Diphenhydramine-Refractory Antipsychotic-Induced Dystonia in an Adolescent Male With Cornelia de Lange Syndrome

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Cornelia de Lange Syndrome is a rare genetic disorder that results in distinctive craniofacial deformities, developmental delay, hirsutism, and other physical abnormalities. Case reports suggest some of these patients exhibit sensitivity and paradoxical reactions to certain psychoactive drugs. This report of a 16-year-old male with Cornelia de Lange is the first to describe dystonia from a first-generation antipsychotic that did not respond to conventional treatment with diphenhydramine. The patient initially presented to the Emergency Department for agitation, which progressively worsened after administration of diphenhydramine, olanzapine, and intramuscular haloperidol. The patient returned to the Emergency Department the following day because of altered mental status and lethargy that progressed to periodic lip-smacking movements and contraction of his upper extremities. His symptoms continued despite administration of diphenhydramine and loading doses of 3 antiepileptic drugs. His abnormal labs included an elevated creatine kinase and a prolonged QTc interval on his electrocardiogram. His symptoms were later deemed a probable drug-induced dystonic reaction to haloperidol once seizures were excluded by an unremarkable electroencephalogram. This case supports previous reports suggesting an association between Cornelia de Lange and paradoxical drug reactions, and it is recommended that clinicians strongly weigh the risks of prescribing first-generation antipsychotics for this patient population. These medications should be carefully titrated, with close patient monitoring to prevent adverse drug effects and other iatrogenic complications because antidotes may be rendered ineffective by this condition.

ABBREVIATIONS CdLS, Cornelia de Lange Syndrome; CK, creatine kinase; ED, emergency department; EEG, electroencephalogram; FGA, first-generation antipsychotic

KEYWORDS adverse drug reaction; antidotes; haloperidol; iatrogenic disease; neurotoxicity syndromes; pharmacology

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Introduction

Cornelia de Lange Syndrome (CdLS) is a rare genetic disorder that is diagnosed in about 1 in 10,000 individuals. Genetic changes in this disorder negatively affect cohesin complex proteins in utero that are responsible for organizing genetic material and guiding physical development. As a result, patients have distinctive facies, including microcephaly, micrognathia, synophrys, and hirsutism. In addition to varying degrees of developmental delay, patients may also experience other complications, such as gastroesophageal reflux, upper extremity malformations, cryptorchidism, hearing loss, and seizures.^{1,2}

Along with the above complications, case reports have suggested that the CdLS may predispose patients to sensitivity to specific drugs, producing paradoxical or toxic effects at normally therapeutic doses. Although no definitive mechanism has been discovered to explain this phenomenon, most reports involve psychotropic drugs, such as benzodiazepines, first-generation anti-

psychotics (FGAs), and local anesthetics. The FGAs in these cases included chlorpromazine, loxapine, and haloperidol. Although such cases typically required routine interventions with little patient harm, at least one patient death has been reported.^{3–8} As a result, some authors in anesthesiology recommend caution regarding the use of depressant drugs in CdLS patients in the operative setting.^{4,5} As discussed in the following case, CdLS may not only predispose patients to exaggerated adverse effects, like drug-induced dystonia, but it could also cause negative or paradoxical effects to drugs that clinicians use to treat such reactions.

This report describes an adolescent CdLS patient who experienced a probable haloperidol-induced dystonic reaction that did not improve after conventional treatment with diphenhydramine. This report suggests pharmacists and other clinicians should carefully review any CdLS patient's allergy and medication history while considering the potential risks of using FGAs in CdLS patients. If used, these medications warrant close monitoring in order to prevent adverse reactions for

Table 1. Patient Home Medication List

Medication	Dosage
Cetirizine 10 mg tablet	10 mg daily by mouth
Dexamethasone 0.1% ophthalmic solution	2 drops twice daily in each ear
Erythromycin ethylsuccinate oral suspension (200 mg/5mL)	180 mg three times daily by mouth
Fluticasone intranasal spray (50 mcg/spray)	1 spray daily in each nostril
Gabapentin oral solution (250 mg/5 mL)	300 mg nightly by mouth
Lubricant eye ointment*	1 app nightly in both eyes
Melatonin 5-mg tablet	5 mg nightly by mouth
Methylphenidate 20-mg tablet (extended-release)	20 mg daily by mouth
Omeprazole 20-mg capsule	20 mg twice daily by mouth
Polyethylene glycol 3350 powder for oral solution†	8.5 g daily by mouth

* LubriFresh PM, Major Pharmaceuticals, Livonia, Michigan.

† Miralax, Bayer Corporation, Whippany, New York.

which treatment may not be effective because of the patient's potential paradoxical reactions.

Case Report

Initial Hospital Encounter. A non-verbal, 16-year-old white male (38 kg, 132 cm) with CdLS presented to the Emergency Department (ED) on day 1 for several episodes of emesis, diarrhea, and violently hitting himself earlier in the day. His past medical history included significant developmental delay, attention deficit hyperactivity disorder, failure to thrive, gastroesophageal reflux disease, Barrett esophagus, hiatal hernia, bilateral hearing loss, and dental caries. His surgical history was notable for orchiectomy in 2012 for a right undescended testis. The patient's home medications are listed in Table 1. In addition to lactose intolerance, the patient's allergy history noted a paradoxical reaction to midazolam and risperidone resulting in severe agitation and screaming, respectively.

After arrival to the ED, he was given diphenhydramine elixir 50 mg by mouth in an attempt to decrease his self-injurious behavior and aggression. Within 20 minutes, he was given a 5-mg oral disintegrating tablet of olanzapine when his aggression worsened. His agitation and behavior continued to escalate, necessitating placement of 4-point restraints and two 5-mg doses of intramuscular haloperidol lactate given roughly 20 minutes apart. A 10 mg/kg oral dose of ibuprofen was also administered in case his agitation was being caused by pain. Within approximately 3 hours he became somnolent enough to warrant removal of his restraints. He was discharged the early morning of day 2 after a restful night sleep.

Second Hospital Encounter. On day 2, approximately 20 hours after the patient's doses of olanzapine and haloperidol, he was noted at home to have altered mental status, lethargy, trouble swallowing, and poor ambulation by his caregiver. He arrived at the ED

roughly 3 hours after the onset of these symptoms. Despite a Glasgow Coma Score of 8, computerized tomography showed no intracranial abnormalities, and abdominal radiographs were unremarkable. Shortly after presentation, the patient had an episode of lip-smacking movements, stiffness of his extremities, headshaking, and tachycardia. Because of concern for a dystonic reaction, he was given 1 mg/kg intravenous diphenhydramine and a 20 mL/kg normal saline bolus without improvement of his symptoms. The failure of diphenhydramine was believed to have ruled out a dystonic reaction, leading to an alternative diagnosis of a seizure disorder. His reaction resolved shortly after a 60 mg/kg loading dose of intravenous levetiracetam. An electrocardiogram revealed a prolonged QTc interval of 502 msec. He was started on an infusion of lactated Ringer with dextrose 5% solution running at 115 mL/hr for an elevated creatine kinase (CK) of 1786 units/L and uric acid of 9.1 mg/dL. Three hours later, he had an identical 2-minute episode that resolved after a 20 mg/kg loading dose of intravenous phenytoin. Many laboratory tests were drawn in the ED, the results of which are presented in Table 2.

After admission to the inpatient pediatric unit on day 3, the patient's home medications were resumed, and a continuous electroencephalogram (EEG) was ordered. Although his lethargy and Glasgow Coma Score slowly improved, his agitation progressively worsened. He continued to have seizurelike episodes that were subsequently treated with loading doses of 60 mg/kg intravenous levetiracetam and 20 mg/kg intravenous valproate sodium. At their peak, these tonic episodes recurred every 5 to 10 minutes, lasting 1 to 2 minutes each. After receiving his valproate dose, an electrocardiogram showed an improved QTc interval of 453 msec and labs showed a phenytoin level of 10.5 mg/L with an increasing CK of 1980 units/L. Evaluation of his continuous EEG by a pediatric neurologist showed no seizure activity during any of these seizurelike episodes, suggesting his

Table 2. Patient Laboratory Values After Second Emergency Department Encounter

Test Performed	Result
Complete blood count with differential	
White blood cells, $10^9/L$	7.3
Neutrophils, $10^9/L$ (%)	5.11 (69.6)
Lymphocytes, $10^9/L$ (%)	1.39 (18.9)
Monocytes, $10^9/L$ (%)	0.71 (9.7)
Eosinophils, $10^9/L$ (%)	0.04 (0.5)
Basophils, $10^9/L$ (%)	0.07 (1)
Red blood cells, $10^{12}/L$	5.69
Hemoglobin, g/dL	16.4
Hematocrit, %	46.8
Platelets, $10^9/mL$	214
Chemistry and electrolytes	
Sodium, mEq/L	139
Potassium, mEq /L	4.2
Chloride, mEq /L	108
Bicarbonate, mEq/L	21
Blood urea nitrogen, mg/dL	19
Creatinine, mg/dL	0.95
Glucose, mg/dL	71
Calcium, mg/dL	9.1
Phosphorous, mg/dL	4.3
Magnesium, mEq/L	1.7
Albumin, g/dL	4.1
Total bilirubin, mg/dL	2.7
Direct bilirubin, mg/dL	0.4
AST, units/L	54
ALT, units/L	30
Alkaline phosphatase, units/L	126
Ionized calcium, mmol/L	1.18
Lipase, units/L	107
Lactate, mmol/L	0.9
Miscellaneous tests	
C-reactive protein, mg/L	11.5
Aspirin serum concentration	Negative
Acetaminophen serum concentration	Negative
Urine toxicology screen	Negative
INR	1.38
PT, sec	17.2

ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; PT, prothrombin time

symptoms were likely dystonia caused by his previous exposure to haloperidol. Later that afternoon he was given diphenhydramine 50 mg intravenously to treat

another possible episode, resulting in increased agitation and little improvement in his dystonia frequency. Through day 3 the patient required multiple doses of

intravenous lorazepam ranging from 1 to 2 mg, with some success in controlling his behavior.

The patient's symptoms improved on days 4 through 6, and he experienced no further seizurelike episodes during that time. His CK improved to 1204 units/L, and intravenous fluids were stopped. During this time, the patient's agitation was controlled using oral disintegrating tablets of olanzapine (2.5- to 7.5-mg doses as needed) and distraction techniques, and he returned to his baseline behavior by the time of discharge on day 6. He was discharged with a diagnosis of toxic encephalopathy from haloperidol and a prescription for olanzapine oral disintegrating tablets with instructions to take 2.5 to 5 mg as needed for agitation. Haloperidol was added to his allergy history, specifying reactions of "severe dystonia" and "possible seizures."

Discussion

This is the first case to describe a CdLS patient who experienced a probable dystonic reaction from haloperidol that was refractory to standard treatment with diphenhydramine. Antipsychotic-induced dystonia is believed to be caused by the antidopaminergic action of these medications in the forebrain, which allows regional cholinergic activity to predominate and cause movement disorders. The symptoms and objective data in this case support the argument that this patient was experiencing such a reaction. First, he was given consecutive doses of haloperidol, a "high-potency" FGA noted for its high risk of extrapyramidal side effects, especially in adolescent males like the case patient.⁹ Olanzapine was considered a less likely offender for this reaction based on his receipt of only one dose, olanzapine's weaker dopaminergic antagonism compared with haloperidol, and haloperidol's roughly quadrupled risk of dystonia compared with second-generation antipsychotics.¹⁰

His presentation with extrapyramidal symptoms (i.e., lip smacking, ataxia), prolonged QTc interval, altered mental status, elevated CK, and upper extremity rigidity parallels the symptoms of the neuroleptic toxidrome. Of note, the patient's erythromycin home medication (Table 1) may have also prolonged his QTc interval in addition to the haloperidol. His onset of dystonia also correlates to the reaction's characteristic time course, with dystonia peaking 24 to 48 hours after drug exposure.¹¹ Finally, the delayed resolution of his symptoms correlates with the slow clearance of intramuscular haloperidol, with an average half-life of approximately 20 hours.¹²

Overall, the above evidence supports the conclusion that the patient had an adverse reaction to haloperidol, and a calculated score of 7 on the Naranjo Adverse Drug Reaction Probability Scale qualifies the reaction as a "probable" case of haloperidol-induced dystonia.¹³ Until seizures were excluded via EEG monitoring, the patient's diagnosis of a seizure disorder was under-

standable given his inability to verbalize his experience, his seizurelike symptoms, and his lack of symptom resolution from diphenhydramine. Such difficulty in distinguishing drug-induced dystonia from seizure disorders has been described in at least one previous case report in a patient without CdLS.¹⁴

Several case reports and investigations support a possible link between CdLS and exaggerated toxic or paradoxical reactions to certain drugs, specifically psychotropic medications. For example, Gaultieri³ performed a survey of 138 CdLS patients, 16 of whom received FGAs, with only 3 patients deriving any benefit from the therapy. In the remaining cohort, the patients experienced intolerable side effects like dystonia, or their behavior had grown much worse. In support of these findings, Sargent⁴ described a 30-year-old CdLS patient who experienced increased agitation after administration of chlorpromazine and haloperidol. Papadimos and Marco⁵ also described this association with FGA adverse effects in a chart review of a 37-year-old male with CdLS that revealed a previous episode of neuroleptic malignant syndrome caused by loxapine. In addition to FGAs, a handful of case reports have described CdLS patients experiencing unpredictable hypotensive and apneic reactions to therapeutic doses of benzodiazepines and local anesthetics, and at least one reported case resulted in a fatal outcome after routine local lidocaine anesthesia.^{4,6-8}

Although drug-induced dystonia is relatively common in patients—especially adolescent males—taking antipsychotics, the association of neuroleptic malignant syndrome, dystonia, and worsening of aggression with FGAs in such a small patient population reveals a discernable risk of unpredictable, paradoxical, and potentially life-threatening drug reactions with CdLS.¹⁰ This is especially concerning because antipsychotics are regularly used to treat aggression and self-injury associated with this syndrome.^{15,16} The pathophysiology behind this potential correlation between CdLS and adverse drug effects has yet to be explained, but the genetic manifestations in this syndrome could have theoretical implications on drug pharmacokinetics and pharmacodynamics. For example, the mutation in the cohesin enzyme seen in CdLS negatively impacts chromosomal organization, which could lead to damaging effects on the expression of a broad range of important genes, including those coding proteins for cellular signaling and drug metabolism.¹² Such theoretical alteration to drug targets and drug pharmacokinetics could result in unpredictable responses to medications.

The intravenous antimuscarinic drugs diphenhydramine and benztropine have been long-recognized, effective antidotes for antipsychotic-induced dystonic reactions.¹⁷ Both medications are efficacious to the extent that symptom relief is considered by some to be diagnostic for antipsychotic-induced dystonia. Although only single doses are usually warranted, some guide-

lines recommend repeating doses of either drug if no relief is achieved after 30 minutes of the initial dose.¹⁸ This notable efficacy was demonstrated in a small Turkish study of 55 pediatric drug-induced dystonia cases, in which 93% were successfully treated with parenteral diphenhydramine, and the remainder successfully received biperiden—a benzotropine analog.¹⁹ Of note, new data have also shown that benzodiazepines can be used to treat drug-induced dystonia. For example, a Korean study of 79 successfully treated pediatric drug-induced dystonia cases noted 67% of the patients received benzodiazepines as their sole pharmacologic treatment.²⁰

The case patient's lack of response to diphenhydramine despite the high success rates of antimuscarinic therapy for drug-induced dystonia, raises the possibility that the adverse and paradoxical reactions noted in CdLS with psychotropic drugs may also affect the response to other medications, like diphenhydramine. The patient's prior reactions to risperidone and midazolam and his sensitivity to haloperidol established that he already has a predisposition to adverse and paradoxical drug reactions. Therefore, it could be theorized that the patient could have an altered response to diphenhydramine. This is supported by the paradoxical increase in his agitation after diphenhydramine administration during both his initial ED visit and on day 2. These occurrences make it conceivable that diphenhydramine not only had paradoxical effects on the patient's behavior, but also on its efficacy as a treatment for dystonia. Of note, this patient never received benzotropine as an alternative treatment for his dystonia. As stated earlier, some guidelines recommend repeating a dose of either drug if there is no effect, yet this was not performed. Hindsight suggests the patient's paradoxical worsening of behavior after diphenhydramine would advocate for trying benzotropine as a first choice for dystonia treatment. However, the patient's prior complex reactions to several medications offer little guarantee that benzotropine would have worked any better. Interestingly, based on the efficacy of benzodiazepines in drug-induced dystonia, the use of intermittent lorazepam may have helped treat this patient's dystonia despite his previous reaction to midazolam, but this remains unconfirmed.

Conclusion

This case report is the first to describe a CdLS patient who experienced a probable haloperidol-induced dystonic reaction that was refractory to conventional diphenhydramine treatment. Other conditions, such as a seizure or structural brain abnormality, were ruled out during his course. His reactions are consistent with previous reports suggesting CdLS patients experience increased sensitivity and paradoxical reactions to psychotropic drugs. This is particularly concerning because CdLS patients, who are regularly treated with

these antipsychotics and have a possible increased risk of reactions like dystonia, may not derive benefit from diphenhydramine treatment. Because of the rarity of CdLS and the complex pharmacologic profile of these patients, pharmacists and other clinicians should carefully consider the possible risks of serious reactions in CdLS when prescribing FGAs. It is recommended to carefully titrate psychotropic medications with close patient monitoring to prevent adverse drug effects in these patients because paradoxical reactions may render reaction antidotes ineffective. Also, using FGAs and routes of administration with a faster rate of elimination should be preferred so that any adverse events may abate more quickly and therefore be easier to manage. Lastly, a careful review of the CdLS patient's medication and allergy history may help predict potential adverse reactions beforehand and identify the best drugs with which to treat them.

ARTICLE INFORMATION

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