

STATUS DYSTONICUS

Study of five cases

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ABSTRACT - Status Dystonicus (SD) is characterized by generalized muscle contractions in dystonic patients. We report 5 cases of SD, two of which in patients with dystonic cerebral palsy, one in a patient with primary segmental dystonia, one in a patient with Hallervorden-Spatz syndrome and one in a patient with Wilson's disease (WD). Three patients were admitted to an intensive care unit and treated with propofol and midazolam, and two were submitted to neurosurgical procedures (bilateral pallidotomy and bilateral pallidal deep brain stimulation). Triggering factors were identified in three patients as follows: infection, stress-induced and zinc therapy for WD. On follow-up, two patients presented with significant improvement of dystonia, whereas the other three cases the clinical picture ultimately returned to baseline pre-SD condition.

KEY WORDS: "status dystonicus", dystonic storm, dystonia.

"Status dystonicus": estudo de cinco casos

RESUMO - O "Status Dystonicus" (SD) é uma situação clínica caracterizada por contração muscular generalizada em pacientes com distonias. Relatamos cinco casos de SD, que ocorreram em dois pacientes com distonia associada à paralisia cerebral, um paciente com distonia segmentar primária, um com síndrome de Hallervorden-Spatz e um com doença de Wilson (DW). Três pacientes foram submetidos a tratamento em terapia intensiva com uso de propofol e midazolam e dois pacientes foram submetidos ao tratamento neurocirúrgico (um paciente com palidotomia bilateral e outro com estimulador cerebral profundo palidal bilateral). Em três casos foram identificados fatores desencadeantes: infecção, estresse acentuado e o uso de zinco no tratamento da DW. Em dois pacientes ocorreu melhora importante do quadro distônico, e outros três retornaram à situação clínica pré-SD.

PALAVRAS-CHAVE: "status dystonicus", tempestade distônica, distonia.

Dystonia is a movement disorder characterized by sustained muscle contractions producing torsional and repetitive movements or abnormal postures¹⁻³. Dystonias can be classified according to bodily distribution as focal, segmental, multifocal, hemi-dystonia or generalized. According to etiology, dystonias can be classified as primary (including genetic and idiopathic forms) or secondary. A third form of classification relates to age of onset: childhood (early onset), adolescence and adulthood (late onset)^{1,3}. Primary or secondary dystonia patients may rarely present with episodes of generalized, intense

and potentially fatal exacerbation of muscle contractions, usually refractory to traditional pharmacological therapy. This clinical situation is referred to as Status Dystonicus (SD) or dystonic storm⁴.

The present report describes five cases of SD evaluated and managed by the authors.

CASES

Five patients with clinical presentations consistent with the diagnosis of SD were studied according the definition of Manji et al.⁴. Table 1 shows the clinical data and outcome of each subject.

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Case 1 – A 57 year-old male with a diagnosis of primary segmentar cranio-cervical dystonia treated successfully with botulinum toxin injections. After intense stress, symptoms worsened significantly and progressed to generalization with prominent, continuous axial involvement, accompanied by profuse diaphoresis. Initial treatment trials with tetrabenazine (75 mg a day), biperiden (10 mg a day), risperidone, clozapine, baclofen, valproic acid, clonazepam and midazolam were unsuccessful. The patient developed an elevation in serum creatine phosphokinase (CK) and was admitted to the intensive care unit (ICU) after his clinical picture deteriorated. Propofol was then tried with transitory improvement but dystonic symptoms recurred and eventually surgical placement of bilateral pallidal deep brain stimulation (DBS) electrodes brought significant improvement complicated by mild left hemiparesis.

Case 2 – A 8 year-old male with a previous diagnosis of epilepsy and spastic cerebral palsy with generalized dystonia taking valproic acid (500 mg a day), clonazepam (4 mg a day), biperiden (15 mg a day) and periciazine (10 mg a day). Without any identifiable triggering event, the patient presented significant abrupt worsening of dystonic symptoms associated with chorea. Symptoms were resistant to combination of diazepam and chlorpromazine as well as to general anesthesia with propofol in the ICU. Elevated serum CK was documented. The patient was then submitted to stereotactic surgery (bilateral pallidotomy) while kept on valproic acid, clonazepam and biperiden with significant improvement.

Case 3 – A 25 year-old male with a previous diagnosis of probable Hallervorden-Spatz disease (HVS) presenting with mental retardation, tetraspasticity and generalized dystonia. Family history was remarkable for a brother with a similar presentation. The patient's symptoms were kept stable with combination therapy that included trihexyphenidyl (20 mg a day), clonazepam (6 mg a day), baclofen (20 mg a day) and carbamazepine (600 mg a day). After a febrile episode (probable viral infection) the patient presented significant deterioration of dystonic symptoms with elevated serum CK. Symptoms were resistant to increasing doses of anti-cholinergics

and clonazepam, as well as to the addition of tetrabenazine, flurazepam, clobazam and pimozide. Haloperidol 15 mg a day brought significant improvement and the patient remained clinically stable with maintenance therapy that included tetrabenazine, flurazepam and carbamazepine.

Case 4 – A 21 year-old male with a 10-month history of swollen cervical lymphonodes. During investigation, persistent low platelet counts were detected (< 50000/mm³) and attributed to hypersplenism. At this point, five months after initial symptoms, the patient was submitted to splenectomy. Liver was roughly nodular and a biopsy was performed during the surgical procedure, showing active cirrhosis. The patient developed neurological symptoms in the immediate post-operative period, with progressive asymmetric left hemidystonia and rigid-akinesia. These symptoms progressed for six weeks and the diagnosis of Wilson's disease (WD) was confirmed after tests of copper metabolism (ceruloplasmin: 3 mg/dl; serum copper: 32 mcg/dl; and urinary copper: 20 mcg/dl) and slit lamp examination showing Kayser-Fleischer ring were performed. Specific treatment with zinc sulfate (210 mg tid) was started. A week later, episodes of intense dystonic contractures developed with hyperthermia of up to 40° C. Such episodes led to acute respiratory failure that required non-invasive ventilatory support and intensive care procedures. Antipyretics and cooling blankets were used for immediate control of fever. Detailed investigation of an infectious etiology was negative and serum CK was elevated. In this context, the diagnosis of SD was confirmed and therapy initially included biperiden in doses up to 24 mg a day, later associated with baclofen (30 mg a day) and levodopa-carbidopa (up to 1 g a day) with partial improvement during the first two weeks and eventually stabilization after the third week.

Case 5 – A 9 year-old male with a past medical history of neuropsychological developmental delay after 6 months of age with increased startle reflex response to tactile and auditory stimuli. A presumed diagnosis of cerebral palsy was established at the age of 18 months. Screening for secondary causes was negative after a second investigation was performed three years later.

Table 1. Status Dystonicus - clinical data and outcome of 5 patients.

Case	Age (year)	Dystonia	Treatment				Outcome
			CK > 3x normal	Clinical	Anesthesia	Surgery	
1	57	primary	+	+	+	+	Excellent
2	8	secondary CP	+	+	+	+	Excellent
3	25	secondary HVS	+	+	-	-	Good
4	21	secondary WD	+	+	-	-	Good
5	9	secondary CP	NP	+	+	-	Good

CP, cerebral palsy; HVS, Hallervorden-Spatz disease; WD, Wilson's disease; CK, creatinophosphokinase; NP, not performed.

At the age of eight years the patient started with right-sided asymmetric generalized dystonia with intermittent periods of exacerbation. Initially treated with midazolam (0.1 mg/kg/dose) during exacerbations and kept on valproic acid (15 mg/kg/day) and clonazepam (0.03 mg/kg/day), without clinical improvement. Later started on haloperidol (0.3 mg/kg/day), again with no significant improvement. On follow up, for no apparent cause, the patient presented abruptly with intense exacerbation of generalized contractures, refractory to the usual therapy leading to admittance to the ICU where he was initially treated with an initial dose of 18 mg of midazolam followed by chlorpromazine (10 mg tid) and additional doses of clonazepam 9 mg until symptoms were controlled during the following 24 hours. The patient was kept on clonazepam (0.03 mg/kg/day), haloperidol (0.05 mg/day), trihexyphenidyl (0.15 mg/kg/day) and levodopa-carbidopa (6 mg/kg/day). After five days, symptoms of SD recurred and were controlled with additional doses of clonazepam and chlorpromazine. The patient was discharged taking trihexyphenidyl (0.7 mg/kg/day), levodopa-carbidopa (15 mg/kg/day) and diazepam (0.23 mg/kg/day).

DISCUSSION

We report clinical features, management and outcome of five cases of SD, a rare complication of dystonia. These cases compile the experience of 4 known Brazilian centers of adult and pediatric neurology, and neurosurgery, thus underlining how uncommon and possibly underreported this potentially fatal neurological emergency is. Most of what is known about the SD comes from single case reports⁵⁻⁹, the only series published in the medical literature is the one from Manji *et al.*⁴ that included 12 patients observed over a 10-year period, also collected from different centers in the United Kingdom. Although the series presented here is relatively small, it represents the first in Latin America and the second largest in the literature.

Jankovic and Penn⁵ reported for the first time in 1982 a case of SD in an 8-year-old boy with primary dystonia complicated by SD and secondary hyperpyrexia, myoglobinuria and acute renal failure. Transient improvement was achieved with tetrabenazine and baclofen, and eventually bilateral thalamotomy had to be performed. Marsden *et al.*¹⁰ published a report of 23 children and 17 adults with dystonia treated with high dose of anticholinergics. From the whole group, 2 children were described as presenting "life-threatening generalized dystonia" treated with combined use of tetrabenazine and pimozide, successful in one of them.

Vaamonde *et al.*⁶ used for the first time the term 'dystonic storm' describing two cases of SD that required anesthesia in the ICU despite trials with benzhexol, tetrabenazine, pimozide, diazepam, baclofen, haloperidol, carbamazepine, primidone and valproic acid. Narayan *et al.*⁷ reported one case of probable SD in an 18-year-old male patient with axial dystonia due to cerebral palsy treated unsuccessfully with anticholinergics and tetrabenazine requiring continuous intrathecal baclofen infusion.

The most frequently reported triggering factors are trauma, surgery, infection, fever, abrupt introduction, withdrawal or change in medical treatment including lithium, tetrabenazine and clonazepam. There are several possible complications of SD including rhabdomyolysis, hyperpyrexia, muscle exhaustion, pain, dehydration, acute renal failure and respiratory insufficiency. The most important differential diagnoses are neuroleptic malignant syndrome and malignant hyperthermia⁴.

Treatment of SD is mainly empirical, variable and collected from anecdotal reports as described above^{4,5-7,10}. Also of note are cases requiring use of continuous infusion of intrathecal baclofen and neurosurgery, including thalamotomy, pallidotomy or placement of DBS electrodes^{4,9,11}. Basic support is also essential and includes adequate fluid balance, analgesia, anti-pyretics, ventilatory support and hemodynamic monitoring^{4,11}. Course and outcome is also highly variable, in the series of Manji *et al.*⁴ 2 out of 12 SD patients died, five returned to their baseline condition, two had complete remission and three remained clinically deteriorated in comparison with their previous dystonic symptoms. Nine required ventilatory support and three required sedation with intravenous chlormethiazole. Two patients were submitted to neurosurgical procedure (thalamotomy), successful in one. Among the 5 patients presented in our series, three were admitted to ICUs, two were treated with propofol and one with intravenous midazolam. Two were submitted to neurosurgical procedures (one with placement of pallidal DBS electrodes and the other with bilateral pallidotomy). In three patients, precipitating factors were identified, namely viral infection, stress and use of zinc for treatment of WD. On our series there were no cases of death, two patients had significant improvement of their dystonia, and three returned to their baseline condition (cases 3, 4 and 5).

One report of SD following the initiation of pharmacological treatment for WD has already been published by Svetel et al.⁸ in 2001, in this case fatal and related to D-penicilamine. Accordingly, D-penicilamine treatment initiation may be known to sometimes worsen the neurological symptoms of patients with WD¹². Case 4 in our series developed SD during zinc sulfate treatment suggesting that the occurrence of such complication in WD is not exclusively related to the use of D-penicilamine and may be part of the natural history of this metabolic disorder. Kyriagis et al.⁹ have recently reported a case of SD in a patient with HVS, as in case 3 from our series. Again, this was described as a dramatic case that did not respond to initial drug trials and required mechanical ventilation, temporary intrathecal baclofen infusion and bilateral pallidotomy.

Although rare, SD requires prompt diagnosis and therapeutic intervention in ICUs if needed, avoiding metabolic, renal and ventilatory complications. Conventional clinical interventions may be ineffective and occasionally stereotactic neurosurgical procedures may be necessary.

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