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# A 12-Year-Old Girl With Encephalopathy and Acute Flaccid Paralysis: A Neuropathological Correlation and Cohort Review

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## Patient Presentation

This 12-year-old girl with a history of mild intermittent asthma presented with five days of fever to 104.2°F, which was initially without associated symptoms but was followed by acute onset headache, neck stiffness, and lethargy on the day of presentation. The patient was evaluated in the emergency department and underwent a lumbar puncture that revealed lymphocytic pleocytosis and increased protein concentrations in her cerebrospinal fluid (CSF) (Table 1). She was admitted to the inpatient ward for presumed viral meningitis and underwent empiric broad-spectrum antimicrobial treatment.

Her condition worsened over the next five days to include progressive encephalopathy associated with acutely developing tachycardia, tachypnea, tremor, and bowel incontinence, leading to endotracheal intubation for airway protection. She concurrently developed fulminant heart failure and required extracorporeal membrane oxygenation for ten days. Despite return of normal heart function and discontinuation of sedatives over the following week, she remained severely encephalopathic with flaccid paralysis and areflexia.

A brain magnetic resonance imaging (obtained two weeks after presentation) showed diffuse patchy T2 signal abnormalities throughout the brain and cerebellum involving both the gray and white matter, including the deep gray nuclei. The entire spinal cord was also affected, with predominant involvement of the anterior cervical cord (Fig 1). Repeat CSF analysis showed persistent lymphocytic pleocytosis and increased protein concentrations. A broad evaluation for infection and markers of autoimmunity were nondiagnostic (Table 1).

Given the severity of her deficits and evidence of inflammation in her CSF, empirical immunomodulatory therapy was initiated with five cycles of plasmapheresis and 2 g/kg of intravenous immunoglobulin (IVIg) to treat a possible immune-mediated process. There was no appreciable short-term treatment response. Another magnetic resonance imaging (five weeks after presentation) revealed dramatic evolution of the signal abnormalities with the emergence of T1 signal voids throughout the neuraxis and profound brain and spinal cord atrophy (Fig 1). Electromyography and nerve conduction study showed diffusely small to absent compound muscle action potentials and normal sensory nerve action potentials. The patient then underwent a frontal lobe brain biopsy after which she received additional immunomodulatory therapy with methylprednisolone (5 g total), plasmapheresis (five cycles), and IVIg (2 g/kg).

## Differential diagnosis

This girl presented with acute-onset meningoencephalitis, myocarditis, and generalized flaccid paralysis. The neurological localization suggested diffuse involvement of the both cerebral hemispheres (leading to encephalopathy) as well as the lower motor neurons (leading to flaccid paralysis), although flaccid paralysis may be secondary to severe encephalopathy alone in the acute phase. The presence of myocarditis further suggested a diffuse or multifocal process. Furthermore, the constellation of high

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**TABLE 1.**
Summary of Diagnostic Studies

| | |
|---|---|
| CSF profile (at the onset of neurological symptoms) | 191 total cells (per μL), 185 nucleated cells (5% neutrophils, 71% lymphocytes, 24% monocytes), glucose 65 mg/dL, protein 119.9 mg/dL |
| Repeat CSF profile (16 days after the onset of neurological symptoms) | 97 total cells, 59 nucleated (1% neutrophils, 92% lymphocytes, 5% monocytes, 2% macrophages), glucose 82, protein 58.1 |
| Infectious studies (not including routine bacterial, fungal, and AFB cultures) (all negative) | *Brain tissue: PCR—enterovirus, JC virus, Ehrlichia, Bartonella, Mycoplasma, parechovirus, FilmArray, HSV, EBV, HHV-6, HHV-7, EV-D68*<br>*CSF: enterovirus, parechovirus, Toxoplasma, HSV, EBV, CMV, VZV, HHV-6, Mycoplasma, EV-D68. Antigen: Cryptococcus. Antibody: arboviruses, measles IgM (IgG positive), VDRL*<br>*Blood/serum: PCR—HIV, enterovirus, adenovirus, HSV, EBV, CMV, VZV, HHV-6, parvovirus, Ehrlichia, EV-D68. Antibodies: arboviruses, EBV, CMV, HIV, LCMV, mumps, Coxiella, RMSF, RPR. Antigen: HIV p24, Quantiferon*<br>*Nasopharyngeal: PCR—influenza, RSV, FilmArray, Mycoplasma, EV-D68*<br>*Stool: PCR—enterovirus, EV-D68* |
| Autoimmune markers (all negative) | Oligoclonal bands (0), CSF and serum paraneoplastic panel, serum NMDA-R Ab, serum NMO IgG, ANA, ANCA, ENA, C3, C4, thyroglobulin Ab |
| Imaging (16 days after the onset of neurological symptoms)—see Fig 1. | Diffuse and patchy diffusion-restriction and T2 hyperintensities throughout brain, brainstem, and whole spine (with anterior cervical cord predominance) and subtle leptomeningeal enhancement |
| Imaging (36 days after the onset of neurological symptoms)—see Fig 1. | Multifocal T1 hypointensities throughout brain, brainstem, and whole spine with profound brain and spine atrophy |
| Echocardiogram (6 days after the onset of neurological symptoms) | Normal segmental anatomy, moderate dilatation of left ventricle, severe decreased systolic function of left ventricle, small pericardial effusion |
| EMG/NCS | Diffusely small to absent CMAPs, normal SNAPs |

Abbreviations:
AFB = Acid-fast bacilli
ANA = Antinuclear antibody
ANCA = Antineutrophil cytoplasmic antibody
CMAP = Compound muscle action potentials
CMV = Cytomegalovirus
CSF = Cerebrospinal fluid
EBV = Epstein-Barr virus
EMG/NCS = Electromyogram/nerve conduction study
ENA = Extractable nuclear antigens
EV-D68 = Enterovirus D68
HHV = Human herpes virus
HIV = Human immunodeficiency virus
HSV = Herpes simplex virus
IgG = Immunoglobulin G
JC = John Cunningham
LCMV = Lymphocytic choriomeningitis virus
NMDA = *N*-methyl-D-aspartate
NMO = Neuromyelitis optica
PCR = Polymerase chain reaction
RMSF = Rocky Mountain spotted fever
RPR = Rapid plasma reagin
RSV = Respiratory syncytial virus
SNAP = Sensory nerve action potential
VDRL = Venereal disease research laboratory
VZV = Varicella zoster virus

fever and CSF pleocytosis indicated either an infectious or a parainfectious, immune-mediated process.

Important considerations among infectious diseases included treatable neuroinvasive disease such as herpes simplex virus encephalitis and varicella zoster virus vasculitis, which prompted antiviral treatment with acyclovir initially.[1] Arboviral infections, such as West Nile virus, were a consideration given the presence of meningitis, encephalitis, and acute flaccid paralysis (AFP). Arboviral infections are also known to rarely cause myocarditis.[2,3] Non-polio enterovirus (likewise, parechovirus) encephalitis was also a consideration, especially in light of concurrent myocarditis.[4] The patient presented in the late summer of 2014 at the peak of the enterovirus D68 (EV-D68) respiratory outbreak when acute flaccid myelitis (AFM) became recognized as a clinical syndrome. She met the case definition for AFM that was later announced in November 2014 by the Centers for Disease Control (CDC) along with two other patients, who presented with more typical features of AFM within a ten-day period. Table 2 summarizes AFM cases presenting to St. Louis Children's Hospital during and preceding the 2014 EV-D68 outbreak.[5]

Another consideration was acute disseminated encephalomyelitis (ADEM), but the prominence of persistent lower motor neuron signs and myocarditis was atypical.[6] A variant of acute inflammatory demyelinating polyradiculoneuropathy, i.e., Miller-Fisher or Bickerstaff variant, was also considered.[7] Evaluation of specific autoantibodies was nondiagnostic. Primary or secondary central nervous system vasculitis was also considered, which contributed to the decision to biopsy. Hopkins syndrome describes a polio-like syndrome occurring after an asthma