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A rare epilepsy phenotype in Gabriele-de Vries syndrome: A new case and literature review

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Abstract

Gabriele-de Vries syndrome (GADEVS) is an extremely rare genetic syndrome characterized by mild-to-profound intellectual disability/developmental delay and a wide spectrum of clinical features. Herein, we report a case involving a rare early childhood epilepsy phenotype in a patient diagnosed with GADEVS based on the typical clinical features and the identification of a pathologic variant of the Yin Yang 1 (YY1) gene. A 3-year-old girl with global developmental delay, failure to thrive, and facial dysmorphism was referred to our rare genetic clinic. She also presented with cognitive impairment, hypotonia, hyperlaxity, strabismus, and autistic features. Whole genome sequencing identified a *de novo* heterozygous missense variant in the YY1 (c.1130A>G; p.His377Arg) gene. Notably, she developed afebrile seizures with abnormal electroencephalogram in early childhood. Currently, she has been seizure-free for more than 2 years with valproic acid. This case expands the epilepsy phenotypic features of GADEVS and reviews the association between the loss-of-function of the YY1 gene and epileptogenesis and possible treatment options.

Keywords: Gabriele-de Vries syndrome; Ying Yang 1; Epilepsy; Neurodevelopmental disorders

INTRODUCTION

With recent remarkable advancements in next generation sequencing (NGS) techniques over the past decade, the genetic causes of intellectual disability (ID) are continuously being revealed.[1] In 2017, Gabriele and de Vries reported patients with haploinsufficiency of the Yin Yang 1 (YY1) gene and cognitive impairment as the core phenotype, and a disease group called Gabriele-de Vries syndrome (GADEVS, MIM #617557) was established.[2] GADEVS is an extremely rare and newly defined autosomal dominant genetic syndrome characterized by mild-to-profound intellectual disability/developmental delay (DD) and a wide spectrum of clinical features, including craniofacial dysmorphism, intrauterine growth restriction/low birth weight, feeding difficulties, neurological manifestations, behavioral problems, and several congenital anomalies.[3,4]

The genetic diagnosis of GADEVS is established by identifying a heterozygous pathogenic variant involving *YY1* or a heterozygous deletion of 14q32.2 involving *YY1* only.[5] The YY1 gene (MIM #600013), located on chromosome 14q32.2, encodes YY1, a deoxyribonucleic acid (DNA)-binding protein that may play a crucial role in early embryogenesis and neurodevelopment.[6-8] Herein, we report a case involving a rare early childhood epilepsy phenotype in a 3-year-old girl diagnosed with GADEVS based on the typical clinical features and identification of a pathologic variant of the YY1 gene.

CASE REPORT

A 3-year-old girl with global DD, failure to thrive, and facial dysmorphism was referred to our rare genetic clinic. She was delivered via cesarean section in the 40th week of pregnancy with a weight of 2,600 g without perinatal problems. Her parents were healthy and nonconsanguineous, and her older sister was also healthy. She had no family history of developmental delays or seizures. She first visited a gastrointestinal clinic at 5 months of age with poor weight gain and

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left eye exotropia. At 13 months of age, she experienced two afebrile seizures characterized by generalized tonic seizures accompanied by facial cyanosis, each lasting less than 5 minutes. An electroencephalogram (EEG) and brain image were normal. The first antiseizure medication (ASM) she was administered was levetiracetam; however, valproic acid was added because of additional seizures. Her early neurodevelopmental milestones were globally delayed. Furthermore, facial dysmorphisms, including facial asymmetry, a broad forehead, low-set and posteriorly rotated ears, a pointed chin, and a thin upper lip, were identified (Figure 1a).

The chromosomal microarray was arr(X,1-22)x2. Whole genome sequencing identified a pathogenic variant of *YY1*, c.1130A>G (p.His377Arg). Paternity validation indicated that the variant was *de novo*.

Currently, she is 4 years old and has been seizure-free for more than 2 years with valproic acid. During the treatment period, an abnormal interictal EEG was observed once. The interictal EEG revealed frequent sharp wave discharges from the bilateral temporal areas (Figure 1b). Despite dysphagia, she continued oral feeding with a thickened liquid. Motor and language development had not improved significantly. She also exhibited cognitive decline and autistic features.

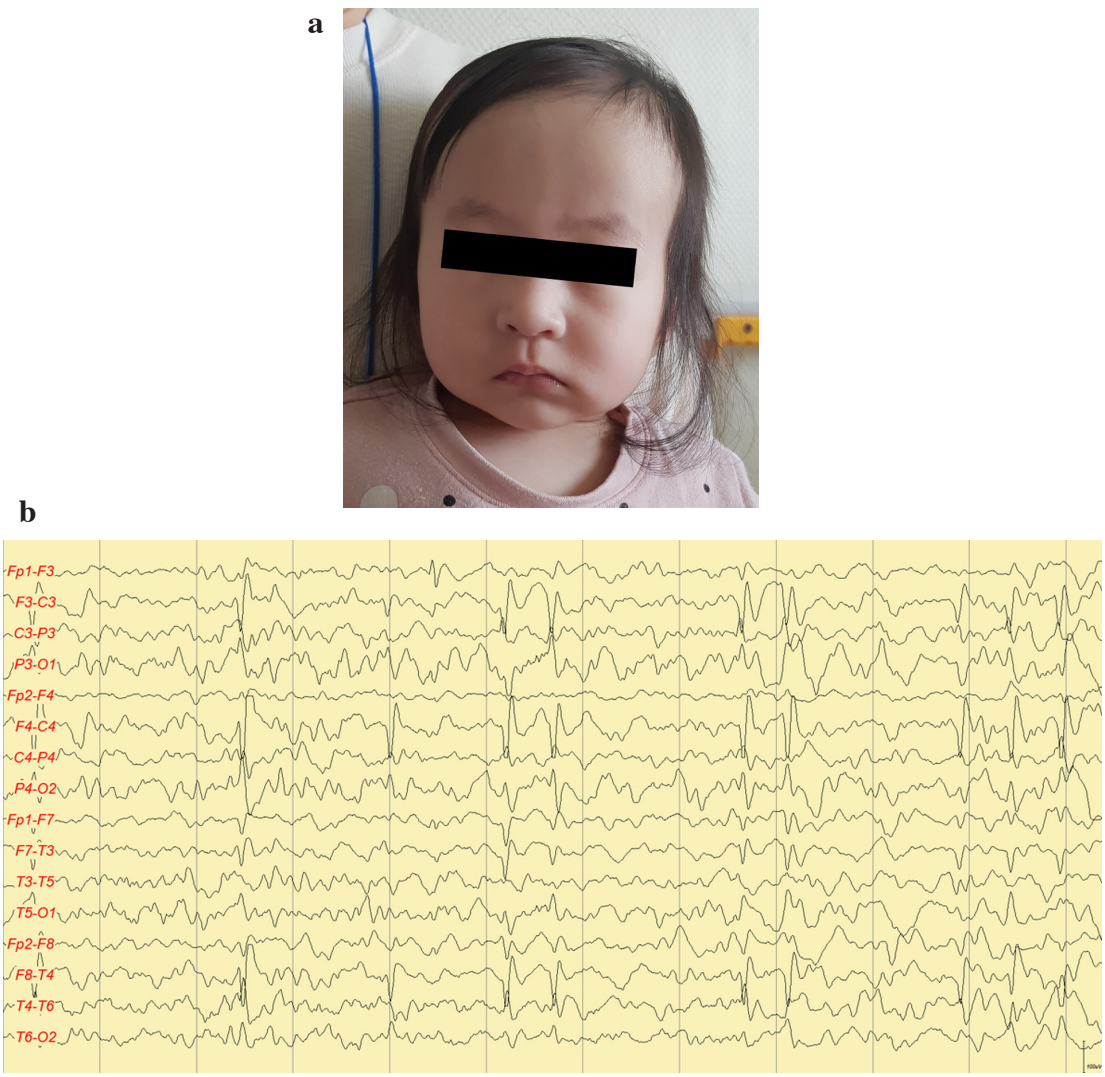

Figure 1. Photograph and electroencephalogram (EEG) of the patient. (a) The dysmorphic facial features, including mild facial asymmetry, a broad forehead, low-set and posteriorly rotated ears, pointed chin, and a thin upper lip (b) Interictal EEG of the patient at 29 months of age showing frequent synchronous or asynchronous medium to high voltage spike and wave discharges from C4T4 and/or C3T3.

DISCUSSION

To date, more than 30 cases of GADEVS with an aberration of the YY1 gene have been reported in the literature.[2-7,9-13] Including our case (p.His377Arg), approximately 80% of these patients have loss-of-function mutations in the zinc fingers,[6] which is a DNA-binding domain of the YY1 gene (Figure 2). Missense mutations were the most common (63.3%), followed by frameshift mutations (26.7%), nonsense mutations (6.7%), and in-frame deletions (3.3%). In addition, one patient had a deletion involving the entire YY1 gene along with adjacent genes.[4] All cases were heterozygous and *de novo*, except for one case of paternal origin.[4] Although several disease-causing variants lead to haploinsufficiency of the YY1 gene, there are no major phenotypic differences associated with the position and type of the variant.[2,4]

The prevalence of each clinical phenotype and characteristic facial feature is shown as a fraction of the total number of cases with available data (Figure 3a).[2-7,9-13] All patients reported to date showed various dysmorphic facial features; however, these could not be considered diagnosis-specific (Fig. 3b). More than half of the patients exhibited ear abnormalities, a broad forehead, a full nasal tip, malar hypoplasia, a long face, and facial asymmetry. Other common clinical symptoms included ID (93%), feeding difficulties (83%), language DD (72%), and behavioral abnormalities (63%) (Figure 2a). Approximately half of the patients (59%, 19/32) had neurological abnormalities (hypotonia, gait disturbance, and seizure) and at least one congenital anomaly of the skeletal system, eye, brain, genitals, or heart. The phenotype of our patient was also associated with typical clinical features, such as profound ID/DD, feeding difficulties with a consequent low body mass index, behavioral problems, hypotonia, strabismus, hyperlaxity, and facial dysmorphic features.

The most notable feature of our patient was the epilepsy phenotype, which developed during early childhood without a family history of epilepsy. The first non-febrile generalized seizure occurred at 13 months of age and initial EEG was normal; however, the EEG performed at the age of 29 months showed frequent sharp-wave discharges in both temporal areas. She has been seizure-free for more than 2 years with valproic acid. Excluding febrile seizures, the only case reported by Dos Santos *et al*. in 2022 exhibited a similar epilepsy phenotype.[12] The patient had an identified pathogenic missense mutation (p.Asn369Ser) in the YY1 gene, had non-febrile seizures in early infancy, and was prescribed valproic acid until the age of 12 years. The EEG showed bilateral focal paroxysmal waves in the anterior and medial temporal areas.

Two genes have been specifically described that explain the role of *YY1* in epilepsy pathogenesis.[8] The first is the matrix metalloproteinase-9 (MMP-9) gene, which encodes an extracellular matrix protease.[8] Aberrant synaptic plasticity is a prominent pathophysiology of epileptogenesis, and MMP-9 is a major molecule involved in matrix remodeling.[14] An excessive activity of MMP-9 contributes to the development of epilepsy.[15] YY1 strongly suppresses MMP-9 transcription by binding to the proximal MMP-9 promoter.[8] The upregulation of hippocampal MMP-9 expression during epileptogenesis is *YY1*-dependent via several methods of histone modification.[12,15] Another epilepsy-implicated gene that acts as a *YY1* partner is the γ-aminobutyric acid (GABA) transporter1 gene (GAT1), which is the major neural GABA transporter in the central nervous system.[16] Aberrant transcriptional activity of GAT1 plays an essential role in GABAergic-related pathologies such as epilepsy.[16] *YY1* enhances or inhibits GAT1 transcription by binding to the GAT promoter.[16]

Patients with GADEVS and non-febrile seizure have childhood epilepsy of a self-limiting nature that responds well to valproic acid treatment.

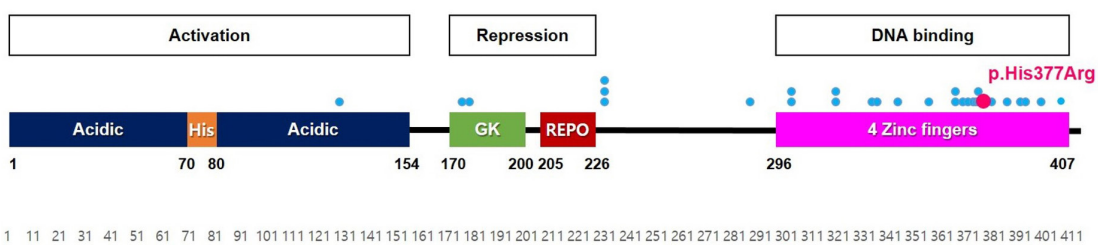

Figure 2. Schematic diagrams showing the structure of the YY1 protein, summarizing the 30 YY1 mutations described in the literature[2-7,9-13] with p.His377Arg highlighted.

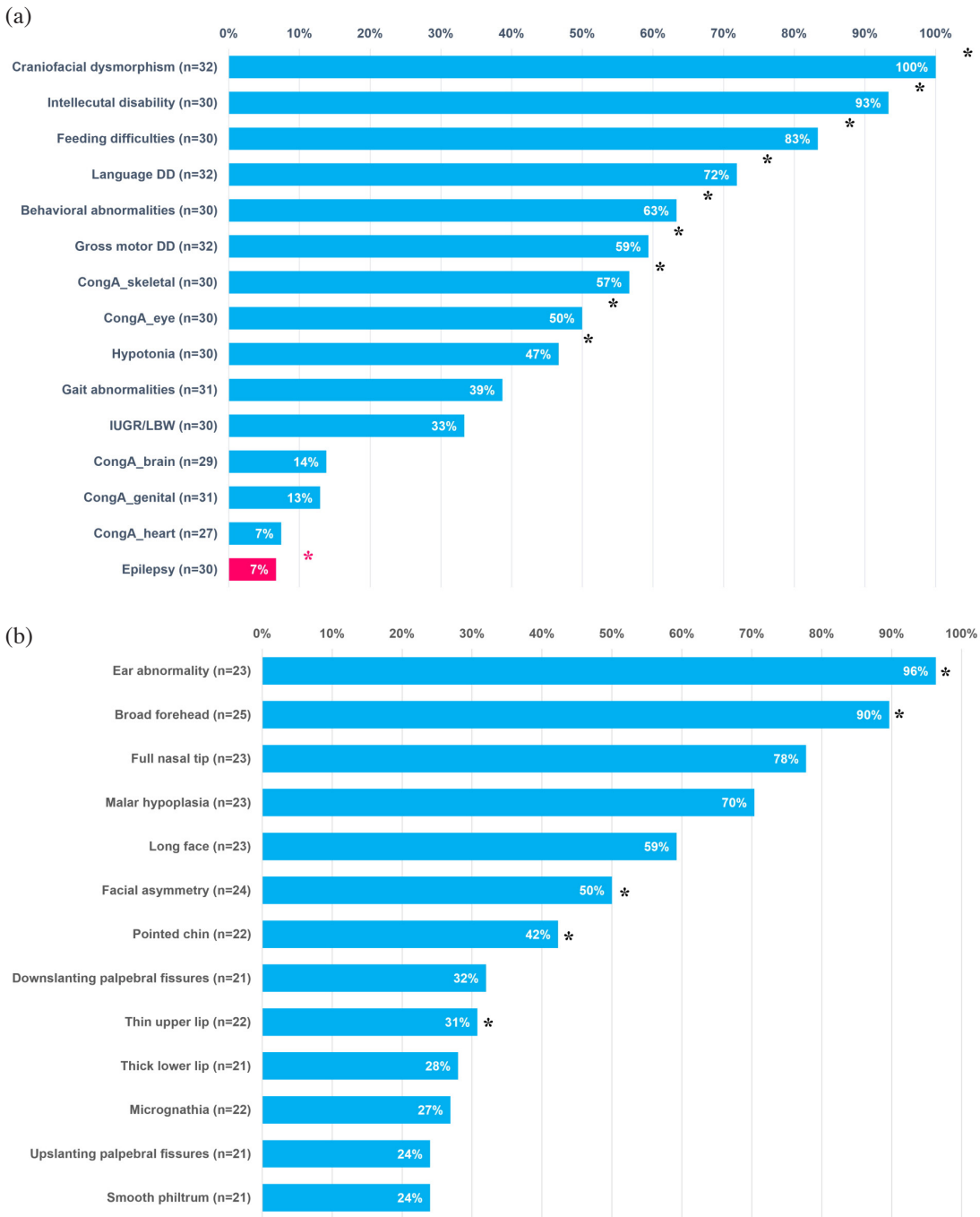

Figure 3. Summary of the clinical features of patients with Gabriele-de Vries syndrome in the literature.[2-7,9-13] (a) Prevalence of the clinical signs and symptoms of the total reviewed cases. (b) Prevalence of the craniofacial dysmorphic features of the total reviewed cases.
(*) Present in our case. DD, developmental delay; CongA, congenital anomaly; IUGR, intrauterine growth restriction; LBW, low birth weight.

Aguirre *et al*. demonstrated that valproic acid regulates *YY1* transcriptional repression via histone deacetylase inhibition.[17] It is unlikely by chance that our patient's seizures were better controlled with valproic acid than with levetiracetam, which was initially used. However, further studies on the functional association between *YY1* haploinsufficiency and valproic acid are required.

In conclusion, the clinical spectrum of

GADEVS is broadening because NGS techniques are actively being used in clinical practice. We reported the case of a patient with GADEVS and an early childhood epilepsy phenotype and reviewed the association between the loss-of-function of the YY1 gene and epileptogenesis and the possible treatment options. We thereby expect to increase clinicians' understanding of GADEVS.

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DISCLOSURE

Ethics: Samples from the patient were obtained in accordance with the Helsinki Declaration. This study was approved by the Institutional Review Board of Chungbuk National University Hospital (2023-07-024), and written informed consent for publication, including photographs with recognizable faces, was obtained from the patient's parents.

Data availability: All data generated or analyzed during this study are included in the references. Further inquiries can be directed to the corresponding author.

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Conflict of interest: None

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