



# Clinical characteristics of acute drug-induced dystonia in pediatric patients

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**Objective** Dystonia is a movement disorder in which muscles contract uncontrollably. Acute drug-induced dystonia (DID) can be diagnosed through detailed history taking and physical examination. This study aimed to identify the clinical characteristics of DID in children, which could help emergency physicians diagnose these conditions more efficiently.

**Methods** We reviewed medical records of children aged below 18 years diagnosed with drug-related dystonia after discharge from the emergency department over 10 years. We collected the patients' age, sex, suspected causative drugs, initial diagnosis of the prescribing physician, duration of drug-taking, diagnostic evaluations, treatment methods, and prognosis.

**Results** Seventy-nine patients were enrolled. The mean age was 11.3±4.9 years (range, 4.0 months to 18.0 years), and 41 patients (51.9%) were boys. The most common cause of DID was gastrointestinal medications in 45 patients (57.0%), followed by antipsychotics in 23 patients (29.1%). Eleven (24.4%) out of 45 patients with DID due to gastrointestinal medications had the initial diagnosis of upper respiratory infection, and seven (30.4%) out of 23 patients with DID due to antipsychotics had the initial diagnosis of non-psychotic diseases. Younger children received more diagnostic procedures and were more frequently admitted. A benzodiazepine (67.1%) was the most common single drug for treatment.

**Conclusion** Physicians should not only acknowledge DID in order to reduce unnecessary workup and admission, but also know that antiemetics and antipsychotics are common causes of DID. Therefore, physicians should try to avoid multidrug prescriptions in children.

**Keywords** Pharmaceutical preparations; Dystonia; Child

Received: 30 March 2017  
 Revised: 15 July 2017  
 Accepted: 10 August 2017

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How to cite this article:

Park HW, Kwak JR, Lee JS. Clinical characteristics of acute drug-induced dystonia in pediatric patients. Clin Exp Emerg Med 2017;4(3):133-137.

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## Capsule Summary

### What is already known

*Dystonia is characterized by involuntary muscle contractions causing twisting and repetitive movements and abnormal postures of the body. Drug-induced dystonia (DID) may occur within minutes or hours or even days of exposure to an inciting drug.*

### What is new in the current study

*Gastrointestinal medications such as metoclopramide and levosulpiride were the most frequent cause of DID. DID responded well to benzodiazepines or benzotropine and had benign courses. A significant proportion of DID cases were caused by prescription drugs not related to the diagnosis.*

## INTRODUCTION

Dystonia, a neurological movement disorder that may cause patients to visit the emergency department (ED), is characterized by involuntary muscle contractions, which result in twisting and repetitive movements and abnormal postures of the neck, jaw, tongue, or the entire body.<sup>1</sup> Dystonia can be the only sign of a disease or one of several manifestations of a clinical syndrome caused by acquired brain lesions, degenerative disorders, drugs, or a psychogenic problem.<sup>2</sup> Therefore, it may be a challenge for the physician to distinguish various causes of dystonia.

Drug-induced dystonia (DID) may occur within minutes or hours or even days of exposure to an inciting drug.<sup>2</sup> Common causes of DID are antiemetic drugs and antipsychotics.<sup>3</sup> Therapeutic ingestions of cough and cold preparations containing dextromethorphan or codeine with antihistamines, decongestants, expectorants, and antipyretics have also been associated with DID.<sup>4</sup> Although there are some case reports referring to various drugs as causes of DID, data on the causes, clinical features, and management of DID are rare, especially in children. If a clinician can diagnose DID on the first medical examination, unnecessary diagnostic evaluations for neurologic causes such as brain imaging and lumbar puncture may be reduced.

We conducted a retrospective review of medical records of our emergency center over 10 years and aimed to identify the suspected causative drugs and clinical characteristics of pediatric DID.

## METHODS

This study was approved by the institutional review board of Ajou University Hospital, Suwon, Korea (AJIRB-MED-MDB-15-307). The informed consent was waived. We reviewed patients who were diagnosed with dystonia when discharged from the ED between January 2005 and December 2014. Our ED is a tertiary regional emergency center. The annual number of patient visits is about 85,000, including 25,000 pediatric patients. Children aged below 18 years of age with suspected drug-related dystonia drugs were selected for analysis. Data such as age, sex, suspected causative drugs, duration of drug intake, diagnostic evaluations, medications for treatment, and disposition from the ED were recorded. Because we focused on why the causative drugs were prescribed, we also collected the initial diagnoses from other hospitals. These data were collected through medical records and previous hospital referrals. The patients were categorized according to age: young children ( $\leq 6$  years) as the first group, school-age children (7 to 12 years) as the second, and adolescents (13 to 18 years) as the third. The collected data were compared among the three groups, and PASW Statistics ver. 18.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis. Categorical variables were described using counts, frequencies, and percentages. The results between the three groups were compared using the Fisher exact test. Statistical significance was determined as a two-tailed P-value of  $<0.05$ .

**Table 1.** Characteristics of drug-induced dystonia patients

Characteristics	Total n = 79	Group 1 ( $\leq 6$ yr) n = 11	Group 2 (7–12 yr) n = 32	Group 3 (13–18 yr) n = 36	P-value
Sex					
Male	41 (51.9)	6 (54.5)	18 (56.3)	17 (47.2)	0.75
Female	38 (48.1)	5 (45.5)	14 (43.7)	19 (52.8)	
Cause of dystonia					
Gastrointestinal medications	45 (57.0)	5 (45.5)	20 (62.5)	20 (55.6)	0.11
Antipsychotics	23 (29.1)	2 (18.2)	8 (25.0)	13 (36.1)	
Common-cold drugs	8 (10.1)	4 (36.4)	3 (9.4)	1 (2.8)	
Others	2 (2.5)	0	1 (3.1)	1 (2.8)	
Unknown	1 (1.3)	0	0	1 (2.8)	
Onset of dystonia (hr)					
0–24	28 (35.4)	5 (45.5)	15 (46.9)	8 (22.2)	0.03
24–72	33 (41.8)	2 (18.2)	9 (28.1)	22 (61.1)	
72–168	6 (7.6)	2 (18.2)	3 (9.4)	1 (2.8)	
Over 168	12 (15.2)	2 (18.2)	5 (15.6)	5 (13.9)	
Initial diagnosis					
Acute gastroenteritis	37 (46.8)	2 (18.2)	19 (59.4)	16 (44.4)	0.09
Upper respiratory infection	21 (26.6)	7 (63.6)	6 (18.8)	8 (22.2)	
Psychiatric disease	16 (20.3)	2 (18.2)	6 (18.8)	8 (22.2)	
Others	5 (6.3)	0	1 (3.1)	4 (11.1)	

Values are presented as number (%).

## RESULTS

During the study period, 79 patients, who visited our emergency center, were diagnosed with DID, of which 41 patients (51.9%) were boys. The mean age was  $11.3 \pm 4.9$  years (range, 4.0 months to 18.0 years). According to age, DID was more common in the school-age and adolescent groups. The proportions between boys and girls in the three groups were similar (Table 1). The most frequent cause of DID was gastrointestinal (GI) drugs in 45 patients (57.0%), followed by Antipsychotics in 23 patients. While common-cold drugs (36.4%) were the second most common drugs in young children, antipsychotics were the second most common drugs in school-age children and adolescents (Table 1). All patients took the medication in therapeutic dosages according to

prescription. The duration from taking the first medication to the onset of dystonia was different among the three groups. Five patients (45.5%) in young children and 15 patients (46.9%) in school-age children presented with dystonia within 1 day after taking the drugs. In the adolescent group, most patients (61.1%) presented with dystonia between the second and third day. In the young children group, most patients had a significantly shorter duration ( $P=0.03$ ) (Table 1).

A total of 71 patients (89.9%) had DID involving the face and neck, while only 8 patients (10.1%) presented with dystonia of the trunk or extremities (Table 2). While 54.5% of the first group and 40.6% of the second group complained of abnormal postures in more than two regions, only 16.7% of the third group presented with dystonia of more than two regions ( $P=0.18$ ).

We compared the causative drugs prescribed by the primary physicians with their initial diagnoses. The causative drugs of 45 patients were GI drugs. Among them, the initial diagnosis of 32 patients was acute gastroenteritis (71.1%), which was appropriate for the prescribed medicines. However, the initial diagnosis of 11 patients (24.4%) was upper respiratory infection (URI). The causative drugs of 23 patients were antipsychotics. Among them, the initial diagnosis of 16 patients (69.6%) was psychiatric dis-

**Table 2.** Affected body regions

Body region	Number (%)
Neck	30 (38.0)
Face	22 (27.8)
Face and other body parts	19 (24.1)
Trunk or extremities	8 (10.1)
Total	79 (100.0)

**Table 3.** Correlation between drug-induced dystonia and initial diagnosis

Causative drug	Acute gastroenteritis	Psychiatric disease	Upper respiratory infection	Others
Gastrointestinal medications	32 (71.1)	0	11 (24.4)	2 (4.5)
Antipsychotics	5 (21.7)	16 (69.6)	2 (8.7)	0

Values are presented as number (%).

**Table 4.** Diagnostic modality and treatment performed before the final diagnosis of drug-induced dystonia

Diagnosis & treatment	Group 1 ( $\leq 6$ yr) n = 11	Group 2 (7–12 yr) n = 32	Group 3 (13–18 yr) n = 36	P-value
Diagnostic imaging				
Computed tomography	8 (72.7)	2 (6.3)	4 (11.1)	<0.01
Magnetic resonance imaging	0	3 (9.4)	1 (2.8)	
None	3 (27.3)	27 (84.4)	31 (86.1)	
Diagnostic procedure				
LP	1 (9.1)	3 (9.4)	0	<0.01
EEG	3 (27.3)	2 (6.3)	0	
None	5 (45.5)	27 (84.4)	36 (100.0)	
LP & EEG	2 (18.2)	0	0	
Disposition				
Discharge	8 (72.7)	27 (84.4)	35 (97.2)	0.06
Admission	3 (27.3)	5 (15.6)	1 (2.8)	
Drug for treatment				
Benzodiazepine	5 (45.5)	19 (59.4)	29 (80.6)	0.02
Benztropine	6 (54.5)	10 (31.3)	6 (16.7)	
Benzodiazepine & benztropine	0	3 (9.4)	1 (2.8)	

Values are presented as number (%).

LP, lumbar puncture; EEG, electroencephalogram.

eases, and the other 7 patients (30.4%) were acute gastroenteritis or URI. In the case of these 7 patients, the antipsychotic drug perphenazine was prescribed by the primary physician for antiemetic effects (Table 3).

When we compared the diagnostic evaluations and treatments, there were significant differences among the three groups (Table 4). In the first group, 8 patients (72.7%) had computed tomography and 6 patients (54.5%) underwent lumbar puncture and/or electroencephalogram. Brain imaging was not performed in 84.4% of the second group and 86.1% of the third group ( $P < 0.01$ ), and lumbar puncture and electroencephalogram were not performed in 84.4% of the second group and 100% of the third group, respectively ( $P < 0.01$ ). All patients were treated with a benzodiazepine or benztropine, but the choices of treatment differed between age groups ( $P = 0.02$ ). While benztropine was more commonly used for treatment in the young children group than a benzodiazepine (54.5% vs. 45.5%), a benzodiazepine was more commonly used in the school-age children group (59.4% vs. 31.3%) and the adolescent group (80.6% vs. 16.7%) than benztropine. Furthermore, among the 79 patients, 70 were discharged from the ED with improvement of symptoms after treatment, and 9 were admitted to the hospital for further evaluation associated with dystonia or treatment of acute infection which had been diagnosed initially. They were all discharged with symptom improvement after treatment. While 3 patients in the first group (27.3%) were admitted, only 1 patient in the third group (2.8%) was admitted. In the younger children groups, relatively more tests were done and more patients were admitted. Moreover, no one diagnosed with DID revisited the ED within 72 hours after discharge.

## DISCUSSION

Our study involved a larger number of patients in a single center and we collected detailed clinical features such as the onset of symptom and disposition compared with previous studies. We also compared the clinical features of pediatric DID in three age groups and analyzed detailed diagnostic evaluations and treatment medications.

In our study, the number of DID patients increased with age, a finding similar to previous studies. This may be attributed to the increase in the number of dopaminergic receptors along with the increase in age. This finding is also supported by adult studies that showed the increased frequency of DID in early adulthood.<sup>1</sup>

In all three groups of children, GI drugs such as metoclopramide and levosulpiride are considered the most frequent cause of DID. Metoclopramide is a benzamide, which is used in infants

and children for the treatment of gastroesophageal reflux disease and as an antiemetic agent in the management of chemotherapy-induced nausea and vomiting.<sup>4</sup> Therefore, physicians must be cautious of prescribing metoclopramide and should consider other antiemetics such as domperidone, which has less frequent extrapyramidal symptoms.<sup>5</sup>

In this study, dystonia occurred in patients who took drugs in therapeutic dosages. Most of the patients developed dystonia within 72 hours after drug ingestion. As with previous studies, DID can be produced at both normal doses and overdoses. This adverse effect is usually seen within the first 24 to 72 hours of drug exposure.<sup>1,4,6</sup> Acute dystonia after taking several medications may occur within 72 hours due to the imbalance between dopamine receptors and cholinergic receptors. When physicians prescribe a drug that has a risk of triggering DID, they should instruct the patient that DID may occur not immediately but within 72 hours after taking the drug. A follow-up of the patient after 3 days to check for the progression and occurrence of DID may be suggested.

When analyzing the initial diagnosis of a primary physician who prescribed the causative medications, we found interesting results. GI drugs were the most common cause of DID, and 11 (24.4%) of 45 cases were actually prescribed GI drugs for URI. In addition, 7 (30.4%) of 23 cases were prescribed antipsychotics for the impression of acute gastroenteritis or URI. The mismatch of diagnosis and prescribed drugs occurred in children over 10 years of age, who have an increased number of dopamine receptors. In pediatric patients, antiemetic drugs are commonly prescribed for various disease entities. Despite the diagnosis of URI, GI symptoms can be often accompanied with URI symptoms. Also, antiemetic drugs are prescribed for GI discomfort in those who receive antibiotics. However, as we noted in this study, multiple medications should not be routinely prescribed in pediatric patients.

DID may be confused with different conditions such as partial seizure, encephalitis, tetany, tetanus, strychnine poisoning, and electrolyte imbalances.<sup>1,4,7-9</sup> In our study, the younger groups had more thorough evaluation such as computed tomography, magnetic resonance imaging, electroencephalogram, and lumbar puncture than the older groups. In addition, the admission rate of the younger groups was higher. These findings may be associated with the physician's unawareness of DID and fear of misdiagnosis, particularly in younger children. Thus, physicians should have a high index of suspicion and knowledge of DID to avoid unnecessary examinations.

DID responds to intravenous or intramuscular injections of anticholinergic drugs. Depending on the availability of medications,

the following agents may be used: biperiden (2.5 to 5 mg), procyclidine (5 to 10 mg), benztropine (1 to 2 mg), trihexyphenidyl (2.5 to 5 mg), or diphenhydramine (25 to 50 mg). Benzodiazepines may also be helpful but are not as effective as anticholinergics.<sup>10</sup> In our study, most of the cases were treated with a benzodiazepine, and only 5.1% of patients were treated with benztropine. This is different from previous studies that often used benztropine or diphenhydramine to treat DID.<sup>1,4,6,10</sup> This difference can be explained by some reasons. In Korea, the intramuscular or intravenous form of benztropine or diphenhydramine is not available. Doctors can only prescribe the oral tablet forms. Therefore, intramuscular or intravenous benzodiazepines may have been used for an anticipated faster effect of treatment. Another reason may be the limited experience of physicians with benztropine or diphenhydramine. In another Korean report, a benzodiazepine was previously used for dystonic reaction after metoclopramide administration.<sup>11</sup> In this study, all patients treated with a benzodiazepine or benzotropine had relief from dystonia in the ED, suggesting that parenteral benzodiazepines can be used for DID and can be as effective as anticholinergic drugs.

This study has several limitations. First, this is a retrospective study in a single center that depended on the records. Our small sample size could not represent all pediatric DID patients, especially in the aspects of treatment and the epidemiology of commonly prescribed causative drugs. Second, we could not analyze the recurrence of DID after using a benzodiazepine. DID might have recurred after injection of a benzodiazepine because of the drug's short half-life. Although we investigated the patients' revisits, we could not investigate visits at other hospitals. Lastly, with the study's grouping of causative drugs such as GI drugs and antipsychotics, it was difficult to ascertain the detailed cause of DID in some cases because the study was researched retrospectively and relied on medical records. For the same reason, information on the dose of the drug was not described in detail. Hence, prospective multicenter studies are needed to confirm these features of pediatric DID.

In summary, GI medications and antipsychotics were the most common drugs causing DID. In children, DID responded well to benzodiazepines or benzotropine and had benign courses. Proper diagnosis through accurate drug history taking and proper knowledge over DID will take key role diagnosing these conditions.

## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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