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Shedding Light on Vici Syndrome: A Rare Neurodevelopmental and Multisystem Disorder Characterized by Agenesis or Underdevelopment of the Corpus Callosum

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Abstract

Dionisi-Vici-Sabetta-Gambarara (Vici) syndrome is an extremely rare autosomal recessive multisystem disorder caused by pathogenic variants in the ectopic P granules protein 5 (EPG5) gene, resulting in impaired autophagy. It is classically associated with five clinically diagnostic findings - corpus callosum abnormalities, cataracts, hypopigmentation, cardiomyopathy, and immunodeficiency - as well as multiple other features such as global developmental delay, hypotonia, and seizures. Diagnosis relies on clinical suspicion with confirmatory genetic testing. Prognosis is poor, with most affected individuals not surviving beyond early childhood, and management remains supportive.

The proband is a 15-month-old male who presented at nine months with global developmental delay, generalized hypotonia, and microcephaly with dolichocephaly. Brain magnetic resonance imaging (MRI) at 10 months revealed dysgenesis of the corpus callosum and white matter diffusely. Subsequent genetic testing revealed compound heterozygous variants in the EPG5 gene, confirming a diagnosis of Vici syndrome, and included a unique novel allele not previously in any genetic database. Despite typical associations, cardiac evaluation at 12 months showed normal structure and function, and immunologic workup was largely unremarkable aside from mildly low immunoglobulin M (IgM). The patient experienced recurrent yet non-severe respiratory infections and demonstrated hyperacusis. He is currently managed with multidisciplinary care, including neurology, cardiology, genetics, and rehabilitation.

This case illustrates a comparatively mild presentation of Vici syndrome, which we speculate is likely due to heterogeneity and mutation variation, as well as multifaceted follow-up and treatment, and highlights the phenotypic variability of this condition. Continued reporting and analysis of such cases is essential to better define genotype-phenotype correlations, identify prognostic indicators, and improve screening, clinical management, treatment, and counseling for affected families.

Categories: Neurology, Genetics, Pediatrics
Keywords: delayed motor milestones, epg5 gene, hypopigmentation, multisystem, musculo-skeletal disorders, neuro development, pediatric genetics, pediatric seizure, pediatrics medicine, vici syndrome

Introduction

Dionisi-Vici-Sabetta-Gambarara (Vici) syndrome remains an exceptionally rare disorder, with approximately 100-150 cases reported worldwide. It is a neurodegenerative and multisystem condition caused by defects in autophagy due to mutations in the ectopic P granules protein 5 (EPG5) gene, which encodes an autophagy regulator [1]. Autophagy serves a vital role in embryologic development and maintenance of many mitotically active structures in the body [2,3], and its absence results in widespread cellular dysfunction affecting the neurologic, cardiac, immune, integumentary, and musculoskeletal systems. Classic Vici syndrome is characterized by a pentad of corpus callosum abnormalities, cataracts, hypopigmentation, cardiomyopathy (often hypertrophic or dilated), and immunodeficiency. Vici syndrome falls under a larger umbrella of EPG5-related disease, which comprises a broader spectrum of phenotypes, including seizures, sensorineural hearing loss, hepatomegaly, cardiomegaly, renal tubular acidosis, and dysmorphic craniofacial features [2,3]. The differential diagnosis includes but is not limited to agenesis versus underdevelopment of the corpus callosum, broader EPG5-related disorders, other neurodevelopmental or musculoskeletal disorders, cerebral palsy, Werdnig-Hoffmann disease, and failure to thrive. The diagnosis is based on screening methods such as cranial ultrasound and brain magnetic resonance imaging (MRI). The gold standard for diagnosis is the identification of biallelic pathogenic mutations in the EPG5 gene. Currently, treatment for Vici syndrome is primarily supportive, with 90% of individuals living less than five years in the reported cases and the oldest reported individual reaching 25 years of age [2], although some variability is noted given the phenotypic variations. This case presents a particularly unique presentation, with a relatively mild phenotype in the context of a novel variant allele and a known pathogenic allele found on genotyping.

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Case Presentation

We present a case of a 15-month-old male diagnosed with Vici syndrome in an attempt to increase awareness of the disease and improve screening and potential treatment options. We also hope our case can shed light on additional risk factors associated with the disease to assist with its possible prevention in the future.

There is a positive family history of dementia (Alzheimer's) in his maternal great-grandmother, maternal great-uncle, and paternal great-grandmother, which is notably linked to mutations in EPG5 [4]; however, there is no family history of Parkinson's disease, which can also be linked [4].

The proband was born at 39 weeks of gestation as the first child to a non-consanguineous couple of Dutch and German descent via induced vaginal delivery (due to failure to progress and concern for high alpha-fetoprotein (AFP) found at 14-16 weeks of gestation). The results of a follow-up ultrasonography (USG) performed at 16 weeks were normal.

At birth, he weighed 3.11 kg (31st percentile), measured 55.1 cm (100th percentile), and had a head circumference of 34.3 cm (45th percentile) based on the World Health Organization (WHO) boys' zero to two years growth chart [5]. Initially, he was bottle-fed, as he was hypotonic at birth. He failed his first hearing screen just after birth, although he passed his repeat several hours later, prior to discharge. However, per his mother, he has hyperacusis, specifically to loud noises such as sneezing, previously seen in one other case [6].

He started breastfeeding at three weeks, using appropriate head support with breastfeeding-friendly pillows. His one-month well visit was unremarkable, with the exception of frequent regurgitation, which was managed conservatively. However, by three months of age, his hypotonia did not improve, and the proband had not attained neck control. Additionally, he was unable to perform tummy time.

At four months of age, he demonstrated gross motor delays, including the inability to support himself on his elbows and wrists when on his stomach and an inability to roll from his stomach to his back. Social delays were also evidenced by a lack of audible laughter. He weighed 6.4 kg (21st percentile), measured 66 cm (85th percentile), and had a head circumference of 40 cm (ninth percentile), based on WHO boys' zero-to-two-year growth charts.

The proband was referred to physical therapy (PT) at six months of age due to persistent generalized hypotonia and hyporeflexia. Strabismus with questionable nystagmus was noted. At the time, he weighed 7.4 kg (26th percentile), measured 71.1 cm (95th percentile), and had a head circumference of 41.9 cm (12th percentile).

At nine months of age, he weighed 8.7 kg (42nd percentile), measured 75.5 cm (94th percentile), and had a head circumference of 42.5 cm (second percentile), as per WHO growth charts. His head circumference later remained at this level, falling off the growth curve by the end of 12 months. A neurology referral was placed for microcephaly and delayed milestones, as well as a parental report of concern for seizures due to abnormal eye movements and left arm convulsions. This was reported by his parents, although it remained unwitnessed clinically. An initial electroencephalogram (EEG) revealed some epileptiform activity, further supporting a probable seizure. An X-ray for evaluation of a dolichocephalic skull and a prominent ridge on his forehead demonstrated patent cranial sutures, ruling out craniosynostosis (plagiocephaly due to premature fusion of cranial sutures), which was considered by his primary physician as the underlying cause of his head shape. He was noted to have esotropia of the left eye, as well as sustained upward gaze, downward tracking, a marked café-au-lait lesion on his left calf measuring 3 × 2 mm, and a nevus simplex.

An MRI of the brain performed at 10 months of age revealed dysgenesis of the corpus callosum, right greater than left white matter volume loss, and small punctate hemorrhages with calcification, with a cephalic index of 0.74, all suggestive of Vici syndrome (Figures *1*-*3*).

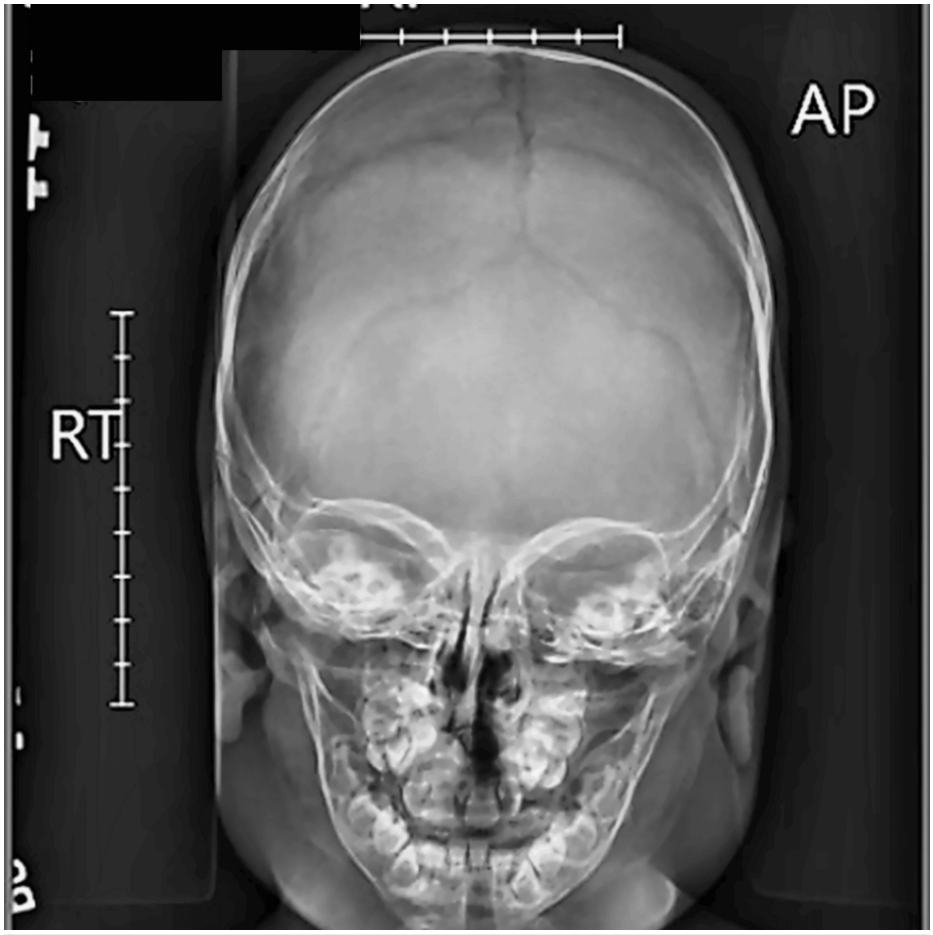


FIGURE 1: Moderate microcephaly and suspected dolichocephaly noted on the scout view (X-ray-style overview image) for brain MRI without contrast.

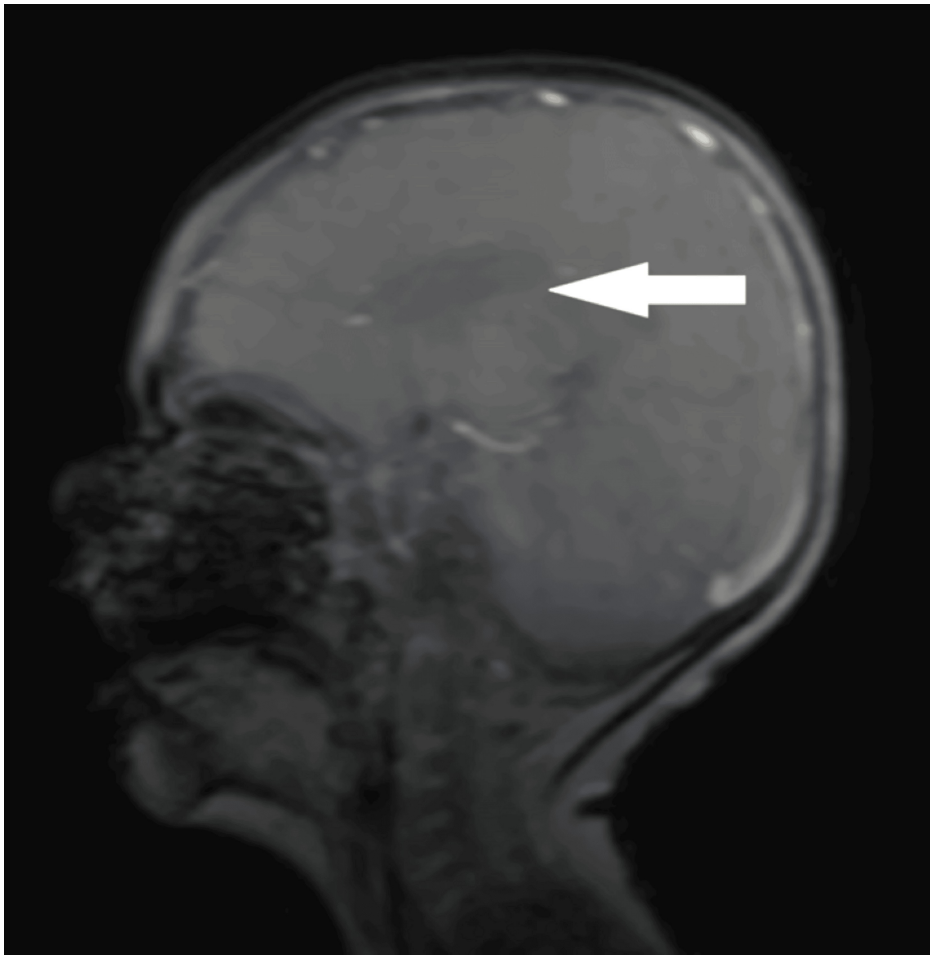


FIGURE 2: Sagittal view of MRI of the brain showing marked hypoplasia of the corpus callosum with diffuse loss of cerebral white matter volume.

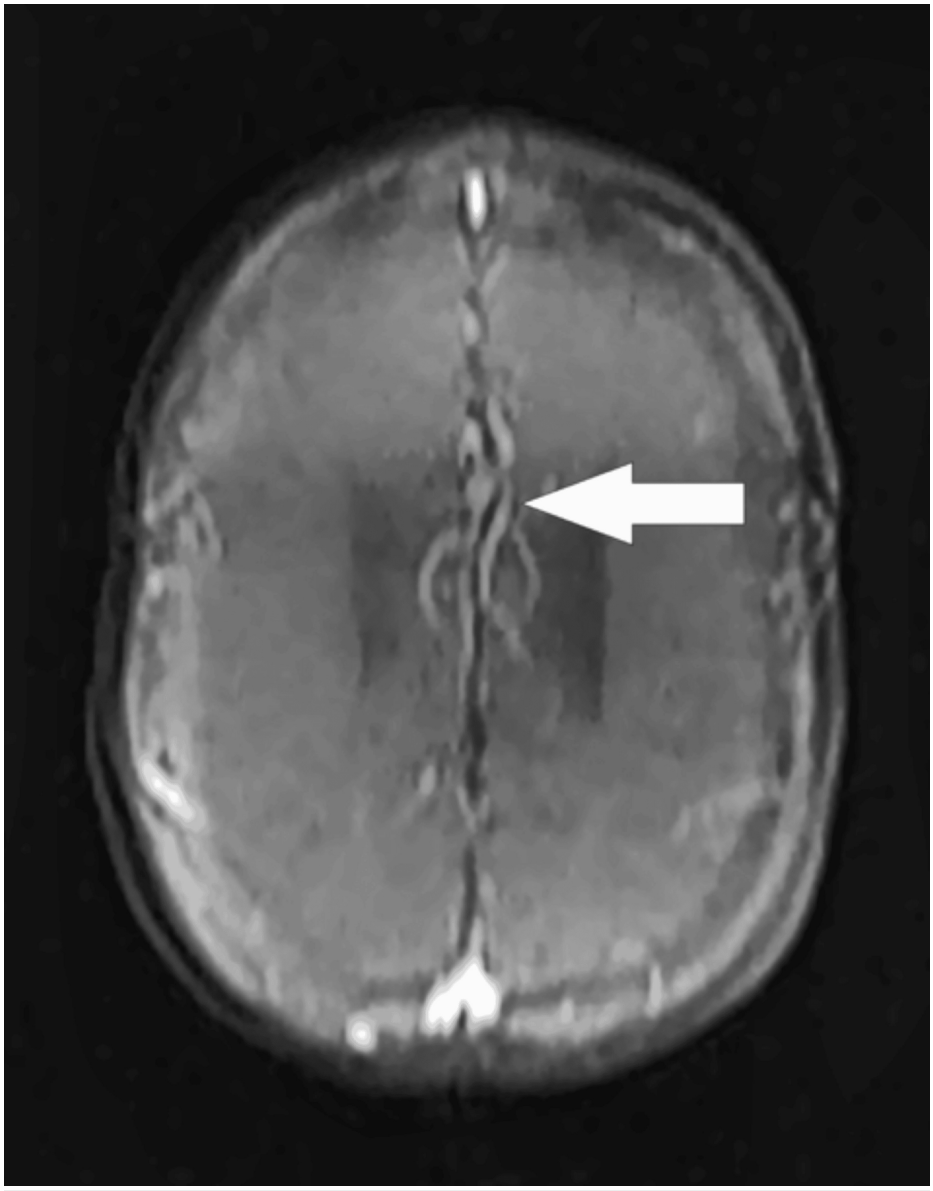


FIGURE 3: Transverse view of MRI of the brain showing marked hypoplasia of the corpus callosum with diffuse loss of cerebral white matter volume.

The proband made progress with PT and is now able to sit independently in the tripod position and started prone-to-supine rolling by 11 months of age. Fine motor skills are delayed, with attainment of palmar grasp, and language skills are limited to monosyllabic vocalizations, without formed words. Neurological examination revealed an alert child with normal bulk and 5/5 muscle strength in all extremities bilaterally. Reflexes were 3+ throughout, with bilateral positive Babinski signs. No adventitious movements were noted on coordination testing. Sensation to touch was intact in all extremities.

Genetic testing revealed mutations in both alleles of the EPG5 gene, most consistent with Vici syndrome. He inherited one defective allele from his father, who harbored a known heterozygous pathogenic variant (Gln2353Ter) (CAG > TAG): c.7057C>T in exon 41, and one allele from his mother, who harbored a heterozygous, unique novel, likely pathogenic variant (Asp1757Tyr) (GAC > TAC): c.5269G>T in exon 30 (Figures *4*-*5*).

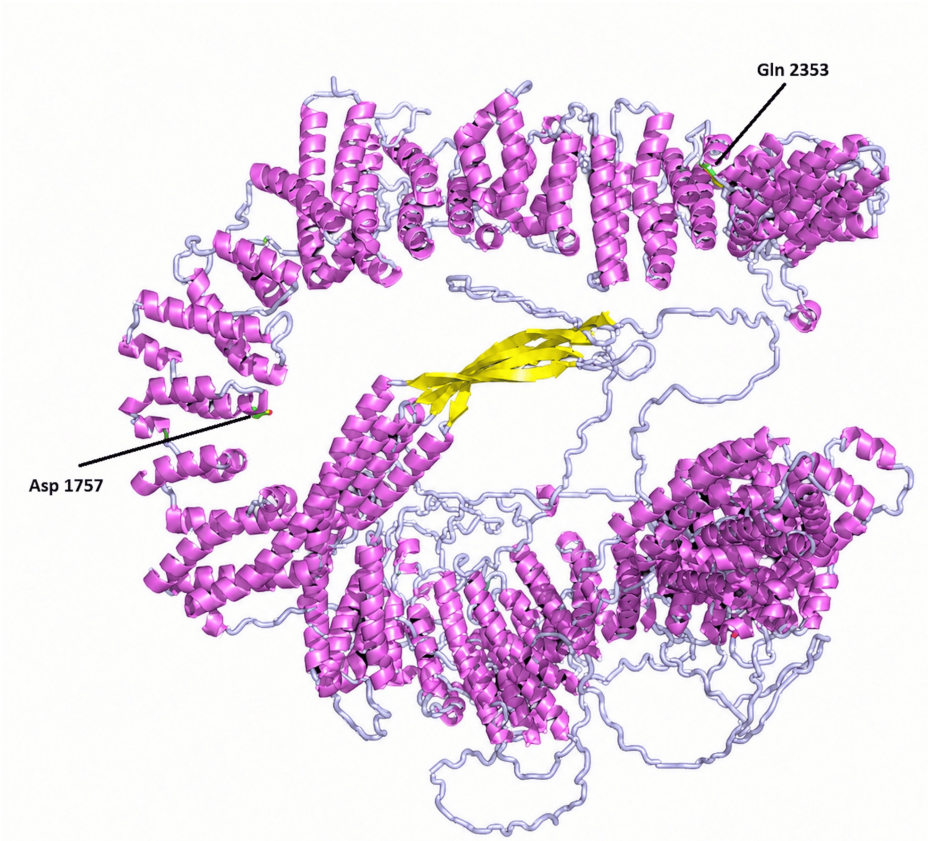


FIGURE 4: AlphaFold-predicted structure of EPG5 demonstrating the location of the p.Asp1757Tyr variant.

Asp1757 resides within a loop connecting adjacent coiled-coil domains. Substitution of a conserved negatively charged aspartate residue with a bulky aromatic tyrosine may alter local structural interactions within this region.

Asp: aspartate; Gln: glutamine; EPG5: ectopic P granules protein 5

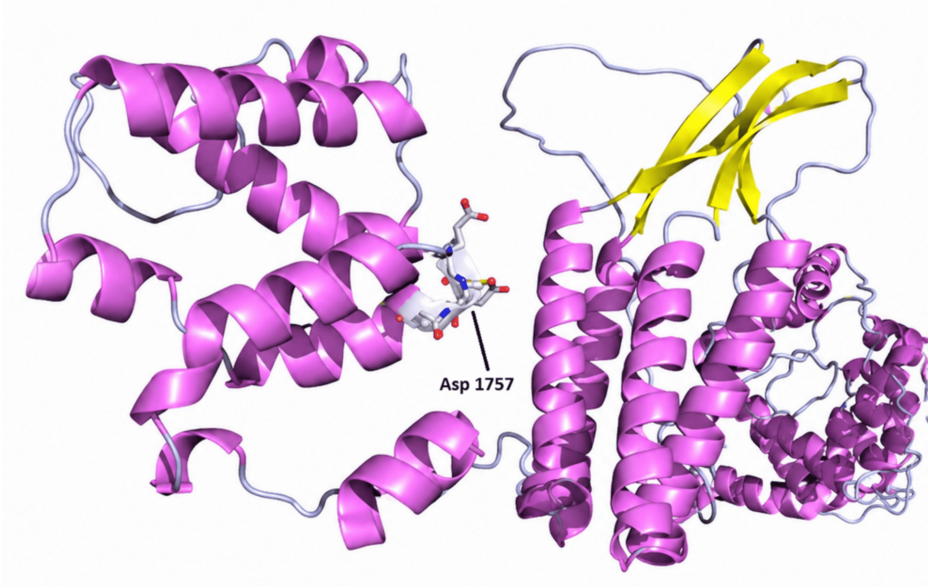


FIGURE 5: Zoomed-in version of Figure 4 highlighting polar hydrogen interactions and the peptide backbone.

Asp: aspartate

Laboratory tests done at 11 months revealed high alanine aminotransferase at 87 U/L (ALT, normal <45), aspartate aminotransferase at 167 U/L (AST, normal <60), creatine kinase of 413 U/L (CK, normal <305), and lactate dehydrogenase 622 U/L (LDH, normal <450), which is consistent with laboratory results reviewed from other Vici syndrome case studies [7]. Hepatomegaly was absent, however, and we speculate that these liver findings are nonspecific and could be related to other causes such as muscle damage, as could be seen with severe hypotonia, rather than liver failure.

At 12 months, he measured 81.5 cm in length (99th percentile) and weighed 9.6 kg (48th percentile) based on the WHO growth chart for boys. Due to associations of Vici syndrome with cardiac manifestations, the patient is closely monitored by a cardiologist, and the evaluations are encouraging. Echocardiography done at 12 months revealed a normal left ventricle with a normal Z score, no cardiomegaly, and a left ventricular ejection fraction of 62%. There was no evidence of dilated or hypertrophic cardiomyopathy, which was reassuring considering the reported pathological association and strongest association with mortality [8]. He is scheduled for regular follow-ups every six months.

The patient had three viral upper respiratory tract infections (URTIs) in the past, one of which was superimposed by a bacterial infection. However, he did not require hospitalization. Due to concerns of immunodeficiency, as is associated with Vici syndrome, the Measles, Mumps, and Rubella (MMR) vaccine was held until immunology workup was received.

Subsequent EEGs at 13 months showed focal epileptiform changes suggestive of potential for focal epilepsies, which is consistent with Vici syndrome (Figure *6*). He started Keppra (levetiracetam) at 13 months of age with therapeutic results. At this time, neurology also listed cerebral palsy as a potential diagnosis given his hypertonia in the left extremities and hypotonia of the right. We suspect this could be secondary to his Vici's, with a relative hypertonicity of the contralateral extremities given the hypotonia in the affected side, although his genetic report also noted that cerebral palsy could be a phenotypic manifestation of his genotype abnormalities.

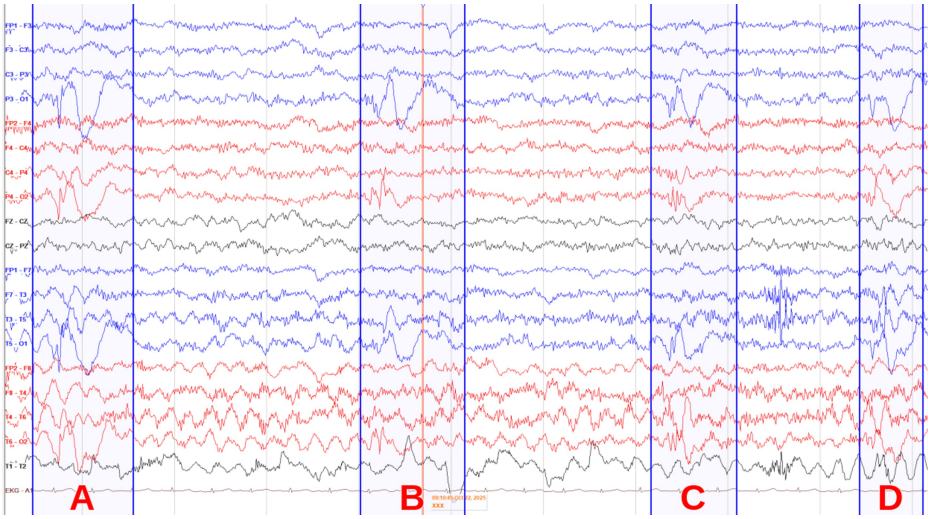


FIGURE 6: EEGs at 13 months: Awake tracing demonstrates a 7 Hz, bilaterally symmetric, reactive posterior dominant rhythm and a preserved anterior-posterior gradient.

The recording is notable for a distinct region of focal slowing in the right hemisphere and increased attenuation in the right paracentral region. There were also focal, independent, and bisynchronous left > right occipital focal epileptiform discharges.

Four complexes were identified at approximately 2 seconds apart. (A) Transient involving P3-O1, P4-O2, T5-O1, and T6-O2, with an initial deflection estimated to last less than 70 ms. (B) Sharp transient involving P3-O1, P4-O2, T3-T5, and T5-O1, with an estimated duration of 70-200 ms. (C) Transient involving P3-O1, P4-O2, T5-O1, T4-T6, and T6-O2, with an initial deflection estimated to last less than 70 ms. (D) Sharp transient involving P3-O1, P4-O2, T3-T5, T5-O1, and T4-T6. An additional polyspike-like transient was observed in F7-T3 and T3-T5; this was considered more consistent with muscle activity or blinking artifact.

EEG: electroencephalogram

Immunological evaluation revealed normal T and B cell counts and normal immunoglobulin levels, with only immunoglobulin M (IgM) mildly low (35 mg/dL; reference range 40-143 mg/dL). He received all childhood vaccines on a slightly delayed schedule and subsequently received his MMR at 13 months. He was scheduled for a one-year follow-up.

As of 15 months of age, he has been continuing intensive PT, with marked improvement in his hypotonia and delayed milestones. He has ongoing multispecialty follow-ups with PT/Occupational Therapy (OT) (including dynamic movement intervention and hydrotherapy), pediatrics, neurology, genetics, nutrition, cardiology, and immunology, and multimodality therapy, including holistic approaches such as eating from their own organic garden and using a reverse osmosis water filter, as per his parents' preference.

Discussion

Vici syndrome is a multisystem disorder caused by defective autophagy, leading to accumulation of abnormal cellular material and dysfunction across the neurologic, cardiac, immune, integumentary, and musculoskeletal systems [2]. It results from autosomal recessive loss-of-function variants in EPG5 (2579 amino acids; chromosome 18q12.3-q21.1) [4,9]. Nearly all reported pathogenic alleles are truncating (nonsense, frameshift, splice-site, or deletion), with a minority being missense [4,6]. Homozygous truncating genotypes, typically in consanguineous families, cause complete loss of function and classic early-onset disease, with a median survival of approximately nine months.

The proband harbors a compound heterozygous genotype, with a truncating paternal allele and a missense maternal allele hypothesized to be less deleterious to EPG5 function. It is speculated that compound heterozygous genotypes retaining a milder allele may yield an attenuated phenotype and longer median survival, up to approximately two years, consistent with this proband's course [10]. Other founder missense variants that preserve partial protein function (e.g., the Ashkenazi p.Gln336Arg) are similarly associated with attenuated phenotypes [3,11].

The paternal variant p.(Gln2353Ter), c.7057C>T, has been classified as pathogenic (LabCorp/Invitae, SCV002183891.5); it is rare in gnomAD (28/1,614,092 alleles; AF 0.00001735; 0 homozygotes) and predicted to cause loss of function, an established mechanism in Vici syndrome [12]. Its proximity to the 3' end of the

transcript is a caveat, though other pathogenic variants lie closer to the terminus [13]. The maternal variant p.(Asp1757Tyr), c.5269G>T, arose de novo, is absent from population databases, and was confirmed in trans; segregation could not be assessed, as the proband was the only affected family member [13].

Computational evidence supports a deleterious effect (CADD PHRED 35) [9]. The change in residue due to the maternal allele (c.5269G>T (p.Asp1757Tyr)) created a nonconservative amino acid change, and analysis with protein sequence alignment showed that the aspartic acid is highly conserved across diverse vertebrate species (Figures *4*-*5*). Structural modeling localizes p.(Asp1757Tyr) between two α-helical coils in the highly conserved C-terminal region (Figures *4*, *5*, *7*, *8*). SpliceAI predicted creation of an in-frame cryptic donor splice site 6 base pairs downstream of the maternal variant (score 0.97), suggesting disruption of normal pre-mRNA splicing that could contribute to partial exon loss or abnormal transcript processing (Figure *7*). This contrasts with the ⩾39 distinct exon mutations reported among the first 50 cases; the proband's variants affect exons 41 and 30 [4]. Splice-site mutations more generally cause exon skipping or large truncations [6].

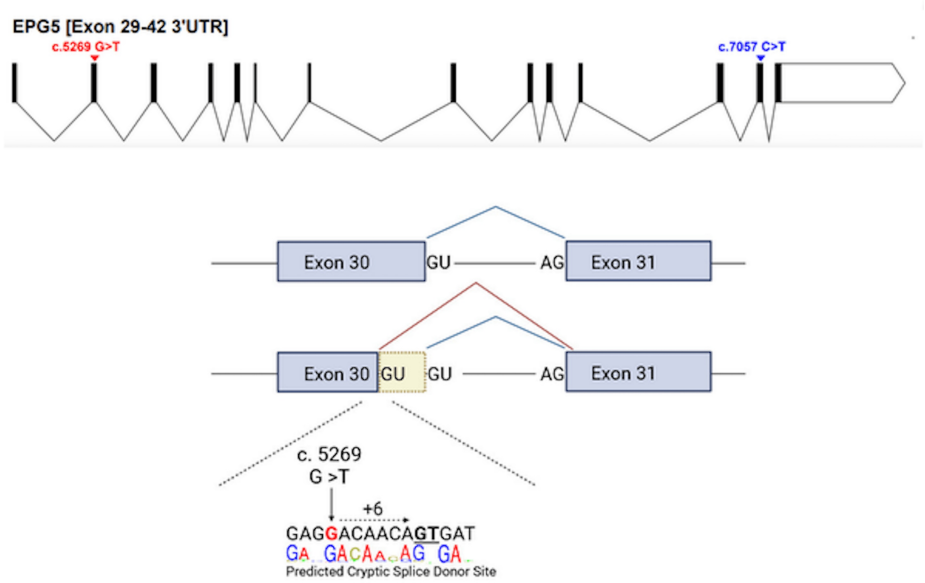


FIGURE 7: Prediction of aberrant splicing associated with the exon 30 variant.

The depicted nucleotide change is predicted to generate a cryptic donor splice site (GT) located 6 bp downstream of the variant, which may alter normal pre-mRNA splicing and transcript structure.

EPG5: ectopic P granules protein 5

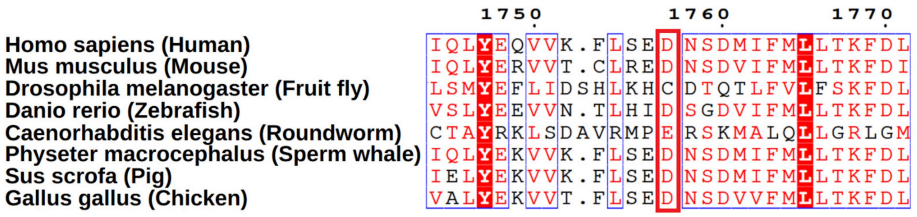


FIGURE 8: Evolutionary conservation of the affected EPG5 residue.

Multiple sequence alignment of EPG5 orthologs from vertebrate and invertebrate species demonstrating strong conservation of the aspartic acid residue across vertebrates, supporting its potential functional importance.

D: aspartic acid residue; EPG5: ectopic P granules protein 5

The proband's presentation is concordant with Vici syndrome, with agenesis of the corpus callosum, progressive microcephaly, features suggestive of oculocutaneous hypopigmentation, recurrent infections,

and poor weight gain. Unlike the many reported cases with consanguineous parentage (Arabic, Turkish, Ashkenazi Jewish) [7,8,11], this patient was born to a non-consanguineous couple, underscoring compound heterozygosity as an important disease mechanism. The comparatively mild early course may reflect variability driven by the specific variants and residual protein function; certain mutation types permitting partial activity have been correlated with prolonged survival [3,14-17], consistent with rare reports of extended lifespan [2].

Elevated CK and liver enzymes, we speculate, may indicate muscle involvement rather than hepatic involvement alone [14], supported by other studies revealing molecular findings of muscle atrophy, loss of muscle spindles, centrally located nuclei, vacuolization/lipidation, and autophagosome accumulation in EPG5-deficient cells [14]. Furthermore, elevated maternal AFP has been inconsistently reported and is nonspecific (also seen with spina bifida, anencephaly, and abdominal wall defects) but warrants further study as a possible prenatal marker [11,14]. Correlations with pregnancy, labor, or delivery complications remain unclear and merit further research to aid earlier detection [1-3,6,14-23].

Phenotypically, affected infants commonly show corpus callosum hypoplasia/agenesis with hypotonia and gross motor delay, cranial and facial dysmorphism, cleft palate, hypopigmentation or albinism (Figures *9*-*10*), hepatomegaly, immunodeficiency with recurrent infections, oculocutaneous abnormalities (cataracts, hypopigmentation), and cardiomegaly/cardiomyopathy (hypertrophic or dilated) (Table *1*) [3]. Fine motor and speech delays and intellectual impairment follow in early childhood, and up to 58% develop seizures (Table *1*) [2]. Most children do not survive past three to five years, with a mean age at death of nine months [1-3,6,14-23].



FIGURE 9: Proband with microcephaly and hypopigmentation demonstrated by fair complexion, pale blond hair, and bright blue eyes. Eczematous plaques are also noted.

Written informed consent was obtained for publication of this identifiable facial image in the open-access journal.



FIGURE 10: Proband with microcephaly and hypopigmentation demonstrated by fair complexion, pale blond hair, and bright blue eyes. Eczematous plaques are also noted.

Written informed consent was obtained for publication of this identifiable facial image in the open-access journal.

Symptoms	Cases	Percent
Core		
Agenesis/dysplasia of corpus callosum [1,2,6,14-19,21-23]	80/80	100.00%
Global developmental delay [2,6,14-16,19,21]	68/80	85.00%
Recurrent infections [1,2,6,16-18,22,23]	67/80	83.75%
Hypopigmentation [1,2,6,14,17,19,22,23]	64/80	80.00%
Common but Variable		
Cardiomyopathy [1,2,6,14,17,19,20,22,23]	57/80	71.25%
Microcephaly [2,6,15-17,19,21,23]	57/80	71.25%
Failure to thrive/Growth retardation [2,15,16,19,20,22]	56/80	70.00%
Less Frequent		
Cataracts [2,6,18,19,21,23]	51/80	63.75%
Seizures [2,6,14-18,21]	47/80	58.75%
Hypotonia [1,2,6,14-17,19-23]	38/80	47.50%
Lab: abnormal LFT [19,20,21]	21/80	26.25%
SNHL [2,6,19,20]	10/80	12.50%
Coarse facies (macroglossia, cleft lip and palate) [2,14,17,19,20,22,23]	5/80	6.25%
Lab: leucopenia [2,6]	4/80	5.00%

TABLE 1: Clinical features noted in each case are tallied and compared for reference.

A comprehensive literature search was conducted on PubMed and supplemented by screening the reference lists of relevant articles to identify case reports and case series of Vici syndrome. Studies were screened and selected based on predefined inclusion criteria: peer-reviewed original case reports or case series with a confirmed diagnosis of Vici syndrome via genetic testing or, where genetic confirmation was unavailable, the presence of the classic pentad of characteristics and availability of patient data regarding clinical presentation and clinical outcomes. Eighty of 100 cases, denoted in 12 articles, met the eligibility criteria.

Disclaimer: It is possible that some cases did not report all findings listed and therefore could be underreported. Furthermore, not all cases may have been 100% confirmed due to inconsistent testing, resource limitations, and financial constraints in some of the settings where the studies took place [1,2,6,14-23].

LFT: liver function tests; SNHL: sensorineural hearing loss

This proband demonstrates several hallmark features, including hypotonia, developmental delay, corpus callosum hypoplasia, epileptiform activity, and possible hypopigmentation (Figures *9*-*10*), but is notable for the relative absence of severe systemic involvement to date. Cardiac evaluation has remained normal, whereas cardiomyopathy affects a substantial proportion of other cases and is a major driver of early mortality [1]. Immune evaluation has likewise been largely preserved, with only mild susceptibility to infection. Seizure activity is a well-documented feature that often emerges in the first year [2], and the neuroimaging findings of corpus callosum abnormalities and diffuse white matter changes are consistent with prior reports of impaired autophagy (Figures *1*-*3*) [14].

The proband is followed by multiple specialists and continues multimodal therapy, with the family open to emerging treatments. Further study of treatment efficacy in Vici syndrome is needed, with attention to both survival and quality of life. This patient's comparatively mild course is encouraging. He is achieving gross motor milestones, albeit with delay, and although nonverbal, he responds to his name and demonstrates comprehension and interactions with body language. While most children do not survive to age five, extended survival has been reported, including a female who lived to 25, attributed to a frameshift mutation yielding a more functional protein product, potentially analogous to this proband's maternal allele, we suspect [2].

This case is distinctive for its unique and novel genomic variant, milder phenotype thus far, and elevated AFP, typically associated with neural tube defects. Despite the absence of a defect such as spina bifida, the

patient nonetheless has a neurodevelopmental abnormality, namely Vici syndrome. If corroborated by further cases, AFP could serve as a screening indicator and should be studied further for significance. Similarly, his dolichocephaly and microcephaly may reflect decreased brain mass, as we postulate, and could warrant earlier brain MRI evaluation to facilitate earlier diagnosis, management, and treatment.

Conclusions

Overall, this case reinforces the hypothesis of significant phenotypic heterogeneity in Vici syndrome and underscores the importance of early recognition, genetic confirmation, and comprehensive multidisciplinary management. Continued accumulation and analysis of case reports are critical to improving understanding of disease progression, identifying prognostic factors, and guiding future therapeutic strategies. We speculate that advancements in gene analysis through 3D modeling and other tools may eventually allow for gene therapy.

Chronic, terminal, and misunderstood diseases can leave patients and their families feeling isolated and alienated. It is important to offer multimodal treatment for a multifaceted disease, including all of the above specialty care as well as online support networks, religious or spiritual groups, social aid, etc. This is part of why it is so critical to raise awareness and increase support for those afflicted with the disease and their families.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Andrea Turel, Camelia Arsene

Acquisition, analysis, or interpretation of data: Andrea Turel, Akhila Jaijith, Pavlo Navrota, Jasmine Kamole

Drafting of the manuscript: Andrea Turel, Akhila Jaijith, Pavlo Navrota, Jasmine Kamole, Camelia Arsene

Critical review of the manuscript for important intellectual content: Andrea Turel, Akhila Jaijith, Pavlo Navrota, Jasmine Kamole, Camelia Arsene

Supervision: Andrea Turel, Camelia Arsene

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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