Parkinsonism and neurosarcoidosis: Cause and effect or coincidence?

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ABSTRACT

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Movement disorders in demyelinating diseases can be coincidental or secondary to a demyelinating lesion. We here report the first case of coincidental association of neurosarcoidosis and idiopathic Parkinson's disease.

Keywords:
Parkinson's disease
Sarcoidosis

Background

Different movement disorders have been reported in demyelinating diseases, with some considered secondary to the disease and improving with its treatment, and some considered coincidental [1]. Parkinsonism has been reported in multiple sclerosis, central pontine and extrapontine myelinolysis [2–5] and post bone marrow transplant demyelinating leukoencephalopathy [6], but in only 4 cases of sarcoidosis [7,8] in which it was probably secondary to the underlying disease.

We here report the first case of coincidental idiopathic Parkinson's disease (PD) and neurosarcoidosis.

Case

A 39 year old male presented with acute diplopia and left arm weakness. A brain magnetic resonance imaging (MRI) was unremarkable, but a cervical spinal cord MRI detected a diffusely enlarged cervical cord with confluent hyperintensity within the cord, extending from the inferior medulla to the level of the second thoracic vertebra on the FLAIR and T2 weighted images; in addition to multiple prominent patchy enhancements at different levels of the cervical spine. A chest X-ray revealed scattered non-necrotizing epitheliod granulomas with negative acid-fast bacillus or fungal cultures. A computed tomography (CT) of the chest with contrast revealed 8 white blood cells, protein at 48 mg/dl (Normal <45), normal IgG index at 0.58 and no oligoclonal bands. In addition, serum screening for HIV, HTLV, syphilis and anti-nuclear antibodies (ANA) was negative, and levels of vitamin B12 and folic acid were normal.

These results were deemed consistent with the diagnosis of pulmonary and neurological sarcoidosis and the patient was started on intravenous then oral corticosteroids with a good response to therapy. 3 years after onset, therapy was changed to weekly oral methotrexate because of steroid induced diabetes. Six years after initial presentation, the patient developed left shoulder pain as well as left hand tremor. These symptoms could not be explained by any structural shoulder lesion, and were treated as a flare of neurosarcoidosis. The patient was treated with steroids over the following 18 months without impact on the tremor.

Propranolol was tried for tremor control without benefit and the patient was referred to our movement disorders clinic 2 years after the onset of the shoulder pain and hand tremor.

During that visit, the patient also reported micrographia as well as a slower gait with decreased left arm swing and hypophonia that developed in the previous months. He also admitted to hypomimia, cervical stiffness and difficulty getting in and out of a car, putting on an overcoat or standing up from a soft chair. He required minimal help with lacing his shoes, getting dressed and cutting his meat. He denied visual hallucinations, cognitive

Abbreviation: PD, Parkinson's disease.
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difficulties, falls or exposure to anti-psychotics or anti-emetics. There were no prominent autonomic symptoms.

The patient’s medication intake was limited to flexeril 10 mg three times a day for neck stiffness with minimal benefits, hydrochlorothiazide 25 mg/day for hypertension, and folic acid. He had stopped taking methotrexate a month prior to his visit to our center, on the advice of another neurologist who suspected a side effect from the medication. He denied any known allergies.

His family history was remarkable only for one brother with epilepsy since childhood but preserved cognition and social functioning. The patient denied drinking alcohol or consuming tobacco products.

On examination, he scored 28/30 on the mini mental status examination, losing one point for recall and another for failure to follow a 3-step command. His examination was remarkable for increased deep tendon reflexes in his knees and ankles, hypomimia, hypophonia, moderate left arm tremor at rest, bradykinesia in the left hand and foot, increased rigidity on the left side and marked cervical rigidity. His gait was slow with mildly reduced left arm swing but he had a normal postural stability on the pull test. An MRI of his brain obtained 2 years after the onset of his tremor was compared to a previous MRI obtained 4 years prior to the onset of his tremor, and showed no interval change or lesions that could explain his parkinsonism.

The patient was diagnosed with idiopathic Parkinson’s disease (PD). Drug-induced parkinsonism secondary to methotrexate exposure was deemed unlikely as he had been on methotrexate for 5 years without any deleterious effect. The patient was still followed in our clinic, 8 years later. Symptoms had since spread to the right side. He has had marked and sustained improvement of the neck stiffness and pain, the shoulder pain and the tremor to dopaminergic drugs. A formal “on/off” levodopa testing documented a 34% improvement in his motor Unified Parkinson’s Disease Rating Scale (UPDRS) after one dose of carbidopa/levodopa/ entacapone 50/200/200. 4 years after his visit to the movement disorders clinic, a routine MRI follow up for neurologic sarcoidosis revealed several small foci of enhancement within the cerebral spinal cord consistent with active neurosarcoidosis and the patient was treated with IVMP. Notably, his parkinsonism did not worsen during this flare. The diagnosis of idiopathic PD rather than secondary parkinsonism was ultimately confirmed by an 1-123-Braint DaT SCAN that showed decreased uptake bilaterally in the caudate and putamen nuclei, more severe on the right.

Discussion

Sarcoidosis is a granulomatous multisystemic disorder of unclear etiology that can involve any part of the nervous system in 5 to 15% of patients with cranial nerves, the hypothalamus and the pituitary gland being most commonly involved. Neurosarcoidosis can be acute or chronic, and is the presenting symptom of sarcoidosis in 50% of patients. The diagnosis of sarcoidosis is made in the presence of compatible clinical and neurological manifestations, with the exclusion of other diseases that could present similarly, and with a biopsy sample demonstrating the presence of non caseating granulomas. In the case of neurological lesions, the pathological sample can be collected form another involved tissue, such as the lung, where the complications from a biopsy are less worrisome.

Papapetropoulos et al. [7] reported one patient with known untreated pulmonary sarcoidosis who presented with akinetic–rigid parkinsonism worse on the left, associated with mild weakness and a Babinski sign on the left. Her brain MRI revealed a hemorrhaging lesion of the right basal ganglia, external capsule and medial temporal lobe with perilesional edema. A stereotactic biopsy of that lesion was consistent with neurosarcoidosis. The parkinsonism markedly responded to oral steroids, and recurred with decrease in the dose of the drug. The existence of a lesion strategically located in the right basal ganglia and the response of the movement disorder to the treatment of neurosarcoidosis argued in favor of a direct relationship between the 2 disorders, with parkinsonism being secondary to neurosarcoidosis. In a case control study specifically examining 22 patients with known neurosarcoidosis for signs of parkinsonism, Drori et al. [8] reported 3 such patients with little to no response to dopamine replacement therapy. Location of brain lesions and response to sarcoidosis treatment were not documented, and DaT scans were not performed in that study, but TNF alpha was suggested as a potential contributor to the neurosarcoidosis-induced parkinsonism [8].

In contrast, our patient’s first symptoms of parkinsonism, namely the stiffness and pain in the left shoulder followed by left hand tremor, resisted to as many as 12 courses of intravenous steroids, but responded dramatcally to dopamine replacement therapy. In addition, the movement disorder did not worsen during subsequent flares of neurosarcoidosis, and there was no basal ganglia involvement by sarcoidosis on brain MRI. Finally, the neurodegenerative nature of the parkinsonism was demonstrated by the abnormal dopamine function on DaTSCAN, confirming the incidental rather than causal nature of parkinsonism and neurosarcoidosis. While our patient has been exposed to methotrexate, it is unlikely to have played a role in the development of his parkinsonism. Indeed, there are only 2 reported cases of methotrexate induced parkinsonism in the literature [11,12]. The first was a cancer patient who received high doses of the drug combined with brain radiation therapy and leucoencephalopathy [11], and the second was a rheumatoid arthritis patient who developed a transient dopamine responsive parkinsonism, but with normal [123I]-B-CIT SPECT excluding neurodegenerative PD [12]. In theory, methotrexate could uncover an underlying idiopathic Parkinson’s disease in our patient with young onset PD, but this was never reported before and could not be confirmed.

Conclusion

When demyelinating diseases and movement disorders co-exist, the question of causal correlation is often raised. It has been suggested that the observed movement disorder is pathophysiologically related to the demyelinating disease if it has an abrupt onset, a temporal and anatomical relationship with a flare of demyelination or a lesion observed on imaging, and responds to the treatment of the demyelinating disease. We here report the first patient with coexisting neurosarcoidosis and PD, and suggest that a coexistence of PD in a patient with neurosarcoidosis should be suspected when parkinsonism does not respond to the treatment of sarcoidosis. This is particularly important to avoid treating the coexisting PD with aggressive and prolonged sarcoidosis-targeted immunosuppressent therapies that have significant side effects [13].

Consent

Informed consent was obtained from the patient for publication of this case report.

Authors’ contribution

R Mehanna: review of the literature, writing of the first manuscript; L Stone: review and critique, I Itin: review and critique. All authors agree with the final version submitted.

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Declaration of competing interest

The authors report no conflict of interest.

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