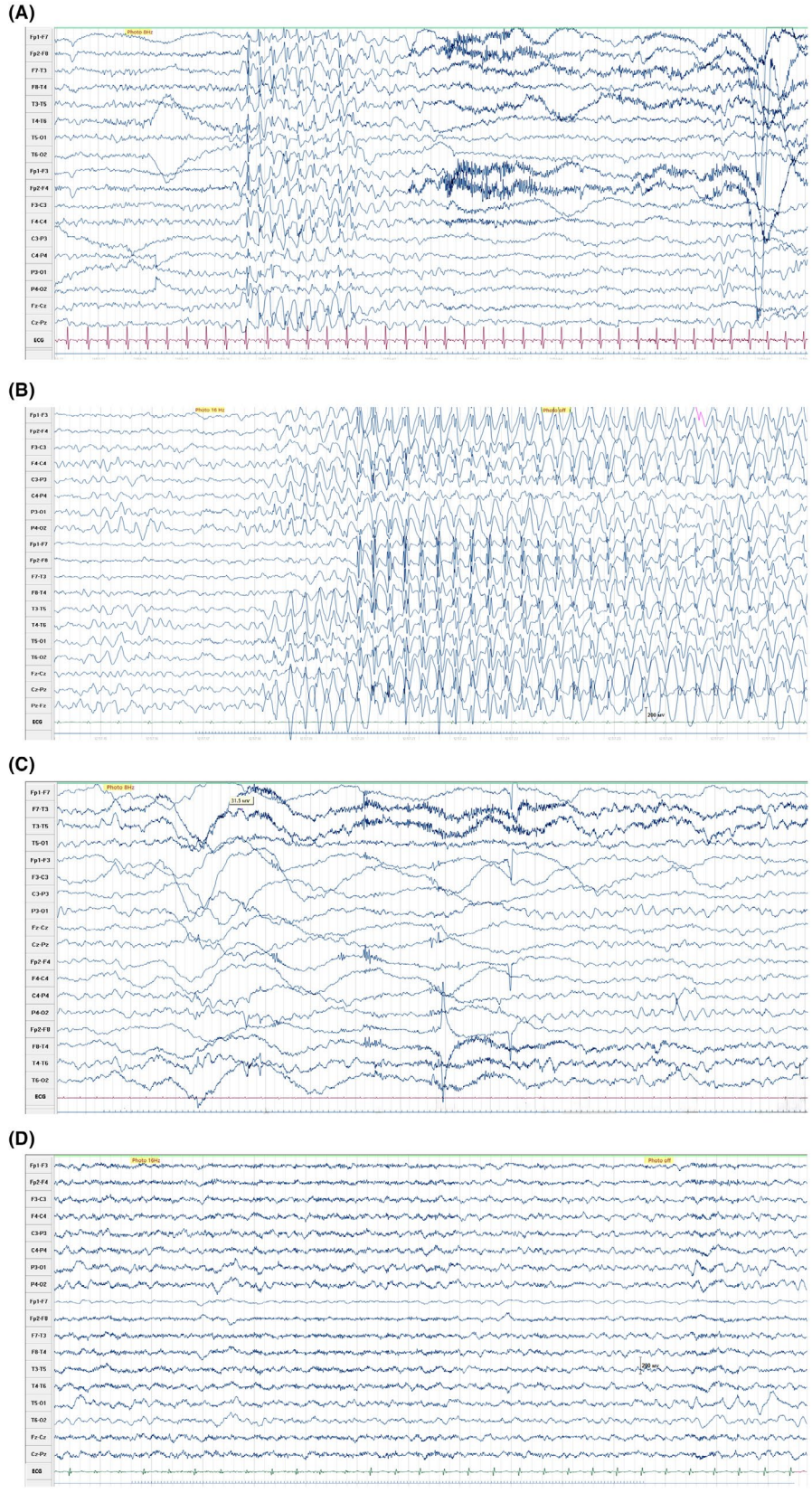

FIGURE 1 EEG tracings from patient #2 (A, C) and patient #3 (B, D) during intermittent photic stimulation (IPS). (A) and (B) show photoparoxysmal responses triggered at 8 Hz in patient #2 and 16 Hz in patient #3, respectively, before acetazolamide (ACZ) treatment. (C) Shows EEG of patient #2 during IPS at 8 Hz while on ACZ treatment. (D) shows EEG of patient #3 during IPS at 16 Hz while on ACZ treatment. Recordings were obtained using a longitudinal bipolar montage according to the International 10–20 system. EEG settings: Sensitivity 20 μV/mm, sweep 30 mm/s, high-pass filter 0.5 Hz, low-pass filter 70 Hz.

At each center, the referring neurologist reviewed the patients' clinical data, based on the medical records, including cognitive development, demographic information, seizure types and frequency, EEG findings, and ASM history before ACZ initiation. On ACZ, seizure reduction was evaluated during routine follow-up visits based on caregiver impressions and the neurologist's assessment. Seizure frequency was primarily quantified using caregiver-maintained seizure

TABLE 1B Acetazolamide treatment and efficacy.

Patient number	ACZ dose (mg/kg/day)	ACZ, treatment duration years/months	Current ASMs	ACZ - seizures	ACZ – ataxia/paroxysmal movement disorder	ACZ -photosensitivity	Adverse events
1	16.5	1 years 9 months	ACZ + OXC	Seizure-free	Improvement/Resolution of episodic ataxia	N/A	None reported
2	22	9 months	VPA + LTG + ACZ	90% reduction	Improvement	Disappeared	None reported
3	13	6 months	LTG + ESM + ACZ	Seizure-free	N/A	Disappeared	None reported
4	20	11 years	LTG + ACZ	Seizure-free	N/A	N/A	None reported
5	9	6 months	ACZ + ESM	50% reduction of both types	No effect	N/A	Weight loss
6	17	6 months	ACZ + VPA	≥75% reduction	Improvement	N/A	None reported

diaries. Only eyelid myoclonus was evaluated according to caregivers' impressions. When photosensitivity was present (assessed on EEG based on the ACNS Guidelines)[19] it was used as another marker of ACZ efficacy and was monitored both before and during treatment.

The primary efficacy criterion was a reduction in seizure frequency by over 50% as compared with the baseline. In patients who exhibited photosensitivity prior to treatment, its resolution was considered a criterion for a positive therapeutic response. Ataxia was evaluated based on caregivers' impressions. Adverse events were based on reports from the referring physicians and caregivers.

Written informed consent for data collection, storage, and publication was obtained from all participants or their parents/legal guardians. The study was conducted according to the Declaration of Helsinki.

3 | RESULTS

Six patients (all females) were recruited from three centers (Table 1A). In all cases, developmental delay preceded seizure onset. Four patients had a history of ataxia, including one who presented with episodic ataxia.

Seizure onset ranged from 12 months to 6 years (mean: 2.4 years). Seizure types included myoclonic seizures ($n = 5$), atypical absences ($n = 5$), and myoclonic–atonic seizures ($n = 3$). No patients experienced bilateral tonic–clonic seizures. All patients experienced daily seizures, with frequencies varying from one to several hundred (Table 1A).

Patients #2 and #3 exhibited eyelid myoclonus with absences and generalized spike–wave discharges on EEGs triggered by photic stimulation at 10–12 Hz, which were fully controlled following treatment with ACZ (Figure 1).

The mean age at the start of treatment was 7 years (range: 2–17 years). In all patients, epilepsy was resistant to multiple ASMs, including valproic acid (used in all 6 patients), lamotrigine (4 patients), levetiracetam (4 patients), ethosuximide (3 patients), topiramate (3 patients), clonazepam (2 patients), clobazam (1 patient), and oxcarbazepine (1 patient), often in various combinations. The median dose of ACZ was 16.75 mg/kg/day, ranging from 9 to 22 mg/kg/day. The median follow-up duration for ACZ treatment was 7.5 months (range: 6–132 months; mean: 30 months; Table 1B).

All patients demonstrated a positive response to ACZ treatment. Three patients achieved complete seizure remission, while patients #5, #6, and #2 experienced seizure reductions of 50%, 75%, and 90%, respectively (Table 1B). The median reduction in seizure frequency was 95% (50–100%). Photosensitivity was fully controlled by ACZ in the two affected patients (Figure 1).

A single adverse event, potentially related to ACZ, was observed: weight loss in patient #5, due to decreased

appetite. This patient had a 50% reduction in seizure frequency. Of the four patients with ataxia, three showed significant improvement compared with baseline. Following the initiation of ACZ, Patient #1 has remained free of further episodic ataxia attacks (Videos S1 and S2). Caregivers also reported improvement in patients' social interaction and school performance in five out of six patients.

In our cohort, all six patients derived clinical benefit from ACZ and continued treatment throughout follow-up; notably, the onset of acetazolamide's clinical efficacy was observed in all six patients within 2 weeks; no nonresponders were identified.

4 | DISCUSSION

GAT1, encoded by *SLC6A1*, plays a critical role in controlling neuronal excitability by limiting GABAergic transmission via reuptake of GABA from the extracellular space in brain tissue, thereby limiting both synaptic and tonic GABAergic inhibition.[1] Disruption of GABAergic neurotransmission is a well-established mechanism leading to epileptic seizures. Interestingly, there is also lots of evidence that excessive GABAergic activity may, somewhat paradoxically, facilitate seizure generation.[13,20] During intense activity of corticohippocampal interneurons, the effect of GABA shifts from inhibition to frank excitation in a HCO_3-dependent manner, and this effect is blocked by ACZ both in vitro and in vivo.[13] Loss-of-function haploinsufficient variants in *SLC6A1* rank among the top 10–20 genes with the highest number of pathogenic variants in the largest epilepsy cohorts,[21] and *SLC6A1* was identified as one of the top 10 genes exhibiting the highest burden of pathogenic variants in individuals with autism spectrum disorder.[22,23]

The most common seizure types in *SLC6A1*-related epilepsy are myoclonic–atonic, myoclonic, and absence seizures. While valproate, lamotrigine, and ethosuximide have shown effectiveness in some patients, approximately one-third of individuals with pathogenic *SLC6A1* variants develop pharmacoresistant epilepsy.[11]

In this case series, we observed a notable reduction in seizure frequency and severity with ACZ, along with improvements in ataxia, social interaction, and school performance, based on caregivers' impressions. These observations suggest that ACZ may target a shared mechanism regulating neuronal excitability, thereby explaining its efficacy across multiple aspects of the SLC6A1-NDD phenotype, including seizures, ataxia, and behavioral disturbances.

By far, most *SLC6A1*-related disease mutations are de novo.[23] In the study by Trivisano et al.,[10] 98 out of 118 (83%) patients in whom inheritance was studied had a de novo variant, and in only 20 cases was the variant inherited from a parent. We have no explanation for the female-only distribution in our cohort, which contrasts with the more balanced sex ratio reported in the literature.[3] It is also worth noting that one patient presented with episodic ataxia, a phenotype which, to the best of our knowledge, has never been reported in patients with *SLC6A1* variants.

Recently, 4-phenylbutyrate, a traditionally used treatment for urea cycle disorders, was evaluated in a prospective, open-label, multiple-dose, single-treatment group case series involving patients with *SLC6A1*-associated epilepsy, and a 70% responder rate was found compared with baseline.[24] Unlike ACZ, which directly modulates neuronal excitability through pH shifts caused by carbonic anhydrase inhibition,[12] 4-phenylbutyrate is thought to act as a chemical chaperone, enhancing the folding and trafficking of misfolded proteins, including disease variants of GAT-1 proteins.[25,26]

SLC6A1 is one of three known monogenic causes of myoclonic–atonic epilepsy (MAE), alongside *NEXMIF* and *SYNGAP1*.[27] Notably, SYNGAP1- and NEXMIF-related epilepsies have also shown favorable responses to ACZ. These findings highlight the potential of repurposing ACZ for the treatment of pharmacoresistant epilepsies associated with monogenic etiology.

It could be of much interest to report the effective dosing of ACZ in the present study alongside previously published cohorts in which this compound was evaluated—specifically, in GLUT1 deficiency syndrome[6] and CHD2-related epilepsy,[7] where its effects on seizure control have been more extensively characterized. In the GLUT1 deficiency cohort, the reported dosing range was 3–28 mg/kg/day, and in the CHD2-related epilepsy cohort, it was 3.5–15 mg/kg/day. In our current SLC6A1 patient cohort, the effective dose ranged from 9 to 22 mg/kg/day. While these ranges show partial overlap across the three studies, no firm conclusions can be drawn regarding potential differences in dosing requirements or efficacy among these disorders, particularly given the small sample size of the current study and the absence of dose–response analysis.

A frequent question in studies on the seizure-suppressing effect of new compounds is the possible development of tolerance, an issue pointed out for ACZ in the treatment of juvenile myoclonic epilepsy.[28] However, in the patients with GLUT1 deficiency, tolerance was observed in 2 out of 17 individuals, with onset occurring at least 1 year after the start of treatment.[6] In the CHD2-related epilepsy cohort, partial tolerance was observed in only 1 out of 12 patients; however, ACZ was continued due to its sustained partial efficacy.[7] In total, tolerance was observed in 3 of 29 patients (10%), including one with partial tolerance and another with restored efficacy after a 1-month ACZ washout and reinitiation.[6,7] These findings

challenge the widely held misconception that tolerance to chronic ACZ use is frequent and uniformly limits long-term efficacy; this does not seem to apply to various monogenic epilepsies.

Given the present findings, it is important to consider whether ACZ's efficacy reflects a general class effect of ASMs with carbonic anhydrase inhibitor properties. However, clinical experience suggests this is unlikely. Topiramate, zonisamide, and even sulthiame, despite their CA-inhibiting properties, have shown little or no consistent benefit in comparable patient populations,[6,7] including the present study in which patients #2, #5, and #6 had been treated with topiramate (see Tables 1A and 1B). Notably, in the GLUT1 deficiency cohort, topiramate was administered in nine cases, and zonisamide in six, with partial or no response in most cases. The one patient with CHD2-related epilepsy showed a limited response to topiramate.[6,7] These observations suggest that (i) the above compounds are not as effective as ACZ in inhibiting critical CA isoforms in the brain,[12] or that (ii) ACZ may have unique mechanisms of action that are particularly relevant in these monogenic neurodevelopmental disorders. Numerous genes related to brain disorders show a striking convergence into a largely shared disease phenotype,[29] and in the three disorders discussed here, ACZ seems to act somewhere in the shared pathways. Whether ACZ will show an even broader potential remains to be seen. Indeed, while the current medical literature is limited and largely anecdotal, insights drawn from epilepsies related to *CHD2*, *GLUT1*, *CACNA1A*, *SYNGAP1*, *NEXMIF*, and *KCNA2* variants support the hypothesis that in genetic neurodevelopmental disorders where pharmacoresistant epilepsy and severe ataxia coexist, ACZ may be a rational but mostly overlooked therapeutic option that warrants further preclinical and clinical investigation.[5,6,12,24,30]

5 | CONCLUSION

This case series indicates that acetazolamide (ACZ) may be a safe and effective adjunctive therapy for drug-resistant seizures in individuals with SLC6A1-NDD. Half of the patients achieved seizure freedom, while the remaining experienced substantial reductions in seizure frequency. Improvements in overall functioning were reported in several cases. No significant adverse effects or signs of tolerance emerged. These preliminary findings warrant further investigation through prospective studies using standardized outcome measures to better define ACZ's long-term efficacy and broader therapeutic potential in this population.

6 | LIMITATIONS

This study offers encouraging evidence supporting the potential role of ACZ in SLC6A1-related epilepsy. However, its interpretation is constrained by the modest sample size, retrospective design, and the absence of standardized outcome measures or a control group. Moreover, the favorable outcomes observed may be subject to publication bias, as cases with positive responses are more likely to be reported than those with limited or no benefit. Future controlled studies with larger cohorts and longer follow-up are essential to confirm these preliminary findings and to better define the long-term efficacy and safety of ACZ in this population.

AUTHOR CONTRIBUTIONS

Gia Melikishvili: Conceptualization; Supervision; Investigation (clinical evaluation); Data curation; Writing – original draft; Writing – review and editing. Olivier Dulac: Validation; Writing – original draft; Writing – review and editing. Otar Koniashvili: Conceptualization; Investigation; Writing – original draft; Writing – review and editing. Giorgi Mamardashvili: Data curation; Visualization; Writing – original draft; Writing – review and editing. Tamar Gachechiladze: Conceptualization; Data curation; Formal analysis; Investigation (clinical data acquisition); Writing – review and editing. Nazhi Tabatadze: Supervision; Resources; Formal analysis; Writing – review and editing. Mariam Melikishvili: Data curation; Project administration; Writing – review and editing. Rimma Gamirova: Investigation (clinical data acquisition); Resources; Data, Writing – review and editing. Tatyana Tomenko: Investigation (clinical data acquisition); Resources; Data; Writing – review and editing. Igor Bakhtin: Investigation (clinical data acquisition); Resources; Data; Writing – review and editing. Amber Freed: Resources; Formal analysis; Writing – review and editing. Elena Bossi: Investigation; Methodology; Resources; Writing – review and editing. Bruria Ben-Zeev: Investigation (clinical data acquisition); Resources; Data; Writing – review and editing. Gerhard Kluger: Investigation (clinical evaluation); Writing – review and editing. Antonio Falace: Writing – review and editing. Antonella Riva: Methodology; Writing – original draft; Writing – review and editing. Kai Kaila: Writing – original draft; Writing – review and editing. Pasquale Striano: Methodology; Supervision; Resources; Formal analysis; Writing – original draft; Writing – review and editing. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work.

AFFILIATIONS

[1]MediClubGeorgia Medical Center, Tbilisi, Georgia

[2]AdPueriVitam, Antony, France

[3]Department of Pediatrics, Stony Brook Children's Hospital, Stony Brook, New York, USA

[4]Tbilisi State Medical University, Tbilisi, Georgia

[5]Department of Neurology with Courses in Psychiatry, Clinical Psychology, and Medical Genetics, Kazan Federal University, Kazan, Russia

[6]Ural Federal University, Yekaterinburg, Russia

[7]Children's Regional Clinical Hospital, Ministry of Health of the Krasnodar Region, Krasnodar, Russia

[8]SLC6A1 Connect, Dallas, Texas, USA

[9]Department of Biotechnology and Life Sciences, University of Insubria, Varese, Italy

[10]Centre for Neuroscience, University of Insubria, Varese, Italy

[11]Sheba Medical Center, Pediatric Neurology, Edmond and Lily Safra Children's Hospital, Ramat Gan, Israel

[12]Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

[13]Department of Pediatrics, Institute of Rehabilitation, Transition and Palliation of Neurologically Ill Children, Member of ERN EpiCARE, Paracelsus Medical University, Salzburg, Austria

[14]Center for Pediatric Neurology, Neurorehabilitation and Epileptology, Schoen Clinic Vogtareuth, Vogtareuth, Germany

[15]IRCCS 'Giannina Gaslini', Full Member of ERN Epicare, Genoa, Italy

[16]Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa, Genoa, Italy

[17]Molecular and Integrative Biosciences (MIBS) and Neuroscience Center (HiLIFE), University of Helsinki, Helsinki, Finland

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CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

PATIENT CONSENT STATEMENT

Written informed consent for publication of clinical details was obtained from all patients (and/or their legal guardians). In addition, written informed consent was obtained from the patient's legal guardian for publication of the accompanying video material.

ORCID

Olivier Dulac https://orcid.org/0000-0001-9512-912X
Kai Kaila https://orcid.org/0000-0003-0668-5955

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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