Title
Reversible dementia with idiopathic hypereosinophilic syndrome.

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these 3, one had epidural spinal cord compression. Four other patients in this series of 1,000 had chloromas but not hypereosinophilia, one of whom had an epidural spinal cord compression.[4]

The table shows that 8 cases with chloromas in the setting of hypereosinophilia had meningeal involvement (cases 1-8). Seven cases of chloroma and hypereosinophilia did not show CNS involvement (cases 9-15). This raises the possibility that hematologic malignancies occurring in the setting of hypereosinophilia have a propensity to involve the CNS as durally based chloromas.

Discussion. The present patient had idiopathic hypereosinophilia for 3 years before developing CNS manifestations of ANLL. On review of the literature, we found a striking association between hypereosinophilia and leukemia or myeloid metaplasia complicated by CNS chloroma.

Leukemia is an unusual sequel to hypereosinophilia, occurring in 1 of 50 patients with idiopathic hypereosinophilia in one report.[5] CNS chloromas are an infrequent complication of leukemia as noted above, but chloromas may occur preferentially in certain subtypes of ANLL. The Fab M2 form of ANLL is associated with hypereosinophilia and chloromas.[4] Also, a subtype of Fab-M4 (AMML) with an abnormality of chromosome 16 is associated with abnormal eosinophils, although the number of eosinophils may not be elevated. It is not known whether chloromas are likely with this subtype. Of note is that Hodgkin's disease is a recognized cause of hypereosinophilia and also has a propensity to form dural-based masses. The apparent high frequency of CNS chloromas in patients with hypereosinophilia and myeloproliferative disorder suggests a biologic association.

Regardless of the reason for the association of hypereosinophilia, ANLL, and meningeal chloromas, the present report demonstrates that CNS involvement with ANLL is a previously unrecognized cause of neurologic symptoms in patients who present with hypereosinophilia. This is clinically relevant, since CNS chloroma may be a presenting manifestation of ANLL in these patients with hypereosinophilia.

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Reversible dementia with idiopathic hypereosinophilic syndrome

Article abstract—A 66-year-old woman with hypereosinophilic syndrome became rapidly demented. Evaluation revealed CSF eosinophilia, background slowing on EEG, and periventricular MRI abnormalities. Following steroid therapy, there was rapid resolution of the dementia and normalization of CSF and EEG. These findings support the concept of a direct neurotoxic effect on the human CNS produced either by eosinophils or possibly by eosinophil-derived neurotoxins.

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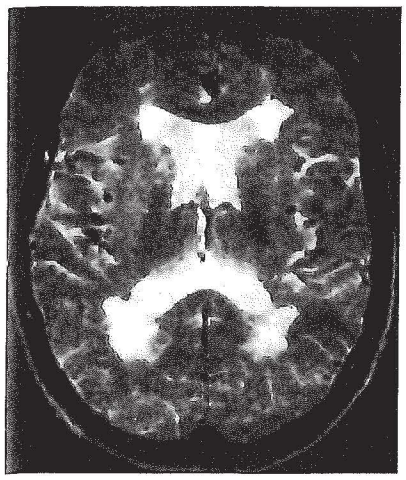
Idiopathic hypereosinophilic syndrome (HES) is characterized by a persistent eosinophilia of 1,500/mm^3 lasting for at least 6 months associated with end organ damage and no other identifiable condition other than eosinophilia.[1,2] Various neurologic abnormalities are associated with this syndrome,[1-6] but dementia with CSF eosinophilia has not been described. We present a case of HES with CSF eosinophilia, dementia, and a rapid response to high-dose steroid therapy, and we comment on possible pathophysiologic mechanisms.



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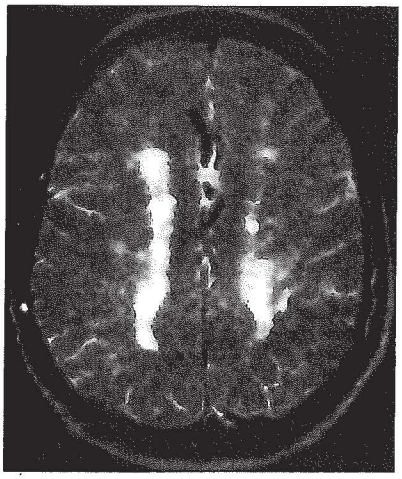

B

Figure. (A and B) MRI in eosinophilic dementia showing confluent increased signal intensity around the ventricles, most marked around the posterior horns.

Case report. A 66-year-old woman was treated with steroids for ulcerative colitis for a number of years before undergoing a total colectomy in 1983. In March 1986, she was hospitalized because of shortness of breath and was found to have severe obstructive and restrictive pulmonary disease. Peripheral blood eosinophilia (65% of 14,300 WBC/μl) was noted. There was no parenchymal infiltrate on chest x-ray. An echocardiogram was normal. There was a clinical response to bronchodilators and the eosinophilia decreased (white cell count 16,100/μl with 7% eosinophils). The presumptive diagnosis was chronic lung disease with hyperactive airways. In May 1986, she was admitted with fatigue, weight loss, dizziness, vertigo, and face and arm numbness. The physical examination was unrevealing, and the neurologic examination was normal. The white cell count was 21,800/μl with 62% eosinophils. Blood chemistries were normal. The rheumatoid factor was positive at 1/160, and the antinuclear antibody (ANA) test was negative. The IgE level was raised at 418 U/ml (normal, <14 U/ml). Trichinosis and *Aspergillus* serologies were negative. *Giardia* had previously been detected in her stool in March 1986, but had been overlooked and were now treated with metronidazole. The chest x-ray was normal. ECG and Holter monitoring revealed no cardiac etiology for her dizziness. Neurologic and ENT evaluations were normal. EEG (June 1986) revealed a 9 Hz background alpha rhythm with intrusion of theta and delta activity during wakefulness. CT of the head showed mild periventricular white matter hypodensity. The etiology of her complaints was unclear, but her symptoms improved during hospitalization. The possibility of HES was entertained, but because there was no evidence of end organ damage, only follow-up without specific therapy was recommended.

Ten months later, the patient's family noted short-lived episodes of mild confusion and forgetfulness. She would call her daughter at night for help, had progressive difficulties managing household chores, and flooded the house after she forgot to turn off a tap. One month later she became belligerent, had auditory hallucinations, talked to nonexistent people, and was incapable of recognizing family members. She developed enuresis and became bedridden.

Three months later, a neurology consult was obtained. Examination revealed an alert woman with little spontaneous speech who was disoriented as to time, place, and person. She could not consistently identify simple objects or body parts. Neuropsychological evaluation was attempted, but was unsuccessful because the patient was too impaired to comprehend and execute the required tasks. The cranial nerve examination was within normal limits. Motor examination showed spontaneous movements of the 4 limbs with no clear wasting or discernible weakness; tone was increased in the 4 extremities. Reflexes were brisk and symmetric in the 4 limbs with indeterminate plantar responses. Upper extremity movements were slow, without dysmetria or tremor. She was unable to stand unassisted.

The peripheral white cell count was 31,000 with 92% eosinophils. CSF revealed glucose 50 mg/dl, protein 146 mg/dl, RBC 7, WBC 86 with 2% polymorphonucleocytes, 63% lymphocytes, 8% monocytes, 2% basophils, and 25% eosinophils. VDRL was unreactive, India ink stain was negative, *Cryptococcus neoformans* latex antigen was negative, and no organisms were seen. EEG (September 1987) was now markedly abnormal, revealing a slow 7 Hz alpha rhythm with marked intrusion of 2 to 3 Hz delta and 4 to 6 Hz theta activity. MRI showed a high-intensity periventricular signal bilaterally, predominantly near the occipital horns (figure, A and B). Nerve conduction testing revealed a mild axonal polyneuropathy.

Within 7 days of starting prednisone at 50 mg/d for treatment of HES, she was "80% recovered," according to her daughter. Reevaluation after 1 week's steroid therapy showed an alert, happy, pleasant, and cooperative patient who was fully oriented. Neuropsychological evaluation 12 days after starting steroid therapy showed dramatic improvement with no cognitive impairment in native intelligence, abstract reasoning, verbal comprehension, reading, writing, repetition, or verbal memory and learning. Motor speed was normal. Sustained attention, confrontational naming, verbal fluency, and visual memory remained impaired.

Cranial nerve examination was normal. There was increased tone and spasticity in the legs. Reflexes remained brisk in all 4 limbs with a right Babinski reflex. Gait was mildly ataxic.

CSF 8 weeks after initiating steroids showed 5 WBC with no eosinophils.

Six months later, the patient was no longer ataxic. Tendon reflexes and tone remained increased. The right Babinski reflex remained. No impairments were found on repeat neuropsychological testing. Nine and 12 months after, EEG was normal with a 9.5 to 10.0 Hz background frequency and no delta or theta activity. MRI was unchanged.

Discussion. *Diagnosis.* The cause of this patient's persistent eosinophilia was unclear. The ulcerative colitis

had been inactive since her colectomy in 1983. The low rheumatoid factor titer with a negative ANA and absence of musculoskeletal involvement made collagen vascular disease unlikely. *Giardia* infections are confined to the lumen of the bowel and consequently are not usually associated with eosinophilia. The stool was negative for other ova and parasites, and the trichinosis serology was negative. Pulmonary disease with airway hyperactivity was a possible etiology, but the persistently high eosinophilia with absolute eosinophil counts as high as 20,000/ml seemed inadequately explained by any of these possibilities. Other causes of hypereosinophilia are not infrequently the forerunners of HES with end organ involvement.[1,2] Our patient had marked eosinophilia for over 1½ years, ultimately developing end organ damage; thus, she demonstrated classic features of HES.

The diagnosis of HES is made in patients with persistently raised eosinophilia—above 1.5 × 10/l without other known cause.[3] There are many reports of neurologic dysfunction in HES.[1-6] In the largest review of patients with HES, Moore et al[3] found 34 affected patients (65%), predominantly with a sensory neuropathy (23 of the 27 patients). Cerebrovascular thromboembolic disease associated with heart involvement affected 6 patients, and a striking primary cerebral dysfunction with marked behavioral changes, memory loss, confusion, ataxia, increased muscle tone, and hyperreflexia affected 7. Several reports mention some form of cerebral dysfunction including "coma, confusion, delusion, and psychosis"[1] and "loss of intellectual ability, impairment of memory, and disorientation to place and time."[5] Most reports omit references to CSF, CT, and EEG findings, and details of neurologic examination of "higher cortical functions" which would permit an accurate determination of the prevalence of cerebral dysfunction. Individual patients in this series and other case reports had abnormal findings including ventricular enlargement on head CT,[3] or slowing of the background rhythm on the EEG,[1,3,5] but none of the 4 patients tested had CSF eosinophilia.[3] Response to treatment with prednisone and hydroxyurea produced only gradual neurologic improvement.[3] In our patient, a striking resolution of the dementia was noted 1 week after starting treatment.

Pathogenesis of dementia. Our patient with HES had a rapidly progressive dementia and ataxia, presumably secondary, in some way, to CSF eosinophilia. EEG showed a slow 7 Hz background activity with intrusion of theta and delta activity, and periventricular abnormalities were seen on MRI. After administration of steroids, there was rapid clinical improvement in mental status, disappearance of CSF eosinophilia, and normalization of EEG with a 10 Hz background and no theta or delta activity. The unique features of our case are the CSF eosinophilia and the dramatic clinical improvement following steroid administration. Previous cases of HES with cognitive changes or dementia had no CSF eosinophils[1,3,5] and cerebral dysfunction has, therefore, not been ascribed to them. The eosinophils probably appeared in the CSF by crossing an altered blood-brain barrier (BBB). If so, this BBB abnormality was presumably reversed by steroid therapy.

The pathogenesis of neurologic dysfunction from eosinophilia is unclear; patients with other diseases may have CSF eosinophilia without dementia.[7] Possible mechanisms of injury to the cerebrum include a direct infiltration of eosinophils, sludging of cells in small vessels, or a toxic effect from infiltration of eosinophils into the CSF and the release of an eosinophil-derived neurotoxin (EDN).[5,8] Potentially neurotoxic proteins derived from eosinophils, including eosinophil cationic protein, major basic protein, as well as EDN, may be implicated in the global dementing process.[5,8] More than 50 years ago, Gordon[9] described the neurotoxic effect of intracerebral inoculation of lymph node preparations from patients with Hodgkin's disease into guinea pigs and rabbits. This produced a severe encephalopathy with ataxia,[9] a remarkable observation which became known as the "Gordon phenomenon." This neurotoxic reaction was subsequently shown to be caused by the eosinophils often found in lymphomatous nodes. Purified eosinophil suspensions from various sources injected intracisternally into rabbits produced forelimb stiffness, incoordination, and ataxia within a few days, with marked tissue damage and spongiform vacuolation in the white matter of the spinal cord and the cerebellar Purkinje cell layer.[8] Recently, protein sequencing has shown that EDN is identical to human nonsecretory ribonuclease.[10]

So far, the Gordon phenomenon has not been identified positively in humans. We postulate that the eosinophil-related dementia in our patient may have been due to the effect of neurotoxic proteins from eosinophils, most likely EDN. Perhaps this patient's symptoms and signs represented an early, reversible stage of the Gordon phenomenon in humans. Conversely, it could be argued that the resolution of her dementia was too rapid for recovery from an established Gordon phenomenon-like process in which permanent cell loss occurs. In animals, EDN causes a minimal inflammatory reaction and steroids do not protect rabbits that are injected with EDN from the Gordon phenomenon (D. Durack, unpublished observations). Nonetheless, in our case there are compelling associations linking CSF eosinophilia and dementia. Possibly, a rapidly reversible dementia (with reversible EEG changes) occurs before the onset of permanent neuronal damage. Structural changes, as documented by MRI in this patient, were not reversed. Further clinical and laboratory observations are needed to establish whether the Gordon phenomenon has a counterpart in human disease.

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Vertical and horizontal epileptic gaze deviation and nystagmus

Article abstract—Periods of epileptic nystagmus consisting of rightward eye deviation and right-beating nystagmus, alternating with upward eye deviation and upbeating nystagmus, occurred in a comatose patient with a left hemisphere subdural hematoma and seizures. The periods of upbeating nystagmus were associated with symmetric, low-voltage 3 to 4 Hz bifrontal spikes. Rightward eye deviation and right-beating nystagmus occurred with diffuse, predominantly left hemispheric 4 to 6 Hz sharp waves. No eye movements occurred in the absence of spike and wave activity. These correlations agree with current concepts of the cortical control of saccadic eye movements in monkeys studied by electrical stimulation.

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Versive horizontal ictal eye movements have been variously correlated with frontal, temporal, parietal, occipital, or generalized seizure discharges,[1-3] but purely vertical movements are rare.[1,2] We present a patient who cycled between periods of horizontal and vertical epileptic gaze deviation with nystagmus. Eye movement abnormality could be correlated with the pattern of EEG activity.

Case report. A 68-year-old chronically alcoholic man sustained a closed head injury after falling to the ground. Over the next 2 weeks he became lethargic. On the day of admission he fell again, lost consciousness, and had a seizure with deviation of the eyes to the right and tonic-clonic limb movements. In the emergency room the patient was given phenytoin and diazepam. CT of the head showed a subdural hematoma in the left temporal region.

Neurologic examination showed a patient unresponsive to pain, with jerking movements of the right arm and leg. There was a left facial weakness and a left Babinski reflex. After limb movements subsided, during coma, the patient manifested 2 types of epileptic gaze deviation and nystagmus. There was deviation of the eyes to the right over 4 to 8 seconds with superimposed right-beating nystagmus for 20 to 40 seconds. The eyes then drifted back towards the midline for 2 to 4 seconds. Subsequently, there was upward deviation of the eyes over 4 to 8 seconds with superimposed upbeating nystagmus for 20 to 40 seconds. Following subdural evacuation and administration of lorazepam and phenytoin, clinical and EEG seizure activity ceased. The patient recovered with only mild residual right arm and leg weakness.

EEG-clinical findings. EEG showed 2 patterns with clinical correlates: (1) prominent medium-voltage 4 to 6 Hz sharp waves, seen maximally over the left parasagittal region with lesser activity over the right hemisphere (figure 1), were associated with rightward eye deviation and superimposed right-beating nystagmus; (2) less prominent low-voltage 3 to 4 Hz sharp waves, bifrontal in distribution (figure 2), were associated with upward eye deviation with superimposed upbeating nystagmus. EEG and clinical findings alternated between these 2 patterns.

Discussion. Although cerebral seizure activity has long been noted to cause contralateral eye deviation, vertical eye deviation and nystagmus are unusual and are only rarely the principal clinical manifestation of seizure activity.[1-3] Most clinical observations have been without an EEG correlate and therefore our understanding of these movements has come from electrical stimulation studies in humans and animals. Review of the literature shows the EEG accompaniment of horizontal epileptic "nystagmus" to be variably over the frontal, temporal, parietal, or occipital scalp region on 1 side.[1-3] Most patients have a nystagmus with the quick phase to the side opposite the ictal EEG discharges. Beun et al[1] note that EEG recordings were usually done on 8-channel machines and a definite scalp localization cannot be certain.

The pulse generator for horizontal saccades and quick phases is in the caudal pons, and for vertical saccades and quick phases in the mesencephalon.[4] Excitatory "burst" neurons lying in the pontine paramedian reticular formation (PPRF) control horizontal