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A young woman with dystonia of a foot

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Case history

A 16-year-old woman was referred to a neurology office by her psychiatrist who was following her for a diagnosis of social phobia. Her social phobia was attributed by her psychiatrist to her "abnormal gait". Initially, the problem with her gait was barely noticeable. When she was 9 or 10 years old, her mother noticed that her shoes were worn unevenly and the right shoe bottom was worn only on the outside. The first time the patient became conscious of this problem was when she was taunted by her classmates because her "walking looked weird". The problem continued and became a major source of psychological distress to the point that she attempted to minimize the amount of walking in public and ended up becoming socially isolated. A diagnosis of social phobia was made by her primary care provider and she was referred to a therapist who referred her to the neurology practice for gait abnormality.

During the neurology visit, she denied any other difficulties except for a change in her dancing skills. She used to enjoy her private dance class. However, she recently noticed that her right foot turned inward during some of the dance moves. When she practiced in the afternoon or after a poor night's sleep, some of the dance moves become impossible to perform. Otherwise she was doing well and the rest of the history, including perinatal life and developmental history, were unremarkable. On examination she was found to have slight inward rotation of the right foot, which became progressively more noticeable with prolonged walking. The tone in her right upper extremity at the wrist was slightly increased. The rest of the general and neurological examination was unremarkable. Blood work including serum copper and ceruloplasmin were within normal limits and magnetic resonance imaging of the brain was unremarkable. The neurologist was clear that the clinical diagnosis was dystonia, but the aetiology was not certain. The main differential diagnosis was between dystonia and juvenile Parkinson's disease (JP). In relation to the dystonia possibility, the main suspicion was of dopamine-responsive dystonia, since there was diurnal fluctuation. JP can present with dystonia without any parkinsonism. She responded minimally to a trial of trihexyphenidyl, but stopped taking it because of side effects. A trial of low-dose carbidopa-levodopa was helpful, but the benefit would wear off after few hours.

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Question 1

Which item in the history is more consistent with a diagnosis of juvenile Parkinson's disease (JP) as opposed to dopamine-responsive dystonia (DRD)?

A. Age of onset

B. Response to low dose of carbidopa/levodopa

C. Response to trihexyphenidyl

D. Wearing off of carbidopa/levodopa effects after 4–6 hours

E. Gender of the patient

F. Diurnal pattern

G. Worsening of dance moves with sleep deprivation

Juvenile Parkinson's disease rarely presents in patients younger than 8 years of age, whereas DRD can present even during infancy [1]. This patient's first symptoms of dystonia probably started around the age of 9 to 10, which can be seen in either condition. Some benefit from anticholinergic agents (trihexyphenidyl) can be seen in both conditions, but side effect profile is the limiting factor in most patients.

Response to levodopa is seen in both of these conditions, though a higher dose is expected to be required to demonstrate benefit in the case of JP. An excellent response to lower doses of levodopa is commonly experienced by patients with DRD. The "wearing off" should not happen in the case of DRD until around 29 hours after the last dose, whereas shorter wearing off periods are more consistent with JP than DRD. Levodopa-induced dyskinesias happen in both conditions, but the dose of levodopa triggering dyskinesias in DRD is much higher than in JP.

JP is more prevalent in males, whereas DRD is more common in females. A diurnal pattern is more frequently seen in DRD, but can happen with JP. Sleep benefit more consistently happens with JP, but can be found in DRD as well.

The correct answer is D.

Question 2

Which test or tests are most likely able to differentiate the two conditions (JP versus DRD)?

A. Genetic study

B. Fluorodopa positron emission tomography (PET)

C. Homovanillic acid (HVA) level in the cerebrospinal fluid (CSF)

D. Phenylalanine test

E. 2 and 4

F. 1 and 3

Comments

Genetic studies (at least the routine ones) are only able to pick up the disease-causing variants in 40–50% of all cases of DRD. Similarly, in many JP cases, a distinct pathogenic variant cannot be found.

Fluorodopa PET studies are abnormal in JP, but are usually normal (can be borderline) in cases of DRD. Alternatively, dopamine transporter (DaT) single-photon emission computed tomography (SPECT) scanning could be done rather than a fluorodopa PET study, and that would be more common in clinical practice.

HVA in the cerebrospinal fluid (CSF) is decreased in both conditions. This is also the case for CSF biopterin.

The phenylalanine test is abnormal in DRD, but is normal in JP. The basis for this test is that tetrahydrobiopterin (BH4) is a cofactor in the metabolism of phenylalanine to tyrosine. In DRD, BH4 deficiency results in accumulation of phenylalanine and reduced production of tyrosine. Therefore, both fluorodopa PET and the phenylalanine test can be used to reasonably differentiate the two conditions.

The correct answer is E.

Further history

A DaT scan ordered by her movement disorder specialist demonstrated decreased dopamine transporter binding in the left striatum, and she was diagnosed with juvenile Parkinson's disease. Genetic studies were unrevealing. After 10 years she came back to the neurology office with a complaint about her chronic migraine headaches, which were now less responsive to the abortive medications. Over the past 10 years, she has been followed up by a movement disorders specialist who recently moved out of the area. In the interval, she started to have resting tremor in the right upper extremity and was now experiencing "on" time dyskinesia taking 300 mg of levodopa 3 times a day.

Question 3

Considering also her Parkinson's disease, what would be the most reasonable prophylactic medication for her migraine headaches?

A. Propranolol

B. Topiramate

C. Zonisamide

D. Verapamil

E. Amantadine

Comment

Zonisamide would be the most reasonable medication in her case, given its headache prophylaxis properties and because it should simultaneously benefit her levodopa-induced dyskinesia [2]. Among the other choices, propranolol, topiramate and verapamil are indicated for prevention of migraine, but none of them are beneficial in her case otherwise.

Verapamil is a non-dihydropyridine calcium channel blocker (CCB) that has not been studied in Parkinson's disease therapeutics. A phase III trial is currently underway to determine whether treatment with isradipine, a dihydropyridine CCB, is neuroprotective in slowing the progression of Parkinson's disease [3].

Amantadine is used for many purposes, including levodopa-induced dyskinesia. It has been shown to decrease the frequency of migraine headaches in sporadic studies [4], but has not been widely investigated and would not be considered first-line treatment.

The best answer is C.

Disclosure statement

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