



# Status Dystonicus in Children with Secondary Dystonia: Reporting 3 Cases of Cerebral Palsy, Leigh Disease and Molybdenum Co Factor Deficiency

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## Authors' contributions

This work was carried out in collaboration among all authors. Author KF designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors MMR and SA managed the analyses of the study. Author MMR managed the literature searches. All authors read and approved the final manuscript.

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Case Study

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## ABSTRACT

**Objective:** Patients with primary and secondary dystonic syndromes occasionally develop severe episodes of generalized dystonia and rigidity which is known as status dystonicus (SD) or dystonic storm. This is a frightening hyperkinetic movement disorder and it is an emergency. Marked, rapid exacerbation of dystonia requires prompt intervention and admission in the hospital. It is critical to recognize early and differentiate dystonic storm from other hyperkinetic movement disorder as it may lead to metabolic complications such as rhabdomyolysis, leading to acute renal failure. This paper has been written to describe three cases of SD, all having secondary dystonia with different etiologies to highlight the mode of presentation, diagnosis, treatment and outcome.

**Methodology:** We report 3 cases of severe secondary dystonia culminating in SD necessitating management in hospital setting. All the three cases were admitted in a tertiary care hospital and

evaluated.

**Results:** One patient was treated in intensive care unit. In brief 1<sup>st</sup> case was a 5 year boy with dyskinetic CP who was treated with trihexiphenidyl (THP), baclofen and midazolam infusion. Second case was a 15 month old boy, diagnosed case of mitochondrial encephalopathy (Leigh disease) who was treated with THP, baclofen, haloperidol, clonazepam and infusion midazolam. The third case was a 13 month old boy, diagnosed case of Molybdenum Cofactor deficiency who was treated with THP, tizanidine but they refused to take midazolam.

**Conclusion:** In this case series, three cases with SD with different etiology have been described with clinical features, modalities of treatment and outcome.

*Keywords: Status dystonicus; cerebral palsy; leigh disease; molybdenum co factor deficiency.*

## 1. INTRODUCTION

Dystonia, traditionally classified as a hyperkinetic movement disorder, manifests in a variety of ways. It is characterized by involuntary sustained or intermittent muscle contractions causing repetitive twisting movements, abnormal postures, or both [1]. Status dystonicus (SD), also known as dystonic storm or dystonic crisis, is a life-threatening movement disorder [2]. SD is characterized by the development of increasingly frequent or continuous severe episodes of generalized dystonic spasms (contractions) and requires urgent (hospital) management [3,4]. It is a rare condition with heterogeneous etiology, pathogenesis, presentation, course and outcome [1].

SD was first described by Jankovic and Penn in 1982 in an 8 year old boy with dystonia musculorum deformans, elevated serum creatine kinase and myoglobinuria [5]. Till date around 100 cases have been reported although there may be a significant number of unreported cases [2]. Several drugs and surgical procedures have been proposed in management of this rare but severe condition. There is limited data till date regarding the management of SD. We are presenting 3 cases of SD who have different aetiology and short review of SD.

## 2. METHODOLOGY

All the three cases were admitted in a tertiary care hospital in Bangladesh between January, 2017 to December, 2019. We are reporting these cases as all three cases had identified and diverse etiology, yet presented with SD. After admission, detailed history of the cases were taken from the caregivers. Physical examination was done at admission and in follow ups. Then in each patient some routine investigation like Complete blood count, liver function test, renal function test, Creatinine phosphokinase (CPK)

and urine routine examination were done. Infection screening of each patient has been done as infection is an important cause of exacerbation of dystonia. For that C reactive protein (CRP), erythrocyte sedimentation rate (ESR), blood culture, urine culture and chest X ray had been done. Targeted investigation to find out the cause for SD was done in individual case. In all patients MRI of brain, electroencephalography (EEG) was done. To find out the genetic basis of disorder, clinical exome sequencing and mitochondrial whole genome sequencing were done in the 2<sup>nd</sup> and 3<sup>rd</sup> cases.

Initially each patient was treated with oral drug as per protocol. Then depending upon the response parenteral drugs for SD was given.

## 3. RESULTS

### 3.1 Case 1

A 5 year old boy, diagnosed as a case of cerebral palsy (mixed-dyskinetic and spastic) with global delay presented with fever for 6 days and severe dystonia. Regarding antenatal history mother had a history of prolonged labour, baby was delivered in a clinic by normal vaginal delivery with history of delayed cry. He was treated in Neonatal ICU for about 12 days. He had delayed milestones of development in all domains. On neurological examination he had spasticity and rigidity. Recently he developed fever which was high grade and continuous in nature. Along with the fever there was acute exacerbation of dystonia which was generalized and severe in nature. On examination, he was conscious, irritable, microcephaly was present, and anthropometry revealed severe wasting and stunting. On nervous system examination, higher psychic function: conscious, not oriented to surrounding. Sensory and cerebellar system was intact. Motor system: bulk of the muscle: decreased in all 4 limbs, tone increased, power 2/5, all jerks

exaggerated, planter extensor. Both truncal and limb dystonia was present. SD was diagnosed; level was 3 as per dystonia severity assessment and planning (DSAP) [6].

Investigation profile revealed: MRI of brain: cortical atrophy, cystic encephalomalacia with hyperintensity of periventricular area (Fig. 1A) EEG: normal, CPK: 3360 IU (raised), serum creatinine: 0.64mg/dl, complete blood count (CBC): Hemoglobin: 8 gm/dl, platelet 7 lac/cu mm, ESR: 120, WBC: 16000. Widal test normal, blood culture was normal, X ray chest: normal. Urine routine examination: protein trace. CRP: 51.24 (raised).

As he had features of infection, he was treated with parenteral antibiotics, ceftriaxone for 7 days. SD was treated with trihexyphenidyl initially, but there was no improvement, then baclofen, diazepam, tizanidine were added. Still SD was persisting. Then the child was treated with midazolam infusion (started with 0.1 mg/kg/hour and was increased upto 0.4 mg/kg/hour). With graded dose of midazolam, patient was improved, SD disappeared on 7<sup>th</sup> day of treatment, however dystonia was persisting along with spasticity, still the severe distressing condition was improved.

### 3.2 Case 2

A 15 month old boy, presented with abnormal posturing since one year of age, loss of acquired skills since 7 month of age and fever for 5 days. He was delivered vaginally at term with average birth weight without any complications. He was attaining his milestones of development normally upto 7 months; started to sit at 6 month, had babbling with normal vision and hearing. At 7 months of age, mother noticed the baby lost his ability to sit, he could not even hold his head straight, stopped to communicate socially. At 1 year of age he started to develop some involuntary movement in the form of abnormal posturing of body and limbs which disappeared in sleep. For the last 5 days, he developed fever which was high grade, associated with cough. His family history revealed that, he was the 2<sup>nd</sup> issue of nonconsanguineous parents, his other sib was healthy. On examination, anthropometry normal, febrile, features of pneumonia was evidenced by tachypnea, crepitation on auscultation. Nervous system examination: higher psychic function: not orientated to surrounding, muscle tone: rigidity present, power:

3/5 in all limbs, jerks: normal, planter: extensor, dystonia (both truncal and limbs) present, DSAP level was 3.

Investigation: CBC: neutrophilic leukocytosis, X ray chest: consolidation, serum/calcium: normal, Parathyroid hormone: normal, s/ammonia: normal, urinary/ketone: normal, s/lactate: increased, CSF lactate: increased, serum electrolytes: normal, arterial blood gas (ABG): normal. Magnetic resonance imaging (MRI) of brain showed bilateral, symmetrical abnormal lesions in the basal ganglia and the brain stem, thalamus with necrosis. The lesions were hyperintense in T2W images, magnetic resonance spectrography (MRS) showed: lactate peak present. (Fig.1 B) Mitochondrial whole genome sequencing revealed: Leigh disease (MT ATP6 gene mutation).

The boy was treated with parenteral antibiotic, ceftriaxone for pneumonia for 7 days, SD was treated with trihexyphenidyl, baclofen, haloperidol sequentially. After the improvement of pneumonia, the boy was treated with midazolam infusion (0.1mg/kg/hour as starting dose which was increased upto 0.3mg/kg/hour) for 4 days. There was improvement of SD, however there was intermittent dystonia persisting. For Leigh disease he was treated with mitochondrial megavitamins (cocktail).

### 3.3 Case 3

A 13 month boy presented with excessive posturing and cry for 1 month. He was the 2<sup>nd</sup> issue of nonconsanguineous parents. He was delivered by cesarean section at term with history of delayed cry. He developed seizure since his 2<sup>nd</sup> postnatal day which persisted upto 3 months. Since his 9 month of age he developed abnormal posturing, twisting movement of all 4 limbs which disappeared in sleep. At 1 year, he developed fever with cough for 7 days; since then there was exacerbation of the posturing, the child could not maintain his normal activity and there was excessive cry along with it. He developed opisthotonus posturing. The child had global developmental delay, there was significant delay in motor, speech and cognition. There was no family history of genetic illness. On examination: the boy was irritable, severe dystonia (DSAP level 4) was present, anthropometry: normal. Nervous system examination: the child was conscious,

bulk of muscle: normal, tone: rigidity present, jerks: exaggerated, planter: extensor.

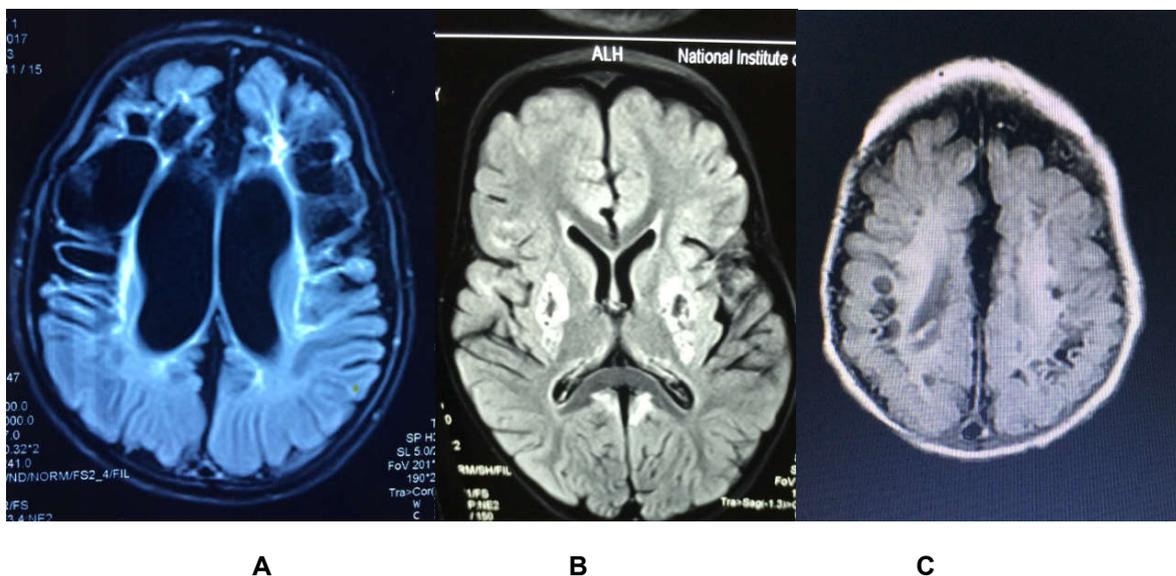
Investigation: CPK: 2010IU (raised), serum creatinine: 0.5mg/dl, serum ammonia and lactate: Normal. EEG: focal epileptic discharge, eye evaluation: normal, cardiac evaluation: normal, MRI of brain: cystic encephalomalacia with periventricular hyperintensity (Fig.1C), genetic study: Molybdenum co factor deficiency (MOCOD), mutation in the sixth chromosome, p21.2 region.

Treatment: He was admitted in pediatric ICU, was treated with phenobarbitone and levetiracetum for epilepsy, trihexyphenidyl and tizanidine for dystonia along with multivitamins. With this treatment, there was minimal improvement of SD. Patient was offered to give midazolam infusion but the parents refused. Baclofen was added and the patient was discharged. The patient was on oral antidystonic and antispasticity drugs after that. There was waxing and waning of dystonia, however he did not have any attack of SD further. The patient expired at 2 year of age with respiratory complications.

#### 4. DISCUSSION

Patients with primary and secondary dystonic syndromes occasionally develop severe episodes of generalized dystonia and rigidity which is known as status dystonicus. It is often refractory to standard drug therapy. SD may be associated with one or more of the following life threatening complications: bulbar weakness compromising upper airway patency with the risk of pulmonary aspiration; progressive impairment of respiratory function leading to the development of respiratory failure, exhaustion and pain; and metabolic derangements. As a consequence of the intense muscle activity, metabolic complications such as rhabdomyolysis, leading to acute renal failure, may ensue [3] Although it is a life threatening disorder but very few number of cases have been reported till date particularly from Bangladesh.

The most important differential diagnoses are neuroleptic malignant syndrome and malignant hyperthermia. Appropriate diagnosis is important because drugs used in the treatment of dystonia, such as tetrabenazine and lithium, as well as levodopa withdrawal, have all been implicated as causing such a malignant syndrome [3,4,7].



**Fig. 1. MRI of brain of the study subjects**

*A: MRI of brain of case 1 showing cortical atrophy, cystic encephalomalacia with hyperintensity of periventricular area B: MRI of brain of case 2 showing bilateral basal ganglia hyperintensity with necrosis . C: MRI of brain of case 3 showing bilateral Cytic encephalomalacia with periventricular leukomalacia*

We are reporting 3 cases with SD. Age range of the patients was 13 month to 5 year at the time of onset, all were male. The underlying etiology were different in these 3 cases: mixed cerebral palsy, Leigh disease and MOCOD. One feature was common in all the children that in each case although there was prior dystonia, SD started with an event of infection. Our finding had similarity with cases reported by Manji H et al who described 2 cases; in one case SD was precipitated by infection in the form of palmer cellulites and in another case exacerbation of severe dystonic spasms was noted with each episode of septicaemia, pneumonia or urinary tract infection [3]. However in other reported cases the cause of exacerbation was introduction of drug like clonazepam, D penicillamine and zinc in wilson disease, abrupt withdrawal of drug like tetrabenazine or reduction of drug dose like lithium [3,4,8,9].

SD usually emerges gradually after weeks or months in the patient with an underlying dystonia diagnosis. However, SD may also present during new onset dystonic disorders without previous or only mild dystonic movements [2,8]. All the three patients we are reporting here had prior form of dystonia. None of the children had recurrence of SD, however there are evidence of recurrent SD in previous publications [2]. The common causes of SD are cerebral palsy, degenerative disorders like Wilson disease, neurodegeneration with brain iron accumulation, mitochondrial disorders, tardive dystonia, post-traumatic dystonia, primary dystonia like DYT1 generalized dystonia, primary generalized DYT1-negative dystonia etc. Among them cerebral palsy is most common [10,11]. Our cases coincide with the literature.

CP is a common cause of SD but MOCOD is rare entity. Very limited cases have been reported till date. Our MOCOD case presented with dystonia at 9 month and SD at 13 month. There is a similar case reported by Carmana KB et al who presented at 10 month of age [12]. However, unlike our case this child had a normal birth history and development until SD developed. MOCOD is a rare autosomal recessive neurometabolic disease. The functions of three enzymes, sulfite oxidase, xanthine dehydrogenase and aldehyde oxidase are altered here. Patients typically present with neonatal seizure, severe neurodevelopmental delay, epileptic encephalopathy, lens dislocation, feeding difficulties and dysmorphism. Movement disorders have been rarely reported as

presenting complaint of MOCOD [13,14,15,16]. Our patient had seizure, which may be explained by delayed cry at birth. Case 2 was diagnosed case of Leigh disease (LD). Dystonia is common in LD but we could not find a case report of SD with LD [17].

The mechanism and neurotransmitter systems involved in dystonic storm remains unknown. The proposed mechanisms are increased pallidal output, spinal-mediated overactivity, dopaminergic blockade leading to hypothalamic storm etc. Various neurotransmitter systems including dopaminergic, serotonergic, GABAergic, glycinergic and glutamatergic systems are likely involved in this disorder [10].

Clinically SD is characterized by increasingly frequent or continuous severe episodes of generalized dystonic spasms (contraction) [3,4]. Phenomenologically it is of two types i) tonic which is manifested by sustained contraction and abnormal posture ii) phasic manifested by rapid and repetitive dystonic contraction [2]. All the 3 cases of this publication was of tonic type.

SD is very painful and uncomfortable. Severe generalized muscle spasms may cause respiratory compromise and severe metabolic disturbances, particularly rhabdomyolysis and acute renal failure. [11]. None of our patients developed renal failure, rhabdomyolysis but one patient developed respiratory complications.

Lumsden et al has reported a simple scoring system of dystonia: DSAP, based upon clinical and investigation features which guided to the treatment based upon the scoring [6]. It is as follows: Grade 1: The child sits comfortably and has regular periods of uninterrupted sleep. Child stable on medication; Grade 2: The child is irritable and cannot settle. Dystonic posturing interferes with sitting activities The child can only tolerate lying despite usual baseline medication; Grade 3: Not able to tolerate lying and/ or unable to get to sleep or sleep disturbed No evidence of metabolic decompensation, with creatinine kinase; Grade 4: Early multi-organ failure: Clinically as above with: Pyrexia (in absence of infection) Evidence of metabolic compromise (e.g. acidosis, elevated potassium, low calcium, evidence of rising creatinine and/or urea) Evidence of myoglobinuria, creatinine kinase >1000 IU/L ;Grade 5: Immediate life-threatening: As above with: Full metabolic decompensation Respiratory, cardiovascular or renal compromise Requires intensive care. Our first and second

cases were in DSAP scale 3 and third one was in DSAP scale 4. Thus the suggested test for SD are empirical tests for rhabdomyolysis and dehydration including renal chemistry, creatine kinase, blood gas analysis, urine and/or blood for myoglobin levels. Further investigations for monitoring are serum calcium, coagulation profile, ECG, infection screening [11].

SD is a life threatening condition which eventually may lead to vital organ failure. Thus achieving sleep without compromising respiration is an important initial measure to combat SD. Drugs used for this are intravenous or enteral clonidine, enteral chloral hydrate, midazolam infusion, anesthetic agents like propofol, barbiturate [6,18]. Patients are preferred to treat in PICU.

Oral polytherapy is suggested with trihexyphenidyl (anticholinergic), tetrabenazine (catecholamine depleter), haloperidol (dopamine receptor blocker), baclofen, benzodiazepine, gabapentin (particularly in Wilson disease), L-dopa.etc [6]. One of our patient was treated in PICU. Rest two were treated in pediatric neurology ward. The drug treatment comprised of oral trihexyphenidyl, baclofen, diazepam, tizanidine, haloperidol etc. In two patient midazolam infusion was given which caused significant improvement of both the cases. Other drugs used in previous studies are benzhexol, pimozide, chlorpromazine, sodium valproate, carbamazepine, risperidone and acetazolamide [3,19]. More intensive step up therapies are administered in refractory SD. These are deep brain stimulation (DBS), Intrathecal baclofen, pallidotomy and thalamotomy [11].None of these have been applied in our cases.

The prognosis of SD is variable and depends upon the etiology, early diagnosis, treatment of precipitating factors and facilities of treatment like ICU and surgery. Mortality is reported at approximately 10%, more in tonic SD and secondary dystonia. Most of the patients revert back to their baseline status and some may improve [2,11].

## 5. CONCLUSION

SD is a severe and life threatening movement disorder. This case series indicates that SD is a difficult to treat condition, early identification and optimum management is important. It often needs ICU admission. Both oral and parenteral drugs are administered. The prognosis is

guarded and depends upon the etiology. However, with time, they revert back to their previous status.

## CONSENT

One patient was treated in Pediatric intensive care unit (PICU) and the rest two were treated in ward. Written informed consent was taken from the guardian of each patient.

## ETHICAL APPROVAL

As per international standard or university standard ethical approval has been collected and preserved by the authors.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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