Original Article

Clinico-Etiological Spectrum and Functional Outcomes of Children with Pre-Status Dystonicus and Status Dystonicus (SD): A Descriptive Study

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Abstract

Background: Status dystonicus (SD) is a life-threatening movement disorder emergency characterized by increasingly frequent and severe episodes of generalized dystonia, requiring urgent hospital admission. The diverse clinico-etiological spectrum, high risk of recurrence, and residual disabilities complicate functional outcomes. **Aim:** We aim to describe the clinico-etiological spectrum, radiology, therapeutic options, and follow-up of patients with pre-status dystonicus (pre-SD) and SD. **Methodology:** A cross-sectional retrospective study was carried out in a tertiary care referral center. The clinical, laboratory, and radiology data of all patients aged less than 18 years with pre-SD and SD from January 2010 to December 2020 were collected. The Dystonia Severity Assessment Plan (DSAP) scale for grading severity and the modified Rankin Scale (mRS) for assessing outcome were used at the last follow-up visit. **Results:** Twenty-eight patients (male:female: 2.1:1) experiencing 33 episodes of acute dystonia exacerbation were identified. The median age at the onset of dystonia and SD presentation was 8.71 (range: 0.25–15.75) and 9.12 (range: 1–16.75) years, respectively. Four patients experienced more than one episode of SD. The etiological spectrum of SD includes metabolic (Wilson's disease—13, L-aromatic amino acid decarboxylase deficiency—one, and Gaucher's disease—one), genetic (neurodegeneration with brain iron accumulation—three and KMT2B and THAP 1 gene-related—one each), structural—three, post-encephalitic sequelae (PES)—four, and immune-mediated (anti-NMDA receptor encephalitis—one). Five patients had pre-SD (DSAP grade 3), and 23 patients had established SD (DSAP grade 4—17 and DSAP grade 5—six). The Rapid escalation of chelation therapy precipitated SD in 11 patients with Wilson's disease. Febrile illness or pneumonia precipitated SD in nine patients. Twenty-three episodes of SD required midazolam infusion in addition to anti-dystonic medications. The median duration of hospital stay was 10 days (range: 3–29). Twenty-three patients had resolution of SD but residual dystonia persisted, while two patients had no residual dystonia at follow-up. Three patients succumbed owing to refractory SD and its complications. **Conclusion:** Early identification of triggers, etiology, and appropriate management are essential to calm the dystonic storm.

Keywords: Dystonic storm, midazolam, status dystonicus, Wilson's disease

Introduction

Status dystonicus (SD) is a life-threatening movement disorder emergency characterized by "increasingly frequent and severe episodes of generalized dystonia, which necessitate urgent hospital admission."[1] Acquired, neurometabolic/degenerative, and genetic etiologies affecting "motor generators/modulators" along the craniospinal axis can result in the dystonic storm either due to the primary pathology itself or precipitated by infection and medication withdrawal.[2] Sustained (tonic) or repetitive/intermittent phasic spasms can lead to exhaustion and pain, which if untreated may progress to life-threatening metabolic derangements and cardiorespiratory compromise. Dystonia Severity Action Plan (DSAP) grades for the severity of SD episodes and acute management protocols are utilized in clinical practice.[3] Neuroimaging and extensive laboratory evaluations are required for metabolic and acquired pathologies. Acute management requires the use of multiple anti-dystonic medications via oral/nasogastric and intravenous, aggressive management of precipitating factors, and intensive care management for life-threatening cardiorespiratory and bulbar compromise. A complete resolution of SD is not achieved in the majority of patients, and they are left with residual dystonia hampering the quality of life. Recurrence is common throughout the etiological spectrum of SD making them prone to readmission and increased morbidity and mortality risks.[4]

Our objective was to describe the clinico-etiological and neuroradiological spectrum, complications during the hospital stay, therapeutic options considered in acute and long-term

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management, and functional outcomes in patients admitted with pre-status dystonicus (pre-SD) and SD.

Subjects and Methods

A retrospective chart review of all patients aged less than 18 years admitted to the Paediatric Neurology Unit, Department of Neurological Sciences from January 2010 to December 2020 with acute dystonia exacerbation at a tertiary care referral center was carried out after approval by the Institutional Review Board (IRB Min No. 14816 dated 31.08.2022).

In accordance with previous studies,[1,4] acute dystonia exacerbation was defined as follows: major worsening of previously existent dystonia; failure of usual medication, requiring dose escalation, and/or medication addition; and hospital admission to a high-dependency unit or intensive care unit. Patients with other movement disorder emergencies, such as neuroleptic malignant syndrome, paroxysmal autonomic instability with dystonia, or malignant hyperthermia, were excluded.

The severity of each episode was retrospectively scored according to the DSAP scoring system.[3]

- DSAP grade 3 (pre-SD) was attributed to episodes of acute dystonia worsening and requiring hospitalization, without evidence of metabolic decompensation.
- DSAP grade 4 was assigned in the presence of fever (not attributed to infection), dehydration, electrolyte disturbances, hyperCKemia (creatine kinase levels >1000 units/liter), or myoglobinuria and evidence of rising creatinine and/or urea.
- DSAP grade 5 was reserved for patients requiring intensive care unit hospitalization for organ support due to respiratory, cardiovascular, or renal compromise.

Patients were classified according to the most severe stage of dystonia during the hospital stay.

We collected data regarding demographic features and underlying dystonic conditions, the phenomenology of other associated movement disorders, known trigger factors, associated metabolic disturbances, follow-up duration, and reoccurrence of SD episodes. All patients with SD were managed as per the proposed algorithm based on literature review and clinical experience outlined in Figure 1.

In addition, acute management of SD episodes and functional status (via a modified Rankin Scale (mRS)) during follow-up were also described. For ascertaining etiology, imaging data and other laboratory parameters were collected.

Statistical analysis

Descriptive statistics were used to describe the aforementioned aspects of the cohort.

Results

Study population and demographics

Twenty-eight patients (male: female ratio—2.1:1) who experienced 33 episodes of acute dystonia exacerbations were identified from hospital records. Four patients experienced more than one episodes of dystonic crisis (Wilson's disease (WD)—two, L- Aromatic amino Acid Decarboxylase deficiency (L-AADC)—one, and Neurodegeration with Brain Iron accumlation (NBIA)—one). Wilson's disease (WD) was the most common cause Pre SD and SD. Combined neurometabolic and genetic etiologies accounted for the majority of cases. The clinico-etiological spectrum of our cohort is represented in Table 1.

The median age at the onset of dystonia and SD was 8.71 years (range: 0.25–15.75) and 9.12 years (range: 1–16.75), respectively. Seventy-five percent of children had a tonic dystonic crisis. Five patients had pre-SD (DSAP grade 3), and 23 patients had established SD (DSAP grade 4—17 and DSAP grade 5—six). None of our pre-SD patients worsened to SD. Seven patients had SD as their initial presentation—three with Japanese Encephalitis Virus (JE) encephalitis, two with WD, and one patient each with extrapontine osmotic demyelination and N- methyl D-Aspartate Receptor (NMDAR) encephalitis. All patients with WD had parkinsonian features. Oromandibular dystonia (WD-8, NBIA, and Thanatos Associated Protein 1 (THAP 1)-related genetic dystonia—one each), choreoathetosis (NBIA-2, Post Encephalitis Sequelae (PES), Lysine Methyl transferase 2B (KMT2B)-related genetic dystonia, and N-methyl-D-aspartate antibody-mediated autoimmune encephalitis (NMDARE)—one each), and lingual dystonia/tremor (WD-3 and PES-2) were other movement disorder phenomenologies observed in the cohort. Ten patients in our cohort had coexisting seizures before or on

Table 1: Clinico-etiological spectrum of pre-SD and SD in our cohort

Category	Number	Total (*n* (%))
Metabolic		
Neurological Wilson's disease	13	15 (53.57%)
L-Aromatic amino acid decarboxylase deficiency (L-AADC)	1	
Neuronopathic Gaucher's disease	1	
Genetic		
Neurodegeneration with brain iron accumulation (NBIA)	3	5 (17.85%)
THAP 1 gene-related generalized dystonia/ DYT 6	1	
KMT2B gene-related generalized dystonia	1	
Infectious (post-encephalitis sequelae)		
Japanese encephalitis	3	4 (14.28%)
Rabies	1	
Structural		
Post-accidental drowning HIE	1	3 (10.71%)
Dyskinetic cerebral palsy	1	
Extrapontine osmotic demyelination syndrome (ODS)	1	
Immune		
N-methyl D-aspartate receptor antibody-associated encephalitis (NMDARE)	1	1 (3.57%)

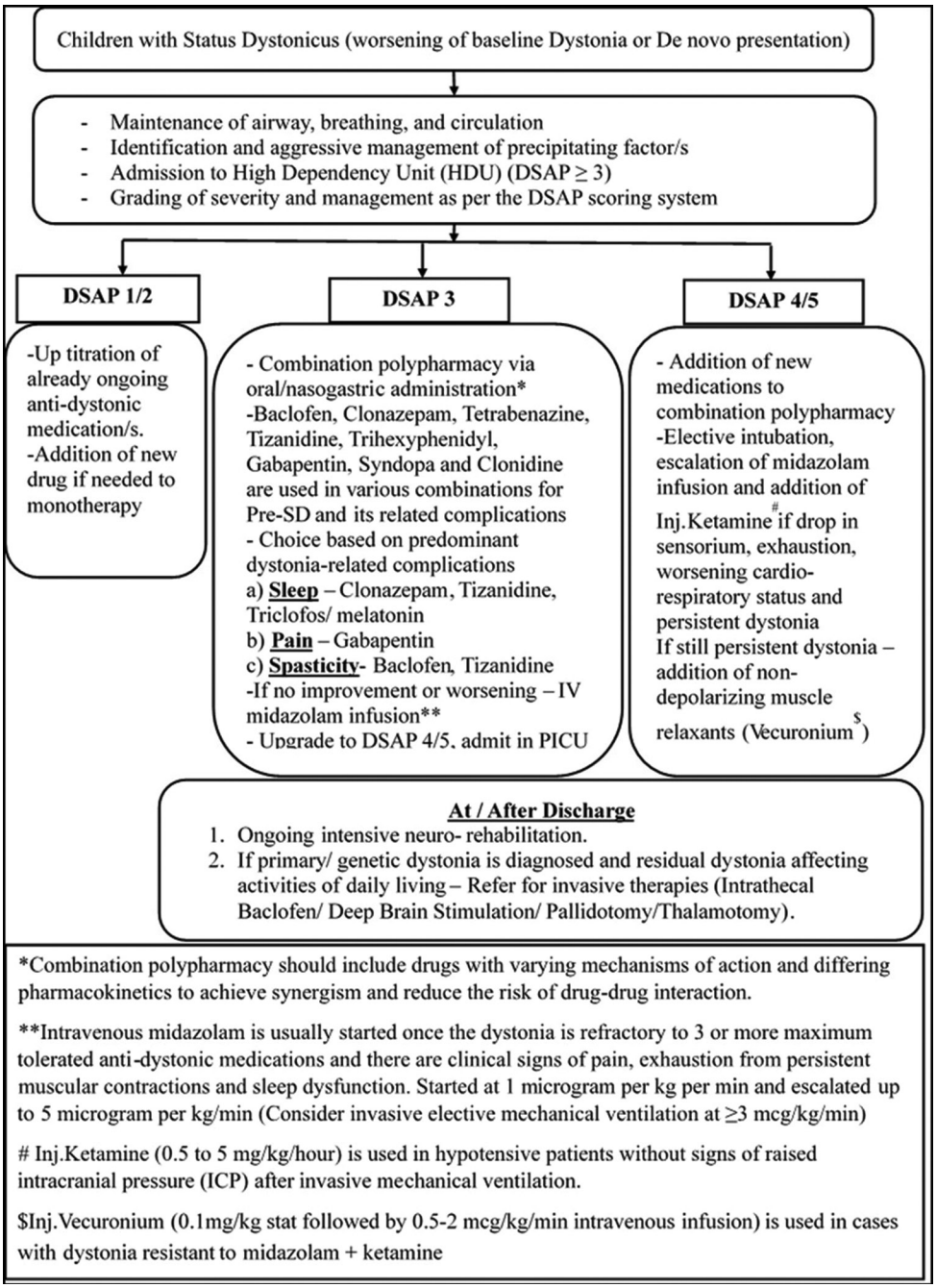

Figure 1: Proposed algorithm for management of pre-SD and SD

admission (WD-4, rabies encephalitis sequelae, post-drowning Hypoxic ischemic encephalopathy (HIE), mixed cerebral palsy (CP), Craniosynostosis syndrome, neuronopathic Gaucher, and PES—one each).

Triggers for dystonic crises

The trigger for dystonia exacerbation was identified in 27 episodes. Rapid escalation of D-penicillamine (Thirteen episodes, n=11) , inadequate dose of chelation (one episode, n=1) and poor drug compliance (one episode, n=1) precipitated SD in WD cohort. Febrile illness and/or associated aspiration pneumonitis precipitated 11 episodes (n=9) of SD. One episode was precipitated by rapid correction of hyponatremia in a postoperative case of craniosynostosis leading to extrapontine demyelination. No Specific triggers were identified in Six (n=5) episodes of SD.

Laboratory evaluation and imaging findings

The median creatine phosphokinase (CPK), aspartate transaminase (AST), and alanine transaminase (ALT) levels were 465U/L (range: 91—1,38,050), 45U/L (range: 24—1930), and 33.5U/L (range: 7—872), respectively. None of the patients had myoglobinuria. All patients with Wilson's disease had features of chronic liver disease on ultrasonography,

but none had overt clinical features of liver dysfunction. Neuroimaging revealed abnormalities predominantly in deep gray nuclei (n = 19) and dorsal brainstem (n = 5). Neuroimaging was not available for one child and was normal in a patient with NMDAR encephalitis. Other sites of neuroaxis involvement and illustrative neuroimaging in a few of our cohort cases are summarized in Table 2 and Figure 2, respectively.

Acute management and complications during a hospital stay

The median duration of hospital stay was 10 days (range: 3 to 29). Twenty-two episodes (n = 23, 82.18%) required intravenous midazolam infusion to control their dystonic crises except for one patient with dyskinetic cerebral palsy (CP) who was managed with intravenous Midazolam and Morphine infusion. A median of 4.5 (Range:2 to 6) anti-dystonia drugs (ADDs) were required for the control of Pre-SD and SD during the hospital stay. Baclofen, trihexyphenidyl, and clonazepam were the most commonly used drugs in our cohort. Data from various anti-dystonic medications used in our cohort are summarized in Figure 3. Five episodes required mechanical ventilation. Dyselectrolytemia (n = 3), shock (n = 2), and hyperpyrexia (n = 1) were other complications observed in our cohort.

Table 2: Spectrum of neuroaxis involvement in neuroimaging (all causes combined)

Sites involved	Number of patients (*n*)*
Basal ganglia (caudate/putamen/globus pallidi/ subthalamic nuclei)	19
Thalamus	8
Posterior fossa	
Brainstem (dorsal pons, substantia nigra (SN), middle cerebellar peduncle)	6
Cerebellum (cerebellar atrophy, rhombencephalitis, dentate nucleus)	3
Corpus callosum	3
Cortex/gray matter	3
Subcortical white matter	3
Periventricular white matter	3
Diffusion restriction	2
Cerebral atrophy	3

*The numbers do not add up as each patient may have multiple sites of neuroaxis involvement in various permutations and combinations

Follow-up

The median duration of follow-up was 11.5 months (range: 0–72). Three patients succumbed, and three were lost to follow-up after admission. Two patients had complete resolution of dystonia at the last follow-up, and twenty patients had residual dystonia at the last follow-up. Three patients (type 2 Gaucher's disease, KMT2B-related primary dystonia, and Wilson's disease with neurological manifestations) succumbed owing to refractory dystonia and probable aspiration pneumonia during follow-up. The modified Rankin score of the cohort (n = 25; three patients lost to follow-up) in the last follow-up is summarized in Figure 4.

Discussion

"Dystonia musculorum deformans," described by Jankovic and Penn[5] in 1982, got renamed "desperate dystonia"/"dystonic storm"[6]/"status dystonicus"[1] in the late 1990s. The majority of literature on this subject is based on anecdotal case reports/series from the Western world.[7-9] Neurometabolic and genetic etiologies predominated in our cohort. More than half of cases had residual dystonia and more than 3/4th cases

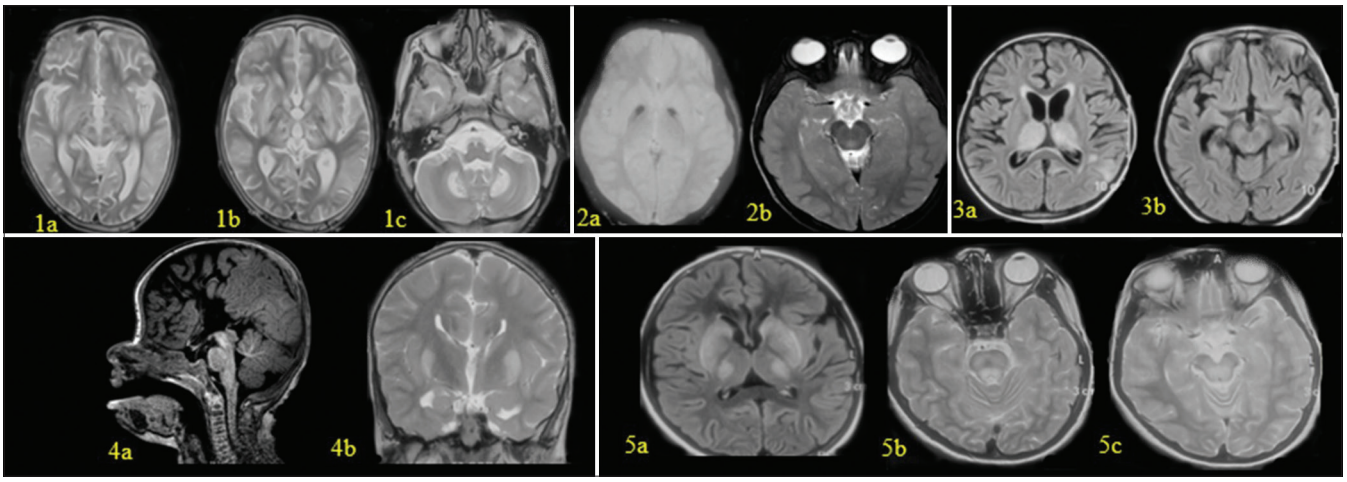

Figure 2: Illustrative neuroimaging features of our pre-SD and SD cohort. 1 (a-c) T2 axial image showing hyperintensities in the bilateral corpus striatum, thalamus, and dentate nuclei in Wilson's disease. 2 (a and b) Bilateral blooming in globus pallidi on gradient recalled echo sequences; T2 hypointensities in substantia nigra (SN) in PANK2-associated NBIA. 3 (a and b) Bilateral thalami and SN hyperintensities on T2 FLAIR axial images in JE virus encephalitis sequelae. 4 (a and b) Extrapontine myelinolysis showing T2 hyperintensities in bilateral putamina after rapid correction of hyponatremia in a child with brachycephaly and corpus callosum agenesis (T1 sagittal). 5 (a-c) Bilateral striatal, ventrolateral thalami, diffuse midbrain, and pontine hyperintensities in post-drowning HIE sequelae

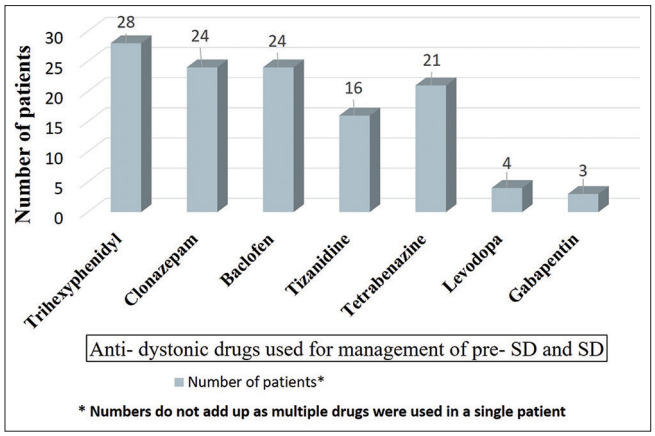

Figure 3: Anti-dystonic drugs used for the management of pre-SD and SD

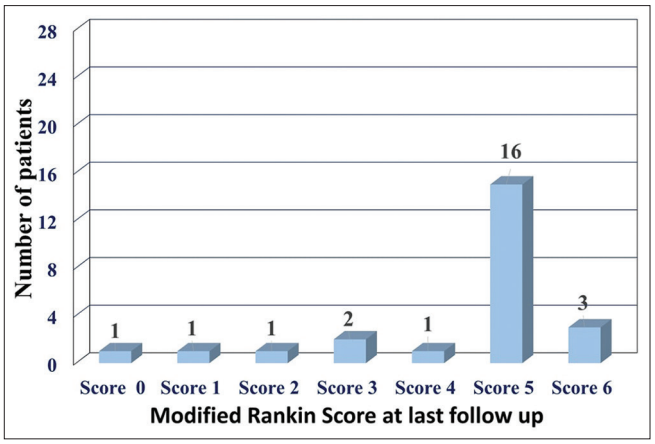

Figure 4: Modified Rankin score at last available follow-up

were completely dependent for all the activities of daily living (ADLs).

Recently published Indian and Italian cohorts had Cerebral plasy contributing to majority of cases in contrast to our cohort wherein neurometabolic and genetic etiologies predominated as etiologies of Pre-SD and SD.[10-12] CP is the most common cause of secondary dystonia and SD in both developed and developing countries.[10-12] Referral bias may explain the paucity of CP cases and predominance of neurometabolic disorders in our cohort. The higher median age at the onset of dystonia and SD with male predominance in our cohort resonates with the epidemiology of Wilson's disease in previously published Indian cohorts.[13,14] Published Indian cohorts observed that decreased mobility, poor nutritional intake and oromotor insufficiency in children with CP probably predisposed them to early age at onset of dystonia and SD.[11,12] Demographic and clinical heterogeneities among published cohorts may be related to referral bias. Tonic SD is frequently described in heredodegenerative cases of SD consistent with 75% of tonic crises in our study.[2,3]

Tremors and Parkinsonism were most frequent movement disorders followed by dystonia in previously published case series of patients with neurological Wilson's disease.[14] Rapid escalation of D-penicillamine, Poor compliance to chelation therapy and disease progression are various factors which may precipitate SD in Wilson's disease.[15,16] The Rapid escalation of D-Penicillamine was the most common trigger for SD precipitation in our Wilson's disease patients. Paradoxical worsening of movement disorders in WD patients with rapid D-Penicillamine escalation has been reported previously by multiple studies.[15-18] Decoppering leads to the efflux of copper from hepatic stores and subsequent deposition of free copper in the basal ganglia, which leads to the generation of free radicals, mitochondrial dysfunction, inflammation, and apoptosis.[19,20] Pallidothalamic dysfunction leading to disinhibition of brainstem tracts and uncontrolled firing of alpha motor neurons results in the precipitation of SD in neurological Wilson's disease.[2,15] Such worsening has also been reported with zinc and trientine, albeit to a lesser extent.[14,15] Slow escalation of chelation therapy and temporary withdrawal may help tide over the crisis.[14,15] Febrile infections with features of aspiration pneumonia precipitated SD in children with the underlying dystonia. Fever and dystonia tend to work together in a positive feedback loop, making it difficult to ascertain the etiology of febrile illness in these patients. Addressing triggers is thus the most important step in the management of SD. However, it is prudent to remember that no trigger may be identified in as many 1/3rd to half of the cases posing diagnostic and therapeutic challenges.[1,10,11]

Fasano *et al*.[10] published 68 patients (89 SD episodes, 59% <15 years) in which first-line medical therapy for established SD was effective in only 10% of cases and mortality was high despite optimal medical and surgical management. As SD is usually a continuum and is difficult to predict progression from DSAP-3 (no metabolic or autonomic disturbances) to be established SD (DSAP-4/5), emergent and optimal protocolized in-patient management may help decrease morbidity and mortality in these cases. Similar in-patient management for DSAP-3 patients was also initiated by Italian and North Indian cohorts.[4,12]

Raised transaminases (AST > ALT) and CPK may be explained by rhabdomyolysis occurring in Pre-SD and SD patients.[21] The absence of urine myoglobinuria may be related to its instability in stored urine samples and deterioration of immunoreactivity with increasing temperatures.[22] A bedside dipstick that detects heme[23] could serve as a surrogate marker of myoglobinuria and could be used as an effective alternative in resource-constraint settings where round-the-clock laboratory processing for urine myoglobin may not be feasible. All WD patients had subclinical evidence of liver parenchymal changes on ultrasound abdomen supporting spillover of copper from hepatocytes before entering the brain and consequent neurological manifestations.[14,15]

Basal ganglia, thalamus, and dorsal brainstem were the most frequently involved structures in neuroimaging in our cohort. Cortical and subcortical white matter, cerebral cortex, corpus callosum, and cerebellum were also involved in neuroimaging in our SD cohort. Disinhibition of "motor

generators/modulators" along the craniospinal axis in a relatively immature pediatric brain has been hypothesized as the main pathophysiological mechanism leading to SD.[24,25] Five (17.85%) children with SD required mechanical ventilation in our study. Between 25 and 40 percent of children required mechanical ventilation/supplemental oxygen in the study by Saini *et al*. and Narayan *et al*.[11,12] Dyselectrolytemia, hyperpyrexia, and shock were observed in a minority of our patients. Protocol-based management helps decrease the rate of complications, long-term morbidity, and mortality.[11] The mortality rate was 10.71% in our cohort, and all of these children had a neurometabolic/genetic etiology of SD. Acquired and heredodegenerative etiologies contributed to around 10 to 20 percent mortality in Western and Indian literature.[3,10] Utility of invasive procedures such as Deep Brain Stimulation (DBS) and intrathecal Baclofen may be limited in children with Pre-SD and SD because of underlying persistent neurodegenration, continuous dystonic spasms and consequent hemodynamic instability. Early identification of these etiologies allows for appropriate genetic counseling and long-term prognosis to families of these children.[26] A child with KMT2B gene-related genetic dystonia persisted to have residual dystonia, and choreoathetosis interfering with ADLs and was referred for deep brain stimulation. Lack of availability, expertise in paediatric DBS and high cost incurred may also beconsidered as limiting factors for genetic generalised dystonia patients amenable to DBS in resource limited settings.

Intravenous sedation forms the mainstay of management for DSAP stage 4/5. Intravenous midazolam formed the cornerstone for achieving sedation along with the optimization of anti-dystonic medications (gabapentin, clonidine, baclofen, and tizanidine) in more than 80% of our SD patients. Rapid onset of action, easy calibration, inherent sedation, and anti-dystonic mechanisms place midazolam infusion as the first choice in the acute management of SD in the literature.[3,10-12]

The median duration of hospital stay was 10 days, which was almost similar to other published Indian cohorts,[11,12] whereas the duration of hospital stay was more than three times in the Italian cohort.[10] Other large cohorts also used morphine, propofol, vecuronium, and barbiturate anesthesia.[3,10,11] Relapse is common in SD patients in those with severe disease at onset reflecting irreversible damage to motor generators. These patients have persistent baseline dystonia after the subsidence of their dystonic crisis. Only four patients experienced a relapse of SD in our cohort, all belonging to the neurometabolic or genetic etiology. Similar high relapse rates were also observed in heredodegenerative and CP cases in Italian and Indian cohorts.[3,10-12] The higher median duration of hospital stay, more frequent relapses, and use of deep sedation in other published cohorts are probably related to more cases with CP and other etiologies leading to the onset of dystonia in early infancy (<2 years). These reflect early disruptions of motor generators/modulators making them prone to brittle dystonia and drug refractoriness, a harbinger of complex severe presentations of SD.[24,27,28]

Persistent baseline dystonia and dependence on ADLs are common sequelae after having a sustained dystonic storm. More than 85% of our children with SD had modified Rankin scores ≥3 making them dependent for ADLs and thus may decrease the quality of life of children and their caregivers.[29] Follow-up of more than five years of our cohort facilitated us to document their long term functional outcomes.

The predominance of neurometabolic/genetic etiologies of SD, sizeable cohort, long follow-up, and inclusion of DSAP-3 SD for inpatient management were strengths of our study. The retrospective nature, attrition of certain data, and possible referral bias were a few limitations that could be addressed via the design of the prospective study.

Conclusion

In conclusion, SD is a complex movement disorder emergency characterized by a high rate of complications and mortality. The Rapid escalation D-penicillamine can worsen neurological symptoms in a subset of children with neurological Wilson's disease and precipitate a Pre-SD and SD. Identification of etiology helps in initiating specific treatment, avoiding triggers, setting realistic targets for improvement from SD, and counseling families regarding long-term prognosis. Early identification of worsening dystonia in DSAP-3 and optimal protocol-based management characterized by addressing triggers, initiation/optimization of ADDs, and/or intravenous sedation form the cornerstone of management of SD.

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Conflicts of interest

There are no conflicts of interest.

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