CASE REPORT

Neuroleptics as a cause of painful legs and moving toes syndrome

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SUMMARY

Painful legs and moving toes syndrome is rare. It is predominantly diagnosed in middle-aged adults following a history of spinal cord surgery or trauma. The syndrome consists of abnormal repetitive movements, most commonly in the lower extremities, accompanied by pain in the affected limb. Pain usually precedes the movements. We report a case in a young patient that we believe was induced by the intake of a low-potency neuroleptic, which was prescribed to him for anxiety. The patient was treated with carbamazepine with mild relief of pain and later on with botulinum injection, which significantly reduced the movements and mildly improved the pain. After stopping the treatment, the beneficial effect lasted for about 3 months after which his condition gradually returned to its initial state.

BACKGROUND

Painful legs and moving toes (PLMT) syndrome is a rare condition that was first described by Spillane *et al*¹ in 1971; it is characterised by abnormal involuntary movements most commonly in the lower extremities associated with pain, but without meeting the criteria for restless leg syndrome (RLS) or other known pathologies. The syndrome has been broadened over the years to include a painless variant and an upper extremity variant, with one case report of a PLMT syndrome with abnormal tongue movement.² The median age of diagnosis was found to be around the late 50s for males and 60s for females.^{1–4} Aetiologies of this disorder are diverse, however, the most common cause mentioned in the literature is idiopathic/cryptogenic followed by trauma. We report a case of a young patient suffering from PLMT syndrome with no evidence of spinal cord lesions or history of trauma, but with temporal association of neuroleptic intake prior to the occurrence of the syndrome.

CASE PRESENTATION

A 23-year-old man presented, 3 years ago, with intermittent movement of his left toes associated with prickly pain in his lower leg and toes and a dull ache extending up his thigh. Based on his report, pain preceded the abnormal toe movements by 3 months but later, the movements increased in proportion to the pain and became continuous. His abnormal movements were more prominent when supine and did not change with rest or walking, but stopped when the patient was asleep. In addition, they became progressively worse during the day and were exacerbated by stressors, sleep deprivation and caffeine intake. Interestingly, they were

also intensified when the patient's bladder was full and relieved subsequent to emptying it. The patient did not have any history of trauma or injuries; however, he was treated with Deanxit (flupentixol/melitracen 0.5/10 mg) at a dose of 2 tablets/day for 3 months prior to the occurrence of his symptoms and signs, which did not regress despite stopping the medication. On presentation, his general physical and neurological examinations were normal. There was no weakness or noticeable strength difference between the two lower limbs. The deep tendon reflexes were normal with a negative Babinski sign. The abnormal movements were limited to the three middle toes of his left foot, and consisted of purposeless writhing with repetitive abduction–adduction. The patient could stop the movements for a brief period of time through conscious effort, but they resumed as soon as he was distracted. He was unable to reproduce them on the unaffected side when asked to do so. The patient showed an abnormal reaction to light stroke and cold pressors on his left leg, but when his leg was rubbed up to the thigh, or lightly stroked, he felt a sharp pricking sensation similar to but less intense than his reaction to cold pressors. An increase in pain and abnormal movements invariably followed cold stimulation, which consisted of applying of ice or acetone on the dorsum of his foot up to his mid shin. The pain elicited by the cold pressors was akin to sharp electric shocks, and differed in intensity and quality from his daily dull, aching pain. Furthermore, he felt the urge to move his leg to stop the uncomfortable sensations induced by the cold pressors.

INVESTIGATIONS

Routine laboratory tests, thyroid-stimulating hormones and lead levels in blood were all normal. Brain and spinal cord MRI with contrast were also normal. Nerve conduction studies (NCS) and electromyography (EMG) of the lower extremities showed no abnormalities.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of a 23-year-old man presenting with left leg pain and abnormal movement of his left toes with no psychiatric disorders besides mild anxiety can be challenging. We briefly discuss the conditions we thought he could be suffering from.

We have divided them into neuroleptic-induced and non-neuroleptic-induced symptoms.

Neuroleptic-induced symptoms:

Acute neuroleptic-induced dyskinesia;
Tardive dyskinesia (TD).

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Non-neuroleptic-induced symptoms:

Wilson's disease
 Hyperthyroidism
 Multiple sclerosis (MS)
 Huntington's disease (HD)
 RLS

Our patient had continuous writhing and rhythmic abnormal movements of his left toes in contrast to diseases that produce myoclonic movements. Furthermore, brain and spinal MRI helped in excluding MS lesions. The absence of family history of HD made this diagnosis unlikely. Wilson's disease and hyperthyroidism can both present with abnormal extremity movements or tremors but these were ruled out by negative laboratory findings along with lack of other symptoms. RLS is associated with pain and might exhibit certain features similar to PLMT syndrome; however, contrary to PLMT syndrome, symptoms are relieved on walking or moving the affected limb and generally worsen at night.

Neuroleptics are known to cause TD; however, TD is considered as a late complication of neuroleptics and, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) V criteria, it requires at least 3 months of drug exposure before diagnosis can be made. While the patient's abnormal movements started intermittently after around 3 months of exposure to flupentixol/melitracen, his symptoms were preceded by a dull aching pain of the affected limb, which is not typically associated with TD but fits the description of PLMT syndrome as reported by Spillane *et al.*¹ Neuroleptics can also cause acute induced dyskinesia, which can occur in 2.3% of patients treated with antipsychotics⁵; however, this acute dyskinesia is dose dependent and remits with dose reduction or cessation of the antipsychotic.

TREATMENT

The patient was started on carbamazepine (200 mg tablets twice daily), which improved his pain but did not have a noticeable effect on the abnormal movements. Three weeks later the medication was stopped because of drowsiness. Botulinum injections in his left extensor digitorum brevis (40 units) and his left flexor digitorum superficialis (30 units), significantly reduced the movements and mildly improved the painful sensations. The beneficial effects lasted for about 3 months after which the movements and pain gradually returned to their initial state.

OUTCOME AND FOLLOW-UP

The patient was followed over the course of 4 years; pain and movements are stable since he initially presented. No other treatment aside from his last botulinum injections was attempted; his neurological examination remains unremarkable except for his abnormal movements.

DISCUSSION

From four main manuscripts discussing PLMT syndrome, there were 162 patients. The mean age of onset in these cases was found to be in the late 50s for men and mid-60s to late 60s for women.¹⁻⁴ Two reports, each on a single patient in his 20s with PLMT syndrome, however, have also been presented by Alvarez *et al.*⁶ and Hassan *et al.*³ We were particularly interested in the research for possible aetiologies in the various syndromes co-existing with PLMT syndrome, especially in young patients.

A main characteristic of PLMT syndrome has been the large number of co-existing aetiologies, but by far the most prevalent has been injury or trauma to the spinal cord, cauda equina or

lumbar nerve roots.^{7 8} As a possible cause of PLMT syndrome, peripheral nerve injury has been suggested to result in a change in the afferent neuronal connections, which can lead to abnormal central processes, which in turn can lead to the abnormal sensations outside the territory of the affected nerve. In our patient, however, there was no history of leg, spinal cord or other trauma or surgical manipulation. Furthermore, brain and spinal MRI and NCS with EMG were all normal, thus ruling out any evidence of trauma or other pathologies in the brain, spinal cord and peripheral nerves.

In addition, the exacerbation of pain and abnormal movements by psychological or emotional stressors and when the patient's bladder was full and the relief subsequently when emptied, further pointed to a possible central aetiology. The disappearance of movements during sleep—a feature commonly reported in this syndrome—could indicate a possible involvement of the reticular formation, which strengthens further the hypothesis of a role of central mechanisms in the development of this syndrome.

Another notable finding was the temporal relation between the onset of pain and abnormal movements with the intake of flupentixol/melitracen, as mentioned previously.

Flupentixol is a first-generation antipsychotic. It is a dopamine receptor antagonist at various sites including D1 to D5. It acts also as an antagonist to serotonin, histamine and epinephrine, with no anticholinergic action. It has been used for the treatment of schizophrenia⁸ and also depression when associated with a tricyclic antidepressant (TCA) such as melitracen. Since TCAs are not known to cause abnormal movements, we were more prone to establish a causal association between the described symptoms and the intake of flupentixol. Usually, first-generation antipsychotics are known to cause a variety of movement disorders such as dystonia, akathisia, TD and parkinsonism.⁹ Flupentixol/melitracen is already banned in the USA and the only cases reported to date of flupentixol inducing abnormal movements have been mainly due to its depot injection, which contains a higher dosage than its oral form, the one present in the medication we are describing; the low dose of flupentixol in Deanxit has been considered to be relatively free of side effects and this is why it is still used in combination with a TCA as an anxiolytic drug in many countries. One particular case of auto-amputation of the tongue as a result of the extra-pyramidal symptoms caused by flupentixol⁹ is worth mentioning. In another study,¹⁰ comparing the efficacy of flupentixol to risperidone, it was found that flupentixol (2 mg orally twice daily), used to treat negative symptoms in schizophrenic patients, was similar and even superior to risperidone, but the side effects were more frequent in the group treated with flupentixol; 75% of patients treated with flupentixol reported adverse effects compared to 56% in the group treated with risperidone.¹⁰ Most of the adverse effects have been movement-related disorders.

The pathology behind PLMT syndrome remains obscure and, to date, cases induced by neuroleptics are seldom reported; Sandyk¹¹ reported the first patient with PLMT syndrome precipitated by molindone in 1990, which was successfully treated with baclofen and clonazepam. Alvarez *et al.*,⁶ in his case series of 14 patients with PLMT syndrome, described two patients having the onset of abnormal movements after long-term intake of a neuroleptic; one patient was taking perphenazine and the other was taking ziprasidone. Similar to our case, those two patients had a normal neurological examination with normal laboratory and radiological tests but contrary to our patient, both of them improved after discontinuation of the antipsychotic drug. Based on our findings, we speculate that

neuroleptics might induce the symptoms of PLMT syndrome but the progression of the disease varies from patient to patient and further studies are needed to understand the cause–effect relationships.

Learning points

- ▶ PLMT syndrome is a rare syndrome but can be diagnosed in young patients.
- ▶ Neuroleptics should be used in caution and can be associated with other movements disorders than tardive dyskinesia and dystonia, in this case PLMT syndrome.
- ▶ The absence of symptoms during sleep, negative findings on EMG, and exacerbation of symptoms when the patient bladder was full could furthermore point to a central origin of the PLMT syndrome.
- ▶ Botulinum injection can be an option for patients suffering from PLMT syndrome.

Contributors RJ established the clinical diagnosis, followed up the patient, performed the EMG and other clinical and therapeutic modalities, she also proposed the neuroleptic medication as cause of the syndrome and reviewed critically the manuscript.

Competing interests None.

Patient consent Obtained.

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