GLUT1 deficiency is a rare neurometabolic disorder that can be effectively treated with ketogenic diet. However, this condition is underdiagnosed due to its nonspecific, overlapping, and evolving symptoms with age. We retrospectively reviewed the clinical course of nine patients diagnosed with GLUT1 deficiency, based on SLC2A1 mutations and/or glucose concentration in cerebrospinal fluid. The patients included eight boys and one girl who initially presented with seizures (44%, 4/9) or delayed development (44%, 4/9) before 2 years of age, except for one patient who presented with apnea as a neonate. Over the clinical course, all of the children developed seizures of the mixed type, including absence seizures and generalized tonic-clonic seizures. About half (56%, 5/9) showed movement disorders such as ataxia, dystonia, or dyskinesia. We observed an evolution of phenotype over time, although this was not uniform across all patients. Only one child had microcephaly. In five patients, ketogenic diet was effective in reducing seizures and movement symptoms, and the patients exhibited subjective improvement in cognitive function. Diagnosing GLUT1 deficiency can be challenging due to the phenotypic variability and evolution. A high index of clinical suspicion in pediatric and even older patients with epilepsy or movement disorders is key to the early diagnosis and treatment, which can improve the patient’s quality of life.

Key Words: GLUT1 deficiency, ketogenic diet, phenotypic variability, SLC2A1
GLUT1 Deficiency Syndrome

possibly due to changes in brain metabolism over time.8

Fortunately, GLUT1 deficiency syndrome has a specific treat-
ment option—a ketogenic diet. Diet therapy is known to be ef-
effective for neurological dysfunctions, such as epilepsy and
movement disorders. However, diagnosing GLUT1 deficiency
syndrome can be challenging due to the variability in clinical
features and age of onset, and phenotypic evolution over time.

Although some authors have suggested diagnostic clues such
as fluctuation associated with fasting or improvement with
meals, in particular, self-induced high-fat diet,9,11 it is not trivial
to find these clues from the patients’ recalls. The disease seems
to be clinically underdiagnosed, even in the era of genomics.12

The aim of our study was to examine and present the pleiotro-
pic and evolving phenotypes of nine patients with GLUT1 de-
ficiency syndrome caused by mutations in SLC2A1.

Nine patients with pathogenic variants in SLC2A1, who vis-
ited the pediatric neurological clinic at Seoul National Univer-
sity Children’s Hospital, were enrolled. We retrospectively re-
viewed their medical records. We collected detailed information
about their prenatal and perinatal history, family history, age of
symptom onset, initial symptoms, psychomotor development,
neurological examination results, brain magnetic resonance
imaging (MRI) findings, electroencephalography (EEG) find-

ings, results of cerebrospinal fluid (CSF) studies, genetic tests,
and treatment outcomes. This study was approved by the Seoul
National University Hospital Institutional Review Board (IRB
No. 1812-119-996), and blood samples were obtained from
enrolled patients and their parents who provided informed
consent. Identified variants through genetic testing were clas-
sified as pathogenic, based on the 2015 guidelines of Ameri-
can College of Medical Genetics and Genomics.13

The patients included eight boys and one girl (Table 1). The
mean age at disease onset was 9.1 months (range, 1–24 months).
The mean age at diagnosis was 9.4 years (range, 13 months to
26 years). Four patients (44%) initially manifested with sei-
zures, four patients (44%) presented with developmental de-
lay, and one patient presented with neonatal apnea. During
the clinical course, all patients developed seizures of the mixed
type, including absence seizures, generalized tonic–clonic sei-
zures, generalized tonic seizures, myoclonic seizures, and fo-
cal seizures. Absence seizures and generalized tonic–clonic sei-
zures were the most common. Seven patients had exhibited
seizures before reaching 2 years of age, and two patients had
developed epilepsy at the age of 7 and 11 years. Seizures were
poorly controlled in most patients, and the average number of
antiepileptic drugs was 3 (range, 1–5). Seven patients had
medically intractable seizures with three or more antiepileptic
drugs. Five patients (56%) exhibited movement disorders
such as ataxia, dystonia, or dyskinesia over time (Fig. 1). Ataxia
was relatively permanent, while dystonia or dyskinesia tended
to be paroxysmal. The mean age of onset of movement symp-
toms was 5.1 years (range, 24 months to 10 years). The pa-
tients had varying severity of delayed psychomotor develop-
ment or intellectual disability. Notably, only one patient had
microcephaly. Other clinical features included oculogyric
movements or apnea. Aggravating factors such as fasting, ex-
ercise, or fatigue were reported in four patients (44%), but no
relieving or aggravating factors were identified in the other pa-
tients. Fluctuation of clinical symptoms along with the meals
was recalled in only three patients (Patients 2, 5, and 7).

Brain MRI showed no abnormalities in six patients, cerebel-
lar atrophy in one patient, and delayed myelination in two pa-
tients (Fig. 2). Interictal EEG was performed in nine patients
with seizures, and showed generalized or focal epileptiform
discharges with or without background slowing. CSF glucose
levels were checked in five patients whose parents gave con-
sent for lumbar puncture. CSF glucose levels ranged from 32
to 46 mg/dL, and CSF-to-serum glucose ratio was <0.4. Ketogenic
diet was applied in five patients (Patients 1–4 and 7), and
was effective in controlling seizures and movement symptoms. All
patients except one (Patient 4) maintained this diet therapy
for >1 year.

Nine pathogenic variants were identified. All nine different
mutations were identified in the nine patients, and four were
novel mutations. Among the eight patients whose parental
tests were performed, seven had de novo mutations, while one
(Patient 3) had a pathogenic variant inherited from his simi-
larly affected mother. The variants were scattered across all
exons (Supplementary Fig. 1, only online) without hot spots.
Although about half of the variants had been identified
through targeted single-gene analysis under the clinical suspi-
cion of GLUT1 deficiency syndrome, the other half were found
via epileptic encephalopathy panel sequencing (Patients 6 and
9) or whole-exome sequencing (Patients 1, 2, and 8).

GLUT1 deficiency syndrome is a treatable neurometabolic
disorder, for which early diagnosis and treatment are very
important. However, due to its nonspecific, overlapping, and
evolving symptoms during development, this disorder re-
mains underdiagnosed.4,12 The diversity of phenotypic fea-
tures, severity, and clinical course, along with the phenotypic
evolution with age mean that an early diagnosis can be chal-
lenging. A long diagnostic odyssey and variable, not uniform,
clinical course have been reported in previous studies.3,4,12 As
in a recent study that reported a median age of diagnosis as 8
years 5 months,7 our study also revealed a substantial delay in
the diagnosis of GLUT1 deficiency syndrome. In our study,
the mean age of disease onset was 9.1 months, but the mean
age of diagnosis was 9.4 years. Alter and colleagues reported
that the earliest symptoms are dominated by seizures and oth-
er paroxysmal events, which are replaced by movement symp-
toms during adolescence.8,14 However, in our study, three out of
five patients who were followed up to adolescence showed an
atypical clinical evolution that differed from the typical course
reported in previous studies. For example, Patients 2 and 7
showed movement abnormalities followed by epilepsy, and
Patient 1 developed epilepsy and ataxia simultaneously. A high

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Table 1. Clinical, Laboratory, Radiological, and Molecular Features of Patients with GLUT1 Deficiency Syndrome

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Age at onset: Dx:Current age or last f/u</th>
<th>Initial symptoms</th>
<th>Movement symptoms (onset age)</th>
<th>Global DD or ID (IQ, if available)/Epilepsy (onset age, sz type)</th>
<th>Microcephaly</th>
<th>Brain MRI</th>
<th>CSF-to-serum glucose ratio</th>
<th>Genotype</th>
<th>Inheritance, Reported [Ref.]</th>
<th>Pathogenicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>6 mon:16 yr:19 yr DD Ataxia (30 mon)</td>
<td>Ataxia</td>
<td>+/- (mild ID, IQ 50)</td>
<td>-</td>
<td>N</td>
<td>0.36</td>
<td>0.36 (34/94)</td>
<td>p.Val131Cysfs</td>
<td>De novo, novel</td>
<td>P</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>18 mon:16 yr:18 yr DD OM Dystonia (24 mon)</td>
<td>Dystonia</td>
<td>+/- (7 yr, A)</td>
<td>-</td>
<td>N</td>
<td>0.36</td>
<td>0.36 (37/102)</td>
<td>c.276-1G&gt;A</td>
<td>De novo, previous report [21]</td>
<td>P</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>12 mon:13 yr:15 yr Dystonia (7 yr)</td>
<td>Dystonia</td>
<td>+/- (mild ID, IQ 54)</td>
<td>-</td>
<td>Cerebellar atrophy</td>
<td>0.4</td>
<td>0.4 (46/114)</td>
<td>p.Arg333Trp</td>
<td>From mother, previous report [22]</td>
<td>P</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>12 mon:3 yr:16 yr DD OM Dystonia (10 yr)</td>
<td>Dystonia</td>
<td>+/- (20 mon, A-F)</td>
<td>-</td>
<td>-</td>
<td>0.4</td>
<td>0.4 (39/97)</td>
<td>p.Phe434Ile</td>
<td>De novo, novel</td>
<td>P</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>24 mon:26 yr:28 yr DD Ataxia (4 yr)</td>
<td>Ataxia (4 yr)</td>
<td>+/- (11 yr, N/A)</td>
<td>-</td>
<td>N</td>
<td>0.36</td>
<td>0.36 (32/87)</td>
<td>p.Gln242*</td>
<td>Unknown, previous report [23]</td>
<td>P</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>1 mon:13 mon: f/u lost after 21 mon Seizure</td>
<td>-</td>
<td>+/- (1 mon, F-GTC-GT)</td>
<td>-</td>
<td>N</td>
<td>N/A</td>
<td>p.Gly419Arg</td>
<td>De novo, novel</td>
<td>P</td>
<td></td>
</tr>
</tbody>
</table>

No., number; Dx, diagnosis; f/u, follow-up; DD, developmental delay; ID, intellectual disability; IQ, intelligence quotient; sz, seizure; CSF, cerebrospinal fluid; M, male; F, female; mon, month(s); yr, year(s); OM, oculogyric movement; N/A, not available; A, absence; GTC, generalized tonic-clonic; F, focal; MC, myoclonic; GT, generalized tonic; N, normal; M, myelination; P, pathogenic.
clinical suspicion and awareness, as well as recognition of phenotypic diversity and evolution over time, are very important for preventing a delayed diagnosis in patients who have seizures, neurodevelopmental problems, or associated abnormal movements with an unexplained etiology at any age.

The mechanism by which phenotypes vary or evolve with

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**Fig. 1.** The graph represents evolving phenotypes of four patients (Patients 1, 2, 4, and 7). Lower axis of the graph represents patient’s age. Red and light blue represent epilepsy and movement disorders, respectively. Orange represents developmental delay (DD) and intellectual disability (ID). Black represents other atypical symptoms. Black arrows represent age at diagnosis, and red arrows denote age during treatment (ketogenic diet). GTC, generalized tonic-clonic.
age is not clear. One possible explanation is that impaired glucose transmission to the brain does not affect prenatal or perinatal development. The brain glucose utilization rate increases from birth until about the age of 4 years, a time in which a child’s cerebral cortex uses more than twice as much glucose as an adult’s cortex; and this rate remains high until age 10, and then declines to reach the adult level at age 16-18 years. Therefore, the ontogeny of cerebral glucose metabolism is similar to the evolving pattern of epilepsy in GLUT1 deficiency syndrome.

GLUT1 deficiency is representative of treatable neurometabolic disorders with intellectual disability. Since the first report by De Vivo, et al.2 in 1991, the effects of ketogenic diet have been supported, and the recently modified Atkins diet has also been known to be effective. Controversy remains on whether diet therapy is highly effective for treating movement symptoms and cognitive impairment, as well as seizures. Four of our patients (Patients 1–3 and 7) started diet therapy in adolescence or adulthood, but they showed favorable outcomes for most of the symptoms, including seizures and movement symptoms, in addition to subjective improvement in cognitive function. Further studies are needed to assess the overall outcome of a ketogenic diet by initiation ages, treatment duration, and type of diet in patients with GLUT1 deficiency syndrome. In addition, medications such as acetazolamide can be applied for paroxysmal movement symptoms for cases with diet therapy failures.

Atypical initial manifestations can be an obstacle to the early diagnosis of GLUT1 deficiency syndrome. In our study, oculogyric movements during neonatal or early infancy were found in four patients (44%). Oculogyric movements or crisis are easily mistaken as strabismus, but can be a key feature of GLUT1 deficiency syndrome. Although microcephaly also emerges during infancy or early childhood in most patients with this syndrome, only one patient in our series had microcephaly. Some symptoms, such as absence seizures, were unnoticed but were later recognized through comprehensive history taking. Our study recapitulates the atypical clinical features and phenotypic evolution of GLUT1 deficiency syndrome. Although a clue-based assumption, followed by CSF analysis and/or targeted single-gene analysis, is the most efficient diagnostic pathway, diagnosis in actual clinical practice remains challenging. As shown in this study, application of next-generation sequencing can be helpful in shortening the time needed for the diagnosis of disorder with phenotypic variability and evolution.

The present study also expands the genotypic spectrum of GLUT1 deficiency syndrome. Whereas missense mutations are often associated with milder symptoms, no clear-cut phenotype-genotype correlations have been established. Although about three-quarters of the patients in our study had missense mutations, they did not show a milder phenotype compared to other patients with truncating mutations. Our patients exhibited interindividual phenotypic variability even though the same mutations have been reported previously, which suggests the presence of genetic modifiers such as secondary genes. Therefore, the genotype does not always predict the phenotype.

In conclusion, GLUT1 deficiency syndrome should be considered in patients with typical phenotypic evolution, such as infantile-onset epilepsy followed by movement symptoms around childhood or adolescence, as well as in atypical patients with early onset movement disorders and/or late onset epilepsy, or even in those with nonspecific and unexplained intellectual disability. Biochemical analysis and recent advances in genomic technology have made it possible to establish a diagnosis efficiently. Early diagnosis that leads to prevention and treatment is important for the neurological improvement, as well as ending the long diagnostic odyssey and providing genetic counseling, in affected children and adults.
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