Status dystonicus: a practice guide

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Status dystonicus is a rare, but life-threatening movement disorder emergency. Urgent assessment is required and management is tailored to patient characteristics and complications. The use of dystonia action plans and early recognition of worsening dystonia may potentially facilitate intervention or prevent progression to status dystonicus. However, for established status dystonicus, rapidly deployed temporizing measures and different depths of sedation in an intensive care unit or high dependency unit are the most immediate and effective modalities for abating life-threatening spasms, while dystonia-specific treatment takes effect. If refractory status dystonicus persists despite orally active anti-dystonia drugs and unsuccessful weaning from sedative or anaesthetic agents, early consideration of intrathecal baclofen or deep brain stimulation is required. During status dystonicus, precise documentation of dystonia sites and severity as well as the baseline clinical state, using rating scales and videos is recommended. Further published descriptions of the clinical nature, timing of evolution, resolution, and epidemiology of status dystonicus are essential for a better collective understanding of this poorly understood heterogeneous emergency. In this review, we provide an overview of the clinical presentation and suggest a management approach for status dystonicus.

UNDERSTANDING AND DIAGNOSING STATUS DYSTONICUS

Dystonia: phenomenology and classification

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] A characteristic feature of dystonia is the presence of muscle co-contraction, exacerbation with the intention to move and/or non-specific afferent stimuli, and complete resolution of dystonia by sleep, irrespective of the mechanism of dystonia. This last observation distinguishes dystonia from lower brainstem, spinal, and intramuscular hyper-activation states. Dystonia distorts voluntary movements and often coexists with other movement and motor disorders such as choreoathetosis in dyskinetic cerebral palsy (CP), myoclonus, or parkinsonism. Dystonic postures may give the impression of hypokinesia.[1,2] Topographically, dystonia may affect a single body site (focal dystonia), several body sites, or be classified as generalized (involving both legs and one or more body region such as axial muscles). Until recently,[3] dystonia was usually classified in terms of whether it occurred as part of a primary dystonia disorder, a dystonia-plus syndrome, a paroxysmal dyskinesia (dystonia), a heredodegenerative disorder, or secondary dystonia (acquired secondary to a symptomatic cerebral, brainstem, or spinal cord insult). Secondary dystonia is more common in children,[4] and CP is the most common cause. This review focuses on the most acute life-threatening complication of dystonia, status dystonicus.

Status dystonicus

Status dystonicus, also known as dystonic storm or dystonic crisis, is a life-threatening movement disorder emergency. Although considered rare (only about 100 published cases), status dystonicus is most likely an underreported condition, heterogeneous in its aetiology, pathogenesis, presentation, course, and outcome. Status dystonicus affects all age groups but up to 60% of patients are between ages 5 years and 16 years, although patients may be younger or older, with a male preponderance.[5] Neurometabolic disorders such as glutaric aciduria type 1 may precipitate status dystonicus as early as 7 months of age and the extensor dystonia is often mistaken for status epilepticus.

Phenomenology and diagnosis

Status dystonicus is characterized by the development of increasingly frequent or continuous severe episodes of generalized dystonic spasms (contractions) and requires urgent (hospital) management.[6,7] Recent phenomenological categorization divides episodes of status dystonicus into either tonic (mainly sustained contractions and abnormal postures) or phasic (rapid and repetitive dystonic contractions) phenotypes. The tonic phenotype is more common in males and in

secondary (acquired) dystonias, and has a potentially worse outcome.[5] The movements of status dystonicus may also overlap with additional, sometimes prominent, hyperkinesias such as choreoathetosis, which can make objective recognition complicated.[6,8,9] Currently, there is no internationally agreed definition for status dystonicus. Criteria, including life-threatening complications proposed by Manji et al. are often cited.[6] All patients in that case series developed one or more of the following: (1) bulbar weakness compromising airway patency, (2) progressive impairment of respiratory function leading to respiratory failure, (3) metabolic derangements, and (4) exhaustion and pain.

In practice, status dystonicus often occurs at the end of a continuum of worsening dystonia. Along such a continuum, a recently described simplified dystonia severity action plan may be useful to assess children at risk of status dystonicus and decide on the level of care required for management (see Fig. 1 and the supplementary material of Lumsden et al. for related clinical vignettes employed to validate the scale).[10] In addition, the sites and severity of the dystonia may be documented using dystonia rating scales such as the Dyskinesia Impairment Scale for patients with cerebral palsy[2] or the Burke-Fahn-Marsden rating scale.[11] Video recordings are important for diagnosis and follow-up of treatment response. The baseline neurological state (coexisting spasticity, etc.) should also be recorded.

Aetiology

Status dystonicus usually emerges gradually after weeks or months in the patient with an underlying dystonia diagnosis. However, status dystonicus may also present during new onset dystonic disorders without previous or only mild dystonic movements.[5,10,12,13] Some patients are prone to recurrent episodes. The acquired dystonias are the most common underlying dystonias leading to status dystonicus (38% of cases), CP being the most common individual secondary cause followed by the previously termed 'heredodegenerative dystonias' (particularly neurodegeneration with brain iron accumulation, Wilson disease, and mitochondrial disorders) and the 'pure primary dystonias'.[5] However, any form of dystonia has the potential to escalate into status dystonicus. If the cause of the underlying dystonia is not established, the history and clinical features will guide appropriate metabolic, genetic, neurophysiological, and neuroimaging investigations.

Trigger factors

Status dystonicus is often a triggered event. The main triggers include infection (particularly gastroenteritis with dehydration) and medication adjustment.[7,13,14] Trauma, surgical procedures, anaesthesia, 'metabolic disorder' decompensation,[15] stress,[7] pain, gastro-oesophageal reflux disease, constipation, and puberty-related deterioration in CP are less commonly reported, but these conditions, as well as discomfort of any cause, should be considered.[6] In about one-third of cases no obvious trigger is identified.[5,13,14]

Medications reported to trigger status dystonicus are important, particularly the dopamine-receptor blockers pimozide (exacerbated status dystonicus)[16] and haloperidol as both can be used to treat dystonia and chorea.[17] Metoclopramide[8] can have the same effect. Clonazepam has been reported as a trigger (possibly coincidental) of status dystonicus.[6,18,19] In Wilson disease the introduction of chelation therapy with penicillamine,[20,21] zinc sulphate,[7] or trientine[22] have also been implicated in status dystonicus. Clozapine treatment has been implicated,[19] as well as withdrawal of lithium and tetrabenazine.[6] Deep brain stimulation failure caused by hardware problems,[5,8] intrathecal baclofen pump failure,[12] as well as routine baclofen, and benzodiazepine withdrawal in general should be considered where relevant.

Complications and related investigations

The muscle spasms or dystonic movements during status dystonicus give rise to complications that are at best painful and uncomfortable, and at worst life-threatening.[5] Severe generalized muscle spasms may cause respiratory compromise and severe metabolic disturbances, particularly rhabdomyolysis and acute renal failure. The initial investigations are based on consideration of the complications, need for monitoring, supportive measures, and likely trigger factors.

Respiratory failure can be a function of dystonic bulbar spasms (pharyngeal, laryngeal), truncal-respiratory muscle spasm, diaphragm dystonia, generalized exhaustion, aspiration pneumonia, and indeed the need for highly sedative and relaxant cocktails of drugs used to control status dystonicus. Relevant respiratory investigations for these complications and triggers include chest X-ray, pulse oximetry, and blood gas monitoring, all of which should be part of the initial and ongoing supportive measures.

The biochemical derangements resulting from significant rhabdomyolysis[23] include elevated creatine kinase (usually >5 times normal range, e.g. >1000 IU/L), myoglobinaemia, myoglobinuria, electrolyte abnormalities, and acid-base disturbances. Muscle spasm-induced exothermia commonly leads to hyperpyrexia and dehydration. As well as clinically monitoring perfusion status (e.g. vital signs, capillary refill time, urine output), empirical tests for rhabdomyolysis and dehydration include renal chemistry, creatine kinase, blood gas analysis, urine and/or blood for myoglobin levels. A positive urine dipstick test for blood without red cells on microscopy is suggestive of recent muscle injury (over several hours).[24] The creatine kinase may need to be repeated if negative at presentation because of a potential lag in elevation. Further monitoring and investigations related to the management of rhabdomyolysis and renal failure (hypocalcaemia, hyperkalaemia, acidosis, haematological derangements, coagulopathy, pancreatic dysfunction, arrhythmias, compartment syndrome, and more) should involve appropriate medical, nephrology, and intensive care input.

Status dystonicus patients are vulnerable to secondary complications such as dysphagia, anarthria, thrombosis, gastric bleeding, injuries, fractures, and sepsis.[16,22,25] Some patients require tracheostomy or gastrostomy and some experience side effects or serious complications of treatment.[6,16] A careful search for systemic or intracranial infection is usually warranted (appropriate septic screen).

Differential diagnosis

A variety of other emergency life-threatening movement disorders can have complications similar to status dystonicus (Table I). These include the neuroleptic malignant syndrome, serotonin syndrome, malignant hyperthermia, and intrathecal baclofen (ITB) withdrawal.[6,12,16,17,26–29] Paroxysmal autonomic instability with dystonia is increasingly recognized in children.[12,30,31] Acute dystonic reactions (usually to drugs) arise dramatically and may cause severe dystonic symptoms (e.g. oculogyric crisis, jaw opening, or closing dystonia). Rhabdomyolysis, muscle rigidity, and stiffness from other causes warrant consideration (Table I).[6,19,29]

In severe status dystonicus the typical patient has an established or evolving dystonia disorder and develops worsening severe generalized dystonia, fever, dehydration, or rhabdomyolysis and respiratory complications. Documentation of the precise evolution of the motor and other features of these disorders is crucial as some children have been diagnosed with neuroleptic malignant syndrome when drugs may not have been involved.[30,32] ITB withdrawal can produce clinical features resembling status dystonicus.[12,27–29]

MANAGEMENT
'Pre-status dystonicus'

In some situations patient-specific management plans are used for known patients with brittle dystonia (characterized as difficult to manage or frequently requiring urgent medical attention) depending on the goals of treatment.[33] In the case of patients who are hospitalized with severe subacute worsening dystonia or pre-dystonic crisis, lighter levels of sedation may be used alone or in combination to help achieve sleep, for example enteral chloral hydrate (30–100mg/kg, administered 3–6 hourly). In addition, oral, enteral or intravenous (IV) clonidine[30] has a less sedating, non-respiratory depressant effect and may prove effective in achieving control or preventing breakthrough dystonia. Doses of 1-5µg/kg/dose may be administered three times daily, but may need to be offered every 3 hours (amounting up to 3,000µg per day in some cases with weights exceeding 70kg). Clonidine can be administered by continuous enteral infusion via NG tube or gastrostomy if necessary by calculating the total daily dose and dividing by 24 hours to deliver. Where the enteral route is unsuitable owing to vomiting, diarrhoea, gastrointestinal bleeding or ileus, the equivalent doses may have to be administered as IV hourly infusion (doses of 0.25–2.0µg/kg/hr), with consideration of higher or bolus doses as tolerated (JP Lin, unpublished data). Chlormethiazole[6] (if available) or trimeprazine may also achieve lighter levels of sedation. Roubertie et al. also suggest effective use of intravenous amitriptyline for painful dystonic spasms.[34] The addition or modification of other antidystonia agents according to the patient plan (e.g. trihexyphenidyl, gabapentin, or baclofen) should be considered. Benzodiazepines also may need to be considered. Although these practical suggestions may help prevent progression to status dystonicus and mostly represent lighter levels of sedation, very little has been published regarding these approaches. For status dystonicus, more prompt and aggressive treatment is often indicated.[9,10,22,34]

Established status dystonicus

As status dystonicus is rarely reported, the evidence for treatment is derived from summation of case reports or series and is therefore empiric. Medical stabilization with supportive care is the initial priority. Figure 1 outlines a practical screening and management approach to status dystonicus.

Stabilization and supportive measures

In order to control an episode of status dystonicus as safely as possible, treatment should take place in the intensive care or high dependency unit. Immediate management of the complications is paramount. Depending on clinical indication (respiratory or systemic compromise, need for comfort or sedation), the initial stabilization measures often, but not always, involve intubation and mechanical ventilation.[6] Intravenous fluid resuscitation, antibiotics, nutritional requirements (nasogastric or parenteral) and antipyretics should be provided early. Rhabdomyolysis requires specific therapy (e.g. intravenous fluids, urine alkalinization, dantrolene, neuromuscular paralysis, and/or dialysis in acute renal failure).[22,35] Trigger factors and other complications should be prevented or identified and treated specifically. Other patient comfort and sleep promoting measures include appropriate positioning and minimal handling, and opioid analgesia may be required. A relatively long intensive care unit course should be anticipated for each presentation.

Temporizing treatments

Status dystonicus exerts its life-threatening effects precisely because sustained active muscle contraction leads to exhaustion and rhabdomyolysis. Depending on the clinical state and complications, an important initial measure is to help the child achieve some sleep without compromising respiration. Judicious use of a few doses of chloral hydrate (see Fig. 1) via nasogastric tube when oral medication is impossible to administer may enable sleep. Oral, enteral or intravenous clonidine (as in the case of pre-status dystonicus) should also be used because of its non-respiratory depressant advantages. In addition, rapid escalation of enteral doses of clonidine as high as 3-5µg/kg/hr (administered in 3-hourly bolus doses) have been tolerated successfully in several children with established status dystonicus, the dose being revised every 3 to 6 hours (JP Lin, unpublished data). If the enteral route is unsuitable, an IV clonidine infusion may be necessary to establish dystonia
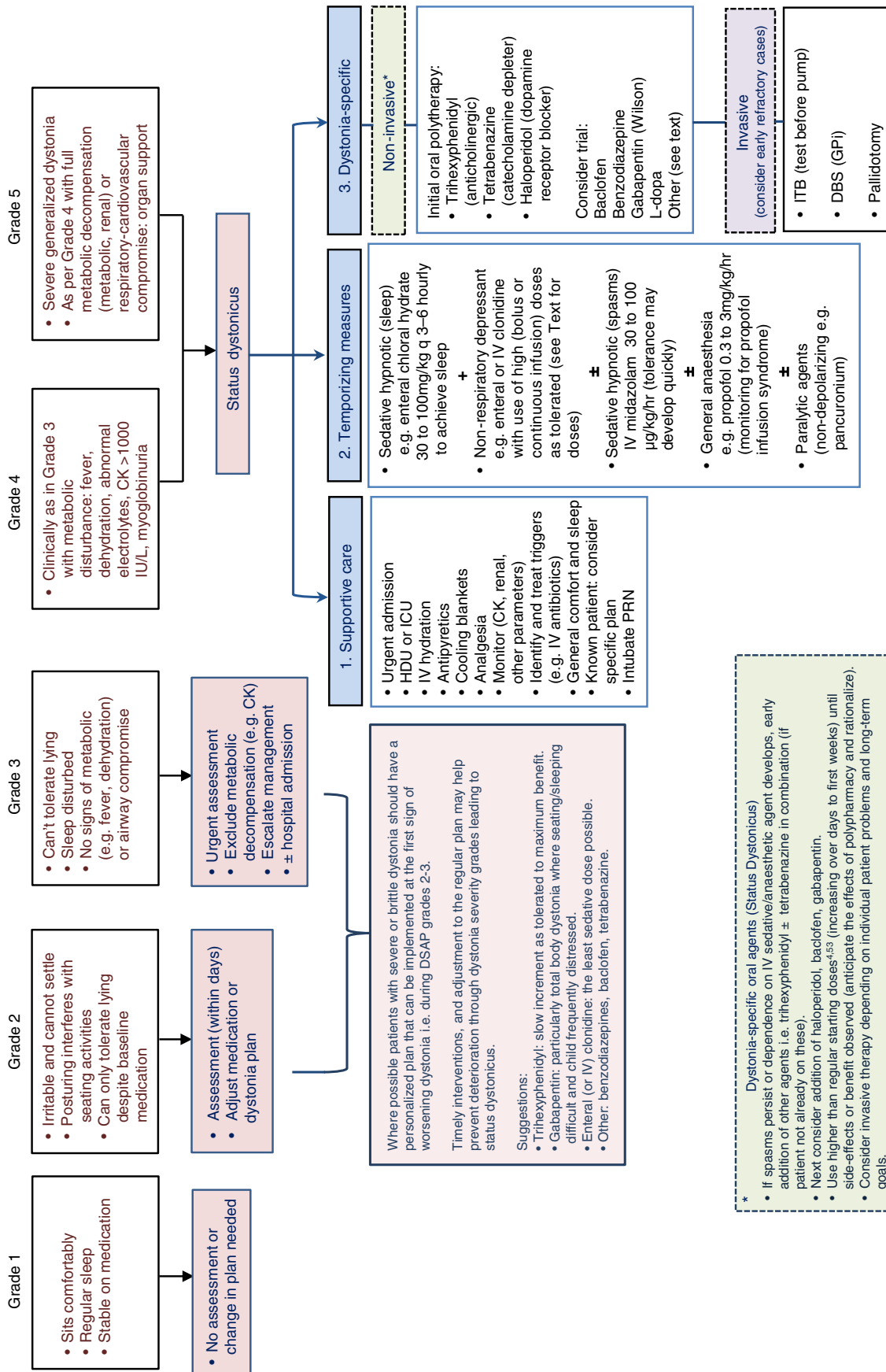
Table I: Differential diagnosis of status dystonicus and core clinical features

Disorder	Motor features	Onset	Trigger/cause	Rhabdomyolysis	Autonomic features	Mental status	Hyperthermia	Other
Status dystonicus	Severe generalized dystonia/other hyperkinesias	Worsening dystonia usually, known patient	Many triggers (must out-rule infection), Underlying dystonia disorder usually (see text)	Significant risk	Unusual (background autonomic symptoms occur in dopamine transporter deficiency)	Usually ok	Common	Respiratory compromise, Treat: see text and Figure 1
Neuroleptic malignant syndrome	Rigidity (trunk/ lower limbs)	Idiosyncratic and variable, usually within weeks of medication introduction or change	Atypical > typical neuroleptics/ dopamine withdrawal, metoclopramide, prochlorperazine. Some drugs used for dystonia (e.g. tetrabenazine, lithium, pimozide)	Significant risk	Prominent (e.g. tachycardia, tachypnoea, labile BP, sweating)	Usually reduced	Common	Respiratory compromise, Treat: stop precipitant, bromocriptine, BZDs, dantrolene, supportive
Serotonin syndrome	Neuromuscular excitability (rigidity, clonus, hyperreflexia, leg myoclonus/ tremor > arms/ trunk)	Within hours, dose related, may resolve quickly when trigger removed. Sometimes longer prodrome (confusion, agitation)	Serotonergic agents (SSRIs, TCAs, MAO-Bi, 'ecstasy' or MDMA, other enhancers), antimigraine medications (e.g. triptans), certain 'cough mixtures', Dose-related	Significant risk	Prominent (e.g. tachycardia, tachypnoea, labile BP, sweating)	Usually reduced, agitation, seizures	Common, a factor in mortality after 'ecstasy' intake	Flushed appearance, respiratory compromise, leucocytosis, transaminitis, Treat: stop precipitant, cyproheptadine, BZDs, supportive
Malignant hyperthermia	Muscle rigidity e.g. masseter, limbs, trunk	Usually intra/ peri-operatively	Genetic predisposition (family history - *RyR1* mutation), depolarizing muscle relaxant, halogenated inhalational anaesthetic	Significant risk	Prominent (tachycardia, tachypnoea, labile BP, sweating)	May be reduced	Very prominent	Respiratory compromise, mixed metabolic -respiratory acidosis, Treat: remove trigger, supportive, dantrolene
Paroxysmal autonomic instability with dystonia (PAID)	Dystonic posturing, extensor posturing, hypertonia	Usually in ICU post brain injury. Manifests in daily cycles over days for diagnosis	Symptomatic brain injury (hypoxia, trauma, infection) Also described rarely in syndromes (e.g. Trisomy 21/ Rett syndrome)	Not usually described	Marked instability (e.g. tachycardia, hypertension, sweating, pupil dilatation)	Usually reduced, agitation	Common	Treat: supportive. May respond to propranolol, clonidine, gabapentin, other adrenergic inhibitors
Intrathecal baclofen (ITB) withdrawal syndrome	Usually severe rebound spasticity, dyskinesia sometimes	Acute (12–24h) or within first few days of ITB interruption	ITB pump failure for any reason	Significant risk	Can be prominent (e.g. tachycardia, tachypnoea, labile BP)	Reduced, delirium, seizures	Common	Pruritis, paraesthesias, multi-organ dysfunction, Treat: supportive, BZDs, other, e.g. dantrolene
Acute dystonic reactions	Acute focal dystonia, e.g. OGC, opisthotonus, oromandibular dystonia, laryngeal	Immediately to hours or days of drug trigger	Neuroleptics and dopamine blockers (metoclopramide), some antidepressants and anticonvulsants	Extremely rare	–	–	–	Can threaten airway, Treat: remove drug, add I.V or I.M anticholinergic or clonazepam in OGC

Other disorders which may cause one or more of muscle rigidity, stiffness, dystonia or rhabdomyolysis:

Medical   Sepsis, meningitis, electrolyte disturbance (hypocalcaemia), thyroid storm. Encephalitis (infective, paraneoplastic or autoimmune particularly NMDAR-Ab mediated). Poisons (e.g. strychnine), drug withdrawal (e.g. opioid), metabolic disorders (myopathies, etc.), tetanus, rabies

Neurological   Tardive dystonia, seizures, stiff person syndrome, hyperekplexia. Parkinson disease (a) Wearing 'off' and 'on' dystonia in late disease (while off L-dopa; severe dystonic spasms of toes (curling or extension) or abdomen/chest or jaw opening dystonia) often eased by L-dopa or S.C apomorphine; (b) hyperpyrexia-dyskinesia syndrome

Psychiatric   Malignant catatonia (from manic state to catatonia with strange posturing, may also resemble NMDAR-Ab mediated encephalitis). Functional disorders

BP, blood pressure; ICU, intensive care unit; OGC, oculogyric crisis; SSRIs, serotonin selective reuptake inhibitors; TCAs, tricyclic antidepressants; MAO-Bi, monoamine oxidase type B inhibitors; BZDs, benzodiazepines; NMDAR-Ab, N-methyl-D-aspartate receptor antibodies; RyR1, ryanodine receptor skeletal muscle mutations (most often); I.V, intravenous; I.M, intramuscular; S.C, subcutaneous.

Grade 1
- Sits comfortably
- Regular sleep
- Stable on medication

→ No assessment or change in plan needed

Grade 2
- Irritable and cannot settle
- Posturing interferes with seating activities
- Can only tolerate lying despite baseline medication

→ Assessment (within days)
- Adjust medication or dystonia plan

Grade 3
- Can't tolerate lying
- Sleep disturbed
- No signs of metabolic (e.g. fever, dehydration) or airway compromise

→ Urgent assessment
- Exclude metabolic decompensation (e.g. CK)
- Escalate management
- ± hospital admission

Grade 4
- Clinically as in Grade 3 with metabolic disturbance: fever, dehydration, abnormal electrolytes, CK >1000 IU/L, myoglobinuria

Grade 5
- Severe generalized dystonia
- As per Grade 4 with full metabolic decompensation (metabolic, renal) or respiratory-cardiovascular compromise: organ support

Status dystonicus

1. Supportive care
- Urgent admission
- HDU or ICU
- IV hydration
- Antipyretics
- Cooling blankets
- Analgesia
- Monitor (CK, renal, other parameters)
- Identify and treat triggers (e.g. IV antibiotics)
- General comfort and sleep
- Known patient: consider specific plan
- Intubate PRN

2. Temporizing measures
- Sedative hypnotic (sleep) e.g. enteral chloral hydrate 30 to 100mg/kg q 3–6 hourly to achieve sleep

+

- Non-respiratory depressant e.g. enteral or IV clonidine with use of high (bolus or continuous infusion) doses as tolerated (see Text for doses)

±

- Sedative hypnotic (spasms) IV midazolam 30 to 100 µg/kg/hr (tolerance may develop quickly)

±

- General anaesthesia e.g. propofol 0.3 to 3mg/kg/hr (monitoring for propofol infusion syndrome)

±

- Paralytic agents (non-depolarizing e.g. pancuronium)

3. Dystonia-specific

Non-invasive*
Initial oral polytherapy:
- Trihexyphenidyl (anticholinergic)
- Tetrabenazine (catecholamine depleter)
- Haloperidol (dopamine receptor blocker)

Consider trial:
Baclofen
Benzodiazepine
Gabapentin (Wilson)
L-dopa
Other (see text)

Invasive (consider early refractory cases)
- ITB (test before pump)
- DBS (GPi)
- Pallidotomy

Where possible patients with severe or brittle dystonia should have a personalized plan that can be implemented at the first sign of worsening dystonia i.e. during DSAP grades 2-3.

Timely interventions, and adjustment to the regular plan may help prevent deterioration through dystonia severity grades leading to status dystonicus.

Suggestions:
- Trihexyphenidyl: slow increment as tolerated to maximum benefit.
- Gabapentin: particularly total body dystonia where seating/sleeping difficult and child frequently distressed.
- Enteral (or IV) clonidine: the least sedative dose possible.
- Other: benzodiazepines, baclofen, tetrabenazine.

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* Dystonia-specific oral agents (Status Dystonicus)
- If spasms persist or dependence on IV sedative/anaesthetic agent develops, early addition of other agents i.e. trihexyphenidyl ± tetrabenazine in combination (if patient not already on these).
- Next consider addition of haloperidol, baclofen, gabapentin.
- Use higher than regular starting doses[4,53] (increasing over days to first weeks) until side-effects or benefit observed (anticipate the effects of polypharmacy and rationalize).
- Consider invasive therapy depending on individual patient problems and long-term goals.

Figure 1: Screening for dystonia severity (grade) and action plan with overview of the management of status dystonicus. DSAP, dystonia severity action plan (for established dystonia patients); GPi, Globus pallidus internus; ITB, intrathecal baclofen; DBS, deep brain stimulation; CK, creatine kinase; ICU, intensive care unit; HDU, high dependency unit; IV, intravenous. Modified with permission from Lumsden et al.[10] and S. Frucht, Movement Disorder Emergencies: Diagnosis and Treatment (2nd edition, NY: Humana Press, 2011).

control (see 'Pre-status dystonicus' for dose considerations). In practice, if additional 'as required' medication is needed to settle a child, the background clonidine dose must be increased to achieve comfort, sleep and metabolic stability.

When more aggressive treatment is indicated, the precise approach depends on individual case severity and degree of complications.[9,10,22,34] Stronger sedation and muscle relaxation or muscle paralysis are the measures most likely to achieve prompt resolution of the dystonic spasms.[5,22] A benzodiazepine, i.e. continuous intravenous midazolam is usually chosen because of its muscle relaxant effect, rapid onset of action, and short half-life, and should be titrated efficiently to control dystonic spasms (see Fig. 1). For refractory spasms, anaesthetic agents (propofol most often) followed by non-depolarizing muscle paralyzing agents (as depolarizing agents, e.g. suxamethonium, are associated with rhabdomyolysis) and barbiturates are then indicated.[22]

The duration of initial intubation and temporizing measures utilized are determined by periodic evaluation of the patient's clinical response while specific antidystonia treatments are being concurrently considered. As ileus may be a serious complication of both status dystonicus and the polypharmacy used in its management, it is essential to keep the combination of drugs to a minimum, using a few drugs at optimal doses, often exceeding usual ranges but titrated against oxygen saturations, heart rate, and blood pressure. Also, it is essential to remember that facilitating regular periods of sleep is a safe and secure mechanism of managing status dystonicus that may need to be maintained for several weeks or possibly months allowing time to explore the underlying problems and management. Some degree of success may be claimed when the child's heart rate dips slightly from baseline wakeful state during true sleep; a feature not obtained if the child is dystonic. Intermittent reductions of the sedative and anaesthetic agents administered should be attempted, as some patients develop dependence on, or tolerance of sedative medications. In others, the status dystonicus abates. Where success is achieved, initial attempts should be made to maintain the beneficial agents by appropriate routes of administration (e.g. oral, nasogastric, or gastrostomy clonidine, midazolam, and/or specific antidystonia drugs).[13]

Dystonia-specific drugs

Although clonidine and midazolam also have specific sometimes effective antidystonia properties, and may control an episode of status dystonicus, other specific oral antidystonia agents are also recommended. The variety of drugs used is broad with success in approximately 10% of cases only,[5] but as they are non-invasive a trial of these agents should be considered in the first instance and before surgery. In our practice, we consider these medications once stabilization measures have been achieved and temporizing treatments described have been initiated and the response observed. The drugs reported to have most success are often used in combination and include an anticholinergic (trihexyphenidyl), a dopamine blocker (haloperidol or pimozide), and a catecholamine depleter (tetrabenazine) (Fig. 1).[5,6,13,14,16,22]

Many other oral drugs have been tried. In Wilson disease several patients with refractory status dystonicus were treated with gabapentin and significantly improved where other antidystonia drugs failed, so it should be used in this condition, and considered in other aetiologies.[21] Other benzodiazepines (clonazepam, flurazepam, diazepam) have been used with[13] and without success.[7,36] Trials of oral baclofen,[25] levodopa, or levodopa-carbidopa have also been suggested, leading to improvement in a few cases.[6,7,37] Primary anticonvulsants including valproate, carbamazepine, primidone, phenytoin,[38] and acetazolamide[6] have been used in various combinations, often with limited benefit. Benztropine, biperidin, lithium, bromocriptine,[6,7] chlorpromazine, olanzapine,[39] clozapine, and risperidone[7] have also been used with mostly limited success. Many of the drugs used to treat dystonia can have significant side effects and some such as pimozide (e.g. cardiac side effects) may exacerbate status dystonicus (see 'Trigger factors').[6,16,22] In such situations the drug should be discontinued.

As the response overall to orally active antidystonia drugs is reported to be poor, with significant risk to patients who develop dependence on sedative or anaesthetic agents and remain in refractory status dystonicus, more invasive step-up surgical therapies including ITB, deep brain stimulation (DBS), or pallidotomy, need to be considered early, once acute or active systemic infections have been clearly excluded or treated.

Invasive therapies

Intrathecal baclofen. Intrathecal baclofen has been tried in a small number (~10%) of patients with refractory status dystonicus with various reports of benefit[12–14,40,41] and failure.[5,6,22,36,38,39,42] Some of these failures have been the result of complications[36] or tolerance,[38] which may potentially limit the use of ITB over long periods. ITB is not without other risks such as over-dosage, withdrawal syndrome, and commonly catheter migration or breakage, although it is considered less invasive than brain surgery.

Deep brain stimulation. Deep brain stimulation has been an effective treatment for status dystonicus in the majority of treated patients (approximately 25).[5,7–9,14,17,19,22,42–50] The globus pallidus interna (bilaterally) is the current anatomical site of choice for this surgical procedure. The effects of DBS were obvious and occurred usually within days or weeks; only occasionally did the effect take months. Although the evidence for DBS in status dystonicus is generated from case reports or series, DBS allowed many patients to become weaned from sedative and anaesthetic agents[8] and in some improvement to baseline or beyond the level of their pre-morbid states.[49] Further plausible evidence for DBS is suggested by device interruption (stimulation or battery), which provoked the appearance of

dystonic spasms, with resolution after switching stimulators back on or by device adjustments.[9,42,45]

Given the observed benefit of DBS, some authors feel that a rapid and aggressive approach is justified to avoid the longer-term complications of status dystonicus and serious morbidity or mortality.[8] However, DBS is not without side effects. Operating on patients with status dystonicus is particularly challenging because of a higher rate of hardware (15%) and other serious complications in already compromised patients.[9] Further challenges exist with urgent DBS surgery in children compared with adults, as a result of anatomical and developmental factors (although it has been used in a child as young as 5 years with status dystonicus).[49] Where the globus pallidus interna was not an option (because of damage), the subthalamic nucleus may be targeted, as recently seen in a 4-year-old with severe methylmalonic acidaemia and refractory dystonia.[51] Thus, evaluation for DBS must be considered on an individual basis.

Pallidotomy and thalamotomy. DBS has largely replaced pallidotomy, thalamotomy, and pallidothalamotomy for the treatment of dystonia. These 'lesional' procedures have been used in approximately 10 cases of status dystonicus with a variety of underlying dystonia disorders with variable outcomes. If DBS is not available, unilateral pallidotomy could be considered.[5–7,14,36,37,42,52]

CONCLUSION

Status dystonicus is a rare but life-threatening movement disorder emergency usually occurring in the context of various established dystonia disorders. Management should be tailored to individual patient characteristics and complications.[5,49] The use of dystonia severity action plans aids the early recognition of worsening dystonia, and communication between health professionals, and may potentially facilitate intervention. For established status dystonicus, sedation in a high dependency or intensive care unit is the most immediate and effective intervention while exploring the specific or individual problems and management issues. The outcome of status dystonicus is variable and for the most part unpredictable. Mortality is reported at approximately 10%, recently suggested to be more common in males with a tonic phenotype and the heredodegenerative and secondary dystonias in which relapses are also more common.[5] Some patients experience progressively worsening dystonia after status dystonicus, but this is not always so. Thankfully the majority of surviving cases gain either partial or complete recovery when compared with baseline neurological status and some improve beyond that.[5] Further reports of the clinical nature and epidemiology of status dystonicus are essential for a better collective understanding of this poorly understood heterogeneous emergency.

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