Acute Postviral Encephalopathy: Pathologic and Radiologic Correlation in an Atypical Case

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Abstract

The authors report a case of fatal acute encephalopathy following influenza infection, with slightly atypical pathological and imaging findings. A healthy 8-year-old boy with probable recent influenza A/B infection admitted for refractory seizures was placed on phenobarbital coma and later developed hemodynamic instability. Magnetic resonance imaging revealed bilateral cerebral and cerebellar white matter lesions and microhemorrhages. Following his demise, the autopsy revealed a large area of necrosis in the right centrum semiovale with similar lesions in the temporal and cerebellar regions. Microscopically, there was extensive coagulative necrosis, compatible with necrotizing white matter encephalopathy, and neuronal loss suggesting superimposed hypoxic–ischemia. The acute progressive neurologic deterioration was partly reminiscent on acute necrotizing encephalopathy, a condition recently associated with influenza A. In acute necrotizing encephalopathy, typical brain findings are characterized by bilateral thalamic necrosis/petechiae with variable white matter edema. The somewhat atypical findings in our case can relate to superadded cardiovascular collapse and hypoxic–ischemic effects.

Acute postinfectious immune disorders are an uncommon group of pediatric conditions, among which acute disseminated encephalomyelitis and its variants are well described. Acute necrotizing encephalopathy of childhood is a more recently described parainfectious condition, which is now considered different from classic acute disseminated encephalomyelitis. It has been most often associated with influenza infections (most commonly influenza A/H1N1 and A/H3N2), but other viral triggers have also been reported, including herpes virus, enterovirus, rotavirus, and parainfluenza.[1–3] Previously, it was estimated that approximately one-tenth of pediatric patients hospitalized with influenza infections develop neurologic deterioration secondary to encephalopathy/encephalitis and approximately 20% of these children with neurologic presentations develop acute necrotizing encephalopathy, which carries a high morbidity and mortality. In a study conducted in the United States, the incidence of neurologic complications in children with influenza was estimated to be 10%, with simple febrile seizures being the most common presentation and with 1% developing acute necrotizing encephalopathy.[4] In most

reported cases with acute necrotizing encephalopathy, brain imaging demonstrates bilaterally symmetric areas of necrosis and hemorrhage in the thalami, basal ganglia, and occasionally the brain stem, with diffuse or focal areas of abnormality or edema in the cerebral and cerebellar white matter.[5] Postmortem reports have typically described areas of brain edema and necrosis. Vasculopathy with breakdown of the blood–brain

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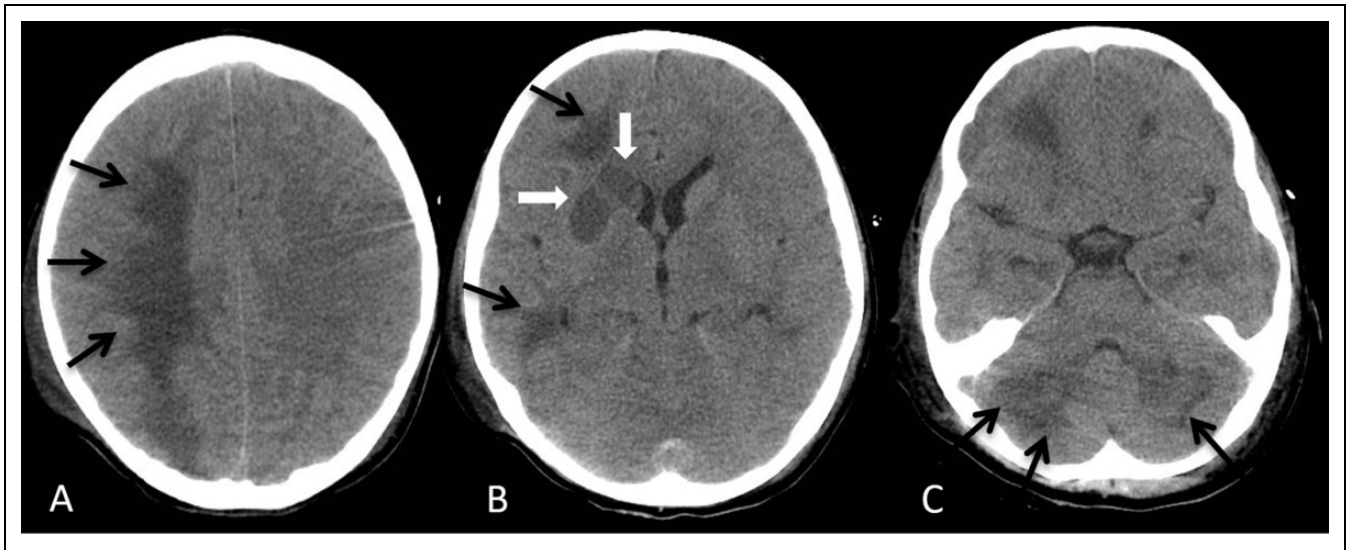
Figure 1. Noncontrast head computed tomography (CT) images. A, Extensive white matter hypodensity in the right centrum semiovale (black arrows). B, Hypodensity in the right caudate head and anterior lentiform nucleus (white arrows) and cerebral white matter (black arrows). C, Patchy hypodensity in the bilateral cerebellar white matter (black arrows).

barrier appears to play a role, but the full pathogenesis of acute necrotizing encephalopathy remains uncertain.

The authors present a case of fatal encephalopathy following influenza infection, which shares some of the clinical aspects of acute necrotizing encephalopathy, but was somewhat atypical in its neuroimaging and neuropathological findings.

Case Report

Hospital Course

The patient was a previously healthy 8-year-old male with reported history of fever for 2 days prior to hospitalization. He was admitted after recurrent generalized tonic–clonic seizures progressed over the course of hours to refractory status epilepticus. On the suspicion that he was having viral encephalitis, a lumbar puncture was performed on the day of admission, which showed slightly elevated cerebrospinal fluid protein of 48.3 mg/dL (normal 15-45 mg/dL) without pleocytosis. A meningoencephalitis panel was positive only for recent or current infection with influenza A/B by antibody enzyme immunoassay. Other routine laboratory testing on admission was normal other than elevations in aspartate transaminase of 406 IU/L (normal 10-40 IU/L) and alanine transaminase of 324 IU/L (normal 7-56 IU/L). The patient was intubated at the time of admission, and pentobarbital and midazolam drips were used to induce electroencephalography suppression, leading to hypotension requiring pressor support. A brain magnetic resonance imaging (MRI) done at this stage of his illness was read as normal, other than gadolinium enhancement of the meninges, consistent with meningoencephalitis. Despite being on high doses of several antiepileptic drugs, his status epilepticus remained refractory to medical treatment. His hemodynamic

instability progressively worsened to the point of cardiovascular collapse, and he was placed on extracorporeal membrane oxygenation. He was being treated with broadspectrum antibiotics for intermittent fevers, a positive sputum culture for *Pseudomonas,* and a posterior scalp ulceration, and there was clinical suspicion for sepsis. When the patient developed dilated pupils and hypertension, computed tomography (CT) and MRI scans of the head were performed, and extensive bilateral brain lesions were seen. Given the refractory nature of his seizures and the severity of his brain damage, the family and medical care team agreed on a decision to withdraw care. The patient died on day 49 of hospitalization. An autopsy was performed on the first day postmortem.

Imaging Studies

The CT head with and without contrast (hospital day 15) showed extensive focal and confluent areas of low density in the cerebellum and right cerebral hemisphere, including the right basal ganglia (Figure 1). Magnetic resonance imaging brain without contrast (hospital day 36) showed diffuse areas of edema and microhemorrhages involving bilateral cerebellar hemispheres, bilateral occipital lobes, right cerebral white matter, right basal ganglia, and left sylvian region. There was mild T2 hyperintensity and suggestion of minimal hemorrhage in both thalami. The findings were nonspecific but suggested possible hypoxia with subsequent hemorrhagic transformation or disseminated intravascular coagulation (DIC); the asymmetric distribution, white matter, and cerebellar involvement were not typical for hypoxic–ischemic injury, which primarily affects the cerebral cortex and deep gray matter structures. The predominant white matter and cerebellar distribution also suggested a possible metabolic abnormality related to the
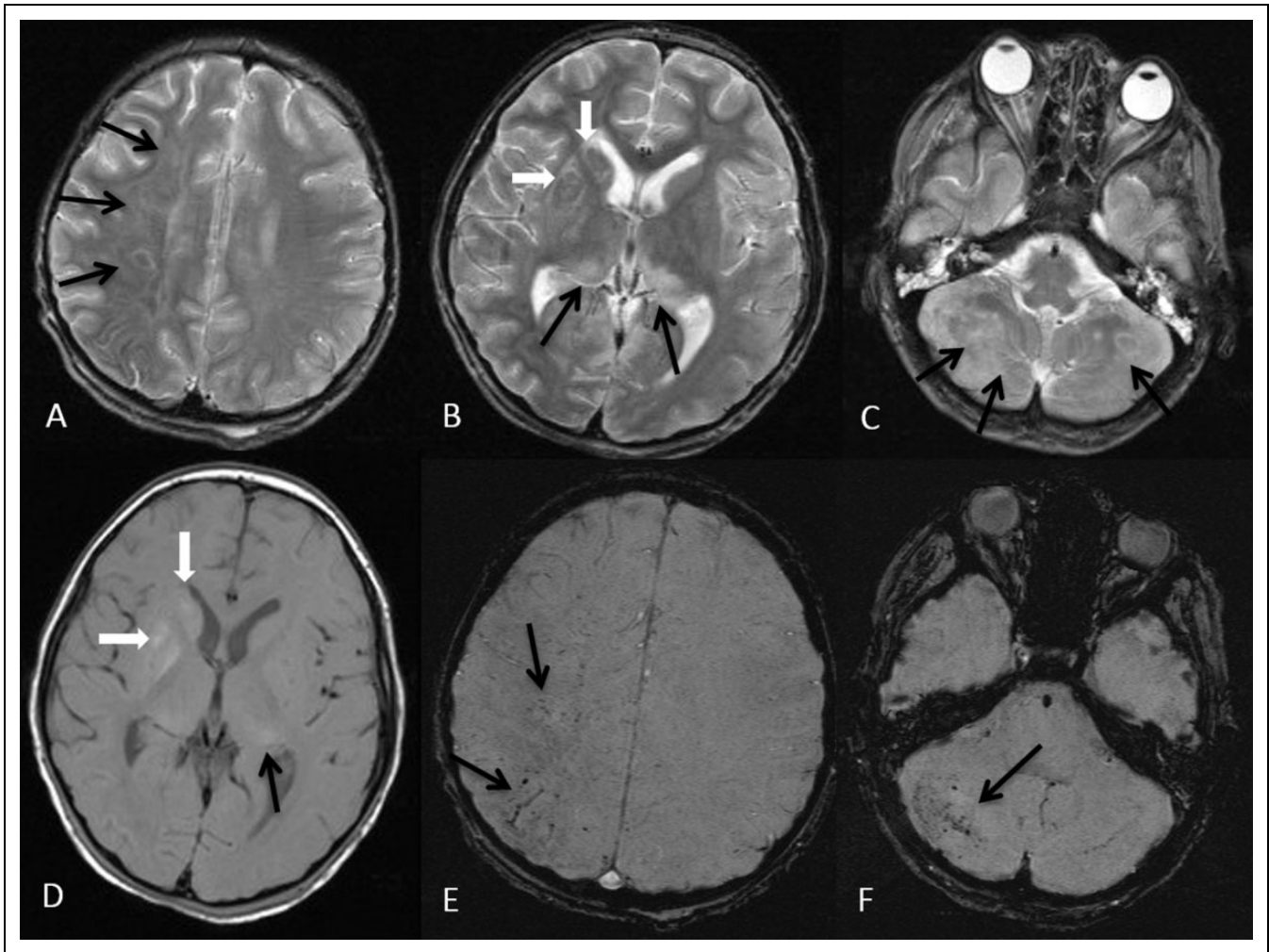
Figure 2. Brain magnetic resonance imaging (MRI). A, T2-weighted axial image showing heterogeneous signal in the right centrum semiovale (black arrows). B, T2-weighted axial image showing patchy T2 hyperintensity in the right basal ganglia (white arrows) and bilateral posterior thalami (black arrows). C, T2-weighted axial image shows bilateral cerebellar patchy T2 hyperintensity (black arrows). D, T1-weighted axial image showing faint hyperintensity in the right basal ganglia (white arrows) and posterior left thalamus (black arrow) consistent with hemorrhage. E and F, Susceptibility weighted images showing scattered hypointensities in the right cerebral hemisphere and bilateral cerebellar hemispheres, right greater than left (black arrows), consistent with petechial hemorrhages.

underlying infection, encephalitis, or autoimmune-mediated reaction (Figure 2). Magnetic resonance spectroscopy (hospital day 36) showed markedly low *N*-acetylaspartate diffusely and a large lactate peak in the mid-occipital gray matter, consistent with hypoxic–ischemic injury.

Autopsy Findings

On gross examination (Figure 3), the brain hemispheres were symmetrical without external or parenchymal hemorrhage or petechiae—the small hemorrhagic lesions noted earlier in the disease course on neuroimaging were not detected and had likely resolved. The leptomeninges were thin and free of exudate, and the cerebral vasculature, including the venous sinuses, was unremarkable and without thrombosis. Sectioning revealed a 2.5-cm-diameter area of yellow necrosis that extended through the right cerebral hemisphere in an almost

continuous lesion approximately 13 cm in length, extending rostrocaudally toward the occipital region. It mostly involved the white matter and extended into the right basal ganglia, obliterating the centrum semiovale. Similar but smaller lesions were seen in the right temporal region and right inferior cerebellar white matter. The thalami were slightly bulging bilaterally.

Microscopic findings of circumscribed, firm, necrotic areas in the right centrum semiovale, basal ganglia, parietal white matter, and cerebellum showed diffuse "glassy" or "mummified" necrosis with prominent central neovascularization and perivascular "rosette-like" infiltrates of plump macrophages (Figure 4A-C). There were prominent perivascular dystrophic calcifications (Figure 4D) arranged peculiarly in linear rows. No striking hemorrhagic lesions were noted. Very little chronic inflammatory response was seen, and essentially no acute inflammation was present. There was no evidence of
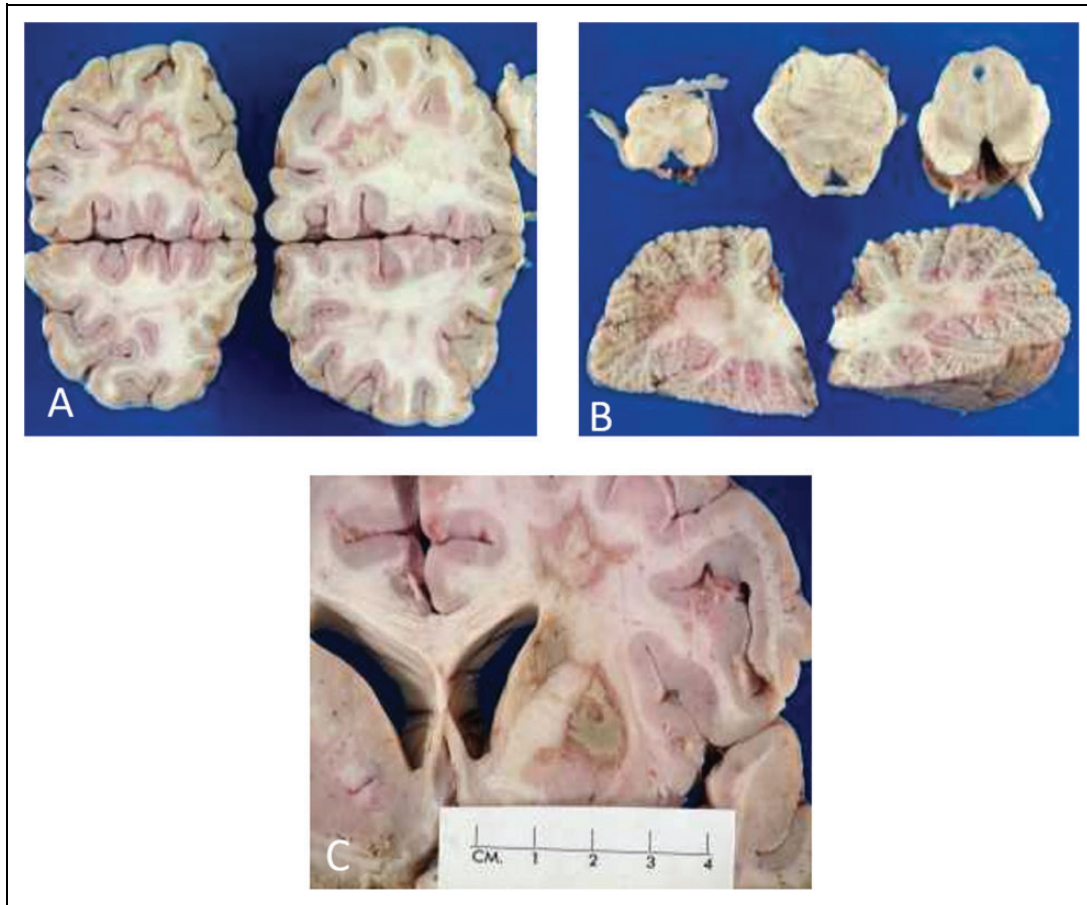
Figure 3. Sections of the brain showing (A) right frontoparietal white matter necrosis; (B) bilateral cerebellar white matter necrosis; and (C) right basal ganglia and thalamus with areas of necrosis.

demyelination or inflammation in perivascular areas or elsewhere in the better preserved white matter. Cavitary lesions typically seen in association with ischemic infarcts were absent. Sections of hippocampi showed decreased numbers of neurons in the cornu amonis 1 (CA1) and proximal CA2 areas with residual neurons displaying changes ranging from ischemia to individual cell necrosis (Figure 5A). The Purkinje cell layer within the cerebellum was almost completely attenuated (Figure 5B). The dentate nuclei showed areas of macrophage infiltration and paucity of neurons. No microorganisms, including fungal elements, were identified on periodic acid-schiff (PAS), Grocott's methenamine silver (GMS), or gram stain in the areas of necrosis.

The multifocal abnormalities were consistent with a form of acute necrotizing encephalopathy, but the pattern of white matter necrosis in the right cerebral hemisphere and cerebellum was not typical, there being only subtle thalamic changes. Changes in the hippocampi and cerebellum suggested superimposed global ischemia.

In addition, examination of the spinal cord revealed subtle "vacuolar" changes in the descending corticospinal tracts, suggesting degenerative axonal pathology (Figure 5C), and sections of the psoas muscle showed diffuse patchy atrophy with a

few admixed hypertrophic fibers (Figure 5D). Type II atrophy is favored due to the lack of "fiber grouping," but an element of denervation effect cannot be excluded, as cryopreserved skeletal muscle was not available for histochemical (enzymatic) confirmation.

Other systemic autopsy findings of significance included a resolving pneumonia with focal pulmonary hemorrhage, bilateral pleural effusions, renal and hepatosplenic enlargements, and thymic atrophy. No ischemic injury of any significance was noted in the major viscera.

Discussion

The authors have presented a unique case of acute postviral encephalopathy with correlative radiologic and autopsy findings, with a view to alerting the medical community of this fatal and somewhat infrequent condition. The conclusion is that an atypical form of acute necrotizing encephalopathy would best explain this presentation, although the authors recognize that more such cases need to be studied before precise terminology is agreed upon. Classic acute necrotizing encephalopathy was first described in 1995 in cases from Japan,[6] where its incidence and mortality appear to remain much higher than
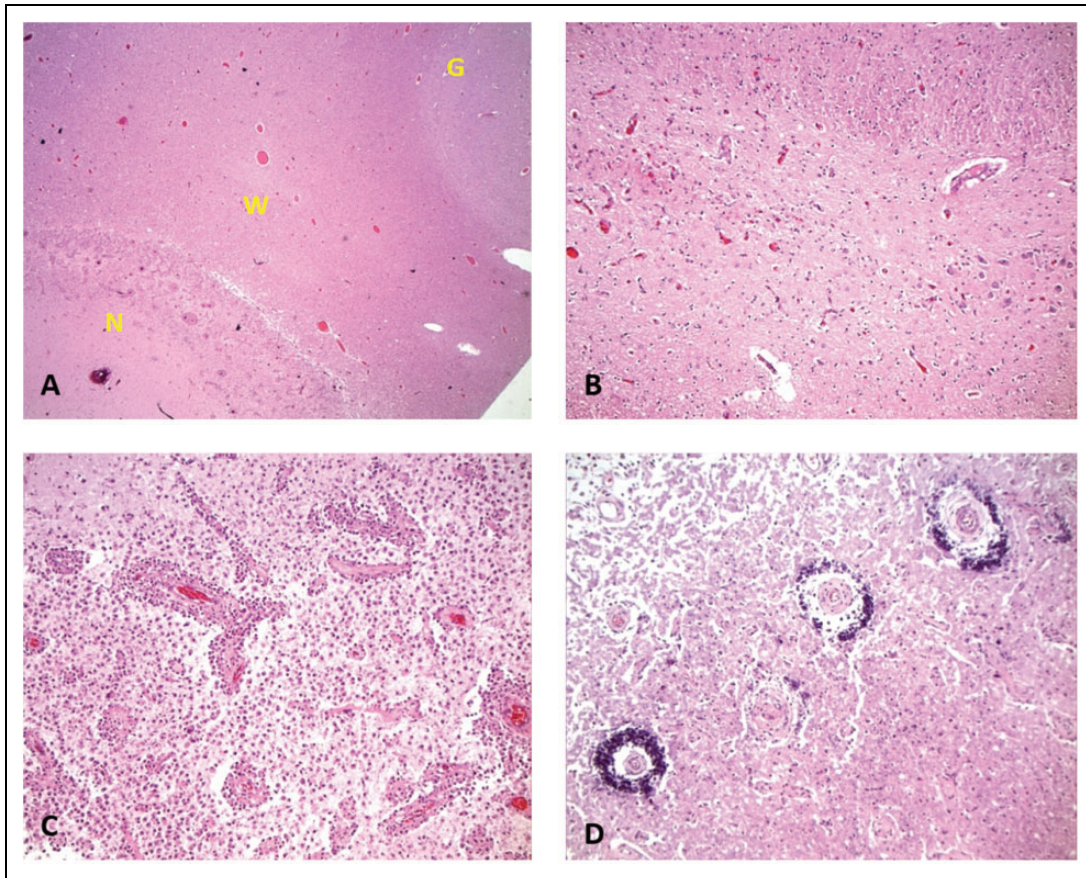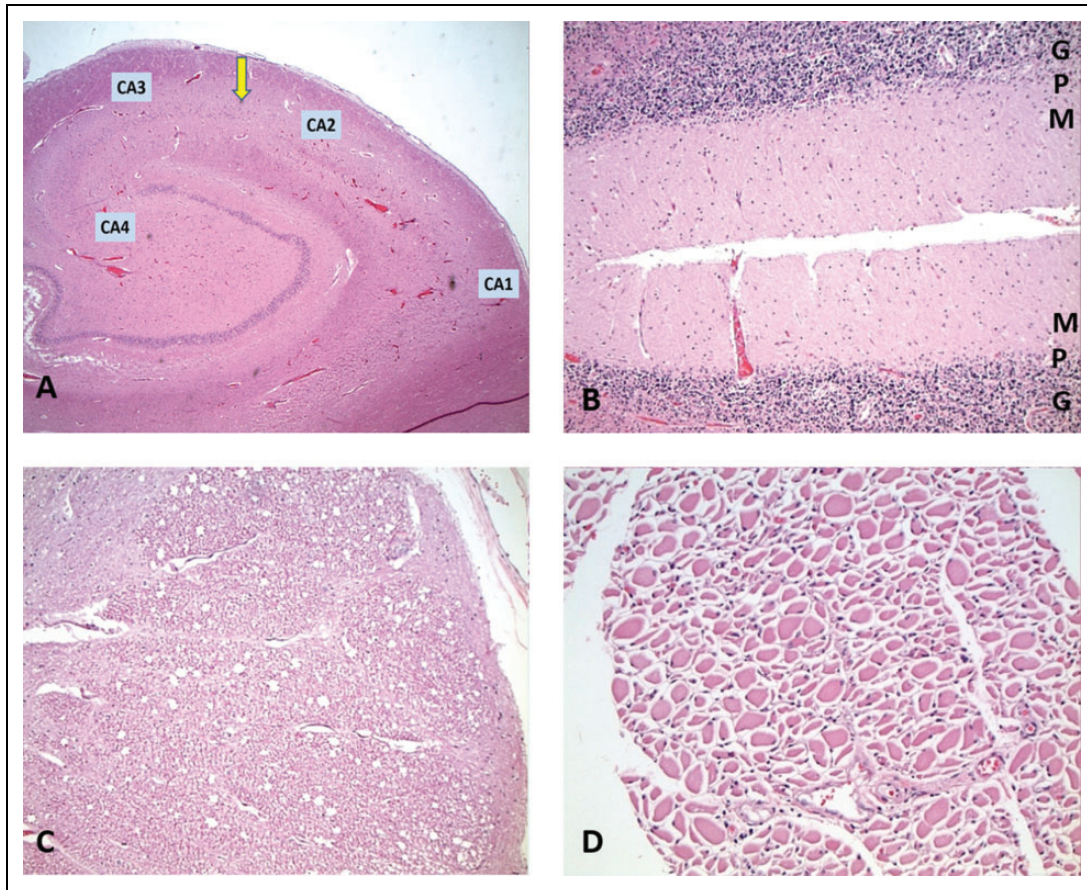
Figure 4. Microscopic images showing (A) abrupt necrosis (N, bottom left) in the white matter (W, middle) and uninvolved cortical gray matter (G, top right; hematoxylin–eosin stain ×40); (B) smooth opaque, "mummified" central necrosis without cavitation and preserved vasculature (hematoxylin–eosin stain ×100); (C) necrosis with peripheral macrophage clustering in an angiocentric fashion (hematoxylin–eosin stain ×100); (D) perivascular calcification—linear rows (hematoxylin–eosin stain × 100).

elsewhere, including the United States.[4] Patients with acute necrotizing encephalopathy present with acute and rapid neurologic deterioration and often intractable seizures preceded by febrile illness. The mortality of acute necrotizing encephalopathy has been as high as 30% in some case series,[6] with severe neurodevelopmental morbidity in most survivors, although some less severe cases have also been described. Recently, acute necrotizing encephalopathy has been most commonly associated with the influenza A (H1N1 and H3N2) outbreaks,[7,8] but it has also been linked to a variety of viral infections, such as herpes virus, varicella zoster, enterovirus, rotavirus, and parainfluenza. Brain imaging and pathological findings are most commonly characterized by bilateral thalamic necrosis and petechial hemorrhage, with variable areas of cerebral and cerebellar white matter edema and congestion, but the literature lacks detailed autopsy studies that address radiologic and neuropathologic correlates of acute postviral encephalopathies in diverse clinical and geographic settings, and this is one of the reasons for documenting this child's brain and systemic findings.

The authors report a case of fatal acute postviral encephalopathy in an 8-year-old male with influenza infection. His imaging and pathological findings are somewhat atypical, with asymmetric prominent necrotic lesions in the cerebral white matter and basal ganglia as well as bilateral cerebellar white matter and only mild involvement of the thalami. Although some of the smaller cortical and subcortical lesions can represent the findings of superimposed hypoxic injury (which was also correlated by magnetic resonance spectroscopy), the large, noncavitating, white matter lesions were believed to be areas of necrosis, consistent with a form of acute necrotizing encephalopathy. There was no evidence of demyelination or inflammation in perivascular areas, or elsewhere in the better preserved parts of white matter, to suggest evolving acute disseminated encephalomyelitis-like changes nor was there evidence of the cavitary lesions typically seen with ischemic infarcts. Mild ischemic overlay may have been present, given the clinical course, and is difficult to exclude, but it is noteworthy that the systemic autopsy findings did not reveal significant ischemic injury in other organ systems (as has been reported in some instances of acute necrotizing encephalopathy[9]). The patient's prolonged refractory status epilepticus, respiratory failure, and cardiovascular collapse likely contributed to vasculopathy and hypoxemia. This can help to explain the atypical pathological

Figure 5. Microscopic images showing (A) hippocampus—massive neuronal loss within the CA1 and proximal CA2 regions (arrow approximately at the CA2/3 interface with neuronal losses and reactive vascular prominence to the right and viable CA3 neurons to the left of arrow; hematoxylin–eosin stain ×20 [inset ×40]); (B) cerebellum—selective, extensive Purkinje cell loss (hematoxylin–eosin stain ×100; M, molecular layer; P, Purkinje cell layer; G, [internal] granule cell layer); (C) spinal cord with myelin pallor, vacuolation, and fiber loss in the lateral corticospinal tract (hematoxylin–eosin stain ×100); (D) skeletal muscle with extensive atrophy (hematoxylin–eosin stain ×100).

findings in this case, which share some features of hypoxic–ischemic encephalopathy. The changes seen in the spinal cord and skeletal muscle may or may not be related to the encephalopathy, and this will ultimately be established through more detailed reporting from other cases.

From a clinical viewpoint, our patient is slightly older than average but within the range of reported ages for acute necrotizing encephalopathy. Our patient's initial blood tests did reveal transaminitis prior to his hemodynamic collapse, and this "hepatic dysfunction" is a finding that has been reported to be variably present in acute necrotizing encephalopathy.[9,10] Also typical for the diagnosis of acute necrotizing encephalopathy was our patient's cerebrospinal fluid analysis showing elevated protein without pleocytosis.[9,10]

Breakdown of the blood–brain barrier secondary to accumulation of cytokines has been proposed as the underlying pathogenesis of acute necrotizing encephalopathy and is likely related to the accompanying vasculitis and hypoxic injury.[11] In addition, the effects of cytokines and macrophage activation causing widespread endothelial damage can also contribute to the systemic response often associated with acute necrotizing

encephalopathy, including cardiovascular collapse and respiratory and renal failure.

Recent studies have established a genetic link between acute necrotizing encephalopathy and an autosomal-dominant mutation of the gene for the protein RAN-binding protein 2. A few familial cases have been described, in which multiple siblings with this mutation have developed acute necrotizing encephalopathy following a nonspecific viral illness.[10,12] Patients with the genetic susceptibility have also been shown to have atypical, recurrent acute necrotizing encephalopathy.[13] Familial cases appear to have a somewhat milder disease course, but this may be due in part to early diagnosis and aggressive treatment.

So far, early therapeutic intervention with high-dose intravenous corticosteroids and intravenous immunoglobulin has been associated with better outcomes compared to supportive therapy alone in patients with acute necrotizing encephalopathy.[14] More recently, brain cooling therapy has also been used with the suggestion of positive results, as it is now considered one of the treatment methods in acute encephalopathy.[15] However, in most nonfamilial cases, the diagnosis of acute

necrotizing encephalopathy is made only late in the disease course, after extensive brain injury is apparent on imaging studies and when a good response to the treatment is less likely. The typical imaging findings of acute necrotizing encephalopathy, bilateral thalamic lesions with microhemorrhages and edema, are the most likely sign to prompt consideration of the diagnosis. Our case had an atypical distribution of lesions, with primarily cerebral and cerebellar white matter necrosis and only mild thalamic involvement, confirmed by autopsy findings. The totality of the imaging findings, medical history, clinical presentation, and pathology encouraged the authors to favor an atypical form of acute necrotizing encephalopathy as the possible diagnosis, although the authors recognize that other differentials may also be in consideration.

In conclusion, typical acute necrotizing encephalopathy still remains a rare but extremely serious complication of acute viral illness in children that is likely more common in certain geographic areas and in genetically susceptible individuals. However, atypical forms, such as the case presented earlier, do exist, and their presentation and outcome can vary, depending on the clinical circumstances. Whether such acute postviral encephalopathies are best categorized as acute necrotizing encephalopathy or a form of hypoxic–ischemic encephalopathy, the authors would like to emphasize that early recognition of the clinical syndrome, its neurologic effects, and potentially fatal complications are critical to save lives. The authors hope that awareness of such atypical presentations will encourage clinicians, radiologists, and pathologists to document more cases of postviral encephalopathies. As more cases are investigated and reported, the authors can hope to see improvements in earlier diagnosis, further elucidation of the pathogenesis, and better treatment outcomes.

Author Contributions

AA wrote the main draft and compiled the clinical, radiological, and pathological data. DM provided clinical information and edited the manuscript. LL aided in gathering the pathological and clinical information. LD assisted in performing the autopsy, brain cutting, preparing illustrations, and pathological interpretation. KO supervised the autopsy examination and pathological interpretations. RR contributed equally to the work; interpreted the neuropathological findings, coauthored and edited the manuscript, and provided support for the project.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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