

MRI reveals multiple reversible cerebral lesions in an attack of acute intermittent porphyria

Article abstract—A 20-year-old woman had an attack of acute intermittent porphyria (AIP) with seizures and hallucinations. MRI revealed multiple lesions in both hemispheres. Both the cerebral clinical abnormalities and the MRI lesions resolved following treatment. These findings suggest that a vascular mechanism may underlie the pathogenesis of cerebral dysfunction in AIP.

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Peter H. King, MD, and Andrew C. Bragdon, MD

Acute intermittent porphyria (AIP) is an uncommon heritable disease in which deficiency of the enzyme porphobilinogen (PBG) deaminase leads to overproduction of the heme precursors δ -aminolevulinic acid (ALA) and PBG by the liver.¹ Neurologic dysfunction is a primary feature of this disease, with seizures and encephalopathy being the hallmarks of cerebral involvement.

The pathogenesis of the cerebral manifestations remains unclear. Some have suggested that metabolic abnormalities produce diffuse neuronal dysfunction through either an overabundance of certain biochemical factors (eg, PBG, ALA, or tryptophan) or a deficiency of other factors (eg, heme or pyridoxal phosphate) stemming from the primary metabolic defect.¹ Others have suggested that multifocal ischemia from a vascular process, possibly vasospasm, is responsible.²⁻⁵

The disparate nature of these hypotheses derives, in part, from the wide range of neuropathologic findings in autopsy studies. Findings of no abnormality² or mild, patchy neuronal loss and demyelination³ have favored metabolic hypotheses, whereas findings of focal ischemic or necrotic cerebral lesions^{4,5} have directed thinking toward a vascular mechanism. However, the pathologic findings may have been biased by problems inherent in autopsy studies. Cases in which cerebral manifestations have been episodic and not clearly proximate to the patients' deaths are potentially biased toward normal or minimal findings. In other cases, complications of chronic illness, such as poor nutrition, and terminal complications, such as sepsis and prolonged hypoxia from ventilatory depression, appear to have contributed to the severe neuropathologic lesions.

MRI provides a sensitive tool to examine changes occurring in the brain at the time of the acute attack without these confounding variables. We now report finding transient, multifocal, cerebral lesions with MRI at the time of an acute attack of AIP with cerebral manifestations. The similarity in appearance of these lesions to those found in known vasculopathies, and their resolution over time, provide support for the vascular hypotheses of the pathogenesis of cerebral dysfunction in AIP.

Case report. A 20-year-old woman was transferred to Duke University Medical Center with a 14-week history of fluctuating weakness, abdominal pain, and hallucinations. At the time of transfer, vital signs were blood pressure, 130/100; heart rate, 100; respiratory rate, 22; and temperature, 37.2 °C. The gen-

eral physical examination was unremarkable. The neurologic examination at this time was notable for normal mental status, diffuse muscle atrophy, flaccid quadriplegia with trace movement of the proximal limbs, and absent deep tendon reflexes. Plantar responses were flexor bilaterally. Pinprick and joint position sensibilities were mildly diminished distally in the extremities. EMG and nerve conduction studies were consistent with a diffuse sensorimotor axonal neuropathy, preferentially involving motor neurons. Lead, mercury, and arsenic in a 24-hour urine sample were all normal.

The diagnosis of AIP was confirmed by the following studies (normal values in parentheses). RBC PBG deaminase was 17.5 nmol uroporphyrin/ml RBC/hr at 37 °C (20.9 to 42.2). A 24-hour urine sample contained ALA 39 mg (<4), PBG 83 mg (<4), uroporphyrin 1,298 μ g (<50), and coproporphyrin 132 μ g (50 to 280). A stool sample contained (per 100 grams wet weight) protoporphyrin 2,160 μ g (<3,416), uroporphyrin 871 μ g (<138), and coproporphyrin 1,620 μ g (<1,002). After treatment with a high carbohydrate diet and two courses of hematin therapy, her biochemical indices of disease activity normalized, but she remained quadriplegic.

Three months after admission, a gastrostomy tube was placed because of persistent difficulty maintaining adequate oral intake. Drugs administered for the procedure were nitrous oxide, 200 μ g of fentanyl given intravenously, and 29 ml of 1% lidocaine injected locally. Abdominal pain and nausea followed for the next few days. On the 5th postoperative day, she had a left adverse seizure with secondary generalization. She was lethargic and confused for several hours afterward but was otherwise unchanged neurologically. Her blood pressure, which normally ranged between 110/70 and 120/90, rose transiently to 170/120. The general physical examination, including the fundoscopic examination, was otherwise normal. Serum chemistries were remarkable for a sodium of 128 mmol/l, a magnesium of 1.2 mg/dl (normal, 1.6 to 2.2 mg/dl), and an arterial PO₂ of 64 mm Hg.

Despite correction of these abnormalities, on the 6th postoperative day she had two more seizures similar to the first. Later that day she experienced visual hallucinations. An EEG showed diffuse slowing at about 1 Hz but no epileptiform activity. A brain CT without contrast enhancement was normal except for a single questionable punctate low density in the left basal ganglia. CSF was normal. An echocardiogram, including a microcavitation study to exclude right-to-left shunting, was normal.

Brain MRI, performed on the 8th postoperative day, revealed seven cortically based, gyriform lesions located primarily in the frontal and parietal areas of both hemispheres (figure, A). The PBG content in a 24-hour urine sample was markedly elevated at 143 mg. After a third course of hematin, her urinary PBG excretion fell to 24.7 mg/24 hr, and her abdominal pain and hallucinations resolved completely. No additional seizures occurred, and she was not placed on anti-

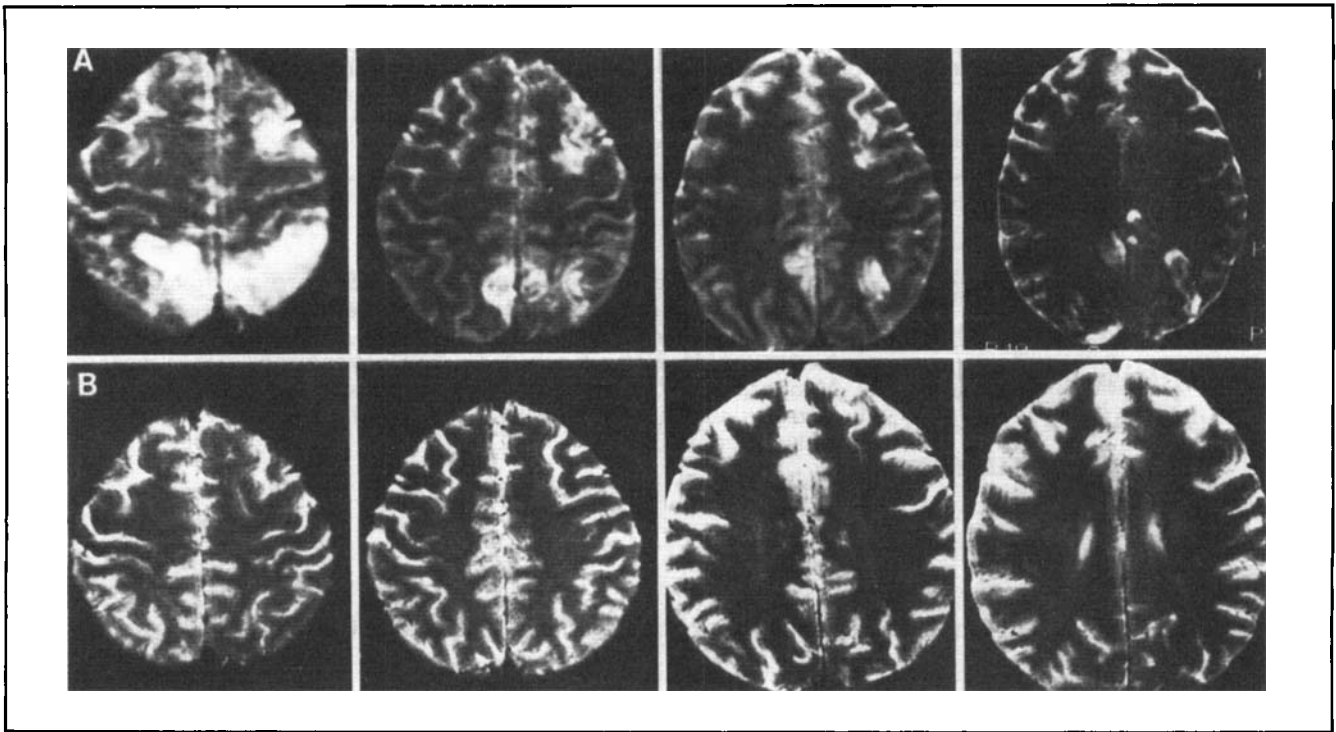


Figure. Axial T_2 -weighted MRI images obtained (A) during the attack, showing multiple areas of increased signal intensity, and (B) 10 days later, showing resolution of these abnormalities.

epileptic medication. MRI repeated on the 18th postoperative day showed that the lesions had resolved completely (figure, B).

Discussion. In this patient, transient cerebral MRI abnormalities occurred coincident with an attack of AIP with typical cerebral manifestations. Although it is not specific for etiology, this pattern of multiple, discrete cortical lesions that resolve with time occurs with vasculopathies, including systemic lupus erythematosus,⁶ CNS vasculitis,⁷ and hypertensive encephalopathy,⁸ suggesting that a vascular process producing multifocal ischemia may have been responsible for the clinical presentation in our case.

The notion that a vascular mechanism with resultant ischemia might underlie the cerebral dysfunction in AIP has been offered by several investigators since the 1940s. This hypothesis has been based in part on the autopsy findings mentioned above but receives further support from some physiologic observations. First, vasospasm occurs peripherally in both skin and retinal vessels during acute attacks of AIP.^{3,4} Second, a rise in blood pressure frequently occurs concurrent with the onset of cerebral manifestations.^{3,4} Moreover, the cerebral manifestations of AIP are quite similar to those of malignant hypertension, a condition in which the pathogenetic mechanism is presumed to be vascular. The mechanisms underlying the hypertension and vasospasm in AIP are unknown. However, parenterally administered porphyrins may cause hypertension.⁹

An alternative explanation is that the lesions were induced by the patient's seizures. However, reports of

reversible imaging abnormalities during or after seizures are rare, and in all such reports we have located, the patients have had focal status epilepticus.¹⁰ There was no evidence of this in our patient.

The present finding of multiple, reversible cerebral lesions provides new fuel for the notion that a vascular mechanism may underlie the cerebral manifestations of AIP, and should rekindle interest in this problem.

From the Division of Neurology (Dr. King), Duke University Medical Center, Durham, NC, and the VA Medical Center and the Departments of Neurology and Pharmacology (Dr. Bragdon), SUNY Health Science Center, Syracuse, NY.

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Address correspondence and reprint requests to Dr. Peter H. King, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195.

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Clinical correlation with serum-soluble interleukin-2 receptor levels in Guillain-Barré syndrome

Article abstract—In patients with Guillain-Barré syndrome (GBS) soluble interleukin-2 receptor (sIL-2R) levels were elevated compared with those of patients with other neurologic diseases (OND), and of healthy controls. Smaller increases in sIL-2R levels occurred in OND patients compared to healthy subjects. Monitoring of GBS patients clearly demonstrated that decreases in sIL-2R levels correlated with clinical recovery. Thus, T-cell activation may be relevant in the pathogenesis of GBS.

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S. Bansil, MD; F.A. Mithen, MD, PhD; S.D. Cook, MD; A. Sheffet, PhD; and C. Rohowsky-Kochan, PhD

Guillain-Barré syndrome (GBS) is a demyelinating polyneuropathy presumably of autoimmune pathogenesis. Increased numbers of DNA-synthesizing lymphoblasts correlating with disease activity are present in the blood of GBS patients.¹

The interleukin-2 receptor (IL-2R) expressed on activated T lymphocytes is shed, resulting in increases in serum-soluble IL-2R (sIL-2R). Increases in circulating IL-2R + T-lymphocytes² and in serum sIL-2R concentrations³ were found in GBS patients.

We assessed serum concentrations of sIL-2R in patients with GBS, other polyneuropathies, and CNS diseases and in healthy controls. Serial serum sIL-2R levels in GBS patients were correlated with clinical disease activity.

Methods. Subjects. The table summarizes the characteristics of patients and controls.

GBS. These patients fulfilled the diagnostic criteria for GBS.⁴ Initial sera were drawn within a mean of 11.4 (\pm 5 [SD]) days after motor onset of disease. Serial samples were obtained from six GBS patients for 3 to 15 months. Disease severity was scored on a clinical scale of 0 to 5, with 0 = healthy and 5 = requiring assisted ventilation.³ Initially, three patients were clinical grade 2, two grade 3, six grade 4, and three grade 5.

Other neurologic disease controls were patients with other polyneuropathies (OND-PNS): monoclonal gammopathy (1), diabetes and sarcoidosis (1), diabetes and hypothyroidism (1), diabetes and multiple myeloma (1), Charcot-Marie-Tooth disease (1), ischemic polyneuropathy (1), neurofibromatosis (1), and unexplained polyneuropathy (1). Patients with CNS disorders (OND-CNS) included those with epilepsy (7), acute strokes (5), dementia (2), Parkinson's disease (2), spondylitic myelopathy (1), and glomus jugular tumor (1).

Family controls were healthy relatives—spouses (2), siblings (2), identical twin (1), and parent (1)—in contact with a GBS patient. One individual had a viral illness similar to that of the paired GBS patient. Serum was drawn within 3 weeks of motor disease onset in the paired GBS patient.

Healthy controls were individuals with no recent contact

with a GBS patient and no medical disease.

Serum collection. Serum was collected, handled identically, and stored at -70°C until testing. GBS and family control samples were collected over 1 to 5 years, and OND and healthy control sera were obtained over 1 to 3 years. Repeated freezing and thawing of sera was avoided.

sIL-2R assay. Serum sIL-2R levels were measured by ELISA using a kit (T Cell Sciences, Cambridge, MA) as described.³ All sera were assayed two or more times with less than 10% variability between testing. All sera were tested undiluted; however, two GBS sera were retested at a 1:10 dilution.

Statistical analysis. Mean sIL-2R levels among GBS, OND-PNS, OND-CNS, and healthy controls were compared by the Kruskal-Wallis test, and mean sIL-2R levels between each group by Fisher's least significant difference. The rank sum test was performed on the six GBS patients and family

Table. Characteristics of patient and control populations

Group*	No.	Sex (F/M)	Mean age (yrs) (range)
Guillain-Barré syndrome	14	7/7	42 (19-77)
Other neurologic PNS diseases	8	2/6	49 (29-74)
Other neurologic CNS diseases	18	4/14	47 (25-76)
Family controls	6	3/3	38 (19-69)
Healthy controls	34	13/21	37 (23-79)

* No individual in the patient or control groups had received corticosteroids, other immunosuppressive therapy, or plasmapheresis at the time of initial blood drawing. No subject in any of the groups was HIV-positive or had risk factors for developing HIV infection.