Clinical characteristics of acute drug-induced dystonia in pediatric patients

Hyun Woong Park, Jae Ryung Kwak, Ji Sook Lee
Department of Emergency Medicine, Ajou University Hospital, Suwon, Korea

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
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. 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. 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. Common causes of DID are antiemetic drugs and antipsychotics. Therapeutic ingestions of cough and cold preparations containing dextromethorphan or codeine with antihistamines, decongestants, expectorants, and antipyretics have also been associated with DID. 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 (≤ 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 (≤ 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 ± 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 (≤ 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.
Drug-induced dystonia in children

Drug-induced dystonia is a condition characterized by involuntary muscle contractions that can occur as a side effect of certain medications. In the pediatric population, this condition is often associated with the use of antipsychotic drugs. A recent study aimed to investigate the incidence of drug-induced dystonia (DID) in children and to determine if there were any differences in symptom onset and disposition compared with previous studies.

In this study, symptoms of dystonia such as movement disorders were identified in 31 patients who received treatment with several medications over a 72-hour period. The primary focus was on identifying the relationship between symptom onset and the prescribing of medications with a high risk of causing dystonia, particularly with the use of benzodiazepine or benztropine. The majority of patients were referred to the emergency department (ED) due to symptoms of dystonia, with 57.7% of patients admitted after an initial ED visit. Interestingly, the first group of patients, aged 1 to 6 years, had a 27.3% admission rate compared to 8% for the second group aged 6 to 10 years and 2.8% for the third group aged 11 to 16 years.

The results showed that dystonia occurred in patients who took drugs in therapeutic dosages. Most of the patients developed dystonia within 72 hours after taking drugs. 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 the brain. Therefore, physicians must be cautious of prescribing metoclopramide and should consider other antiemetics such as domperidone, which has less frequent extrapyramidal symptoms.

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.1,4,6 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.1,4,7-9 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. 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.10 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.11 In this study, all patients treated with a benzodiazepine or benztropine 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 benztropine because of the drug’s short half-life. Although we investigated the patients’ revisits, we could not visit 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 benztropine 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.

REFERENCES

1. Derinoz O, Caglar AA. Drug-induced movement disorders in children at paediatric emergency department: ‘dystonia’. Emerg Med J 2013;30:130-3.
2. Moosavi SM, Ahmadi M, Monajemi MB. Acute dystonia due to citalopram treatment: a case series. Glob J Health Sci 2014;6:295-9.
3. van Harten PN, Hoek HW, Kahn RS. Acute dystonia induced by drug treatment. BMJ 1999;319:623-6.
4. Yis U, Ozdemir D, Duman M, Unal N. Metoclopramide induced dystonia in children: two case reports. Eur J Emerg Med 2005;12:117-9.
5. Reddymasu SC, Soykan I, McCallum RW. Domperidone: review of pharmacology and clinical applications in gastroenterology. Am J Gastroenterol 2007;102:2036-45.
6. Low LC, Goel KM. Metoclopramide poisoning in children. Arch Dis Child 1980;55:310-2.
7. Kirkham FJ, Haywood P, Kashyape P, et al. Movement disorder emergencies in childhood. Eur J Paediatr Neurol 2011;15:390-404.
8. Dingli K, Morgan R, Leen C. Acute dystonic reaction caused by metoclopramide, versus tetanus. BMJ 2007;334:899-900.
9. Schneider SA, Udani V, Sankhla CS, Bhatia KP. Recurrent acute dystonic reaction and oculogyric crisis despite withdrawal of dopamine receptor blocking drugs. Mov Disord 2009;24:1226-9.
10. Burkhard PR. Acute and subacute drug-induced movement disorders. Parkinsonism Relat Disord 2014;20 Suppl 1:S108-12.
11. Jo YY, Kim YB, Yang MR, Chang YJ. Extrapyramidal side effects after metoclopramide administration in a post-anesthesia care unit: a case report. Korean J Anesthesiol 2012;63:274-6.