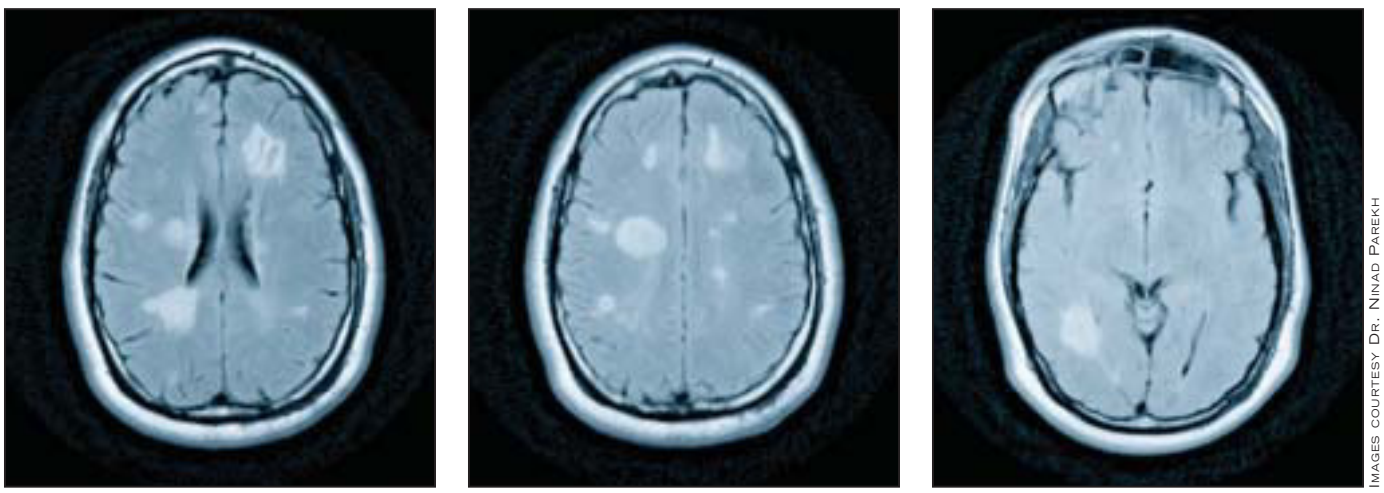
IMAGE OF THE MONTH

MRI Seals MS Diagnosis After Unclear Exams



IMAGES COURTESY DR. NINAD PAREKH

MRI revealed multiple large lesions indicative of multiple sclerosis, although the lesions did not correlate with the very limited neurologic deficits that were detected on physical exam.

The man also complained of visual difficulty, including double vision and blurring of vision in the left eye. He denied having any dysphagia or dysarthria.

He had been seen in the emergency department 3 months prior, complaining of severe nausea and vertigo. At that time, a CT scan showed decreased attenuation along the right periventricular area. The radiologist recommended correlation with MRI to exclude acute infarction. However, at that time, the patient did not have any weakness and was treated symptomatically for the diagnosis of acute labyrinthitis. He is otherwise healthy, with no history of STDs, known drug allergies, or family history of neurologic disease.

On physical exam, his vital signs were within normal limits. An eye exam revealed a normal reactive pupil and incomplete left homonymous hemianopia. Cranial nerves III, IV, V, VI, VII, IX, X, and XII were intact.

Rinne and Weber tests showed abnormal lateralization to the left with decreased bone and air conduction in the left ear. On the left upper and lower extremities, the patient had a 20% reduction in power and strength and decreased sensation to touch, pinprick, and temperature. His deep tendon reflexes were 2+ in both upper extremities and 3+ in both lower extremities, and his plantar reflexes were flexor bilaterally. He had dysmetria and past-pointing on his left side. The Romberg sign was positive, with a tendency to fall toward left. He also had an ataxic gait with limping of his left leg. Initial laboratory data showed mild hypokalemia and elevated creatinine phosphokinase. His blood chemistry was otherwise normal.

A CT scan of the head showed patchy areas of decreased attenuation involving the left frontal lobe and the periventricular region, including on the right side posteriorly and on the left side in the region of the left frontal lobe and the centrum semiovale. There was no evidence of acute infarction. The radiologist recommended that the possibility of vasculitis should be excluded with a follow-up MRI. Neurology was consulted to rule out vasculitic cause of the symptoms. The patient's history and physical examination suggested findings consistent with upper motor neuron disease, and possible demyelination, according to the consulting neurologist Dr. Victor Jaramillo and internal medicine resident Dr. Ninad Parekh of Conemaugh Memorial Hospital, Johnstown, Pa.

Follow-up MRI findings met four of the McDonald MR imaging criteria for the diagnosis of multiple sclerosis. However, the multiple large lesions found on the brain MRI did not correlate with the very limited neurologic deficits that were detected on physical exam. A cervical MRI also showed multiple areas of increased signal, while a thoracic MRI appeared normal.

The recommended diagnostic criteria for multiple sclerosis, published as guidelines from the international panel on the diagnosis of multiple sclerosis—more commonly known as "McDonald criteria"— were modified in 2005 to simplify and increase rapidity of diagnosis of MS while at the same time maintaining adequate sensitivity and specificity.

According to the modified McDonald criteria, "the revised MRI criteria for dissemination in time are detection of gadolinium enhancement at least 3 months after the onset of the first clinical event or detection of a new T2 lesion appearing at any time, compared with a reference scan done at least 30 days after the onset of the initial clinical event" (Ann. Neurol. 2005;58:840-6). "The revised MRI criteria for dissemination in space are three of the following: (1) one or more gadolinium-enhancing lesions or nine T2 hyperintense lesions; (2) one or more infratentorial lesions; (3) one or more juxtacortical lesions; or (4) three or more periventricular lesions."

The patient was started on a high dose of intravenous steroids (1,000 mg/day methylprednisolone) for 5 days, followed by tapering does of oral prednisone. His neurologic symptoms were completely resolved at the follow-up visit 15 days later. He had no neurologic symptoms at a visit 2 months later. Three months later he was seen in the ED for cervical strain and urticaria, but at that time he was not having any neurologic symptoms.

—Kerri Wachter

Study Provides Insight Into Vitamin D's Link to MS Risk

BY JEFF EVANS

Vitamin D appears to interact directly with a key susceptibility locus for multiple sclerosis, serving as an environmental influence that may decrease the risk of the disease in individuals with certain haplotypes, according to a study reported online in PLoS Genetics.

The findings provide "more direct support for the already strong epidemiological evidence implicating sunlight and vitamin D in the determination of MS [multiple sclerosis] risk, and implies that vitamin D supplementation at critical time periods may be key to disease prevention," Sreeram V. Ramagopalan, D.Phil., of the University of Oxford (England) and associates reported (PLoS Genetics 2009 Feb. 6 [doi:10.1371/journal.pgen.1000369]).

The prevalence of MS has been shown to decrease across a north-to-south gradient in the northern hemisphere and increase across a north-to-south gradient in the southern hemisphere. Other studies found that patients with MS are deficient in vitamin D, and dietary intake of the vitamin reduces MS risk. Data also suggest that MS risk in the northern latitudes of the northern hemisphere may vary with the season of birth.

However, the association between MS risk and the chromosomal region that the researchers focused on is "weak at best," even though it is the region known to be most strongly associated with MS in Northern Europeans, Dr. Mark S. Freedman said in an interview.

"As you go around the world…there may well be other HLA susceptibility genes, but we just haven't been able to identify the exact ones," said Dr. Freedman, director of the multiple sclerosis research unit at Ottawa (Ont.) Hospital and professor of neurology at the University of Ottawa. He was not involved in the study.

Dr. Freedman also noted that the association between vitamin D and MS does not explain why dark-skinned people can develop MS.

In a cell line that carried HLA-DRB1*15, Dr. Ramagopalan and colleagues discovered a functional vitamin D response element (VDRE) near the transcription start of the gene HLA-DRB1, which is located in the large genomic region containing major histocompatibility complex (MHC) class II genes.

The sequence of the VDRE was the same in 322 individuals with or without MS who were homozygous for the HLA-DRB1*15 risk allele. However, nucleotide changes in the VDRE sequences were detected in 168 individuals who were homozygous for other HLA-DRB1 alleles. In a cell line that carried the HLA-DRB1*15 haplotype, the putative VDRE was able to bind to vitamin D receptor, which is known to influence "the rate of transcription of vitamin D responsive genes by acting as a ligand activated transcription factor," according to the investigators.

Dr. Ramagopalan and coinvestigators then showed that the addition of 1,25-dihydroxyvitmin D_3, or calcitriol, to HLA-DRB1 gene constructs with this VDRE significantly increased expression of the HLA-DRB1 gene by 60%. Treatment with 1,25-dihydroxyvitamin D_3 also significantly increased the expression of HLA-DRB1 by 30% on the surface of cells that were homozygous for the HLA-DRB1*15 haplotype.

"Given the results of this study, variable expression of HLA-DRB1 could affect central deletion of autoreactive T cells. It is plausible that a lack of vitamin D in utero or early childhood can affect the expression of HLA-DRB1 in the thymus, impacting on central deletion. For MS in HLA-DRB1*15 bearing individuals, a lack of vitamin D during early life could allow autoreactive T cells to escape thymic deletion and thus increase autoimmune disease risk."

"The intriguing possibility that vitamin D responsiveness rather than any antigen specificity determines the increased MS risk of the HLA-DRB1*15 haplotype warrants consideration and can be tested in the infrequent haplotypes bearing the VDRE on other non–HLA-DRB1*15 haplotypes," the researchers concluded.

The study was funded by the Multiple Sclerosis Society of Canada Scientific Research Foundation and the Multiple Sclerosis Society of the United Kingdom. ■