Central nervous system ischemia after varicella infection and desmopressin therapy for enuresis

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A 7-year-old boy had a left-sided cerebrovascular accident 48 hours after beginning intranasal desmopressin acetate (DDAVP) therapy for persistent secondary nocturnal enuresis and approximately 2 weeks after varicella infection. A possible connection between desmopressin therapy or varicella infection (or both) and the patient's neurologic symptoms is discussed, as is the relationship of desmopressin with hypercoagulability. Suggestions for patient/parent education, medical history taking, and patient surveillance are offered to prescribing physicians.

(Key words: Desmopressin acetate, DDAVP, enuresis, ischemia, varicella)

Intranasal administration of the synthetic polypeptide desamino-D-arginine vasopressin, or desmopressin acetate (DDAVP), is considered an effective, safe treatment for persistent nocturnal enuresis.¹ No reported cases of serious morbidity or mortality associated with intranasal desmopressin therapy for children with nocturnal enuresis was found. Intracerebral hemorrhage relating to an antecedent varicella infection has been uncommonly reported in association with

acute onset of hemiplegia.² This report details the case of a 7-year-old boy who sustained mild hemiplegia and other neurologic deficits after the initiation of intranasal desmopressin therapy for secondary nocturnal enuresis and following a recent varicella infection. Varicella is a likely etiology for the reported neurologic sequelae; however, a role for desmopressin must also be considered.

Report of case

A 7-year-old boy was brought to the hospital emergency department by his parents with complaints of left facial paralysis, dizziness, and fatigue that began 24 hours earlier. Forty-eight hours before the symptoms appeared, the patient had begun intranasal desmopressin therapy (0.10 µg in 0.2 mL at bedtime) to control recurrent secondary nocturnal enuresis of 2 years' duration. Medical history was noncontributory and specifically negative for other current medication or for hematologic, cardiovascular, neurologic, gastrointestinal, or renal disease. Alternative treatment of enuresis had not been attempted before the initiation of desmopressin therapy.

Physical examination revealed an alert, apparently well-nourished, and healthy white male child with normal findings on eye, ear, nose, throat, heart, lung, abdominal, and sensorimotor extremity examinations. Vital signs were as follows: blood pressure, 102/60 mm Hg; pulse rate, 88 beats per minute; respirations, 28/min; and rectal temperature, 99.2°F. Neurologic examination demonstrated all cranial nerves to be intact except for a left central facial weakness; and muscle stretch reflexes were equal and symmetric (2+/4+) bilaterally. Gait was noted to be without deficit. Complete blood cell count showed normal leukocyte count (6900/mm³) and differential, hemoglobin level (12.7 g/dL), and hematocrit (36.9%); blood chemistry reflected normal levels of glucose (110 mg/dL), sodium (138.9 mg/L), potassium (3.72 mEq/dL), chloride (105.8 mEq/dL), carbon dioxide (26.9 mEq/dL), blood urea nitrogen (13 mg/dL), creatinine (0.5 mg/dL), and calcium (9.4 mg/dL). Results of homocystinuria examination were negative. Prothrombin and activated partial thromboplastin times were not obtained. Lipid and cholesterol testing revealed normal levels of high- (30 mg/dL) and low-density lipoproteins (109 mg/dL) and of cholesterol (169 mg/dL), whereas the triglyceride level was slightly elevated (187 mg/dL). Sinus radiographs showed no abnormality.

After an initial diagnosis of Bell's palsy, the child was discharged from the hospital, with imaging studies scheduled for the next day. The child's symptoms had progressed the day after hospital discharge, with the onset of left upper extremity paresthesia and left leg weakness. The child was returned to the hospital; the parents reported his impaired verbal expression and left-foot drag in gait. Computed tomography (CT) scans of the head revealed a hypodense lesion within the head of the right caudate nucleus extending into the putamen, with some effacement of the right anterior horn, suggesting a mass or infarct (Figure).

Immediately after hospital readmission, desmopressin therapy was discontinued. Laboratory testing revealed pro-

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thrombin time of 11.8 seconds (control, 11.67 seconds), activated partial thromboplastin time of 25.1 seconds (control, 26.7 seconds), and erythrocyte sedimentation rate of 4 mm/h. Neurologic examination revealed left-sided central upper motor neuron weakness of the facial muscles manifested by facial droop, widened palpebral fissure, diminished muscular control of facial expression, right uvular deviation, impaired left grip and upper extremity strength (4/5), and difficulty with left finger-to-nose testing. Sensation to pinprick and light touch was intact, muscle stretch reflexes bilaterally were equal and symmetric (2+/4+), Babinski response was negative, and bowel and bladder functions were normal. Magnetic resonance imaging (MRI) revealed an enhanced mass lesion in the right putamen and head of the caudate nucleus, with mild mass effect and evidence of compression of the anterior horn of the lateral ventricle, consistent with an acute vascular ischemic event. Subsequent cerebral angiography supported this finding, revealing lateral deviation of several right thalamostriate vessels.

The child's hospital course was otherwise uncomplicated. He was discharged 3 days later in stable condition with evidences of progressively improving strength, such as: range of motion, normal; activities of daily living (ADL)—dressing, bathing, and feeding—independent; right upper and lower extremity strength, 5/5; left upper extremity strength, 4/5; left lower extremity strength, 4-/5, except left gluteus maximus, gluteus medius, and gastrocnemius, 4/5; coordination, sensation, proprioception, muscle stretch reflexes, and sitting/standing balance intact. An outpatient physical therapy program for strengthening and improvement of balance and gait was prescribed.

Two weeks later, the patient was again admitted to the emergency department with complaints of left-sided facial numbness and drag in gait as well as history of a fall. Detailed questioning of the parents disclosed that the patient had an uncomplicated varicella infection 2 weeks before initial presentation. On this examination, the patient was alert and coop-

Figure. Initial computed tomography scan of head revealing hypodense lesion in caudate nucleus, extending into the putamen with anterior horn effacement suggesting infarct.

erative, exhibiting mild left-sided weakness that was most apparent in the gluteus medius, gluteus maximus, and plantar flexors (4/5); left lower extremity hyperreflexia (3+/4); and impaired left upper extremity rapid alternating movements. Proprioception and sensation were normal, as were balance, and bowel and bladder functions; ADL were independent. The patient remained medically stable during a 3-day hospital stay. He was discharged from the hospital with appropriate outpatient physical therapy maintenance prescribed. The child's neurologic symptoms gradually resolved within several weeks.

Brain MRI 8 weeks subsequent to final hospital discharge showed markedly decreased mass effect and signal changes in the right basal ganglia, compatible with resolving infarct. Neurologic examination demonstrated stable, nearly normal (4+/5), left-sided strength and normal sensation. No further episodes of neurologic deficit or impairment of ADL occurred. The patient complied with prescribed outpatient physical therapy, achieving complete independence in mobility and ADL with full resolution of all symptoms.

Discussion

Childhood strokes are uncommon. Those that do occur manifest typically as hemiplegia and produce other serious seque-

lae. Strokes in children, embolic or thrombotic (or both), usually involve venous circulation that is often associated with embolic occlusive disease, such as sickle cell anemia or congenital cardiac abnormality.³

Lesions of the middle cerebral artery (that supplies the entire caudate nucleus and all but the lower part of the putamen by way of the lateral striate branches) and of the anterior cerebral artery (that supplies the lower caudate nucleus and putamen by way of the medial striate branches) can cause central facial paralysis and hemiparesis. In addition, impaired input from the reticular activating system may result in motor compromise.

Acute hemiplegia in a previously healthy child has been linked to varicella infection.² However, of an estimated 3.5 million cases annually among American children (aged 5 to 9 years), most resolve after a short course of mild fever and vesicular exanthem.⁴

In a study of 103 children (60 boys and 43 girls; mean age, 3.6 years), Jackson and associates⁵ reported complications in 29 of the subjects after varicella infection. In descending order of incidence, the complications included skin or soft tissue infections (*Staphylococcus*; *Streptococcus*) or pneumonia (or both), central nervous system (CNS) dysfunction (most often encephalitis), dehydration, Reye's syndrome (associated with aspirin use), acute cerebellar ataxia, thrombocytopenia, coagulopathy, and intracerebral insult with hemiplegia. Significantly, hemiplegia has occurred most commonly in children younger than 9 years of age.¹ However, Jackson and colleagues⁵ qualify that 19% of the study population had had stable, preexisting diseases (such as metabolic defect, congenital anomaly, failure to thrive, and eczema) that were possibly contributory to the subjects' complications after varicella infection.

Desmopressin acetate, a synthetic analog of the natural posterior pituitary substance vasopressin, effectively suppresses urine production for 7 to 10 hours.⁹ Desmopressin elicits a greater antidiuretic response than does natural vasopressin

and increases water reabsorption by the renal collecting tubules, resulting in increased urine osmolality and decreased urine flow.⁷ Desmopressin is rapidly absorbed from mucosal surfaces in the nose and mouth, reaching plasma levels approximately 45 minutes after administration; its half-life is 4 to 6 hours, and duration of action is 6 to 24 hours.⁸

Although desmopressin therapy has been associated with few adverse effects, there is evidence of a link with enhanced coagulation through increased platelet aggregation, with resultant central thrombotic events.⁹ Desmopressin causes a dose-dependent increase in plasma factor VIII and plasminogen activator of 1.2 to 2.8 times basal levels following intranasal administration, particularly in persons with von Willebrand's disease or hemophilia. In fact, desmopressin is indicated for the treatment of von Willebrand's disease (type I) and hemophilia A because of its induction of platelet aggregation.¹⁰ Byrnes and coworkers¹¹ have reported cerebral thrombosis in a patient who was given desmopressin for a bleeding disorder, positing increased platelet aggregation and levels of von Willebrand factor as putative causes of this thrombotic activity. Other authors⁸ have shown normalization or shortening of prolonged bleeding times in patients with various platelet function disorders.

Thus, although desmopressin could have caused, or at least contributed to, this patient's hemiplegia and infarctive lesions, history of varicella infection presents another possible etiology for the observed neurologic symptoms.

Clearly, desmopressin therapy is not entirely benign, despite its documented effectiveness in treating nocturnal enuresis, and should therefore be prescribed with caution. Moreover, desmopressin is inappropriate for first-line treatment of enuresis. Before recommending desmopressin therapy, organic causes should be ruled out, fluid intake should be monitored and adjusted when necessary, and behavior modification techniques or classical conditioning therapy (or both) should be considered. Before instituting desmopressin therapy, patients or parents (or both) should be informed of the

potential complications, including increased coagulation, hyponatremia, water intoxication, as well as of the need to monitor other electrolytes. Close surveillance is indicated as soon as desmopressin therapy is begun, particularly if there is medical or family history of atherosclerosis, von Willebrand's disease, or other platelet or clotting disorders. Parents should be advised that the posttreatment relapse rate is very high, with enuresis resuming in a third of the patients.

Comment

Although antecedent varicella infection is not an absolute contraindication to desmopressin use, we suggest that patients or parents (or both) be questioned about varicella history before initiation of desmopressin therapy. We also recommend informing patients/parents of the low risk of neurologic complications, as previously described. Further, we favor inquiring about history of varicella infection or desmopressin therapy (or both) if faced with an acutely hemiparetic pediatric patient with subjective or objective evidence of CNS insult. Finally, additional investigations to support or refute the role and safety of desmopressin for treatment of enuresis in patients with history of coagulation disorders, are indicated in order to assess the appropriateness of this therapy.

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