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A Novel Case of Pediatric CMV Encephalitis, Encephalopathy, and Brain Infarction in a Child With Homozygous CARMIL2 Splice-Site Mutation: Case Report and Review of the Literature

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ABSTRACT

Biallelic loss-of-function variants in CARMIL2/RLTPR impair CD28-mediated T-cell costimulation and cause a combined immunodeficiency with variable infectious and inflammatory phenotypes. CNS viral disease and cerebrovascular complications are sparsely documented in this setting.

Here, we are reporting an eight-year-old Saudi girl of consanguineous parentage presented with febrile illness, rapid-onset encephalopathy, focal deficits, and refractory focal seizures. Neuroimaging showed diffuse atrophy with cortical/subcortical T2/FLAIR hyperintensities and features compatible with ischemic injury. CSF PCR detected CMV DNA. Immunology revealed leukopenia/lymphopenia with normal quantitative immunoglobulins but abnormal T/B/NK subsets. Whole-exome sequencing identified homozygous splice-site variants CARMIL2 (NM_001013838.2:c.958+1G>A) and PRMT7 (NM_001290018.1:c.282+1G>A). She received ganciclovir with corticosteroids/IVIg and antiseizure therapy; partial stabilization was followed by protracted encephalopathy and death from severe chest infection and respiratory failure one year later.

Conclusions: This fatal case supports CARMIL2 deficiency as a predisposing condition for severe CMV CNS disease and cerebrovascular injury in children. Early recognition of inborn errors of immunity (IEI) in pediatric encephalitis—especially in consanguineous populations—may enable timely antivirals, tailored immunomodulation, consideration of HSCT in selected phenotypes, and informed genetic counseling.

KEYWORDS: CARMIL2; RLTPR; inborn errors of immunity; pediatric encephalitis; cytomegalovirus; vasculopathy; infarction; consanguinity.

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INTRODUCTION

CARMIL2 (RLTPR) encodes a scaffolding adaptor essential for CD28-mediated co-stimulation and actin-dependent immune synapse formation. Human CARMIL2 deficiency is an autosomal-recessive inborn error of immunity characterized by impaired T-cell activation/NF-κB signaling, diminished memory T cells and regulatory T cells, and variable B- and NK-cell perturbations. Clinically, patients present with recurrent sinopulmonary and mucocutaneous infections, recalcitrant warts/HPV disease, EBV-associated smooth-muscle tumors, dermatitis/eczema, and very-early-onset inflammatory bowel disease.

Severe CNS viral disease has been rarely detailed in confirmed CARMIL2 deficiency. We report a child harboring a novel homozygous CARMIL2 splice-site variant with CMV CNS infection, encephalopathy, and brain infarction, and we synthesize literature relevant to pathophysiology, diagnosis, and management.

CASE PRESENTATION

Patient and background: Eight-year-old Saudi girl; consanguineous parents; Arabic descent. Developmental history included global delay, intellectual and speech delay, assisted ambulation since age three. Past medical history included recurrent chest infections, chronic diarrhea, atopic dermatitis, gastroesophageal reflux disease, and proximal esophageal stricture.

Index illness: Three days of fever, cough, and sputum production followed by acute confusion, dysarthria, left hemiparesis, and focal left-sided tonic-clonic seizures with rapid progression to a catatonic state.

Initial management: Empiric coverage for autoimmune encephalitis/vasculitis and infectious etiologies with high-dose corticosteroids, IVIg, broad-spectrum antibiotics, and acyclovir. Seizures ceased on levetiracetam, phenobarbital, and lacosamide, but encephalopathy persisted.

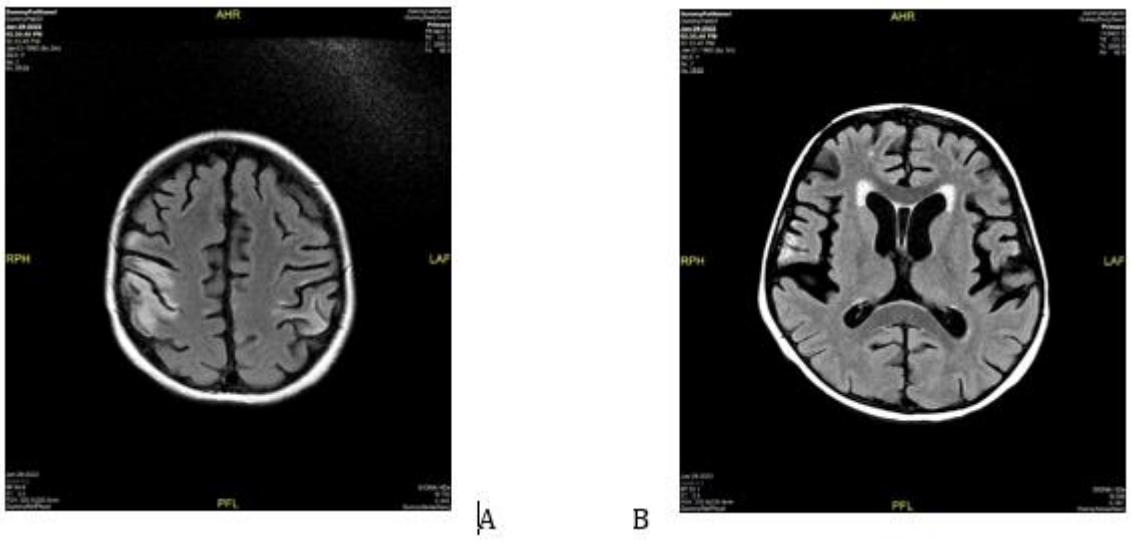
Neurologic examination: GCS 9/15; symmetric facies; central tongue protrusion; normal limb power with reduced tone; diminished reflexes; plantar flexor responses; no meningeal signs.

Respiratory: Decreased air entry on the left; oxygen requirement 5 L/min by mask.

CSF/virology: Bacterial studies negative; CMV DNA detected in CSF; serum CMV IgM/IgG positive; CSF HSV/EBV PCR negative; HIV DNA negative. Respiratory PCR positive for rhinovirus/enterovirus. Transaminitis present.
Immunology: Leukopenia/lymphopenia; normal IgG/IgA/IgM; lymphocyte subset abnormalities across T/B/NK lineages; oxidative burst normal—pattern consistent with combined cellular immunodeficiency typical of CARMIL2 deficiency.

Neuroimaging: MRI revealed generalized brain volume loss with bilateral cortical/subcortical T2/FLAIR hyperintensities (right>left) and periventricular and frontal subcortical white matter changes compatible with post-encephalitic inflammatory injury and ischemic involvement. (A,B)

Genetics: Whole-exome sequencing identified homozygous splice-site variants CARMIL2 c.958+1G>A and PRMT7 c.282+1G>A.



Antivirals and immunomodulation: Ganciclovir 10 mg/kg/day for six weeks; continued IVIg and prednisone with careful balancing of immunosuppression risks amid active viral CNS disease. Foscarnet/cidofovir would be considered if resistance suspected (e.g., UL97), guided by genotypic testing.

Supportive care: Initial antibacterials and acyclovir; Bactrim prophylaxis; respiratory support; multidisciplinary neurology and immunology follow-up.

Outcome: Seizures controlled and partial neurological improvement; persistent encephalopathy and death at approximately 12 months due to severe lower respiratory infection and respiratory failure.

DISCUSSION

CARMIL2 (RLTPR) encodes a cytosolic scaffolding protein that regulates actin polymerization and facilitates CD28-mediated co-stimulatory signaling, which is indispensable for optimal T-cell activation, regulatory T-cell (Treg) differentiation, and maintenance of immune homeostasis. Homozygous loss-of-function variants result in a distinct form of combined immunodeficiency characterized by impaired cellular immunity, defective epithelial and mucosal barrier function, and recurrent infections with inflammatory manifestations such as dermatitis and very early-onset inflammatory bowel disease (1–4). Although the canonical features of CARMIL2 deficiency have been well documented, central nervous system (CNS) involvement has not been previously recognized as a defining component of this immunodeficiency. The present case highlights a novel phenotype—cytomegalovirus (CMV) encephalitis and brain infarction in a child with homozygous CARMIL2 splice-site mutation—broadening the clinical spectrum of this disorder and underscoring the intersection between immune dysregulation and neurotropic viral susceptibility.

At the molecular level, CARMIL2 deficiency disrupts CD28-dependent co-stimulation, leading to impaired T-cell activation, reduced cytokine production, and defective Treg development (3,5). CARMIL2 interacts with actin capping protein and other cytoskeletal regulators, supporting the formation of the immunological synapse and stable antigen-presenting cell (APC) engagement. Consequently, affected individuals exhibit a state of quantitative and functional T-cell deficiency with preserved immunoglobulin levels but limited antiviral control. This immune phenotype predisposes to chronic or severe viral infections, particularly those requiring robust cytotoxic T-cell responses such as herpesviruses and CMV (3,6–8). In addition, epithelial barrier dysfunction, a recurring feature of CARMIL2 deficiency, may facilitate systemic viral dissemination, compounding infection risk.

CMV is an opportunistic pathogen capable of causing CNS disease in neonates and immunocompromised hosts. In pediatric transplant and primary immunodeficiency settings, CMV encephalitis and encephalopathy manifest as altered consciousness, seizures, and radiological evidence of periventricular and white-matter injury (9–13). CNS disease typically results from viral reactivation or dissemination in the context of impaired T-cell–mediated immunity. In this setting, CMV-driven inflammation can extend beyond parenchymal infection to induce vasculitic or vasculopathic complications culminating in cerebral infarction (14–17). While such vascular sequelae have been reported in transplant recipients, their occurrence in a genetically defined primary immunodeficiency, as observed in this patient, is unprecedented. The combination of CMV encephalitis and brain infarction thus represents an expansion of the recognized neurological and infectious phenotype of CARMIL2 deficiency.

Our patient's presentation—fever, encephalopathy, refractory seizures, and radiographic evidence of global cerebral injury—exemplifies the clinical consequences of profound immune dysregulation on CNS viral control. Despite broad-spectrum antimicrobial and antiviral therapy, the disease course progressed rapidly, suggesting that delayed immune-mediated viral clearance, rather than drug resistance, was the principal driver of CNS pathology. The patient's immunologic profile, characterized by lymphopenia with preserved immunoglobulins but deficient T-cell subsets, aligns with prior reports describing defective CD28 signaling and Treg paucity (3,5,7,8). This immune substrate plausibly impaired containment of CMV replication within neural tissue, allowing for both encephalitic inflammation and secondary vascular compromise.

The literature to date includes several case series delineating the immunological and clinical features of CARMIL2 deficiency (1–8,18,19). Schober et al. (3) first described the syndrome, demonstrating defective CD28 signaling and cytoskeletal organization. Subsequent cohorts, including Kolukisa et al. (4) and Ben Arous et al. (7), have expanded the spectrum of manifestations to include mucocutaneous inflammation, dermatitis, EBV-driven lymphoproliferation, and inflammatory bowel disease. However, none have reported CNS infection as a primary feature. Therefore, the current case provides the first documentation of CMV CNS disease in a child with genetically confirmed homozygous CARMIL2 mutation, extending the clinical phenotype to include neuroinvasive viral disease.

Mechanistically, the impaired CD28 co-stimulatory axis in CARMIL2 deficiency compromises both effector T-cell expansion and Treg-mediated regulation. The resultant imbalance may facilitate unrestrained viral replication and exaggerated inflammatory responses within the CNS. In addition, CARMIL2-deficient epithelial and endothelial barriers could contribute to viral penetration of the CNS compartment. Together, these mechanisms provide a biologically coherent explanation for susceptibility to CMV encephalitis and vasculopathy in this context. While the exact pathogenic link between CMV and cerebrovascular injury remains incompletely defined, histopathologic data from CMV-associated vasculitis in pediatric cohorts support endothelial infection, cytokine-mediated vascular injury, and prothrombotic activation as plausible mediators (14–17).

From a clinical standpoint, this case underscores the need for vigilance toward CNS infection in CARMIL2-deficient patients presenting with neurological symptoms. Routine viral surveillance, including plasma CMV PCR during febrile or neurological episodes, should be incorporated into clinical monitoring protocols. Early cerebrospinal fluid analysis and neuroimaging are critical to differentiating infectious from inflammatory etiologies. Empirical initiation of ganciclovir or valganciclovir therapy remains the mainstay of treatment for suspected CMV CNS disease, with escalation to foscarnet or cidofovir in resistant cases (12,20). In severe phenotypes, hematopoietic stem cell transplantation has shown potential for immune reconstitution and restoration of viral control (21). Preventive strategies, including antiviral prophylaxis and vaccination optimization, merit consideration in high-risk pediatric populations with primary T-cell co-stimulatory defects.

In summary, this report delineates a previously unrecognized neurologic manifestation of CARMIL2 deficiency—CMV encephalitis complicated by cerebral infarction—highlighting the critical role of CD28 co-stimulation in neuroimmune defense. The case expands the clinical phenotype of CARMIL2 deficiency and reinforces the importance of early diagnostic vigilance and aggressive antiviral management in children with unexplained encephalitic presentations and underlying immunologic anomalies. Future research should aim to define the prevalence, pathophysiologic mechanisms, and optimal management strategies for viral CNS disease in patients with co-stimulatory pathway defects.

CONCLUSIONS

In children with homozygous CARMIL2 deficiency, cytomegalovirus (CMV) central nervous system (CNS) disease—manifesting as encephalitis, encephalopathy, or brain infarction—represents a critical but underrecognized complication. The present case expands the clinical phenotype of CARMIL2 deficiency to include severe CMV-associated neurological involvement, illustrating how impaired CD28-mediated co-stimulation and defective regulatory T-cell function may permit uncontrolled CMV replication and inflammatory injury within the CNS.

Early recognition of neurologic symptoms in this patient population is essential. Diagnostic vigilance should include cerebrospinal fluid CMV PCR testing and neuroimaging when encephalitic features arise. Prompt antiviral therapy with ganciclovir or valganciclovir, escalation to alternative agents in resistant cases, and multidisciplinary coordination—including infectious disease, neurology, and immunology teams—are critical to optimize outcomes. In select patients with progressive immunodeficiency, hematopoietic stem-cell transplantation (HSCT) offers a potential route to durable immune reconstitution and viral control.

Although reports of CMV CNS disease in CARMIL2-deficient children remain limited, accumulating evidence from broader immunodeficiency and HSCT literature supports a proactive, preventive approach. Continued aggregation of clinical experiences

and systematic research into CARMIL2-related immune dysregulation will be essential to establish diagnostic algorithms, refine antiviral strategies, and elucidate long-term neurological outcomes in this rare but high-risk population.

ETHICS AND CONSENT

Written informed consent for publication was obtained from the patient's legal guardians; the case is presented in a fully de-identified manner.

SUMMARY OF REPORTED CARMIL2 DEFICIENCY CASES

Table 1 summarizes the clinical spectrum of CARMIL2 deficiency reported in the literature from 2016 to 2025, highlighting the diversity of infectious, inflammatory, and dermatologic manifestations across cohorts and individual cases.

Author (Year)	Region	No. of Cases	Age at Presentation (years)	Clinical Manifestations	Notes
Sowte et al., 2016	Europe	4	6–12	Dermatitis, warts, Molluscum contagiosum	Cutaneous viral infections predominant
Wong et al., 2016	Asia	6	5–15	Cutaneous & pulmonary infections, allergy, tuberculosis, fungal infections	Variable immune deficiency severity
Schober et al., 2017	Europe	4	1–5	Epstein–Barr viremia, smooth muscle tumors	EBV-related lymphoproliferation
Anas et al., 2018	Middle East	7	3–10	Eczema, dry dermatitis, skin abscesses	Recurrent staphylococcal infections
Alazami et al., 2018	Saudi Arabia	1	2	Dermatitis, respiratory infection, eczema, allergic rhinitis, bronchopleural fistula	Middle Eastern cohort
Alina et al., 2019	Europe	1	1	Infantile colitis	Severe gastrointestinal phenotype
David K et al., 2019	North America	1	12	Smooth muscle tumors and eosinophilic esophagitis	Late childhood onset
Magg et al., 2019	Europe	1	1.5	Very early-onset inflammatory bowel disease	Severe early-onset immune dysregulation
Rastogi et al., 2021	India	1	8	Refractory infections, lymphopenia; successful HSCT	Improved after HSCT
Kolukısa et al., 2022	Turkey	1	7	Combined immunodeficiency, dermatitis, CMV, EBV infections	Multi-pathogen susceptibility
Vinayagamoorthy et al., 2023	India	1	9	IBD, respiratory infections, oral thrush, dermatitis, warts, pulmonary TB	Broad infectious phenotype
Zhu et al., 2024	China	1	10	CMV meningitis	CNS CMV involvement
Current case, 2025	Saudi Arabia	1	8	Severe CMV encephalitis, encephalopathy, brain infarction	First CNS infarction in CARMIL2 deficiency

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