Hyperpyrexia Associated With Sustained Muscle Contractions: An Alternative Diagnosis to Central Fever

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Muscle activity is the principal source of body heat production, and elevated core body temperatures may occur in healthy exercising persons. Hyperpyrexia from sustained tonic muscle contractions can also occur in a number of pathological conditions. The present case of hyperpyrexia associated with dystonic posturing and sustained muscle contraction in a child with encephalopathy illustrates the importance of recognizing muscular activity in the generation of fever of unknown origin following central nervous system injury. The pathophysiology, clinical features, and management of this uncommon cause of fever are discussed.

CASE REPORT

The patient was a previously healthy 2-year-old boy whose near drowning resulted in severe hypoxic encephalopathy. An initial computed tomography (CT) brain scan on day 1 postinjury was unremarkable. Follow-up CT brain scans showed progressive cerebrocortical and central atrophy, periventricular deep white matter infarctions, and bilateral basal ganglia hemorrhagic infarcts progressing to encephalomalacia. The patient developed progressive spasticity and tremors in the first 2 weeks postinjury; a gradually increasing body temperature reached 39.5 degrees C during the third week. An extensive work-up for infection and other causes of fever failed to identify an etiology. He was placed empirically on intravenous vancomycin and ceftazidime for 7 days with no response. Serum lactic acid dehydrogenase (LDH) was 1,382U/L in a nonspecific pattern; serum creatine kinase (CK) was 2,685IU/L. Other liver enzymes were only mildly elevated. Before further medications for spasticity were initiated, he had spontaneous resolution of the tonic opisthotonic posturing, severe tonic spasticity, and diaphoresis. On one occasion before anticonvulsants were initiated, his electroencephalogram (EEG) showed generalized paroxysmal activity and multifocal spikes indicative of multifocal seizures. Despite the addition of phenobarbital and carbamazepine with therapeutic blood levels and phenobarbital, dystonic posturing and fever returned for a 24-hour period only when clonazepam was added and gradually increased to 0.04 mg/kg/day by day 86, the child exhibited no further posturing or fever. Posturing and fever returned for a 24-hour period only when clonazepam was temporarily held for gastrostomy tube placement. The CK decreased to 742IU/L on day 87 and to 180 on day 100. LDH decreased to 215U/L on day 114. At 10 months postinjury, the child remained at Rancho Level 3 and continued on clonazepam with no further posturing or unexplained fevers.

DISCUSSION

Body temperature is a balance between heat loss and heat production. Heat loss is a function of radiation, conduction, convection, and evaporation. About 95% of body heat loss...
HYPERPYREXIA SECONDARY TO SPASTICITY, Sneed

normally occurs through the skin: 60% to 65% occurs by radiation and 20% to 30% by evaporation, with evaporation by sweating playing a greater role at higher environmental temperatures. Body heat production results from the interaction of the heat production from: the basal rate of metabolism (BMR) of all body cells; hormonal influences such as an increased metabolism from thyroxin; increased metabolism from catecholamines including epinephrine and norepinephrine; extra metabolism of the body cells themselves; and muscular activity.

Of these, muscular activity is the major producer of body heat in the normal environment. Shivering, a form of involuntary muscle contraction, is the principal means of thermogenesis in cold exposure. Intense muscular exercise may increase heat production 10 to 15 times so that body temperature may increase to as high as 41 degrees C (105.8 degrees F) in long distance runners, with no adverse effects and with only a mild increase in skin temperature. Fever from exercise, unlike fever of infection, does not seem to respond as well to salicylates.

Hyperpyrexia associated with sustained muscular activity previously has been associated with several etiologies. Among these are *Clostridium tetani* infection (tetanus), strychnine poisoning, malignant hyperthermia, neuroleptic malignant syndrome, idiopathic lethal catatonia, baclofen withdrawal, prolonged status epilepticus, and autonomic seizures. Mandac et al describes a patient with two episodes of secondary hyperthermia as a product of baclofen withdrawal. They postulated that the increased spasticity that followed led to a sympathetic response, triggering catecholamine production and a concomitant hypermetabolic state.

Studies of patients with traumatic brain injury have shown increased plasma levels of norepinephrine (NE) and dopamine B-hydroxylase, along with increased sympathetic activity. Blood pressure, pulse, and body temperature were elevated directly in proportion to the plasma NE levels. However, in these studies temperature levels were not consistently reported, and fluctuations in body tone/spasticity reviewed in relation to the hyperpyrexia, hypertension, tachycardia, or diaphoresis were not evaluated.

When discussing hypermetabolic states, drugs, increased circulatory catecholamines, and hormones as factors in core body temperature elevations, most investigators do not describe increases of more than 1 degree to 2 degrees C, if recordings are reported at all. Also, one must be certain that other causes of heat regulation, such as a loss of skin area and sweating for heat dispersion in burn patients, have not been altered, and that hypermetabolism is not coexisting or secondary to other factors like muscular activity (as in this case report), rather than as a primary cause of heat increase.

Experimentally induced prolonged seizure states of greater than 1 hour in cats and primates produce hyperpyrexia after sustained muscle activity. Clinical reviews of humans in prolonged status epilepticus also show tachycardia, hypertension, and hyperpyrexia. In status epilepticus the EEG may show a variety of abnormalities from focal or generalized slowing to bilateral spike-wave discharges. As Aminoff and Simon note, the elevated temperatures, coupled with concomitant seizure induced leukocytosis, may lead to a mistaken diagnosis of infection. Muscle tissue may break down with increased CKs, myoglobinuria, and renal failure. Phenobarbital, phenytoin, or carbamazepine are usually the first choices for prolonged treatment of generalized tonic-clonic seizures. Secondary drugs such as clonazepam or valproic acid may be required to control refractory patients, particularly of severe mixed or multifocal seizures, or if a myoclonic component is present.

A syndrome labeled variously as diencephalic (autonomic) seizures, hypothalamic-midbrain dysregulation syndrome, and acute hyperthermia syndrome with autonomic dysfunction has been recognized in various forms of brain injury including trauma, tumor, and hydrocephalus. Although hypertension, diaphoresis, tachycardia, and tachypnea are present, severe muscle rigidity and hyperthermia are the principal features in most reported cases. EEGs show only generalized slowing. Bullard and Talman and coworkers noted that hyperthermia was most severe when decerebrate extensor posturing was present.

Among hypoxic encephalopathies, the most frequently observed neurological sequelae include extrapyramidal rigidity and movement disorders such as action, intention, or generalized myoclonus, decerebrate rigidity, and the possibility of seizures. This child was believed to have a diencephalic seizure as well as multifocal complex seizure disorder secondary to severe hypoxic encephalopathy, with a questionable myoclonic component. This resulted in episodic rigid extension posturing of all four extremities, truncal opisthotonus, and intermittent tongue protrusion, accompanied by increased pulse rate, respiratory rate, and diaphoresis, all of which were quite distinct from his usual relaxed quadraparetic state. Temperature increases never preceded but always followed from 1 to 12 hours after the onset of rigid posturing, with time of onset and height directly proportional to the severity and sustainability of the posturing. Temperatures always decreased shortly after relaxation was achieved. Marked increases in LDH and CK always occurred after the onset of posturing, and decreased once relaxation occurred. With other enzymes relatively unaffected, muscle damage was suspected as the source.

Hyperpyrexia accompanied by spasticity should not be dismissed as "central fever" until both central and peripheral treatable causes, including sustained muscle contractions, have been considered. If muscle contractions are prolonged, elevated CKs from muscle damage, tachycardia, diaphoresis, hypertension, and secondary hypermetabolism also may coexist. Treatment of the condition must be specific to the etiology whenever possible and not just to the effects. If the patient is on antihypertensive medications for control of secondary blood pressure increase, medication induced hypotension may occur when the diencephalic firing and rigidity periodically dissipate. Conceivably, dantrolene may have lessened the spasticity with secondary fever reduction, but this would constitute masking rather than treating the central cause. Even chloral hydrate, phenobarbital, and carbamazepine provided only temporary relief. Only when clonazepam was added was the problem corrected.

Clonazepam and sodium valproate facilitate the GABAergic (Y-aminobutyric acid) transmittal system and may also affect the serotonin precursor 5-HTP (5-hydroxytryptophan). They may exert positive effects on injured serotonin and GABA neurotransmission pathways causing excessive excitation or diminished inhibition in the reticular and...
thalamie areas of the brain stem. Pranzatelli and colleagues have previously focused on the potential role of pharmacological treatment of neurotransmitters and modulators, including the serotonin and GABA systems, in central hyperthermia and decerebration in diencephalic brain stem injury, although their focus was on propranolol use. Clonazepam and valproic acid have been used for absence and myoclonic seizures and for posthypoxic myoclonus. There are no reports of their use in diencephalic seizures, as in this case. In view of the similarities of areas of brain damage involvement and response to clonazepam in this case, a trial of one or both of these medications may be worthy of consideration in the diencephalic syndrome, particularly in posthypoxic encephalopathies.

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References