A complication of severe brain injury, regardless of etiology, is a syndrome of marked agitation, diaphoresis, hyperthermia, hypertension, tachycardia, and extensor posturing. To capture the main features of this syndrome, derived through literature review and our own case series, we propose the term *paroxysmal autonomic instability with dystonia*. We reviewed reports of autonomic dysregulation after brain injury and extracted essential features. From the clinical features, consistent themes emerge regarding signs and symptoms, differential diagnosis, and pharmacological therapies. We used these findings to make recommendations regarding diagnosis and treatment. Paroxysmal autonomic instability with dystonia appears to be a distinctive syndrome after brain injury that can mimic other life-threatening conditions. Early recognition may lead to fewer diagnostic tests and a rational approach to management. Prospective trials of specific drugs are needed to determine optimal efficacy.

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A complication of severe brain injury, re-
gardless of etiology, is a syndrome of
marked agitation, diaphoresis, hyper-
thermia, hypertension, tachycardia, and
tachypnea accompanied by hypertonia and
extensor posturing. Usually episodic, it first
appears in the intensive care setting but
may persist into the rehabilitation phase
for weeks to months after injury in indi-
viduals who remain in a low-response
state. The syndrome engenders alarm be-
cause it may be difficult to distinguish from
life-threatening conditions such as sep-
sis, impending herniation, or epileptic sei-
zure. These manifestations could lead to
secondary hypertensive or hyperthermic
encephalopathy and even death.

Various labels have been applied to
this phenomenon, such as *paroxysmal symp-
thetic storms, diencephalic seizures,* or
*midbrain dysregulatory syndrome.* How-
ever, the syndrome remains poorly un-
derstood and underrecognized, despite its
distinctive and characteristic features. The
lack of a standardized nomenclature is a
major problem with research into this con-
dition.\(^1\) Based on a review of limited ex-
isting literature, generally consisting of re-
ports of a single or only a few cases, and
of our own case series, we propose the fol-
lowing name for this syndrome: *paroxys-
mal autonomic instability with dystonia* (PAID). We will define its characteristics as precisely as possible, provide guidelines for distinguishing it from other conditions with similar characteristics, and suggest a rational treatment approach.

The pathophysiology of PAID can be
best explained by dysfunction of auto-
nomic centers in the diencephalon (thala-
mus or hypothalamus) or their connec-
tions to cortical, subcortical, and brainstem
loci that mediate autonomic function. Bullard\(^2\) suggested a release phenomen-
on in which loss of cortical and sub-
cortical control of vegetative functions
occurs, including regulation of blood
pressure and temperature. Boeve et al\(^3\)
expanded this concept by speculating that
the mechanism likely involves activ-
tion (or disinhibition) of central sym-
pathoexcitatory regions such as the para-

From the Kluge Children's Rehabilitation Center, Department of Pediatrics (Drs Blackman, Patrick, and Buck), and the Division of Pediatric Neurology, Department of Neurology (Dr Rust), University of Virginia, Charlottesville.
ventricular hypothalamic nucleus, lateral periaqueductal gray substance, lateral parabrachial nucleus, or rostral ventricular medulla. Cortically provoked release of adreno-medullary catecholamines during PAID episodes may contribute to the rise in blood pressure as well as tachycardia and tachypnea.1,5

Thermoregulatory dysfunction may also be produced by hypothalamic dysfunction, as has been demonstrated experimentally6 and clinically. The temperature elevations associated with PAID may also be explained, at least in part, by the hypermetabolic state that accompanies sustained muscular contractions.

Rigidity and decerebrate posturing are seen experimentally and clinically with lesions in the midbrain, blocking normal inhibitory signals to pontine and vestibular nuclei.7 This allows these nuclei to become tonically active, transmitting facilitatory signals to the spinal cord control circuits. Spinal reflexes become hyperexcitable, evoked by sensory input signals that are usually below the threshold for excitation of a motor response.

**LITERATURE REVIEW**

Episodic agitation, diaphoresis, hyperthermia, tachycardia, tachypnea, and rigid decerebrate posturing after severe brain injury were first noted in a report by Strich in 1956.8 He called these events **brainstem attacks**. Subsequently, this constellation of clinical signs has received a variety of labels, including **autonomic dysfunction syndrome**, **fever of central origin**, **neurostorming**, **acute midbrain syndrome**, **hypothalamic-midbrain dysregulation syndrome**, **hyperpyrexia associated with sustained muscle contractions**, **dysautonomia**, **sympathetic storms**, **paroxysmal sympathetic storms**, **acute hypothalamic instability**, and **diencephalic seizures**.

**Table 1** provides a summary of the clinical features of relevant case reports. We have included a series of our own patients. Permission was obtained from the Human Investigation Committee, University of Virginia, Charlottesville, to review patient records for this report. Because some of these patients received intensive care at other hospitals and their daily nursing and physician notes were not available, it was not possible to determine the time of initial onset of PAID signs or their total duration.

Although some heterogeneity in manifestations has been noted, there is a sufficient degree of uniformity to justify viewing these cases as a syndrome. The cases have in common autonomic dysregulation and rigidity due to dystonia (involuntary sustained muscle contraction and extensor posturing). The PAID syndrome has been reported in children and adults. Traumatic and hypoxic brain injury account for most cases, but some were due to tumors, intracranial hemorrhage, or hydrocephalus. It is most likely to be encountered after processes that produce diffuse axonal or brainstem injury.

The onset of PAID signs often occurs in the first week after severe brain injury, when differential diagnosis is most difficult, and continues for weeks to months, in some cases for longer than 1 year. We have found that the episodes tend to persist the longest in patients with brain injury due to anoxia. Early diagnosis is challenging because the various constituent parts of the syndrome may be caused by a wide variety of processes that may occur in these very ill patients, including seizures, infection, the effects of drugs, withdrawal from drug therapy, pain, or agitation. PAID signs occur at a time when the patient's mental status is abnormal, and tests such as electroencephalography may be difficult to obtain or coordinate with the intermittent phenomena. These signs invariably include temperature elevation (as high as 41°C), increases in heart and breathing rates, hypertension, diaphoresis, agitation, and extensor posturing. Creatine kinase levels are rarely reported; in one case these values were within the reference range, and in another, elevated.

The most commonly used drugs for treatment of PAID are morphine sulfate, bromocriptine mesylate, propranolol hydrochloride, clonidine hydrochloride, lorazepam, and dantrolene sodium. Each one of these drugs is rational and addresses a component of the PAID syndrome (**Table 2**).

Opioid receptors are found in brain cardiovascular nuclei, the heart, and blood vessels.20 Opiates such as morphine, when peripherally injected into healthy animals, produce hypotension.21 Morphine induces analgesia, respiratory depression, and bradycardia. Its analgesic properties may interfere with pain as an exciting factor, and its sedative effects may counter the tachycardia and tachypnea. Constipation is a problematic adverse effect of morphine and narcotic dependency. Withdrawal from opiate therapy may provoke signs that falsely suggest PAID.

The use of dopamine antagonists or the withdrawal of dopamine agonist therapy may also result in neuroleptic malignant syndrome (NMS), the clinical features of which suggest PAID. Thus, it is not surprising that the use of bromocriptine, a dopamine agonist, has been found to be helpful in PAID.

Because excitation of the sympathetic nervous system appears to be a major feature of PAID, the uses of β-adrenergic blockade, such as propranolol (nonselective β-adrenergic blockade) or labetalol hydrochloride (nonselective β- plus α, β-adrenergic blockade), are logical choices and have proven clinically useful in the amelioration of some of the most important clinical signs (eg, hypertension), but not cholinergic signs (eg, diaphoresis) of PAID. In the experience of Do et al,6 β, β-adrenergic selective antagonists (eg, metoprolol or atenolol) are not effective, as in mitigating autonomic dysregulation.

Clonidine, an α, β-adrenergic agonist, reduces blood pressure, has a behavior-stabilizing effect, and causes sedation. These features treat the sympathetic signs and may interrupt feedback into the system that otherwise would perpetuate the cycle of autonomic dysregulation.

The benzodiazepines, such as lorazepam, have anxiolytic and sedating effects and muscle relaxant properties that may account for benefits observed in treatment of PAID.

In addition to its direct muscle relaxant properties, dantrolene may diminish fever due to prolonged muscle contraction and may also reduce the somatosympathetic spinal reflexes that contribute to sympathetic excitation.

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<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Subjects</th>
<th>Age, y</th>
<th>Origin</th>
<th>Onset, d</th>
<th>No. of Cycles per Day</th>
<th>Duration of Each Episode</th>
<th>Total Duration</th>
<th>Signs</th>
<th>Treatment or Drugs</th>
<th>Term Used to Describe</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Virginia</td>
<td>7</td>
<td>9-29</td>
<td>MVC, near drowning, hanging, assault</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>T, 38°C-41.8°C; HR, 161-216 beats/min; BP, 123-171/78-101 mm Hg; rigid or decerebrate posturing; diaphoresis; agitation</td>
<td>Atenolol, lorazepam, diazepam, methadone hydrochloride, propranolol hydrochloride, clonidine hydrochloride</td>
<td>NA</td>
</tr>
<tr>
<td>Thorley et al,12 2001</td>
<td>1</td>
<td>20</td>
<td>MVC</td>
<td>1</td>
<td>NA</td>
<td>Seconds to hours</td>
<td>2 wk</td>
<td>T, 40.0°C; HR, 156 beats/min; extremity posturing; diaphoresis; agitation; CPK, 61 U/L</td>
<td>Midazolam, lorazepam, morphine sulfate, oxycodone, bromocriptine mesylate, dantrolene sodium</td>
<td>Acute hypothalamic instability</td>
</tr>
<tr>
<td>Cuny et al,11 2001</td>
<td>4</td>
<td>17-37</td>
<td>MVC</td>
<td>24-60</td>
<td>2-16</td>
<td>1-8 wk</td>
<td>Labetalol hydrochloride</td>
<td>T, 39.1° C; HR, 140-160 beats/min; BP, 170-180/100 mm Hg; diaphoresis; flexor posturing</td>
<td>Hyperthermia; hypertension; tachycardia</td>
<td>Dysautonomia</td>
</tr>
<tr>
<td>Do et al,9 2000</td>
<td>1</td>
<td>21</td>
<td>MVC</td>
<td>450</td>
<td>3</td>
<td>1-2 h</td>
<td>NA</td>
<td>Hyperthermia; hypertonia; tachycardia</td>
<td>Labetalol hydrochloride</td>
<td>Paroxysmal sympathetic storm</td>
</tr>
<tr>
<td>Baguley,1 1999</td>
<td>14</td>
<td>NA</td>
<td>Hypoxia, TBI</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Classic features described by Boeve et al (1998)</td>
<td>NA</td>
<td>Paroxysmal sympathetic storms</td>
<td>NA</td>
</tr>
<tr>
<td>Goh et al,10 1999</td>
<td>1</td>
<td>7</td>
<td>Midbrain glioma</td>
<td>3</td>
<td>NA</td>
<td>NA</td>
<td>T, 38.4°C-39.5°C; HR, 150-180 beats/min; BP, 170-180/100 mm Hg; diaphoresis; flexor posturing</td>
<td>Phenytoin sodium, diazepam, lorazepam, clonidine</td>
<td>Diencephalic seizures</td>
<td></td>
</tr>
<tr>
<td>Boeve et al,3 1998</td>
<td>1</td>
<td>17</td>
<td>MVC</td>
<td>5</td>
<td>1-3</td>
<td>2-4, 8-10 h</td>
<td>12 mo</td>
<td>T, 39°C-42°C; HR, 140-190 beats/min; RR, 26-40 breaths/min; SBP, 150-170 mm Hg; increased decerebrate/opisthotonic posturing</td>
<td>Morphine, bromocriptine, dantrolene sodium</td>
<td>Paroxysmal sympathetic storms (diencephalic seizures)</td>
</tr>
<tr>
<td>Scott et al,213 1997</td>
<td>1</td>
<td>11</td>
<td>Hydrocephalus, tumor</td>
<td>NA</td>
<td>2-4</td>
<td>2-6 h</td>
<td>NA</td>
<td>T, 39°C-42°C; HR, 140-160 beats/min; RR, 30-60 breaths/min; SBP, 160 mm Hg; DBP, 110-120 mm Hg; diaphoresis; increased muscle tone; tremors; muscle spasms; decorticate posturing; nystagmus; teeth grinding</td>
<td>Chlorpromazine hydrochloride, bromocriptine, propranolol, levodopa/ carbidopa</td>
<td>Hypothalamic storming</td>
</tr>
<tr>
<td>Sneed,14 1995</td>
<td>1</td>
<td>2</td>
<td>Near drowning</td>
<td>14</td>
<td>Days to a week</td>
<td>85 wk</td>
<td>T, 39.5°C</td>
<td>Tachycardia; T, 38.9°C-40.6°C; sweating; decorticate posturing; focal hyperthermia</td>
<td>Clonazepam</td>
<td>Hyperpyrexia associated with sustained muscle contractions</td>
</tr>
</tbody>
</table>
| Meythaler and Stinson,15 1994 | 3               | 15, 20, 21 | TBI                              | NA       | NA                    | NA                       | NA            | T, 38.9°C-40.6°C; sweating; decorticate posturing; 

(continued)
DIFFERENTIAL DIAGNOSIS

The following clinical entities have features in common with PAID and may share underlying pathophysiological mechanisms (Table 3).

### Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome is a severe disturbance of motor tone seen in patients taking dopamine receptor-blocking agents, i.e., phenothiazines such as thioridazine hydrochloride (Mellaril) and prochlorperazine (Compazine) and butyrophenones such as haloperidol (Haldol). This syndrome consists of fever, muscle rigidity, autonomic instability, alteration of consciousness, and elevation of serum creatine phosphokinase levels. Formerly, neuroleptics such as haloperidol were frequently used to treat agitation in brain-injured patients. The decline in this practice has diminished the occurrence of NMS in such patients. Because a considerable number of safer agents are now available, the use of neuroleptics in this setting is generally considered to be contraindicated.

Several cases have been reported with withdrawal of dopamine agonists (levodopa/carbidopa22 and amantadine hydrochloride.23 Numerous reports also associate the syndrome with the use of the dopamine receptor antagonist metoclopramide hydrochloride (Reglan),24-27 a drug commonly used to stimulate gastric emptying and reduce aspiration risk in patients with brain injury. Two case reports implicating metoclopramide involved children,28,29 and in 1 case symptoms were likely triggered by metoclopramide but did not reach their full manifestation until after the therapy was discontinued.30

Neuroleptic malignant syndrome apparently results from deficient compensatory mechanisms after blockade of dopaminergic regulation of muscle tone and...
autonomic function. Neuroleptic malignant syndrome occurs in only 1% of individuals taking neuroleptics. The incidence of NMS is likely lower than this with the newer antipsychotic drugs. Cases have been reported in children as young as 1 year after a single accidental dose. Symptoms usually occur 3 to 9 days after starting therapy. Extrapyramidal signs may be associated with other NMS clinical features. With early recognition and appropriate treatment, mortality due to NMS is low. Treatment includes stopping the neuroleptic therapy and providing supportive care.

**Malignant Hyperthermia**

Malignant hyperthermia (MH) is a disease of skeletal muscle characterized by hypermetabolism that occurs with...
exposure to a triggering agent such as inhalational anesthetic agents or depolarizing muscle relaxant drugs (eg, succinylcholine chloride), usually during induction or sometimes within 2 to 3 hours and rarely more than 24 hours later. After surgery, MH has been reported to occur in the absence of administration of a known triggering agent and may continue for several days.33

Malignant hyperthermia may also follow head injury without any exposure to anesthesia or surgery.34 A 21-year-old man became agitated and diaphoretic 36 hours after head injury. His temperature rose to 42.3°C; he was tachycardic, hypotensive, tachypneic, and displayed decerebrate posturing. Rhabdomyolysis and renal and liver failure developed. Results of a muscle biopsy confirmed the diagnosis of MH, including a characteristically abnormal response of muscle to halothane in vitro.

Malignant hyperthermia tends to occur most commonly in younger persons; 52% were younger than 15 years in 1 case series.35 Inheritance of MH is primarily autosomal dominant, although it may also be autosomal recessive, polygenic (genes on chromosomes 3, 17, and 19 have been implicated), or sporadic.36-39

Abnormal calcium regulation appears to be the basic underlying defect resulting in tonic muscle contraction with production of excessive heat, resulting in a rise in body temperature to as high as 44°C. Skeletal muscle rigidity can be local or diffuse, and is often first observed in the masseter muscles, extremities, and chest. Damaged muscles release large amounts of tissue thromboplastin, leading to coagulopathy, and myoglobin, leading to myoglobinuria and acute tubular necrosis.

Apart from discontinuing the triggering agent, if known, the use of dantrolene is the only effective treatment for MH. Dantrolene blocks calcium release from the sarcoplasmic reticulum causing muscle relaxation, and has reduced mortality due to MH dramatically.

**Diencephalic Seizures**

The PAID syndrome frequently has been termed and confused with true diencephalic seizures. In 1929, Penfield40 described a 41-year-old women with a tumor of the third ventricle who displayed paroxysmal discharges of the vegetative nervous system that he described as autonomic epilepsy. Subsequent case reports of episodes characterized by irregular respirations, altered heart rate, labile blood pressure, hypothermia, and diaphoresis were associated with neoplasms of the diencephalon,41 agenesis of the corpus callosum,42-44 trapped third ventricle,45 and a suprasellar arachnoid cyst. The key features of hypothermia and profuse sweating generally responded to anticonvulsants, although electroencephalographic studies did not typically show epileptiform discharges. One case of periodic hypothermia, described as diencephalic epilepsy, responded only to total sympathectomy.46

Several cases of what appears to us to be the PAID syndrome have been described in the literature as diencephalic seizures.2-3 Goh et al10 described a 7-year-old child with repeated episodes of sympathetic hyperactivity due to a midbrain glioma as having a variant of diencephalic seizures. They acknowledged in the discussion that the term seizure is a misnomer, because there has never been a demonstration of an epileptogenic focus during a PAID episode, and most patients with PAID do not benefit from antiepileptic medications. Thus, diencephalic seizures constitute a syndrome distinct from PAID.

**Autonomic Dysreflexia**

Autonomic dysreflexia (AD) occurs in individuals with spinal cord injury at the level of T6 through T8 or above. Any noxious stimulus below this level, such as a distended bladder, may initiate reflexive sympathetic activity resulting in life-threatening hypertension uncontrolled by feedback parasym pathetic activity.47 Other manifestations of AD include headache, flushing and sweating of the face and upper torso, and apprehension. Removing the inciting stimulus relieves AD. Patients with spinal cord injury may have brain injuries as well, predisposing them to sympathetic dysregulation at the spinal cord and brain levels.

**Central Fever**

Fever is common after central nervous system trauma.48 Causes include wound infection, meningitis, blood in the cerebrospinal fluid, drug fever, and pneumonia/atelectasis. Central fever is a diagnosis of exclusion, attributed to trauma if it affects the base of the brain or the hypothalamus. The fever, often very high and persisting for weeks after injury, is relatively resistant to antipyretic therapy and occurs in the absence of perspiration.

**Agitation**

The clinical sign that is probably most often confused with PAID is simple agitation. After emergence from true coma (return of sleep/awake cycles) with returning—albeit sometimes very slowly—arousal and awareness, the patient typically becomes agitated with extensor posturing and thrashing about the bed. The following tabulation shows the levels of cognitive functioning of the Rancho Los Amigos Scale.

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No response</td>
</tr>
<tr>
<td>II</td>
<td>Generalized response</td>
</tr>
<tr>
<td>III</td>
<td>Localized response</td>
</tr>
<tr>
<td>IV</td>
<td>Confused, agitated</td>
</tr>
<tr>
<td>V</td>
<td>Confused, inappropriate</td>
</tr>
<tr>
<td>VI</td>
<td>Confused, appropriate</td>
</tr>
<tr>
<td>VII</td>
<td>Automatic, appropriate</td>
</tr>
<tr>
<td>VIII</td>
<td>Purposeful, appropriate</td>
</tr>
</tbody>
</table>

If the patient is at level II, there may be no purposeful movements. The lack of autonomic instability (ie, excessive rise in temperature and blood pressure) distinguishes agitation from PAID. Pain or discomfort from any source (eg, musculoskeletal, visceral, or headache) can produce agitation. When purposeful movements are observed with agitation, such as pulling out tubes or hitting, as seen at Rancho Los Amigos levels III and IV, PAID is clearly not the cause of agitation. Another possible cause of agitation is narcotic withdrawal, as almost all patients with severe brain trauma accompanied by other in-
juries such as fractures receive narcotics in the intensive care setting, and they are weaned from the drugs as they progress toward rehabilitation.

In acute brain injury, the pathophysiology of PAID may be similar in some ways to that of NMS or MH. Drug exposure or withdrawal or even stress may initiate aspects of these conditions, confusing the diagnosis. Any of the single features of PAID, such as hypertension, agitation, or hypothermia, could stimulate the full-blown syndrome. This might explain why a single drug that addresses 1 feature (eg, dantrolene for hypertonia) could interrupt and perhaps abort the process, especially if therapy is initiated early. Four cases of posttraumatic dysautonomia successfully treated with intrathecal baclofen, a muscle relaxant, illustrate this point.11 Most often, more than 1 drug is required for control.

It is clear that PAID is not associated with seizure activity and, thus, the term diencephalic or hypothalamic seizure is not appropriate to describe this condition. Unless there are comorbid seizures, antiepileptic drugs for PAID are not a rational choice except for use as mood stabilizers, possibly treating the agitation feature.

CRITERIA FOR PAID

It seems useful clinically and for future research to establish a single name that encompasses and clearly denotes the main features of the clinical phenomena described in this report. Paroxysmal autonomic instability with dystonia appears to accomplish this. Based on the literature review and our own experience, we propose specific criteria for the PAID syndrome. Within the clinical setting of traumatic brain injury, signs of PAID syndrome include (1) severe brain injury (Rancho Los Amigos level, <IV), (2) temperature of at least 38.5°C, (3) pulse of at least 130 beats/min, (4) respiratory rate of at least 140 breaths/min, (5) agitation, (6) diaphoresis, and (7) dystonia (ie, rigidity or decerebrate posturing). The duration is at least 1 cycle per day for at least 3 days. Finally, other conditions must be ruled out. In addition to recognizing consistent features of PAID, it is as important to recognize signs of other diseases or conditions that require prompt attention and a different diagnostic or treatment approach.

ASSESSMENT AND TREATMENT

Differential diagnosis is challenging, especially in the phase of acute brain injury. Because patients may be heavily sedated for ventilation or pain management, temperature elevation is usually the first concern, prompting body fluid cultures, leukocyte counts, and various imaging studies to rule out sepsis. If these test results are negative, fever may be attributable to noninfectious causes.

As sedation and analgesia are withdrawn, more typical cycles of PAID may become evident. Typically, the next sign of concern is elevated blood pressure, leading to the initiation of antihypertensive therapy. Gradually, the cyclical nature of the PAID signs becomes evident with episodes daily or several times daily and with the return of vital signs to normal between episodes.

Before accepting PAID as a diagnosis, alternative causes of autonomic dysregulation should be consid-er, especially treatable intracranial abnormalities such as hydrocephalus, increased intracranial pressure, or extraxial blood or fluid accumulation. Other treatable irritants, such as dehydration, constipation, fracture site pain, or uncomfortable casts must be alleviated. Drugs or anesthetics that might precipitate or exacerbate PAID should be avoided, and caution should be used in the sudden withdrawal of dopamine agonist therapy.

As described earlier, a finite number of drugs have been used singly or in combination to alleviate PAID. No clear evidence suggests that one medication regimen is superior to another, and drugs seem to work well for some patients but not others. The goal is to maximize effectiveness while minimizing adverse effects. For example, sedation medications that are administered as needed, like narcotics or benzodiazepines, may quiet an episode but depress arousal and awareness between episodes. Clonidine will reduce blood pressure effectively, but also is sedating. Dantrolene as a muscle relaxant may be preferable to baclofen because it does not sedate; however, its use may be limited by toxic effects to the liver. β-Blockers will lessen sympathetic features, but should be used with caution in patients with asthma or diabetes.

A logical approach is to choose target signs, consider safety of particular drugs for the individual, and set a time frame for determination of efficacy before a drug is changed or a second drug is added. In our center, we try to devise a regimen that will prevent or ameliorate rather than rely on as-required drugs that may overtreat the condition.

Greater awareness of PAID and appropriate early intervention may minimize repetitive and expensive tests (eg, sepsis workups), ease nursing management, avoid pharmacological excess, prevent secondary injury, and allay the anxiety of parents and health care workers observing repeated episodes.

Further research is needed to evaluate individual or combination pharmacotherapy for PAID. A clearer definition of this syndrome may facilitate cross-institutional studies.

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