individuals; probability calculations assumed independent trials so cannot be interpreted strictly.

To our knowledge, this is the first epidemiologic study of HD in an American Indian tribe and the only report detailing the absence of HD in any population. Taken with studies of amyotrophic lateral sclerosis³ and Parkinson disease,⁴ these data point to differentially distributed neurodegenerative disorders among American Indians and other populations. Research into the reasons underlying these contrasts could yield better understanding of often cryptogenic and universally incurable brain disorders.

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CNS DEMYELINATION AND ENHANCED MYELIN-REACTIVE RESPONSES AFTER IPILIMUMAB TREATMENT

Ipilimumab is a monoclonal antibody that prolongs survival in patients with metastatic melanoma.¹ It targets the coinhibitory receptor cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4). CTLA-4 signaling induces a state of T-cell unresponsiveness, which facilitates tumor escape from immune surveillance. Blockade of CTLA-4 is believed to shift the immune status from T-cell exhaustion to a functional antitumor response. Anti-CTLA-4 therapy is associated with immune-related adverse events in 64% of patients. Autoimmunity involving the nervous system has a low incidence and manifests predominantly as peripheral inflammatory neuropathy.² We report new-onset inflammatory CNS demyelination in an ipilimumab-treated melanoma patient (figure), confirmed by histology and associated with enhanced responses of myelin-reactive CD4⁺ T cells.

Methods. A 76-year-old woman was diagnosed with stage III melanoma in 1997 for which she underwent

surgery and received adjuvant vaccination. The patient did well until May 2014, when she was found to have kidney, spleen, and peritoneal masses. A kidney biopsy confirmed metastatic melanoma with BRAF^{V600K} mutation. The patient underwent 4 cycles of ipilimumab immunotherapy from June to August 2014. Restaging 2 weeks after completion of immunotherapy demonstrated partial responses but also a new enhancing lesion in the left posterior cingulate gyrus (figure, A) that was assumed to represent metastatic disease. Treatment was switched to dabrafenib and trametinib in mid-September and gamma knife stereotactic radiosurgery (SRS) was administered to the left posterior cingulate gyrus 2 weeks later (margin dose 20 Gy). Two weeks after SRS, the patient was readmitted with fatigue, memory loss, and vision changes and repeat MRI demonstrated new signal abnormalities in the left optic nerve, left inferior frontal lobe, and splenium of the corpus callosum, which extended into the parietal lobe and bordered on the SRS-treated lesion that by now was no longer

Figure Inflammatory CNS demyelination and enhanced myelin-reactive T-cell responses in a patient with melanoma treated with ipilimumab (IP)

Three-tesla MRI scans obtained 2 weeks (scan A) and 6 weeks (scan B) after completion of IP therapy. (A) Axial fluid-attenuated inversion recovery (FLAIR) at the level of the peritrial white matter of the lateral ventricles demonstrate an abnormal focus of increased T2 signal in the left posterior cingulate gyrus (arrow) with corresponding enhancement on T1 postgadolinium imaging (arrowhead). In addition, several scattered foci of abnormal FLAIR signal are seen in the periventricular and subcortical white matter consistent with small vessel ischemic disease. (B) FLAIR images demonstrate increased T2 signal changes seen in the intracanalicular segment of the left optic nerve, the left orbital gyrus of the inferior frontal lobe, and splenium of the corpus callosum (arrows). Changes related to stereotactic radiosurgery are present in the left posterior parietal lobe (arrowhead) with evidence of faint residual enhancement in this region on postcontrast sequences (not shown). The green dot indicates the site of the biopsy taken 1 week after this MRI. (C-F) Representative section of the corpus callosum biopsy. (C) Low-power magnification with a large area of demyelinated white matter, indicated by absence of myelin basic protein (MBP), and an abundance of infiltrating CD68⁺ macrophages (MBP, brown; CD68, purple). Scale bar 2 mm. (D) Detail from (C) shows MBP⁺ myelin debris within phagocytosing macrophages (arrowheads) as well as streaks of myelin still connected to axons (arrow). Scale bar 40 μ m. (E) Immunolabeling for CD3 shows a cluster of tissue-infiltrating lymphocytes. Scale bar 150 μ m. (F) High-power magnification demonstrates demyelinated but mostly preserved axons (arrowheads) separated by foamy macrophages (arrows). Bielschowsky stain. Scale bar 75 μ m. C-E counterstained with hematoxylin (blue). (G, H) Phenotypic analysis of myelin-reactive CD4⁺ T cells from the IP-treated patient, patients with multiple sclerosis (MS), and healthy controls (HC). CCR6⁺ memory T-cell libraries were generated and cultured with irradiated autologous monocytes with or without a myelin peptide pool (MBP₈₅₋₉₉, myelin oligodendrocyte glycoprotein [MOG]₉₇₋₁₀₉, MOG₂₂₂₋₂₄₁, proteolipid protein [PLP]₃₀₋₄₉, PLP₁₂₉₋₁₄₈, and PLP₁₈₀₋₁₉₉) and with *Candida albicans* as control as described.⁷

Continued

enhancing (figure, B). A 5-day course of high-dose Solu-Medrol did not improve clinical symptoms. A biopsy of the left splenic lesion was performed, 1 month after radiosurgery and 2 months after the last ipilimumab dose, revealing acute/subacute inflammatory demyelination without evidence of tumor cells (figure, C–F). The patient was treated with cyclophosphamide and discharged to rehabilitation. She entered hospice care in January 2015, 3 months after admission, and died 1 month later.

Results. We compared the functional profiles of the patient's myelin-reactive T cells to those of myelin-reactive T cells from 14 age-/sex-matched patients with multiple sclerosis (MS) and healthy controls by generating T-cell libraries from peripheral blood of all participants and measuring their responses to myelin peptides. Proliferation rates and proinflammatory cytokine production of myelin-reactive CD4+ T cells from the ipilimumab-treated patient were higher than that of myelin-reactive CD4+ T cells from healthy subjects and similar to those from patients with MS in response to myelin antigens (figure, G and H). Conversely, fewer T cells from the ipilimumab-treated patient and patients with MS than from healthy controls produced the anti-inflammatory cytokine IL-10, without differences in T-cell responses to *Candida albicans* (figure, G), confirming the specificity of the T-cell response to myelin peptides. Thus, myelin-reactive T cells from the ipilimumab-treated patient exhibited an enhanced autoimmune response similar to that observed in patients with MS and distinct from healthy controls.

Discussion. Treatment with immune checkpoint inhibitors is currently revolutionizing cancer therapy.³ CTLA-4 is the best-characterized inhibitory pathway for T-cell activation and has been shown experimentally to play a key role in limiting T-cell reactivity in MS and its animal models.⁴ Moreover, a recent report of a patient with stable relapsing-remitting MS who had a severe relapse after ipilimumab treatment for metastatic melanoma suggests that blocking CTLA-4 signaling can induce MS exacerbations.⁵

The presentation of this patient is complicated by administration of SRS, which can induce

inflammatory demyelination in susceptible individuals in the vicinity of the radiation field, typically 9–18 months after SRS.⁶ The white matter lesions reported here occurred 2 weeks after radiosurgery at multiple sites, including optic nerve and left frontal lobe, too early to be induced by SRS.

Finally, functional profiling of myelin-reactive CD4+ T cells revealed an inflammatory T_H1/T_H17 phenotype that resembled that of myelin-reactive T cells in patients with MS. This phenotype has been shown to be pathogenic in an animal model of MS, suggesting that demyelination in this patient was induced by an ipilimumab-associated pathogenic T-cell response against myelin. It would be interesting to examine whether this pathogenic phenotype is absent in ipilimumab-treated patients who did not develop inflammatory demyelination.

As the use of immune checkpoint inhibitors for cancer treatment increases, neurologists must be aware that immunotherapy can induce de novo inflammatory demyelination and worsen existing MS. Presence of new brain lesions after ipilimumab treatment requires careful evaluation to distinguish among brain metastases, SRS-induced encephalopathy, and inflammatory demyelination.

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Figure legend, continued:

(G) Heat map details functional responses of multiple T-cell libraries from a healthy control, a patient with MS, and the IP-treated patient, all age-, sex- and race-matched. Proliferation measured by ³H-thymidine incorporation on day 5 and culture supernatants examined on day 7 by ELISA for interferon (IFN)- γ , interleukin (IL)-17, granulocyte-macrophage colony-stimulating factor (GM-CSF), and IL-10. Data were z score-normalized for each parameter. A total of 96 T-cell libraries were tested for each individual. Each bar per column represents one T-cell library. Each row represents the different measurements that were performed on an individual library. (H) Percentage of proliferating and cytokine production of myelin-reactive T-cell libraries from the IP-treated patient compared to 14 matched patients with MS and healthy controls. Data are shown as mean $\pm$ SEM. CPM = counts per minute; N.D. = not detectable. * $p < 0.05$, ** $p < 0.01$, unpaired Mann-Whitney test.

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GLOBAL CEREBRAL EDEMA FROM HYPERCAPNIC RESPIRATORY ACIDOSIS AND RESPONSE TO HYPEROSMOLAR THERAPY

Hypercapnic respiratory acidosis (HRA) causes cerebral vasodilation via perivascular extracellular pH changes.¹ Its ability to precipitate global cerebral edema (GCE) in the absence of acute brain injury is rare. Treatment in these reports involves mechanical ventilation.² We describe a rare case of HRA-induced GCE in a patient without brain injury and the efficacy of hyperosmolar treatment after mechanical ventilation failed.

This case provides Class IV evidence. This is a single observational study without controls.

Case report. A 32-year-old quadriparetic man with cervico-thoracic syringomyelia and ventriculoperitoneal shunt (VPS) presented with recurrent dyspnea. Prior episodes were treated with noninvasive positive pressure ventilation (NIPPV). However, he presented 6 hours after symptom onset, much later than prior episodes. He denied new sensorimotor or constitutional symptoms. He was afebrile, tachycardic, tachypneic, and without evidence of hypoxia or dysautonomia. General examination revealed rapid, shallow breathing. Mental status and cranial nerves were intact with baseline spastic quadriparesis and hyperreflexia.

Arterial blood gas (ABG) on room air revealed HRA (pH: 7.18, PaCO₂: >96 mm Hg, PaO₂: 128 mm Hg, HCO₃: 42 mEq/L). Routine laboratory studies, cardiopulmonary, and infectious workup were unrevealing. NIPPV failed to improve HRA. A previous do not intubate order was reversed after discussion with the patient. After 65 hours of HRA, the patient progressed to coma and was intubated. CT brain (figure, A) revealed GCE and he was transferred to the neurointensive care unit.

Despite HRA resolution after intubation (ABG: pH: 7.58, PaCO₂: 42 mm Hg), the patient had a Glasgow Coma Scale (GCS) score of 3T. A total of

30 mL of 23% NaCl on arrival provided transient improvement of GCS to 7T (motor localization) before returning to GCS 3T. Metabolic workup and EEG were unrevealing. MRI brain at 96 hours revealed diffuse subcortical hyperintensities despite HRA resolution for over 30 hours (figure, B). There was no evidence of hypoxic injury, thrombosis/infarct, infection, or hydrocephalus. VPS was functional via shunt series examination. MRI spine revealed stable syringomyelia. Persistent coma and prior response to hyperosmolar therapy prompted scheduled hyperosmolar therapy. Thirty milliliters of 23% NaCl at 103 hours improved the GCS from 3T to 10T within an hour (following commands). The GCS worsened from 10T to 7T at 105 hours and mannitol 80 g (1g/kg) was given, improving the GCS back to 10T within 3 hours.

Alternating scheduled 23% NaCl and mannitol were continued every 6 hours with titration to clinical response. The patient returned to his neurologic baseline in 24 hours but required a tracheostomy and phrenic nerve pacer placement for ventilator support. A 2-month follow-up CT scan revealed resolution of GCE (figure, C).

Discussion. Etiologies for edema such as hydrocephalus, cervical dysautonomia, infection, stroke, toxins, and hepatic failure³ were excluded in our patient. Without other provoking factors, his delayed presentation and subtle extension of the syringomyelia (not appreciated on imaging) resulted in severe HRA. Central respiratory drive was intact, but was limited by neuromuscular weakness resulting in GCE.

PaCO₂ >80 mm Hg increases cerebral blood flow up to 6 times its baseline⁴ via pH-induced chemoregulatory cerebrovasodilation. Hyperemia in conjunction with increased vascular permeability from severe vasodilation allowed for resultant edema formation and subsequent elevated intracranial pressure. The length of time required to precipitate GCE from HRA is unknown. Our patient had