CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 24-2007: A 20-Year-Old Pregnant Woman with Altered Mental Status

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PRESENTATION OF CASE

A 20-year-old pregnant woman was admitted to this hospital at 26 weeks of gestation because of dizziness, confusion, and difficulty walking.

Ten weeks before admission, the patient had a positive result on a home pregnancy test and presented to a neighborhood health center for prenatal screening. Tests for sickle cell trait, syphilis, and human immunodeficiency virus (HIV) and hepatitis B and C virus antibodies were negative. Serologic tests for varicella–zoster virus and rubella IgG were positive. Two weeks later, an endocervical specimen was positive for *Chlamydia trachomatis* infection and negative for gonorrhea. The patient missed follow-up appointments, and treatment with azithromycin was initiated 4 weeks later.

Six weeks before admission, she moved into a shelter for pregnant women. Staff members described her as happy, with a childlike affect, a poor memory, confusion, and odd movements of her head. During the next 2 weeks, nausea and vomiting occurred daily and were controlled with metoclopramide. Four days before admission, dizziness and weakness on the left side developed; she began to fall to her left and vomited several times. The next day, she went to the emergency department of another hospital. On evaluation, the patient was oriented to location but not to date, day, or month, and she provided inconsistent information about her medical history. The uterus was gravid, and the remainder of the physical examination was normal. An electrocardiogram revealed sinus tachycardia and counterclockwise rotation with T waves in the right precordial leads. Urinalysis showed a protein level of 30 mg per deciliter and a glucose level of 100 mg per deciliter (5.6 mmol per liter). Tricyclic metabolites were present on toxicology screening of a urine specimen. Computed tomographic (CT) scanning of the head revealed a slight, diffuse prominence of the ventricular system. There was no intracranial mass or other focal brain lesion.

On the second hospital day, the patient was alert, calm, cooperative, and oriented to person, location, and current events but was not aware of details of her life. There were no tremors or extrapyramidal signs. Ultrasonographic examination revealed normal fetal anatomy and growth, corresponding to a gestation of 25 weeks 6 days. On the third day, the weakness, nausea, and vomiting had resolved,

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and the patient was thought to have returned to her baseline mental status. She was discharged to the shelter with a recommendation to schedule a follow-up neurologic evaluation. At the shelter, she was dizzy, had difficulty walking, and fell into a chair. That evening, she was brought to the emergency department of this hospital.

In the emergency department, the patient reported feeling "woozy" and nauseated. She noted a mild headache of gradual onset, extending bandlike across the brow. The history as given by the patient was inconsistent; the history was then provided by staff members of the shelter, and many details were lacking. The patient was a native of Cape Verde who had immigrated to this country 3 years previously. She had had measles at 4 months of age and varicella infection in childhood. At 7 years of age, she injured her head in a fall but was said to have recovered fully. Immunizations included polio vaccine and diphtheria, pertussis, and tetanus vaccine series; measles vaccine (at 11 months of age); measles, mumps, and rubella vaccine combination; and hepatitis B vaccine (between 2 and 3 years before admission, on enrollment in high school).

The patient had attended school through the 10th grade and was unemployed. During the 3 years before admission, she had lived with relatives, friends, and a boyfriend, as well as in shelters. She was single, and she no longer maintained a social relationship with the father of the fetus. Her parents and seven siblings were alive but not in contact with her at the time of admission. No family medical history was available. She had no known allergies and did not use alcohol, illicit drugs, or tobacco.

On examination in the emergency department, the patient was alert but somewhat uncooperative, with involuntary head movements. Her mental status was not formally assessed, but her level of cognitive function was said by a friend to be at baseline. The blood pressure was 107/81 mm Hg, the pulse 84 beats per minute, and the temperature 36.3°C; the respirations were 18 per minute, and the oxygen saturation was 100% while the patient was breathing ambient air. Acneiform lesions were present on her face. The abdomen was soft, gravid, and not tender; the fetus appeared to be healthy. The 1st cranial nerve was not tested, and the 2nd through 12th nerves were intact. Strength was intact, and the gait was unsteady. The remainder of the examination was normal.

Results of laboratory tests are shown in Table 1. After premedication with lorazepam at a dose of 1 mg to control involuntary movements, magnetic resonance imaging (MRI) of the brain was performed without administration of contrast material. On T_2-weighted, fluid-attenuated inversion recovery (FLAIR) images, hyperintense signal was seen in the left hippocampus and parahippocampal gyrus as well as in the posterior limb of the left internal capsule. There was no evidence of restricted diffusion.

Examination by a neurology consultant showed that the patient was oriented to person and place, with a childlike affect. Her speech was fluent, and naming was intact. She could read a short sentence and do simple addition. She was left-handed, could write her name but not a sentence, and followed simple and complex commands. Her attention was variable, and testing of her memory showed recollection of zero of three items at 5 minutes on repeated examination. There was mild asymmetry of the face with flattening of the right nasolabial fold. Smell and taste were not tested. The function of the other cranial nerves was intact. There were choreiform movements of the head and neck, poor performance of rapid alternating movements, and apraxia. Hypertonia and hyperreflexia with clonus were noted in the right leg. The gait was wide-based, with postural instability and leaning toward the left. She was unable to stand on one foot. She was admitted to the neurology service.

On the second hospital day, a lumbar puncture was performed. Results of cerebrospinal fluid analysis are shown in Table 2; other test results are listed in Table 1. An enzyme-linked immunosorbent assay for serum antibodies against HIV was negative. An electroencephalogram showed diffuse theta slowing and frontal intermittent rhythmic delta activity, which was more prominent in the right hemisphere than in the left. There was no epileptiform activity (Fig. 1). Repeated MRI of the brain after the administration of gadolinium showed no changes and no evidence of abnormal enhancement. Acyclovir was administered intravenously.

The next day, a serum Lyme antibody test, a test of a throat swab for *Mycoplasma pneumoniae* nucleic acid, and cultures of blood and urine were negative; results of other tests are listed in Table 1. On the fifth day, the patient's condition appeared to be improved. She was oriented and remembered details of her past; dysmetria and truncal

ataxia were reduced. Results on a repeated electroencephalogram were unchanged. The next day, a repeated lumbar puncture was performed (Table 2).

Between the 7th and 18th hospital days, the patient's motor function gradually worsened, right-sided neglect developed, she became unable to feed herself, her responsiveness and ability to follow commands decreased, and she became incontinent. She began lying in a fetal position, moaning and crying out unintelligible sounds. A skin test for tuberculosis, a test of a nasopharyngeal specimen for respiratory viral antigens, and a viral culture of a stool specimen were negative. Nucleic acid testing for HIV RNA and tests for antinuclear antibodies were negative. Levels of free and total thyroxine were normal, and the thyroglobulin level was elevated (54.7 ng per milliliter; normal range, 4 to 40). On the 12th day, the acyclovir was discontinued, and ceftriaxone, at a dose of 2 g, was administered intravenously. A repeated electroencephalographic study showed increased attenuation of background activity and less abundant frontal intermittent rhythmic delta activity. MRI on the 13th day showed new hyperintense signal in the pons and middle cerebellar peduncles with associated restricted diffusion of water on T_2-weighted FLAIR images. Restricted diffusion was also noted in the posterior limb of the left internal capsule. There was atrophy in the left medial temporal lobe, with resolution of the abnormal hyperintense signal on FLAIR images. On the 14th day, a third lumbar puncture was performed.

On the 18th hospital day, a test result was received.

DIFFERENTIAL DIAGNOSIS

Dr. Andrew J. Cole: I was involved in this patient's care from the time of her admission and am therefore aware of the diagnosis. I will discuss the case as it unfolded in order to illustrate the diagnostic process and therapeutic decision making that took place. The patient lived semi-independently until she became pregnant 27 weeks before admission. Her level of function at that time was unknown, and because of the lack of information, it was not possible to determine either her level of function before her illness or the tempo of her disease.

Neurologic differential diagnosis relies primarily on the physical examination for localization of lesions and on the history, especially the nature of onset and pace of progression, to identify the disease process. This patient's neurologic examination showed abnormal cognitive function indicating dysfunction of the cortical and subcortical gray matter, abnormal motor function indicating dysfunction of the pyramidal motor system, and choreiform movements indicating dysfunction of the extrapyramidal motor systems. This examination also showed a clumsy gait and difficulty performing rapid alternating movements, indicating dysfunction of the cerebellum or its connections. With the limited information about the pace of her disease, we needed to consider inherited, congenital, and acquired diseases that could be acute, subacute, or chronic, with static, episodic, or progressive tempos. We had to base our differential diagnosis on the neurologic examination, initial laboratory testing, and electroencephalographic and MRI studies.

CEREBROSPINAL FLUID EXAMINATION

The results of the cerebrospinal fluid analysis in this patient showed a lymphocytic pleocytosis with few red cells, a mildly elevated protein level, and a normal glucose level. These findings are characteristic of aseptic meningitis. We were thus concerned about viruses, rickettsia, spirochetes, partially treated bacterial infection, a parameningeal focus of infection, certain autoimmune illnesses such as systemic lupus erythematosus or Behçet's disease, vasculitides, carcinoma, a reaction to the toxic effects of certain medications such as nonsteroidal antiinflammatory drugs, and chemical meningitis related to the rupture of a cyst. Although they were nonspecific, the cerebrospinal fluid findings provided support for the possibility of acute or subacute infection or inflammatory illness. The presence of an inflammatory response made chronic degenerative diseases such as Huntington's disease, Wilson's disease, and systems abiotrophies such as multisystem atrophy unlikely.

ELECTROENCEPHALOGRAPHIC STUDIES

The initial electroencephalogram was markedly abnormal, but the findings were nonspecific (Fig. 1). The slow and attenuated posterior dominant rhythm suggests cortical gray-matter disease, whereas the intermittent frontal rhythmic delta activity suggests subcortical gray-matter disease. The monomorphic slow waves also suggest that initially the subcortical white matter

Table 1. Results of Laboratory Tests.*

Variable	Reference Range for Adults†	On Admission	On Hospital Day 2
Hematocrit (%)	36.0–46.0 (in women)	37.4	35.2
Hemoglobin (g/dl)	12.0–16.0 (in women)	13.2	12.1
White-cell count (per mm^3)	4500–13,000	8,100	7,600
Differential count (%)			
Neutrophils	40–62	72	
Lymphocytes	27–40	21	
Monocytes	4–11	6	
Eosinophils	0–8	1	
Basophils	0–3	0	
Platelet count (per mm^3)	150,000–350,000	236,000	192,000
Mean corpuscular volume (μm^3)	80–100		89
Erythrocyte sedimentation rate (mm/hr)	1–25		26
Glucose (mg/dl)	70–110	78	73
Sodium (mmol/liter)	135–145	135	137
Potassium (mmol/liter)	3.4–4.8	3.5	3.4
Chloride (mmol/liter)	100–108	106	104
Carbon dioxide (mmol/liter)	23.0–31.9	26.0	25.2
Urea nitrogen (mg/dl)	8–25	8	4
Creatinine (mg/dl)	0.6–1.5	0.5	0.6
Bilirubin (mg/dl)			
Total	0.0–1.0	0.1	
Direct	0–0.4	0.0	
Protein (g/dl)			
Total	6.0–8.3	7.7	7.4
Albumin	3.3–5.0	3.5	
Globulin	2.6–4.1	4.2	
Phosphorus (mg/dl)	2.6–4.5	3.0	
Magnesium (mmol/liter)	0.7–1.0	0.75	
Calcium (mg/dl)	8.5–10.5	9.2	
Creatine kinase (U/liter)	40–150 (in women)		62
Alkaline phosphatase (U/liter)	30–100	96	
Aspartate aminotransferase (U/liter)	9–32	18	
Alanine aminotransferase (U/liter)	7–30	15	
Lipase (U/dl)	1.3–6.0	7.5	
Amylase (U/liter)	3–100	79	
Rapid plasma reagin			Nonreactive
Human chorionic gonadotropin, quantitative (IU/liter)	<6 (in nonpregnant women); 6–15 (borderline)	32,907	
Toxicology screen		Negative	
Partial-thromboplastin time lupus anticoagulant			None
Anticardiolipin IgG antibodies (GPL units)	0–15		7.9

Table 1. (Continued.)

Variable	Reference Range for Adults†	On Admission	On Hospital Day 2
Anticardiolipin IgM antibodies (MPL units)	0–15		10.6
Ceruloplasmin (mg/dl)	27–50		84
Iron (μg/dl)	30–160		61
Iron-binding capacity (μg/dl)	228–428		464
Vitamin B_{12} (pg/ml)	>250		430
Ferritin (ng/ml)	10–200		9
Transferrin (mg/dl)	188–341		361
Antistreptolysin O (IU/ml)	<200		208
Thyrotropin (μU/ml)	0.40–5.00		0.2
Serum protein electrophoresis (mg/dl)			
IgA	69–309		109
IgG	614–1295		1490
IgM	53–334		93
Herpes simplex virus type 1 antibody IgG			Positive (>6.00)
Herpes simplex virus type 2 antibody IgG			Negative

* To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for total and direct bilirubin to micromoles per liter, multiply by 17.1. To convert the values for phosphorus to millimoles per liter, multiply by 0.3229. To convert the values for magnesium to milliequivalents per liter, multiply by 2. To convert the values for calcium to millimoles per liter, multiply by 0.250. To convert the values for iron and iron-binding capacity to micromoles per liter, multiply by 0.1791. To convert the values for vitamin B_{12} to picomoles per liter, multiply by 0.7378.

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. The ranges therefore may not be appropriate for all patients.

was relatively spared. Dr. Henson, may we review the radiologic studies?

Dr. John W. Henson: Axial T_2-weighted FLAIR images from the MRI studies of the brain on the day of admission, performed without the administration of gadolinium, revealed a region of hyperintense signal in the left medial temporal lobe (Fig. 2A) and subtle increased signal in the posterior limb of the left internal capsule corresponding to the location of the corticospinal tract. These foci did not show restricted diffusion or abnormal enhancement on a gadolinium-enhanced study performed the next day. The appearance of the pons was unremarkable, and no other clinically significant findings were noted. Magnetic resonance venography of the head was normal.

By day 13, there had been marked changes. There was a region of abnormal signal in the pons (Fig. 2B), with areas of restricted diffusion on the diffusion-weighted image and apparent-diffusion-coefficient maps. The hyperintensity of the left medial temporal lobe had resolved, and there was volume loss in the region of the hippocampal formation. There was restricted diffusion in the left corticospinal tract (Fig. 2C); no abnormal enhancement was detected. These findings were interpreted as resulting from a subacute encephalitis caused by an infection or an autoimmune disorder.

Dr. Cole: In summary, this patient has a disturbance of cognitive function, pyramidal tract and cerebellar dysfunction, and a choreiform-movement disorder, and both laboratory tests and electroencephalographic and imaging studies suggest an infectious or autoimmune encephalitis.

DISORDERS OF MOVEMENT

Chorea is a hyperkinetic movement disorder that may result from a number of neurologic diseases; it may appear or worsen during pregnancy, a condition known as chorea gravidarum. Most patients

Table 2. Results of Cerebrospinal Fluid Tests.

Test*	Normal Range	Hospital Day 2	Hospital Day 6	Hospital Day 14
Opening pressure (mm H_20)		17		
Appearance	Colorless	Colorless, slightly turbid	Pink, slightly turbid	Slightly pink, clear
Red-cell count (per mm^3)				
Tube 1	None	650	2250	2360
Tube 4	None	28	2438	1100
White-cell count (per mm^3)				
Tube 1	0–5	40	100	36
Tube 4	0–5	37	46	10
Differential count (%)				
Neutrophils				
Tube 1	None	0	6	7
Tube 4	None	0	6	4
Lymphocytes				
Tube 1	None	82	80	61
Tube 4	None	88	82	76
Reactive lymphocytes				
Tube 1	None	11	0	18
Tube 4	None	3	0	8
Monocytes				
Tube 1	None	7	7	9
Tube 4	None	9	4	9
Other hematic cells (%)			Large mononuclear cells with abundant cytoplasm and nucleoli	Large mononuclear cells with basophilic cytoplasm and prominent nucleoli
Tube 1	None		7	5
Tube 4	None		6	3
Unidentified cells (%)				
Tube 1	None		0	
Tube 4	None		2	
Protein (mg/dl)	5–55	66	100	76
Glucose (mg/dl)	50–75	53	73	65
Venereal Disease Research Laboratory test		Nonreactive	Nonreactive	
IgG (mg/dl)	0.0–8.0	38.9		
Albumin (mg/dl)	11.0–50.9	16.4		
Oligoclonal bands on agarose electrophoresis	None seen in 80× concentrate	Several seen in 63× concentrate		
Gram's stain		No organisms	No organisms	No organisms
Acid-fast bacilli stain		No organisms		No organisms
Varicella–zoster virus (PCR)		None detected		None detected
Enterovirus RNA (PCR)		None detected		
Cytomegalovirus DNA		None detected	None detected	
Epstein–Barr virus DNA		None detected	None detected	

Table 2. (Continued.)

Test	Normal Range	Hospital Day 2	Hospital Day 6	Hospital Day 14
Human herpes virus type 6 DNA (PCR)			None detected	
Herpes simplex virus (PCR)		None detected	None detected	None detected
Mycoplasma pneumoniae (PCR)			None detected	
Encephalitis antibodies				
Eastern equine encephalitis		None detected		
West Nile virus IgM		None detected		
Cultures				
Routine		No growth	No growth	No growth
Fungal		No growth		No growth
Adenoviral			No growth	
Enteroviral			No growth	
Mycobacterial		No growth		

* PCR denotes polymerase chain reaction.

with this condition present during the second trimester with an isolated movement disorder that resolves after delivery. The most common causes are acute rheumatic fever (Sydenham's chorea) and the antiphospholipid-antibody syndrome. We also considered other illnesses associated with chorea, including systemic lupus erythematosus, Huntington's chorea, and Wilson's disease, although the latter two illnesses were ruled out by the cerebrospinal fluid and other findings.

Sydenham's chorea is a late complication of infection with group A streptococcus; the onset occurs months after acute infection. Most cases occur in childhood, but up to 30% of patients may have recurrent chorea months or years after the initial episode.[1] This patient had only a minimally elevated antistreptolysin-antibody titer, with no other evidence of recent streptococcal infection or cardiac disease. The antiphospholipid-antibody syndrome[2] may be primary or secondary to systemic lupus erythematosus, and it may become manifest during pregnancy. This patient had no symptoms or signs of systemic lupus, but lupus confined to the central nervous system is well recognized and may worsen during the course of pregnancy. Antiphospholipid-antibody testing and all laboratory studies for lupus were negative.

ACUTE VIRAL ENCEPHALITIS

Herpes simplex encephalitis was initially considered as one of the acute infectious encephalitides because of the abnormality detected in the left hippocampus on MRI. Unlike the arboviral encephalitides and West Nile virus encephalitis, which occur in the summer and fall, when mosquitoes are abundant, herpes simplex encephalitis occurs sporadically throughout the year. The negative results on cerebrospinal fluid testing for herpes simplex virus nucleic acid and the lack of response to acyclovir made this diagnosis unlikely. Other common causes of viral encephalitis, including enteroviral and echoviral infections, as well as infection with coxsackievirus, typically pro-

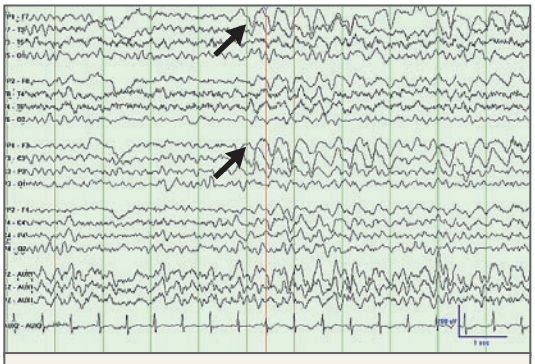

Figure 1. Electroencephalogram Obtained on the Second Hospital Day.

The electroencephalogram is markedly abnormal, showing modest slowing of the posterior dominant background rhythm with bursts of frontal intermittent rhythmic delta activity (arrows), sometimes maximal on the right and other times relatively symmetric bilaterally. There are no epileptiform features and no periodic discharges.

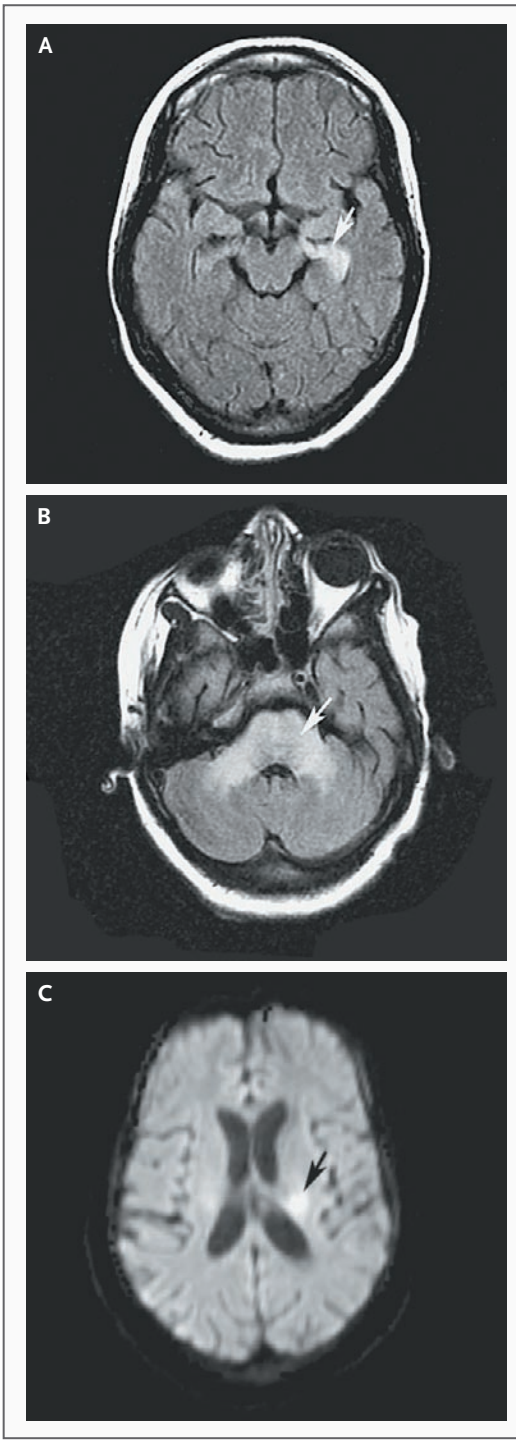

Figure 2. Brain Imaging Studies.
An axial T_2-weighted FLAIR image (Panel A) obtained on the day of admission showed a region of abnormal, hyperintense signal in the left hippocampus (arrow) and in the posterior limb of the left internal capsule (not shown). On the 13th hospital day, there was a new region of hyperintense signal on T_2-weighted FLAIR images in the pons and middle cerebellar peduncles (Panel B, arrow) and restricted diffusion in the middle cerebellar peduncle and posterior limb of the internal capsule as shown on the diffusion-weighted images (Panel C, arrow).

duce prominent signs of meningeal irritation, with photophobia, meningismus, nausea, and headache, but only minimal signs of focal cerebral dysfunction, which may be fleeting and are not progressive. Serologic tests in this patient ruled out these agents.

SUBACUTE ENCEPHALITIDES

Paraneoplastic Encephalitis

Paraneoplastic limbic encephalitis may precede the appearance of a tumor by months or even years. Psychiatric symptoms, memory failure, confusion and drowsiness, disordered respiration, ataxia, and cranial-nerve palsies have been reported. There may be a modest increase in protein in the cerebrospinal fluid, but few cells are detected. This patient's clinical and cerebrospinal fluid findings were not consistent with paraneoplastic encephalitis.

Postinfectious Encephalitis

Several infections may be associated with postinfectious encephalitis syndromes, including measles, mumps, and rubella; influenza; Epstein–Barr virus; and varicella–zoster virus. Acute disseminated encephalomyelitis may occur after a variety of viral infections and after the administration of rabies and smallpox vaccines.[3] It usually begins with nonspecific symptoms such as fever, headache, stiff neck, vomiting, and anorexia. Neurologic examination may show optic neuritis, ataxia, and focal weakness; seizures and decreased consciousness may develop. This patient did not have a recent history of immunizations or a viral infection or evidence of optic neuritis, and the imaging findings were not typical of acute disseminated encephalomyelitis.

The cerebrospinal fluid findings were an important clue to the diagnosis in this case. Although the protein level in the initial cerebrospinal fluid specimen was modestly elevated, the IgG component was markedly elevated. Dr. Roehrl, would you discuss the analysis and implications of this finding?

Dr. Michael H.A. Roehrl: Cerebrospinal fluid levels of total protein, albumin, and IgG obtained on the second hospital day are shown in Table 2.

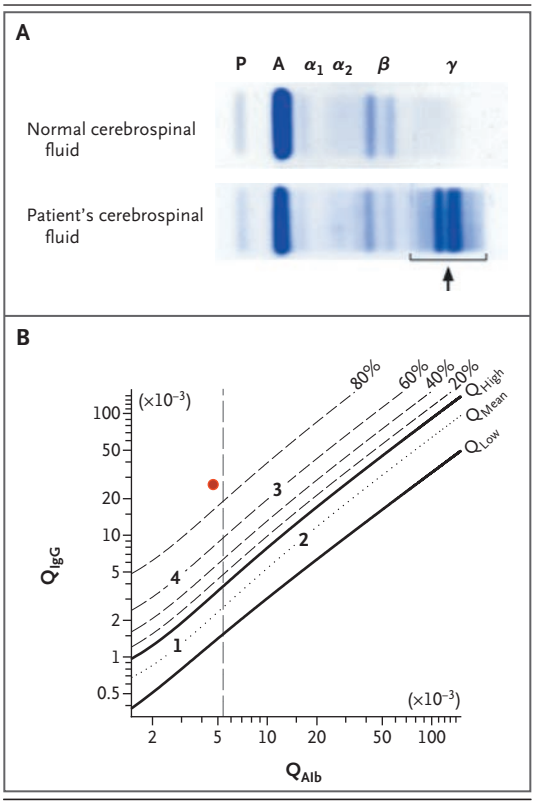

Figure 3. Results of Cerebrospinal Fluid Electrophoresis.

Panel A shows the results of agarose-gel electrophoresis of a specimen of the patient's cerebrospinal fluid collected on the second hospital day (concentrated to 1/63 of the original volume) and cerebrospinal fluid from a normal control (concentrated to 1/80 of the original volume). P, A, α_1, α_2, β, and γ denote the electrophoretic prealbumin, albumin, alpha-1, alpha-2, beta, and gamma regions, respectively. The arrow shows the position of several strong bands in the gamma region, indicating the presence of multiple oligoclonal immunoglobulins. There is also a relative decrease of the level of albumin in the patient's cerebrospinal fluid. Panel B shows a double-logarithmic graph designed according to the method proposed by Reiber (also called a Reibergram), in which cerebrospinal fluid to serum mass concentration quotients for albumin (Q_{Alb}) and IgG (Q_{IgG}) are plotted along the abscissa and ordinate, respectively. Upper limits (Q_{High}) and lower limits (Q_{Low}) of normal values are shown as solid lines, with the dotted line indicating mean normal values (Q_{Mean}). The isopercentiles (dashed lines) correspond to various relative amounts of intrathecal IgG production (20 to 80%). The vertical dashed line denotes the age-adjusted upper limit of Q_{Alb}, separating normal function (left) and abnormal function (right) of the blood–brain barrier. The patient (red dot) had markedly increased intrathecal IgG synthesis (intrathecal production fraction, 87.7%) without evidence of significant dysfunction of the blood–brain barrier (zone 4). Zone 1 denotes normal function, zone 2 denotes pure blood–brain barrier dysfunction, and zone 3 denotes a combination of increased intrathecal IgG synthesis and blood–brain barrier dysfunction.

Agarose-gel electrophoresis of cerebrospinal fluid revealed oligoclonal bands in the gamma region (Fig. 3A). The cerebrospinal fluid to serum mass concentration quotients for albumin and IgG concentrations were $Q_{Alb}=4.7\times10^{-3}$ and $Q_{IgG}=26.1\times10^{-3}$, corresponding to an IgG index of 5.6 (normal value, <0.85).[4] On the basis of an analysis developed by Reiber,[5-7] this patient's results (Fig. 3B) indicated markedly increased intrathecal IgG synthesis (intrathecal production fraction, 87.7%) without evidence of clinically significant blood–brain barrier dysfunction. The mass concentration ratio of IgG to total protein in the cerebrospinal fluid was 58.9%.

Dr. Cole: The diseases that can elicit an intrathecal response of this magnitude are syphilis, chronic rubella panencephalitis, and subacute sclerosing panencephalitis.[8-11] This patient did not have syphilis, as shown by negative results on serologic testing and a symptom complex that was inconsistent with the disease. Postrubella encephalitis[12,13] may affect patients with history of remote or congenital rubella infection and presents with progressive dementia, ataxia, chorea, retinal degeneration, and seizures. Examination of the cerebrospinal fluid shows pleocytosis and a moderately elevated protein level, with up to 50% of the cerebrospinal fluid protein composed of immunoglobulins. The diagnosis is confirmed by a high antirubella-antibody titer in the cerebrospinal fluid.

SUBACUTE SCLEROSING PANENCEPHALITIS

Measles causes three distinct diseases of the central nervous system: postinfectious encephalomyelitis, subacute measles encephalitis, and subacute sclerosing panencephalitis.[14] Subacute sclerosing panencephalitis is typically seen 7 to 10 years after infection with measles, and patients present most commonly with declining performance in school, behavioral changes, headache, adventitious movements, and sometimes seizures.[15] Characteristic findings include myoclonic jerks that are often periodic and are associated with periodic lateralized or bilateral epileptiform discharges on an electroencephalogram. Although most cases occur in childhood or adolescence, cases beginning as late as the fifth decade of life have been described.[16,17] The incidence of subacute scleros-

ing panencephalitis has decreased with widespread vaccination against measles; however, it persists in places where measles vaccination is uncommon.[18] The incidence of this condition is increased as much as 10 times in patients in whom measles develops before the age of 2 years; this patient had measles at 4 months of age. The illness may present during pregnancy, possibly as a result of altered immune status.[8,19]

In summary, this patient presented with a subacute progressive neurologic disease characterized by widespread dysfunction of the central nervous system, inflammatory features in the cerebrospinal fluid, and an extremely high level of cerebrospinal fluid IgG. My colleagues and I favored the diagnosis of subacute sclerosing panencephalitis, a delayed consequence of her infection with measles at 4 months of age. This condition may have been exacerbated by her pregnancy. Specimens of serum and cerebrospinal fluid from the 14th hospital day were sent for testing of levels of antibodies against measles.

Dr. Roehrl: The measles-specific cerebrospinal fluid to serum IgG antibody index was elevated at 31.8 (normal value, <1.4)[7] (Table 3). Measles-specific IgM antibodies were not detected in the serum. This profile indicates a chronic immune response to measles infection in the cerebrospinal fluid compartment. A comparison with mumps titers shows the specificity of the immunologic process. The results confirm the diagnosis of subacute sclerosing panencephalitis in the patient. The disease was a late consequence of persistent infection with measles virus.

Table 3. Results of Blood and Cerebrospinal Fluid Tests for Measles and Mumps Antibodies on Hospital Day 14.

Test	Result	
	Blood	Cerebrospinal Fluid
Measles		
IgM	Negative	1:512
IgG	>1:800,000	1:81,920
Mumps		
IgM	Negative	Negative
IgG	1:512	1:32

DISCUSSION OF MANAGEMENT

Dr. Cole: Cell-mediated immunity stimulated by T-helper cell type 1 (Th1) inducing cytokines is crucial for the clearance of measles virus in the weeks after infection, whereas cytokines that induce type 2 helper T (Th2) cells are implicated in antibody production. Several reports have suggested that treatment with intrathecal interferon alfa-2 (a cytokine that promotes Th1 activity), with or without treatment with the antiviral immunomodulatory agent inosine pranobex, may slow or even arrest the progression of subacute sclerosing panencephalitis.[20-25] However, no definitive data are available to show the efficacy of this treatment approach.

When we made the diagnosis in this patient, she was at 28 weeks of gestation, and her condition was deteriorating rapidly. We believed that an attempt at treatment was in the best interest of the patient and her fetus. We treated her with interferon and inosine pranobex for 8 weeks, without any clear clinical benefit. After the delivery of a healthy baby by elective cesarean section at 34 weeks' gestation, a decision was made to discontinue treatment, with the consent of the patient's mother. The patient died 6 weeks later.

DR. ANDREW J. COLE'S DIAGNOSIS

Subacute sclerosing panencephalitis.

PATHOLOGICAL DISCUSSION

Dr. Matthew P. Frosch: The autopsy revealed inflammatory infiltrates containing macrophages, plasma cells, and lymphocytes around vessels, with neuronal destruction and reactive gliosis that were most prominent in the brain stem (Fig. 4A). No viral inclusions of the type usually seen in acute measles encephalitis (and occasionally present in subacute sclerosing panencephalitis) were seen in the nuclei or cytoplasm of any cell types (neurons, glia, or vascular endothelial cells). Unlike other measles-associated diseases, subacute sclerosing panencephalitis is caused by the persistence of defective viruses that do not form complete viral particles but may infect adjacent cells by direct contact.[26,27] In the cerebral cortex, neuronal populations were preserved, but there was marked gliosis with reactive astrocytes (Fig. 4B). The brain stem was softened by the pathologic process, but the hemispheric white matter was firmer than normal; this was most evident when the brain was cut in the fresh state. This firmness corresponds to the sclerosis in the name, subacute

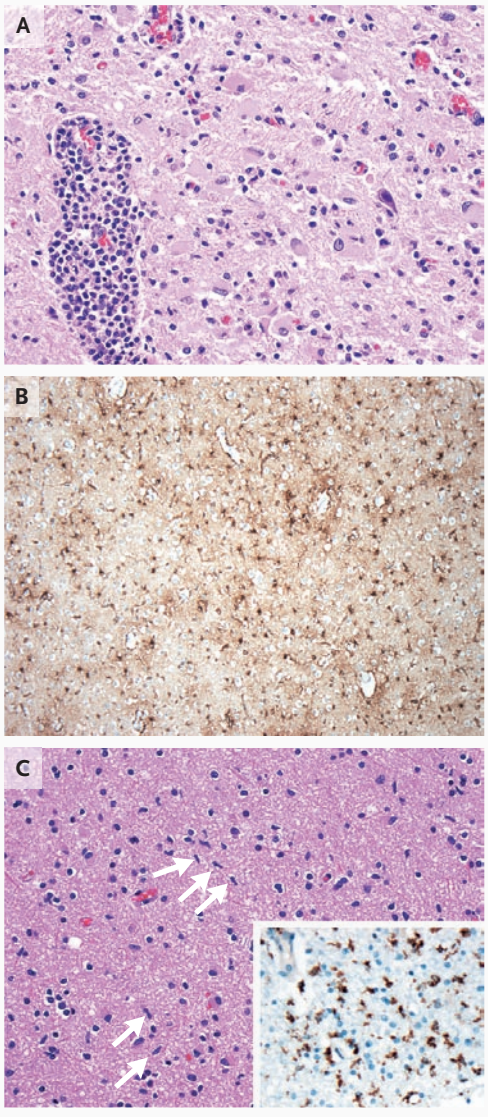

Figure 4. Findings in the Brain at Autopsy.

A marked inflammatory infiltrate around the vessels and neuronal destruction are most prominent in this section of the brain stem, which contains macrophages, plasma cells, and lymphocytes; there is prominent perivascular cuffing by lymphocytes (Panel A, hematoxylin and eosin). In the cerebral cortex, neuronal populations are preserved, but a marked gliosis is present (Panel B, immunohistochemical analysis for glial fibrillary acidic protein). Marked microglial activation is present in the subcortical white matter with rod-shaped CD68-positive cells (Panel C, arrows; hematoxylin and eosin) (inset, immunohistochemical staining for CD68).

sclerosing panencephalitis. The subcortical white matter also showed reactive gliosis and extensive microglial activation (Fig. 4C). These findings are nonspecific, but together with the serologic studies, they are consistent with a diagnosis of subacute sclerosing panencephalitis.

Fixed and frozen specimens of brain tissue were sent to Dr. William Bellini at the Centers for Disease Control and Prevention for immunohistochemical and molecular diagnostic studies.[14,28-30] Immunohistochemical analysis for measles virus nucleoprotein antigen was negative. Molecular diagnostic studies performed to detect portions of the measles genome were negative in repeated attempts at amplification of regions of the measles nucleoprotein gene. Weak signals were detected in a real-time reverse-transcriptase–polymerase-chain-reaction assay, but there were insufficient amounts of amplified DNA product to perform a sequence analysis. As a result, it was not possible to definitively establish the presence of measles virus in this case.

Dr. Nancy Lee Harris (Pathology): Dr. Cort, who prepares the case histories for these exercises, was able to obtain some additional history, which was not available to the patient's caregivers.

Dr. Alice M. Cort (Internal Medicine): Two years before admission, the patient was seen in the emergency department of another hospital because of an episode of loss of consciousness that was associated with rolling of the eyes and arching of the back. On examination, there were intermittent involuntary movements of the head and neck and jerking movements of the arms. Deep-tendon reflexes were brisk and symmetric. CT scanning of the head and an electroencephalogram were normal. Further testing showed an early pregnancy, which was electively terminated. During the next 20 months, the patient was lost to medical follow-up, and it is not known whether the abnormal movements stopped.

Dr. Harris: Dr. Cole, is it possible that subacute sclerosing panencephalitis began during this patient's previous pregnancy, stabilized, and then worsened with the second pregnancy?

Dr. Cole: Subacute sclerosing panencephalitis is almost always a chronically progressive disease, although plateaus in the clinical course have been described. The duration of the disease can be years, however, and in retrospect, her symptoms 2 years earlier may have been an earlier manifestation of the same disease. The effect of the patient's treatment on the appearance of the brain at autopsy and on the ability to detect viral antigens or DNA is not known.

ANATOMICAL DIAGNOSIS

Subacute sclerosing panencephalitis secondary to measles virus infection.

Dr. Cole reports receiving consulting fees from GlaxoSmithKline, Abbott Laboratories, and Supernus Pharmaceuticals and lecture fees from GlaxoSmithKline, Abbott Laboratories, and Ortho-McNeil; Dr. Henson, consulting fees from GlaxoSmithKline; and Dr. Frosch, consulting fees from Biogen Idec and Bristol-Myers Squibb. No other potential conflict of interest relevant to this article was reported.

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REFERENCES

1. al-Eissa A. Sydenham's chorea: a new look at an old disease. Br J Clin Pract 1993; 47:14-6.
2. Levine JS, Branch DW, Rauch J. The antiphospholipid syndrome. N Engl J Med 2002;346:752-63.
3. Menge T, Hemmer B, Nessler S, et al. Acute disseminated encephalomyelitis: an update. Arch Neurol 2005;62:1673-80.
4. Thompson EJ, Riches PG, Kohn J. Antibody synthesis within the central nervous system: comparisons of CSF IgG indices and electrophoresis. J Clin Pathol 1983;36: 312-5.
5. Reiber H. The discrimination between different blood-CSF barrier dysfunctions and inflammatory reactions of the CNS by a recent evaluation graph for the protein profile of cerebrospinal fluid. J Neurol 1980;224:89-99.
6. *Idem*. Flow rate of cerebrospinal fluid (CSF) — a concept common to normal blood-CSF barrier function and to dysfunction in neurological diseases. J Neurol Sci 1994;122:189-203.
7. Reiber H, Peter JB. Cerebrospinal fluid analysis: disease-related data patterns and evaluation programs. J Neurol Sci 2001;184:101-22.
8. Case Records of the Massachusetts General Hospital (Case 15-1998). N Engl J Med 1998;338:1448-56.
9. Fishman RA. Cerebrospinal fluid in diseases of the nervous system. 2nd ed. Philadelphia: W.B. Saunders, 1992.
10. Norrby E, Vandvik B. Relationship between measles virus-specific antibody activities and oligoclonal IgG in the central nervous system of patients with subacute sclerosing panencephalitis and multiple sclerosis. Med Microbiol Immunol 1975; 162:63-72.
11. Wolinsky JS. Progressive rubella panencephalitis. In: Vinken PJ, Bruyn GW, Klawans HL, McKendall RR, eds. Viral disease. Amsterdam: Elsevier, 1989:405-16.
12. Townsend JJ, Baringer JR, Wolinsky JS, et al. Progressive rubella panencephalitis: late onset after congenital rubella. N Engl J Med 1975;292:990-3.
13. Weil ML, Itabashi H, Cremer NE, Oshiro L, Lennette EH, Carnay L. Chronic progressive panencephalitis due to rubella virus simulating subacute sclerosing panencephalitis. N Engl J Med 1975;292:994-8.
14. Honarmand S, Glaser CA, Chow E, et al. Subacute sclerosing panencephalitis in the differential diagnosis of encephalitis. Neurology 2004;63:1489-93.
15. Swoveland PT, Johnson KP. Subacute sclerosing panencephalitis and other paramyxovirus infections. In: Vinken PJ, Bruyn GW, Klawans HL, McKendall RR, eds. Viral disease. Amsterdam: Elsevier, 1989:417.
16. Gagnon A, Bouchard RW. Fulminating adult-onset subacute sclerosing panencephalitis in a 49-year-old man. Arch Neurol 2003;60:1160-1.
17. Prashanth LK, Taly AB, Ravi V, Sinha S, Arunodaya GR. Adult onset subacute sclerosing panencephalitis: clinical profile of 39 patients from a tertiary care centre. J Neurol Neurosurg Psychiatry 2006;77:630-3.
18. Bellini WJ, Rota JS, Lowe LE, et al. Subacute sclerosing panencephalitis: more cases of this fatal disease are prevented by measles immunization than was previously recognized. J Infect Dis 2005;192:1686-93.
19. Wirguin I, Steiner I, Kidron D, et al. Fulminant subacute sclerosing panencephalitis in association with pregnancy. Arch Neurol 1988;45:1324-5.
20. Gokcil Z, Odabasi Z, Demirkaya S, Eroglu E, Vural O. Alpha-interferon and isoprinosine in adult-onset subacute sclerosing panencephalitis. J Neurol Sci 1999; 162:62-4.
21. Anlar B, Yalaz K, Oktem F, Köse G. Long-term follow-up of patients with subacute sclerosing panencephalitis treated with intraventricular alpha-interferon. Neurology 1997;48:526-8.
22. Gascon G, Yamani S, Crowell J, et al. Combined oral isoprinosine-intraventricular alpha-interferon therapy for subacute sclerosing panencephalitis. Brain Dev 1993; 15:346-55.
23. Yalaz K, Anlar B, Oktem F, et al. Intraventricular interferon and oral inosiplex in the treatment of subacute sclerosing panencephalitis. Neurology 1992;42:488-91.
24. Steiner I, Wirguin I, Morag A, Abramsky O. Intraventricular interferon treatment for subacute sclerosing panencephalitis. J Child Neurol 1989;4:20-4.
25. Panitch HS, Gomez-Plascencia J, Norris FH, Cantell K, Smith RA. Subacute sclerosing panencephalitis: remission after treatment with intraventricular interferon. Neurology 1986;36:562-6.
26. Ueda S, Okuno Y, Hamamoto Y, Oya H. Subacute sclerosing panencephalitis (SSPE): isolation of a defective variant of measles virus from brain obtained at autopsy. Biken J 1975;18:113-22.
27. Hirano A, Ayata M, Wang AH, Wong TC. Functional analysis of matrix proteins expressed from cloned genes of measles virus variants that cause subacute sclerosing panencephalitis reveals a common defect in nucleocapsid binding. J Virol 1993; 67:1848-53.
28. Zaki SR, Bellini WJ. Measles. In: Connor DH, Chandler FW, Schwartz DA, Manz HJ, Lack EE, eds. Pathology of infectious diseases. Stamford, CT: Appleton & Lange, 1997:233-44.
29. Bellini WJ, Rota JS, Lowe LE, et al. Subacute sclerosing panencephalitis: more cases of this fatal disease are prevented by measles immunization than previously recognized. J Infect Dis 2005;192:1686-93.
30. Hummel KB, Lowe L, Bellini WJ, Rota PA. Development of quantitative gene-specific real-time RT-PCR assays for the detection of measles virus in clinical specimens. J Virol Methods 2006;132:166-73.