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Case Report

Drug Induced Acute Dystonic Reactions

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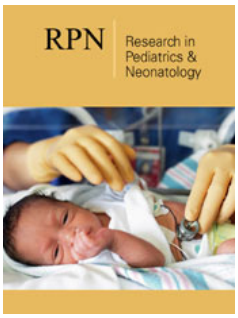

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Abstract

Objectives: The aim of the present study is to understand the main pharmacologic triggers for drug induced dystonia (DID), the most common clinical manifestations, and the need for specific treatment.

Methods: We performed a cross-sectional study at the emergency paediatric department of a level II Portuguese hospital and reviewed all clinical records of children who were discharged from our emergency department (ED) with the diagnosis of DID in a 10-years period (2011-2020). The following data were studied: gender, age, trigger for dystonic reaction, type of dystonic reaction, pharmacological approach to reverse the dystonic effects and need of hospital admission. The study protocol was approved by our hospital ethics committee.

Results: We obtained a total of seven patients with a median age of 15 years old. Four patients (57.1%) presented the dystonic reaction after the administration of risperidone. Two patients (28.5%) presented the DID after the administration of a correct dose of haloperidol and one (14.2%) patient after the administration of metoclopramide in a correct dose. Three patients (42.8%) had generalized dystonia (in at least two different body sites), while the remaining four patients (57.1%) presented a focal DID. The most frequent clinical presentation (57.1%) was a buccolingual crisis that included persistent tongue protrusion, tongue fasciculations, tongue deviation, pain, and paralysis. Five patients (71.5%) were treated with intravenous biperiden at the emergency department with clinical resolution. Two patients (28.5%) had an initial spontaneous resolution of the dystonic reaction, but with a recurrence within hours, leading to biperiden treatment as well.

Conclusion: Although drug-induced dystonia is rare among the paediatric population, its occurrence often causes anxiety or pain. Close communication is essential to the early recognition and treatment of DID, avoiding unnecessary investigations for this potentially reversible condition.

Keywords: Acute dystonic reactions; Drug induced dystonia; Antipsychotics; Adverse reactions

Introduction

Dystonia is a neurological movement disorder characterized by involuntary and sustained muscle contractions affecting one or more sites of the body, like the extremities, face, neck, abdomen, pelvis, or larynx in either sustained or intermittent patterns that lead to abnormal movements or postures [1-4]. A new classification scheme for dystonia uses two branches to facilitate clinical recognition, diagnostic evaluation, and treatment. The first branch considers the clinical characteristics of each patient into four categories: age at onset, body distribution, temporal pattern and associated features including the presence of other movement disorders, neurological or systemic manifestations. The second branch focus on aetiology, classifying dystonia as inherited, acquired, or idiopathic [5]. Inherited dystonia's are the ones with proven genetic origin, acquired dystonia's have an identified nongenetic cause and idiopathic dystonia's have no known cause [5].

Drug-induced dystonic reactions are the most common cause of acute acquired dystonia [1,6]. The aetiology is thought to be due to dopaminergic-cholinergic imbalance and reactions usually occur shortly after the initiation of the offending agent (up to 96 hours) or after an increase in dose [1,2]. The most common causative drugs include antipsychotic and antiemetic agents but others such as anti-malarial, antidepressants, antihistamines, and anticonvulsants

have also been implicated in cases of acute dystonic reaction [1-3,6-8].

Anticholinergic agents and benzodiazepines are the most used agents to reverse or reduce symptoms in acute dystonic reaction [1,3,9]. Intramuscular or intravenous administration of anticholinergic drugs (for example biperiden) are usually effective within 20 minutes [1,9]. Drug induced dystonic reactions are often transient but can cause significant distress to the patient and their parents [3]. The aim of the present study is to understand the main pharmacologic triggers for DID, the most common clinical manifestations, and the need for specific treatment.

Material and Methods

We performed a cross-sectional study at the emergency paediatric department of a level II Portuguese hospital with a hospital catchment area serving 334081 inhabitants, 61225 of them in the paediatric age range (from birth to 18 years old).

We revised all clinical records of children who were discharged from our emergency department (ED) with the diagnosis of DID in a 10-years period (2011-2020). We searched by ICD9 codification using the following codes: Dystonia: acute due to drugs 333.72; acute neuroleptic-induced 333.72, deformans progressive 333.6, lenticularis 333.6, Musculo rum deformans 333.6, torsion (idiopathic) 333.6, acquired 333.79, fragments (of) 333.89, genetic 333.6 and symptomatic 333.79. There was a mean of 41195 ED admissions per year in the mentioned period.

The following data was extracted from the clinical file: gender, age, trigger for dystonic reaction, type of dystonic reaction, pharmacological approach to reverse the dystonic effects and need of hospital admission. The study protocol was approved by our hospital ethics committee. Statistical analysis was performed using IBM SPSS Statistics version 23. Categorical variables are presented as frequencies and percentages and continuous variables as medians as they were non-normally distributed. Normal distribution was evaluated using Kolmogorov Smirnoff test or through analysis of skewness and kurtosis.

Results

We obtained a total of seven patients, five males (71.5%) and two females (28.5%). The median age was 15 years (minimum 8 years; maximum 17 years). Considering the total number of admissions at the ED, DID represented 0.017% of them. Concerning the trigger for the occurrence of dystonic reaction, four patients (57.1%) presented the dystonic reaction after the administration of risperidone. Among these patients, one of them presented this adverse effect after the first administration of the drug and another one after the third administration of risperidone. One patient had an DID after restarting risperidone following a long period of discontinuation and the fourth patient after the administration of a 10-times higher dose than the correct prescribed dose.

Two patients (28.5%) presented the DID after the administration of a correct dose of haloperidol and one (14.2%) patient after the administration of metoclopramide in a correct dose. Regarding the clinical presentation, three patients (42.8%) had generalized dystonia (in at least two different body sites), while the remaining four patients (57.1%) presented a focal DID. The most frequent clinical presentation (57.1%) was a buccolingual crisis that included persistent tongue protrusion, tongue fasciculations, tongue deviation, pain, and paralysis. Three patients (42.8%) presented with a torticollis crisis characterized by abnormal asymmetric neck position. Two patients (28.5%) presented the acute dystonic reaction as an oculogyric crisis with spasm of the extraocular muscles resulting in ocular deviation upward. Finally, two patients (28.5%) presented with labial commissure deviation. All the mentioned patients had, beside the dystonic features, a normal neurological examination.

Five of the seven patients (71.5%) were treated with intravenous biperiden in an age adjusted dose at the emergency department with clinical resolution. Two patients (28.5%) had an initial spontaneous resolution of the dystonic reaction, but with a recurrence within hours, leading to biperiden treatment as well. None of the patients had the need of a second dose of biperiden. Only two patients needed hospital admission, one due to a cunfusional status after biperiden administration and one adolescent for surveillance of associated behavioural changes.

Discussion

Dystonia is a heterogeneous movement disorder characterized by sustained muscle contractions affecting one or more sites on the body [2]. The diagnostic evaluation of childhood dystonia is challenging due to the phenotypic variability and heterogeneous aetiologies [4]. It is primarily a clinical diagnosis based on history, examination, and pattern recognition [4].

Concerning the aetiology of acquired DID, they are most often caused by dopamine receptor blocking neuroleptics, antiemetic, and antipsychotic drugs [3,4]. Antipsychotics are among the most reported causes of drug related dystonic reactions in children and adolescents [6]. First-generation antipsychotics like haloperidol are associated with a higher risk of acute dystonic reaction than second-generation antipsychotics, such as risperidone. However, it is well known that this risk increases with higher doses and with the combination of different antipsychotics [3,4,6,7]. The diagnosis of acute dystonia caused by antipsychotic can only be made if the patient has been treated with antipsychotics within the past few days [1]. In our study the most common causative agent of acute dystonia was risperidone (57.1%) with haloperidol being responsible for two dystonic reactions (28.5%). This may be explained by the fact that risperidone is prescribed more frequently in outpatient setting, while haloperidol is usually reserved for inpatient settings as an acute antipsychotic agent in psychomotor agitation. Some antiemetic agents like metoclopramide are also common triggers for DID [3,6] and they are the most common type of extrapyramidal reaction associated with the use of metoclopramide [10]. In our sample only one patient presented an DID after the administration of a correct dose of metoclopramide. This can be explained by the

less frequent use of this drug as an antiemetic agent in our hospital and outpatient setting.

There is an estimated 6.8% prevalence of acute dystonic reactions in adults treated with antipsychotics [6], but there are no studies in paediatric age. DID represented only 0.017% of total of ED admissions, probably explained by the less frequent use of antipsychotic drugs in paediatric patients. Also, some of DID can be managed in the primary care setting or because they were time-limited and remitted spontaneously before attending to the ED. DID typically develop two to four days after starting a new antipsychotic drug or increasing dose and 90% occur within the first three days [6,9]. These timings are consistent with our findings.

Male sex and younger ages (patients aged between 10-19 years compared with patients aged 39-39) are well recognized risk factors for acute drug-induced dystonia [1,3,11]. Likewise, in our study, we had a male sex predominance with a median age of 15 years. Drug-induced dystonic reactions can happen in all muscle groups but are typically observed in the head and neck area [1] and can lead to a variety of clinical presentations such as torticollis, trismus, dystonia, dysarthria, oculogyric crisis, blepharospasm, and swallowing difficulties [1,7]. All our patients had their DID localized to the head and neck. Treatment of acute dystonic reaction consists in restoring the disrupted dopaminergic-cholinergic balance and discontinuation of the offending agent [3,9]. Drug-induced dystonia usually responds well to treatment with anticholinergics [4,6,12]. Symptoms usually improve within 10 to 30 minutes after administration of parenteral anticholinergics [3]. Anticholinergics have a relatively high frequency of adverse effects, such as blurry vision, dry mouth, urinary retention, constipation, cognitive impairment, confusion, and delirium [1,12]. All patients in our study were treated with intravenous biperiden and only one (14.2%) presented with significant adverse event (cunfusional status) that led to hospital admission, however remitted quickly and without sequelae.

To the best of our knowledge, this is the first study on acute drug-induced dystonia in a Portuguese paediatric population, which is important to estimate the prevalence of this complication in our population. Also, the identification of the most common causative drugs enables us to perform a thorough medication history when evaluating patients with DID in the ED. Clinicians need to be alert to the possibility that these reactions may occur in patients who were already taking the drug, but who stopped and recently resumed taking it. Alternatives to the most common causative drugs must also be considered in therapeutic regimens. There are some weaknesses in our study, such as a small sample, selection bias (discharge diagnosis), place of performance (many cases probably do not reach the ED) and its retrospective design.

Conclusion

Although drug-induced dystonia is rare among the paediatric population, its occurrence can disturb the relationship between the Paediatrician, the caregiver, and the patient as it often causes anxiety or pain. Also, it may require drug changes and therefore limit treatment options. As with any acute medical condition, close communication is essential to the early recognition and treatment of acute dystonic reactions, avoiding unnecessary investigations for this potentially reversible condition.

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