

Low-Dose Amitriptyline-Induced Acute Dystonia in a Patient with Metachromatic Leukodystrophy

Gerarda Cappuccio · Nicola Brunetti-Pierri ·
Gaetano Terrone · Alfonso Romano ·
Generoso Andria · Ennio Del Giudice

Received: 01 August 2012 / Revised: 23 September 2012 / Accepted: 25 September 2012 / Published online: 30 October 2012
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Abstract Acute dystonia is an abrupt event mainly related to toxicity of drugs such as antiemetics, antipsychotics, anti-acids, and, more rarely, tricyclic antidepressants. Use of amitriptyline in metachromatic leukodystrophy (MLD), a lysosomal storage disorder (LSD) due to arylsulfatase A deficiency, is suggested to control neurological pain and irritability. We describe a patient with MLD who experienced acute dystonia as a side effect of low dosage of amitriptyline. The distribution of psychotropic drugs, including antidepressants, depends upon lysosomal trapping which is inefficient in LSD. The defective lysosomal depot might raise cerebral levels of amitriptyline, thus enhancing its adverse effects.

Physicians caring for children with MLD treated with psychotropic drugs should be aware of such adverse events which are potentially related to lysosomal dysfunction. This experience raises a potential concern about the appropriate dose of amitriptyline in patients with MLD.

Introduction

Drug-induced dystonic reactions are the most common causes of acquired dystonia in childhood (van Harten et al. 1999).

Side effects profile of amitriptyline includes sedation, dry mouth, impaired cardiovascular and central nervous system (CNS) function (Gore et al. 2006); among extrapyramidal manifestations, acute dystonia has been reported in cases of long-term or overdose of amitriptyline treatment (Ornadel et al. 1999; Finder et al. 1982; Lee 1988). In the literature, two cases of pediatric amitriptyline poisoning are described (Baysal et al. 2007; Doherty et al. 2012).

Metachromatic leukodystrophy (MLD) is an autosomal recessive lysosomal storage disorder (LSD) due to arylsulfatase A (ARSA) enzyme deficiency, resulting in rapid and progressive neurologic and cognitive deterioration. Irritability and neurologic pain are significant problems for the management of patients in advanced stages of the disease and evidence-based treatment options for these issues are lacking. Practical hints can be found in the document by the Evanosky Foundation (The Evanosky Foundation 2008). Listing of the suggested medications include: myorelaxant agents (Dantrium, Baclofen), anti-reflux, anti-seizure, and anti-inflammatory medications. Amitriptyline is suggested to control irritability and pain.

We report a 3.7-year-old girl affected by MLD who presented with an acute episode of dystonia related to amitriptyline which was given to control irritability and pain.

Case Report

A 3.7-year-old girl affected by the late infantile form of MLD, confirmed by both biochemical and molecular analyses, is regularly followed at the Department of Pediatrics of Federico II, University of Naples, Italy. Progressive spasticity had led to permanent plantar flexion of the feet at rest, despite baclofen treatment at the dosage of 2 mg/kg/day. Moreover, the girl began to

Communicated by: Verena Peters

Competing interests: None declared

G. Cappuccio (✉) · N. Brunetti-Pierri · G. Terrone · A. Romano ·
G. Andria · E. Del Giudice
Department of Paediatrics, University of Naples Federico II,
Via s. Pansini, 5, 80131, Naples, Italy
e-mail: gerardacappuccio@gmail.com

N. Brunetti-Pierri
Telethon Institute of Genetics and Medicine, Naples, Italy



Fig. 1 Girl affected with MLD presenting with an acute dystonia following amitriptyline treatment. Note the opisthotonos with forced head and gaze deviation to the right, grimacing, and trismus

suffer from bouts of crying lasting for several hours during the night.

We used a modified Ashworth scale (Lee et al. 1989) to rate her severity of hypertonia: on the right side, passive movement was difficult and scored 3, on the left, range of motion and spasticity matched to a score of 4. After an extensive workup carried out in order to exclude treatable causes of pain, including gallbladder stone (Kim et al. 1996) dantrolene sodium (6 mg/kg/day) was added to therapy, and resulted in some improvements on the Ashworth scale: spasticity improved within 2 days to a score of 3 bilaterally.

Treatment with amitriptyline was started to improve crying and neurological pain, as suggested by the Evanovsky paper (The Evanovsky Foundation 2008). The starting dose was 0.2 mg/kg daily orally for the first 2 days, gradually raised to 0.4 mg/kg daily in the third and the fourth day, lower doses than those recommended for pediatric age (Fournier-Charrière 2010).

After 4 days of treatment, muscular tone further improved (bilaterally score 2 according to Ashworth scale). However, on the morning of the fifth day of amitriptyline treatment, the patient experienced generalized malaise, vomiting, profuse sweating, tachycardia (heart rate 190/min), tachypnea (respiration rate about 28/min), and mydriasis. A few hours later, she abruptly developed worsening of hypertonia with severe generalized muscle contractions and opisthotonos (score 4 bilaterally, according to the Ashworth scale). Furthermore, a forced head and gaze deviation to the right with horizontal nystagmus ensued, followed by trismus, and buccolingual automatisms (Fig. 1). Oxygen saturation was in the normal range (about 99–100%). The patient appeared unresponsive to her surroundings with an ill-defined state of consciousness. The video/EEG monitoring showed high amplitude, background activity of 3 to 4 Hz, with an excess of muscular

artifacts. In view of the absence of epileptic abnormalities, a diagnosis of acute generalized dystonia was entertained and treatment with 0.16 mg/kg of diazepam intravenously was started.

As an amitriptyline-induced dystonic reaction could be reasonably foreseen, the drug was immediately discontinued. Common antidotes as anticholinergic benztropine were not used because of the tachycardia.

The patient showed a gradual reversion of the opisthotonos and resolution of all autonomic symptoms and signs. Video/EEG recording was repeated after 1 week from the acute episode and did not show any epileptic abnormalities.

The Naranjo scale (Naranjo et al. 1981) indicated that the adverse event was probably caused by amitriptyline (causality algorithm yielded a score of 7).

The chronic unexplained irritability in the little child has been treated subsequently with Gabapentin, 5 mg/kg per dose as previously described (Hauer et al. 2007), achieving successful results in decreasing irritability and crying, bettering nocturnal sleep.

Discussion

Drugs inducing extrapyramidal symptoms include anticonvulsants (Van Harten et al. 1999), antiemetic and anti-nausea drugs (Patel et al. 2011), atypical and typical antipsychotics, tricyclic antidepressants (TCAs) (Arnone et al. 2002), triptans (Garcia et al. 1994), antitussive drugs (Polizzi et al. 2001), histamine H₂-receptor antagonists (Kapur et al. 1999), and antihistamine agents (Esen et al. 2008). Misdiagnosis is common, and video/EEG monitoring is useful to rule out epileptic fits.

Amitriptyline, a TCA, has pronounced side effects that tend to be most acute in the elderly because they frequently require multiple medications that increase the potential

drug-drug interactions (Gore et al. 2006). Tremor, dysarthria, and akathisia due to amitriptyline have been observed. Only few cases of acute dystonia due to amitriptyline have been reported in adults, ascribed to overdose and/or long-term therapy, drug interactions (Ornadel et al. 1999; Finder et al. 1982; Lee 1988).

List of medications potentially interacting with amitriptyline includes baclofen (Gore et al. 2006). In our young patient, concurrent administration of baclofen with the amitriptyline may have lowered the threshold for this unwanted adverse effect.

Among pediatric patients, acute neurological manifestations, like tonic-clonic seizures, due to amitriptyline overdose (47 mg/kg and 14 mg/kg respectively) have been described sporadically (Baysal et al. 2007; Doherty et al. 2012). In children, doses of 5 mg/kg are potentially toxic while severe toxicity is encountered at 20 mg/kg dose (Vernon and Gleich 1997). In the case herein reported, the patient presents with acute dystonia at dosage of amitriptyline within 0.2–0.4 mg/kg daily.

The causal relationship between acute dystonia and amitriptyline in our patient is based on (1) close temporal correlation between drug administration and onset of the dystonia, (2) improvement following drug withdrawal, (3) no recurrence of symptoms after the drug was discontinued, and (4) exclusion of other possible causes. In addition, according to the Naranjo adverse drug reaction probability scale, the event is assigned as probable (Lee et al. 1989).

Dystonia has been rarely described as a feature of MLD (Baumann et al. 2002). This may suggest a particular predisposition for dystonia episodes in MLD patients following centrally acting drugs.

A possible pathomechanism underlying this unexpected toxic effect of low-dose amitriptyline may depend upon lysosomal dysfunction of MLD. Tissue distribution of psychotropic drugs depends on phospholipid binding and lysosomal trapping, which play an important role, particularly for drug biodistribution within the central nervous system (CNS) (Daniel et al. 2001). A decrease in the concentration of psychotropic drugs in lysosomes, as a result of lysosomal dysfunction in LSDs, may result in altered intracellular distribution and/or drug uptake in neuronal and glial cells, which ultimately might lead to enhancement of the drug biological effect (Daniel 2003). Therefore, we speculate that impaired lysosomal trapping of amitriptyline in the patient reported might lead to increased drug CNS levels, which resulted in drug intoxication. This mechanism of drug toxicity could be responsible for the onset of extrapyramidal signs also in other previously reported patients with other LSDs, receiving psychotropic drugs.

In their review of 20 patients with mucopolysaccharidosis type III, treated with neuroleptic drugs (lamotrigine, risperidone, and olanzapine), Tchan and Silence (2009)

reported five patients with a clear relationship between drug assumption and extrapyramidal symptoms (included acute dystonia). Moreover, Shapiro et al. (2006) reviewed 44 adults with late-onset Tay-Sachs disease who experienced worsening of neurologic symptoms (weakness, incoordination, imbalance, tremor, dysarthria, cognitive decline, and dystonia) following treatments with medications such as haloperidol, risperidone, and chlorpromazine.

The above-mentioned psychotropic drugs have been proved to share lysosomotropic properties (Daniel et al. 2001). We suggest that adverse extrapyramidal manifestations reported in patients with LSDs taking psychotropic drugs could be related to defective lysosomal drugs uptake and disposal.

In summary, we report a patient with MLD who developed acute dystonia following amitriptyline therapy. Patients with a defective lysosomal depot might be prone to drug toxicity even at doses falling within or lower the recommended dose range. Treatment of irritability and neurological pain in patients with MLD is often difficult, since it may require the use of multiple medications (increasing potential drug-drug interactions), appropriate dosage, and monitoring for undesirable medical consequences.

References

- Arnone D, Hansen L, Kerr JS (2002) Acute dystonic reaction in an elderly patient with mood disorder after titration of paroxetine: possible mechanisms and implications for clinical care. *J Psychopharmacol* 16:395–397
- Baumann N, Turpin JC, Lefevre M, Colsch B (2002) Motor and psychocognitive clinical types in adult metachromatic leukodystrophy: genotype/phenotype relationships? *J Physiol Paris* 96:301–306
- Baysal T, Oran B, Doğan M, Cimen D, Elmas S, Karaaslan S (2007) Beta-blocker treatment in an adolescent with amitriptyline intoxication. *Anadolu Kardiyol Derg* 7:324–325
- Daniel WA (2003) Mechanisms of cellular distribution of psychotropic drugs significance for drug action and interactions. *Prog Neuropsychopharmacol Biol Psychiatry* 27:65–73
- Daniel WA, Wójcikowski J, Pałucha A (2001) Intracellular distribution of psychotropic drugs in the grey and white matter of the brain: the role of lysosomal trapping. *Br J Pharmacol* 134:807–814
- Doherty S, Cave G, Harvey M (2012) Paediatric amitriptyline overdose. *Open J Pediatrics* 2:170–174
- Esen I, Demirpence S, Yis U, Kurul S (2008) Cetirizine-induced dystonic reaction in a 6-year-old boy. *Pediatr Emerg Care* 24:627–628
- Finder E, Lin KM, Ananth J (1982) Dystonic reaction to amitriptyline. *Am J Psychiatry* 139:1220
- Fournier-Charrière E (2010) Neuropathic pain in children. *Arch Pediatr* 17:665–666
- Garcia G, Kaufman MB, Colucci RD (1994) Dystonic reaction associated with sumatriptan. *Ann Pharmacother* 28:1199
- Gore M, Dukes E, Rowbotham D, Tai KS, Leslie DL (2006) Prevalence of contraindicated medical conditions and use

- of precluded medications in patients with painful neuropathic disorders prescribed amitriptyline. *Pain Pract* 6:265–272
- Hauer JM, Wical BS, Charnas L (2007) Gabapentin successfully manages chronic unexplained irritability in children with severe neurologic impairment. *Pediatrics* 119:e519–e522
- Kapur V, Barber KR, Peddireddy R (1999) Ranitidine-induced acute dystonia. *Am J Emerg Med* 17:258–260
- Kim TS, Kim IO, Kim WS, Choi YS, Yeon KM, Hwang YS (1996) Involvement of the gallbladder in childhood metachromatic leukodystrophy: ultrasonographic findings. *J Ultrasound Med* 15:821–825
- Lee HK (1988) Dystonic reactions to amitriptyline and doxepin. *Am J Psychiatry* 145:649
- Lee K, Carson L, Kinnin E, Patterson V (1989) The Ashworth Scale: A Reliable and Reproducible Method of Measuring Spasticity. *Neurorehabil Neural Repair* 3:205–209
- Naranjo CA, Busto U, Sellers EM et al (1981) A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Therapeutics* 30:239–245
- Ornadel D, Barnes EA, Dick DJ (1999) Acute dystonia due to amitriptyline. *J Neurol Neurosurg Psychiatry* 55:414
- Patel A, Mittal S, Manchanda S, Puliye JM (2011) Ondansetron-induced dystonia, hypoglycemia, and seizures in a child. *Ann Pharmacother* 45:e7
- Polizzi A, Incorpora G, Ruggieri M (2001) Dystonia as acute adverse reaction to cough suppressant in a 3-year-old girl. *Eur J Paediatr Neurol* 5:167–168
- Shapiro BE, Hatters-Friedman S, Fernandes-Filho JA, Anthony K, Natowicz MR (2006) Late-onset Tay-Sachs disease: adverse effects of medications and implications for treatment. *Neurology* 67:875–877
- Tchan MC, Sillence D (2009) Extrapyrarnidal symptoms and medication use in mucopolysaccharidosis type III. *J Intellect Dev Disabil* 34:275–279
- The Evanosky Foundation (2008) Pain and symptoms management. <http://www.evanoskyfoundation.org/MLD%20Care%20Plan%20031408.pdf>
- Van Harten PN, Hoek HW, Kahn RS (1999) Acute dystonia induced by drug treatment. *BMJ* 319:623–626
- Vernon DD, Gleich MC (1997) Poisoning and drug overdose. *Crit Care Clin* 13:647–667