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Research Paper

Stroke and Stroke-Like Episodes: Recurrent Manifestations in GLUT1 Deficiency Syndrome

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ABSTRACT

Background: Since the initial description of glucose transporter-1 deficiency syndrome (Glut1-DS) the phenotype of the condition has expanded, even leading to the recognition of atypical manifestations. We report on eight patients with Glut1-DS who experienced at least one episode of acute focal neurological deficits.
Methods: We conducted a retrospective analysis, collecting clinical, electrophysiological, neuroradiological, and genetic information. We focused in particular on three well-documented cases.
Results: Among 42 patients with Glut1-DS, eight individuals aged between six and 38 years presented with an acute onset of neurological disturbances: dysarthria/aphasia, oral dyskinesia, swallowing difficulties, paresthesia, facial palsy, hemi/monoplegia, vomiting, headache, and behavioral disturbances. When performed, magnetic resonance imaging (MRI) revealed signs of venous congestion and hypoperfusion and electroencephalography showed focal contralateral slowing. Deficits were transient in all patients but one. Four patients (50%) were on a ketogenic diet (KD), and two of these patients had lower than usual ketonemia levels during the episode. In two patients, MRI demonstrated the presence of an ischemic brain lesion.
Conclusions: In Glut1-DS, stroke-like episodes are a recurrent manifestation, particularly during early adulthood, and they were reported in 19% of the patients in our cohort. Stroke mimics should be considered a key feature of Glut1-DS, as other paroxysmal disorders. It remains to be established whether a KD can prevent the recurrence of episodes and, if so, at what level of ketosis. Further observations are needed to confirm the correlation between Glut1-DS and ischemic stroke.

Introduction

Glucose transporter-1 deficiency syndrome (Glut1-DS) is a rare genetic metabolic disorder characterized by impaired glucose transport across the blood-brain barrier and into astrocytes.[1,2] Glut1-DS is usually caused by *de novo* heterozygous pathogenic variants in the *SLC2A1* gene; however, in some cases it is inherited in an autosomal dominant fashion, and an autosomal recessive inheritance is reported in rare cases.[3-5] Diagnosis of the disorder is

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confirmed by the presence of characteristic clinical signs, hypoglycorrhachia documented by lumbar puncture, and heterozygous pathogenic variants in *SLC2A1*.

The classic Glut1-DS phenotype, characterized by persistent symptoms across three domains (epileptic seizures, movement disorders, and cognitive behavioral impairment), has expanded over recent years, leading to recognition of patients with milder symptoms.[6] Atypical features have also been identified, such as writer's cramp, intermittent ataxia, total body paralysis, parkinsonism, nocturnal painful muscle cramps, confusion, fatigue, and recurrent headaches.[3,7]

Consequently, Glut1-DS currently has a broad phenotypic spectrum,[8,9] and even related patients may present different clinical phenotypes[9,10]; more recently, episodes classified as alternating hemiplegia of childhood (AHC), hemiplegic migraine (HM), cyclical vomiting, or more generally stroke-like events (also referred to as stroke mimics) have been related to *SLC2A1* variants.[11,12]

We report the clinical, genetic, electrophysiological, and neuroradiological features of eight patients with Glut1-DS who presented single or multiple episodes of acute focal neurological deficits.

Methods

A retrospective case study was performed, based on data drawn from the Glut1-DS patient database kept at the Paediatric Neurology Unit, "Vittore Buzzi" Children's Hospital, Milan, Italy. We collected relevant clinical, electroencephalographic (EEG), and neuroradiological data.

Written informed consent was obtained from all patients (or parents where applicable). The study complied with institutional regulations for anonymized retrospective studies and was approved by the Milan Area 1 ethics committee (2021/ST/214). The study adheres to the principles of the Helsinki Declaration.

Results

Among the 42 patients in our database, we identified six females and three males, aged 10 to 42 years, who presented single or multiple episodes of acute focal neurological deficits; of these, one male patient was excluded due to the presence of patent foramen ovale. Table details the remaining eight patients' features and acute episodes.

Next-generation sequencing epilepsy gene panels were used to screen all the patients, two of whom were sisters (Patients 4 and 5). Sequencing analysis identified seven different variants (six missense and one frameshift) in *SLC2A1* (OMIM #138140; 1p34.2), which encodes glucose transporter-1 (GLUT1). This protein, belonging to the GLUT transporter superfamily, is composed of 12 α-helical transmembrane domains, separated by a large intracellular loop between helices 6 and 7, and it is involved in glucose uptake into the brain. Three of the identified variants (42.8%), encoded by exon 4, are located on transmembrane helix (TMH) 4 and TMH5, and another three (42.8%), encoded by exons 6 and 7, are located on TMH7; the remaining variant is situated on intracellular domain 5.[10] According to the American College of Medical Genetics criteria, five of the variants were classified as pathogenic and two as likely pathogenic.

Five patients underwent lumbar puncture, which showed diagnostic cerebrospinal fluid/blood glucose ratio values; Patients 3, 5, and 6 did not undergo the procedure, but they carry the same genetic variant as first-degree family members with hypoglycorrhachia values indicative of Glut1-DS. No mutations were identified in the *CACNA1A*, *SCN1A*, or *ATP1A2* genes.

Six patients (75%) presented seizures, with a mean age at onset of 2.2 years (range: 10 months to 6 years). One patient had paroxysmal eye-head movements. Seven patients (87.5%) presented movement disorders, with a mean age at onset of 11.21 years (range: 14 months to 25 years), the most common being paroxysmal exertion-induced dyskinesia (PED) (75%). Intellectual functioning was normal in three patients (37.5%), whereas two (25%) had borderline intellectual functioning and three (37.5%) had mild intellectual disability (ID); no patient had moderate or severe ID. Five patients (62.5%) had a history of headache. Three patients (37.5%) reported almost daily fatigue.

The patients' mean age at the first episode of focal neurological deficits was 20.25 years (range: 6 to 38 years). The patients presented with various clinical manifestations, namely, paresthesia (62.5%), hemiplegia (62.5%), dysarthria (50%), facial palsy (50%), vomiting (37.5%), behavioral abnormalities (25%), aphasia (25%), oral dyskinesia (12.5%), swallowing difficulties (12.5%), and monoplegia (12.5%). Four patients (Patients 1, 3, 4, and 7) presented headache either as the initial symptom or during the course of the episode; Patient 7 had also experienced four episodes without headache.

The acute focal neurological deficits were transient and self-limiting in all but one patient (Patient 3). Patient 3 presented a single focal neurological episode due to an ischemic stroke; this evolved into a persistent neurological deficit. In one individual (Patient 2), magnetic resonance imaging (MRI) findings were indicative of a previous ischemic insult.

Transient focal neurological deficits lasted between one and three hours in four patients (57.1%) and from 12 to 24 hours in three (42.9%).

Three of our eight patients (37.5%) presented an isolated episode, three (37.5%) between two and four episodes, and two (25%) multiple episodes.

Specific triggers of the acute focal neurological events could not always be identified, but fatigue and poor sleep were reported in Patient 7. Four of the eight patients (50%) were on a ketogenic diet (KD). Among these, Patients 1, 2, and 7 displayed ketonemia levels lower than their usual values before the events. In Patient 1 ketonemia was 0.7 mmol/L before the last episode. In Patient 2, ketonemia levels of around 1.3 mmol/L were reported in the weeks before the episodes, versus an average value of 2 mmol/L. Patient 7 had several episodes, during one of which a ketonemia value of 0.4 mmol/L was documented, followed two hours later, after almost complete resolution of the symptoms, by a value of 1.9 mmol/L. Patient 1 presented episodes only before starting the KD.

We here report in detail the clinical history of Patients 1, 2, and 3.

Patient 1

Patient 1 is an 11-year-old girl who was diagnosed with Glut1-DS at age nine years. She shows clumsiness and poor eye-hand coordination and has a learning disability. Her intelligence quotient is normal.

At age six she presented an acute episode characterized by left parietal-temporal headache, followed by upper and lower right limb paresthesia and, a few minutes later, right hemiplegia; nausea, vomiting, and expressive aphasia then occurred. The episode lasted 12 hours. An emergency brain computed tomography scan was negative; gadolinium-enhanced T2-weighted fluid-attenuated inversion recovery MRI performed during the episode showed circumscribed contrast enhancement deep in some vertex mesial frontoparietal sulci on the left side, which could be due to venous congestion; magnetic resonance angiography (MRA) was normal; and pseudocontinuous arterial spin labeling was not performed. No other pathologic finding was observed.

TABLE.
Patients' Clinical and Instrumental Data

Patient	Sex and Current Age	*SLC2A1* Gene Variant (Type)	Age at Diagnosis	CSF/ Blood Glucose Ratio	Glut1-DS Phenotype	KD Diet	Age at First Stroke-Like Event	Acute Symptoms	Number and Duration of Episodes	Neuroimaging During Episode	EEG During Episode
1	F 11 y	c.971C>T p.Ser324Leu (missense)	9 y	0.46	Average IQ (IQ 97), clumsiness, poor coordination	Yes	6 y	First episode: headache, vomiting, aphasia, paresthesia, and right hemiplegia In one episode: headache confusion, vomiting, dysarthria, left hemiplegia, aggressive behavior	5 Episodes, 1-12 h	Cranial CT and MRI: circumscribed contrast enhancement in the depth of some vertex mesial frontoparietal sulci on the left side due to venous congestion. MRI during the fifth episode: diffuse reduced perfusion of the left cerebral hemisphere; MRA: diminished representation of the peripheral branches of left middle cerebral artery	Slow left hemisphere activity
2	F 17 y	c.457C>T p.Arg153Cys (missense)	5 y 5 m	0.39	Average IQ (IQ 104), seizure (onset 12 m: DS, GTCS, ABS), MD (onset 16 m: PED), ataxia, headache	Yes	16 y	First episode: dysarthria, paresthesia with monoplegia (right upper limb)Second episode: aphasia and headache	2 episodes, 3 h	MRI (3 h after clinical onset of first episode): decreased perfusion in the left hemisphere, cortical alteration on the right cerebellum (gliosis and atrophy)	EEG (1 day after first episode): slower activity on the left anterior regions and on the vertex
3	F 41 y	c.884C>T p.Thr295Met (missense)	40 y	NA*	Normal IQ, MD (onset 16 y: PED), headache	No	25 y	Headache, photophobia, vomiting, paresthesia with hemiplegia and facial palsy (left lower limb propagating to upper limb and face)	1 Episode	Cranial CT during episode: millimetric hypodensity on right uncus Brain MRI: acute cytotoxic alteration in the right thalamocapsular region MRA: normal	Not performed
4	F 39 y	c.493G>A p.Val165Ile (missense)	25 y	0.44	Mild ID (IQ 55), seizure (onset 1 y: GTCS, ABS), MD (onset 25 y: PED), headache	No	28 y	Headache, aphasia, right hemiplegia	1 Episode, 24 h	Cranial CT: negative	Not performed
5	F 35 y	c.493G>A p.Val165Ile (missense)	21 y	NA†	BIF (IQ 72), seizure (onset 6 y: ABS), MD (onset 20 y: PED), headache, fatigue	No	32 y	Paresthesia with hemiplegia and facial palsy (left upper limb propagating to left lower limb and face)	2 Episodes, 3 h	NA	Not performed
6	F 42 y	c.388G>A p.Gly130Ser (missense)	39 y	NA‡	Mild ID, seizure (onset 2 y: GTCS), MD (onset 7 y: PED), fatigue	No	38 y	Paresthesia (face), facial palsy	Several episodes, 2-3 h	NA	Not performed
7	M 10 y	c.1458_1459insT p.Gly487Trpfs*3 (frameshift)	4 y 10 m	0.37	BIF (IQ 72), seizure (onset 10 m: FS, GTCS), MD (onset 8 y: PED), eye-head movements, headache	Yes	7 y	Pallor, dysarthria, oral dyskinesia, paresthesia, facial palsy In two episodes: autoaggressiveness and agitation In one episode: headache and vomiting	Several episodes, 1-3 h	Cranial CT: negative	Normal
8	F 10 y	c.847C>A p.Gln283Lys (missense)	1 y 7 m	0.37	Mild ID (IQ 77), seizures (onset 2y, 6 m: MyAbs), MD (onset 14 m: PNKD)	Yes	10 y	Dysarthria, swallowing impairment, left hemiplegia	1 Episode, 24 h	Not performed	Not performed

Abbreviations:
ABS = Absences
BIF = Borderline intellectual functioning
CSF = Cerebrospinal fluid
CT = Computed tomography
DS = Dyscognitive seizure
EEG = Electroencephalography
F = Female
FSs = Focal seizures
GLUT1-DS = Glucose transporter-1 deficiency syndrome
GTCS = Generalized tonic-clonic seizure
ID = Intellectual disability
IQ = Intelligence quotient
KD = Ketogenic diet
M = Male
MD = Movement disorder
MRI = Magnetic resonance imaging
MyAbs = Myoclonic absences
MRA = Magnetic resonance angiography
NA = Not available
PED = Paroxysmal exercise-induced dyskinesia
PNKD = Paroxysmal nonkinesigenic dyskinesia
* Patient 3 has a daughter with Glut1-DS with the same *SLC2A1* variant and documented hypoglycorrhachia (39 mg/dL).
† Patient 5 is the sister of Patient 4, with whom she shares the same gene variant.
‡ Patient 6 has a daughter with Glut1-DS who has the same *SLC2A1* variant and a CSF/blood glucose ratio of 0.39.

The following day an EEG was performed, showing prevalence of delta activity with higher amplitude on the left central-frontal and posterior regions (occipito-temporal). Two days later the EEG normalized, and a diagnosis of an episode of HM was made.

At age eight, she had a further episode, characterized by right parietal-occipital headache associated with confusion, vomiting, dysarthria, left hemiplegia, and auto- and heteroaggressive behavior. In the emergency room intravenous midazolam and fentanyl were administered, she fell asleep, and the episode resolved. At age nine years, another two, milder, episodes occurred, each lasting one hour. One last episode occurred at age 11 years, when she was admitted to the emergency room after experiencing right arm motor impairment, left facial paresis, and aphasia, followed by five episodes of vomit. The parents reported that in the morning before the episode she had low ketonemia (0.7 mmol/L). Brain MRI showed diffuse reduced perfusion of the left cerebral hemisphere cortex; MRA detected a diminished representation of the peripheral branches of the left middle cerebral artery. The clinical picture regressed to normality within approximately 24 hours. A control brain MRI was taken five days after the episode, and the hypoperfusion was not detectable anymore. MRI findings are shown in Fig 1.

Analysis of *SLC2A1* detected a likely pathogenic *de novo* variant (c.971C>T, p.Ser324Leu); Glut1-DS was confirmed by cerebrospinal fluid glucose analysis. Follow-up brain MRI and MRA were negative.

The patient started a 2:1 KD and has since presented episodes of headache associated with vomiting but no other associated symptoms.

Patient 2

Patient 2 is a 17-year-old girl with average intellectual functioning, who was diagnosed with Glut1-DS at age five years.

From age one and a half month she presented generalized tonic-clonic seizures in fever and, from age 12 months, also in apyrexia. Seizures were controlled with valproic acid and carbamazepine. From age four, she showed PED and episodes of intermittent ataxia. After being diagnosed with Glut-DS at age six, she started a KD, while discontinuing the antiseizure medications. She has not presented seizures or movement disorders since. At age 16, she attempted to switch from a 2:1 KD to a modified Atkins diet (MAD). Two months later, she experienced an episode of sudden dysarthria, paresthesia, and right upper limb plegia. The deficits resolved in approximately three hours. No headache, vomiting, or fever occurred, even though she had complained of a mild headache and general malaise during the previous two months. During the previous week, the patient's ketonemia level had been around 1.3 mmol/L, versus an average value of 2 mmol/L. She was admitted to hospital, and brain MRI/MRA was performed around two hours after the onset of the acute clinical manifestations. Susceptibility-weighted imaging showed prominence of some venous structures in the area of the left cerebral cortical sulci, associated with signs of left hemisphere hypoperfusion on pseudocontinuous arterial spin labeling images, more evident in the frontal lobe, without evidence of any supratentorial parenchymal abnormality on morphologic images. The distal middle cerebral artery branches were found to be asymmetrically represented on MRA, being less evident on the left side (Fig 2). A predominantly cortical alteration characterized by gliosis and atrophy involving the right middle cerebellar folia was detected. This feature, certainly a stable sequela of previous cerebellar damage, had not been present on previous brain MRI performed at age two years. The EEG recording, performed the day after the episode, showed an overall slower pattern compared with the previous recordings, and an asymmetry between the two hemispheres, with slower activity on the left anterior regions and vertex.

Thrombophilia screen, coagulation factors, cardiological evaluation, transcranial Doppler, and supra-aortic trunk echo-Doppler were performed, revealing no pathologic findings.

Follow-up brain MRI was performed one month later, when the left cerebral hemisphere hypoperfusion was no longer detectable. Venous structures in the susceptibility-weighted imaging sequence and arterial vessels appeared symmetrically represented, as did the peripheral branches of the middle cerebral artery in the MRA sequence; only minimal perfusion reduction in the right cerebellar hemisphere was detected, corresponding to the gliotic-atrophic lesion.

At age 17, the patient had an episode characterized by aphasia lasting 10 minutes, followed by headache lasting around two hours. Ketones were 0.5 mmol/L. Brain MRI showed no new clinical findings.

Patient 3

Patient 3 is a 42-year-old woman with average intellectual functioning, who was diagnosed with Glut1-DS at age 40, following

her daughter's diagnosis. She experienced febrile seizures and lower limb PED from age 16. She has no cardiovascular risk factors. From age 17 she started presenting episodes of frontal/temporal headache with photophobia. From age 17 to 21 she presented at least three 10- to 15-minute episodes of sudden imbalance, on one occasion accompanied by impaired lower limb coordination.

At age 25, she experienced an episode of right frontotemporal headache, which worsened in 15 to 20 minutes. She took acetaminophen and fell asleep for an hour. Upon awakening, the headache was only partially resolved, and she started presenting paresthesia and motor difficulties affecting the lower left limb. At the emergency room, photophobia, nausea, and vomiting occurred. Urgent noncontrast head computed tomography was performed during the episode, detecting millimetric hypodensity on the right uncus.

The neurological examination, performed about five hours after the headache onset, showed left facio-brachio-crural hemiparesis and homolateral ataxia.

Brain MRI showed signal alteration in the right thalamocapsular region, compatible with acute cytotoxic injury (Fig 2). MRA was normal.

Thrombophilia screen, autoimmune screen, cardiological evaluation, transesophageal and transthoracic echocardiogram, and epiaortic vessel echo-Doppler were performed, and all were normal.

She was discharged with a diagnosis of right thalamocapsular stroke, with a hypothesis of migrainous infarction. Treatment with clopidogrel (due to acetylsalicylic acid allergy) and rehabilitation therapy were started. Repeat brain MRI after six months demonstrated malacic evolution of the lesion with signs of anterograde degeneration along homolateral centrum semiovale white matter fibers (Fig 3).

This patient still presents mild upper left limb hemiplegia, associated with a tremor-like movement disorder, previously treated unsuccessfully with propranolol and levetiracetam, and now partially responsive to piracetam.

Discussion

The spectrum of paroxysmal disorders in Glut1-DS is gradually expanding beyond seizures and motor and nonmotor disorders. Pons in 2010[5] reported patients with complex transient neurological symptoms, comprising ataxia, hemiparesis, limb weakness, sudden paralysis, dysarthria, dysphoria, and headache. More recently atypical manifestations such as AHC, HM, cyclical

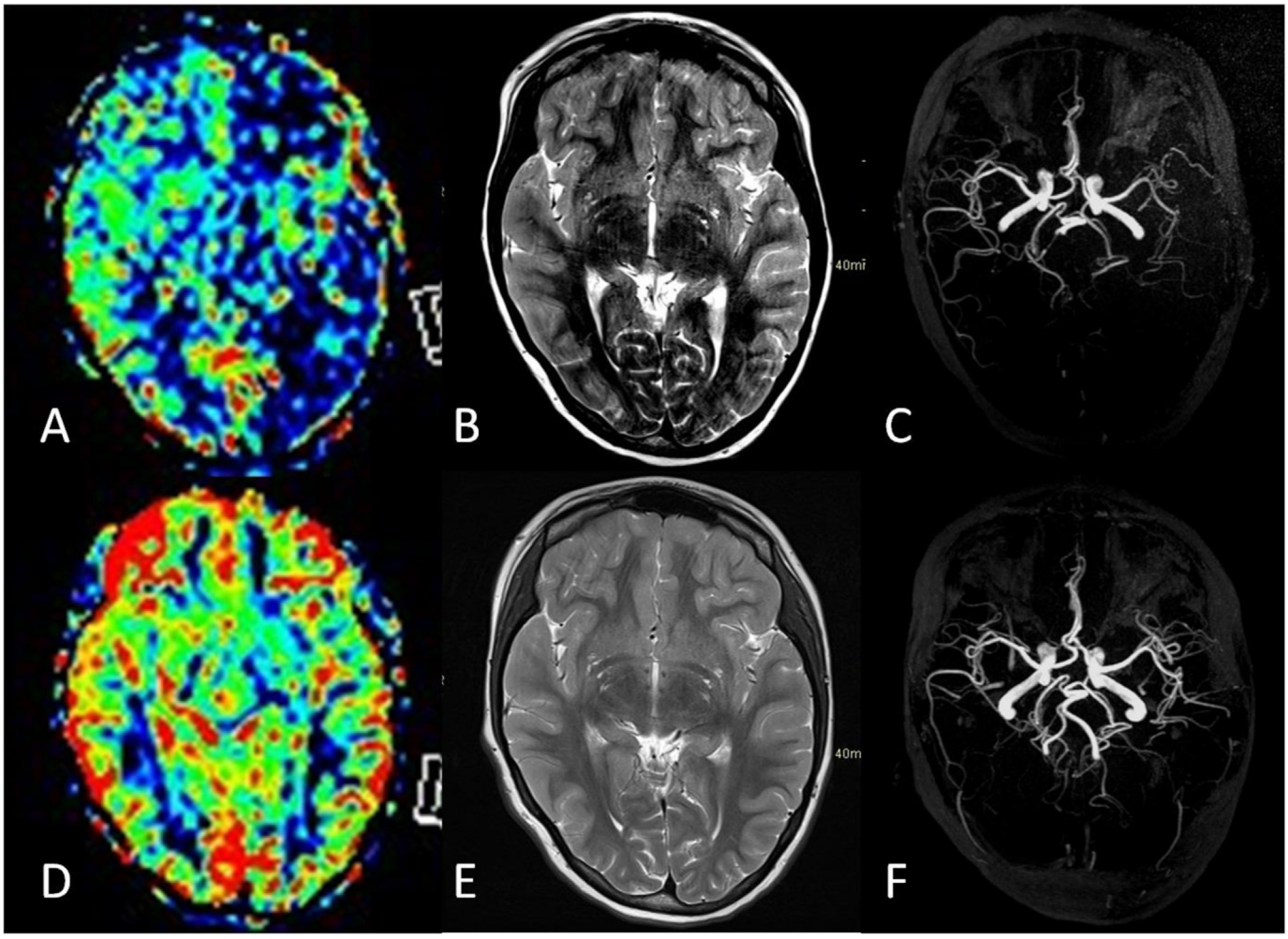

FIGURE 1. Axial T2-weighted images (A, D), pseudocontinuous arterial spin labeling (B, E) images at the level of the subthalami, and 3D-time-of-flight (C, F) images acquired during symptoms (top row) and after four days (bottom row) show no evidence of parenchymal lesions associated with left hemisphere hypoperfusion and asymmetric representation of the distal middle cerebral artery branches, less evident on the left side in the first examination and no longer evident at subsequent follow-up examination. The color version of this figure is available in the online edition.

vomiting, and stroke-like episodes have increasingly been described.[5,11,12]

Our case series comprised individuals with a definitive diagnosis of Glut1-DS with clinical, metabolic, and genetic characteristics fully compatible with the disorder. During the course of the disease, they presented isolated or recurrent episodes characterized by variable combinations of headache, mono-/hemi-/tetraplegia, and speech and behavioral disorders, referred to as "stroke mimics" or stroke-like episodes. These focal neurological episodes are well-identifiable phenomena, so much so that they should be considered not as an additional disorder but as fully part of the Glut1-DS clinical phenotype, especially in young adulthood but also in childhood. In our database they were found to be recurrent events, occurring in about one fifth of the patients, a frequency not dissimilar to that of other disturbances associated with Glut1-DS, such as paroxysmal abnormal eye movements, which are described in about one third of patients and considered a key feature of the disorder.[6] In our series, we found a stroke-like episode in about 19% of the patients, which is higher than the 9% previously reported in the literature.[12] Interestingly, we noticed that the stroke-like episodes never occurred as an onset symptom, but during the course of the illness, and in the majority of the cases (six of eight) it affected female subjects in postpubertal age.

During the acute/subacute phase of these events, we documented the simultaneous presence of both neuroradiological and electrophysiological changes.

In the acute/subacute phase, Patients 1 and 2 had an EEG characterized by a pattern of focal unilateral slowing, while MRI revealed signs indicative of venous congestion and signs of hypoperfusion on the hemisphere contralateral to the deficit, without concomitant diffusion abnormalities or areas of abnormal T2 signal. In both patients, these changes were no longer visible on repeat EEG and MRI.

In the clinical evaluation of stroke-like episodes, it is imperative to distinguish them from ictal and postictal manifestations. In our case series, stroke-like episodes have not been temporally associated with seizures and their clinical presentation differs from the

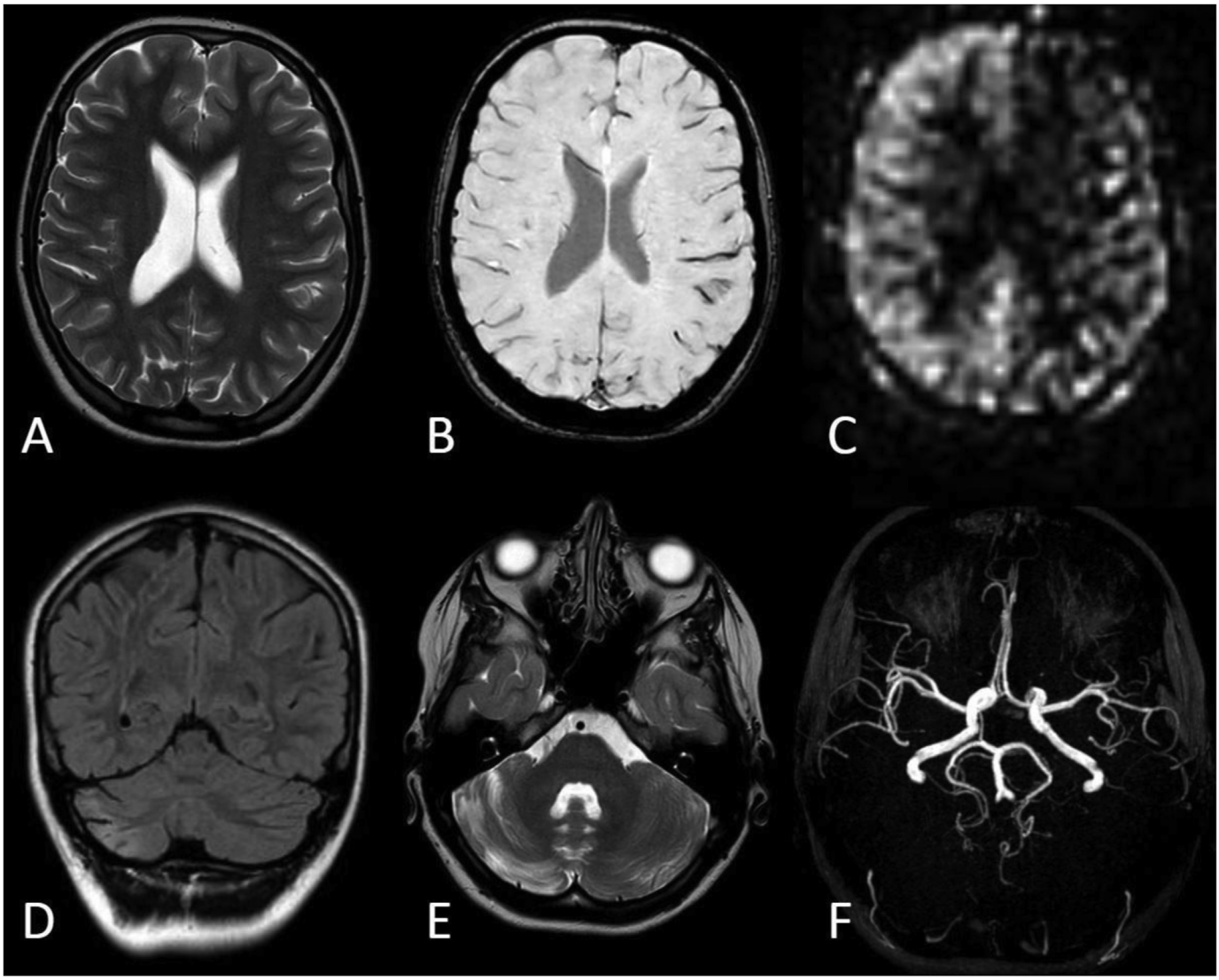

FIGURE 2. Axial T2-weighted (A), susceptibility-weighted imaging (B), and pseudocontinuous arterial spin labeling (C) images at the level of the middle cells of the lateral ventricles show no evidence of parenchymal lesions in (A) and prominence of some venous structures in the area of the left cerebral cortical sulci (B), associated with hypoperfusion on the left side, more evident in the frontal lobe (C). Coronal fluid-attenuated inversion recovery (D) and axial T2-weighted images (E) show cortical gliosis and atrophy of the right middle cerebellar folia. The distal middle cerebral artery branches are asymmetrically represented on MRA (F), being less evident on the left side.

typical ictal manifestations reported by patients and their caregivers. These episodes are typically characterized by one or more focal deficits with preserved consciousness. EEG during a stroke-like episode does not reveal evidence of rhythmic or recruiting epileptic abnormalities, or overt epileptic seizures. However, it does demonstrate focal slow activity leading to interhemispheric asymmetry, as commonly observed in transient vascular alterations.

Currently, it is recommended that in the event of a sudden onset of new neurological symptoms in a patient with Glut1-DS, further investigation including brain MRI with perfusion and angiographic studies should be pursued. This investigation is essential for confirming clinical suspicion and assessing the condition's progression over time.

Perfusion abnormalities without any other alteration and lateralized vascular pruning on MRI[13] as well as the finding of unilateral theta-delta slowing on the EEG contralateral to the affected side of the body have been reported anecdotally in Glut1-DS cases presenting stroke-like episodes.[14-16] The fact that similar findings are observed during episodes of HM and AHC may suggest a common pathophysiologic mechanism based on glucose deficiency and consequent cerebral hypometabolism.[17,18] Topakian et al. reported diffuse reduced glucose metabolism of the supratentorial cortex and marked hypometabolism of the left cerebellum in a patient during an HM attack.[19] Cerebral glucose deficiency in AHC, suggested by low glucose metabolism in the frontal lobes, putamen, and cerebellum,[20] may explain the efficacy of KD/MAD in a patient with familial AHC due to *ATP1A3* mutation[21] and in a patient with

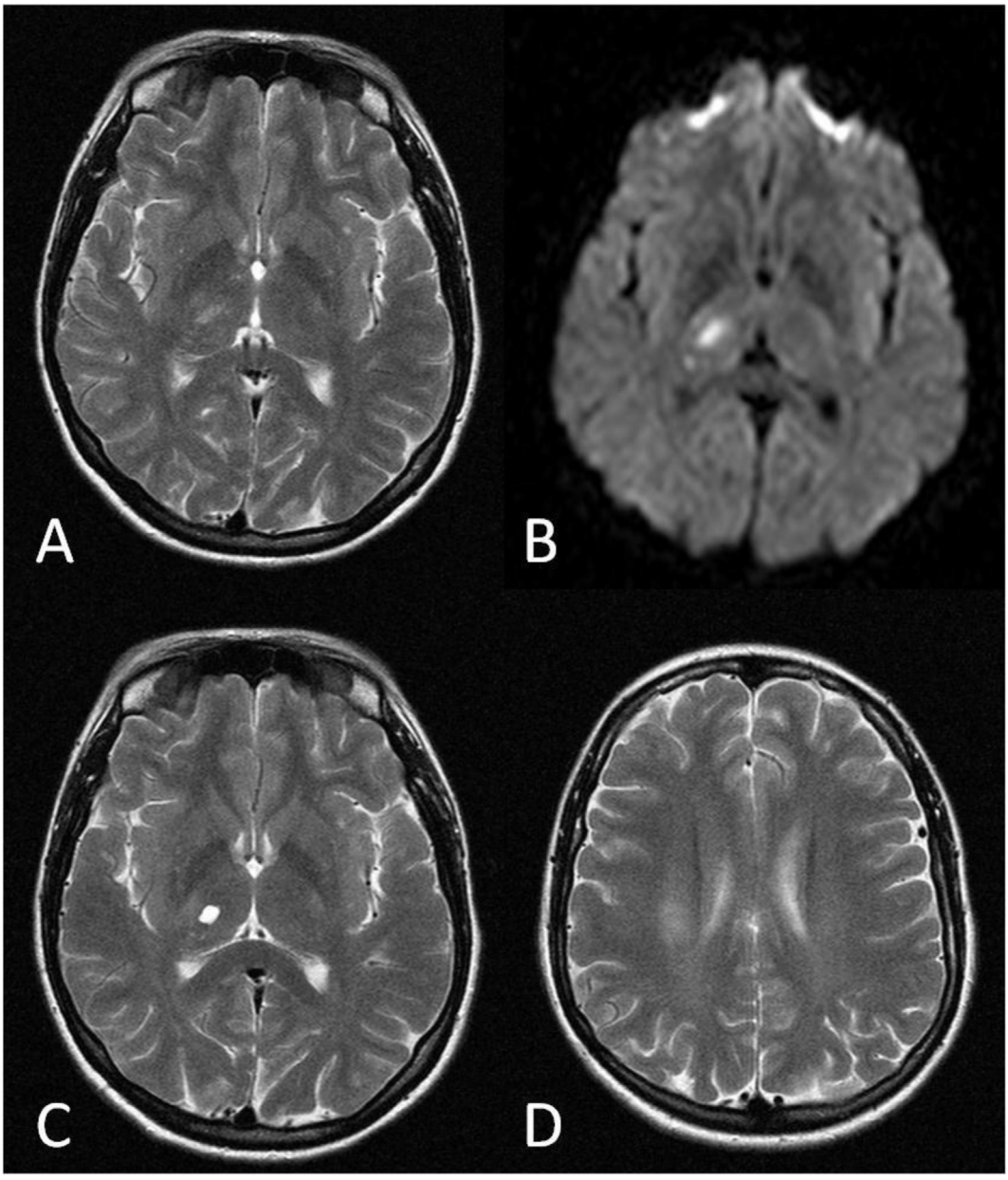

FIGURE 3. A, B) Brain MRI acquired five hours after the onset of symptoms. Axial T2-weighted image (A) shows a thalamic hyperintense lesion on the right side; axial diffusion-weighted image shows that the lesion is characterized by restricted proton diffusivity. (C and D) Follow-up brain MRI performed after six months. Axial T2-weighted image (C) shows malacic evolution of the lesion with signs of anterograde degeneration along homolateral centrum semiovale white matter fibers (D).

AHC harboring a *de novo* pathogenic variant in *ATP1A3*, together with a duplication and insertion in *SLC2A1*.[22]

Some authors have investigated the pattern of glucose hypometabolism in Glut1-DS,[23,24] in which it seems to be present symmetrically in the thalamus, cerebellum, and frontal and temporal cortex, even though its degree varies between brain regions. These regional differences in glucose uptake and the extent of glucose depletion may explain the different neurological manifestations.

Some reports suggest that in patients on a KD, stroke-like episodes might be facilitated by a decrease in ketonemia, and that adequate dietary compliance might prevent their recurrence,[14,25] as already documented in other paroxysmal disorders (e.g., epilepsy, PED, migraine).[12] Patients 2 and 7, during the episodes, were found to have ketonemia levels lower than their usual values. In Patient 2, it is not possible to establish when the cerebellar ischemic lesion occurred and therefore what relationship, if any, it may have with the KD. However, the first clinical episode certainly occurred during an attempt to switch from KD to MAD; a low ketone level was then documented during a further episode characterized by aphasia lasting 10 minutes, followed by headache. Assuming this to constitute a metabolic trigger, some authors suggested that medium to high ketone levels (ketone bodies >3 mmol/L) would be preferable and that lower ratio diets may be inadequate to prevent further episodes.[25] However, other authors have suggested that the KD, at least in a subset of patients, may cause vascular damage in the form of an increase in arterial stiffness.[26] Our case series, in which half of the patients were on a KD and half were on a free diet, does not allow us to judge whether or not the KD can be said to support or protect against stroke and stroke-like episodes.

The therapeutic mechanisms of ketogenic dietary treatments in Glut1-DS are far to be completely elucidated.

Recent studies on animal models, focusing in particular on the causative mechanisms of seizures, state that the neural hyperexcitability in Glut1-DS is caused by a reduction of inhibitory circuits due to decreased brain glucose and glycogen storage. The seizure amelioration observed with ketogenic dietary treatments in Glut1-DS can be explained because ketone bodies augment brain acetyl coenzyme A production normalizing neurotransmitter release.[27] To understand the paroxysmal manifestations in Glut1-DS, it is necessary to study not only the role of neurons but also the contribution of other cellular compartments such as glial cells, red blood cells, and endothelial cells that are rich in Glut1.[28]

From a genetic perspective our findings are fully comparable with those described in the literature: missense mutations represent the most frequent variant (88.2% in the literature and 85.7% in our case series), followed by frameshift and nonsense mutations (11.8% in the literature and 14.3%, albeit only frameshift ones, in our case series). Although genetic features may be expected to be a predominant contributing factor in stroke-like episodes, we failed to detect a clear genotype-phenotype correlation. The role of epigenetic mechanisms (DNA hypermethylation and noncoding RNA)[29,30] in patients with Glut1-DS presenting stroke-like episodes could help to clarify this constitutional susceptibility. The pathophysiology underlying episodes of transient neurological symptoms in association with focal cerebral hypoperfusion in patients with Glut1-DS is not fully elucidated.

In all patients with Glut1-DS with acute neurological deficits described in the literature, stroke and seizures were excluded by MRI and EEG. However, in our Patient 2, MRI showed, alongside signs of venous congestion and hypoperfusion, the presence of a gliotic-atrophic cerebellar lesion, not present on a previous brain MRI and certainly a stable sequela of cerebellar infarction. Retrospectively, no medical history emerged that could explain this finding.

Patient 3 presented with a single episode of severe headache that evolved into left facio-brachio-crural paresis. Emergency MRI revealed an altered signal in the right thalamocapsular region, compatible with acute cytotoxic injury that eventually evolved into a malacic lesion. Extensive investigations failed to detect a cause, and a diagnosis of right thalamocapsular stroke was made, hypothesis of migrainous infarction. The patient could, at that time, be diagnosed as an HM, but was then diagnosed as a Glut1-DS, with confirmed laboratory findings. More than 20 years later, this patient still has a plegic left arm and a tremor-like movement disorder.

Stroke events have been described in patients with migraine, particularly migraine with aura[31] and HM,[32-34] but the exact mechanism underlying migraine-induced stroke has yet to be determined. Cortical spreading depression (CSD) and endovascular dysfunction are among the theories suggested to explain the migraine-stroke relationship. CSD is a depolarization wave associated with a transient increase in energy metabolism followed by prolonged cerebral oligemia that may favor ischemic events.[35] In animal models, increased cerebral glucose availability has been shown to make the cerebral tissue resistant to CSD.[36] In migraine, endothelial dysfunction and reduced endothelial repair are hypothesized to be factors contributing to the development of stroke. Glut1 has a primary effect on cerebral vasculature, and it is particularly abundant in cerebral vessel endothelial cells. Angiogenesis is highly reliant on glycolysis. *In vivo* models corroborate that low Glut1 protein arrests cerebral angiogenesis during brain development, resulting in a profound diminution of the brain microvasculature that further aggravates neuroglycopenia.[37] In this scenario affected individuals may be more susceptible to episodes of transient vasospasm eventually evolving into an ischemic event.

From an etiopathogenic point of view it is plausible that the metabolic derangement leading to inadequate cerebral glucose availability, and the presence of endothelial dysfunction, may predispose to stroke events.[38] In this scenario, the presence of *SLC2A1* mutations could potentially be a risk factor for the development of ischemic stroke.

Nevertheless, this hypothesized ischemic predisposition must be validated by further observations. We hope that this first report will encourage clinicians to investigate ischemic attacks in patients with Glut1-DS and in their relatives, and, primarily, to consider the possibility of Glut1-DS in cases of stroke of undetermined aetiology.

Conclusion

In our experience, the identification of stroke-like episodes in patients with Glut1-DS is a recurrent feature, up to about one fifth of patients, both in childhood and in young adulthood, therefore it should be considered a key feature of the disorder. In particular, it occurred during the disease's course, with a prevalence in post-pubertal females.

The exact pathophysiologic mechanism underlying stroke-like events in Glut1-DS remains to be clarified, but presumably involves both metabolic and vascular alterations.

Further studies will be needed to assess whether habitual ketosis, suitable for controlling epilepsy and paroxysmal movement disorders, is an adequate means of preventing stroke-like episodes.

Our report of an association between Glut1-DS and ischemic stroke needs further confirmation to ascertain a predisposing role of Glut1-DS. In cases of ischemic stroke with no definite cause, we suggest that Glut1-DS should be ruled out, especially if there is a family history of this disorder or a family or personal history of epilepsy, ID, or chronic or paroxysmal movement disorders.

New research on epigenetic factors and metabolomics studies could help to shed more light on these newly recognized manifestations of Glut1-DS.

CRediT authorship contribution statement

Sara Olivotto: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Anna Freddi:** Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft. **Roberto Previtali:** Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Alessia Mauri:** Formal analysis, Writing – original draft. **Cristina Cereda:** Methodology, Writing – review & editing. **Ramona De Amicis:** Data curation, Formal analysis, Writing – review & editing. **Simona Bertoli:** Conceptualization, Writing – review & editing. **Chiara Doneda:** Data curation, Investigation, Methodology, Writing – review & editing. **Pierangelo Veggiotti:** Conceptualization, Data curation, Methodology, Writing – review & editing.

Declaration of competing interest

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