Clinical/Scientific Notes

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IDIOPATHIC EOSINOPHILIC MENINGOENCEPHALOMYELITIS FOLLOWING WELL SYNDROME

Eosinophilic meningitis is an uncommon condition often associated with helminthic infections. We present a patient with idiopathic eosinophilic meningoencephalomyelitis occurring 9 months after an episode of Well syndrome, an idiopathic eosinophilic cellulitis. The disorder mimics Gordon phenomenon, an experimentally induced encephalitis in animals associated with eosinophil-derived neurotoxicity.

Case report. A 55-year-old woman developed a rash on her legs. Skin biopsy revealed an eosinophilic cellulitis consistent with Well syndrome (figure, A and B). A peripheral eosinophilia of 1,134 cells/μL was present. The cellulitis resolved with a short course of oral steroids, and the eosinophilia diminished.

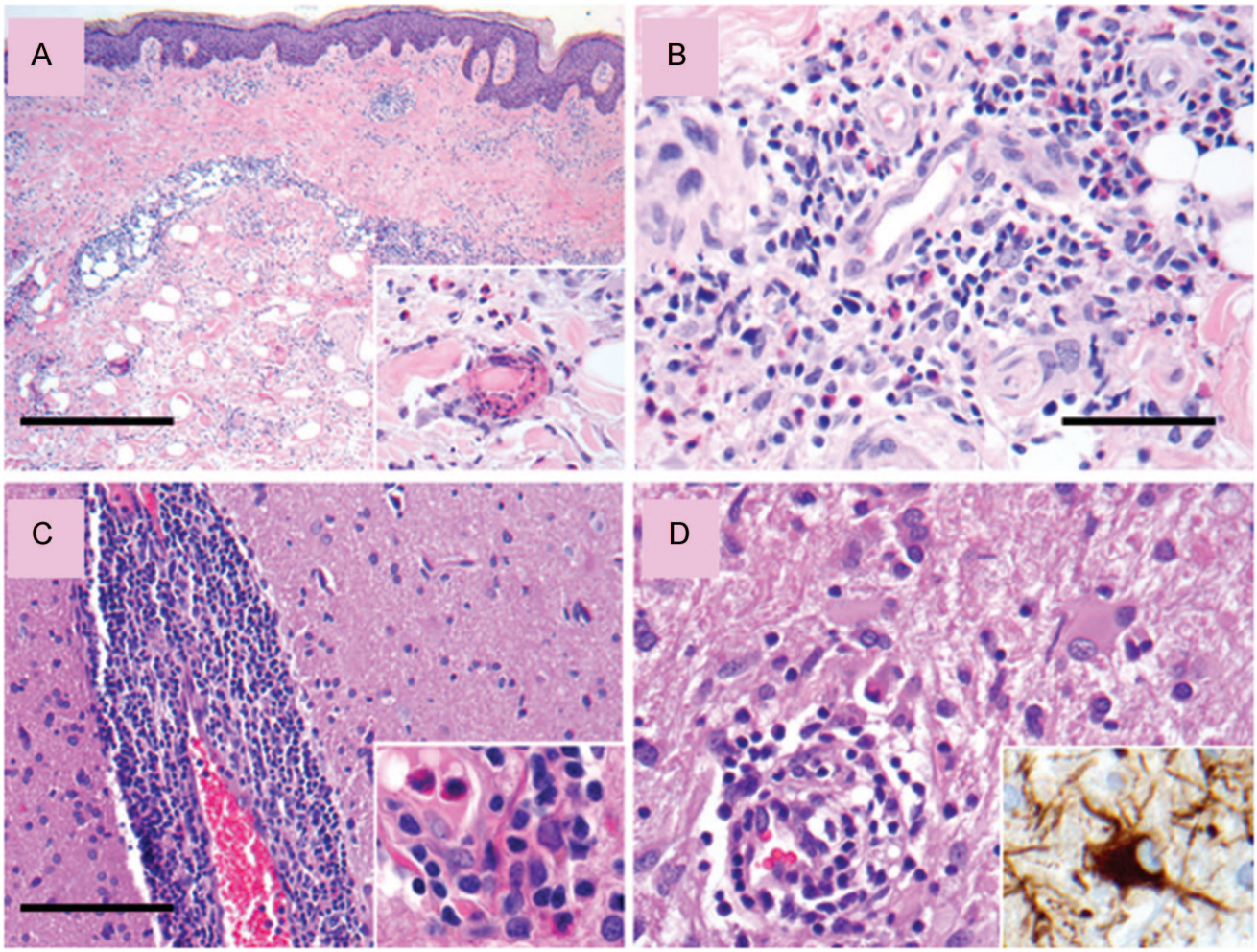
Nine months later, she developed vertigo and ataxia, followed by progressive dysarthria, double vision, headache, and tinnitus. A peripheral eosinophilia of 1,900 cells/μL was present. An initial brain MRI was unremarkable. Two weeks later, the MRI showed mild leptomeningeal enhancement and 2 globoid temporal white matter lesions. The CSF revealed a lymphocytic pleocytosis with 140 white blood cells and protein of 104 mg/dL. Three weeks later, the eosinophilic fraction increased (351 cells; 81% lymphocytes, 8% eosinophils, 8% monocytes). Cytology was negative for malignancy. A FiP1L1 platelet-derived growth factor receptor test was negative, making eosinophilic leukemia unlikely.[1] After a short course of empiric IV methylprednisolone, the patient was transferred to our hospital.

On admission, 5 weeks after onset, her examination revealed cerebellar dysarthria, extremely slow saccades in all directions, profound dysmetria, and gait ataxia. Despite an empiric course of albendazole, these findings gradually worsened, and she developed downbeat nystagmus and mild left hemiparesis. Serial CSF examination revealed 76, 78, and 61 white blood cells, with an increasing eosinophilic fraction (4%, 24%, 33%). Oligoclonal bands were present. An infectious evaluation was negative for strongyloides, toxocara, *Bartonella*, enterovirus, Whipple, coccidiomycosis, cysticercosis, Epstein-Barr virus, cytomegalovirus, varicella zoster virus, JC virus, parvovirus, hepatitis B and C, HIV, Lyme, syphilis, toxoplasma, mycoplasma, rickettsia, and histoplasmosis. Rheumatologic serologies and paraneoplastic testing were unremarkable. Whole body CT scan and breast ultrasound revealed no abnormalities. MRI 8 weeks after presentation revealed mild cerebellar vermal enhancement, new enhancement of the right temporal lesion, and 2 nonenhancing cervical spine lesions. Biopsy of the right temporal lobe revealed a brisk leptomeningeal, perivascular, and intraparenchymal mixed infiltrate with florid gliosis (figure, C and D). High-dose IV methylprednisolone was initiated 1 week after completing albendazole, and the patient's saccades improved rapidly. She was discharged on oral prednisone. The eosinophilic cellulitis recurred after tapering the prednisone several months later, but resolved after reinitiating it. Eighteen months after presentation, she continued to improve neurologically, with mild downbeat nystagmus, dysmetria, and ataxia. The white matter lesions improved and enhancement resolved on MRI. Peripheral eosinophilia has not recurred.

Discussion. Our patient presented with eosinophilic meningoencephalomyelitis 9 months after a bout of Well syndrome, an eosinophilic cellulitis. Well syndrome may occur as reaction to medications or malignancy, or be idiopathic, as in our patient.[2] One of the unusual features of our patient was the prominent cerebellar findings in the absence of an obvious cerebellar inflammatory infiltrate. This observation is consistent with experimental evidence that neurologic damage associated with eosinophilia may result from neurotoxic factors such as eosinophil-derived-neurotoxin (EDN) and the eosinophil cation protein (ECP).

The association between eosinophils and neurotoxicity was discovered serendipitously after Gordon[3] injected lymph node suspensions from patients with Hodgkin disease into rabbits' thecal sacs. Some of the rabbits developed a neurologic syndrome characterized by diffuse spongiform demyelination, most prominent in the cerebellum, brainstem, and spinal cord.[4] This "Gordon phenomenon" was only observed when an eosinophilic infiltrate was found in the lymph nodes. Subsequently, Durack et al.[5] puri-

Figure Histopathology of eosinophilic cellulitis and meningoencephalitis



(A, B) Skin biopsy showed a dermal eosinophilic infiltrate associated with necrotic collagen (so-called "flame figures," shown in inset) consistent with Well syndrome. Stains for microorganisms were negative. (C) Right temporal leptomeningeal and neocortical biopsy revealed a mixed inflammatory infiltrate comprised of lymphocytes, eosinophils (see inset), plasma cells, and macrophages with a prominent perivascular distribution. (D) The inflammatory infiltrate was associated with a florid astrocytic gliosis, highlighted by glial fibrillary acid protein staining (inset). Detailed staining did not reveal evidence for an infectious cause or malignancy. Scale bars: 500 μm (A), 62.5 μm (B, D), 125 μm (C).

fied the specific toxin, EDN. Injection of purified EDN in rabbits produces similar clinical and histopathologic findings found in the Gordon phenomenon including ataxia. Pathologically, spongiform lesions in the white matter and loss of cerebellar Purkinje cells have been noted. Our patient had prominent cerebellar findings without an obvious inflammatory disease burden in this location, suggesting that some of her deficits may have resulted from the remote effect of eosinophilic neurotoxicity.

Recently, ECP was demonstrated in the eosinophils of an inflammatory infiltrate from a brain biopsy of a patient with idiopathic hypereosinophilic syndrome. Histologic examination revealed perivascular and parenchymal inflammatory infiltrates without tissue or neuronal damage.[6] The lack of correlation between the eosinophilic infiltrates and tissue damage seen in eosinophilic encephalitis along with the role of the EDN and ECP in experimental and clinical cases suggests that nervous system injury associated with eosinophilia may result from remote injury from toxins secreted by such cells.

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1. Peros-Golubicic TA, Smojver-Jezek SB. Hypereosinophilic syndrome: diagnosis and treatment. Curr Opin Pulmonary Med 2007;13:422–427.
2. Moossavi M, Mehregan DR. Well's syndrome: a clinical and histopathologic review of seven cases. Int J Dermatol 2003;42:62.
3. Gordon MH. Remarks on Hodgkin's disease: a pathogenic agent in the glands, and its application in diagnosis. BMJ 1933;1:641–644.
4. Durack DT, Sumi SM, Klebanoff SJ. Neurotoxicity of human eosinophils. Proc Natl Acad Sci USA 1979;76:1443–1447.
5. Durack DT, Ackerman SJ, Loegering DA, Gleich GJ. Purification of human eosinophil-derived neurotoxin. Proc Natl Acad Sci USA 1981;78:5165–5169.
6. Tamaru Y, Nakashita M, Ito H, Okumura R, Matsumoto S, Imai T. Spontaneous remission of a massive CNS inflammation with eosinophilic infiltrate. Intern Med 2003;42:424–427.

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LIMBIC ENCEPHALITIS ASSOCIATED WITH ANTIBODIES TO THE NMDA RECEPTOR IN HODGKIN LYMPHOMA

Convulsions, fever, and memory loss after chemotherapy are usually due to opportunistic infection, and often attributed to infection even if CSF viral PCR examination is negative. We describe a case of limbic encephalitis in a patient with relapsed Hodgkin lymphoma, in whom antibodies to the NMDA receptor were identified in serum and CSF, and whose anterograde memory improved with aggressive immunotherapy. Paraneoplastic limbic encephalitis in Hodgkin lymphoma has been reported before,[1,2] but no target antigen identified. The case adds to the clinical associations of NMDA receptor antibodies.

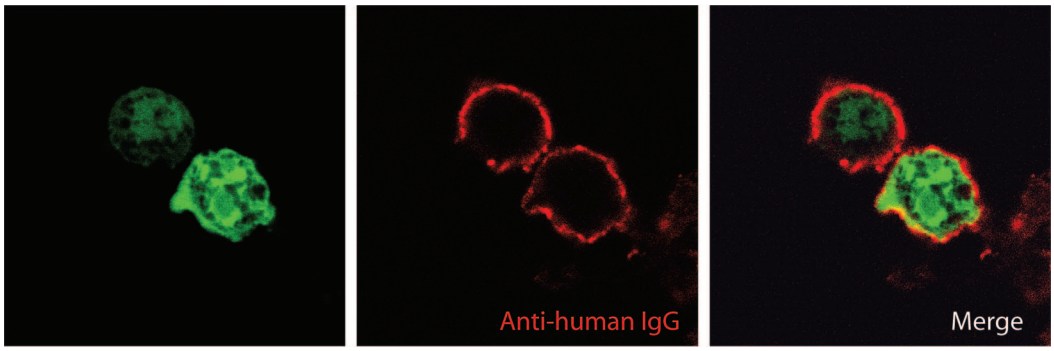
Case report. A 49-year-old man developed an amnesic syndrome temporally related to a second relapse of nodular sclerosing Hodgkin lymphoma. Eight years previously he had developed a large cervical lymph node and was successfully treated with mantle radiotherapy. He received chemotherapy to treat an abdominal relapse 2 years later, and maintained remission for 5 years. Last year he relapsed with a large abdominal para-aortic mass, and 3 weeks after his first cycle of treatment, with gemcitabine and cisplatin, he developed confusion and disorientation over 2 days, culminating in a generalized seizure while driving. Initial confusion and memory loss was assumed to be postictal, but his anterograde memory deficit persisted and worsened: at worst he could encode 4 of 7 parts of an address but could not recall or recognize any components at 5 minutes. He had no evidence of a movement disorder. There was no neutropenia. Erythrocyte sedimentation rate was 75 mm/hour (1–7), C-reactive protein 187 mg/L (0–6). MRI revealed abnormal signal bilaterally in the temporal lobes on T2 and fluid attenuation inversion recovery imaging (figure e-1 on the *Neurology*® Web site at www.neurology.org). CSF examination revealed 4×10^6/L white cells. He was treated with IV acyclovir and sodium valproate for possible herpes encephalitis. Initial EEG was within normal limits. CSF examination a few days later demonstrated 10×10^6/L lymphocytes, normal protein and glucose, and was sterile on culture; viral PCR was subsequently negative for herpes simplex and varicella zoster virus DNA, and enterovirus RNA. No malignant cells were seen. There were oligoclonal bands in the CSF, unmatched in the serum. Serum sodium, thyroid stimulating hormone, immunoglobulins, protein electrophoresis, B12, and red cell folate were normal. Lactate dehydrogenase was 306 U/L (120–240). Blood cultures were negative. Serum antibodies to thyroid peroxidase, Hu, Yo, Ri, voltage gated potassium channels, amphiphysin, Ma, CV2/CRMP5, tissue transglutaminase, and antiphospholipid antibodies were negative. There was no immunohistochemical evidence of anti-Tr. Serum and CSF antibodies to the NMDA receptor were present on a direct immunofluorescence cell based assay, in which serum was tested against NR1 and NR2b subunits expressed on human embryonic kidney cells (figure).[3]

He received immunosuppression with high dose oral steroids, followed by IV immunoglobulin. Symptoms and further EEG and MRI were unchanged. He underwent 10 days of plasma exchange after which his neurologic symptoms started to improve: he could encode all 7 parts of an address, and recall 3 parts at 5 minutes, with a contemporaneous MRI showing marked resolution of the temporal lobe high signal. He received radical chemotherapy and then in December 2008 preparation for autologous stem cell transplantation, but unfortunately had radiologic evidence of significant abdominal disease and entered palliation. His anterograde memory has continued to improve functionally to date (at least 6 months after initial presentation).

Discussion. Limbic encephalitis in Hodgkin lymphoma was first described, and termed the Ophelia

Supplemental data at www.neurology.org

Figure Immunofluorescence cell-based assay



Human embryonic kidney (HEK) cells cotransfected with NR1/2B and EGFP cDNA (green). The patient's antibodies bound strongly to the surface of the cells, as detected with Alexa Fluor–568 conjugated antihuman immunoglobulin G (red).

syndrome, by the pathologist Ian Carr in an account of his daughter's illness.[1] Paraneoplastic limbic encephalitis is most commonly due to small cell lung cancer, and rarely due to other cancers which express proteins that share epitopes with neurons and glia, including Hodgkin lymphoma.[2,4] Here, we describe limbic encephalitis associated with relapsed Hodgkin lymphoma, with antibodies to the NMDA receptor and response to plasmapheresis. This case adds to the clinical associations of anti-NMDAR encephalitis,[5] and should prompt antibody testing with a cell-based assay[6] in cases of relatively pure limbic encephalitis. Anti-NMDAR encephalitis was first described in young women with ovarian teratomata who exhibited a rhythmic movement disorder, hypoventilation requiring ventilation, and autonomic instability, although both sexes and a wider age range has now been reported.[5] The case for pathogenicity of anti-NMDAR antibodies is based on the surface expression of the targeted antigens and the often impressive response of patients to immunosuppression, in comparison to paraneoplastic degenerations where the neuronal target is intracellular.[7] This case should raise a wider recognition of paraneoplastic and autoimmune processes in patients whose symptoms might otherwise be attributed to chemotherapy or infection.

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1. Carr I. The Ophelia syndrome: memory loss in Hodgkin's disease. Lancet 1982;1:844–845.
2. Gultekin SH, Rosenfeld MR, Voltz R, Eichen J, Posner JB, Dalmau J. Paraneoplastic limbic encephalitis: neurological symptoms, immunological findings and tumour association in 50 patients. Brain 2000;123:1481–1494.
3. Dalmau J, Tüzün E, Wu HY, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol 2007;61:25–36.
4. Ances BM, Vitaliani R, Taylor RA, et al. Treatment-responsive limbic encephalitis identified by neuropil antibodies: MRI and PET correlates. Brain 2005;128:1764–1777.
5. Dalmau J, Gleichman AJ, Hughes EG, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol 2008;7:1091–1098.
6. Takahashi Y. Epitope of autoantibodies to N-methyl-D-aspartate receptor heteromers in paraneoplastic limbic encephalitis. Ann Neurol 2008;64:110–111; author reply 111–112.
7. Dalmau J, Rosenfeld MR. Paraneoplastic syndromes of the CNS. Lancet Neurol 2008;7:327–340.

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INTRAMEDULLARY SJÖGREN SYNDROME

Sjögren syndrome (SS) is a systemic autoimmune disorder predominantly affecting the exocrine glands, involving the CNS in 20%–25% of cases. Previous neuropathologic specimens in Sjögren myelopathy have suggested a vasculitic pathophysiology.

Case report. A 66-year-old woman developed sicca symptoms followed by subacutely evolving neck pain, paraparesis, and paresthesias below her neckline. She had 5 similar attacks over ensuing months, partially improved by IV methylprednisolone, but gradually became cane dependent and noted anesthesia below her chest. Her only regular medication was benazepril.

One year later, her symptoms recurred, and she presented to our institution. On examination, there was flaccid hyporeflexic upper extremity paresis with areflexic paraplegia. A T5 sensory level was noted. There was no optic disc pallor, dysmetria, or dyssynergia.

Brain MRI was unremarkable except for small vessel disease. Spinal MRI showed multiple patchily enhancing, longitudinal white matter lesions (several extending over 3 corresponding vertebral body segments) from the medullary spinal junction to the conus medullaris.

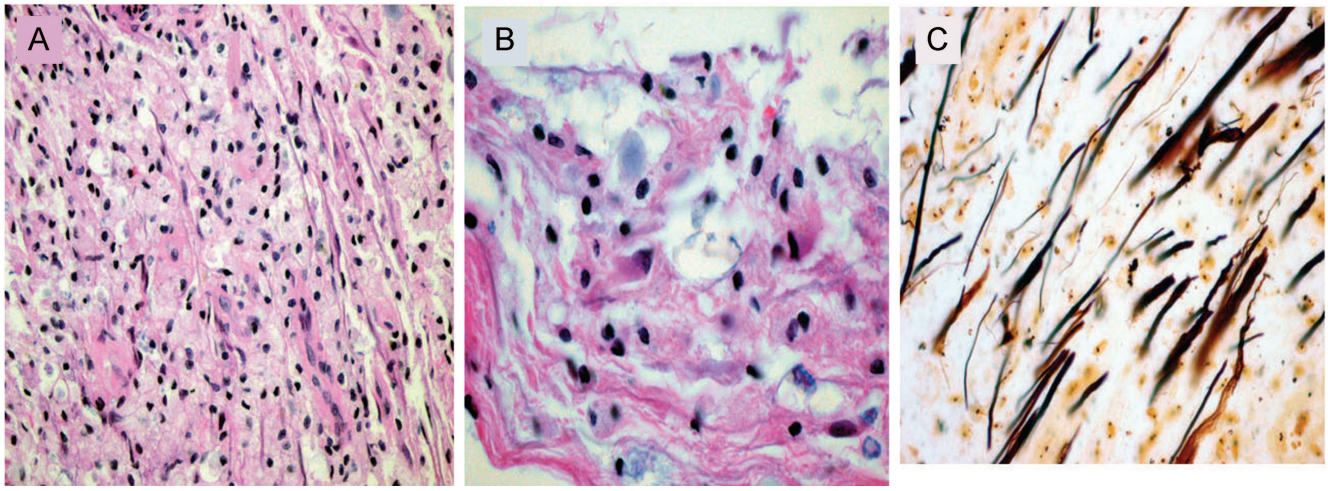
CSF showed protein 208, glucose 79, 9 erythrocytes, and 9 leukocytes, including 6 lymphocytes, 2 histiocytes, and 1 neutrophil. CSF de novo immunoglobulin G (IgG) synthesis was 45.6 (−9.9 to 3.3 mg/day) and CSF IgG index was 0.8 (0.0–0.7). Possible matching IgG bands in serum and CSF were seen. SSA, SSB, antinuclear antibodies (1:320, normal 1:40), Smith (1:50), and RNP (1:100) were positive. Serum NMO IgG antibody was negative.

A biopsy of dura, epidura, and (T8–T10) spinal cord revealed extensive demyelination without evidence of vasculitis or malignancy (figure). A minor salivary gland biopsy was consistent with SS. The patient was subsequently treated with cyclophosphamide and hydroxychloroquine for 6 months without improvement.

Discussion. Our patient presented with relapsing inflammatory myelopathy initially responsive to steroid therapy. While MS or NMO were considered, we believed a diagnosis of Sjögren myelopathy was more likely due to the clearcut associated SS diagnosis (serology and biopsy proven), older patient age, and lack of NMO antibodies or historical optic neuritis. However, the possibility of a primary form of NMO in evolution, or of overlapping comorbid NMO spectrum disorder, remains possible since serum NMO antibody positivity is not invariably present in patients with clinically established NMO, and given that NMO seropositivity is less frequent in those with isolated recurrent longitudinally extensive transverse myelitis (LETM).[1] CSF NMO antibody testing is occasionally diagnostic in seronegative NMO patients without optic nerve involvement, but was not obtained in our patient.[2]

SS is an autoimmune connective tissue disorder characterized by lymphocytic infiltration of exocrine glands and B-lymphocyte hyperactivity. CNS involvement has been estimated to affect 10%–25% of SS patients.[3] Common associated neurologic manifestations of SS are sensory neuropathy and trigemi-

Figure Spinal cord biopsy



Hematoxylin-eosin stain (A) revealed spinal cord tissue composed of axons with numerous foamy macrophages. The Luxol Fast Blue stain (B) demonstrates aggregates of myelin within macrophages and a loss of axonal myelin. The Bielschowsky stain (C) demonstrates numerous axons.

nal neuropathy. Spinal cord presentations may include acute transverse myelopathy, chronic progressive myelopathy, and Brown-Sequard syndrome.[3,4]

Peripheral nerve biopsies in patients with SS with peripheral nervous system symptomatology have revealed vasculitis or perivascular mononuclear cell infiltration.[4]

The pathogenesis of CNS SS has remained unclear. CNS involvement by SS has been postulated to have a vasculitic pathophysiology similar to previously reported pathologic specimens from peripheral nerve and other organs. Previous pathology in CNS SS has shown vasculitis or a perivascular mononuclear infiltration. Microinfarcts and microhemorrhages with hypertrophic or damaged endothelial cells have also been seen.[3,4]

CNS involvement in SS could also arise from autoimmune demyelination. Recently published cases have linked SS to Devic neuromyelitis.[5] Another case of SS revealed necrosis and demyelination of the cerebellar white matter postmortem.[6]

A longitudinal study suggested that anti-CNS antibodies may be an important marker for cerebral involvement in connective tissue diseases.[7] Demyelination could represent one stage of pathogenesis in a vasculitic myelopathy. However, the biopsy in our patient was performed following subacute deterioration after months of illness, and no evidence of active or previous blood vessel involvement such as areas of infarctions, hemorrhage, or perivascular lymphocytic infiltrates were seen, making a vasculitic pathophysiology unlikely.

SS should be considered in the differential diagnosis of inflammatory myelopathy, especially in the presence of sicca symptoms. The intramedullary demyelination unassociated with NMO antibodies seen in our case expands the spectrum of known pathophysiology seen in CNS SS. Additional tissue from future biopsies and autopsies are needed to clarify the pathogenesis of Sjögren myelopathy and hopefully guide more specific treatments.

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1. Lennon VA, Wingerchuk DM, Kryzer TJ, et al. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. Lancet 2004;364:2106–2112.
2. Klawiter EC, Alvarez E 3rd, Xu J, et al. NMO-IgG detected in CSF in seronegative neuromyelitis optica. Neurology 2009;72:1101–1103.
3. Govoni M, Padovan M, Rizzo N, Trotta F. CNS involvement in primary Sjögren's syndrome: prevalence, clinical aspects, diagnostic assessment and therapeutic approach. CNS Drugs 2001;15:597–607.
4. Niemela RK, Hakala M. Primary Sjögren's syndrome with severe central nervous system disease. Semin Arthritis Rheum 1999;29:4–13.
5. Gökçay N, Çelebisoy A, Gökçay Y, Kabasakal Y, Öder G. Primary Sjögren's syndrome presenting as neuromyelitis optica. Pediatr Neurol 2007;36:58–60.
6. Ichikawa H, Ishihara K, Fujimoto R, et al. An autopsied case of Sjögren's syndrome with massive necrotic and demyelinating lesions of the cerebellar white matter. J Neurol Sci 2004;225:143–148.
7. Weiner SM, Klein R, Berg PA. A longitudinal study of autoantibodies against central nervous system tissue and gangliosides in connective tissue disease. Rheumatol Int 2000;19:83–88.

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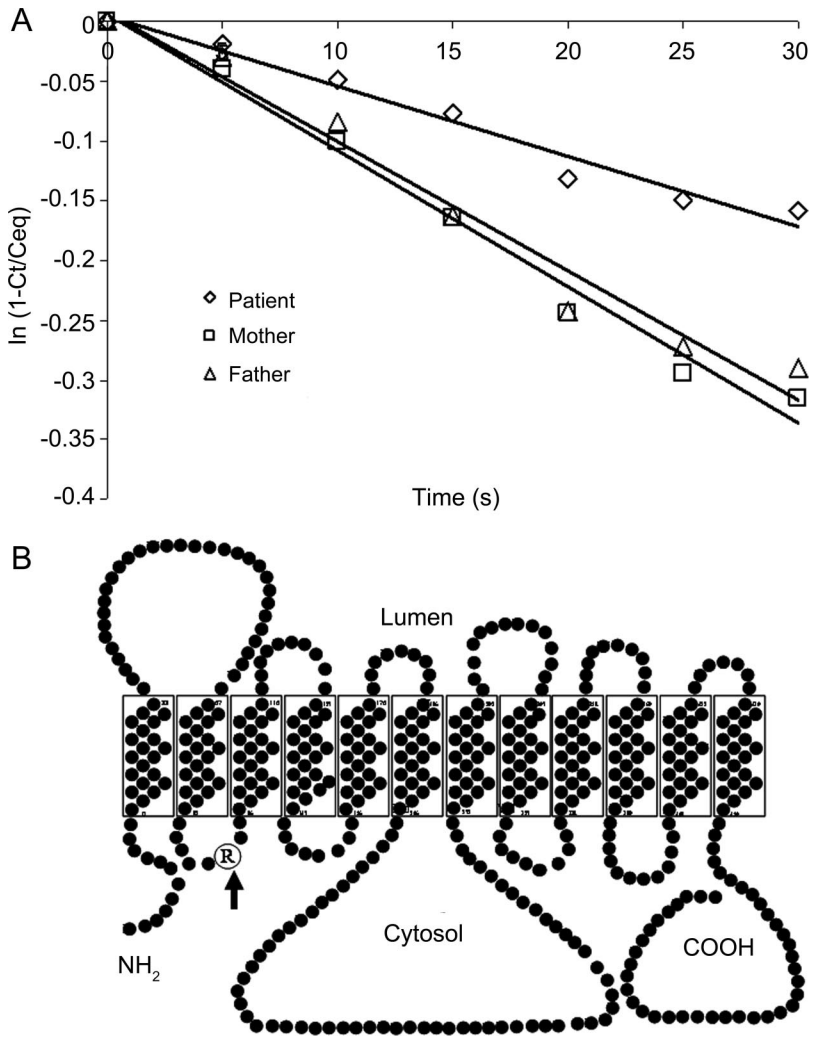
GLUT1 DEFICIENCY AND ALTERNATING HEMIPLEGIA OF CHILDHOOD

Alternating hemiplegia of childhood (AHC) is a neurodevelopmental syndrome of uncertain etiology.[1] It is characterized by onset of hemiplegic, tonic, or dystonic episodes occurring before the age of 18 months. Progressive ataxia and cognitive impairment are frequent. AHC has been reported to be caused by mutations in the *ATP1A2* and the *CACNA1A* genes,[2,3] but most cases of AHC remain genetically undiagnosed.

Glut1 deficiency syndrome (Glut1 DS, OMIM 606777) is a disorder of brain energy metabolism caused by impaired glucose transport into the brain mediated by the facilitative glucose transporter Glut1, encoded by the *GLUT1* gene.[4] The hallmark of the disease is low CSF glucose concentration.[5] Classic presentation of Glut1 DS includes epilepsy, developmental delay, acquired microceph-

Figure Glut1 protein: Functional and structural analysis



(A) 3-O-methyl-D-glucose uptake into red blood cells, which was performed as described elsewhere.[4] Decreased uptake rate in patient is shown compared with parents serving as control. The data are expressed as the natural logarithm of the ratio of intracellular radioactivity at time T/equilibrium vs time in seconds (2 determinations/data point). (B) The proposed Glut1 protein configuration with the R93W mutation (arrow) situated in the first cytosolic loop.

aly, cognitive impairment, spasticity, ataxia, and dystonia. Paroxysmal movement disorders with or without epilepsy have been described as well, such as paroxysmal episodes of abnormal head or eye movements, intermittent ataxia,[4] and paroxysmal exercise-induced dyskinesias.[5] The ketogenic diet may have a beneficial effect on symptom control and development.[4]

We report a child with AHC found to have a mutation in the *GLUT1* gene.

Case report. The patient is now 10 years old. There is no pertinent family history. The perinatal period and initial development were normal. He walked unassisted at 14 months and was noted to fall more frequently than his peers. At 2 years he began having episodes of ataxia and slurred speech, lasting for 10–15 minutes. From 2.5 years asymmetry was noted during the episodes, with right or left sided hemiplegia, unilateral facial weakness, and slurred speech lasting for 3–4 hours. The episodes included pallor and irritability. Upon awakening he was asymptomatic, and within an hour would start to show unilateral weakness. Episodes were mitigated or aborted by beverages or candy. There were no eye movement abnormalities. He was diagnosed with AHC. Treatment with flunarizine made the events milder and shorter. He has shown gradual cognitive deterioration. Current neuropsychologic evaluation showed full-scale IQ of 51. He has gradually developed a mild ataxic gait. Head circumference has decreased from the 50th percentile to below the third percentile. Brain MRI was normal. Two lumbar punctures showed CSF glucose concentrations of 35 and 39 mg/dL, and serum glucose concentrations of 99 and 80 mg/dL. CSF lactate was 1.07 mM. The ketogenic diet was poorly tolerated with severe weight loss. The patient is currently supplementing his diet with cornstarch, which has made the events milder and less frequent. We evaluated him at age 10 years for Glut1 DS.

Methods. Erythrocyte 3-O-methyl-D-glucose uptake and *GLUT1* mutational analysis were performed as described elsewhere.[4]

Results. Patient uptake of 3-O-methyl-D-glucose was 53% (figure, A), Vmax for 3-O-methyl-D-glucose uptake was 52% (patient: 500 fmol/s/10^6 cells, controls: 1,000 fmol/10^6 cells, 909 fmol/10^6 cells), and Km was 97% (patient: 1.3 mM, controls: 1.4 mM and 1.3 mM). *GLUT1* mutational analysis revealed a single nucleotide replacement CGG>TGG at nucleotide 277, resulting in a heterozygous R93W missense mutation in exon 4. Parents' analysis was normal. This mutation is located in the first cytosolic loop of Glut1 (figure, B). R93W or R93Q mutations have been described previously in Glut1 DS associated with a typical epileptic phenotype.[6]

Discussion. AHC patients may have cerebral glucose deficiency. Low glucose metabolism was found in the frontal lobes, putamen, and cerebellum of patients with AHC as measured by ^{18}F-fluorodeoxyglucose PET.[7] This pattern of cortical and cerebellar glucose hypometabolism also has been described in Glut1 DS.[6] We describe a child with Glut1 DS presenting with episodes of alternating hemiplegia, progressive ataxia, cognitive deterioration, and decelerating head growth. Other than the

episodes starting after the age of 18 months, the phenotype is typical for AHC.[2] The hallmark of Glut1 DS is low CSF glucose concentration, usually below 40 mg/dL.[4,5] A literature search of AHC cases failed to show CSF findings in this population. Episodes of AHC are triggered by physical activity, environmental stress, and certain foods but not by fasting.[2] We recommend that children with AHC be tested for hypoglycorrhachia, especially if symptoms are induced by physical activity or fasting. If the glucose concentration is low, further evaluation as described in this case should be performed. Early treatment with the ketogenic diet should be considered in all children with Glut1 DS.

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1. Sweney MT, Silver K, Gerard-Blanluet M, et al. Alternating hemiplegia of childhood: early characteristics and evolution of a neurodevelopmental syndrome. Pediatrics 2009;123:e534–e541.
2. Swoboda KJ, Kanavakis E, Xaidara A, et al. Alternating hemiplegia of childhood or familial hemiplegic migraine? A novel ATP1A2 mutation. Ann Neurol 2004;55:884–887.
3. de Vries B, Stam AH, Beker F, et al. CACNA1A mutation linking hemiplegic migraine and alternating hemiplegia of childhood. Cephalalgia 2008;28:887–891.
4. Wang D, Pascual JM, Yang H, et al. Glut1 deficient syndrome: clinical, genetic, and therapeutic aspects. Ann Neurol 2005;57:111–118.
5. De Vivo DC, Wang D. Glut1 deficiency: CSF glucose. How low is too low? Rev Neurol Paris 2008;164:877–880.
6. Pascual JM, Van Heertum RL, Wang D, Engelstad K, De Vivo DC. Imaging the metabolic footprint of Glut1 deficiency on the brain. Ann Neurol 2002;52:458–464.
7. Sasaki M, Sakuma H, Fukushima A, Yamada K, Ohnishi T, Matsuda H. Abnormal cerebral glucose metabolism in alternating hemiplegia of childhood. Brain Dev 2009;31:20–26.

CDC, AAN to Health Care Professionals: Monitor Patients for GBS

The Centers for Disease Control and Prevention (CDC) and the American Academy of Neurology (AAN) collaborated to reach out to neurologists across the US to monitor and report any possible new cases of Guillain-Barré syndrome (GBS) following 2009 H1N1 flu vaccination.

Neurologists and health care professionals nationwide who diagnose patients with vaccine-associated GBS should use the CDC and FDA Vaccine Adverse Event Reporting System (VAERS) to report their observations.

In addition, neurologists and all health practitioners in the 10 Emerging Infections Program (EIP) states—California, Connecticut, Maryland, Minnesota, New Mexico, New York, Colorado, Oregon, Georgia, and Tennessee—are asked to report all new cases of GBS, regardless of vaccination status, to their state's surveillance officer.

The AAN hosted a series of webinars providing an in-depth look at H1N1 vaccination and how it may pose a risk for GBS and information about the vaccination monitoring campaign.

For additional information about the monitoring campaign, or to watch the webinars or download VAERS form and information on reporting to surveillance officers in your state, visit the AAN's GBS toolkit page, *www.aan.com/view/gbstoolkit*.