Aims and scope

Annals of Child Neurology is an interdisciplinary peer-reviewed biomedical journal publishing articles in the fields of child neurology, pediatric neuroradiology, child psychiatry, pediatric neuropsychology, developmental and behavior pediatrics, pediatric neuroscience, and developmental neurobiology. The aims of Annals of Child Neurology are to contribute to the advancements in the fields of pediatric neurology through the scientific reviews and interchange of all of pediatric neurology. It aims to reflect the latest clinical, translational, and basic research trends from worldwide valuable achievements. In addition, genome research, epidemiology, public education and clinical practice guidelines in each country are welcomed for publication.

Focusing on the needs of neurologic patients from birth to age 18 years, Annals of Child Neurology covers topics ranging from assessment of new and changing therapies and procedures; diagnosis, evaluation, and management of neurologic, neuropsychiatric, and neurodevelopmental disorders; and pathophysiology of central nervous system diseases.

Area of specific interest include the following: behavioral neurology & neuropsychiatry, clinical neurophysiology, epilepsy, headache medicine, neurocritical care, neurodevelopmental disabilities, neurogenetics, neuroimaging, neuromuscular medicine, neuroimmunology and inflammation, neuro-oncology, sleep medicine, vascular neurology, as well as other diseases affecting the developing nervous system.

Acceptance for publication of submitted manuscript is determined by the editors and peer reviewers, who are experts in their specific fields of pediatric neurology. The journal includes the following sections: original articles, reviews, letters to the editor. The editorial board invites articles from international studies or clinical, translational, and basic research groups. Supplements can be published when they are required.

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Publisher

Korean Child Neurology Society

Editor-in-chief

Soonhak Kwon, Kyungpook National University, Korea

Editorial office

The Korean Child Neurology Society
50-1, Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
Tel: +82-2-2019-3350  Fax: +82-2-2019-4881  E-mail: editor@annchildneurol.org

Printing office

M2community Co.
8th FL, DreamTower, 66 Seongpil-ro, Seongdong-gu, Seoul 04784, Korea
Tel: +82-2-2190-7300  Fax: +82-2-2190-7333  E-mail: journal@m2community.co.kr

Published on OCTOBER 1, 2020

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This paper meets the requirements of KS X ISO 9706, ISO 9706-1994 and ANSI/NISO Z39. 48-1992 (Permanence of paper)
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Deep Phenotyping in 1p36 Deletion Syndrome

Youngkyu Shim, MD¹, Young Jun Go, MD¹, Soo Yeon Kim, MD¹,², Hunmin Kim, MD³, Hee Hwang, MD³, Jeun Choi, MD⁴, Byung Chan Lim, MD¹,², Ki Joong Kim, MD¹, Jong-Hee Chae, MD¹,²

¹Department of Pediatrics, Pediatric Clinical Neuroscience Center, Seoul National University Children’s Hospital, Seoul National University College of Medicine, Seoul, Korea
²Research Center for Rare Diseases, Seoul National University Hospital, Seoul, Korea
³Department of Pediatrics, Seoul National University Bundang Hospital, Seongnam, Korea
⁴Department of Pediatrics, Seoul Metropolitan Government Seoul National University Boramae Medical Center, Seoul, Korea

Purpose: Although 1p36 deletion syndrome is the most common terminal deletion syndrome, unexplained phenotypic variability still occurs. We aimed to delineate the phenotype of this syndrome in detail and to characterize the phenotype-genotype correlation.

Methods: We retrospectively reviewed 15 patients diagnosed with 1p36 deletion syndrome confirmed by chromosomal microarray.

Results: All 15 patients revealed delayed attainment of motor milestones and speech. Seven patients (46.7%) never walked alone and only two (13.3%) could express a simple two-word sentence. They all showed subsequent intellectual disability. Two patients with large deletions of both distal and proximal critical regions of the 1p36 region shared severe intellectual disability with Rett syndrome-like behavioral features. Seizures, although frequent (73.3%), were well-controlled except in one patient with infantile spasms. Facial dysmorphism (92.9%) and ventricular mild dilatation with corpus callosum anomaly (46.7%) were common. Heart problems were identified in 14 patients, including structural abnormalities and/or functional problems associated with the gene encoding PR domain-containing protein 16. Two patients developed severe cardiac dysfunction requiring heart transplantation in their late teens. One patient with a 400 Kb deletion partly overlapping with the gene encoding calmodulin-binding transcription activator 1 did not have facial dysmorphism and presented with mild developmental delay and ataxic gait. One patient had a choledochal cyst, which was resected due to neonatal cholestasis.

Conclusion: Although the phenotype of 1p36 deletion syndrome is quite consistent with previous reports, additional manifestations such as certain behavioral features, ataxic gait, and severe cardiac dysfunction at an early age should be considered.

Keywords: Chromosome 1p36 deletion syndrome; Phenotype; Genotype

Introduction

The 1p36 deletion syndrome (OMIM 607872, also referred to as monosomy 1p36 syndrome) is the most common chromosome terminal deletion syndrome. This syndrome has some notable features. The estimated prevalence ranges from 1 in 5,000 to 1 in 10,000 [1-3]. Previous reports described the characteristic features of 1p36 deletion syndrome, which include developmental delay/intellectual disability (ID), epilepsy, craniofacial anomaly, and structural or functional heart problems [1,4,5]. However, some
unexplainable phenotype variability still occurs. It is important to delineate clinical and genetic heterogeneity in terms of earlier recognition of the disorder, individualized surveillance testing for co-morbidities, and counseling on the prognosis. Recent advanced chromosomal microarray (CMA) enables physicians to detect interstitial deletions located in the far proximal site, identify complex rearrangements of the deletion site, and measure the extent of the deletion, which can precisely identify the involved genes compared to G-banded chromosomal analysis or telomere fluorescence in situ hybridization. We report our patients’ phenotypic spectrum of the 1p36 deletion syndrome with noticeable findings along with the exact breakpoint of chromosomes as detected by CMA. We also attempted to compare our results to previously reported findings in other literature.

Materials and Methods

Fifteen patients diagnosed with the 1p36 deletion syndrome by using CMA were retrospectively reviewed. The CMA test was conducted using Agilent Human Genome oligonucleotide comparative genomic hybridization microarray 244, 80, or 60 K (Agilent Technologies, Santa Clara, CA, USA) with 8.9, 13, or 41 Kb over median probe spacing, respectively. All copy number variants were called and based on human assembly GRCh37 (hg19). Thirteen patient’s CMA data with exact chromosome deletion size and location were demonstrated with involved genes. Two patients’ clinical characteristics without detailed CMA data were also reviewed in attempt to review the phenotype variability. This study was approved by the Institutional Review Board of Seoul National University hospital (IRB No: H-2005-143-1125). Informed consent was waived by the board.

Patients’ clinical characteristics and ancillary tests were retrospectively reviewed. Available cerebral magnetic resonance imaging (MRI), electroencephalography, echocardiography, abdominal ultrasonography, and laboratory results were all reviewed. Phenotypes with related genetic breakpoints and responsible genes described in previous literature were analyzed

Results

1. Patients’ demographics

Of the 15 patients we recruited into the study, nine were female and six were male, giving a female to male ratio was 3:2. The median age at diagnosis was 4 years and ranged from 2 months to 15 years. The median follow up duration was 4.5 years and ranged from 0.8 to 9.9 years. All patients were aged more than 4 years and four patients were over 18 years old at the last follow-up. Eight patients’ parental tests were available and all were reported as de novo deletions in the 1p36 region. All 15 patients’ demographic data and overall clinical features are provided in Table 1.

2. Neurological problems

All 15 patients were reported to have varying degrees of developmental delay or ID. Delayed attainment of motor milestones and speech was apparent in all 15 patients. Although all patients could

### Table 1. Overview of the clinical features of the 15 patients with 1p36 deletion (n=15)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>9 (60)</td>
</tr>
<tr>
<td>Age at diagnosis (yr)</td>
<td>4.0 (0.2–15.0)</td>
</tr>
<tr>
<td>Follow-up duration (yr)</td>
<td>4.5 (0.8–9.9)</td>
</tr>
<tr>
<td>Age at last follow-up (yr)</td>
<td>8.5 (4.4–21.1)</td>
</tr>
<tr>
<td>DD or ID</td>
<td>15 (100)</td>
</tr>
<tr>
<td>No ambulation</td>
<td>7 (46.7)</td>
</tr>
<tr>
<td>Walking with or without assistance</td>
<td>8 (53.3)</td>
</tr>
<tr>
<td>Aphasia or a few words</td>
<td>13 (86.7)</td>
</tr>
<tr>
<td>Sentence expression</td>
<td>2 (13.3)</td>
</tr>
<tr>
<td>Seizure</td>
<td>11 (73.3)</td>
</tr>
<tr>
<td>Seizure onset age (mo)</td>
<td>8 (2–204)</td>
</tr>
<tr>
<td>Facial dysmorphism</td>
<td>13/14 (92.9)</td>
</tr>
<tr>
<td>Brain abnormality</td>
<td>10/12 (83.3)</td>
</tr>
<tr>
<td>Corpus callosum abnormality</td>
<td>4</td>
</tr>
<tr>
<td>Ventricular dilatation</td>
<td>3</td>
</tr>
<tr>
<td>Simplified gyral pattern</td>
<td>3</td>
</tr>
<tr>
<td>PVWM T2HSI</td>
<td>2</td>
</tr>
<tr>
<td>Migration anomaly</td>
<td>1</td>
</tr>
<tr>
<td>Heart problems</td>
<td>14/14 (100)</td>
</tr>
<tr>
<td>PDA</td>
<td>8</td>
</tr>
<tr>
<td>ASD or VSD</td>
<td>6</td>
</tr>
<tr>
<td>LVNC or CMP</td>
<td>4</td>
</tr>
<tr>
<td>Valve problems</td>
<td>2</td>
</tr>
<tr>
<td>Needed treatment (operation or medication)</td>
<td>9/14 (64.3)</td>
</tr>
<tr>
<td>Finger or toe abnormality</td>
<td>7</td>
</tr>
<tr>
<td>Eye problems</td>
<td>4</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>4</td>
</tr>
<tr>
<td>Cryptorchidism</td>
<td>3</td>
</tr>
<tr>
<td>Choledochal cyst</td>
<td>1</td>
</tr>
<tr>
<td>Inguinal hernia</td>
<td>1</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>1</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>1</td>
</tr>
</tbody>
</table>

Values are presented as number (%) or median (interquartile range). DD, developmental delay; ID, intellectual disability; PVWM T2HSI, periventricular white matter T2 high signal intensity; PDA, patent ductus arteriosus; ASD, atrial septal defect; VSD, ventricular septal defect; LVNC, left ventricular noncompaction; CMP, cardiomyopathy.

*Overriding, curly, or contracture deformity of fingers or toes.
sit with or without support eventually, seven patients (46.7%) were not able to get walking ability even after their age of 4 years. Those patients also showed limited language acquisition. At the most, a few word expression was possible. Eight patients (53.3%) could walk with or without assistance; however, only two patients were able to express a simple sentence consisting of two basic words.

One patient (Patient 6) with the smallest chromosome deletion (400 Kb, chr1:6499296-6900414) who presented with slow catch-up development could walk alone at his age of 31 months and revealed the mildest ID among 15 participants. Other 14 patients showed severe ID without developmental regression (Table 2).

A noticeable feature was found in two relatively older children aged 10 and 13 years that visited (Patient 2 and 3, respectively). They presented with Rett syndrome-like behavioral features including severe ID with hand automatism or bruxism showed large deletions that overlapped both distal [6] and proximal [7] critical regions. Other behavioral features such as aggressive behavior (Patient 5) and attention deficit hyperactivity disorder (Patient 6) were also described. The available CMA data of thirteen patients are depicted in Fig. 1.

Seizures occurred in 11 patients (11/15, 73.3%). Every first-time seizure occurred before the age of five except in one patient (Patient 2, seizure onset at 17 years old). In seven patients (63.6%), seizure was noticed before the age of one and the earliest onset age was 2 months. Seizure semiology was variable, including focal clonic, generalized tonic or clonic, hypomotor, or spasm. Only one patient (Patient 1) had infantile spasms and was detected hypsarrhythmia in electroencephalography. Combination of vigabatrin, zonisamide, and prednisolone were required in this patient whose deletion size was the largest one (10.5 Mb) of all the study participants. Except in this patient, seizures were well-controlled with zero (n = 2) to two (n = 2), mostly one (n = 6), antiepileptic drug (AED). Three patients were able to discontinue AED after 3 years from their initial treatment. There was no correlation between seizure onset age and seizure severity.

### 3. Facial dysmorphism

Facial dysmorphism was noticed in 13 patients with flat and pale faces, deep-set eyes, small-slit eyes, hypertelorism, flat noses and nasal bridges, low set ears with small or large cupped ears, thickened ear helices, small mouths, or pointed chins. Although some previously delineated dysmorphic facial features were noticed, we could not identify any shared facial anomaly between the patients. There was no relationship between the deletion sizes and facial dysmorphism. However, one patient (Patient 6) with the smallest size of deletion (400 Kb) did not have any apparent craniofacial anomaly.

### 4. Brain structural abnormality

Brain structure was able to assess in 12 patients with MRI. Among

<table>
<thead>
<tr>
<th>No.</th>
<th>Age at last FU (yr)</th>
<th>Walka</th>
<th>Sentenceb</th>
<th>Behavior</th>
<th>Seizure onset</th>
<th>Seizure type</th>
<th>AEDc</th>
<th>FD</th>
<th>Brain MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7.2</td>
<td>–</td>
<td>–</td>
<td>NA</td>
<td>2 mo</td>
<td>Spasm, hypomotor</td>
<td>VGB ZNS (PD)</td>
<td>+</td>
<td>CC hypoplasia, Vd, SG</td>
</tr>
<tr>
<td>2</td>
<td>20.7</td>
<td>–</td>
<td>–</td>
<td>RS-like</td>
<td>17 yr</td>
<td>Tonic</td>
<td>CLB VPA LTG</td>
<td>+</td>
<td>Vd</td>
</tr>
<tr>
<td>3</td>
<td>21.1</td>
<td>–</td>
<td>–</td>
<td>RS-like</td>
<td>1 yr</td>
<td>NA</td>
<td>VPA</td>
<td>+</td>
<td>CC dysgenesis</td>
</tr>
<tr>
<td>4</td>
<td>8.9</td>
<td>–</td>
<td>–</td>
<td>RS-like</td>
<td>4 yr</td>
<td>Hypomotor</td>
<td>VPA</td>
<td>+</td>
<td>Migration anomaly</td>
</tr>
<tr>
<td>5</td>
<td>5.1</td>
<td>–</td>
<td>–</td>
<td>ADHD</td>
<td>4 yr</td>
<td>Hypomotor</td>
<td>–</td>
<td>+</td>
<td>SG</td>
</tr>
<tr>
<td>6</td>
<td>8.5</td>
<td>+</td>
<td>+</td>
<td>NA</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Normal</td>
</tr>
<tr>
<td>7</td>
<td>10.9</td>
<td>+</td>
<td>+</td>
<td>NA</td>
<td>3 mo</td>
<td>Clonic, hypomotor</td>
<td>VPA OXC</td>
<td>+</td>
<td>CC splenium dysgenesis</td>
</tr>
<tr>
<td>8</td>
<td>4.6</td>
<td>–</td>
<td>–</td>
<td>NA</td>
<td>2 mo</td>
<td>NA</td>
<td>VPA</td>
<td>+</td>
<td>NA</td>
</tr>
<tr>
<td>9</td>
<td>9.5</td>
<td>+</td>
<td>–</td>
<td>NA</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>CC rostrum dysgenesis, Vd</td>
</tr>
<tr>
<td>10</td>
<td>6.2</td>
<td>–</td>
<td>–</td>
<td>NA</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>Normal</td>
</tr>
<tr>
<td>11</td>
<td>19.0</td>
<td>+</td>
<td>–</td>
<td>NA</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>Normal</td>
</tr>
<tr>
<td>12</td>
<td>4.1</td>
<td>+</td>
<td>–</td>
<td>NA</td>
<td>2 mo</td>
<td>Focal clonic</td>
<td>LEV</td>
<td>+</td>
<td>PVM T2 high signal</td>
</tr>
<tr>
<td>13</td>
<td>19.6</td>
<td>+</td>
<td>–</td>
<td>NA</td>
<td>3 yr</td>
<td>Tonic</td>
<td>–</td>
<td>+</td>
<td>SG</td>
</tr>
<tr>
<td>14</td>
<td>4.4</td>
<td>–</td>
<td>–</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>15</td>
<td>5.5</td>
<td>–</td>
<td>–</td>
<td>NA</td>
<td>4 mo</td>
<td>NA</td>
<td>LEV CLB</td>
<td>n/a</td>
<td>NA</td>
</tr>
</tbody>
</table>

FU, follow-up; AED, antiepileptic drug; FD, facial dysmorphism; MRI, magnetic resonance imaging; NA, not available; VGB, vigabatrin; ZNS, zonisamide; PD, prednisolone; CC, corpus callosum; Vd, ventricular dilatation; SG, simplified gyral pattern; RS, Rett syndrome; CLB, clobazam; VPA, valproate; LTG, lamotrigine; ADHD, attention deficit hyperactivity disorder; OXC, oxcarbazepine; LEV, levetiracetam; PVM, periventricular white matter.

*Able to walk with or without assistance at the last follow-up; *Able to speak a sentence at the last follow-up; *Generalized seizures, unless otherwise described; *Underlining indicates prescribed medications at the last follow-up.

https://doi.org/10.26815/acn.2020.00108

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them 10 patients (83.3%) had some abnormalities including four patients with corpus callosum abnormalities (hypoplasia or dysgenesis), three patients with ventricular dilatation, three patients with simplified gyrus patterns, two patients with periventricular white matter T2 high signal intensity, and one patient with migration anomaly. Two patients including one patient (Patient 6) with the smallest size of interstitial deletion (400 Kb) did not have any brain structural abnormality.

5. Heart problems
Except for one patient who did not undergo echocardiography, all patients had a certain degree of heart anomalies or functional problems. Patent ductus arteriosus was the most common problem (57.1%) followed by atrial septal defect (ASD) or patent foramen ovale (35.7%), ventricular septal defect (VSD; 28.6%), left ventricular noncompaction (LVNC), or dilated cardiomyopathy (DCMP; 28.6%), and valve anomaly (14.3%; severe mitral valve stenosis, bicuspid aortic valve). Nine patients required either corrective operations for cardiac anomalies or pharmacological treatments for cardiac dysfunction (9/14, 64.3%). Of the three patients (Patient 7, 11, and 13) with DCMP, two patients (Patient 11 and 13) had end-stage cardiac dysfunction impending heart transplantation at their ages of 19.6 and 19.0 years, respectively. All four patients with either LVNC or DCMP revealed that their deleted chromosome sites were involved with the gene encoding PR domain-containing protein 16 (PRDM16), previously well known as one of the major genes responsible for cardiomyopathy. Patient 6, with the smallest interstitial deletion (400 Kb), had ASD and VSD. However, those defects did not require any treatment, and closed spontaneously.

6. Other phenotypes
Almost half of the patients (7/15, 46.7%) had either finger or toe anomaly. The phenotypic descriptions were either overriding, curly, or contracture deformity of fingers or toes. Amblyopia or esotropia was also found in four patients. Sensory neural hearing loss was another problem in four patients. Cryptorchidism (n = 3), inguinal hernia (n = 1), hypothyroidism (n = 1), and type 2 diabetes mellitus (n = 1) were reported as well. A choledochal cyst with neonatal cholestasis was observed in Patient 12. None of them was reported to have neuroblastoma. The patients’ non-neurological clinical phenotypes were provided in Table 3.

Discussion
In patients with the 1p36 deletion syndrome, a certain phenotype with a responsible deleted region or a causative gene was still under investigation along with cumulating CMA data [5,8]. Although deletion size is not linearly correlated with the clinical severity, critical regions and involved genes in 1p36 region were reported in previous studies [7-10]. Moderate to severe ID is present universally in the patients with

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Fig. 1. Chromosomal terminal deletion of the 1p36 region in 13 patients with candidate gene locations. Thirteen patients' chromosome breakpoint and location data are depicted based on available chromosomal microarray test results. Each solid bar represents the deletion point and size. Interstitial deletion is illustrated with a solid green bar. Previously reported proximal/distal critical regions (CRs) and known candidate genes are shown in solid red and blue color bars, respectively. Calmodulin binding transcription activator 1 (CAMTA1; chr1: 6,845,384–7,829,766) was partially deleted (chr1: 6845384–6900414) in patient 6. Other previously reported candidate genes are also depicted with their size and location. UBE4B, ubiquitination factor E4B; RERE, arginine-glutamic acid dipeptide repeats; KCNAB2, potassium voltage-gated channel subfamily A regulatory beta subunit 2; PRDM16, PR domain-containing protein 16; SKI, SKI proto-oncogene; GABRD, gamma-aminobutyric acid receptor delta; MMP23B, matrix metalloproteinase 23B.

https://doi.org/10.26815/acn.2020.00108
Table 3. Detailed non-neurologic phenotypes of the 15 patients with 1p36 deletion syndrome

<table>
<thead>
<tr>
<th>No.</th>
<th>Age at last FU (yr)</th>
<th>Heart problem</th>
<th>Limb anomaly</th>
<th>Eye problem</th>
<th>Hearing loss</th>
<th>GI or GU problem</th>
<th>Endocrine problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7.2</td>
<td>PDA&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Overriding toe</td>
<td>-</td>
<td>+</td>
<td>Cryptorchidism&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>20.7</td>
<td>Closed PDA, VSD</td>
<td>Clindactyly</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>21.1</td>
<td>NA</td>
<td>Hand deformity</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>8.9</td>
<td>PDA&lt;sup&gt;a&lt;/sup&gt;, bicuspid AV</td>
<td>Curly toe</td>
<td>-</td>
<td>-</td>
<td>Inguinal hernia&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>5.1</td>
<td>Large PDA, severe MS&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-</td>
<td>Amblyopia</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>8.5</td>
<td>Closed ASD, VSD</td>
<td>-</td>
<td>Amblyopia</td>
<td>-</td>
<td>Cryptorchidism</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>10.9</td>
<td>DCMP&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Clindactyly</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>4.6</td>
<td>ASD</td>
<td>-</td>
<td>Amblyopia</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>9.5</td>
<td>VSD, ASD</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Cryptorchidism</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>6.2</td>
<td>LVNC, PFO</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>19</td>
<td>PDA&lt;sup&gt;a&lt;/sup&gt;, DCMP&lt;sup&gt;b&lt;/sup&gt;, arrhythmia&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Finger contracture</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>4.1</td>
<td>PDA&lt;sup&gt;a&lt;/sup&gt;, small ASD or PFO</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>Choledochal cyst&lt;sup&gt;a&lt;/sup&gt;</td>
<td>T2DM&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>13</td>
<td>19.6</td>
<td>DCMP&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Overriding toe</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>14</td>
<td>4.4</td>
<td>VSD, ASD, PDA&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-</td>
<td>Esotropia</td>
<td>-</td>
<td>-</td>
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<td>15</td>
<td>5.5</td>
<td>PDA&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-</td>
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<td>-</td>
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</tr>
</tbody>
</table>

FU, follow-up; GI, gastrointestinal; GU, genitourinary; PDA, patent ductus arteriosus; VSD, ventricular septal defect; NA, not available; AV, aortic valve; MS, mitral valve stenosis; ASD, atrial septal defect; DCMP, dilated cardiomyopathy; LVNC, left ventricular noncompaction; PFO, patent foramen ovale; T2DM, type 2 diabetes mellitus.

<sup>a</sup>Managed with surgical methods; <sup>b</sup>Managed with medications, including two patients (marked in bold) with end-stage cardiac dysfunction.

1p36 deletion syndrome [1]. Shimada et al. [8] described the genomic regions responsible for ID and associated possible modifier genes, potassium voltage-gated channel subfamily A regulatory beta subunit 2 (KCNAB2; chr1:6,052,358–6,161,253; OMIM# 601142). They reported that patients with terminal deletions larger than 6.2 Mb from telomere showed no ambulation and poor prognosis of neurodevelopmental status. We noticed the similar findings in our five patients (Patient 1 to 5) with larger deletions including KCNAB2 gene. They were having severe neurocognitive delay prominent with speech delay and not able to gain walking ability at last follow-up in their age of 7, 20, 21, 8, and 5 years, respectively. Patient 14 (4 years old) and 15 (5 years old) were not able to walk at their last follow-up; however, no detailed information of deletion size was available. We could assume that they might have larger than 6.2 Mb deletions.

Behavioral problems were not easy to be specified due to severe ID. However, an unknown cause of female ID with Rett syndrome like behavioral features could be another behavioral phenotype of the 1p36 deletion syndrome. Patients 2 and 3 presented with severe ID with hand automatism, bruxism, and abnormal breathing pattern. It was clinically indicated Rett syndrome. In contrast to Rett syndrome, they showed early onset developmental delay without regression and mild anomalies in face, fingers, or brain. Patients 2 and 3 were tested negative for the MECP2 deletion/duplication and had large deletions of 9.9 and 9.8 Mb, respectively in the 1p36 region. This finding is another possible behavioral expression of the 1p36 deletion syndrome along with the Prader-Willi syndrome-like behavioral expression ([11,12]). Further investigation of genes responsible for behavioral expressions should be performed in the future study.

Seizures were a common manifestation reported from 50% to 79% [1,4,8]. Infantile spasms and refractory epilepsy (20.9%) were associated with poor clinical outcomes in a previous study [13]. Our study also showed a high rate of occurrence of seizures (11/15, 73.3%). However, except for one patient presenting with infantile spasms having the largest deletion size, seizures were well-controlled, or even resolved spontaneously. Four patients were required AED at last follow-up and their deletion size were over 5.9 Mb. Although it demands a larger cohort study to establish statistical significance, the severity of seizure seems to be related to the size of the deletion rather than to the onset age of the seizure.

We noted that each patient had some shared facial appearances with reported features. However, not all patients were able to be suspicious of the 1p36 deletion syndrome based on facial features only. There was no specific pattern of congenital brain structural abnormality either. One patient (Patient 6) with a small interstitial deletion of 400 Kb (chr1:6499296-6900414) showed a normal facial appearance and brain structure.

Cardiac assessment is crucial at initial evaluation and also during long term follow-up period in 1p36 deletion syndrome. Structural anomaly with or without left ventricular dysfunction is a major
concern in 1p36 deletion syndrome patients in view of their long
term prognosis. Previous literature reported heart problems as
prevalent manifestations with up to 75% of structural anomaly and
23% to 31% of cardiomyopathy [4,5,14]. Our report showed the
possible severity of cardiomyopathy as an end-stage severe heart
dysfunction in two patients. These two patients were impending
heart transplantation as they were approaching adulthood. Cardiac
dysfunction in two other patients was not severe; however, the old-
er patient required medications at the age of 10 years during the
last follow up. Due to well-controlled seizures in early childhood
and absence of symptoms with slowly progressing heart dysfunc-
tion, follow up might be irregular, and as such early prophylactic
medical treatment may be missed. Encouraging regular follow-up
with explanations of possible heart involvement in 1p36 deletion
syndrome in late teenage should be included in patients’ and par-
ents’ education, even in a patient without any symptom or sign.

One patient (Patient 6) with a small interstitial deletion of 400
Kb (chr1:6499296-6900414) was presented with relatively mild
phenotype, including mild global developmental delay, ataxic gait,
unilateral cryptorchidism, ambyopia, and spontaneously-closed
ASD and VSD. Brain MRI was normal and he had no history of
seizure. The deleted position revealed 11 involved genes including
three high pLI (loss of function intolerance) genes; PHD finger
protein 13 (PHF13), DnaJ heat shock protein family member C11
(DNAC11), calmodulin-binding transcription activator 1 (CAM-
TA1). Among them, CAMTA1 was previously reported as the
cause of non-progressive congenital ataxia with or without ID
[15,16], which was consistent with the phenotype of this patient
having mild global developmental delay and unexplainable ataxic
gait. This deleted region was not regarded as a critical region in the
previous literature. This patient showed ambyopia and cryptorchi-
dism as well. However, there was no shared deleted region among
patients who had ambyopia and cryptorchidism. This finding
might be another explanation for the shared phenotype with dif-
ferent involved genes [17].

The 1p36 deletion syndrome showed a tendency of contiguous
gene deletion syndrome presenting a more severe phenotype in
case of larger deletion size. However, there was often discordance
between deletion size and clinical features. Even cases with small
deletion sizes had most of the clinical features of 1p36 deletion
syndrome. Beyond this very critical terminal region, continu-
ous efforts to delineate phenotype variability with exact genotyp-
ing is crucial in a variable range of deletion sizes, and an inconsis-
tent breakpoint of the chromosome 1p36 region.

Conflicts of interest

No potential conflict of interest relevant to this article was report-
ed.

ORCID

Youngkyu Shim, https://orcid.org/0000-0002-3414-4702

Jong-Hee Chae, https://orcid.org/0000-0002-9162-0138

Author contribution

Conceptualization: YS, YJG, SYK, HK, HH, JC, BCL, KJK, and
JHC. Data curation: YS, YJG, SYK, HK, HH, JC, BCL, KJK, and
JHC. Formal analysis: YS, SYK, and JHC. Methodology: YS, SYK,
and JHC. Project administration: YS. Visualization: YS. Writ-
ing-original draft: YS. Writing-review & editing: YS and JHC.

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Serum Uric Acid as a Predictive Factor for Rotaviral or Noroviral Benign Convulsions with Mild Gastroenteritis

Si Yoon Yoo, MD*, Dong Hyun Kim, MD*, Yeongseok Lee, MD, Ga Hee Lee, MD, Dong Jun Ha, MD, Young Se Kwon, MD

Department of Pediatrics, Inha University Hospital, Inha University School of Medicine, Incheon, Korea

Purpose: This study investigated the relationship between serum uric acid levels and benign convulsions with mild gastroenteritis (CwG) caused by rotavirus and norovirus.

Methods: This retrospective study identified 89 patients with CwG at Inha University Hospital from January 1999 to December 2019. We analyzed serum uric acid levels in patients with CwG and in patients with acute gastroenteritis without seizures according to the causative virus.

Results: Among the 2,790 patients with rotavirus or norovirus gastroenteritis, 89 patients (3.2%) were diagnosed with CwG. The serum uric acid levels were significantly higher in CwG patients than in acute gastroenteritis patients (8.20±2.34 mg/dL vs. 5.44±2.69 mg/dL, P<0.001). When examined according to the virus type, serum uric acid levels were higher in the CwG group than in the acute gastroenteritis group in patients with rotavirus (8.05±2.48 mg/dL vs. 5.48±2.78 mg/dL) and norovirus (8.43±2.13 mg/dL vs. 5.31±2.36 mg/dL) infections (P<0.001). However, there were no significant differences in uric acid levels between patients with CwG caused by rotavirus and those with CwG caused by norovirus.

Conclusion: Patients with CwG, caused either by rotavirus or norovirus, showed significantly higher serum uric acid levels than those with acute gastroenteritis without seizures. Elevated serum uric acid levels could be a useful indicator for diagnosing CwG.

Keywords: Seizures; Gastroenteritis; Rotavirus; Norovirus; Uric acid

Introduction

Convulsions are a common problem in children. Benign convulsion with mild gastroenteritis (CwG) was first reported in Japan in 1982 [1], and is defined as an afebrile convulsion accompanied by symptoms of gastroenteritis in a child without a previous history of neurological disease or electrolyte abnormalities, moderate to severe dehydration, or metabolic acidosis. Long-term prognosis is favorable without serious sequelae. Most cases of CwG have been described in patients with rotavirus infection [2-4], but cases of CwG caused by norovirus have increased recently [2,5-8].

The diagnosis of CwG is generally made by confirming the presence of convulsions in a child with gastrointestinal symptoms. No specific biomarker for CwG has been identified to date, and multiple studies have evaluated changes in the laboratory results of CwG patients. Specifically, studies related to uric acid levels have been reported [9,10]. In this study, we evaluated the serum uric acid levels of CwG patients compared to those of patients with acute gastroenteritis without convulsions. Our goal was to...
investigate the relationship between serum levels of uric acid and CwG and examine the differences in uric acid levels depending on the viral pathogen that caused the gastroenteritis (rotavirus or norovirus).

**Materials and Methods**

The study included infants and children under the age of 7 who were admitted for the treatment of gastroenteritis caused by rotavirus or norovirus at the Pediatric Department of Inha University Hospital between January 1999 and December 2019. CwG was defined as (1) recurrent or non-recurrent convulsive seizures without fever within 5 days from the first day of the onset of acute gastroenteritis symptoms in healthy children without underlying neurological diseases; (2) no evidence of moderate or severe dehydration of more than 5% due to gastroenteritis; (3) no acid-base imbalance and no abnormality in cerebrospinal fluid, serum electrolytes, or blood sugar; (4) no suspected encephalopathy or meningitis, based on neurological examination; and (5) good prognosis and treatment outcome [11]. Exclusion criteria were (1) developmental delay or neurological abnormality; (2) electrolyte or blood sugar abnormality; and (3) body temperature measured in the ear, drum or axillary region of 38.0°C or higher; and (4) neonate (under the age of 1 month).

A total of 2,790 patients were diagnosed with acute gastroenteritis caused by either rotavirus (2,100 cases) or norovirus (690 cases). The CwG group consisted of 50 patients with rotavirus enteritis and convulsions and 39 patients with norovirus enteritis and convulsions. The remaining 2,701 patients without convulsions were selected as the control group. To exclude patients with confirmed duplicate infection, the rotavirus-positive group included only patients with no viruses except for rotavirus and the norovirus-positive group included only patients with no viruses except for norovirus.

**1. Methods and statistics**

The medical records of patients hospitalized with non-febrile seizures associated with symptoms of acute gastroenteritis were retrospectively reviewed to identify (1) the cause of gastroenteritis, pathogenicity of convulsions after gastroenteritis; (2) blood test results at the time of admission (e.g., electrolyte imbalance, hypoglycemia, uric acid levels); and (3) the degree of dehydration. If additional blood tests were performed during hospitalization, the results were excluded from the survey. The causative gastroenteritis pathogens were identified through stool antigen tests for rotavirus and norovirus.

Rotavirus antigen detection tests for stool samples were conducted using immunochromatography assay kits (SD BIOLINE® Rotavirus, Standard Diagnostics Inc., Yongin, Korea) until 2010; between 2011 and 2019 an enzyme immunoassay was used (Ridascreen® Rotavirus, R-Biopharm Aktiengesellschaft, Darmstadt, Germany). Rotavirus real-time reverse transcription-polymerase chain reaction (RT-PCR) was conducted using the Allplex GI-Virus Assay (Seegene, Seoul, Korea) since June 2014.

Statistical analyses were performed to compare the differences in serum uric acid levels among the CwG patient group with rotavirus infection, the CwG patient group with norovirus infection, and the control group. The receiver operating characteristics (ROC) analysis was performed to obtain the cut-off value for distinguishing CwG patients from acute gastroenteritis patients. All statistical analyses were conducted using SPSS version 19.0 (IBM Co., Armonk, NY, USA), and the t-test was used to determine statistical significance ($P < 0.05$).

This study was approved by the Institutional Review Board of the Inha University Hospital (IRB No. 2020-04-012). Written informed consent by the patients was waived due to a retrospective nature of our study.

**Results**

Among the 2,790 gastroenteritis cases, 2,100 cases were caused by rotavirus and 690 cases were caused by norovirus. Among the patients who had convulsions, 89 patients were diagnosed with CwG (male:female = 43:46); when categorized based on the type of the virus, 50 patients (male:female = 24:26) had CwG caused by rotavirus and 39 patients (male:female = 19:20) had CwG caused by norovirus. This corresponded to 2.38% rotavirus-positive patients and 5.65% norovirus-positive patients diagnosed with CwG, and the number of CwG cases caused by norovirus was 2.3 times higher than that caused by rotavirus ($P < 0.05$).

The ages, sex ratio, and uric acid levels in the patient and the control groups are presented in Table 1. The average uric acid level for all CwG patients was $8.20 \pm 2.34$ mg/dL (95% confidence interval [CI], 7.69 to 8.72), while that of acute gastroenteritis patients was $5.44 \pm 2.69$ mg/dL (95% CI, 5.34 to 5.54). When categorized by virus type, the uric acid level in rotavirus CwG group was $8.05 \pm 2.48$ mg/dL (95% CI, 7.34 to 8.77), while that of the rotavirus gastroenteritis group was $5.48 \pm 2.78$ mg/dL (95% CI, 5.36 to 5.60). The uric acid level in norovirus CwG group was $8.43 \pm 2.13$ mg/dL (95% CI, 7.67 to 9.19), while that of norovirus gastroenteritis group was $5.31 \pm 2.36$ mg/dL (95% CI, 5.12 to 5.49).

The uric acid level in CwG patients was measured to be higher than the normal range (3.4 to 7.9 mg/dL), while the uric acid level...
in CwG patients was higher compared to that in the group with acute gastroenteritis without seizures ($P < 0.05$). However, when uric acid levels between the rotavirus CwG group and norovirus CwG group were compared, significant differences were not found between the groups ($P > 0.05$) (Fig. 1).

In ROC analysis, the optimal cut-off value of the serum uric acid level that can distinguish between CwG and acute gastroenteritis was 7.35 mg/dL; with a sensitivity of 70.7% and specificity of 77.7%. The area under the curve was 78.9% (95% CI, 74.5% to 83.3%) (Fig. 2).

**Discussion**

Patients with CwG have no abnormalities in the cerebrospinal fluid and on electroencephalography, and seizures do not recur after the resolution of gastroenteritis symptoms [2]. Long-term anticonvulsant medications are rarely required, and the prognosis is very good. Recently, the range of ages for diagnosis has been widened from 6 months–3 years to 1 month–6 years. Cases of CwG have been predominantly reported in East Asian countries including Japan and Korea, and have been reported in Hong Kong and Taiwan. Although some studies have identified cases in Europe and the USA, these are rare, suggesting that regional or racial differences may affect the incidence of CwG [12].

The majority of CwG cases have been reported in patients with rotavirus infection [4,13-15], but gastroenteritis caused by norovirus is more common in winter months, which has led to an increased number of CwG reports caused by norovirus [6-8]. Some studies have reported that the incidence of norovirus-related CwG is higher than that of rotavirus-related CwG [5-8,16]. This finding is consistent with our own observation that CwG accompanied by

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CwG</th>
<th>Acute gastroenteritis</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male:female</td>
<td>43:46</td>
<td>1,534:1,167</td>
<td>0.112</td>
</tr>
<tr>
<td>Age at onset (mo)</td>
<td>20.43 (1–53)</td>
<td>19.75 (1–83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum uric acid (mg/dL)</td>
<td>8.20 ± 2.34</td>
<td>5.44 ± 2.69</td>
<td>&lt;0.050</td>
</tr>
<tr>
<td>Rotavirus</td>
<td></td>
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<tr>
<td>Male:female</td>
<td>24:26</td>
<td>1,160:890</td>
<td>0.226</td>
</tr>
<tr>
<td>Age at onset (mo)</td>
<td>22.84 (1–53)</td>
<td>13.71 (1–82)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum uric acid (mg/dL)</td>
<td>8.05 ± 2.48</td>
<td>5.48 ± 2.78</td>
<td>&lt;0.050</td>
</tr>
<tr>
<td>Norovirus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male:female</td>
<td>19:20</td>
<td>374:277</td>
<td>0.285</td>
</tr>
<tr>
<td>Age at onset (mo)</td>
<td>17.33 (4–32)</td>
<td>19.74 (1–83)</td>
<td>0.156</td>
</tr>
<tr>
<td>Serum uric acid (mg/dL)</td>
<td>8.43 ± 2.13</td>
<td>5.31 ± 2.36</td>
<td>&lt;0.050</td>
</tr>
</tbody>
</table>

Values are presented as median (range) or mean±standard deviation.

CwG, convulsions with mild gastroenteritis.
RNA in the cerebrospinal fluid. Another theory is that disruption of sial as not all cases of rotavirus CwG had evidence of rotavirus transmitters dysregulation. However, this hypothesis is controver-

promotes seizure development by inducing neurotoxicity and neu-

stimulate the production of nonstructural protein (NSP4) that

CwG patients

RNA was detected by PCR in the cerebrospinal fluid of rotavirus

caused encephalitis, encephalopathy, or seizure. In fact, rotavirus

the bloodstream after penetrating the gastrointestinal tract and

was hypothesized that the rotavirus can invade the CNS through

the absence of severe electrolyte imbalance or dehydration is not

known. One possible explanation may be that children in this age

group are undergoing a period of rapid growth and development

of the central nervous system (CNS), and brain immaturity may

have some effect on seizure development in CwG patients

have been implicated in CwG including norovirus, which is known

to be related to adenovirus, astrovirus, sapovirus, and coxsackievir-

us [13]. More research is necessary to identify the specific mecha-

nisms whereby each of these viruses exerts its effect in CwG pa-

tients. In particular, a better understanding of the mechanism of

seizures in CwG patients with norovirus is essential given the in-

creasing prevalence of norovirus-associated CwG.

CwG is diagnosed clinically. Laboratory investigations, lumbar

puncture, electroencephalography, magnetic resonance imaging,

and other tests are not essential in diagnosing CwG. To date, few

studies have evaluated the clinical utility of blood tests in diagnos-

ing CwG or predicting patient prognosis.

No clear evidence has been found regarding the relationship be-

tween CwG and serum sodium levels. For example, while some

studies have demonstrated an association of mild hyponatremia

with CwG but not simple gastroenteritis [22], others failed to

show a significant difference in sodium levels between groups [23-

25]. Further, one study demonstrated that seizure duration was

prolonged in patients with CwG with hyponatremia [26], but oth-

er studies showed no significant relationship between hyponatre-

mia and seizure semiology, frequency, and duration [27].

Previous studies have also explored the effect of ketone bodies in

CwG [28]. Lee et al. [28] found a significant association of ketosis

with mild hyponatremia and low blood glucose levels in CwG pa-

tients, which was thought to be caused by the metabolic response
to poor oral intake or hyponatremia in this group. However, there

was no clear interaction between severe ketosis and seizure recur-

rence.

Recent studies have investigated the relationship between uric

acid and CwG. Tsujita et al. [23] reported that blood tests from

CwG patients had significantly high levels of uric acid. In a 2014

norovirus infection accounted for 5.65% of all norovirus infections,

while CwG accompanied by rotavirus infection accounted for

2.38% of all rotavirus infections. These differences may be because

uptake of the rotavirus vaccine has resulted in a reduction in the

number of gastroenteritis cases caused by rotavirus, or due to the

increased accessibility of the norovirus test which has identified

more cases of norovirus-related CwG [7,17].

The mechanism of seizure development in CwG patients in the

absence of severe electrolyte imbalance or dehydration is not

known. One possible explanation may be that children in this age

group are undergoing a period of rapid growth and development

of the central nervous system (CNS), and brain immaturity may

have some effect on seizure development in CwG patients [18]. It

was hypothesized that the rotavirus can invade the CNS through

the bloodstream after penetrating the gastrointestinal tract and

cause encephalitis, encephalopathy, or seizure. In fact, rotavirus

RNA was detected by PCR in the cerebrospinal fluid of rotavirus

CwG patients [19]. After invasion into the CNS, the rotavirus can

stimulate the production of nonstructural protein (NSP4) that

promotes seizure development by inducing neurotoxicity and neu-

rotransmitter dysregulation. However, this hypothesis is controver-

sial as not all cases of rotavirus CwG had evidence of rotavirus

RNA in the cerebrospinal fluid. Another theory is that disruption of

calcium homeostasis caused by NSP4 secretion after rotavirus

infection induces hypocalcemia which may play a significant role

in seizure development [20]. However, research on the relation-

ship between calcium homeostasis and rotavirus CwG is lacking,

and further studies are required to explain the mechanism of hypocalcemia on seizure pathogenesis. Additionally, results suggesting that nitric oxide may be the cause of seizures in rotavirus CwG have been reported. Nitric oxide may have a role in the neuro-pathogenesis of brain inflammation. According to one study, nitric oxide levels were significantly high in both the serum and cerebrospinal fluid of the rotavirus-associated seizure patient group when compared with meningitis, encephalitis, and febrile seizure groups [21].

Taken together, the above evidence suggests that direct virus invasion, the increase in mediators such as NSP4, and the increase in nitric oxide are the main mechanisms to explain the etiology of seizures in rotavirus-associated CwG. However, other viruses have also been implicated in CwG including norovirus, which is known to be related to adenovirus, astrovirus, sapovirus, and coxsackievirus [13]. More research is necessary to identify the specific mechanisms whereby each of these viruses exerts its effect in CwG patients. In particular, a better understanding of the mechanism of seizures in CwG patients with norovirus is essential given the increasing prevalence of norovirus-associated CwG.

![Receiver operating characteristic curve of the capacity of serum uric acid levels to predict convulsions with mild gastroenteritis instead of acute gastroenteritis. The optimal cutoff value is indicated by a red dot.](image)

Fig. 2. Receiver operating characteristic curve of the capacity of serum uric acid levels to predict convulsions with mild gastroenteritis instead of acute gastroenteritis. The optimal cutoff value is indicated by a red dot.

Serum uric acid cut-off: 7.35 mg/dL
Sensitivity: 70.7%
Specificity: 77.7%

Serum uric acid levels to predict convulsions with mild gastroenteritis instead of acute gastroenteritis.

![Sensitivity and specificity graph](image)
report, CwG patients showed significantly high serum uric acid levels (uric acid level ≥ 5.8 mg/dL in all patients in the CwG group), but only 44.7% of the patients in the control group showed hyperuricemia [10]. In the latest publication by Yoo et al. [9], found that the elevation of serum uric acid was not due to dehydration, nor to postictal phenomenon (Serum uric acid was not elevated in febrile seizure group in their study).

Consistent with previous studies, the total CwG group had a higher serum uric acid level than the simple gastroenteritis group, and this was maintained after further stratification into rotavirus and norovirus-associated CwG. However, when rotavirus CwG was compared with norovirus CwG, the serum uric acid levels between the groups did not show a significant difference. This finding demonstrates that hyperuricemia per se is insufficient to predict the viral pathogen responsible for CwG.

The results obtained in this study suggest that a serum uric acid level of ≥ 7.35 mg/dL may be a useful marker for predicting CwG in patients with gastroenteritis symptoms or seizure alone. Although the diagnosis of CwG cannot be made solely on the presence of a high serum uric acid level in acute gastroenteritis patients, being aware of this abnormal result may help clinicians better understand the pathophysiology of CwG and identify at-risk patients. Hyperuricemia is known to be related to gout, chronic metabolic diseases, Down syndrome, congenital heart disease, hemato-oncologic disorders, and metabolic syndrome in children, but the relationship between hyperuricemia and seizures has not yet been definitively proven. It has been reported that hyperuricemia may increase the secretion of tumor necrosis factor-α, which can cause seizure or endothelial dysfunction [29]. Studies in mice have also reported that elevated serum uric acid levels are associated with the occurrence of generalized seizures [30]. Additional research is needed to determine the relationship between hyperuricemia and seizures.

Uric acid levels change with growth [31,32]. Comparing the total CwG and acute gastroenteritis group, the result was that age at onset was higher in the CwG group. However, the age gap is not large enough to cause the difference in uric acid levels to the extent identified in our study results. In addition, in the norovirus group, the age of onset of acute gastroenteritis was higher, although not statistically significant. Therefore, it seems difficult to conclude that age of onset caused a difference in uric acid levels between CwG and acute gastroenteritis groups.

This study has several strengths. First, our study was conducted using a large number of cases of CwG and acute gastroenteritis accumulated over 21 years at a single center. Second, we analyzed serum uric acid levels for each virus implicated in CwG. However, this study was a retrospective study, and therefore we were unable to establish a clear causal relationship and temporal relationship between CwG and serum uric acid. In addition, there was no statistically significant difference in gender distribution between CwG and acute gastroenteritis group, and age at onset was not significantly different in norovirus group. It can be considered as a limitation that no control group has been established to correct this. Future prospective studies that address these limitations are warranted.

Serum uric acid measurements in this study were higher in CwG patients compared to simple acute gastroenteritis patients, but there was no difference in serum uric acid levels between rotavirus and norovirus CwG. These results strongly suggest that uric acid can be a predictive factor in the diagnosis of CwG. Therefore, it is important to measure uric acid levels in patients presenting with gastroenteritis associated with an afebrile seizure. In addition, a stool antigen test should be performed to confirm the causative virus.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

ORCID

Si Yoon Yoo, https://orcid.org/0000-0003-3184-0750
Dong Hyun Kim, https://orcid.org/0000-0001-9883-0229
Young Se Kwon, https://orcid.org/0000-0003-4570-7037

Author contribution

Conceptualization: YSK. Data curation: GHL. Formal analysis: YL. Methodology: DHK and YSK. Project administration: YSK. Visualization: SYY. Writing-original draft: SYY and DHK. Writing-review&editing: YSK.

Acknowledgements

This study was supported by INHA University Research Grant.

References


Effectiveness of Intravenous Immunoglobulin Therapy for Pediatric Viral Encephalitis

Ji Eun Byun, MD, Kyung Yeon Lee, MD

Department of Pediatrics, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, Korea

Purpose: Intravenous immunoglobulin (IVIg) is considered as a first-line therapy for autoimmune encephalitis. However, its effectiveness in viral encephalitis has yet to be evaluated. Therefore, we investigated the effectiveness of IVIg therapy for pediatric viral encephalitis.

Methods: We retrospectively reviewed the records of 35 pediatric patients who were hospitalized with confirmed or suspected viral encephalitis. Twenty patients (57.1%) were treated with IVIg in conjunction with conventional therapy (IVIg-treated group), and 15 patients (42.9%) were treated with conventional therapy (non-IVIg-treated group). We compared the clinical characteristics of the groups at admission and their clinical outcomes.

Results: Compared to the non-IVIg-treated group, the IVIg-treated group had more critical clinical features at admission, with a lower score on the pediatric Glasgow Coma Scale (mean±standard deviation, 9.1±2.3 vs. 10.8±2.7, P=0.025), longer fever duration (3.5±2.2 days vs. 1.8±1.1 days, P=0.022), and higher incidence of magnetic resonance imaging abnormalities (14/19 [73.7%] vs. 3/15 [20.0%], P=0.002). Nevertheless, the clinical outcomes of the IVIg-treated group were comparable to those of the non-IVIg-treated group in terms of mortality rate (1/20 [5.0%] vs. 0/15 [0%]), neurological deficits at discharge (2/20 [10.0%] vs. 1/15 [6.7%]), and occurrence of epilepsy (5/20 [25.0%] vs. 2/15 [13.3%]). Fourteen (70.0%) and 13 (85.7%) patients in the IVIg-treated and the non-IVIg-treated groups, respectively, achieved complete recovery without any neurological complications.

Conclusion: IVIg may be considered as a potential immunomodulating agent when treating critical pediatric viral encephalitis to improve neuropsychological outcomes.

Keywords: Encephalitis, viral; Immunoglobulins, intravenous; Treatment outcome; Immunomodulation

Introduction

Encephalitis is a clinical syndrome resulting from the inflammation of the brain parenchyma [1,2]. It presents with neurological dysfunctions, such as altered consciousness. The global incidence of encephalitis was reported to be 4.3 million cases in 2015, of which 150,000 patients had died [3,4]. Encephalitis is caused by direct invasion of microorganisms, such as viruses, bacteria, or fungi into the brain parenchyma. Alternatively, it can be caused by overactivation of the host immune system in the brain due to post-infection processes, such as acute disseminated encephalomyelitis, or noninfectious conditions such as anti-N-methyl-D-aspartate receptor encephalitis [2]. In fact, the cause of encephalitis is unknown in approximately half of the cases [5]. A recent report revealed that the
prevalence of autoimmune encephalitis is similar to that of infectious encephalitis in adults [6]. In children, however, the most common cause of encephalitis is an infection by microorganisms [7]. Viral encephalitis accounts for 20% to 50% of the cases with a known cause [5]. Herpes simplex virus infection is the most common sporadic cause of viral encephalitis, accounting for 50% to 75% of identified viral cases. Varicella-zoster virus (VZV), enterovirus, Epstein-Barr virus, and cytomegalovirus (CMV) are also common causes [5]. The prognosis of viral encephalitis, including mortality and neurological complications varies according to the causative pathogens [1,5].

The basis of therapy for viral encephalitis is the use of antiviral agents, such as acyclovir. The mortality rate of patients with herpes simplex virus encephalitis has sharply decreased from 70% to 10%–20% since the introduction of acyclovir in the 1970s [8]. However, despite acyclovir therapy, 69% to 89% of survivors still suffer from a wide range of neuropsychological sequelae [9,10]. Moreover, there is a lack of evidence on the effectiveness of specific antiviral agents for other viral causes [1]. Hence, the application of additional treatment strategies other than conventional antiviral agents is highly desirable for the treatment of viral encephalitis.

During viral infection, the host’s immune response is crucial to eliminate invading viruses. However, since excessive host immune response can be harmful to the host cells, immunomodulation is also important when treating viral infection. Intravenous immunoglobulin (IVIg) is a well-known example of an immunomodulating agent [11]. It has been used in a variety of systemic diseases, such as immunothrombocytopenia and Kawasaki disease [12]. It has also been used when treating inflammatory neurological diseases, such as Guillain-Barré syndrome [13]. Although IVIg is considered as a first-tier therapy for autoimmune encephalitis, there is thus far a lack of studies on its effectiveness in viral encephalitis. This study aimed to evaluate the potential efficacy of IVIg therapy in the treatment of viral encephalitis.

Materials and Methods

1. Participants

We retrospectively reviewed the records of 89 pediatric patients with acute inflammatory brain diseases who were admitted to the Ulsan University Hospital between January 2012 and December 2019. Among the 89 patients, 26 had bacterial meningoencephalitis, 14 had acute disseminated encephalomyelitis, three had autoimmune encephalitis, three had acute cerebellitis, and one had a brain abscess. These 47 patients were excluded from the study (Fig. 1). The remaining 42 patients had confirmed or suspected viral encephalitis. Seven of these were transferred to other hospitals and were thus excluded from the study. Finally, 35 patients with confirmed or suspected viral encephalitis were included in the analysis. All patients included in this study were otherwise healthy before the appearance of the cause of admission and had no history of immunoglobulin therapy.

2. Methods

In this study, we applied modified diagnostic criteria for encephalitis, adapted from the International Encephalitis Consortium [2]. When the following major and minor criteria were fulfilled, patients were diagnosed with encephalitis. Major criteria included altered mental status for at least 12 hours (defined as decreased or altered level of consciousness, lethargy, or altered personality) with no alternative cause identified. Minor criteria were considered to be fulfilled when two or more of the following six criteria were met: (1) fever ≥ 38°C within the 72 hours before presenting with altered consciousness; (2) generalized or partial seizures not fully attributable to a preexisting seizure disorder; (3) new onset of focal neurological deficits; (4) cerebrospinal fluid (CSF) pleocytosis; (5) abnormality of brain parenchyma in magnetic resonance imaging (MRI) suggestive of encephalitis; and (6) abnormality on electroencephalography (EEG) indicating encephalitis and not attributable to another cause. In this study, a diagnosis of viral encephalitis was made based on clinical features and various test results, including MRI, EEG, and routine CSF analysis; and reasonable exclusion of other causes of encephalitis, regardless of confirmatory diagnostic test results.

To determine the etiology of encephalitis, specific tests were
performed based on the clinical manifestations and initial test results, such as the previously mentioned MRI, EEG, and routine CSF analysis. All patients underwent routine CSF analysis that included white blood cell count, total protein level, and bacterial culture. CSF pleocytosis was defined as the presence of \( \geq 5 \) white blood cells/mm\(^3\) in CSF. To identify the causative viruses for encephalitis, the following analyses were performed: (1) CSF polymerase chain reaction (PCR) for enterovirus (n = 32), herpes simplex virus (n = 23), VZV (n = 8), and CMV (n = 1); (2) CSF mycoplasma-specific immunoglobulin M (IgM) tests (n = 6); (3) serological tests for measles (n = 4), Chlamydia pneumoniae (n = 3), mumps virus (n = 3), rubella virus (n = 2), parvovirus B19 (n = 2), and toxoplasma (n = 1); (4) PCR for enterovirus in stool samples (n = 12); (5) rotavirus antigen test in stool samples (n = 3); and (6) PCR for CMV in urine samples (n = 2). For genome detection and genotyping of enterovirus, real-time quantitative PCR using the Taq-Man probe technology was attempted on stool and CSF samples obtained from 12 patients. Genotyping of the enterovirus was conducted at the Division of Enteric and Hepatitis Viruses, Korea Centers for Disease Control and Prevention (Osong-eup, Cheongwon, Korea).

MRI was performed on either a 3.0 Tesla system (Intera Achieva, Philips, Best, The Netherlands) or a 1.5 Tesla system (Intera Achieva, Philips). The protocol included T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR), and contrast-enhanced T1-weighted and FLAIR imaging. MRI was performed in all patients except one (97.1%). This patient could not undergo MRI because of her critical condition due to enterovirus 71 brainstem encephalitis. In this study, meningeal enhancement without brain parenchymal lesion was not considered as an abnormal MRI finding. EEG was performed in 27 patients (77.1%). Eight patients (22.9%) who had suspected or confirmed enterovirus 71 brainstem encephalitis did not undergo EEG.

The participating patients were divided into two groups on the basis of the inclusion of IVIg in their therapy regime. IVIg treatment was selectively used in patients with more severe neurological manifestations, according to the pediatric neurologist’s judgment instead of specifically defined criteria. Corticosteroids were not used in any patient as an acute treatment for encephalitis. Twenty patients (57.1%) were treated with IVIg (2 g/kg) in conjunction with conventional therapy (IVIg-treated group), whereas 15 patients (42.9%) were treated with conventional therapy only (non-IVIg-treated group). Conventional therapy included intravenous acyclovir and/or antibiotic therapy and conservative management. We compared the groups for manifestations at admission, including clinical features (altered consciousness, fever, seizure, and focal neurologic signs) and severity (Pediatric Glasgow Coma Scale score, duration of altered consciousness, duration of fever, presence of status epilepticus, and the need for treatment at the intensive care unit [ICU]), MRI and EEG findings, and CSF profiles. In addition, we compared the groups for the clinical outcomes, including interval from admission to recovery of consciousness, interval from admission to disappearance of fever, neurological deficits at discharge, occurrence of epilepsy after discharge, and mortality. Lastly, we evaluated in detail the characteristics of patients included in the IVIg-treated group.

This study was approved by the Institutional Review Board of Ulsan University Hospital (IRB No. 2020-04-043). Informed consent was waived by the board due to the study’s retrospective nature.

3. Statistical analysis
Data were analyzed using IBM SPSS version 21.0 (IBM Co., Armonk, NY, USA). The Pearson’s chi-square test was used to compare the groups for patients’ age, clinical symptoms, EEG abnormalities, the number of patients admitted to the ICU. The Fisher’s exact test was used to compare the presence of seizures, CSF pleocytosis, MRI abnormality, mortality, neurological deficits at discharge, and occurrence of epilepsy. The independent t-test was used to compare the duration of fever, duration of altered consciousness, and the number of seizures at admission. The Mann-Whitney U test was used to compare the sex of the patients, Pediatric Glasgow Coma Scale score, the number of patients who had status epilepticus at admission, and the interval from admission to disappearance of fever and recovery of consciousness. Continuous variables are reported as the mean ± standard deviation. Differences with \( P < 0.05 \) were considered statistically significant.

RESULTS

1. Patient demographics
The mean ages were 6.7 ± 4.8 and 7.7 ± 4.9 years in the IVIg-treated and the non-IVIg-treated groups, respectively. There were 13 (65.0%) males in the IVIg-treated group and 10 (66.7%) males in the non-IVIg-treated group (Table 1).

2. Comparison of clinical features and MRI, EEG, and laboratory findings between the groups at admission
A comparison between the groups for clinical manifestations and MRI, EEG, and laboratory findings at admission is summarized in Table 1. At admission, the IVIg-treated group had more critical clinical features than the non-IVIg treated group. The IVIg group had a lower Pediatric Glasgow Coma Scale score (9.1 ± 2.3 vs. 10.8 ± 2.7, \( P = 0.025 \)) and longer duration of fever (3.5 ± 2.2 days.
Moreover, the IVIg-treated group had higher incidence of MRI abnormalities (14/19 [73.7%] vs. 3/15 [20.0%], \(P = 0.002\)). The IVIg-treated group tended to have a higher rate of ICU admission compared to the non-IVIg-treated group (13/20 [65.0%] vs. 5/15 [33.3%]), but this trend was not statistically significant (\(P = 0.064\)). Nine patients (45.0%) had seizures in the IVIg-treated group at admission, whereas 12 patients (80.0%) had seizures in the non-IVIg-treated group (\(P = 0.036\)). White blood cell counts in blood and CSF were higher in the IVIg-treated group than those in the non-IVIg-treated group, whereas C-reactive protein levels did not differ between the groups. No difference was observed in the incidence of fever, status epilepticus, focal neurological signs, CSF pleocytosis, and EEG abnormalities between the groups.

3. Comparison of clinical outcomes between the groups
A comparison between the groups for clinical outcomes is summarized in Table 2. Of the total 35 patients, only one patient (2.9%) included in the IVIg-treated group died. No difference was observed in the mortality (1/20 [2.9%] vs. 0/15 [0%], \(P = 1.000\)), neurological deficits at discharge (2/20 [10.0%] vs. 1/15 [6.7%], \(P = 1.000\)), and occurrence of epilepsy (5/20 [25.0%] vs. 2/15 [13.3%], \(P = 0.672\)) between the groups. Also, there was no significant difference in the time from admission to recovery of consciousness (2.8 ± 3.2 days vs. 3.0 ± 4.9 days) and disappearance of fever (1.6 ± 2.0 days vs. 1.5 ± 3.1 days) between the groups. Fourteen (70.0%) and 13 (86.7%) patients achieved complete recovery without any neurological complications in the IVIg-treated and non-IVIg-treated groups, respectively.

4. Characteristics of the IVIg-treated group
1) Clinical features and laboratory, MRI, and EEG findings at admission
Clinical features and laboratory, MRI, and EEG findings of the 20 patients treated with IVIg at admission are described in detail in Table 3. The patients’ age ranged between 3 months and 15 years. The Pediatric Glasgow Coma Scale scores ranged between 4 and 10. The Pediatric Glasgow Coma Scale scores were 9.1 ± 2.3 in the IVIg-treated group and 10.8 ± 2.7 in the non-IVIg-treated group (\(P = 0.025\)).

Table 1. Comparison of demographics, clinical features, and laboratory, magnetic resonance imaging, and electroencephalographic findings between the IVIg-treated and non-IVIg-treated groups at admission.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients treated with IVIg (n = 20)</th>
<th>Patients treated without IVIg (n = 15)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>6.7 ± 4.8</td>
<td>7.7 ± 4.9</td>
<td>0.400</td>
</tr>
<tr>
<td>Male sex</td>
<td>13 (65.0)</td>
<td>10 (66.7)</td>
<td>0.918</td>
</tr>
<tr>
<td>Clinical manifestations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Altered consciousness</td>
<td>20 (100.0)</td>
<td>15 (100.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Fever</td>
<td>18 (90.0)</td>
<td>13 (86.7)</td>
<td>1.000</td>
</tr>
<tr>
<td>Seizures</td>
<td>9 (45.0)</td>
<td>12 (80.0)</td>
<td>0.036</td>
</tr>
<tr>
<td>Focal neurological signs</td>
<td>4 (20.0)</td>
<td>3 (20.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Severity of clinical manifestation at admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pediatric GCS score</td>
<td>9.1 ± 2.3</td>
<td>10.8 ± 2.7</td>
<td>0.025</td>
</tr>
<tr>
<td>Duration of altered consciousness (hr)</td>
<td>17.9 ± 16.9</td>
<td>8.8 ± 9.2</td>
<td>0.157</td>
</tr>
<tr>
<td>Duration of fever (day)</td>
<td>3.5 ± 2.2</td>
<td>1.8 ± 1.1</td>
<td>0.022</td>
</tr>
<tr>
<td>Status epilepticus (≥ 30 min)</td>
<td>2 (10.0)</td>
<td>1 (6.7)</td>
<td>1.000</td>
</tr>
<tr>
<td>ICU care</td>
<td>13 (65.0)</td>
<td>5 (33.3)</td>
<td>0.064</td>
</tr>
<tr>
<td>CSF, MRI, and EEG abnormalities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSF pleocytosis’</td>
<td>16 (80.0)</td>
<td>8 (53.3)</td>
<td>0.144</td>
</tr>
<tr>
<td>Abnormalities on brain MRI</td>
<td>14/19 (73.7)</td>
<td>3/15 (20.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>Abnormalities on EEG</td>
<td>9/13 (69.2)</td>
<td>13/14 (92.9)</td>
<td>0.165</td>
</tr>
<tr>
<td>Laboratory findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC count in blood</td>
<td>12,951.5 ± 5,699.5</td>
<td>9,056.9 ± 4,025.2</td>
<td>0.039</td>
</tr>
<tr>
<td>WBC count in CSF</td>
<td>87.2 ± 110.2</td>
<td>29.6 ± 66.8</td>
<td>0.023</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>0.3 ± 0.3</td>
<td>1.9 ± 3.9</td>
<td>0.987</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number (%). IVIg, intravenous immunoglobulin; GCS, Glasgow Coma Scale; ICU, intensive care unit; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; EEG, electroencephalography; WBC, white blood cell.

\(WBC ≥ 5 \text{cells/mm}^3\);  \(\text{The patient who did not undergo brain MRI had died}\);  \(\text{Most patients with confirmed or suspected enterovirus 71 brain stem encephalitis did not undergo electroencephalography}\).
13. Nine patients (45.0%) had seizures, which evolved into status epilepticus in two of the patients (22.2%). Four patients (20.0%) had focal neurological signs. One patient had ataxia, two had weakness of the right arm, and the other patient showed tremor of the tongue and the right leg after his consciousness had altered.

Enterovirus 71 was detected in stool samples of six patients (30.0%). Herpes simplex virus was identified by a serological test (23- and 48-fold increase of herpes simplex virus-specific IgG titer along with positive result in IgM) in two patients (10.0%). The mean CSF white blood cell count was 87.4 cells/mm$^3$ (range, 0 to 430). Sixteen patients (80.0%) had CSF pleocytosis. The mean protein level was 63.2 mg/dL (range, 16.3 to 149.0). Nine patients (45.0%) showed increased protein levels (>50 mg/dL).

Seven of the 19 patients (36.8%) who underwent MRI showed increased signal intensity in the posterior region of the brain stem and the bilateral cerebellar dentate nuclei on T2-weighted and FLAIR imaging. Six patients (31.6%) showed increased signal in the cerebral cortex. Four patients (21.1%) showed only leptomeningeal enhancement without parenchymal lesions. One patient (5.3%) had lesions in both basal ganglia, and one patient (5.3%) displayed normal images.

Nine of the 13 patients (69.2%) who were examined by EEG showed an abnormality in the test. All nine patients had background slowing on the EEG. One patient (7.7%) had focal spikes. Four patients (30.8%) had normal EEG findings.

2) Clinical outcomes and complications

Clinical outcomes of the IVIg-treated group are described in detail in Table 4. A dose of 2 g/kg of IVIg was administered for 2 to 5 days to 18 patients (90.0%). One patient received 2.4 g/kg of IVIg for 6 days, and one patient, who expired a day after admission, received 1 g/kg of IVIg for one day. The mean interval between admission and commencement of IVIg treatment was 24.6 hours (range, 4 to 100). The mean time from IVIg administration to recovery of consciousness was 3.0 days (range, 1 to 13). In four patients (20.0%), IVIg treatment was commenced after regaining consciousness. The mean interval between IVIg administration and disappearance of fever was 2.4 days (range, 1 to 6). In 10 patients (50.0%), IVIg treatment was commenced after the fever had already subsided. Thirteen patients (65.0%) were admitted to the ICU. The mean length of stay at the ICU was 4.2 days (range, 1 to 16). Two patients (10.0%) required ventilator management during the time at the ICU. The mean length of hospital stay was 15.5 days (range, 1 to 57). None of the patients had adverse effects from the IVIg therapy during the treatment.

One patient (5.0%) with enterovirus 71 brainstem encephalitis died due to pulmonary hemorrhage, acute heart failure, and shock 17 hours after admission. One patient (5.0%) experienced pneumonia and sepsis during hospitalization. These were completely resolved with antibiotic therapy. Two patients (11.1%) showed neurological deficits at discharge. One patient had weakness in his right arm. The other one had a tremor in his right leg, but this tremor had completely subsided by the time of a follow-up visit to the outpatient clinic two months later. Fourteen patients (70.0%) achieved complete recovery without any neurological complications. Anti-epileptic medication was prescribed to six patients (30.0%) at the time of discharge. Five patients (25.0%) were newly diagnosed with epilepsy after discharge.

Discussion

In the present study, at admission, although the IVIg-treated group had a more critical clinical condition than the non-IVIg-treated group, the clinical outcomes of both groups were comparable. Only one (5.0%) of the 20 patients treated with IVIg in conjunction with acyclovir had died, one (5.0%) had residual neurological deficits, and five patients (25.0%) were newly diagnosed with epilepsy. Otherwise, 14 patients (70.0%) achieved complete recovery without any neurological complications. Considering that the mean Pediatric Glasgow Coma Scale score in the patients treated with IVIg was approximately 9 at admission, 14/19 patients (73.7%) had brain parenchymal lesions on MRI, and 13 patients
<table>
<thead>
<tr>
<th>Pt. no.</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Pediatric GCS score</th>
<th>Fever</th>
<th>Seizure</th>
<th>Status epilepticus</th>
<th>Focal neurologic signs</th>
<th>Identified viruses</th>
<th>CSF WBC count (cell/mm³)</th>
<th>Total protein (mg/μL)</th>
<th>CRP (mg/dL)</th>
<th>EEG findings</th>
<th>Location of lesions on MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>0</td>
<td>9</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>91</td>
<td>95.4</td>
<td>0.05</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>1</td>
<td>9</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>260</td>
<td>42.9</td>
<td>0.28</td>
<td>ND</td>
<td>Pons, dentate nucleus in cerebellum</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>1</td>
<td>11</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>21</td>
<td>27.3</td>
<td>0.17</td>
<td>ND</td>
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</tr>
<tr>
<td>4†</td>
<td>F</td>
<td>2</td>
<td>12</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>EV71</td>
<td>60</td>
<td>149</td>
<td>0.37</td>
<td>ND</td>
<td>Midbrain, pons, dentate nucleus in cerebellum, ME</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>2</td>
<td>10</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>Ataxia</td>
<td>EV71</td>
<td>56</td>
<td>61.5</td>
<td>0.2</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>3</td>
<td>8</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Right arm weakness</td>
<td>–</td>
<td>2</td>
<td>42.2</td>
<td>0.13</td>
<td>Normal</td>
<td>Left frontal cortex and left thalamus</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>3</td>
<td>12</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>EV71</td>
<td>150</td>
<td>33.7</td>
<td>0.15</td>
<td>Normal</td>
<td>Pons, dentate nucleus in cerebellum</td>
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<tr>
<td>8</td>
<td>F</td>
<td>3</td>
<td>7</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>HSV</td>
<td>20</td>
<td>45.7</td>
<td>0.9</td>
<td>Delta slowing over both cerebral hemispheres</td>
<td>Both diffuse cerebral cortex</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>3</td>
<td>11</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>86</td>
<td>49.5</td>
<td>&lt;0.02</td>
<td>Delta slowing over both anterior head regions</td>
<td>Both basal ganglia, ME</td>
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<td>M</td>
<td>3</td>
<td>8</td>
<td>+</td>
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<td>–</td>
<td>–</td>
<td>230</td>
<td>57.9</td>
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<td>&lt;0.02</td>
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<td>Right temporal cortex</td>
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Pt., patient; GCS, Glasgow Coma Score; CSF, cerebrospinal fluid; WBC, white blood cell; CRP, C-reactive protein; EEG, electroencephalography; MRI, magnetic resonance imaging; EV71, enterovirus 71; ND, not done; ME, meningeal enhancement; HSV, herpes simplex virus.

†Except patient 1, all patients with confirmed or suspected enterovirus 71 brain stem encephalitis did not undergo electroencephalography; †Patient 1 was 3 months old at admission; †The patient died 17 hours after hospitalization.
<table>
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<th>Pt. no.</th>
<th>Dose of IVIg</th>
<th>Interval between admission and IVIg commencement (hr)</th>
<th>Interval between IVIg administration and recovery of consciousness (day)</th>
<th>Interval between IVIg administration and disappearance of fever (day)</th>
<th>Duration of stay in ICU (day)</th>
<th>Duration of hospitalization (day)</th>
<th>Occurrence of complications</th>
<th>Complications during admission</th>
<th>Administration of AED at discharge</th>
<th>mRS on discharge</th>
<th>Occurrence of epilepsy</th>
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<th>Occurrence of other adverse effects</th>
<th>Occurrence of other adverse effects before IVIg administration</th>
<th>Death</th>
<th>Administration of AED at discharge</th>
<th>mRS on discharge</th>
<th>Occurrence of epilepsy</th>
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</tbody>
</table>

IVIg, intravenous immunoglobulin; Pt., patient; ICU, intensive care unit; AED, antiepileptic drug; mRS, modified Rankin Scale.

*a* Recovery of consciousness before IVIg administration is presented as “-.”

*b* Disappearance of fever before IVIg administration is presented as “-.”

+ Pneumonia, sepsis
(65.0%) were treated in the ICU, the mortality and morbidity results look promising. It is, however, hard to conclude whether IVIg treatment was effective for the treatment of pediatric viral encephalitis because this study was a retrospective observational study at a single center. In addition, the study included only a small number of patients with encephalitis caused by a diversity of viruses, including herpes simplex virus, enterovirus 71, and, most commonly, unidentified viruses. Nevertheless, this study implies that IVIg could at least be considered as an additional medication in support of the conventional antiviral agents to improve the clinical outcome of patients with critical viral encephalitis.

During acute viral infection, immune system is activated through pathogen-sensing by various pattern-recognition receptors, such as Toll-like receptors. Innate immune cells, such as macrophages and dendritic cells, produce interferon-α and -β via the nuclear factor-κB and the interferon regulating factor signaling pathway [14]. The release of proinflammatory cytokines and chemokines then activates the innate immune and adaptive immune responses. Although cytokines and chemokines are produced mainly by immune cells, during acute viral infection, they are also produced in the central nervous system by the microglia and astrocytes [15-17]. The chemokines produced during viral infection induce the migration of leukocytes from the vascular lumen to the infected brain parenchyma, across the blood-brain barrier. This migration is achieved through the adhesive molecular interactions between the leukocytes and the endothelial cells [18-20]. While the recruited immune cells play a key role in eliminating infected brain cells, they might also damage uninfected surrounding cells in the process. Hence, the immunomodulation is critical during the management of viral encephalitis. Indeed, in a study on herpes simplex virus encephalitis in mice, mortality was associated with the severity of inflammatory responses, but not the virus titer [21]. In Japanese encephalitis, inflammation contributed to disease severity by disrupting the integrity of the blood-brain barrier, inducing neuronal cell death, and inhibiting the proliferation and differentiation of neural progenitors [22].

IVIg has been used for the treatment of a broad range of autoimmune and systemic inflammatory diseases, including rheumatoid arthritis, systemic lupus erythematosus, immunohumortombocytopenia, autoimmune hemolytic anemia, and Kawasaki disease [23]. In addition, it has been applied to the therapy of autoimmune and inflammatory neurological disorders, such as Guillain-Barré syndrome, myasthenia gravis, chronic inflammatory demyelinating polyneuropathy, and autoimmune encephalitis [24]. Although IVIg has been used off-label for the treatment of encephalitis caused by enterovirus 71, Japanese encephalitis virus, and West Nile virus, there is a lack of clinical studies on the efficacy and safety of IVIg for viral encephalitis [25-27]. Since 2015, the first randomized controlled trial, has been conducted to evaluate the effect of IVIg treatment in pediatric encephalitis of any cause [28]. This clinical trial included 308 children (6 months to 16 years) across 30 hospitals in the United Kingdom. It planned to recruit patients over 42 months and conduct follow-up of each participant for 12 months post-randomization.

IVIg is prepared from pools of serum IgG, retrieved from 3,000 to 60,000 healthy blood donors. A cold ethanol precipitation step is used to enrich for the serum IgG fraction [29,30]. This step is followed by several viral inactivation, depletion of blood coagulation factors, and removal of IgG aggregates. Besides IgG, various amounts of other immunoglobulin isotypes, mostly notably IgA, can be found in the IVIg preparation [31].

Despite the widespread use and therapeutic success of IVIg, the mechanism of IVIg action is not well understood. IgG molecules have two functional domains, The F(ab′)2 fragment (antigen-binding fragment), which is responsible for antigen recognition, and the Fc fragment, which is crucial for activating the innate immune system [31]. In IVIg preparation, the F(ab′)2 fragments of the IgG molecules recognize and bind not only to foreign antigens but also to a wide range of self-antigens. F(ab′)2 fragment-dependent mechanisms of IVIg activity include the killing of target cells by antibody-dependent cytotoxicity, blocking cell interactions by inhibiting cell-surface receptors, such as CD95 and CD95 ligands, eliminating anaphylatoxins, such as C3 and C5, and neutralizing cytokines and autoantibodies [31,32]. The Fc fragment of the IgG binds the family of Fcγ receptors (FcγR), which are broadly expressed by most cells of the innate immune system, including eosinophils, neutrophils, monocytes, and macrophages. In humans, the FcγR family consists of several activating receptors and one inhibitory receptor, FcγRIIB [33,34]. Fc-dependent mechanisms of action include expanding the regulatory T cell population, blocking the binding of immune complexes to FcγR, modulating dendritic cell activation via activation of FcγRII, and modulating the activating and inhibitory FcγRII expression on innate immune cells and B cells [31].

In general, IVIg infusion is well tolerated. The common side effects of IVIg are mostly transient and mild. It includes flushing, headache, malaise, fever, chills, fatigue, and lethargy [35]. However, in some rare cases, serious side effects, such as renal failure, transfusion-related acute lung injury, thrombosis, and arrhythmia have been reported [35]. Early assessment of risk factors, slow infusion, and premedication may lessen side effects. Fortunately, in this study, no side effects were observed in the patients treated with IVIg.

As briefly mentioned above, this study has considerable limita-
tions. First, in this study, to identify the etiology of encephalitis, different tests were selectively conducted among patients with encephalitis based on their clinical manifestations and initial test results instead of following an established diagnostic protocol to screen for all known etiologies of encephalitis, including autoimmune encephalitis. In addition, this study included patients with suspected viral encephalitis, a diagnosis made based on clinical, laboratory, and MRI features along with reasonable exclusion of other causes without confirmatory test results. This might lead to inclusion of misdiagnosed viral encephalitis. Second, IVIg treatment was selectively used in patients who showed more severe neurological conditions according to the treating physician’s judgment. No specific criteria were used for the initiation of this treatment. We, therefore, could not include suitable controls for appropriate outcome-comparison with the patients treated with IVIg. Third, as this study included only a small number of patients from a single institute, selection bias may have occurred. Fourth, in this study, the identified causative virus was mostly enterovirus 71. However, in 55% cases, no specific virus could be identified. This precludes the possibility of evaluating what kind of viral encephalitis responds effectively to IVIg therapy. Fifth, autoantibody tests for autoimmune encephalitis were performed only in a few patients who had clinical manifestations suggesting such an etiology, such as abnormal psychiatric behavior, cognitive dysfunction, and movement disorder. Lastly, in patients whose parents did not complain of their having any neuropsychological symptoms, testing for those diseases were not performed. Therefore, neuropsychological complications, such as attention deficit hyperactivity disorder and learning disability could be underestimated in this study.

In conclusion, this study demonstrated the relatively low mortality (5.0%) and morbidity (30.0%) rates in children with critical viral encephalitis who were treated with IVIg in conjunction with conventional treatment. None of the patients had adverse effects to the IVIg therapy. This suggests the possibility of using IVIg as a potential immunomodulating agent for the treatment of pediatric viral encephalitis, aiming to improve clinical outcomes. Although IVIg therapy was described in several studies on viral encephalitis [36,37], including enterovirus 71 and Japanese B encephalitis, to the best of our knowledge, this is the first Korean study to focus on the efficacy of IVIg therapy in patients with viral encephalitis. Well-designed randomized control trials with a larger number of participants and a longer duration of follow-up are needed to determine whether IVIg therapy can improve the neuropsychiatric outcome of patients with viral encephalitis. In addition, further investigations are required to identify the mechanisms of action of IVIg in viral encephalitis treatment.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

ORCID

Ji Eun Byun, https://orcid.org/0000-0001-9747-8681
Kyung Yeon Lee, https://orcid.org/0000-0001-6821-1056

Author contribution

Conceptualization: KYL. Data curation: JEB and KYL. Formal analysis: JEB and KYL. Funding acquisition: KYL. Methodology: KYL. Visualization: JEB. Writing-original draft: JEB and KYL. Writing-review & editing: KYL.

Acknowledgements

This work was supported by the 2019 Ulsan University Hospital Research Grant (UUh-2019-08). We thank the patients and their families for placing their trust in us.

References

and a comparison to infectious encephalitis. Ann Neurol 2018;83:166-77.
Cerebral sinovenous thrombosis (CSVT) is an uncommon disease (0.4 to 0.7 cases per 100,000 live births) characterized by blood clotting in the cerebral venous sinuses [1]. The diagnosis is often delayed owing to its nonspecific symptoms. However, fatal neurological sequelae, including developmental delays, visual impairment, and cerebral palsy, may develop [1]. Diabetes mellitus (DM) can be responsible for this hypercoagulable state [1]. A certain gene involved in the insulin synthesis and secretion pathway might be involved in some cases and can contribute to CSVT treatment. Particularly, neonatal DM (NDM) is a rarer disease, which is encountered with hyperglycemia within the first 6 months of life [2]. Herein, we report the case of a male infant diagnosed with CSVT caused by NDM. He was treated promptly owing to early detection, without finding a causative gene yet.

A 50-day-old boy visited our emergency center with an abruptly sunken anterior fontanelle. He was a first-born child and had no specific underlying diseases and family DM history, despite his small size considering the gestational age at birth (37 weeks, 2,040 g). His weight, height, and head circumference were within 3 percentiles. Although his initial vital signs were stable, he seemed severely dehydrated with dry lips and mottled skin. His mental state was alert and neurological examination was unremarkable. Eye tracing and social smile were possible, indicating normal development.

The initial laboratory analysis revealed severe hyperglycemia (1,352 mg/dL) and hypernatremia (160 mEq/L). Blood gas analysis revealed metabolic acidosis (pH, 7.2; bicarbonate concentration, 17.5 mmol/L), and urinalysis revealed glycosuria without ketonuria. Serum ketone tracing led to the suspicion of diabetes. The possibility of metabolic diseases was eliminated using negative tandem mass spectrometry. He-moglobin A1c (HbA1c) and fasting C-peptide levels were 5.8% and 0.7 ng/mL, respectively. Antibody tests for islet cells and insulin, and anti-glutamic acid decarboxylase were negative. He was treated with normal saline (10 cc/kg) infusion for the first hour, followed by continuous intravenous infusion of regular insulin (0.05 U/kg/hr) with half-normal saline according to the principle of diabetic ketoacidosis treatment.

Meanwhile, he suddenly developed seizure-like trembling movements in both legs. This generalized tonic-clonic seizure disappeared after 3 days; however, repetitive saw-tooth-like electrical seizure activities with sudden lower and upper margin elevation were recorded for 7 days on the
amplitude-integrated electroencephalograph (aEEG) followed by a marked depression on aEEG tracing (Fig. 1), corresponding to non-convulsive electrical status epilepticus. Diffusion brain magnetic resonance imaging (MRI) was performed immediately, and lesions suspicious of venous thrombosis were observed. Subsequent contrast-enhanced MRI revealed extensive CSVT (Fig. 2).

Continuous intravenous heparin and anticonvulsant treatments were administered promptly. The heparin loading dose (75 U/kg over 10 minutes) was followed by a maintenance dose for 4 weeks, determined by the activated partial thromboplastin time (aPTT) according to the Protocol for Systemic Heparin Administration and Adjustment in Children [3]. Intravenous phenobarbital was started and lorazepam was intermittently administered when a convulsive movement presented. As this was not well-controlled, topiramate and levetriacetam were added. The electroclinical seizures disappeared and lesions improved on follow-up MRI at 4 weeks. Finally, he was discharged after switching to subcutaneous injection of 1 mg/kg low-molecular weight heparin twice a day. The insertion of an insulin pump ensured good blood sugar control. Despite receiving regular basic rehabilitation, the patient demonstrated delayed milestones, i.e., those of a 7-month-old when he was 28-month-old, for all the developmental areas (gross motor, fine motor, cognition, language, sociality, and self-care) on the Korean Developmental Screening Test for Infants and Children. He still requires 0.5 to 0.6 U/kg of insulin per day for normoglycemia maintenance. All known genetic tests related to NDM, such as ABCC8, KCNJ11, 6q24 methylation, and targeted exome sequencing, were negative.

Among CSVT treatments, use of anticoagulation therapy in children is still controversial and limited. However, several studies have reported better outcomes and safety with careful aPTT monitoring [3]. Determining the etiology of various underlying conditions causing CSVT in children is also crucial for the treatment. Dehydration is found in a sizable proportion of neonates and can induce sinovenous occlusion by altering systemic circulation [1]. Considerable elevation of random blood sugar levels alone led to the NDM diagnosis in this case. Importantly, when NDM is accompanied by severe dehydration despite the absence of certain neurological symptoms, neuroimaging and cerebral function monitoring should be conducted promptly. Treatment strategies including thrombolysis should be established and at least be considered even in newborns [1].

NDM can be classified into transient (45%), permanent (45%), and syndromic forms (10%). Our patient can be considered to have permanent NDM, as the blood sugar level elevation lasted for more than 6 months. Further HbA1c elevation to 6.5% over 6 months suggests that type 1 DM had occurred at a very early age.

This report has some limitations. First, genetic analyses of the

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Fig. 1. Amplitude-integrated electroencephalography (aEEG) of the patient. Several repetitive saw-tooth-like electrical seizure activities (triangles) were detected on the aEEG (A) and its corresponding raw electroencephalography (EEG) channel (B) without clinical seizures.
patient’s parents were not conducted. Second, the extent of whole exome sequencing was not sufficient to detect a potential mutation.

There are three reports on CSVT resulting from hyperglycemia [2,4,5]. Anik et al. [2] described the case of a 2-month-old patient who presented with focal clonic seizures, which was the most similar to ours. Conversely, Sasiadek et al. [4] and Keane et al. [5] described the cases of patients aged > 5 years, who lost consciousness a few hours after visiting the hospital.

Neuroimaging examinations, such as computed tomography or MRI, were necessary for diagnosis and performed immediately after the appearance of each symptom; CSVT was confirmed in all cases.

Subcutaneous enoxaparin [2] and heparin [4,5] were used to dissolve cerebral thrombosis. Treatment was switched to sulfonylurea administration in one study [2] because the genetic analysis revealed a de novo ABCC8 (modulator of the potassium channel) mutation. Most patients with channelopathy responded well to sulfonylurea treatment. Several known genes linked to NDM development were analyzed in our patient, without any satisfactory results.

In conclusion, prompt neurological evaluation including neuroimaging studies and cerebral function monitoring should be performed for appropriate NDM management with severe dehydration, before the manifestation of neurological symptoms. Molecular gene analysis for rare diseases may assist in determining targeted-treatment strategies.

This case report was approved by the Institutional Review Board of Bundang CHA Medical Center (CHA 2018-06-008) after agreement with the infant’s parents.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

ORCID

Chaeri Yoo, https://orcid.org/0000-0003-0299-7775
Kyu Young Chae, https://orcid.org/0000-0003-3243-5853
Mo Kyung Jung, https://orcid.org/0000-0001-5904-4946

Author contribution

Conceptualization: SR, EGY, KYC, and MKJ. Data curation: CY, SR, EGY, and MKJ. Formal analysis: SR and MKJ. Funding acquisition: KYC. Methodology: KYC and MKJ. Project administration: SR, EGY, KYC, and MKJ. Visualization: CY, SR, HJC, KYC, and MKJ. Writing-original draft: CY. Writing-review & editing: CY, HJC, KYC, and MKJ.

Acknowledgements

This work was supported by the Institute for Information & Communications Technology Promotion (IITP) grant funded by the Korean government (2018-2-00861, Intelligent SW Technology Development for Medical Data Analysis).

References


Riboflavin (vitamin B2) is the solitary precursor for the biologically active cofactors known as the flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD) molecules [1]. These cofactors are required in oxidation-reduction (redox) reactions and act as cofactors for the electron transfer flavoprotein (ETF) and its dehydrogenase (ETFDH) [2]. The ETF and ETFDH form electron transport pathways for at least 12 mitochondrial flavoprotein dehydrogenases involved in amino acid, fatty acid, and choline metabolism [3]. Variations of the ETF or ETFDH cause multiple acyl-CoA dehydrogenation deficiencies (MADDs), and riboflavin metabolism or transport genetic defects can also cause MADD or varying degrees of progressive neurodegenerative diseases such as riboflavin transporter deficiency (RTD) [3].

There are three human riboflavin transporter (RFVT) homologs: RFVT 1 to 3, encoded by genes SLC52A1 to SLC52A3, respectively [4]. RFVTs are widely distributed in the body and SLC52A1 is highly expressed in the placenta and intestine [3]. SLC52A2 is rather ubiquitously expressed, mainly in the brain, and, although SLC52A3 is most highly expressed in the testes, which also expressed in the intestine and prostate [3]. There are three types of RTDs and these are caused by autosomal dominant, heterozygous (SLC52A1 [OMIM: 615026]), and autosomal recessive (AR), biallelic (SLC52A2 [OMIM: 614707] and SLC52A3 [OMIM: 211500 and 211530]) mutations corresponding to RTD1, RTD2, and RTD3, respectively [4]. Although 24 cases of RTD2 and 49 cases of RTD3 have been reported, only two cases of RTD1 have been reported so far [3-5]. The first case was published in 2007, and in 2011 a maternal RTD was identified, caused by a heterozygous microdeletion of the maternal SLC52A1, with transient neonatal-onset MADD [5]. The second case reported a transient neonatal-onset riboflavin-responsive MADD caused by maternal riboflavin deficiency, with detection of heterozygous intronic variations of both the maternal and fetal SLC52A1 [3]. To the best of our knowledge, this is the first case report of a homozygous exon 3 deletion in SLC52A1 in an infant in the absence of maternal RTD. It may have occurred due to AR inheritance via paternal heterozygous exonal deletions and a 25% decrease in the concentration of DNA in exon 3 in the mother, a mosaic heterozygous exon 3 deletion that could affect the homozygous deletion of exon 3 in the patient was considered.

A previously healthy 4-month-old girl present-
ed to our hospital with repeated seizures. Two days prior to presenting to the hospital, while she was asleep in the car on a family trip, she experienced left eyeball deviation accompanied by a generalized tonic-clonic seizure lasting for 2 minutes. On the day of her visit, when she woke up from a nap, she experienced, for 1 minute, a focal clonic seizure of the right extremities. Her consciousness recovered well and no febrile illness was observed before and after these two episodes. At the time of the hospital visit, her blood pressure, pulse rate, respiratory rate, body temperature, and oxygen saturation were 80/50 mm Hg, 124 beats/minute, 32 breaths/min, 36.9°C, and 97%, respectively.

The infant was born, by cesarean section, at the gestational age of 38+1 weeks, weighing 3,300 g. There were no prenatal or perinatal problems. Tandem mass spectroscopy was normal and she showed normal growth and development. There was no family history of seizures or other neurologic diseases. Her body weight, height, head circumference, and neurologic examination were within the normal range.

Blood biochemical analysis revealed white blood cell 10,840/mm³, hemoglobin 11.5 g/dL, platelet 467,000/mm³, C-reactive protein 0.063 mg/dL, aspartate aminotransferase 59 IU/L, alanine aminotransferase 61 IU/L, and glucose 121 mg/dL. Electrolyte levels were normal. Venous blood gas analysis showed compensated metabolic acidosis with pH 7.275, PCO2 36.3 mm Hg, bicarbonate 17.0 mmol/L, base excess –8.4, and elevated ammonia 170 μmol/L. No specific lesion was observed in the brain magnetic resonance imaging, and electroencephalography (EEG) showed interictal epileptiform discharges (IEDs) over the midline central region.

Hyperammonemia was considered due to the transient elevation after the seizure. Epilepsy was the suspected diagnosis and we started administering oxcarbazepine. After an intravenous infusion of 5% dextrose water with electrolytes throughout the day, serum ammonia decreased to 94 μmol/L. However, after the discontinuation of the dextrose fluid with full enteral feeding, ammonia level became elevated, at 208 μmol/L on day 2. Treatment of hyperammonemia was initiated, with fasting for 24 hours and sufficient administration of glucose to prevent additional hyperammonemia via protein catabolism. In addition, nitrogen scavenger arginine was administered intravenously and carnitine was administered to buffer toxic acyl-CoA intermediates. On day 3, serum ammonia decreased to 88 μmol/L and feeding resumed. Serum ammonia was maintained as 52 to 74 μmol/L for a month thereafter. A metabolic workup for serum and urine taken to find the cause of hyperammonemia showed normal results. Gene panel tests for inborn errors of metabolism and epilepsy did not detect any gene mutations. A variation was observed on partial exome sequencing for 5,447 genes using copy number variation (CNV) analysis based on the human GRCh37: 17p13.2(4936243-4937911) × 1, 1.7kb, containing SLC52A1 exons 2, 3, 4, 5. During the CNV analysis, statistically meaningful values were derived by comparing the sequencing depths with other sample data; the eXome-Hidden Markov Model (XHMM) algorithm was used for the analysis (PMID: 23040492). Subsequent droplet digital polymerase chain reaction (ddPCR) revealed a homozygous exon 3 deletion in SLC52A1 and heterozygous deletions in exons 1, 2, 4, and 5 (Fig. 1). Finally, the patient was diagnosed with RTD1 and started taking additional riboflavin. Targeted CNV analysis and ddPCR of her parents revealed heterozygous deletions in exons 1–5 of SLC52A1 in her father and a 25% decrease in the concentration of DNA in exon 3, which was suggestive of a mosaic heterozygous exon 3 deletion that could affect the homozygous deletion of exon 3 (Fig. 1). Her brother had no mutation. Thus, the proband’s phenotypic characteristics may be attributed to the homozygous single exonal deletion of SLC52A1 with a probable underlying AR inheritance. This study was approved by the Institutional Review Board (IRB) of Kosin University Gospel Hospital (IRB no., 2020-06-014). Informed consent was waived due to the retrospective nature of the study.

Since then, she has been seizure-free and her development has been normal. We continued oxcarbazepine therapy because of occasional IEDs identified in the EEG, which may be caused by mildly sustained hyperammonemia, and might lead to seizure recurrence. Serum ammonia remained between 57 and 61 μmol/L for about 18 months. She is currently 22 months old, with a head circumference in the 5th percentile, and takes 100 mg of riboflavin, 900 mg of carnitine, and 96 mg of oxcarbazepine per day. After increasing riboflavin dosing to 100 mg per day, her serum ammonia dropped to 44 μmol/L; therefore, we planned to discontinue oxcarbazepine treatment if her serum ammonia and EEG findings were maintained within the normal limits. RFVT3 plays a major role when riboflavin is absorbed into the epithelial cells of the small intestine. Afterward, riboflavin migrates to the bloodstream, either assisted by RFVT1 or RFVT2, or directly through conversion to the FAD coenzyme via FMN [3]. RFVT2 plays a major role in blood-brain barrier passage, for reaching the brain tissue [3]. When the maternal riboflavin passes through the placenta, RFVT1 becomes the only way to the fetus [3]. If a maternal RTD1 exists, fetal MADD may occur, sometimes causing fetal death in fatal cases [3]. When RTD1 presents only in a child, transport of riboflavin from small intestinal epithelial cells into the blood would be partially impaired, because of the transportation by RFVT2 or direct passing through conversion to FAD [1]. This is why an RTD1 without maternal RTD1 displays relatively mild symptoms and an infant with RTD1 can be treated effectively. In this case, RTD1 was diag-
nosed in an infant, without maternal riboflavin deficiency, and gene testing suggested paternal inheritance in the initial diagnosis. Her father was healthy and had no symptoms related to this mutation. The homozygous deletion in exon 3 of SLC52A1, which was only found in the proband, may have accounted for her symptoms, especially when her parents were asymptomatic. In two previously reported cases of RTD1, both mothers were also symptom-free and the infant with RTD1 were treated until 3 years of age. However, in our case, the mutation was a homozygous deletion, which may have influenced a different clinical course of the disease. While RTD1 may be a transient disorder with a heterozygous mutation, further studies pertaining to the clinical courses are needed.

Children with RFVT1 deficiency due to the heterozygous mutation of SLC52A1 may be asymptomatic, but maternal RFVT1 deficiency should be considered when a neonate has hyperammonemia, metabolic acidosis, or a convulsive history of unknown etiology. The neonate and the mother can be healthy if treated with proper supplementation of riboflavin. Children with RFVT1 deficiency due to the homozygous variation of SLC52A1 can present with hyperammonemic seizures and it is important for them to take sufficient riboflavin to control hyperammonemia, and in turn to be seizure-free with normal development.

**Conflicts of interest**

No potential conflict of interest relevant to this article was reported.

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**Fig. 1.** The droplet digital polymerase chain reaction results of exons 1 and 3 of SLC52A1. DNA concentrations of exon 1 in the (A) patient and (B) her father were approximately half of that of the control, and this is consistent with a heterozygous deletion. (C) The DNA concentration of exon 1 in her mother was equal to that of the control, which means that there was no deletion. (D) The DNA concentrations of exon 3 were 39.4 and 38.9 copies/μL in the patient and 228 and 228 copies/μL in the control, which is consistent with a homozygous deletion. (E) Her father’s DNA concentration of exon 3 was approximately half of that of the control, which is consistent with a heterozygous deletion. (F) The DNA concentrations of exon 3 were 234 and 238 copies/μL for her mother and 305 and 288 copies/μL for the control. These results may be due to the mosaic heterogeneous deletion of exon 3, which may have affected the patient’s homozygous deletion.
Author contribution

Conceptualization: UK, DHY, and GMY. Data curation: UK, DHY, and YJL. Formal analysis: SON and GMY. Methodology: UK, DHY, SON, and GMY. Project administration: DHY, SON, YJL, and GMY. Visualization: DHY and YJL. Writing-original draft: UK and GMY.

Acknowledgements

We would like to thank Dr. Chang Ahn Seol (Genome Research Center, GC Genome) for analysing gene mutation of the patient.

References

Head and neck bruits are well known findings in diagnostics. A cranial bruit can also cause one to sense a thrill; thus, self-diagnosis is possible in adults or in severe cases among pediatric patients. However, it is very hard to detect a cranial bruit in infants or young children, because it can only be diagnosed using a stethoscope. A bruit is caused by turbulence in intracranial or extracranial vessels and is mostly associated with the systolic phase. Innocent cranial bruits can be heard in a high cardiac output situation, but sudden onset of cervical bruits, particularly bruits during the systolic phase or detected throughout the entire head and neck including both eyeballs, must be considered to indicate life-threatening conditions such as carotid artery stenosis, an arteriovenous fistula, and an intracranial hemangioma [1,2].

A 7-month-old boy was admitted to our hospital because of the sudden onset of an audible rhythmic sound in the occipital area 1 week ago, which was detected by his mother. He was born at full term by uncomplicated delivery. Before admission, he had been healthy and had normal neurodevelopment. He had neither other symptoms nor a history of trauma. Family history showed nothing particular, except for subarachnoid hemorrhage in his grandmother.

Upon physical examination, his vital signs were as follows: heart rate, 136 beats per minute; blood pressure, 94/66 mm Hg; body temperature, 36.8°C; and respiration rate, 34 breaths per minute. He showed regular heartbeats without any murmur. However, systolic bruits were detected across the entire scalp, particularly in the left posterior auricular area, but thrills were not detected. After recording with an electronic stethoscope (3M™ Littmann® Electronic Stethoscope Model 3200, 3M, St. Paul, MN, USA), acoustic analysis using a Computerized Speech Lab (CSL™, CSL models 4500, Kay-PENTAX, Montvale, NJ, USA), confirmed that the bruits matched the heartbeats (Fig. 1). His mental status was alert without any abnormalities in cranial nerve function tests. Motor power showed grade 5 in all extremities, tone was normal, and deep tendon reflexes were normal. No pathologic reflexes were present.

There was no specific finding in routine laboratory investigations, including bleeding tendency, blood glucose level, and lipid profile. Brain magnetic resonance imaging (MRI) did not show any definite intracranial lesions. However, brain magnetic resonance angiography (MRA) showed arterial stenosis at the left internal carotid artery that may have been due to focal arterial dissection (Fig. 2A and B). Transcranial Doppler ultraso...
nography (TCD) showed that the peak blood flow velocity of the left internal carotid artery was 109 cm/sec and that of the right internal carotid artery was 91.5 cm/sec, but TCD did not show any stenotic lesions. Electroencephalography (EEG) showed normal symmetric background activities for his age, and interictal brain perfusion single-photon emission computed tomography (SPECT) showed symmetric perfusion in brain parenchyma.

Previous reports suggest that if the internal carotid artery shows a peak blood flow velocity of 125 cm/sec or higher, it can be said that the internal carotid artery has more than 50% stenosis in an adult [3,4]. They recommended antiplatelet treatment in such a situation [3,4].

His vital signs were stable, and he had no remarkable neurological abnormalities. His peak blood flow velocity of the left internal carotid artery was less than 125 cm/sec. Therefore, we recommended observation and a follow-up brain MRA without any medication or intervention, as previous reports have recommended observation in a similar situation [3-5].

After about 5 months of follow-up, the bruits gradually started to decrease, and after 7 months of follow-up, no more bruits could be heard using a stethoscope. Follow-up brain MRA, which was conducted at around 8 months after the initial MRA, confirmed that the previously seen vascular lesion had fully recovered (Fig. 2C).

We reported a case of a 7-month-old boy visiting our hospital for an abnormal sound in the occipital area. Brain MRA showed partial stenosis of the left internal carotid artery that may have been caused by focal dissection. Brain MRI, EEG, TCD, and brain SPECT were performed to evaluate brain function, and they showed no specific findings. At follow-up after 8 months, the stenotic lesion and bruits had improved without any medication or intervention. During follow-up observations, this patient showed suitable development for his age, without any abnormalities.

This study was approved by the Institutional Review Board of Jeonbuk National University Hospital (IRB No: 2020-07-029). Informed consent was waived by the board.
Conflicts of interest

No potential conflict of interest relevant to this article was reported.

ORCID

Kyo Un Cho, https://orcid.org/0000-0002-5565-0081
Sun Jun Kim, https://orcid.org/0000-0002-7673-8728

Author contribution

Conceptualization: KUC and SJK. Data curation: KUC and SJK. Formal analysis: KUC and SJK. Methodology: KUC and SJK. Project administration: KUC and SJK. Visualization: KUC and SJK. Writing-original draft: KUC and SJK. Writing-review & editing: KUC and SJK.

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Craniosynostosis involves premature closure of cranial suture lines, causing increased intracranial pressure and hydrocephalus. This results in the skull or facial bones changing from a normal appearance to a more triangular forehead, termed as trigonocephaly. A newborn male was delivered prematurely at 35 weeks and 3 days gestational age, weighing 2.3 kg at birth. The cranial contour showed evidence of trigonocephaly. Magnetic resonance imaging (MRI) findings portrayed complete fusion of the metopic sutures, mid-sagittal sutures, lambdoidal sutures and partial fusion of the coronal sutures. Clinically, a fusion of the calvaria along the auroculoauricular suture is referred to as the coronal suture fusion. Conversely, a metopic suture fusion presents with a triangular forehead, a palpable midline ridge, hypotelorism-induced ethmoidal hypoplasia and minimal anterior cranial fossa. Diagnosis of craniosynostosis is based on typical facial and cranial morphology and can be done through Caldwell-Luc antrostomy as well. Early calcification of developing sutures occurs with oxidative stress due to postnatal ventilation in premature births. Altered calcification leads to trigonocephaly with metopic suture fusion, which is treated with metopic craniosynostosis surgical repair: Caldwell-Luc antrostomy was performed as a diagnostic and therapeutic approach. This repair confirmed and treated the metopic craniosynostosis; however, the surgery was complicated by post-operative hydrocephalus in this patient at age 2 years. Although currently inaccessible, the brain MRI was indicative of hydrocephalus. Evidence of high intracranial pressure such as papilledema secondary to optic disc swelling and left abducens nerve palsy appeared secondary to intracranial pressure. Due to the severity of this post-operative hydrocephalus, an external ventricular drain and a ventriculoperitoneal shunt were urgently placed in this patient to reduce intracranial pressure. Maternal use of opioids is shown to have an association with opioid use in the National Birth Defects Prevention Study from 1997 to 2005, a case control study of 17,449 case mothers showed statistical significance of conoventricular septal defects, hypoplastic left heart syndrome and spina bifida. This study showed statistically significant ratios associating congenital malformations with maternal opioid treatment one month before pregnancy and during the first trimester. Pre-natal nutritional status was within normal limits and the pre-delivery medications consisted of only Tylenol (Johnson & Johnson, Brunswick, NJ, USA) as needed. The atypical nature of post-operative hydrocephalus in this patient warranted an examination of possible syndromic craniosynostosis; however, syndromic craniosynostosis was ruled out through single nucleo-
tide polymorphism genotyping analysis and whole genome sequencing. Other differentials were ruled out by routine newborn screening and verification of epicanthal folds, a normal cephalic index despite biparietal broadening, the surprised coon sign and concurrent bitemporal shortening. This suggests that maternal opioid dependence may be associated with other congenital malformations such as the metopic craniosynostosis seen in this case [5]. A year later the patient presented with macro-encephaly. The patient also needed occlusive therapy to correct his severe strabismus. The patient was obese at > 97th percentile with a tendency to gain weight easily, and also short in stature. Weight control strategies were implemented.

Neuropsychological signs of craniosynostosis include affected development of behavior, speech and language; deficiencies in cognition; neurodevelopmental delays such as attention deficit hyperactivity disorder, oppositional defiant disorder, autism spectrum disorder, and conduct disorder [5]. Some of these signs were seen in this patient. The patient experienced extensive speech delay as well: at 2 years old he was able to say only two words.

After revision surgery of the trigonocephaly, despite management of the complication of post-operative hydrocephalus, this patient with non-syndromic craniosynostosis had persistent, related conditions including obesity, speech delay and a need for occlusive therapy.

The patient was informed and agreed to voluntary disclosure for the purpose of research publication and the betterment of healthcare.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

ORCID

Trissa Paul, https://orcid.org/0000-0002-2884-5756
Sarabjot Singh Makkar, https://orcid.org/0000-0003-0008-4876

Author contribution

Conceptualization: TP. Data curation: TP and SSM. Formal analysis: TP and SSM. Funding acquisition: SM and PM. Methodology: TP and SSM. Project administration: SM and PM. Visualization: TP, SSM, SM, and PM. Writing-original draft: TP and SSM. Writing-review & editing: TP and SSM.

References

Instructions to authors

Enacted: January 31, 2019

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The abstract should be a single paragraph of less than 250 words, and describe concisely, the purpose, methods, results, and conclusion of the study, in a structured format. Abbreviations, if needed, should be kept to an absolute minimum, and their first use should be preceded by the full term in words. The abstract should not include footnotes, references, or tables. The abstract can be modified by an English language reviewer who is appointed by the editorial board. A maximum of 5 keywords should be listed at the end of the abstract to be used as index terms. For the selection of keywords, refer to Medical Subject Headings (MeSH; https://meshb.nlm.nih.gov/search).

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Clearly describe the selection of observational or experimental participants (healthy individuals or patients, including controls), including eligibility and exclusion criteria and a description of the source population. Because the relevance of such variables as age, sex, or ethnicity is not always known at the time of study design, researchers should aim for inclusion of representative populations into all study types and at a minimum provide descriptive data for these and other relevant demographic variables.

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Examples of reference styles

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REFERENCES
1) Kwon and Son, Biomol Ther 21(3), 181-189 (2013), in vivo : rat, dog
2) DA9701_FU_III_CSR_Final (Ver 2.0), Phase III Clinical Trial Comparing the Efficacy and Safety of DA-9701 and Itopride in Patients with Functional Dyspepsia.
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SMN2 pre-mRNA에 결합하여 정상 SMN 단백질 생성을 촉진하는 세계 최초의 SMA 치료제

신생아부터 성인까지의 SMA 환자를 대상으로 치료 효과 확인

10개 임상연구 총 346명 규모의 임상을 통해 최대 6년의 양호한 안전성 프로파일 확인

*At the age of photoshoot
SMA, spinal muscular atrophy; SMN, spinal motor neuron
6. SPINRAZA® Product Information (2020)
스핀라자주 (뉴시너센나트륨)

[원료약품 및 그 분량]
1 바이알(5 mL) 중, 주성분: 뉴시너센나트륨 (별규) 12.63 mg  (뉴시너센으로서 12 mg)

[성상]
무색투명한 액이 무색투명한 유리 바이알에 든 주사제

[효능•효과]
5q 척수성 근위축증의 치료

[용법•용량]
이 약은 척수성 근위축증 치료 경험이 있는 의사에 의해서만 투여하여야 한다. 요추 천자로 경막내 투여한다.

투여 요법
이 약의 권장용량은 1회 12 mg (5 mL)이다. 척수성 근위축증으로 진단 후 가능한 빨리 0일, 14일, 28일, 63일에 4회 도입 용량(loading dose)으로 투여를 시작하며, 이후에는 4개월마다 유지용량으로 투여한다.

투여 기간
이 약의 장기간 유효성에 대한 정보는 없다. 치료의 지속성에 대한 필요성은 환자의 임상 증상 및 치료에 대한 반응에 따라 정기적으로 검토되어야 하며 개별적으로 고려되어야 한다.

투여 지연
도입용량의 투여가 지연되거나 누락된 경우에는 가능한 빨리 이 약을 투여하여야 한다. 투약 사이는 적어도 14일 간격이어야 하고, 처방된 투여 빈도에 따라 투여를 지속하여야 한다. 유지용량 투여 기간 중 계획된 투여가 지연 또는 누락된 경우 가능한 한 빨리 투여를 재개하여야 한다. 투여 기간은 4개월까지로, 이후에는 4개월마다 투여를 지속하여야 한다.

[사용상의 주의사항]
다음 환자에는 투여하지 말 것:
이 약의 주성분 또는 구성성분에 과민반응이 있는 환자

일반적 주의:
1) 이 약의 운전과 기계사용 능력에 미치는 영향에 대한 연구는 실시되지 않았다. 2) 요추천자시술: 요추천자시술로 인한 이상반응(예, 두통, 요통, 구토; '2. 이상반응' 항 참조)이 보고되어 있다. 이러한 투여방법은 매우 어린 환자 및 척추 측만증 환자에게 잠재적 어려움이 있을 것으로 보인다. 의사의 판단 하에 이 약의 경막 내 투여를 보조하기 위한 초음파 또는 다른 영상기법의 사용을 고려할 수 있다. 3) 혈소판감소증 및 응고장애: 급성 중증 혈소판감소증을 포함한 혈소판감소증 및 응고장애가 기타 안티센스 올리고뉴클레오티드의 피하주사 또는 정맥주사 후에 관찰되었다. 임상적으로 필요한 경우, 이 약의 투여 전에 혈소판 및 응고 검사가 권고된다. 4) 신장독성: 신장독성이 기타 안티센스 올리고뉴클레오티드의 피하주사 및 정맥주사 후에 관찰되었다. 임상적으로 필요한 경우, 요단백 검사(기상 후 첫 소변을 이용하는 것이 좋음)가 권고된다. 요단백이 지속적으로 증가하는 경우 추가적인 평가를 고려하여야 한다. 5) 수두증: 이 약을 투여한 환자의 시판 후 조사에서 뇌수막염 또는 출혈과 관련 없는 교통수두증이 보고되었다. 일부 환자는 뇌실복강션트를 시행 받았다. 의식이 저하된 환자는 수두증에 대한 평가를 하여야 한다. 뇌실복강션트를 시행한 환자에서 이 약의 투여에 대한 위해성-유익성은 현재 알려지지 않았으며, 투여 유지는 신중히 고려되어야 한다.

전체 허가사항은 제품설명서를 참조하시기 바랍니다.

[제조의뢰자] Biogen Netherlands B.V., Prins Mauritslaan 13, 1171 LP Badhoevedorp, 네덜란드


[수입자] 바이오젠코리아 유한회사 서울특별시 영등포구 국제금융로 10, 23층 (여의도동, 투아이에프씨)

6. SPINRAZA® 제품설명서(2020년 3월 16일)

*At the age of photoshoot
SMA, spinal muscular atrophy; SMN, spinal motor neuron

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Ultra-broad spectrum of activity
High stability to ESBLs
Well tolerated, Low incidence of nausea and vomiting
“Premium anticonvulsant!”

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Levetiracetam

큐팜정 250mg 500mg 750mg 1000mg
큐팜액 100mg/mL
큐팜주사 500mg/5mL
큐팜XR서방정 500mg 750mg

명인제약(주)
ACCP* Guideline 권고거담제.
기관지염치료에 “Grade of recommendation A”- 엘도스

- Muco-modulatory activity
- Anti-oxidant activity
- Bronchial anti-inflammatory activity
- Bacterial anti-adhesion activity

*ACCP=American college of chest physicians


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모토 audition는 제거하기 전, 상세 제품정보를 참조하시기 바랍니다. 최종개정연월일:2015.07.23

시간 동안 발생. 두드러기, 수포음, 빈맥, 산소포화도 감소, 기관지연축, 빠른 호흡, 눈주위 부종, 고혈압을 포함한 중대한 주입반응이 보고됨. 임상시험 중 가장 흔하게 관찰된 중대한 이상반응: 폐렴, 호흡부전, 호흡곤란, 카테타 관련 감염, 호흡기 세포융합바이러스 감염, 위소장염, 발열, 가장 흔하게 나타난 이상반응: 발열, 설사, 발진, 구토, 기침,

모토 audition은 제거하기 전, 상세 제품정보를 참조하시기 바랍니다. 최종개정연월일:2015.07.23


관련반응 3) 중심 정맥에 카테타를 설치하기 위한 전신마취 중 심장부정맥과 급성심장사의 위험 4) 급성 심폐부전의 위험

금기 재투여에 실패하였을 당시, 이 약에 대한 생명을 위협하는 과민반응(아나필락시스 반응)을 경험한 환자 이상반응 영아발병형 폼페병: 이상반응은 대부분 경증-중등도였으며 거의 모든 이상반응은 주입 중 또는 주입 후 2


동안 발생. 두드러기, 수포음, 빈맥, 산소포화도 감소, 기관지연축, 빠른 호흡, 눈주위 부종, 고혈압을 포함한 중대한 주입반응이 보고됨. 임상시험 중 가장 흔하게 관찰된 중대한 이상반응: 폐렴, 호흡부전, 호흡곤란, 카테타 관련 감염, 호흡기 세포융합바이러스 감염, 위소장염, 발열, 가장 흔하게 나타난 이상반응: 발열, 설사, 발진, 구토, 기침,

소아.청소년기 후기 발병형 폼페병

만약 아이가 달리기나 운동하는데 어려움을 느끼는 등의 근육 악화가 있다면, 폼페병 검사를 서둘러 주세요.

폼페병 검사를 서둘러 주세요.

폼페병은 치료 가능한 질환입니다.3-5 조기 진단과 치료는 특히 운동기능과 호흡기능 결과를 개선시킬 수 있습니다.3-6

POMPE

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자주 넘어지고, 늘어지기나 운동하는데 어려움을 느낄 때

호흡곤란/ 반반한 호흡기 감염

설명할 수 없는 피로

지속적인 설사

소아.청소년기 LOPD에서 흔히 나타나는 증상"
소아. 청소년기 후기 발병형 폼페병
시간 동안 발생. 두드러기, 수포음, 빈맥, 산소포화도 감소, 기관지연축, 빠른 호흡, 눈주위 부종, 고혈압을 포함한 중대한 주입반응이 보고됨. 임상시험 중 가장 흔하게 관찰된 중대한 이상반응: 폐렴, 호흡부전, 호흡곤란, 카테타 관련 감염, 호흡기 세포융합바이러스 감염, 위소장염, 발열, 가장 흔하게 나타난 이상반응: 발열, 설사, 발진, 구토, 기침.

관련반응 3) 중심 정맥에 카테타를 설치하기 위한 전신마취 중 심장부정맥과 급성심장사의 위험
4) 급성 심폐부전의 위험

금기 재투여에 실패하였을 당시, 이 약에 대한 생명을 위협하는 과민반응(아나필락시스 반응)을 경험한 환자

상상병형 폼페병: 이상반응은 대부분 경증-중등도였으며 거의 모든 이상반응은 주입 중 또는 주입 후 2

도를 높이는 계단식 방식으로 투여되어야 함. 초기 주입 속도는 최대 1mg/kg/hr, 내약성을 고려하여 매 30분마다 2mg/kg/hr씩 증가하여 최대속도 7mg/kg/hr에 도달하게 함. 주입관련 반응이 나타날 경우에는 주입 속도를 늦추고/거나 일시적으로 주입을 중단할 수 있음.

사용상의 주의사항
경고 1) 아나필락시스 반응 및 알러지 반응
2) 주입

다. 이 약으로 치료받은 대부분의 환자에게서 혈청전환이 나타날 것으로 예상된다. 이 약에 대한 IgE 항체를 발현한 환자는 이 약을 재투여 할 경우, 주입관련 반응의 발생 위험이 더 크므로, 이 환자는 이 약의 투여 중 더욱 면밀히 모니터링 되어야 한다. 면역조절 면역억제제로 치료받는 폼페병 환자는 중증 감염으로 발열 위험이 증가할 수 있으므로, 면역억제제 약물 사용 시는 증상을 주의 깊게 모니터링

폐렴, 중이염, 상기도 감염, 위소장염, 산소포화도 감소 후기발병형 폼페병: 위약대조임상시험에서 이상반응을 경험한 환자수는 두 군간에 유사하였으며,가장 흔한 이상반응은 주입관련반응이었음. 대부분이 경증-중등도이었고 자연적으로 치유되었음. 면역원성 임상시험에서 대부분의 환자는 전형적으로 치료 3개월 이내에 IgG 항체를 발현하였으며, 3개월 이상의 치료 후에는 IgM 항체가 더 많이 나타났음. 이 약의 치료는 폼페병의 진단 후 가능한 한 빨리 시작하는 것이 중요함. 보다 자세한 사항은 제품설명서 전문을 참고하시기 바랍니다.

REFERENCES
트리렐탈은 NICE GUIDELINE에서 성인 및 소아부분 발작 환자에서 일차 단독요법 또는 보조요법으로 권고되고 있습니다.

1) 임부 또는 임신하고 있을 가능성이 있는 여성, 임신을 원하는 여성
2) 수유부
3) 간염이나 간부전이 의심되는 환자 혹은 중증의 간장애 환자
4) 심장 전도 장애 병력이 있는 환자 혹은 방실 전도 억제 약물 복용중인 환자
5) 심부전 환자
6) 중증의 신장애 환자
7) 저나트륨혈증 환자 혹은 혈청 나트륨을 저하시킬 수 있는 약물 또는 NSAIDs를 투여중인 환자
8) 고령자, 특히 신장 기능 장애가 있는 고령의 환자

High Dose
I.V.-Globulin SN inj. 10%

- First High Dose immunoglobulin in Korea
- High Volume I.VIG
- Reduced Infusion time
- Reduced Volume load

Product Information
Synergistic Seizure Control

Simple, Once-daily
엑시그란과 피코판패이의 1일 1회 용법이 가능한 극초단 치료제입니다.2,3

Synergy of Zonisamide & Perampanel
In vivo 시험에서 Zonisamide와 Perampanel 병용 시
시너지 효과가 관찰되었다.3

Greater effectiveness and lower risks
엑시그란의 Broad Spectrum 작용기전과
피코판패이의 Unique한 작용기전이 만나 시너지 효과를 제공할 수 있습니다.5,6

References
서방형 제형으로 하루 한 번 간편하게 처방하세요!

▶ 하루 한 번 복용의 편의성
▶ 24시간 안정적인 혈중농도 유지
▶ 우수한 내약성
▶ 다양한 Seizure type의 치료

FDA에서 승인받은 Seizure치료의 1차 선택제
- 하루 한 번 데파코트® ER

“오랜 경험이 리더를 만듭니다!”
이젠 달라졌습니다.
친구들 곁에서 밤 미소를 얻지 않도록
선생님의 도움이 필요합니다.
 국내최초 Premix Bag

아세트펜프리믹스 주* 1g/100ml
acetaminophen 100ml
0.5g/50ml

에이치케이에이노엔 최초 50ml 출시

원내감염으로부터 안전한 국내최초 Premix Bag 해열 진통 주사제로 발열 및 통증 을 유의하게 조절합니다.*

Drug Information

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