CASE REPORT/*OPIS PRZYPADKU*

Acute focal dystonia induced by a tricyclic antidepressant in a patient with Wilson disease: a case report

Ostra dystonia ogniskowa wywołana trójpierścieniowym lekiem przeciwdepresyjnym u pacjenta z chorobą Wilsona – opis przypadku

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Abstract

The authors present the case of a 19-year-old patient with Wilson disease (WD) who developed symptoms of acute focal dystonia of the left hand (a 'starfish' hand presentation) shortly after treatment with the tricyclic antidepressant clomipramine. The diagnosis of WD was made 8 months earlier based on abnormal copper metabolism parameters and was confirmed by genetic testing. Initially, the patient presented with akathisia, sialorrhea, oromandibular dystonia (occasionally grimacing) and slight dysarthria. The patient's symptoms diminished after treatment with d-penicillamine was initiated. No further deterioration was observed after copper-chelating therapy was started.

The authors diagnosed acute focal dystonia induced by clomipramine.

Botulinum toxin and intensive rehabilitation was initiated; complete regression of hand dystonia was observed. Based on the case, the authors suggest that care should be exercised with regard to starting medications that could potentially impact the extrapyramidal system in WD patients.

Key words: Wilson disease, dystonia, clomipramine.

Streszczenie

W pracy przedstawiono przypadek 19-letniego pacjenta z chorobą Wilsona, u którego po włączeniu trójpierścieniowego leku przeciwdepresyjnego – klomipraminy – wystąpiły objawy ostrej dystonii ogniskowej w postaci ręki „rozgwiazdy". Chorobę Wilsona rozpoznano u pacjenta 8 miesięcy wcześniej na podstawie nieprawidłowego metabolizmu miedzi i badań genetycznych. Początkowo chory prezentował dyskretne objawy neurologiczne: akatyzję, ślinotok, dystonię ustno-żuchwową oraz dyzartrię. Po włączeniu leczenia d-penicylaminą nie obserwowano pogorszenia stanu neurologicznego, a początkowe objawy w trakcie leczenia chelatującego znacznie się zmniejszyły, dlatego rozpoznano u pacjenta ostrą dystonię ogniskową indukowaną klomipraminą. Pacjenta leczono toksyną botulinową oraz rehabilitowano z dobrym efektem, objawy dystonii ogniskowej całkowicie ustąpiły w ciągu roku. Autorzy proponują zachowanie szczególnej ostrożności w stosowaniu leków potencjalnie wpływających na układ pozapiramidowy u pacjentów z chorobą Wilsona.

Słowa kluczowe: choroba Wilsona, dystonia, klomipramina.

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Introduction

Wilson disease (WD) (OMIM 277900) is an inherited autosomal recessive copper metabolism disorder that results in copper accumulation in many organs (brain, liver, cornea, kidney and heart) with secondary damage of the affected tissues [1-4].

There is a wide spectrum of WD phenotypic presentation, including clinical signs and symptoms ranging from predominantly asymptomatic hepatic presentation or asymptomatic increased level of aminotransferases to acute liver failure, or to a predominantly neuropsychiatric presentation, including various involuntary movements and psychiatric symptoms [2,4-7]. At diagnosis, up to 40% of WD patients present with neurological symptoms, very often including multi-segmental or general dystonia, which apart from tremor is the most frequent and most severe presentation of WD [5]. Approximately 15% of WD patients present with psychiatric manifestations [4,5]. These patients often require treatment with antipsychotics or antidepressants. However, due to damage within the dopaminergic system in patients with WD, such treatments should be used and introduced very carefully due to the possibility of medication-induced movement disorders (MIMDs) [8-12].

Medication-induced dystonia has been previously described and, in most cases, is caused by drugs blocking the action of dopamine, especially those blocking D_2 (dopamine) receptors in the caudate, putamen and globus pallidus [8-11]. The other drugs that cause dystonia include pharmaceutics that change the balance between serotonin and dopamine or between dopamine and acetylcholine in the basal ganglia [13-21]. In the literature, there are reports of acute dystonia produced by (1) neuroleptics, (2) antiemetics, (3) antidepressants such as tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOs), selective serotonin reuptake inhibitors (SSRIs), serotonin antagonist and reuptake inhibitors (SARIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), (4) antiepileptic drugs (phenytoin, carbamazepine, diazepam), and (5) antimigraine drugs (sumatriptan), among others [13-22]. In patients with neurodegenerative disorders such as WD in whom symptoms of acute dystonia develop during treatment, the following question should be considered: Are the symptoms related to the progression of the disease or to a movement disorder that is a side effect of treatment?

We report the case of a patient with WD with slight extrapyramidal syndrome (akathisia and oromandibular dystonia) in whom focal acute hand dystonia occurred after treatment with the tricyclic antidepressant clomipramine.

Case report

A 19-year-old patient was admitted to our department of neurology in September 2005 because of acute focal left hand dystonia with spreading of his fingers in a 'starfish' pattern (Fig. 1). This symptom appeared in July 2005 within 5 days of initiating clomipramine therapy (20 mg/day) and then progressed to complete loss of left hand function.

We first diagnosed the patient with Wilson disease in January of 2005. The first clinical symptoms of WD developed in March 2004 and included akathisia (involuntary movements of both upper extremities), sialorrhea and signs of dystonia, such as abnormal neck posture, oromandibular dystonia with occasional face grimacing and slight dysarthria (his speech was inaudible). At the time of diagnosis, no signs of left hand dystonia were present. The diagnosis of WD was confirmed by biochemical test results showing abnormal copper metabolism parameters: the serum ceruloplasmin level was 0.009 g/L (normal: 0.092-0.164 g/L), the serum copper was 5 μg/dL (normal: 70-140) and the copper excretion in urine was 580 μg/24 h (normal: 0-50). An ophthalmologic slit lamp examination revealed the presence of Kayser-Fleischer rings bilaterally. Additionally, a brain MRI showed changes typical of WD (Fig. 2). Finally, genetic testing revealed homozygosity for the p.H1069Q mutation in both alleles of the *ATP7B* gene.

Beginning in January 2005, the patient was treated with copper chelator d-penicillamine with a gradually

Fig. 1. Left hand dystonia with a 'starfish' presentation: acute phase

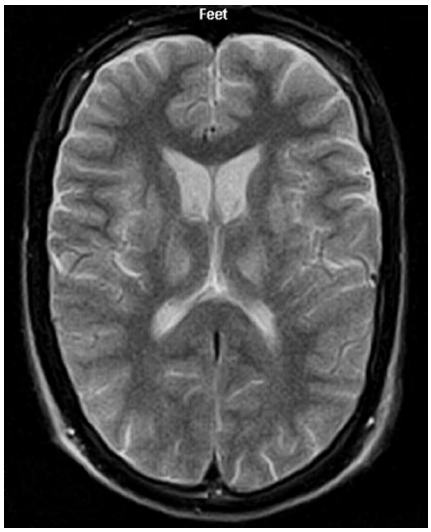

Fig. 2. Brain MRI showing increased signal intensity on T2-weighted images both in deep structures and in the thalamus

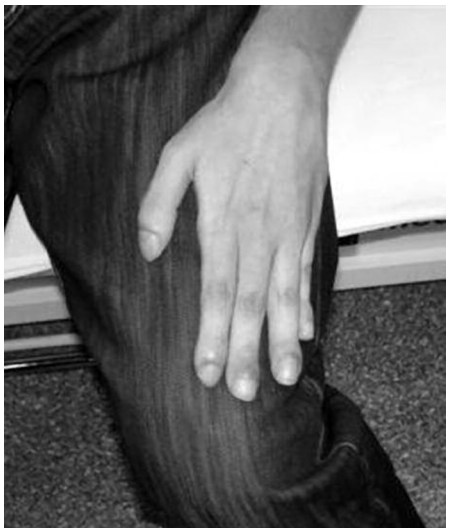

Fig. 3. Complete recovery of the affected hand after one year

increasing dose that started from 100 mg/day and reached 1000 mg/day in February 2005.

In the summer of 2005, his parents observed a decline in his mood. The consulting neurologist decided to introduce antidepressive treatment with clomipramine (20 mg/day). Five days later, the patient developed acute focal dystonia of the left hand.

The patient was seen again in our department. A neurological examination at admission revealed severe dystonia of the left hand with spreading of his fingers in a 'starfish' configuration (the hand was not functional), hypomimia, and the continued presence of Kayser-Fleischer rings in both eyes. Akathisia, sialorrhea, oromandibular dystonia and dysarthria (observed at initial diagnosis) and other clinical signs of WD were not present.

We again measured copper metabolism parameters. His urine demonstrated continued increased copper excretion at a level of 676 μg/24 h (normal: 0-50), which we attributed to good patient compliance with d-penicillamine treatment. The overall clinical picture suggested the occurrence of acute dystonia induced by clomipramine. Because the dystonic symptoms persisted for a relatively long time (3 months), we decided not to treat this patient with anticholinergic drugs. We started with intensive rehabilitation and gave him a series of injections with botulinum toxin (Dysport), and complete recovery of the affected hand was observed over the course of a one-year observation period (Fig. 3).

Discussion

We present this case as an example of an MIMD, specifically a complication of treatment with the antidepressant clomipramine in a patient with WD.

In clinical practice, MIMDs can be divided into five types [11]:

1) Acute focal dystonia, which starts rapidly within the first 7 days (typically 96 hours) after medication treatment (with antipsychotics, antidepressants and other drugs). Muscle spasms produce abnormal postures with pain. Fear and fever have also been reported.
2) Tardive dyskinesia, which is the late onset of a neuroleptic-related movement disorder. This MIMD is usually observed a few months or years after neuroleptic treatment. The symptoms include involuntary movements of mouth and face (very difficult to treat).
3) Intermediate-onset types of movement, the symptoms of which occur between 1 and 3 months after treatment with medication that causes extrapyramidal symptoms. Two forms of this MIMD may be distinguished: neuroleptic-induced parkinsonism (symmetrical signs) and akathisia (uncontrolled restlessness with compulsive movement of feet and fingers).
4) Neuroleptic malignant syndrome, which is a movement disorder that can occur at any time. This disorder presents as coma, fever, high blood pressure, or muscular rigidity.

5) Tremor, which includes high-amplitude postural tremor occurring after treatment with valproic acid, lithium, amphetamine, or tricyclic antidepressants.

As mentioned in the introduction, most MIMDs occur after neuroleptic use, but they can also occur during treatment with other drugs that impact neurotransmitters in the basal ganglia. Antidepressant-induced extrapyramidal symptoms are relatively rare (incidence 1/1000), but failure to recognize these symptoms and their etiology could significantly impact a patient's quality of life [13]. The first recorded case was described in 1959 as a coarse tremor after imipramine treatment [14]. The authors described this phenomenon as a "manifestation of the dystonic type of motor disturbance". However, it has been reported that different antidepressants elicit different extrapyramidal symptoms or MIMDs [13-21]. Patients treated with tricyclic antidepressant can present with dyskinesia, akathisia, 'rabbit syndrome' and acute dystonia. These adverse events are not frequent, are related to drug dosage and could occur more often in patients with previous exposure to neuroleptics, lithium, or estrogens. In patients treated with MAOs, there are reports of akathisia, acute dystonia and parkinsonism. SARIs can produce dystonia, parkinsonism, oculogyric crisis, torticollis and chorea, in addition to akathisia. Finally, SSRIs can produce dystonic reactions, parkinsonism, akathisia and tardive dyskinesia [13].

The mechanisms underlying the adverse effects of antidepressants are not known, but changes in the balance between neurotransmitters such as serotonin and dopamine or dopamine and acetylcholine in the basal ganglia have been proposed. It is conceivable that these drugs impact receptors in the brain, thereby modulating dopaminergic functions. For example, TAC is a high-affinity antagonist of serotoninergic (5-HT_2, 5-HT_6, 5-HT_7), adrenergic (α_1-adrenergic), histaminergic (H_1 and H_2 receptors) and cholinergic receptors. SSRIs and SARIs produce increased 5-hydroxytryptamine inhibition of nigrostriatal dopaminergic neurons [13].

The most common MIMD, which is particularly common in younger patients, is acute focal dystonia, especially in response to neuroleptics, but also, as mentioned above, in response to antidepressants and other drugs [11]. The symptoms of acute focal dystonia usually start rapidly within the first 7 days (often within 96 hours) after treatment initiation (with antipsychotics, antidepressants and others). The muscle spasms produce abnormal postures with pain and occasionally fear and fever.

In our patient, an MIMD (in the form of acute focal dystonia of the left hand) was induced by clomipramine treatment. Several risk factors for this type of adverse drug reaction have been previously identified, including male sex, young age (10-20 years old), use of cocaine, and history of extrapyramidal syndrome [11,13]. In patients with these risk factors, drug-induced dystonia can be prevented by introducing anticholinergic therapy (i.e., biperiden) during the first seven days of treatment with potentially hazardous pharmaceuticals.

The treatment of acute dystonia induced by medication is usually effective if it is initiated early [11, 16,20]. Intramuscular injections of anticholinergic drugs resolve the symptoms in several minutes, and repeated injections are usually not needed. Oral treatment with anticholinergic drugs should be introduced and continued from 48 hours to 7 days to prevent recurrence of the symptoms [11]. Treatment with the offending drug should be discontinued. If dystonia persists in the patient or if the symptoms persist or reoccur after a few months (as they did in our patient), then treatment with botulinum toxin should be considered. In each case, the possibility of other underlying causes of dystonia should be considered [11].

It should be noted that d-penicillamine can also cause neurological deterioration in patients suffering from WD, especially during the first months of treatment [4-7,23]. These symptoms are caused by the rapid release of copper from tissues into the blood, which produces a secondary increase in brain copper concentration and toxic brain damage [4-6].

Effective anti-copper treatment (as evidenced by high copper excretion in the urine) as well as the recovery of initial neurological signs and a lack of any new WD neurological symptoms strongly confirmed that the dystonia symptoms in this patient were closely related to clomipramine treatment without prophylaxis with anticholinergic drugs. The delay in neurological consultation after the onset of dystonia contributed to the persistence of the symptoms over a long period of time. Finally, treatment with botulinum toxin and rehabilitation was effective and completely ameliorated the signs of dystonia.

In summary, we suggest that care should be exercised when beginning any pharmacologic agent that could produce EPS in WD patients due to the risk of medication-induced movement disorders.

Disclosure

The authors report no conflict of interest.

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