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A rare presentation of herpes simplex virus encephalitis occurring in a pediatric patient on dupilumab for atopic dermatitis

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Abstract

A 4-year-old female with a history of atopic dermatitis developed herpes simplex virus (HSV) encephalitis while being treated with dupilumab and concomitant topical steroids. There was no prior history of HSV infections or immunodeficiency. To our knowledge, this is the first case of HSV encephalitis in a patient receiving dupilumab.

KEYWORDS
atopic dermatitis, drug reaction, infection- viral

1 | INTRODUCTION

Dupilumab is a monoclonal antibody that targets the IL-4 receptor alpha-chain subunit common to IL-4 and IL-13 receptors. The cytokines IL-4 and IL-13 are integral to the Th2-mediated inflammation pathway, which contributes to pathogenesis of atopic dermatitis. Levels of these cytokines are directly correlated with atopic dermatitis disease activity.[1] Although dupilumab was approved for atopic dermatitis for use in children aged 6–11 in May 2020, it has not yet been approved for use in children under the age of 6. Initial safety data in children and adolescents appear similar to adults, but data are comparatively limited in off-label younger cohorts.[2] Large analyses pooling randomized controlled trial data in adults reveals that severe all-cause infections may be reduced with dupilumab compared to placebo, while non-severe all herpes viral infections are slightly higher in treatment groups.[3] However, the safety of dupilumab in children less than 6 years of age is less understood and limited to small phase 2 studies.

2 | CASE DESCRIPTION

A 4-year-old girl with a history of severe atopic dermatitis treated with dupilumab 9 mg/kg administered subcutaneously every 2 weeks presented with fever and dehydration. Her eczema had been well-controlled with dupilumab for approximately 1 year. Four days prior to presentation, she developed headache, poor oral intake, fever (T_{max} 40.6°C), and difficulty walking, prompting emergency evaluation. Her last dupilumab injection was 2.5 weeks prior to hospital admission. She was febrile (39.6°C) and tachycardic (126 bpm) at presentation and her neurologic status deteriorated rapidly (lethargy and unresponsiveness to verbal stimuli) prompting urgent non-contrast head CT imaging. Her imaging revealed intraparenchymal hemorrhages into the parietal lobe and temporal lobe concerning for herpes simplex virus (HSV) encephalitis, bacterial meningitis, or septic emboli. Therapy with empiric ceftriaxone and acyclovir was initiated promptly and the patient was transferred to a tertiary care hospital. Shortly after transfer, the patient was intubated for airway

protection due to worsening mental status. Polymerase chain reaction (PCR) of the cerebral spinal fluid was positive for HSV-1 supporting the MRI findings of HSV encephalitis with subsequent hemorrhagic transformation. Severity of disease shown on MRI (Figures 1 and 2) prompted continuous video electroencephalography, seizure prophylaxis with levetiracetam and intracerebral pressure (ICP) monitoring. Acyclovir 15 mg/kg every 8 h was continued for 21 days with suppressive dosing for 6 months. Despite seizure prophylaxis, the patient developed seizures requiring levetiracetam titration and the addition of fosphenytoin and lacosamide. Her clinical status improved after several days, allowing for extubation and eventual transfer to a rehabilitation hospital. Following discharge from the rehabilitation hospital, the patient had a significant decline in her normal health. including impairment of activities of daily living (ADLs), ongoing seizures, weakness, hearing deficits, vocalization and mobility deficits, inability to focus, and increased agitation.

3 | DISCUSSION

Over the past few years, treatment options for moderate to severe atopic dermatitis have expanded to include small molecule inhibitors and biologics such as dupilumab. Dupilumab is a monoclonal antibody that inhibits signaling of IL-4 and IL-13, two cytokines integral to the pathogenesis of atopic dermatitis. Dupilumab randomized controlled trials (RCTs) have revealed herpes viral infections as treatment-emergent adverse events in both adult and pediatric atopic populations. Clinically significant herpes viral infections may include herpes zoster, eczema herpeticum, and now, HSV encephalitis.

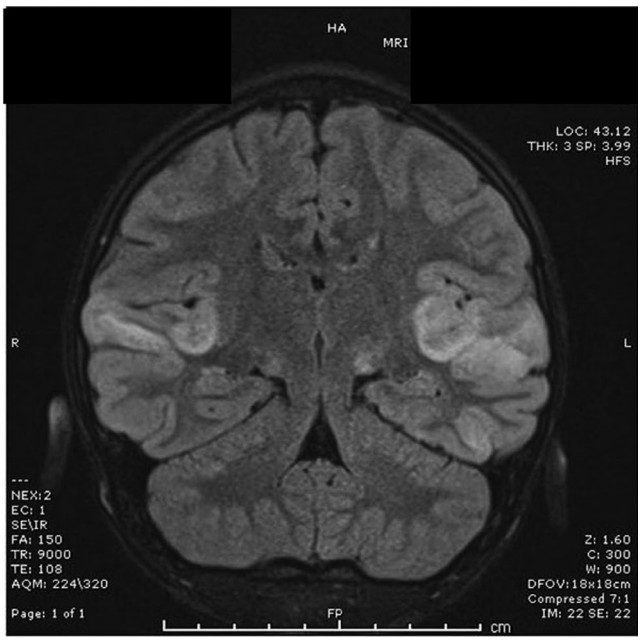

FIGURE 1 Coronal View of MRI: MRI reveals bilateral diffusion restriction and edema associated most extensively within bilateral temporal lobes, frontal and temporal cortices along the sylvian fissures, the left inferior temporal lobe, and bilateral thalami. Perfusion sequences demonstrate hyperemia in the temporal lobes and Sylvian fissures. These findings are most consistent with herpes encephalitis with subsequent hemorrhagic conversion

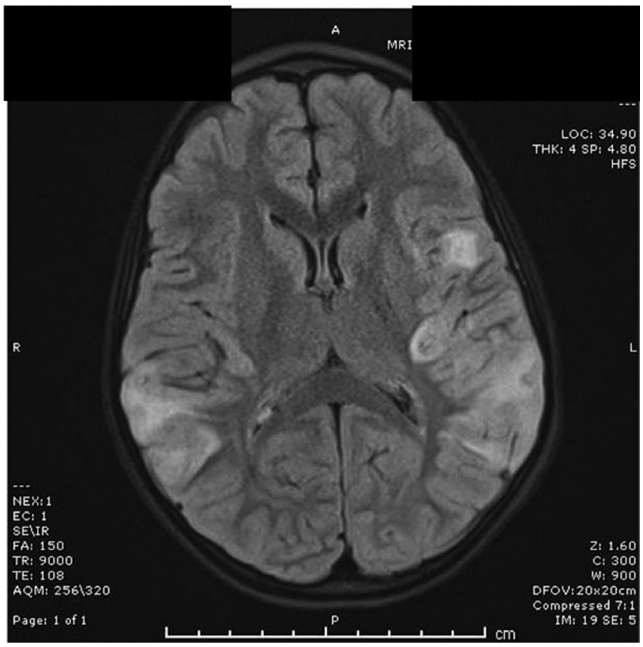

FIGURE 2 Axial View of MRI: MRI reveals regions of diffusion restriction and edema noted along the atria and occipital horns of the lateral ventricles bilaterally, likely revealing intraventricular spread of infection

The complex relationship between herpes viral infections, dupilumab, and atopic dermatitis is still being elucidated. Pooled analyses in adults with moderate to severe atopic dermatitis reveals that the incidence rate of all herpesvirus infection is slightly higher in dupilumab treatment groups compared to placebo; however, the difference is less than 1%. Furthermore, the majority of these infections were mild (herpes labialis), while the incidence of more severe infections (herpes zoster and eczema herpeticum) was higher in the placebo group suggesting uncontrolled atopic dermatitis as a greater risk factor.[3] Lower HSV incidence was also noted in the randomized control trial LIBERTY AD PEDS, which included children aged 6–11 years with atopic dermatitis. Patients were randomized 1:1:1 with placebo and topical corticosteroid (TCS), 300 mg dupilumab every 4 weeks and TCS, or weight-based dosing of 100/200 mg every 2 weeks and TCS. Herpesvirus infection occurred in 5% of the placebo group, in 1.7% of the group receiving dupilumab 300 mg every 4 weeks, and in 3.3% in the group receiving dupilumab 100/200 mg every 2 weeks. Consistent with results from trials in adults and adolescents, herpes viral infection incidence was again lower in groups treated with dupilumab compared to the placebo group.[4] There are little data, however, regarding dupilumab use in children aged 6 months to <6 years. Phase III safety data are yet to be published in this cohort and Phase II trials are limited by design. The LIBERTY AD PRE-SCHOOL is limited by its duration, single dosing, and low power.[5]

Since this is the first case to our knowledge of a patient on dupilumab developing HSV encephalitis, we considered other confounders such as underlying immunodeficiency (inborn error of immunity). However, immunodeficiency was considered unlikely given the lack of prior herpes viral infections and a negative immunology work-up. Immunology workup, including toll-like receptor function, natural killer cell function including CD107a, CD2, CD3, CD4, CD8, and immunoglobulin counts (IgA, IgG, IgM), was within normal laboratory limits. Additionally, we could not explain the severity of her encephalitis. Typical neuroimaging in patients with HSV encephalitis reveals hemorrhage and involvement of temporal lobes and spares the parietal lobes. It is known that immunocompromised patients may have atypical manifestations of HSV encephalitis. Such patients may present with fewer prodromal symptoms and fewer focal deficits. They may also have more extensive involvement of the brain, extending to the cerebellum, brainstem, or atypical regions in the cerebrum leading to higher morbidity and mortality.[6] Our patient's age, previous healthy predisposition, severity of disease, and concurrent use of dupilumab raise concerns that our understanding of dupilumab and its interaction with developing immune systems in children less than 6 years is still incomplete.

We present this case so that providers are exhaustive in their patient education and are aware of rare but salient adverse events. Typically, dupilumab-specific adverse event education focuses on injection site reactions, conjunctivitis, and clinically relevant cutaneous herpes viral infections (HSV and herpes zoster). We recommend educating caregivers on the warning signs of HSV encephalitis in addition to cutaneous herpes infectious signs especially in younger cohorts. We look forward to the growing safety data from dupilumab phase III trials for children 6 months to <6 years and further long-term surveillance as we better understand Th2 immune modification at a young age.

ACKNOWLEDGMENTS

The authors hereby consent to publication of this work.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

CONSENT STATEMENT

Informed consent was obtained from the patient's legal guardian.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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