

Status dystonicus: management and prevention in children at high risk

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Summary. *Background:* Status dystonicus (SD) is a movement disorder emergency associated with significant morbidity and life-threatening events that requires immediate and effective treatment. Nevertheless, SD is currently an under-recognized and undertreated condition, partly due to the lack of a standard definition and because it can be the acute complicated course of both primary and secondary dystonias. In subjects with SD, due to the delay of identification and lacking prevention of trigger and precipitant factors, intensive care management is consistently required. *Objectives:* We performed a critical review of this topic, outlining clinical features and linked genetic disorders to recognize subject at higher risk of SD, describing precipitant and trigger factors and proposing potential pharmacological treatment strategies in order to prevent hospitalization. *Results:* Genetic predisposition included: primary dystonias particularly in the case of TOR1A mutation; epileptic encephalopathy such as ARX and GNAO1 genetic variants and neurodegenerative disorders as PANK2. Early recognition of SD should be oriented by the following sign and symptoms: fever, tachycardia, respiratory change, hypertension, sweating and autonomic instability, elevated serum CK. Pain, fever and dehydration are main trigger factors that have to be prevented or quickly controlled. Achieving sleep could be the first therapeutic option in those with high risk of developing SD. Recently, enteral or transdermal clonidine as safety and efficacy therapeutic alternative was proposed. *Conclusion:* Recognizing high risk children for Status dystonicus from the onset of subtle signs and avoiding trigger factors could drive towards better management avoiding intensive treatments. (www.actabiomedica.it)

Key words: childhood, treatment, dystonia

1. Introduction

Status dystonicus (SD), is currently defined as “increasingly frequent and severe episodes of generalized dystonia, which necessitate urgent hospital admission (1). Many other terms have been used to refer to this condition, such as dystonic storm (2), life-threatening dystonia (3), desperate dystonics, and dystonic state (4).

SD commonly arise from both primary and secondary dystonias and rarely it is a complication of acute symptomatic dystonia related to infections, brain injuries, drowning or drugs (4).

Inside primary and secondary dystonias, many authors reported different genetic disorders at high risk of developing SD, although a systematic review has not been performed yet (4, 5). Underlying pathophysiology is not completely understood even because different precipitant factors could be the reasons of arising SD (6).

Up to now, there are no epidemiological studies on the prevalence of SD. Even if SD could not be referred as an age-dependent disorder, it is shown to be more frequent in childhood, probably due to the major risk of trigger factors and vulnerability of the developmental brain (1).

Furthermore, there is lack of high quality evidenced base medicine guidelines to inform management strategies. Dopaminergic modulation operated by antidyskinetic drugs could be a transient or ineffective therapeutic option (4, 5, 7), moreover usually introduced too late. Different drugs are commonly reached out in the way to allow muscular relaxation, sleep sedation or handle pain due to sustained muscle contraction. Ideally, such treatments should be performed in paediatric intensive care settings (6).

Our work propose the most recent update on SD in children based on a systematic review of the literature until the end of year 2017 and on our personal experience. The search was limited to articles published in english language and it was performed on PubMed database using the following terms: [Status dystonicus; dystonic storm; dystonia; life-threatening dystonia]. Seventy-five articles have been identified and from these we selected reviews and studies reporting SD in childhood. Single case reports were excluded. Our aims are: outlining clinical features and linked genetic disorders to recognize subject at higher risk of SD; describing precipitant and trigger factors that could be easily treated and proposing potential pharmacological strategies in order to prevent hospitalization in Pediatric Intensive Care Unit (PICU). In table 1 we reported strengths and limits of the principal reviews on this topic.

2. Status Dystonicus: clinical features and genetic predisposition

Dystonia is characterized by involuntary sustained or intermittent muscle contractions causing repetitive twisting movements, abnormal postures, or both (7). Dystonia is usually a fluctuating state, where clinical severity grows up over minutes, hours or days and there is paucity of available diagnostic biomarkers. Several conditions may mimic SD (e.g. status epilepticus, neuroleptic malignant syndrome, serotonin syndrome, acute parkinsonism or other dyskinesias): the phenomenology of the underlying movement disorder, associated neurological symptoms and signs, age of the patient and history of triggers are helpful clues to differentiate SD from other hyperkinetic movement disorder (6). Some patients are prone to SD, due to

acquired or genetic underlying condition. The acquired dystonias (e.g. dystonic cerebral palsy) are the most common underlying dystonias leading to SD (8, 9). Another important information comes from genetic background other than acquired individual vulnerability in the pediatric age. In the largest series, describing 68 patients with isolated or recurring SD, 26% of subjects had primary dystonias (82% DYT1-TOR1A genetic mutation) and 35% hereditary degenerative disorders, particularly pantothenate-kinase-associated neurodegeneration (PANK2 genetic mutations) and Wilson diseases (ATP7B genetic mutations), typically after initiation of D-penicillamine (8). An increasing number of reports documented that different epileptic encephalopathies of genetic origin could present SD. A high risk of SD in patients with ARX gene mutation, infantile spasm and expansion of the trinucleotide repeat that codes for the first PolyA tract has been highlighted (10). Missense mutations in GNAO1 were described in patients with epileptic encephalopathy and even in subjects with distinctive and severe movement disorder marked by episodes of severe, refractory ballismus requiring intensive care unit admissions that could lead to necessary deep brain stimulation (11, 12). Another important clue in this group of patient is the high recurrence of SD in almost 20% (8).

3. Precipitating factors

SD appears more commonly in children due to the vulnerability of the homeostatic systems and it could develop often as a triggered event. In that way many factors could potentially act as a trigger and generate a SD. Even if in about one-third of SD appears suddenly and without apparent causing factors, avoiding or treating the potential triggers as soon as possible must be considered as the first therapeutic choice. The main triggers are infections (particularly gastroenteritis with dehydration) and therapeutic adjustments (e.g. dopamine-receptor blockers such as pimozide and haloperidol, metoclopramide and clonazepam) (6, 8). In specific metabolic disorders such as Wilson disease, chelation therapy with penicillamine, zinc sulphate or trientine have also been linked to the development of SD (6). Other potential triggers are: trauma with head

Table 1.

Reviews (year)	Strengths	Limits of the study	Practical utility
Mariotti P. et al. Movement Disorders 2007	First critical review Accurate description of two personal cases with one year of follow-up	No clear information about dosage of drugs No information about trigger factors and warning sign	Not available
Grosso S. et al. European Journal of Paediatric Neurology 2012	Detailed description of personal cases with dosage of drugs and clinical course Flow chart management	Limited number of subjects No clear information about dystonia-targeted therapy No description about how to prevent SD	Therapy in PICU
Fasano A. et al. Movement Disorders 2012	Comprehensive systematic analysis of SD Large case series Information about successful treatment strategies Outcome description	No information about dosage of drugs and timing of pharmacological intervention No specific for pediatric population	Diagnosis
Allen ML. et al. Developmental Medicine & Child Neurology 2014	First description about how to prevent SD in hospitalized child Screening for dystonia severity (grade) and action plan with overview of the management of SD and how to treat complications	No distinction in management depending on underlying etiology	Diagnosis and Therapy
Lopez MR and Fasano A. Movement Disorders 2017	Update on. phenomenology, progression and outcome Underlying etiology and pathophysiology Differential diagnosis	No description about how to prevent SD No information about dosage of drugs and timing of pharmacological intervention	Diagnosis
Lumsden DE et al. Curr Opinion Neurology 2017	Whole update on SD Screening for dystonia severity and action plan	No information about treatment outside PICU and dosage of dystonia-targeted therapy or calibrating sedation	Multilevel intervention and pharmacological management in PICU

injury, surgical procedures, anesthesia, ‘metabolic disorder’ decompensation, pain, gastro-esophageal reflux disease and constipation. Puberty-related deterioration in CP is less commonly reported but this condition as well as discomfort of whatsoever origin should be considered (9). Among all, pain, fever and dehydration are the most frequent trigger factors (4, 8), that could be prevented and quickly controlled. However, in 32,6% of SD an apparent precipitating factor remains unrevealed (8).

4. Therapeutic options outside PICU

Recent phenomenologic categorization divides episodes of SD into either tonic (mainly sustained contractions and abnormal postures) or phasic (rapid and repetitive dystonic contractions) phenotypes (8). In different studies it was underlined the importance to recognize and treat as soon as possible the life-

threatening aspect and the development of one or more of the following signs: bulbar weakness, respiratory failure, metabolic derangements, exhaustion and pain (1, 4). In these well-defined life-threatening events an admission to PICU is otherwise unavoidable.

Frequently the first-line pharmacological treatment is able to achieve a well recovery in only 10% of the patients.

The other patients need sedation (benzodiazepines and propofol were the most used, followed by barbiturate anesthesia), neurosurgery (either DBS or ablations), and more rarely intrathecal baclofen (ITB) (8).

In order to control an episode of SD as safely as possible, treatment should take place either in the intensive care unit or in a high dependency unit (13).

A practical therapeutic multiphasic approach in PICU could be summarized as follows (4, 6):

- Address precipitants (particularly accurate pain control loop)

- Begin supportive care
- Calibrate sedation
- Dystonia specific medications.

In that way intravenous fluid, antibiotics, nutritional requirements (nasogastric or parenteral) and antipyretics should be provided as early as possible but opioid analgesia might be also required (5, 6, 8).

In SD the sustained active muscle contraction leads to exhaustion and rhabdomyolysis: an important initial measure is to help the child to sleep without compromising respiration (13).

In some cases early recognition of SD and its prompt treatment could prevent serious complications and intensive care might be not necessary (14).

Our purpose is to identify early the subjects at high risk in order to prevent SD;

Basically, our strategy act on four items:

- 1) Periodic clinical check-up focused on patients at high risk due to brain damage, genetic or environmental factors. Particular attention should be given to the first three years of age and during pubertal spurt. Clinical evaluation has to consider: developmental abilities, functional skills and night-time sleeping pattern.
- 2) Prevention of precipitant factors through the early recognition of trigger (e.g. fever and dehydration). This aspect must be managed especially by the parents and for this reason specific 'parent training' could be helpful.
- 3) Sustained muscular contraction should be avoided and use of oral benzodiazepine could be helpful. Oral baclofen was reported to improve gait and lower-limb dystonia in children with primary dystonia (15). Pain control could be obtained not only with oral paracetamol or others nonsteroidal anti-inflammatory agents but also promoting correct sleep-wake pattern [e.g. administration of melatonin (16)].
- 4) Early administration of anti-dyskinetic drugs. Different aspects must be taken into account before the administration of anti-dyskinetic drug: mixed motor disorders are frequent (e.g., dystonia associated with spasticity); the course of dystonia might be influenced by ongoing brain maturation and by the remarkable plasticity of young brain; drug tolerability and

effectiveness can be different in children; the therapeutic strategy must be discussed with both patient (according to their cognitive/intellectual ability) and parents (17, 18). Clinical evaluation is the starting point to define the therapeutic strategy, to delineate the topography, type (hyperkinetic/fixed dystonia) and severity of the dystonic manifestations, and degree of functional impairment in daily life (16). Trial with L-dopa should be always tried in children with dystonia of unknown or as-yet undiagnosed etiology due to the clinical variability of the dopa-responsive dystonias. In children with mixed movement disorders trihexiphenidyl is more effective on speech and upper-limbs function than on lower-limbs function. Different studies documented the utility of tetrabenazine for mobile dystonia (but not fixed) and particularly with facial involvement or delayed-onset dystonia (19). D2 dopamine receptor blockers (e.g. Pimozide, aloperidol) could be of some benefits in patients with acute exacerbations and/or painful dystonic spasms (5, 6); and botulinum toxin injection for patients with focal dystonia (20). Intrathecal baclofen pump can be helpful in children with secondary dystonia, especially when associated with spasticity (8).

For children with severe drug-resistant primary generalized dystonia, early pallidal DBS is recommended before the onset of fixed skeletal deformities and major educational or social setbacks (8, 13).

Recently high dose of clonidine in the acute management of severe exacerbations of childhood dystonia or in SD, administered via different routes, has been proposed. This therapeutic option allowed a good response without bearing significant cardio-respiratory depression (21, 22).

Pediatric drug doses and side effects are shown in Table 2.

5. Conclusion

Our review gives an updated information about how to recognize children at high risk of SD and to

Table 2.

<i>Drugs</i>	<i>Initial and Target daily dosage</i>	<i>side effect</i>	<i>Precautions for use</i>
<i>Melatonin</i>	<ul style="list-style-type: none"> If used as chronobiotic administer melatonin 3 or 4 h before actual sleep onset time. Start with a low dose of 0.2-0.5mg fast release melatonin 3 - 4 h before bedtime; increase by 0.2-0.5 mg every week as needed (maximum 3 mg; adolescents: 5 mg) until effect. If no response after 1 week: increase dose by 1 mg every week until effect appears. When 1 mg is effective: try lower dose. Maximum dose: <40 Kg: 3 mg; >40 Kg: 5 mg If used as sleep inductor start with 1-3 mg 30 min before bedtime 	<i>morning drowsiness</i> ; slight transient headache and gastrointestinal symptoms during the first days of the treatment. Rarely reported dizziness, rash, and hypothermia	<ul style="list-style-type: none"> 6 months
<i>L-dopa</i>	<ul style="list-style-type: none"> 1 mg/kg/day of L-dopa (for classical DOPA responsive disorder) mg/kg/day up to 3–5 mg/kg/day, or even 8–10 mg/kg/ proceeding by very small increments and six intakes/day 	Gastrointestinal disorders	<ul style="list-style-type: none"> Could be toxic in mitochondrial disorders
<i>Trihexiphenidyl</i>	<ul style="list-style-type: none"> Start 0.03–0.06 mg/kg/day up to 0.05–0.7 mg/kg/day by increments of 0.03–0.05 mg/kg/week in two to three daily intakes 	Anticholinergic side effects: Drowsiness, Memory impairment, Blurred vision, Dry mouth, Urinary retention, Constipation	<ul style="list-style-type: none"> Efficacious if administered early at onset of movement disorders
<i>Baclofen</i>	<ul style="list-style-type: none"> 0.3 mg/kg/day 0.5 to 1.5 mg/kg/day, by increments of 0.1 mg/kg/week, in two to three intakes 	Drowsiness, Gastrointestinal Disorders.	<ul style="list-style-type: none"> Worsening of axial hypotonia,
<i>Tetrabenazine</i>	<ul style="list-style-type: none"> Start 0.5 mg/kg/day 4–5 mg/kg/day (without exceeding 150–200 mg/day) by increments of 0.5 mg/kg/week, beginning with one intake then two 	Drowsiness, Asthenia, Parkinsonian syndrome, Depression	<ul style="list-style-type: none"> Caution in patients with akinetic-rigid syndrome
<i>Pimozide</i>	<ul style="list-style-type: none"> Start 0.5 to 1 mg/day 2–8 mg/day in two intakes 	Drowsiness, Weight Gain Long QT syndrome	<ul style="list-style-type: none"> Suspected susceptibility to malignant hyperthermia

identify early the subtle clinical signs before the onset of a SD. Moreover, specific therapeutic strategies could prevent the need of intensive therapy.

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