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Postinfectious Encephalopathy in a Child following *Campylobacter jejuni* Enteritis

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Summary: We report a case of acute postinfectious encephalopathy in a child following *Campylobacter jejuni* enteritis. Serial MR scans showed lesions involving predominantly gray matter and the adjacent subcortical white matter—findings different from those in other immune-mediated disorders, such as systemic lupus erythematosus, in which either white or gray matter may be involved, and acute disseminated encephalomyelitis, in which white matter abnormalities predominate with involvement of the subcortical white matter.

Index terms: Magnetic resonance, in infants and children; Brain, diseases; Pediatric neuroradiology

The *Campylobacter* species of bacteria has become a well-known group of infectious agents. It is now recognized that *Campylobacter jejuni* is a leading cause of diarrheal illness, both in developing and industrialized countries around the world. While *C jejuni* enteritis is generally benign and self-limited, complications can arise, including bacteremia, vasculitis, arthritis, and septic abortions (1, 2). Infection and the inflammatory response to infection can lead to neurologic complications, including meningitis, stroke, empyema, encephalopathy (3), and Guillain-Barré syndrome and its variants (4). *C jejuni* enteritis leading to postinfectious encephalopathy is an unusual complication.

Postinfectious encephalomyelitis is an acute, inflammatory, demyelinating disease of the central nervous system (CNS) which occurs most commonly in childhood, but is occasionally seen in adults. The clinical onset is usually 5 days to 2 weeks after a nonspecific upper respiratory infection, viral illness, or vaccination, but is not specific to these events and has been reported following bacterial infections and drug and serum administrations (5). The terms acute disseminated

encephalomyelitis (ADEM), acute demyelinating encephalomyelitis, and perivascular myelinolysis are names coined to describe the pathologic features and probably refer to the same disorder (5). We will describe the magnetic resonance (MR) findings in a young child in whom acute encephalopathy developed due to immune complex-mediated vascular injury largely confined to the gray matter and the immediate subcortical white matter following *C jejuni* enteritis. In this case, the antecedent infection was well documented and the subsequent encephalopathy was extensively studied by cultures, serum and cerebrospinal fluid (CSF) serologies, brain biopsy, and serial MR scans.

Case Report

A 4-year-old white girl with a history of cerebral palsy since birth was admitted to the hospital for left-sided partial complex seizures which began 2 to 3 days after a diarrheal illness characterized by a fever of 101°F and abdominal discomfort. Stool cultures revealed numerous leukocytes and heavy growth of *C jejuni*. Treatment with erythromycin resulted in prompt resolution of her enteritis; her seizures were controlled with dilantin and phenobarbital therapy. An MR scan showed increased signal in the right posterior frontoparietal region (Figs. 1A and 1B). She was dismissed after 7 days with no fever, diarrhea, or seizures.

The patient was readmitted 10 days later with a fever of 103°F, skin rash over the lower abdominal wall, palmar and plantar erythema, and new onset of seizures involving the entire right side and left arm and face. Positive laboratory studies included erythrocyte sedimentation rate (ESR) of 150 mm/hour, elevated liver enzymes, antinuclear antibody (ANA) titer (1:320) with a diffuse pattern, antismooth muscle antibody (1:80), and C-reactive protein (5.7). Negative studies included normal CSF, and negative cultures for bacteria, fungus, and multiple viruses. Immunoelectro-

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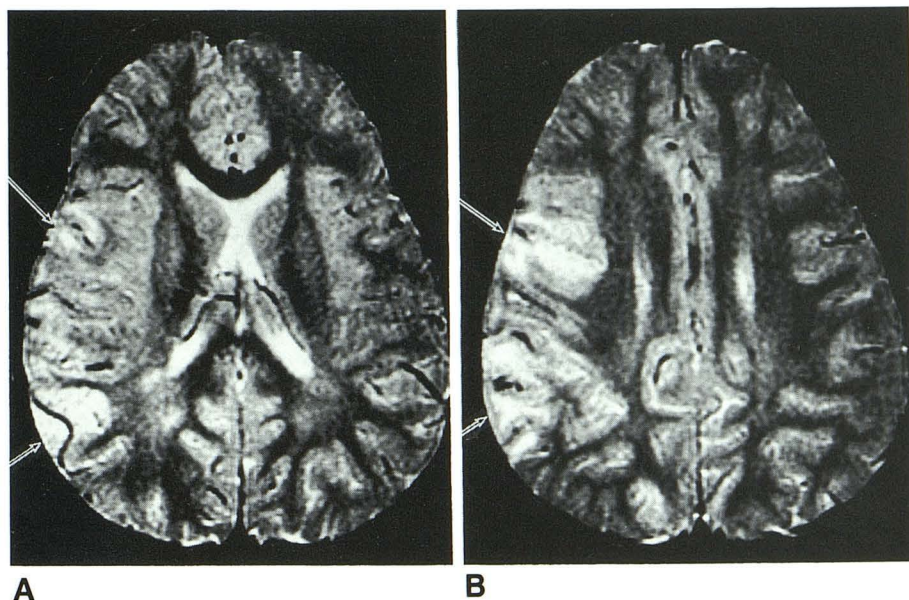


Fig. 1. MR images for the first hospital admission.

A and B, Axial T2-weighted images (2500/80; TR/TE) from the first hospital admission showing large areas of involvement in the right posterior frontoparietal lobe and immediate subcortical white matter (arrows).

phoresis of the CSF showed no oligoclonal bands, and no increase of the CSF immunoglobulin G antibodies was seen. A repeat MR scan on day 2 of the second admission (Figs. 2A-2D) showed regression: previous generalized areas of increased signal on T2 images seen in the right posterior frontoparietal lobe in the first scan had become three smaller, separate areas of increased signal involving the gyri. In addition, new areas of increased T2 signal were present diffusely throughout the gray matter in the left frontal, parietal, and occipital lobes. Gd-DTPA produced no enhancement of the brain parenchyma, although there was pial and dural enhancement.

On the basis of the fever, skin rash, positive ANA, and acute phase reactants, the patient was thought to have an infectious or immune-related inflammatory process involving the central nervous system. Empiric treatment with gancyclovir was initiated on the supposition the encephalopathy could be secondary to herpes group (cytomegalovirus and herpes simplex virus) virus invasion of the CNS. A brain biopsy on day 5 showed evidence of vasculopathy characterized by involvement of the gray matter, reactive gliosis, extensive spongiosis, and blood vessels showing scattered lymphocytes and hemosiderin-laden macrophages in the perivascular space (Fig. 3). Perivascular cuffing and viral inclusions typically seen in viral encephalitis were not present. No microorganisms or granulomatous reactions were seen on special stains. Electron microscopy showed cerebral edema and electron-dense deposits in the basement membranes of blood vessels, consistent with immune complex deposition (Fig. 4). No viral particles were seen in nuclei or cytoplasm. After the brain biopsy and negative culture results were obtained, gancyclovir was discontinued and methylprednisolone therapy (350 mg intravenously daily) was initiated. The patient also received high dose (200 mg/kg) intravenous immunoglobulin for 5 days. Her fever improved dramatically, and the seizure activity, which previously had been refractory to aggressive anticonvulsant therapy, rapidly came

under control. The ESR fell quickly to 24 mm/hour, and her rash resolved. An MR scan on day 10 of the second admission showed persistent signal abnormalities on the left side, especially involving the left occipital lobe (Fig. 5). At that time, the ESR was 10 mm/hour and the ANA was negative. Prednisone was gradually discontinued over 6 weeks.

Discussion

C jejuni is a ubiquitous bacterial pathogen that is known to be a leading cause of diarrheal illness. The number of isolates of *C jejuni* in the United Kingdom, mostly from patients with diarrhea, exceeded the number of reported isolates of *Shigella* and approached the number of *Salmonella*. Studies from the United States and Europe of patients with diarrhea found *C jejuni* isolated in 4.3% to 13.9% (6). While *C jejuni* enteritis is generally a benign, self-limited infection that can be easily treated with erythromycin, some strains are invasive, with 20% to 30% of patients having a dysenteric type of diarrhea with inflammatory cells and blood in the stool (7). This invasiveness can account for the occasional septicemia, bacteremia, and rare cases of meningitis. Dysfunctional host immune response to *C jejuni* has been implicated in a number of CNS syndromes. *C jejuni* enteritis has been shown to precede the onset of Guillain-Barré syndrome by 1 to 3 weeks in 38% of patients in one study. Those patients with serologic evidence of antecedent *C jejuni* infection are thought to manifest a more severe form of Guillain-Barré syndrome (8). Variants of Guillain-Barré syndrome, such as cases with pri-

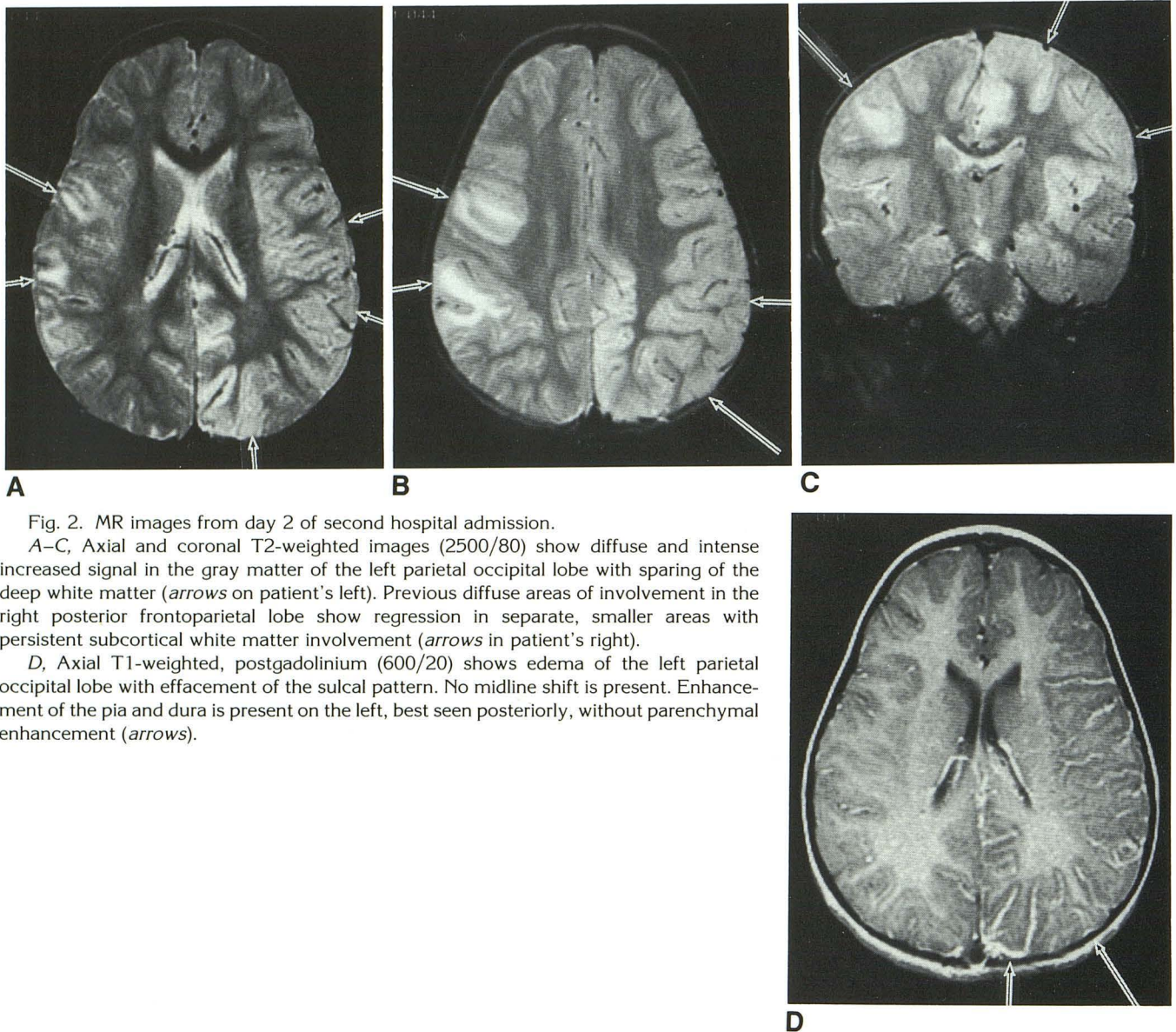


Fig. 2. MR images from day 2 of second hospital admission.

A–C, Axial and coronal T2-weighted images (2500/80) show diffuse and intense increased signal in the gray matter of the left parietal occipital lobe with sparing of the deep white matter (arrows on patient's left). Previous diffuse areas of involvement in the right posterior frontoparietal lobe show regression in separate, smaller areas with persistent subcortical white matter involvement (arrows in patient's right).

D, Axial T1-weighted, postgadolinium (600/20) shows edema of the left parietal occipital lobe with effacement of the sulcal pattern. No midline shift is present. Enhancement of the pia and dura is present on the left, best seen posteriorly, without parenchymal enhancement (arrows).

marily cranial nerve involvement, have been reported following *C jejuni* enteritis (9), as have several cases of Miller-Fisher syndrome, a rare variant of Guillain-Barré syndrome consisting of ophthalmoplegia, ataxia, and areflexia (4, 10). Cross-reactivity between an antigen from *C jejuni* and the body's own proteins and lipids has been theorized as a possible pathophysiologic mechanism by which these syndromes can arise. Although cross-reactivity between nerve proteins and *C jejuni* has not been firmly established, antibodies against GM1 gangliosides (11) and acidic glycolipids have been demonstrated (12).

This patient had documented heavy growth of *C jejuni* on stool culture, with neurologic symptoms beginning several days after the onset of

gastrointestinal symptoms. On subsequent readmission, she had clinical evidence of a systemic inflammatory process manifested by the previously described skin rash, new onset seizures, + ANA, and elevated ESR. The brain biopsy showed histologic evidence of a vasculitis with immune complex deposition in the blood vessel walls. Other possible causes for the patient's encephalopathy were eliminated by culture and histologic findings. The complete clinical resolution of this process with a short course of immunomodulating, antiinflammatory therapy suggests that the patient had a severe immune reaction to a clearable antigen consistent with *C jejuni*, resulting in an immune complex encephalopathy. Immune complex deposition in blood vessels was seen in

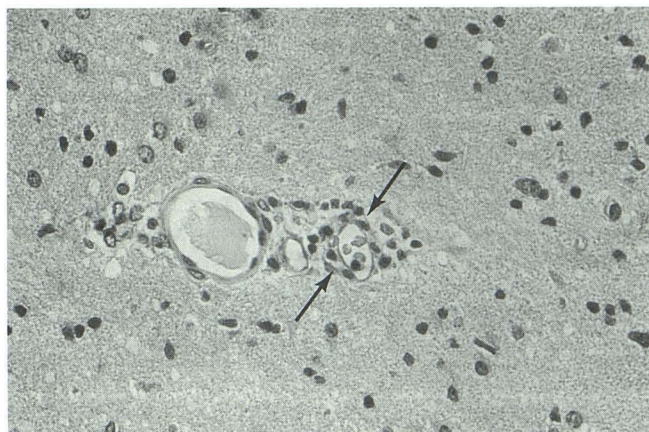


Fig. 3. Light microscopy of the brain biopsy shows a mixture of lymphocytes and plasma cells surrounding blood vessels (arrows). (Hematoxylin eosin, $\times 400$.)



Fig. 4. Electron microscopy reveals electron dense deposits in the basement membranes of the blood vessel, consistent with immune complex deposition. *Thick arrows*: electron dense deposits; *thin arrow*: blood vessel lumen; *arrowheads*: blood vessel wall.

a case of vasculitis of the leg following *C jejuni* gastroenterocolitis infection (2). The mechanism is probably similar in this case.

Since *C jejuni* encephalopathy is an immune-mediated condition, a distinction should be made from other more commonly known entities such as ADEM and systemic lupus erythematosus. ADEM can be seen after an antecedent viral infection or vaccination, or more commonly after a nonspecific upper respiratory infection where

the etiologic agent is unknown. Historically, ADEM is thought to account for one third of the cases of encephalitis in the United States (5). As adults often have immunity to the childhood viral illnesses, this may account for the higher prevalence of ADEM in children. The pathogenesis of ADEM is not clearly understood, but the disturbance of immune regulation appears to play an important role.

Previous reports of the MR findings in ADEM have emphasized the involvement of the white matter tracts, with some tendency to involve the gray-white matter junction as well (13–15). This distribution is not specific and can be seen in CNS lymphoma, progressive multifocal leukoencephalopathy, and severe multiple sclerosis, among other diseases (16).

Our case of *C jejuni* encephalopathy differs from ADEM in that there is an intense T2 signal predominantly in the gray matter in a gyriform pattern with some simultaneous areas of subcortical white matter involvement. These findings were confirmed by brain biopsy, which revealed vasculitis involving gray matter. Electron microscopy showed electron-dense deposits in the basement membranes of the blood vessel, consistent with immune complex deposition. The pattern of enhancement of ADEM differs from our case in that in ADEM some subcortical white matter lesions may enhance (17), while in our case there was some pial and dural enhancement without involvement of the parenchyma.



Fig. 5. Axial T2-weighted image (2500/80) on day 10 of second admission following steroid therapy shows persistent abnormal signal in the gray matter seen in previously affected areas. The brain biopsy site is seen on the left posteriorly (arrow).

A second immune-mediated condition that should be contrasted to our case is systemic lupus erythematosus, which is a chronic immune dysfunction disease characterized by vascular injury due to immune complex deposition. A pattern of multiple, focal, white matter abnormalities or large areas of white matter infarction can be seen, as can focal signal abnormalities in the gray matter alone (18). The pattern of predominant gray matter lesions with some concomitant subcortical white matter involvement seen in our case is not characteristic of systemic lupus erythematosus.

In summary, we report a case of postinfectious encephalopathy in a young child following *C jejuni* enteritis, comparing the histopathologic and serologic findings with the sequential changes in the brain seen on MR. The combination of predominant gray matter involvement and concomitant focal areas of subcortical white matter involvement is a notable finding and is different from the pattern of signal abnormalities seen in other diseases of immune dysfunction, such as ADEM and systemic lupus erythematosus.

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