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Fatal Acute Hemorrhagic Leukoencephalitis Following Immunization Against Human Papillomavirus in a 14-Year-Old Boy

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Abstract

Human papilloma virus (HPV) is a prevalent pathogen whose persistent infection can lead to a variety of cancers. To protect against this threat, an HPV vaccine has been developed and is routinely administered to adolescents. The HPV vaccine has a reassuring safety profile, but reports have emerged of acute disseminated encephalomyelitis following its administration. Acute hemorrhagic leukoencephalitis (AHLE) is a severe inflammatory disease of the central nervous system and the most fulminant form of ADEM. We report a previously healthy 14-year-old boy who developed headache, fatigue, focal weakness, and confusion 3 weeks after receiving the HPV vaccine. Neuroimaging demonstrated multifocal demyelination. Despite treatment with high-dose steroids, his encephalopathy worsened. He developed severe cerebral edema and died of cerebral herniation. Postmortem histology revealed perivenular sleeves of tissue damage, myelin loss surrounding small parenchymal vessels, and diffuse hemorrhagic necrosis, consistent with AHLE. This is the first report of AHLE following HPV vaccination.

Keywords

autoimmune, neuroimmunology, children, encephalitis, neuroimaging

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Human papilloma virus (HPV) infection is common, and the prevalence of high-risk, oncogenic genital HPV infection is 22.7% in American adults.[1] Persistent HPV infection with an oncogenic strain is associated with the development of cervical cancer and a substantial number of anogenital and oropharyngeal cancers. In response to this threat, the Centers for Disease Control and Prevention (CDC) recommends that adolescent boys and girls receive vaccination against HPV as part of their routine immunizations.[2] While the HPV vaccine has a reassuring safety profile,[3] there have been case reports of acute disseminated encephalomyelitis (ADEM) following bivalent and quadrivalent HPV vaccination.[4,5,6,7]

Acute hemorrhagic leukoencephalitis (AHLE) is a rare, frequently fatal central nervous system inflammatory disorder thought to be the most fulminant form of ADEM. While the precise pathogenic mechanism underlying AHLE is unknown, it is an autoimmune process and is often triggered by a preceding respiratory tract infection or vaccination.[8] This report describes the clinical, imaging, and neuropathological features of a 14-year-old boy who developed AHLE leading to severe cerebral edema and death several weeks after receiving the nonavalent HPV vaccine. To our knowledge, this is the first report of AHLE in association with HPV vaccination.

Case Presentation

A 14-year-old boy who was previously healthy developed a persistent headache 3 weeks after receiving the 9-valent human papilloma virus (HPV) vaccine (Gardasil 9 ®, Merck and Co, 0.5 mL intramuscularly). Over the following 2 weeks,

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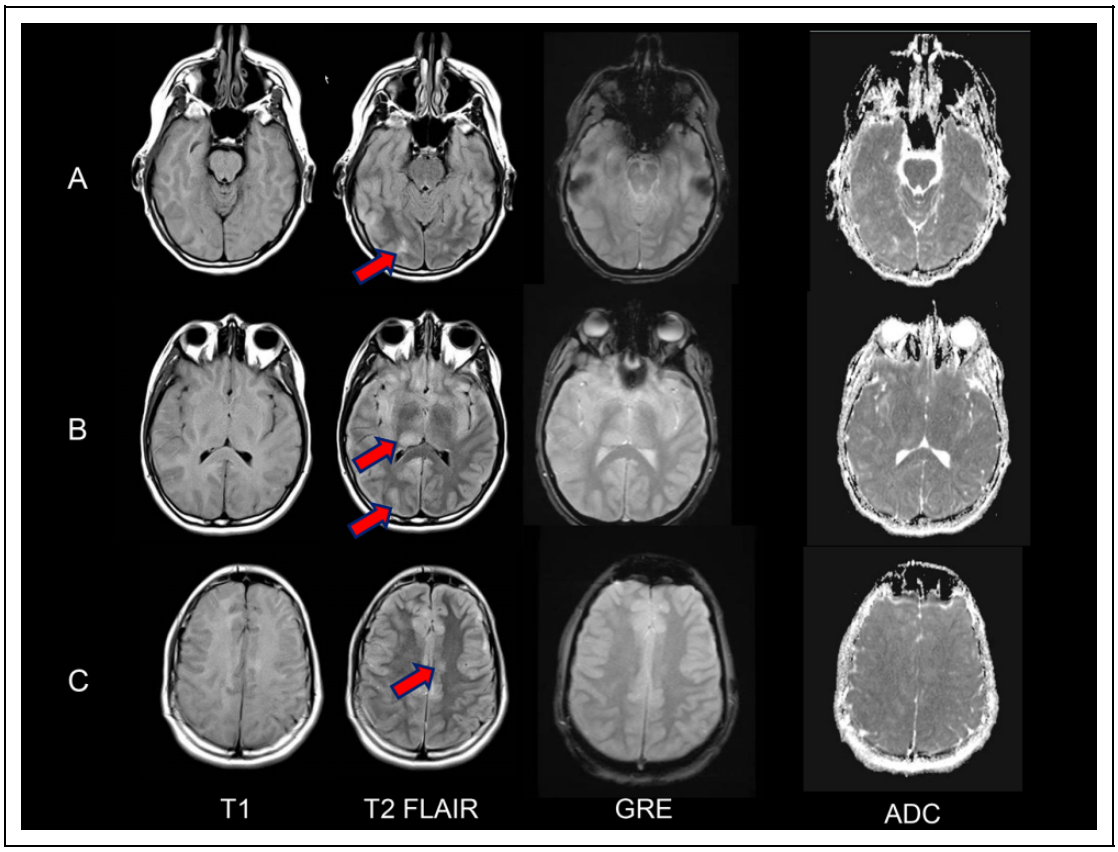

Figure 1. Neuroimaging findings. MRI scan of the brain revealed diffuse signal abnormalities within the subcortical white matter, thalamus, and basal ganglia. T1-weighted, T2 FLAIR, gradient echo sequence, and ADC images at the level of midbrain (A), basal ganglia (B) and centrum semiovale (C). Bilateral asymmetric foci of increased T2-signals are demonstrated (arrows) involving the thickened cortices, thalami, and globus pallidi but sparing the posterior fossa structures (not shown), brainstem or centrum semiovale. Gradient echo sequence images showed no hemorrhagic areas. The areas of T2-prolongation did not show diffusion restriction or contrast enhancement (not shown).

the patient's headache worsened, and he became increasingly fatigued.

On the day of presentation (40 days post-vaccination), he developed left-sided weakness, urinary incontinence, and confusion, which prompted his family to bring him to a local emergency department. There, head CT was normal and labs, including CBC, complete metabolic panel, and urine toxicology screen, were unremarkable. He was then transferred to our tertiary children's hospital for further evaluation and management.

Neurologic exam upon admission was notable for left-sided extremity weakness, tremors of left extremities, and mild confusion. Brain MRI revealed diffuse hyperintensities on T2 and FLAIR sequences within the subcortical white matter, thalamus, and basal ganglia (Figure 1). Cerebrospinal fluid examination showed a lymphocytic pleocytosis with 56 WBC (reference range 0-5), 77% of which were lymphocytes, along with normal protein and glucose. Extensive serologic and nucleic acid amplification testing of his CSF for bacterial and viral pathogens was negative, as were blood cultures. CRP was normal.

Given the combination of his clinical picture, neuroimaging, and laboratory results, the patient was diagnosed with acute disseminated encephalomyelitis (ADEM) and started on treatment with intravenous methylprednisolone, 1 gram daily. Despite this treatment, the patient's encephalopathy worsened, necessitating transfer to the Pediatric Intensive Care Unit (PICU) on the second day of hospitalization. Upon transfer to the PICU, the patient was non-verbal and only intermittently following commands. Exam at the time was notable for left-sided facial weakness, increased tone in the left extremities, bilateral ankle clonus, and left patellar hyperreflexia. After an episode of bilateral shoulder twitching concerning for seizure, continuous video electroencephalogram monitoring was initiated and revealed severe multifocal disturbance of cerebral function, but no epileptiform activity.

On the third day of hospitalization, the patient had a rapid deterioration in his neurologic exam and developed agonal breathing, emesis, tachycardia, and fixed and dilated pupils. Emergent non-contrast head CT showed severe cerebral edema with impending cerebral herniation, for which he was treated with hyperventilation, hypertonic saline and intravenous mannitol. An emergent right hemicraniectomy was performed. Post-operatively, 400 mg/kg of intravenous immunoglobulin (IVIG) daily was added as treatment for ADEM, but the patient had no neurologic recovery. Neurologic exam performed

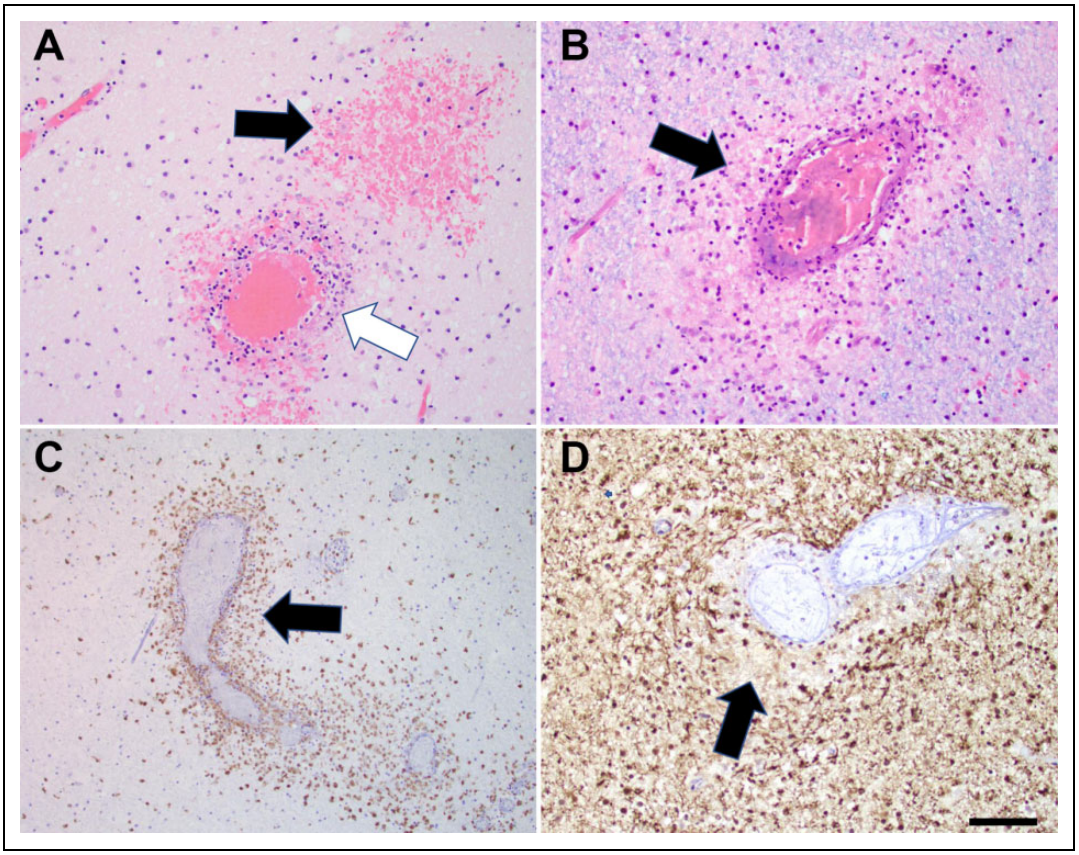

Figure 2. Histopathologic findings from a biopsy specimen of the right parietal lobe. (A) A section stained with H&E revealed that parenchymal vessels were surrounded by a marked mixed inflammatory infiltrate with fibrinoid necrosis (white arrow) and perivascular hemorrhage (black arrow). (B) A section stained with Luxol fast blue and H&E revealed peri-vascular demyelination (arrow). (C) A section immunohistochemically stained for CD68 antigen revealed a marked macrophage infiltrate (arrow). (D) A section immunohistochemically stained for neurofilament revealed patchy axonal loss (arrow).

3 days post-operatively was consistent with brain death. Following the patient's death, the family consented to autopsy.

Neuropathologic examination revealed an acute vascular inflammatory process with fibrinoid vascular necrosis, marked macrophage infiltrates, parenchymal necrosis, numerous hemorrhages, and areas of myelin and axonal loss **(**Figure 2**),** consistent with acute hemorrhagic leukoencephalitis.

Discussion

Acute hemorrhagic leukoencephalitis (AHLE) is a rare, fulminant disease, thought to be the most severe form of the central nervous system demyelinating diseases.[9] A hyperacute subform of acute disseminated encephalomyelitis, AHLE represents only 2% of ADEM cases.[10] ADEM and AHLE both are characterized by multifocal neurologic symptoms, including encephalopathy, along with neuroimaging showing multiple areas of demyelination. Both entities are frequently preceded by an upper respiratory tract infection, viral illness, or vaccination.

While there are numerous similarities between ADEM and AHLE, there are epidemiological, clinical, pathologic, and prognostic differences.[11] The mean age at presentation of ADEM is 5 to 8 years old, while AHLE is most frequently diagnosed in adolescents and young adults. The opening pressure is most often normal in ADEM, while it is often elevated in AHLE. Cerebrospinal fluid white blood cell counts are typically normal to slightly elevated and associated with lymphocytic predominance in patients with ADEM, while the CSF often has a more notable pleocytosis with neutrophilic predominance in AHLE. Patients with AHLE are also more likely to have an elevated ESR and peripheral leukocytosis with neutrophilic predominance, though this was not seen in our patient. Finally, while the mortality rate for ADEM is only 1-3%, death occurred in 66% of patients with AHLE in the only published pediatric case series.[12]

Definitive differentiation of AHLE from ADEM requires a brain biopsy. Histopathology in both disorders includes perivenular sleeves of tissue damage and myelin loss surrounding small parenchymal vessels. However, pathology in AHLE also includes diffuse hemorrhagic necrosis, which is absent in ADEM.[13]

Death from AHLE can occur within hours to days after symptom onset, highlighting the importance of rapid recognition and aggressive treatment. Among recent case reports of pediatric AHLE survivors, use of high dose corticosteroids

(standard therapy for ADEM) was universal. Adjunctive treatments used in case reports of survivors have included administration of IVIG, plasmapheresis, therapeutic hypothermia, decompressive craniectomy, hyperosmolar therapy, and use of interleukin-1 receptor antagonist.

ADEM is a rare disease with an annual incidence of 0.6-0.8 per 100,000 individuals, and an antecedent vaccination is reported in 5-19% of cases.[14] Vaccinations are thought to trigger ADEM through molecular mimicry, wherein certain pathogenic antigens contained in the vaccine share sequence homology with endogenous human CNS proteins, leading to immune cross-reactivity and subsequent autoimmune demyelination. Gardasil 9 is a recombinant vaccine that includes the major capsid (L1) protein of 9 HPV types in highly purified virus-like particles. Sequence homologies between astrocyte water channel aquaporin 4 and several of the HPV L1 capsid proteins have been identified,[15] suggesting that molecular mimicry is a biologically plausible mechanism by which HPV vaccination could trigger demyelinating disease.

It is unclear why some individual patients develop ADEM or AHLE in response to an antigenic stimulus while most do not, but is likely due to differences in genes regulating the immune response. Indeed, ADEM has been associated with several specific major HLA histocompatibility class II alleles.[16] In addition, partial complement factor I (FI) deficiency was identified in 2 pediatric patients with AHLE who were generally healthy prior to presentation. Other genes, besides those regulating the immune response, may also play a role in predisposing individuals to ADEM and AHLE. Mutation of the Ran binding protein (RANBP2) gene, which encodes a protein important for energy homeostasis in neurons, predisposes patients to AHLE.[17]

The HPV vaccine has a reassuring safety profile.[3] The safety of HPV vaccines was extensively investigated pre-release and has been monitored through post-licensure surveillance programs.[18,19] The multiple post-licensure studies, based on information from spontaneous reporting systems, have found no association between demyelinating disease and HPV vaccination.

While the epidemiologic data have failed to show a significant statistical association between HPV vaccination and ADEM or AHLE on a population basis, there have been multiple case reports published describing patients who have developed ADEM in the weeks following HPV vaccination.[4,5,6,7] These case reports strongly suggest that the HPV vaccination played a causal role in the onset of ADEM in the patients described. It is likely that the HPV vaccine can trigger demyelinating CNS disease in genetically susceptible individuals. Further research is needed to elucidate what those specific genetic factors are. Here, we present the first reported case of AHLE following immunization against HPV.

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