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T2 hyperintensity in the globus pallidus after Agent Orange exposure

Introduction

Previous reports concluded to the absence of strong evidence establishing an association between Agent Orange exposure and clinical neurological disorders, but did not review brain MRI. We here report a case of bilateral heterogenous hyperintense lesions in the T2 sequence on brain MRI, likely secondary to Agent Orange exposure.

Case

A 53 year old left - handed veteran developed left hand action tremor that subsequently involved his right hand and his head, while sparing his voice and legs. The tremor worsened with anxiety and seemed to improve with alcohol. Impact of caffeine on his tremor was unclear, since he rarely drank. He denied any motor slowness, stiffness, gait change, cognitive complaints, depression or anxiety. He was never exposed to tremorigenic drugs. He was diagnosed with essential tremor and started on primidone with some benefits initially. Because of poor tremor control and worsening of his tremor with age, topiramate then propranolol were successively added without satisfactory response. At 68 years of age, 15 years after the onset of his symptoms, the patient presented to our movement disorder center to be evaluated for Deep Brain Simulation for refractory tremor.

The patient denied history of encephalitis or meningitis, head trauma, current or past exposure to dopamine receptor blocking agents, heavy metals, insecticides, pesticides or carbon monoxide, but reported massive exposure to Agent Orange he was spraying when serving as a helicopter pilot during the Viet Nam war. Objective quantification of the exposure was impossible, but the patient reported multiple exposures per week and enough exposure every time so that the cockpit would be full of smoke and he could barely see through it.

His paternal grandmother, 3 siblings and 2 of his 4 children were diagnosed with essential tremor. His father was killed in a car accident at age 29 and did not have any tremor at that time. There was no family history of dystonia, parkinsonism or chorea.

At the time of his visit, the patient was on primidone 50 mg three times a day, topiramate 50 mg daily and propranolol 10 mg three times a day, in addition to niacin-simvastatin 500–20 mg daily and lisinopril 5 mg daily.

His examination was remarkable for a bilateral 3–10 cm amplitude high frequency postural and kinetic hand tremor, as well as a 1–3 cm amplitude head tremor. Motor power, tone and bulk, sensory examination, deep tendon reflexes, coordination and gait were normal. There was no evidence of parkinsonism. The rest of his examination was normal.

A basic work up, including TSH and T4 levels, as well as a complete blood cell count and comprehensive metabolic panel were normal.

A brain MRI, ordered as part of the pre-operative work up, revealed bilateral globus pallidus heterogenous hyperintense lesions in the T2 sequence, surrounded by a hypointense rim (Fig. 1).

The differential diagnosis of this incidental finding was chronic carbon monoxide intoxication, heavy metal accumulation, neurodegenerative disease with brain iron accumulation (NBIA) or mitochondrial disease. These lesions were stable on a repeat imaging preformed 9 months later, arguing in favor of a more static phenomenon. Levels of ferritin, parathyroid hormone, lactate, pyruvate, methemoglobin, copper and manganese were normal, and the patient was negative for the kinase-associated neurodegeneration 2 (PKAN 2) mutation. A CT scanner of the brain did not show any abnormality in the basal ganglia.

We concluded that the changes incidentally found on MRI were possibly caused by the patient's prior exposure to massive amounts of Agent Orange.

Discussion

Agent Orange is a powerful herbicide that was used during Viet Nam war to destroy foliage under which enemy soldiers might have taken shelter [1]. A report from the institute of medicine concluded to the absence of strong evidence establishing an association between herbicides used in Vietnam and clinical neurological disorders [2], but no study looked at a possible association between Agent Orange exposure and abnormal brain MRI. In a series of 643 Korean veterans form the Viet Nam war with Parkinson's disease, Yang et al. [3] compared the characteristics of Parkinson's disease in 143 veterans exposed to Agent Orange and 500 veterans who were not exposed to it. Brain MRIs were performed on all patients but no results were reported. However, patients exposed to Agent Orange had a lower 18F-N-(3-fluoropropyl)-2βcarboxymethoxy-3β-(4-iodophenyl) nortropane positron emission tomography (18F-FP-CIT-PET) uptake in the caudate and putamen with higher asymmetry in the putamen uptake between both sides. While not directly evaluating the globus pallidus on imaging, these finding suggest that Agent Orange exposure could have an impact on basal ganglia. Indeed, rat studies have demonstrated that gastric exposure to 2,3,7,8-Tetrachlorodibenzo-p-dioxin, which is one of the most toxic by-products of Agent Orange [3], led to up-regulation of methionine-enkephalin-like immunoreactivity in various brain areas, including the globus pallidus [4].

Our patient presented with a personal and family history suggestive of essential tremor, confirmed by a thorough examination and the exclusion of other frequent causes of tremor such as medications or hyperthyroidism. However, and likely unrelated to his clinical presentation, his brain MRI revealed bilateral heterogenous hyperintense lesions in the T2 sequence, surrounded by a hypointense rim, reflecting globus pallidus gliosis of neurodegenerative origin. In addition to being a well described aspect in

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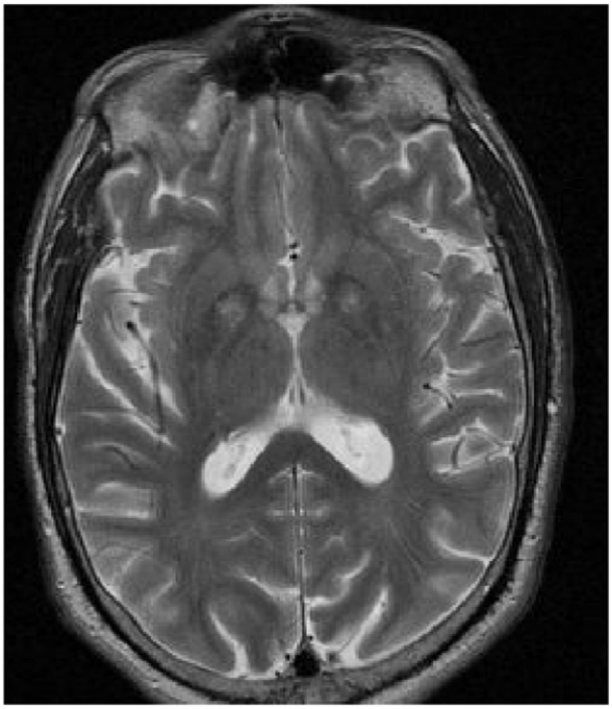

Fig. 1. T2 weighted MRI of the basal ganglia reveals hyperintensity in the globus pallidus, a pattern previously described with carbon monoxide intoxication, neurological degeneration with brain iron accumulation and perinatal hypoxic injury, but not with Agent Orange exposure.

NBIA, specifically in PKAN-2 and neuroferritonopathy [5], this aspect had also previously been described in patients with chronic carbon monoxide intoxication [6] or cerebral palsy secondary to perinatal injury [7]. While the patient has a family history of essential tremor, we are not aware of any familial condition that would have caused this aspect on MRI and that was not already ruled out by the work up above. In addition, while new genetic syndromes are always a concern, there was not high enough suspicion to obtain a whole exome sequencing on this patient, particularly that the MRI findings were considered incidental and not contributing to his symptomatology and disease. Finally, family members were not available for genetic testing, precluding any meaningful conclusion should a new variant be detected in this patient.

Cerebral palsy, NBIA, carbon monoxide chronic intoxication having been ruled out in our patient by history, examination and blood tests when appropriate, it is possible that the changes observed on MRI might have been caused by prior exposure to massive amounts of Agent Orange. However, one case alone cannot support this conclusion and more cases need to be reported to confirm this association. We encourage other authors to share their findings in an attempt to better understand the effect of Agent Orange on the brain.

Disclosures related to this manuscript

The authors have nothing to disclose.

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