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Case Report

Status Dystonicus: A Rare and Underdiagnosed Complication of Dystonia

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ABSTRACT

Dystonia is characterized by sustained muscle contractions which produce repetitive twisting movements or abnormal postures. If it is associated with intense frequent episodes refractory to standard drug therapy and requires urgent hospital management, it is known as status dystonicus (SD). Pediatric SD remains underdiagnosed and is a potentially life-threatening crisis. SD is very painful and uncomfortable to the patient and very much distressing to the care givers. Complications of SD include bulbar weakness compromising the upper airway, pulmonary aspiration, respiratory failure, metabolic derangements such as rhabdomyolysis, myoglobinuria, dehydration, acute renal failure and hyperpyrexia. The efficacy of medical management of SD is only 10% and mortality remains at about 10%. We report on 2 dystonic cerebral palsy children who presented to us with SD: one in respiratory failure who needed immediate intubation and a second case who was under diagnosed at admission, later diagnosed during an intensive care unit stay who partially responded to midazolam infusion and polypharmacotheraphy.

Keywords: Dystonia, status dystonicus (SD), complications, midazolam, rhabdomyolysis

Introduction

Dystonia is characterized by involuntary sustained or intermittent muscle contractions causing repetitive twisting movements, abnormal postures, or both (1,2). Status dystonicus (SD) is a severe episode of dystonia, characterized by the development of increasingly frequent or continuous severe episodes of generalized dystonic spasms refractory to standard drug therapy which necessitate urgent hospital admission (3,4). SD, which is also known as dystonic storm, is infrequently reported in children (5). Pediatric SD remains underdiagnosed, is potentially fatal, needs prolonged intensive care unit (ICU) stays and has a mortality rate of 10% (1,5,6). We report on 2 cerebral palsy (CP) children who presented with SD; one with respiratory failure who needed immediate intubation and a second case who was underdiagnosed at admission, and later diagnosed as SD who partially responded to midazolam infusion and polytherapy.

Case Reports

Case 1

A 4-year and 10-month-old female child born to non-consanguineous parents at term gestation with bilirubin encephalopathy, diagnosed with dystonic quadriplegic CP with Gross Motor Function Classification System (GMFCS) level 5 presented with fever and cough over the prior 6 days and convulsions over the prior 2 hours before admission. The convulsions were tonic posturing of the limbs and opisthotonic posturing lasting for 10 minutes, accompanied by moaning and biting of the lips. On examination, the following vitals were recorded: Temp: 106 °F, PR 128/min,

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RR 20/min, BP 98/44 mmHg and capillary filling time 3 seconds. The patient was pale with dental caries in the right lower molar region. The child's weight was 12.6 kg and head circumference was 45 cm (<3rd percentile). Central nervous system examination revealed hypertonia of all four limbs with brisk tendon reflexes and extension of the neck with excessive irritability. The patient had been on tablet form gabapentin and tablet form tetrabenazine for 1 year for dystonia. The child was given one dose of IV midazolam. A provisional diagnosis of dystonic CP with seizure disorder was made. The patient was started on IV Fluids, Ceftriaxone injection, amikacin injection, tablet form doxycycline and fosphenytoin injection. The investigations are shown in Table I. On the second day, the child was febrile with intermittent dystonia. Tablet form clonazepam was added. On the fourth day, there were no seizures/posturing but the patient had persistent fever. On the 6th day, the child had swelling of the left thigh without evidence of cellulitis. By the 10th day, the patient remained afebrile for 72 hours and was started on Ryle's tube feeding, and was slowly transitioned to oral feeds. On day 14, the patient had one high fever spike with increasing dystonic posturing, irritability with inconsolable crying and acute distension of the urinary bladder. Dystonic storm was suspected and we initiated IV midazolam infusion (1 microgram/kg/hour), increased the dose of fosphenytoin, with tetrabenazine tablet form, gabapentin tablet form and baclofen tablet form added. The bladder was catheterized and one liter of urine was drained. On the 15th day, on midazolam infusion, the patient's dystonic movements improved, and tube feeding was restarted. On the 17th day, spontaneous eye opening was present, on midazolam infusion, no abnormal posturing/dystonia was seen.

Case 2

A 4-year and 4-month-old male child born to non-consanguineous parents at term gestation with perinatal asphyxia and bilirubin encephalopathy, diagnosed as mixed quadriplegic CP with GMFCS level 5 presented with multiple episodic tonic movements of the bilateral upper & lower limbs over the prior 4 days. Each episode lasted 20 to 30 seconds along with arching of neck, associated with excessive crying. There was also the presence of multiple tongue bites. One day prior, he had had a fracture of the left neck femur. There was history of multiple (8 times) clavicular fractures and a right ankle fracture over the prior 2 years. He had received syrup phenobarbitone for the first 2 years of life. Subsequently, he was on tablet form baclofen for 2 years and then switched over to Ayurveda treatment 15 days prior to admission. At admission, he had multiple tongue bites with bleeding, his Glasgow coma scale was 3/15 with poor respiratory efforts, therefore, the child was intubated and put on a ventilator. His vitals were measured as follows: Temperature 103 °F, PR 172/minutes with feeble pulse volume & cold peripheries. Only a systolic BP of 84 was recordable. His capillary blood sugar (CBG) was 65 mg/dL. He received 20 mL/kg of normal saline and 2 mL/kg 10% dextrose. After 20 minutes, his CBG was 120 mg/dL and BP 88/40 mmHg. The child was started on injections of fosphenytoin and ceftriaxone with a paracetamol suppository. His ankle, knee, biceps and triceps reflexes were brisk. His investigations are shown in Table II. He was on ventilator support and had high fever spikes (Temp 105 °F not responding to paracetamol). He developed hypotension again and was started on dopamine infusion at 10 micro/kg/minute. Hypernatremia correction was started with N/2 saline. A Thomas splint was applied for the femur fracture. He had acute kidney injury (AKI) and rhabdomyolysis for which conservative treatment was given. The following day, the child's guardians wanted to take the child home against medical advice.

Discussion

Secondary dystonias are the most common cause of SD and CP accounts for 59.3% of patients (7). Both of our cases were tonic type dystonic CP with a past history of bilirubin encephalopathy. SD usually occurs in known dystonia patients and ***de novo*** presentation is rare (6). Fever, infection, surgery and trauma are the frequent triggering factors (3,5). Fever was the trigger in our first child. Femur fracture and fever were the triggers in the second child. SD is a potentially life-threatening crisis which is associated with excessive exhaustion and severe pain (1). SD remains underdiagnosed in children (5). In the first case, the child was diagnosed as dystonic quadriplegic CP and had been on tablet form gabapentin, and tablet form tetrabenazine for the prior year for dystonia. The patient presented to us with tonic posturing of the limbs and opisthotonic posturing lasting for 10 minutes, which was accompanied by moaning and biting of the lips. The child was treated as status epilepticus with IV midazolam and fosphenytoin. We continued gabapentin and tetrabenazine in tablet form and added clonazepam. The patient had continuous inconsolable crying for hours, possibly due to severe pain which we could not diagnose early. We believe that the patient's condition was SD and not status epilepticus. On the 14th day, high fever spike was present along with increasing dystonic posturing, irritability with inconsolable

Table I. Haematological and biochemical investigations

	Case 1					Case 2
Investigations (normal value)	**Day 1**	**Day 3**	**Day 5**	**Day 9**	**Day 14**	**Day 1**
Hb (11-14 g/dL)	8.8	7.6		7.7		8.0
PCV (34-40%)	29	27		26		30.4
TLC (4,000-11,000 cells/mm^3)	12,230	6,970		14,400		6,200
Platelets (150,000-450,000/mm^3)	1.68	2.38		9.12		3.36
CRP (0-5 mg/L)	0.42			2.8		174
ESR (<10 mm in 1 hour)	100					100
Blood urea (12-42 mg/dL)	70	21	10			141
Serum creatinine (0.2-0.7 mg/dL)	0.83	0.57	0.42			1.65
Uric acid	5.6	1.5	0.7			15.6
Serum sodium (136-145 mEq/L)	159		133			159
Serum potassium (3.5-5 mEq/L)	3.4		4.4			4.0
Blood sugar (70-140 mg/dL)	230	129				240
AST (0-40 U/L)	739		2,618	681	556	273
ALT (0-40 U/L)	188		1,600	1,052	311	75
PT/control, INR (15 seconds/1.01)	13.2/13.3, 1.01					16.8/13.3, 1.33
aPTT/control (30 seconds/1.0)	43.8/31.8, 1.3					40.2/31.8, 1.28
Serum mg (1.5-2.6 mg/dL)	2.1				1.3	2.8
Serum phosphorous (2.5-7.7 mg/dL)	4.4					4.8
Serum calcium (ionized) (8.4-10.2 mg/dL), ionized (1.16-1.32)	8.3 [1.16]				7.5	7.3 [1.06]
CK-NAC (20-200 U/L)	>22,000		>22,000			>22,000
CK-MB (up to 4.9 ng/mL)	193					91.46
Blood lactate (4.5-19.8 mg/dL)	20					20
Troponin-T (0.0127-0.0249 ng/mL)	0.114			0.145		0.311
Vitamin D	3					-
LDH (135-214 U/L)				1132		-

PCV: Packed cell volume, TLC: Total leucocyte counts, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, PT: Prothrombin time, aPTT: Activated partial thromboplastin time, Hb: Hemoglobin, CK: Creatine kinase, NAC: N-acetyl-cystein-activated, MB: Myocardial band

crying and acute distension of the urinary bladder. At this junction, we reviewed our diagnosis. Dystonic storm was suspected and IV midazolam infusion (1 microgram/kg/hour) was started. Additionally, we increased the dose of fosphenytoin, and tetrabenazine, gabapentin and baclofen in tablet form were added. The patient also had increased levels of creatine kinase (CK)-N-acetyl-cystein-activated (more than 22,000 U/L), which may have been due to the severe generalized muscle spasms. The patient responded to our treatment. In the second case, our diagnosis was SD at admission in view of multiple episodic tonic movements of the bilateral upper & lower limbs, arching of the neck, excessive crying, multiple tongue bites and fracture of left neck femur. However, the relatives of the child wanted to take the child home against medical advice.

Complications of SD include bulbar weakness compromising the upper airway, pulmonary aspiration, respiratory failure, metabolic derangements such as rhabdomyolysis, myoglobinuria dehydration, acute renal failure and hyperpyrexia (2-4).

In SD, severe generalized muscle spasms may cause rhabdomyolysis and this may lead to acute renal failure. Significant rhabdomyolysis leads to elevated CK [usually >5 times the normal range (>1,000 IU/L)], myoglobinuria, electrolyte abnormalities, and acid-base disturbances (2).

Table II. Additional investigations

	Case 1	Case 2
CSF analysis	Cell count=3/mm^3 all lymphocytes, protein=16, sugar=95, chloride=136, culture=no growth, Gram-stain negative	
COVID RT-PCR	Negative	
ABG	-	pH=7.31, PO_2=66.6, PCO_2=24, HCO_3=11.9, Base excess=-13
H1N1 RNA PCR, Influenza A Influenza B	Negative	
Abdominal sonography	Normal diffuse edema left thigh, Doppler venous left lower limb normal	
Sonography of the thigh	Normal	
Venous doppler of the lower limbs	No thrombosis	
Other tests	Blood, CSF and stool culture sterile, Widal and Weil Felix negative Dengue NS1 and IgM negative Leptospira IgM ELISA negative Serology for HAV, HbSAg, HCV and HEV negative	Blood and stool culture sterile, Dengue NS1 negative
Femur X-ray		Left femur neck fracture

CSF: Cerebrospinal fluid, COVID: Coronavirus, ABG: Arterial blood gass, RT-PCR: Real time-polymerase chain reaction, HCV: Hepatitis C virus, Ig: Immunoglobulin, ELISA: Enzyme-linked immunosorbent assay

Both our children had CK levels >220,000 IU/L along with significant elevation of cardiac enzymes (Table I). The first case also had AKI and hypernatremia. Most likely, cardiac muscles also undergo spasms which were the cause of elevated cardiac enzymes in both cases. In SD, dystonic spasms of the upper airway and respiratory muscles result in alveolar hypoventilation and hypoxemia thereby necessitating tracheal intubation and ventilation (2,4). In our second case, SD occurred continuously for 4 days in their home which led to hypoventilation which necessitated intubation and ventilation. Hyperpyrexia occurs due to muscle spasm-induced exothermia (2). Both of the current cases had high fever spikes of 105 °F which did not respond to paracetamol. Therefore, in order to monitor these complications, SD patients should be managed in an intensive care setting (3,6).

SD should be differentiated from other disorders such as neuroleptic malignant syndrome and malignant hyperthermia (3) as those drugs used in the treatment of dystonia (tetrabenazine) (used in first child) have been implicated in the cause malignant syndrome (3,4). SD typically occurs in children. Further clues include the phenomenology of the underlying movement disorder, associated neurological symptoms and signs, a history of triggers, and time durations (2,6).

Lumsden et al. (8) proposed a Dystonia Severity Assessment Plan (DSAP) based on clinical and laboratory investigations which guide its treatment. Grade 1: The child sits comfortably with regular periods of uninterrupted sleep. Grade 2: The child is unable to sit, can only tolerate lying and able to sleep at night. Grade 3: Unable to sleep or sit comfortably, no evidence of metabolic decompensation. Grade 4: Early multi-organ failure, metabolic decompensation (e.g., acidosis, hyperkalemia, hypocalcemia, AKI, myoglobinuria, and creatinine kinase >1,000 IU/L); Grade 5: SD & multi-organ failure, requires pediatric ICU (1,8). Both of our cases were Grade 5. In a study by Goswami et al. (5), out of 23 SD children, 8 of them had CP and 50% had identifiable triggers. All of them were in DSAP 4/5 grades and needed polypharmacotherapy with >4 drugs (5).

The strategy of management includes the first 24 hours and the next 2-4 weeks (6). Intravenous midazolam is the first choice due to its muscle relaxation effect (5,6). Midazolam infusion is titrated to achieve a cessation of dystonia followed by tapering on achieving DSAP Grade 3 and a switch to an intermittent dosing schedule (5). If dystonia is not controlled, propofol is the second line drug. Third line drugs are non-depolarizing paralytic agents such as pancuronium and barbiturates (6). The duration of sedation is determined by the frequent evaluation of the child by intermittently reducing the dose of sedation. Our

first case responded to midazolam infusion. Management over the next 2-4 weeks is aimed at symptomatic dystonia control and supportive therapies. Specific dystonia treatment includes anticholinergics, dopamine receptor blockers, tetrabenazine, clonidine, baclofen and assorted drugs. A triad of drugs (the Marsden cocktail) benzhexol, tetrabenazine and pimozide may be useful (6). Our first child was on polypharmacy therapy without much benefit which led us to try Ayurveda treatment. Goswami et al. (5) observed that SD occurred in 43% children while on anti-dystonic drug therapy (5). In fact both our children were on anti-dystonic drug therapy. Deep brain stimulation can be considered early on during the first 24 hours (5,9). However financial issues and the requirement of an experienced neurosurgery team may be challenging (5). The efficacy of medical management of dystonic storm is only 10% and mortality remains at about 10% (6,8).

Conclusion

Most likely, an early identification of SD in the first case would have decreased morbidity and early pediatric consultation could have prevented mortality in the second case. There is no clear-cut demarcation between dystonia and dystonic storm and it is difficult to predict if the patient will progress to SD. Continuous monitoring by the care-givers and clinicians, and good clinical judgment is required in order to identify the life-threatening dystonic storm.

Ethics

Informed Consent: Informed consent was obtained.

Footnotes

Authorship Contributions

Concept: J.K.K., N.H.R., Design: M.V., A.A.S., Data Collection or Processing: J.K.K., N.H.R., Analysis or Interpretation: M.V., N.H.R., A.A.S., Literature Search: J.K.K., N.H.R., Writing: J.K.K., A.A.S.

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