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REVIEW

Movement disorders in GLUT1 deficiency syndrome: a systematic review of the literature

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Abstract

Background and objectives Movement disorders (MDs) are a prominent feature of GLUT1 Deficiency Syndrome (GLUT1DS), a rare and treatable neurometabolic disorder caused by impaired glucose transport across the blood–brain barrier. We aimed to provide a comprehensive overview of the prevalence, clinical features, and treatment response of MDs in GLUT1DS.

Methods A systematic review was conducted across five databases in accordance with PRISMA guidelines. The protocol was registered in PROSPERO (CRD42025644449). Studies reporting individual patient data on MDs in GLUT1DS were included. Descriptive and comparative analyses were performed.

Results Of 1178 records screened, 68 studies were included, comprising 94 published patients and two additional unpublished cases (n = 96). MDs were the presenting symptom in 34.4% of cases. The most frequent phenotypes were paroxysmal dyskinesias (63.5%) and ataxia (47.9%). Patients with MD-onset showed a later age at onset and fewer cognitive features. Non-missense variants were associated with earlier disease onset and a higher frequency of ataxia, whereas missense variants were independently associated with paroxysmal dyskinesias (OR 3.02, 95% CI 1.09–8.35). Ketogenic dietary therapies were associated with improvement in motor symptoms in most reported cases, although outcome data were heterogeneous and non-standardized.

Discussion MDs in GLUT1DS are highly heterogeneous and frequently overlap, with distinct patterns across clinical and genetic subgroups. While ketogenic therapies appear beneficial for motor symptoms, current evidence is limited by methodological variability and potential reporting bias, highlighting the need for prospective studies with standardized outcome measures.

Keywords Ataxia · GLUT1 deficiency syndrome · Movement disorders · Ketogenic diet · Paroxysmal dyskinesia

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Introduction

GLUT1 Deficiency Syndrome (GLUT1DS; OMIM 606777) is a genetic and treatable neurometabolic disorder caused by pathogenic variants in the *SLC2A1* gene, which encodes glucose transporter type 1 (GLUT1), the principal glucose transporter expressed in endothelial cells of the blood–brain barrier and astrocytes [1]. Impaired GLUT1 function reduces glucose transport into the central nervous system, leading to chronic cerebral energy deficiency and a broad spectrum of neurological manifestations. Since the initial two cases described by De Vivo et al. in 1991 [2], awareness of the clinical variety of this syndrome has increased, and the recognized phenotype now includes early-onset drug-resistant epilepsy, abnormal eye movements, neurodevelopmental delay, and movement disorders (MDs) [3].

Epidemiologic data remain limited and are largely derived from pediatric cohorts with epilepsy or developmental disorders [4, 5]. Prevalence is likely underestimated because of the broad range of ages at onset, phenotypic heterogeneity, and relatively recent availability of advanced diagnostic tools. Available registry data show an approximately equal sex distribution [6, 7].

In about 90% of cases, GLUT1DS results from a de novo heterozygous *SLC2A1* variant, whereas inherited forms are usually autosomal dominant; autosomal recessive inheritance has been reported only rarely [8, 9]. Pathogenic sequence variants are identified in most patients, whereas gene deletions or duplications account for a smaller proportion [9–11]. Previous genotype–phenotype studies suggest that missense variants are generally associated with milder phenotypes, whereas truncating variants, splice-site defects, insertions/deletions, and complete gene microdeletions are associated with more severe manifestations [3].

The diagnosis of GLUT1DS is established by identifying a pathogenic *SLC2A1* variant and/or by demonstrating hypoglycorrhachia, with low-normal CSF lactate and abnormal CSF-to-blood glucose ratio [3, 9]. Electroencephalography and brain magnetic resonance imaging are not part of the diagnostic criteria, since no specific findings are associated, although they play a role in supporting differential diagnosis.

Neurological manifestations may be persistent or paroxysmal, likely reflecting different consequences of cerebral energy failure. Sustained neuroglycopenia during neurodevelopment has been associated with region-specific metabolic and functional network abnormalities involving basal ganglia and cerebellar circuits [12, 13]. Conversely, paroxysmal symptoms are thought to reflect acute energy crises during periods of increased metabolic demand [14].

GLUT1DS also shows age-dependent clinical evolution: early-onset epilepsy often regresses or decreases in frequency over time, whereas MDs become more prominent during childhood or adolescence [9]. This has led to the recognition of an infantile-onset form dominated by seizures and developmental impairment, and a late-childhood-to-adulthood form in which MDs predominate. Additionally, in milder phenotypes MDs may occur as isolated manifestations, representing the primary source of disease burden. The motor spectrum is broad and heterogeneous. Phenomenologically, ataxia, dystonia, chorea, dysarthria and tremor are the most common manifestations, while temporally these disorders predominantly follow an intermittent course, with paroxysmal exercise-induced dyskinesia being the typical presentation. Despite their clinical relevance, MDs in GLUT1DS remain insufficiently characterized, and their response to symptomatic and disease-specific treatments is poorly defined.

Ketogenic dietary therapies (KDTs), which provide ketone bodies as an alternative cerebral energy substrate, have been shown to be effective particularly for seizure control [15] and constitute the first-line disease-specific treatment for GLUT1DS [3, 7]. The best outcomes are achieved with early initiation and strict adherence to the dietary regimen [7, 16], making prompt diagnosis essential. In contrast to their well-established efficacy in epilepsy, the effects of KDTs on MDs appear more variable and less consistently reported [17, 18]. Alternative ketogenic approaches, such as the Modified Atkins Diet, have been explored to improve adherence, although their effectiveness remains insufficiently validated [19]; other therapeutic strategies for GLUT1DS have also been proposed but remain investigational [20].

Therefore, in this systematic review we offer a comprehensive description of the movement-disorder spectrum associated with GLUT1DS, focusing on clinical features and therapeutic responses.

Methods

The systematic review of the literature was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We searched Medline, Embase, CINAHL, Scopus, and Web of Science for eligible studies published through October 10, 2025. The search strategy combined keywords and Medical Subject Headings related to MDs and GLUT1DS and is provided in the Supplementary Materials. The review protocol was registered in PROSPERO (CRD42025644449).

Three reviewers (ZB, FC, AG) independently screened records and assessed eligibility. Inclusion criteria were: (i)

presence of MDs; (ii) description of movement-disorder phenomenology; (iii) diagnosis of GLUT1DS based on hypoglycorrhachia and/or a pathogenic *SLC2A1* variant; (iv) human subjects. We excluded reviews, editorials, opinion pieces, non-English articles, and studies reporting only aggregated data without individual clinical information.

Disagreements were resolved by consensus with a senior author (FV). Reference lists of included studies were screened for additional eligible reports. Data extraction was performed by two authors (ZB, FC) and reviewed by a senior author (RE). Extracted data included demographics, diagnostic data (including CSF glucose and mutation type), brain MRI findings, neurological features, and treatment response.

MDs were classified according to international consensus criteria [21–23]. Episodic hyperkinetic MDs with preserved consciousness—featuring dystonic, choreic, ballistic components, or mixed combinations—were categorized as paroxysmal dyskinesias (PxDs) and subclassified as exercise-induced, kinesigenic, or non-kinesigenic [24]. Paroxysmal oculomotor disturbances were not included as a separate category, as they have been specifically characterized in dedicated studies and represent early, age-dependent manifestations of GLUT1DS, with available longitudinal data suggesting that they often decrease in frequency or resolve during childhood [25].

Treatment data included reported effects of KDTs on epilepsy, intellectual disability, and MDs, as well as pharmacologic and surgical interventions for specific motor phenotypes.

Study quality was qualitatively assessed using selected domains from the Joanna Briggs Institute critical appraisal tools for case reports and case series [26]. Quality assessment was used to contextualize the evidence and not as an exclusion criterion.

For analytical purposes, patients were grouped by clinical onset and genotype. Clinical onset was classified as MD-onset or non–MD-onset according to the first reported neurologic symptom or, when manifestations were simultaneous, the presenting complaint. For genotype–phenotype analyses, the primary comparison was between missense and non-missense variants (including deletions, nonsense, frameshift, insertion, and splice-site variants). Variants were also categorized by predicted functional consequence. Variants expected to result in loss of function (LoF), including nonsense, frameshift, splice-site variants, and large deletions, were classified as LoF; the remainder were considered non-LoF. As an exploratory analysis, patients were further stratified into 3 mutation groups: missense variants, deletions, and other mutation types [10].

Statistical analyses were performed using IBM SPSS Statistics (IBM, Armonk, NY, USA). Because most continuous variables were non-normally distributed, nonparametric methods were used. Continuous variables are reported as mean ± SD, median, and range; categorical variables as frequencies and percentages. Two-group comparisons used the Mann–Whitney U test for continuous variables and the Pearson χ^2 or Fisher exact test for categorical variables. Associations between mutation type and continuous clinical variables were assessed using Spearman rank correlation. Multivariable logistic regression was used to evaluate whether genotype was independently associated with selected motor phenotypes, with mutation type (missense vs non-missense) as the main predictor and sex and age at disease onset as covariates; results are reported as odds ratios (ORs) with 95% confidence intervals (CIs). Exploratory 3-group analyses used the Kruskal–Wallis test for continuous variables and the Pearson χ^2 test for categorical variables, with post hoc Mann–Whitney U testing when appropriate. All tests were 2-tailed, and $p < 0.05$ was considered significant.

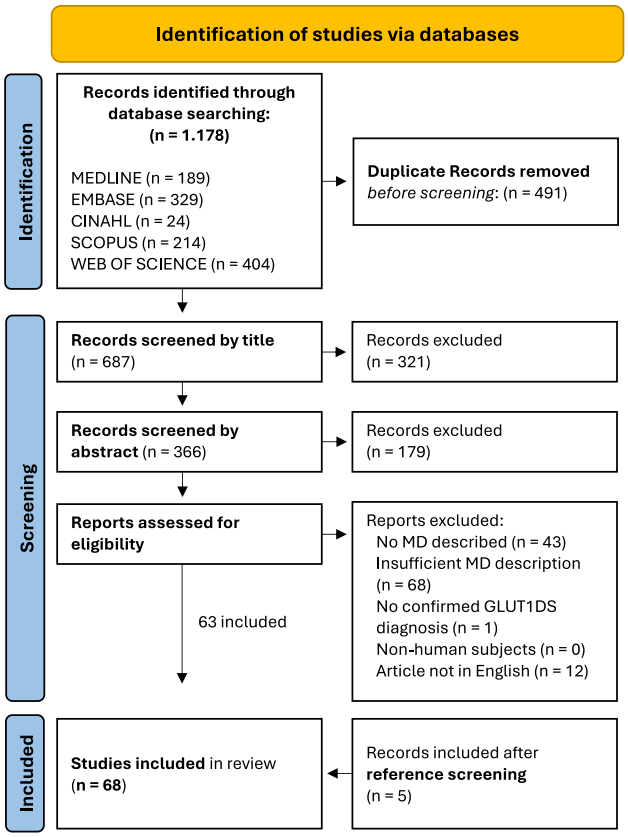

Fig. 1 The PRISMA flow diagram summarizes the study selection process. From the 1178 records initially identified, 68 studies were included after title, abstract, and full-text screening according to the predefined eligibility criteria

Results

A total of 1178 records were identified. After duplicate removal, title and abstract screening, 187 full-text articles were assessed, and 63 met inclusion criteria. Five additional studies were identified through reference screening (Fig. 1). Two unpublished cases from our center who met the same eligibility criteria were included, yielding a final cohort of 96 patients.

Demographics and clinical characteristics

Among 96 patients, 51% were female. Mean age at symptom onset was 3.1 ± 4.5 years, whereas mean age at diagnosis was 17.0 ± 14.5 years. The mean diagnostic delay was 14 ± 12.9 years, ranging from near-simultaneous diagnosis to a delay of up to 61 years. Most diagnoses (96.9%) were genetically confirmed. Missense variants were the most common (58.3%), followed by deletions (17.7%) and nonsense variants (5.2%).

Epilepsy was reported in 74% of cases, typically with early onset. The most common seizure types were absence and generalized tonic–clonic seizures. Frequent associated features included intellectual disability and dysarthria (Table 1). Rare comorbid conditions were occasionally reported, including hemiplegic migraine (in one case associated with a CACNA1A variant), Wilson disease, and presence of anti–glutamate receptor antibodies. Brain MRI findings were normal in most cases (66%), with nonspecific abnormalities reported in a minority, most commonly mild generalized atrophy, T2 white matter hyperintensities, and delayed myelination patterns.

Phenotypic spectrum of movement disorders

MDs represented the presenting symptom in 34.4% of cases, and multiple motor phenotypes frequently co-occurred (37.5%), with up to four distinct MDs observed in a small number of patients. The most common phenotypes were PxDs (63.5%) and ataxia (47.9%), whereas other manifestations included tremor (16.7%), dystonia (14.6%), chorea (7.3%), and myoclonus (6.3%). Rarely observed MDs included tics, ballism, stereotypies, restless legs syndrome, and functional MDs (Fig. 2).

Paroxysmal dyskinesias

Paroxysmal dyskinesias (n = 61) had a mean age at onset of 8.0 ± 5.5 years. Clinical, genetic, and comorbidity profiles were similar to the overall cohort, with a higher prevalence of missense variants and a lower frequency of dysarthria. PxDs were typically characterized by mixed phenomenology, most frequently dystonic (78%), with heterogeneous body distribution, often involving multifocal (31%) or bilateral lower limbs (29%) patterns. Exercise-induced forms predominated, although non-kinesigenic and kinesigenic presentations were also observed (Table 2). Pharmacologic treatments were variably effective: among treated patients (19/61, 31%), levodopa showed modest benefit in 2 of 7 treated patients, acetazolamide yielded partial or transient responses in 3 of 6 treated patients, and carbamazepine or oxcarbazepine showed limited benefit (one responder each). Rare abortive responses were described with oral glucose and medium-chain triglycerides [27, 28].

Ataxia

Ataxia (n = 46) tended to have an earlier onset, a shorter diagnostic delay, and a higher prevalence of intellectual disability, microcephaly, and dysarthria. A subset of patients (n = 12) also exhibited spastic features mainly with distal distribution and often described as ataxic–spastic gait.

Tremor

Tremor (n = 16) showed a marked female predominance (81.3%), with a tendency toward later disease onset and diagnosis. When characterized, it most often involved the upper limbs and presented as segmental or generalized tremor, with intention and postural components predominating (Table 2). Pharmacologic treatments for tremor were not systematically reported.

Dystonia

Dystonia (n = 14) typically had later onset without significant diagnostic delay. It was most often multifocal, although focal, generalized, and hemidystonic forms were also observed, with frequent task-specific and diurnal variability. Pharmacologic treatments showed limited efficacy, with one partial response to biperiden; botulinum toxin and GPi-DBS were used in selected cases with heterogeneous outcomes.

Myoclonus

Myoclonus (n = 6) showed variable onset and distribution, including multifocal and generalized patterns, and was typically intermittent. Activation patterns were inconsistently reported. Partial responses were observed in 3 patients treated with antiseizure medications (clobazam, clonazepam, valproate, ethosuximide, lamotrigine), while 1 case was drug-resistant.

Table 1 Age-related variables, CSF parameters, and demographic and clinical characteristics of the total cohort and major movement disorder subgroups

Characteristic	Total cohort N = 96	Paroxysmal Dyskinesias N = 61	Ataxia N = 46	Tremor N = 16	Dystonia N = 14
	n/N (%); mean [SD]; median {range}				
Age at first symptom (months)	36.9 [54.7]; 16 {0.4–300}	40.2 [53.2]; 18{0.4–240}	17.6 [20.9]; 12 {1–96}	40.2 [46.7]; 20 {1–144}	43.8 [48.7]; 24 {2–144}
Age at first symptom (years)	3.1 [4.6]; 1.3 {0.03–25}	3.3 [4.5]; 1.5 {0.1–20}	1.5 [1.7]; 1 {0.1–8}	3.4 [3.9]; 1.7 {0.1–12}	3.6 [4]; 2 {0.2–12}
Age at GLUT1DS diagnosis (years)	17 [14.5]; 10.5{0.7–68}	20.8 [15]; 18 {2.5–68}	11.5 [10.4]; 8 {2–44}	25.5 [19.5]; 22{0.7–68}	16.5 [12.7]; 11 {0.7–44}
Diagnostic delay (years)	14 [12.9]; 8.7{0.49–61}	17.6 [13.7]; 15.2 {1–61}	10.1 [9.8]; 5.5 {1.7–38}	22 [18.6]; 19.9 {0.5–61}	13.4 [12.5]; 7.8 {0.49–38}
Age at KDT initiation (years)	11.6 [10.4]; 8 {0.6–53}	14.2 [10.2]; 11 {2.5–53}	10 [9.5]; 7 {2–44}	14.8 [15.1]; 7.5 {0.6–44}	15.6 [15.1]; 11 {0.6–44}
Age at epilepsy onset (months)	31.5 [55.4]; 16 {0.4–420}	38.2 [67.5]; 18 {0.4–420}	20.2 [19.6]; 12{2–72}	63.5 [117.5]; 16 {2.5–420}	38 [39.6]; 24 {2–96}
Age at specific MD onset (years)	NA	8 [5.5]; 6 {1–20}	NA	9.4 [8.3]; 12 {0.07–16}	12.2 [8.5]; 10 {1.5–27}
CSF glucose (mmol/L)	1.93 [0.31]; 1.9 {1.4–2.7}	1.95 [0.35]; 1.9 {1.4–2-6}	1.85 [0.30]; 1.88 {1.4–2.7}	1.97 [0.44]; 1.89 {1.5–2.7}	1.75 [0.15]; 1.77 {1.5–1.94}
CSF/Blood Glucose Ratio	0.4 [0.07]; 0.4 {0.23–0.57}	0.41 [0.08]; 0.41 {0.23–0.57}	0.38 [0.07]; 0.39{0.23–0.53}	0.42 [0.12]; 0.43{0.23–0.57}	0.34 [0.05]; 0.34 {0.25–0.40}
CSF lactate (mol/L)	1.03 [0.25]; 1.02 {0.56–1.83}	0.95 [0.24]; 0.94 {0.56–1.4}	1.06 [0.26]; 1.05 {0.68–1.83}	1.03 [0.3]; 1.2 {0.68–1.22}	0.98 [0.16]; 0.92 {0.8–1.2}
Female	49/96 (51%)	32/61 (53%)	24/46 (52%)	13/16 (81%)	7/14 (50%)
Intellectual disability	71/96 (74%)	43/61 (71%)	39/46 (85%)	13/16 (81%)	8/14 (57%)
Microcephaly	23/96 (24%)	10/61 (16%)	16/46 (35%)	3/16 (19%)	4/14 (29%)
Epilepsy	71/96 (74%)	45/61 (74%)	35/46 (76%)	13/16 (81%)	11/14 (79%)
Dysarthria	31/96 (32%)	15/61 (25%)	21/46 (46%)	8/16 (50%)	5/14 (36%)
Movement disorder as first symptom	33/96 (34%)	20/61 (33%)	15/46 (33%)	7/16 (44%)	4/14 (29%)
Genetic performed	93/96 (97%)	61/61 (100%)	43/46 (94%)	16/16 (100%)	13/14 (92%)
Missense	56/96 (58%)	42/61 (69%)	19/46 (41%)	9/16 (56%)	7/14 (50%)
Nonsense	7/96 (7.3%)	6/61 (9.8%)	5/46 (11%)	NA	NA
Deletion	17/96 (18%)	8/61 (13%)	9/46 (20%)	4/16 (25%)	4/14 (29%)
Insertion	5/96 (5.2%)	2/61 (3.3%)	4/46 (8.7%)	2/16 (13%)	1/14 (7.1%)
Duplication	NA	NA	NA	NA	NA
Frameshift	1/96 (1%)	NA	1/46 (2.2%)	NA	NA
Splice site	1/96 (1%)	NA	1/46 (2.2%)	NA	NA
Not reported or not applicable	9/96 (9.4%)	3/61 (4.9%)	7/46 (15%)	1/16 (6.3%)	2/14 (14%)
MRI performed	62/96 (65%)	38/61 (62%)	30/46 (66%)	9/16 (56%)	9/14 (64%)

Continuous variables are presented as mean [SD] and median {range}. Categorical variables are reported as n/N (%), based on available data. Subgroups include paroxysmal dyskinesias, ataxia, tremor, and dystonia. For genetic data, "not applicable" indicates patients without genetic testing, and "not reported" indicates cases in which testing was performed but the mutation type was not specified

Ketogenic dietary therapy

Reporting of ketogenic dietary therapy effects was limited, with variable levels of detail across studies. KDT was started in 67 patients (70%); treatment was discontinued in 10 patients, due to difficulties in diet adherence. The mean age at initiation of KDT was 11.6 ± 10.4 years. Among patients with available outcome data, seizure reduction was reported in 41/45 (91%) individuals with epilepsy. Improvement in intellectual disability was

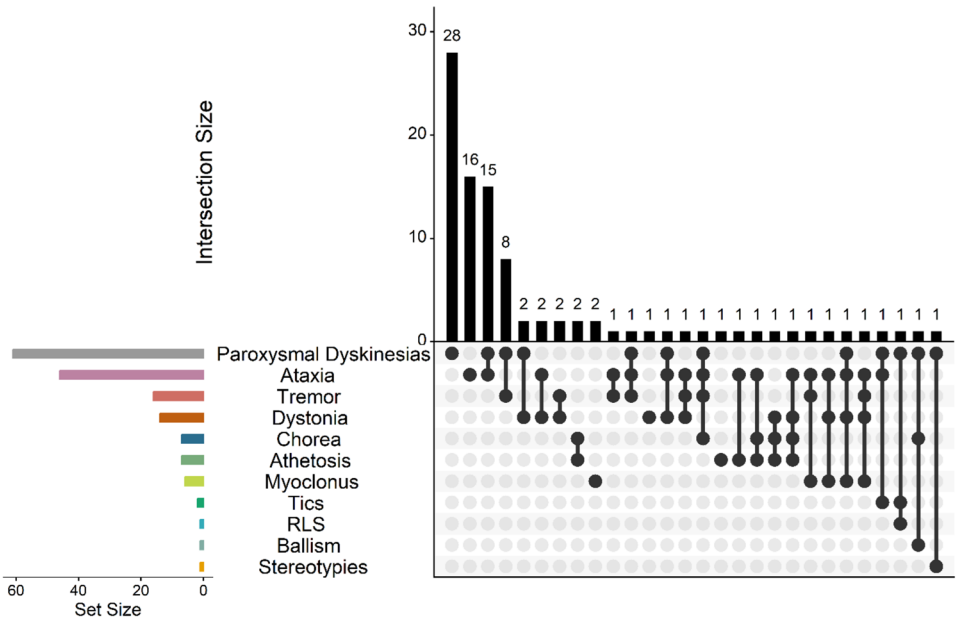

Fig. 2 UpSet plot showing the distribution and co-occurrence of movement disorder phenotypes. Horizontal bars indicate the number of patients with each movement disorder. Vertical bars indicate the number of patients with the specific combinations of phenotypes shown below (intersection size)

documented in 21/29 patients with available data (72%). Regarding MDs, improvement was reported in 50/55 patients with available motor outcome data (91%; including 43 complete and 7 partial responses), corresponding to 50/67 KDT-treated patients (75%) when unreported outcomes were included in the denominator. This estimate should be interpreted cautiously because outcomes were derived predominantly from case-based evidence, with a high risk of reporting bias. Qualitatively, improvement in MDs mainly consisted of a reduction in the frequency of paroxysmal episodes and amelioration of gait disturbances. Detailed KDT outcomes by movement disorder phenotype are provided in Supplementary Table 2.

Comparison between patients presenting with or without movement disorders at onset

Compared with the non–MD-onset group, patients with MD-onset had a significantly older age at first GLUT1-related symptoms ($p < 0.001$), as well as higher CSF glucose concentrations ($p = 0.021$) and CSF-to-blood glucose ratios ($p = 0.014$). Regarding categorical variables, patients with MD-onset showed a significantly lower frequency of intellectual disability (61% vs. 81%, $p = 0.031$) and microcephaly (6.3% vs. 35%, $p = 0.002$) compared with those with non–MD-onset. The response to ketogenic dietary therapies for movement disorder control was comparable between groups: improvement was reported in 16/17 MD-onset patients (94%) and 35/39 non–MD-onset patients (90%) with available motor outcomes, or 16/21 (76%) and 35/46 (76%) of treated patients after including unreported outcomes. All results of between-group comparisons are reported in the Supplementary Material.

Genotype–phenotype associations

In the two-group analysis, non-missense variants were negatively correlated with age at first symptom onset ($\rho = -0.42$, $p < 0.001$), age at epilepsy onset ($\rho = -0.29$, $p = 0.027$), and age at GLUT1DS diagnosis ($\rho = -0.34$, $p = 0.002$), indicating earlier clinical onset and diagnosis compared with missense variants. PxDs were more frequent in patients with missense variants (75.0% vs 51.6%, $p = 0.048$). In a multivariable logistic regression model adjusted for sex and age at onset, missense variants remained independently associated with PxDs (OR = 3.02, 95% CI 1.09–8.35, $p = 0.033$). In the additional analysis based on predicted functional consequence, patients carrying LoF variants showed a lower frequency of PxDs than non-LoF carriers (48.3% vs 75.0%, $p = 0.012$), and this association remained after adjustment (OR = 0.285, 95% CI 0.103–0.793, $p = 0.016$). Conversely, ataxia was more frequent among patients with non-missense variants (64.5% vs 33.9%, $p = 0.01$) although this association did not reach statistical significance in multivariable analysis ($p = 0.055$). Detailed results of the missense versus non-missense comparison are presented in Table 3.

In the three-group analysis the frequency of dysarthria differed significantly across groups ($p = 0.013$, Cramer's $V = 0.315$), being higher in patients with mutation types other than missense variants or gene deletions (64.3%) compared with those carrying missense variants (25.0%) or gene deletions (23.5%). Similarly, ataxia differed significantly across the three mutation groups ($p = 0.008$,

Table 2 Clinical characteristics of each movement disorder phenotype in GLUT1DS

Paroxysmal dyskinesias	Patients (N = 61)
Phenomenology, n/N (%)	50/61 (82%)
Dystonic	39/50 (78%)
Choreic	13/50 (26%)
Athetotic	9/50 (18%)
Myoclonic	6/50 (12%)
Ballistic	1/50 (2%)
Body Distribution, n/N (%)	49/61 (80%)
Multifocal	15/49 (31%)
Bilateral Lower Limbs	14/49 (29%)
Generalized	8/49 (16%)
Focal	7/49 (14%)
Hemiparoxysmal	5/49 (10%)
Trigger, n/N (%)	45/61 (74%)
Exercise-Induced	35/45 (78%)
Non-Kinesigenic	7/45 (15%)
Kinesigenic	3/45 (7%)
Tremor	**Patients (N = 16)**
Body Distribution, n/N (%)	10/16 (63%)
Segmental	6/10 (60%)
Generalized	3/10 (30%)
Focal	1/10 (10%)
Activation Condition, n/N (%)	8/16 (50%)
Intention	7/8 (88%)
Postural	4/8 (50%)
Simple Kinetic	2/8 (20%)
Rest	1/8 (13%)
Frequency, n/N (%)	2/16 (13%)
4–8 Hz	2/2 (100%)
Dystonia	**Patients (N = 14)**
Body Distribution, n/N (%)	14/14 (100%)
Multifocal	5/14 (36%)
Generalized	3/14 (21.3%)
Segmental	3/14 (21.3%)
Focal	3/14 (21.3%)
Course, n/N (%)	10/14 (71%)
Static	7/10 (70%)
Progressive	3/10 (30%)
Variability, n/N (%)	12/14 (86%)
Task-specific	8/12 (67%)
Diurnal	4/12 (33%)
Myoclonus	**Patients (N = 6)**
Age at onset, n/N (%)	4/6 (67%)
Infancy (birth-2 years)	3/4 (75%)
Childhood (3–12 years)	1/4 (25%)
Course, n/N (%)	3/6 (50%)
Stable	2/3 (67%)
Improving	1/3 (33%)
Body Distribution, n/N (%)	4/6 (67%)
Multifocal	2/4 (50%)
Generalized	1/4 (25%)
Proximal	1/4 (25%)
Activation, n/N (%)	4/6 (75%)
Rest	3/4 (75%)
Action	1/4 (25%)
Temporal Profile, n/N (%)	3/6 (50%)
Paroxysmal	3/3 (100%)

Data are reported as counts and percentages (n/N, %) based on available data. Denominators vary across variables. Phenomenological features and activation patterns may co-occur within the same patient; therefore, percentages may exceed 100%

Cramer's V = 0.332), with the highest prevalence among patients with mutation types other than missense variants or gene deletions (78.6%), compared with patients carrying missense variants or gene deletions. With regard to treatment response, the three-group comparison demonstrated a significantly higher frequency of response to the ketogenic dietary therapy among patients carrying other mutation types (100%) and missense variants (84.4%) compared with those with gene deletions (53%, p = 0.031), with a moderate effect size (Cramer's V = 0.35). For continuous variables the Kruskal–Wallis test showed significant differences across groups in age at first symptom onset, age at GLUT1DS diagnosis, and CSF glucose concentration. Post hoc pairwise comparisons using Mann–Whitney U tests demonstrated that patients carrying missense variants had a significantly higher age at first symptom onset compared with patients with gene deletions (p = 0.005) and those with other mutation types (p = 0.001); and a higher age at diagnosis compared with both gene deletions (p = 0.013) and other mutation types (p = 0.023). CSF glucose concentration was significantly higher in patients with missense variants compared with those carrying gene deletions (p = 0.049) with no significant difference between missense and other mutation types.

Discussion

In this systematic review, we synthesize the clinical profile of 96 patients with GLUT1DS and movement disorders. Overall demographic features were consistent with registry data, whereas age at diagnosis was markedly higher, with a mean of 17 years, compared with Italian and international

Table 3 Demographic, clinical, biochemical, and KDT-related characteristics of patients with GLUT1DS, comparing missense mutation versus other mutations

	Missense Mutation N = 56 n/N (%); mean [SD]; median {range}	Other Mutation N = 31	p value
Age at first symptoms (months)*	52.6 [65.5]; 24{1–300}	14.7 [18.4]; 7 {0.4–72}	**< 0.05**
Age at GLUT1DS diagnosis (years)*	20.4 [15.6]; 15 {2–68}	12 [11.6]; 8 {0.7–44}	**< 0.05**
Age at KDT initiation (years)*	13.4 [10.8]; 10 {2–53}	9.8 [9.7]; 7 {0.4–44}	0.09
Age at epilepsy onset (months)*	43.7 [71]; 24 {2–420}	18.1 [18.6]; 9.5 {0.4–72}	**< 0.05**
CSF glucose (mmol/L)*	2.01 [0.3]; 2 {1.49–2.7}	1.84 [0.3]; 1.88 {1.4–2.6}	0.059
CSF/Blood Glucose Ratio*	0.42 [0.07]; 0.41 {0.25–0.57}	0,39 [0.08]; 0.39 {0.23–0.57}	0.19
CSF lactate (mol/L)*	1.1 [0.25]; 1.08 {0.8–1.83}	0.94 [0.27]; 0.96 {0.56–1.22}	0.3
Female†	26/56 (46.4%)	17/31 (54.8%)	0.59
MD as first symptom	21/56 (37.5%)	10/31 (32.3%)	0.79
Intellectual disability†	38/56 (67.9%)	25/31 (80.6%)	0.3
Microcephaly†	9/54 (16.7%)	11/31 (35.5%)	0.059
Epilepsy†	40/56 (70.1%)	24/31 (77.4%)	0.72
Dysarthria†	14/56 (25%)	13/31 (41.9%)	0.16
Paroxysmal Dyskinesias†	42/56 (75%)	16/31 (51.6%)	**< 0.05**
Ataxia†	19/56 (33.9%)	20/31 (64.5%)	**< 0.05**
Tremor†	9/56 (16.1%)	6/31 (19.4%)	0.93
Dystonia†	7/56 (12.5%)	5/31 (16.1%)	0.88
Ketogenic Dietary Therapy†	34/56 (60.7%)	27/31 (87.1%)	**< 0.05**
Effect of KDT on seizure†	18/32 (56.3%)	18/27 (66.7%)	0.075
Effect of KDT on intellectual disability†	9/20 (45%)	9/19 (47.4%)	0.45
Effect of KDT on MDs†	27/32 (84.4%)	19/27 (70.4%)	0.073
KDT discontinuation†	6/13 (46.2%)	4/10 (40.0%)	0.94

Continuous variables are reported as mean [SD] and median {range}, and categorical variables as n/N (%). *P* values were obtained using the Mann–Whitney U test for variables marked with an asterisk (*) and the chi-square test for variables marked with a dagger (†); bold values indicate statistically significant results. For diet discontinuation, patients with unreported discontinuation status were included as a separate category in the chi-square test

registries [6, 7]. This likely reflects the inclusion of older reported cases with lower diagnostic awareness, but more importantly the greater diagnostic challenge posed by later-onset MD phenotype compared with early epileptic forms.

Paroxysmal dyskinesias and ataxia were the most prevalent motor manifestations. The largest study specifically focused on MDs in GLUT1DS was a retrospective single-center study including 57 patients [17], in which gait abnormalities, dystonia, chorea, and tremor were the most frequently reported MDs, whereas PxDs were observed in only 28% of cases. Their higher prevalence in our cohort (63.5%) likely reflects a broader classification of paroxysmal motor phenomena within the PxD spectrum. This distinction is supported by the characteristic GLUT1DS phenomenology, in which paroxysmal events are often mixed, variable, and trigger-dependent, and may represent a clinically relevant window for targeted acute metabolic interventions.

Less common motor manifestations in GLUT1DS, including tremor, dystonia, myoclonus, and choreoathetosis, should not be overlooked. Difficulties in applying standard diagnostic criteria highlight the need for structured movement-disorder assessments in clinical practice, with potential therapeutic implications. Although GLUT1DS benefits from disease-specific metabolic therapy, the role of symptomatic treatments remains incompletely defined, particularly whether they provide adjunctive benefit for selected motor manifestations.

Our comparison between MD-onset and non–MD-onset presentations partially supports the distinction between a later, primarily motor phenotype and an earlier epileptic phenotype. MD-onset cases presented later but had fewer cognitive features, while non–MD-onset patients showed lower CSF glucose levels, suggesting a more severe metabolic defect [29, 30]. Nevertheless, movement disorders occurred across phenotypes and showed marked heterogeneity, supporting the concept of GLUT1DS as a continuum rather than discrete clinical categories, particularly regarding its motor manifestations.

Genotype–phenotype analyses provided additional insights within the marked phenotypic variability of

GLUT1DS. Non-missense variants were associated with earlier onset and diagnosis, lower CSF glucose levels and a higher frequency of ataxia (64.5% vs 33.9%), consistent with a more severe phenotype [3]. Conversely, the finding of a higher proportion of missense variants (58.3%) compared with previous studies reporting a higher frequency of MDs in patients carrying deletions or other non-missense variants [10], likely reflects differences in cohort composition and the inclusion of all motor phenotypes. Notably, missense variants were associated with more frequent paroxysmal dyskinesias (75.0% vs 51.6%), predominantly exercise-induced, supporting the notion that, in patients with partially preserved transporter function, motor manifestations may be preferentially triggered by metabolic stressors [31]. Consistently, variants classified as LoF were associated with a lower frequency of paroxysmal dyskinesias compared with non-LoF variants. Although exploratory, this finding is consistent with the hypothesis that more disruptive mutations may lead to more severe and persistent phenotypes, whereas variants preserving partial transporter function may predispose to metabolically triggered paroxysmal manifestations.

This interpretation gains further relevance considering the higher responsiveness of MDs to KDT in patients with missense variants and other non-deletion mutation types, in whom paroxysmal motor manifestations are frequent but often coexist with more persistent features such as ataxia. In this context, the therapeutic role of KDT appears broad and largely unexplored, potentially encompassing both paroxysmal and non-paroxysmal motor manifestations. However, available data are incomplete, non-longitudinal, and based on non-standardized assessments; therefore, reported effectiveness should be interpreted with caution and considered hypothesis-generating.

Indeed, Pons et al. [17] documented dietary treatment benefits mainly for gait disturbances, whereas earlier uncontrolled studies of triheptanoin reported marked reductions in paroxysmal motor events in GLUT1DS [32, 33]. However, the subsequent phase 3 randomized placebo-controlled trial of triheptanoin showed no benefit over placebo for paroxysmal movement disorders in GLUT1DS [18]. In our review, reported motor improvement was most often described as reduced frequency of paroxysmal episodes, consistent with the spectrum of benefits described in observational studies. These findings argue against dismissing ketogenic approaches as ineffective for MDs in GLUT1DS, especially considering that the mechanisms underlying the ketogenic dietary therapy are likely not exclusively metabolic and remain far from fully understood [34]. Consistent with this evolving therapeutic landscape, emerging investigational approaches include preclinical AAV-mediated *SLC2A1* gene therapy [35], red blood cell exchange transfusion [36], and continuous glucose monitoring–guided diazoxide therapy [37]. These strategies highlight the need for standardized motor outcomes in future trials.

This review is limited by the predominance of case reports in the literature, with associated risks of selection and reporting bias. Clinical data were often incomplete and heterogeneously reported, resulting in variable denominators and limiting the precision of several estimates, particularly for movement disorder classification and treatment response. In addition, the observational nature of the included studies and small sample sizes limit the strength of genotype–phenotype analyses and preclude causal inference. Overall, these findings highlight the need for prospective, multicenter studies with standardized phenotyping and outcome measures to better define the clinical spectrum, underlying mechanisms, and optimal management of movement disorders in GLUT1DS.

Conclusion

This systematic review provides a comprehensive overview of movement disorders in GLUT1DS, highlighting several methodological nuances that warrant critical reflection. Our analysis reveals significant heterogeneity in clinical data provided by each report, highlighting the need for standardized motor assessment protocols. Exploratory genotype–phenotype analyses suggest variant-specific differences in motor expression, although these findings require validation. Furthermore, the variability in ketogenic dietary therapy implementation and assessment underscores the necessity for controlled, longitudinal research designs that can definitively establish treatment efficacy across different motor manifestations. Given the predominance of case-based evidence, the overall certainty of these findings remains low. Future investigations should prioritize developing structured evaluation frameworks that can capture the complex, dynamic nature of movement disorders in GLUT1DS, moving beyond narrative descriptions to quantitative, reproducible metrics to better define underlying pathophysiological mechanisms and facilitate targeted therapeutic strategies.

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Declarations

Conflicts of interest The authors declare that there are no conflicts of interest relevant to this work.

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