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HUNTINGTON DISEASE AMONG THE NAVAJO: A POPULATION-BASED STUDY IN THE NAVAJO NATION

Huntington disease (HD) has a protracted course that imparts substantial personal and economic burden.¹ Disease rates vary by geographic location. In Western countries, prevalence approximates 5.7/100,000; rates are tenfold lower in Asia.² Epidemiologic studies from the United States report on mostly white populations.² Few studies give rates of HD among minorities, and there are no comprehensive descriptions of HD in American Indians. Better understanding of how the disease affects discrete populations could produce hypotheses for new approaches to treatment.

The goal of this study was to describe the epidemiology of HD among Navajo people living in the Navajo Nation, at 27,000 square miles, the largest reservation for American Indians in the United States.

Methods. The e-Methods on the *Neurology*[®] Web site at Neurology.org and previous articles by this group^{3,4} describe the methodology in detail. We sought to determine average annual incidence and point prevalence rates of HD among Navajo residents of the Navajo Nation during 2001–2011. The Indian Health Service National Patient Information Reporting System provided the data, which captured 98% of eligible Navajo during the planned study period.

Post hoc analyses estimated prevalence rates in American Indians living on or near reservations across the United States (2001–2011), determined whether any HD-associated inpatient visits occurred in the Navajo Nation from 1980–2000, and estimated the probability of the primary findings on prevalence day, July 1, 2006, under different rate assumptions. The Navajo Nation Human Research Review Board approved the study.

Results. The primary analysis found no cases of HD (average annual incidence rate = 0.0/100,000 [95% confidence interval (CI) 0.0–0.21]; point prevalence = 0.0/100,000 [95% CI 0.0–1.8], Navajo Nation, 2001–2011). Post hoc analyses identified 57 cases among American Indians nationwide (estimated prevalence rate = 4.1/100,000); none was Navajo (estimated

nationwide prevalence rate among Navajo = 0.0/100,000; estimated prevalence in non-Navajo American Indians = 4.9/100,000). Examination of Navajo Nation inpatient data, 1980–2000, found no cases.

The probability of finding no cases on prevalence day in the Navajo Nation ranged from 0.0004% assuming mutation rates found in people of European descent to 42% assuming rates in Asia (table e-1).²

Discussion. We found no cases of HD among Navajo people. We initially limited the analyses to the 11-year period, 2001–2011, because the data capture nearly all 275,000 eligible people in the Navajo Nation.⁵ Post hoc analyses captured approximately 350,000 Navajo nationwide and extended the Navajo Nation analysis over 30 years.

We estimated the probability of finding no HD in the Navajo Nation on prevalence day under different rate assumptions to provide context for our findings. It is improbable that we missed rare cases on prevalence day but it is much less likely that we missed cases over the entire 30-year investigation.

American Indians emigrated from Asia.⁶ The rate of HD in non-Navajo American Indians indicates that they acquired the mutation from people of European and not Asian ancestry. Approximately 10% of HD is sporadic, due to spontaneous expansion of a CAG triplicate repeat in the *HTT* gene from an intermediate to a disease-causing tract size.⁷ CAG instability varies by haplotype, which vary according to ethnicity. A stable gene haplotype with short tract sizes explains the low prevalence in Asia.⁷ The absence of HD among Navajo people could be due to low spontaneous tract expansion from inheritance of the stable Asian haplotype and serendipitous avoidance of the European mutation carried by later-arriving immigrants because of an isolated existence.

Our findings deserve cautious interpretation. Cases could have been overlooked or misdiagnosed, or patients could have received health care elsewhere. However, a nationwide search found no Navajo with HD and, because of the remoteness of the reservation, essentially all eligible Navajo are captured by the Navajo Nation data. The findings were not verified by genetic investigation because American Indian tribes in the United States do not yet permit their genes to be analyzed. Genetic inheritance creates dependency between

Supplemental data
at Neurology.org

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