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Benign Intracranial Hypertension Associated With Budesonide Treatment in Children With Crohn's Disease

ABSTRACT

Oral budesonide in adult studies is a potent corticosteroid with decreased systemic bioavailability and an improved adverse effect profile in comparison with prednisone. It has recently been introduced for the treatment of inflammatory bowel disease in Europe, Canada, and Israel. Benign intracranial hypertension has rarely been associated with corticosteroid therapy but has not been reported in association with budesonide therapy. Three adolescents with Crohn's disease and poor nutritional status developed benign intracranial hypertension while receiving oral budesonide. All three patients had previously received multiple courses of prednisone during the course of their disease, without developing intracranial hypertension. Benign intracranial hypertension resolved after medication withdrawal and did not recur with subsequent use of prednisone. Evaluation for benign intracranial hypertension should be considered in patients with inflammatory bowel disease who develop headache while receiving oral budesonide. This side effect may be associated with poor nutritional status. (*J Child Neurol* 2001;16:458–461).

Corticosteroids are frequently used for exacerbations of Crohn's disease.[1,2] Benign intracranial hypertension is characterized by increased cerebrospinal fluid pressure, normal cerebrospinal fluid composition, and signs and symptoms referable to raised intracranial pressure. Benign intracranial hypertension is not commonly associated with corticosteroid therapy. Symptoms and signs include headache, vomiting, blurred vision, transient visual obscurations, dizziness, diplopia, and bilateral papilledema. Abducens paresis is a less common but well-recognized finding.[3] Neuroimaging studies show no evidence of a mass lesion, hydrocephalus, or any obvious structural cause for the elevated intracranial pressure.[3–5]

Benign intracranial hypertension has been described in Crohn's disease but only in isolated reports and in association with standard corticosteroid therapy.[6,7] Budesonide is a new-generation potent corticosteroid that has a local effect, low systemic bioavailability, and decreased corticosteroid-related toxicity.[1,2] This profile would appear to be safer and could lead to increased use in children. Oral budesonide was introduced in Israel in 1997. During early 1999, all pediatric gastroenterology out-patient centers in Israel were contacted. We identified and describe three patients with benign intracranial hypertension among the estimated 50 children with Crohn's disease who had received oral pH modified-release budesonide (Dr. Falk Pharma, Freiburg, Germany).

Case Reports

Case 1

Case 1 is a 14-year-old girl with glycogen storage disease type 1b and Crohn's disease who presented with a 2-week history of retro-orbital pain. She had received mesalamine 1 g daily and oral budesonide 9 mg/day for over 2 months. The latter was discontinued 1 week prior to admission because of headache. On physical examination, she was afebrile and appeared stunted and wasted, and her weight and height were below the third percentile for age (body mass index, 15). Her blood pressure was 105/63 mm Hg. The liver was palpated 10 cm below the costal margin. Neurologic examination demonstrated generalized weakness and bilateral papilledema. Contrast head computed tomography (CT) showed no structural lesion, mass effect, brain edema, or hydrocephalus. Cerebrospinal fluid opening pressure was 37 cm H_2O. Cerebrospinal fluid analysis showed 3 monocytes/μL, protein of 28 mg/dL, and glucose of 94 mg/dL. Plasma hemoglobin was 7.2 g/dL, and mean corpuscular volume was 76 fL. White blood cells were 3300/μL, total serum iron was 17 mg/dL, and total iron binding capacity was 193 mg/dL. Serum aminotransferases, bilirubin, ammonia, blood urea nitrogen, creatinine, electrolytes, and vitamin D were within normal range. Albumin was 2.4 g/dL. Therapy with furosemide was started because of increased intracranial pressure. Methylprednisolone was administered intravenously. There was gradual clinical improvement. The headache and papilledema all but disappeared within weeks. Two months after admission, there were no neurologic complaints. She has since been treated uneventfully with a course of prednisone.

Case 2

Case 2 was a 15-year-old boy with a 4-year history of Crohn's disease involving the small bowel and colon who presented with a 2-week history of severe frontal headache that awakened him from sleep. Six weeks earlier, he had suffered from intermittent abdominal pain, anorexia, and diarrhea and was started on budesonide 3 mg/tid and a polymeric formula supplement, in addition to mesalamine and 6-mercaptopurine, all of which he had received the previous year. Pain and diarrhea had resolved, and he had discontinued budesonide 3 days prior to admission because of headache. His height and weight were at the 25th and below the 3rd percentiles, respectively (body mass index, 15.3). Physical and neurologic examinations were normal except for bilateral papilledema. His blood pressure was 113/70 mm Hg. Pertinent laboratory examination revealed a hemoglobin of 12.0 g/dL and albumin of 3.3 g/dL. Serum vitamin D and A levels were both normal. An intravenous rapid corticotropin test ruled out adrenal suppression. A contrast CT scan of the brain and sinuses was normal; the

patient refused a lumbar puncture. The headache gradually disappeared. One month after admission, he consented to an elective lumbar puncture; his opening pressure was 14 cm H_2O with 2 cells/μL, protein 14 g/dL, and glucose 72 mg/dL. Papilledema gradually resolved over the next 2 months. He has since been treated uneventfully with several courses of prednisone.

Case 3

Case 3, a 13-year-old boy with a 6-year history of predominantly small bowel Crohn's disease, was admitted for severe headache and vomiting. He had finished a course of prednisone for an exacerbation 2 months prior to admission, at which time he had been placed on budesonide 9 mg/day, in addition to mesalamine and azathioprine, which he was already receiving. Weight and height were both well below the 3rd percentile (body mass index, 18.5). Physical examination was normal except for papilledema. Blood pressure was 100/60 mm Hg. Hemoglobin was 13.4 g/dL, and albumin was 3.8 g/dL. Serum iron and vitamin A and D levels were normal. Computed tomography of the brain and sinuses was normal. Cerebrospinal fluid opening pressure was 28 cm H_2O, cerebrospinal fluid glucose was 52 mg/dL, and protein was 23 mg/dL, with 1 cell/μL. He received acetazolamide with symptomatic improvement. Papilledema was slow to resolve. Magnetic resonance imaging of the brain was normal.

Discussion

Many predisposing factors have been associated with benign intracranial hypertension in the pediatric population. Acute and chronic diseases, endocrine disorders, medications, and obesity have all been linked to benign intracranial hypertension[3–13] (Table 1). Nevertheless, in most cases, a predisposing factor cannot be discerned.[5,8] Corticosteroid therapy has also been described in association with benign intracranial hypertension, which may occur during active treatment or during medication withdrawal.[6–8]

We present three patients with inflammatory bowel disease and benign intracranial hypertension that developed during oral budesonide therapy. Although a lumbar puncture was not performed on case 2 during the acute episode, the onset of acute persistent severe headache with resolving papilledema, normal blood pressure, and a normal contrast CT scan makes this diagnosis likely.

Multiple confounding factors could be related to the appearance of benign intracranial hypertension in patients with inflammatory bowel disease, such as iron deficiency anemia or vitamin D deficiency. Two of our patients were not anemic at presentation, and vitamin D levels were normal in all three. We cannot exclude iron deficiency anemia as a contributing etiologic factor for benign intracranial hypertension in case 1.

Hypervitaminosis A can occur due to vitamin supplementation. However, the only patient receiving supplementation had a normal serum vitamin A level. Adrenal insufficiency due to pituitary-axis depression was excluded by a corticotropin stimulation test performed in two of the patients, making this an unlikely mechanism. Behçet's disease can mimic Crohn's disease and cause benign intracranial hypertension; however, diagnostic criteria such as uveitis, genital ulcers, or pathergy were absent in our patients.[16] Common denominators in all patients in this study were the presence of Crohn's disease and treatment with mesalamine and budesonide. All three patients had received prednisone in the past without developing headache, and none were in the withdrawal phase of steroid therapy.

Crohn's disease itself could theoretically be a risk factor for benign intracranial hypertension. It has been associated with central nervous system manifestations including venous and arterial thrombosis and vasculitis.[17] However, previously reported cases of benign intracranial hypertension occurring in inflammatory bowel disease have been related to corticosteroid therapy. Both Liu et al[6] and Newton and Cooper[7] described multiple cases occurring during prednisone therapy or taper in patients with inflammatory bowel disease, including one patient with multiple episodes of benign intracranial hypertension on corticosteroid withdrawal. None of these patients were receiving mesalamine at the time.

Hence, it is very likely that our patients developed benign intracranial hypertension due to the corticosteroid therapy they were receiving at the time, namely budesonide. Oral budesonide is a potent corticosteroid with a low systemic bioavailability of 10%. It is efficiently metabolized during first-pass metabolism, and its by-products are nearly inactive; therefore, it is often considered a form of topical intestinal therapy.[1] These characteristics allow a superior side-effect profile in comparison with standard corticosteroid therapy. This has been validated in several studies.[18,19]

It is unclear why a topical corticosteroid with low systemic bioavailability might cause benign intracranial hypertension. An unexplained increase in absorption, decrease in first-pass effect, or difference in patient population could all explain increased bioavailability. Although this may seem inconsistent with the fact that glucocorticoid side effects were not present and the pituitary-adrenal axis was not suppressed, it is not clear that they need to be evident during corticosteroid-induced benign intracranial hypertension. Case 1 had concurrent liver disease, which, theoretically, may have altered first-pass metabolism.

Table 1. Conditions Associated With Benign Intracranial Hypertension

Endocrine disorders
Adrenal insufficiency
Hyperadrenalism
Hypoparathyroidism
Obesity
Obstruction to venous drainage
Cerebral venous sinus thrombosis
Aseptic (hypercoagulability)
Septic (otitis media or mastoiditis)
Increased right heart pressure
Trauma to jugular veins
Medications
Amiodarone
Aspirin
Corticosteroids (mostly withdrawal)
Cyclosporine
Growth hormone
Levothyroxine
Lithium
Methylphenidate
Nalidixic acid
Sulfa antibiotics
Tetracyclines
Vitamin A
Vitamin D
Other conditions
Antiphospholipid antibody syndrome
Behçet's disease
Human immunodeficiency virus
Iron deficiency
Sleep apnea
Systemic lupus erythematosus
Turner's syndrome

One possible explanation may have to do with the patient population treated. Our patients were adolescents and had significantly low weight for age. Two patients had poor nutritional status at the onset of treatment and were hypoalbuminemic. Budesonide is bound to albumin and is considerably more lipophilic than prednisone. In the presence of hypoalbuminemia, the volume of distribution may have decreased, thus leading to higher availability for central nervous system penetration. Although less may be absorbed into the systemic circulation, budesonide has a glucocorticoid receptor affinity 21 times greater than that of methylprednisolone,[20] and the glucocorticoid receptor concentration is high in the brain.[21] The relationship, if any, between corticosteroid dose and benign intracranial hypertension is unclear at present.[6,7]

The mechanisms leading to benign intracranial hypertension are still enigmatic. The process by which corticosteroid drugs raise intracranial pressure is unknown. This puzzling situation becomes even more confusing by the fact that corticosteroids are also effective in the treatment of benign intracranial hypertension.[2,5]

Although the pathogenesis of increased intracranial pressure in benign intracranial hypertension has not been established, several potential mechanisms have been proposed. Studies of cerebral white matter in two patients with benign intracranial hypertension who died unexpectedly showed no evidence of any type of cerebral edema.[5] Mann et al found increased resistance to cerebrospinal fluid outflow, possibly due to impaired absorption by the arachnoid villi.[22]

Elevated venous pressure appears to play an important role in diminishing cerebrospinal fluid outflow.[23] More recently, impaired lymphatic drainage has also been implicated.[24] Finally, the finding of elevated vasopressin in the cerebrospinal fluid but not in the serum of patients with benign intracranial hypertension raises the possibility that brain water transit may also be altered in these cases.[5]

Whatever the mechanism may be, it appears that oral budesonide may be capable of causing benign intracranial hypertension in children with inflammatory bowel disease. Prospective studies involving children with inflammatory bowel disease and close follow-up of children receiving inhaled budesonide should cast further light on the incidence and significance of this phenomenon. Until these data become available, physicians should be aware of this potential adverse effect and thoroughly evaluate children who develop headache while on budesonide. It may be prudent to reduce the dose in malnourished or small children receiving prolonged therapy.

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Acute Necrotizing Encephalopathy Presenting as a Basal Ganglia Syndrome

ABSTRACT

Acute necrotizing encephalopathy is a relatively new disease. The characteristic clinical findings are of febrile illness followed by rapid deterioration in mental status and seizures. The hallmark of the disease is multifocal bilateral symmetric lesions affecting the thalamus, hypothalamus, brainstem tegmentum, cerebral white matter, and cerebellum. The etiology is unknown, but immune-mediated mechanism was suggested. We present a 12-year-old previously healthy girl who developed increased sleepiness progressing to stupor and coma. Magnetic resonance imaging (MRI) of the brain showed the characteristic findings previously described in acute necrotizing encephalopathy. Her mental status improved dramatically with steroid treatment, and the MRI findings resolved completely within 6 months. Following the acute illness, she developed a complex neuropsychiatric disorder consistent with basal ganglia syndrome. (*J Child Neurol* 2001;16:461–462).

We describe a case of a previously healthy 12-year-old girl who presented with a 3-week history of progressive sleepiness culminating in stupor and coma. Magnetic resonance imaging (MRI) of the brain showed a hyperintense signal involving the midbrain, hypothalamus, thalamus, caudate, and lenticular nuclei bilaterally. This picture was previously described as characteristic of acute necrotizing encephalopathy, a new disease entity proposed by Mizuguchi et al in 1995.[1] Stereotactic biopsy of the caudate showed inflammatory changes. The clinical outcome was consistent with a neuropsychiatric syndrome manifested by transient hemiparesis, chorea, jerky involuntary movements, preservative speech, echolalia, obsessive-compulsive symptoms, poor insight, attention deficit and hyperactivity, impulsiveness, poor judgment, and hypersexuality. Such symptoms were recently described as basal ganglia syndrome.[2] Although the acute illness improved with steroid treatment and the MRI findings resolved, the behavioral problems characteristic of basal ganglia syndrome persist.

Case Report

A 12-year-old African-American girl with no significant past medical history presented with mild fever and diarrhea, progressively increasing sleepiness, and tiredness of 3 weeks' duration, prompting her admission to the hospital. On admission, she was afebrile, sleepy, but arousable to painful stimuli. The examination revealed bilateral ptosis, brisk reflexes, ataxia, and retropulsion. She rapidly deteriorated to stupor and coma over the next few days. Laboratory findings showed blood glucose 83 mg/dL, glutamic-pyruvic transaminase 64 U, glutamic-oxaloacetic transaminase 83 U, ammonia 43 μmol/L, lactate 2.1 μmol/L, and normal vitamin B_{12}. The cerebrospinal fluid showed normal glucose, no pleocytosis, and protein of 64 mg/dL. Viral cultures and titers (IgM) for influenza, measles, cytomegalovirus, Epstein-Barr virus, mycoplasma, and herpes virus as well as Lyme titer, were all negative in blood and cerebrospinal fluid. C3 and C4 levels were normal; antinuclear antibody and anti-DNA antibodies were negative. Magnetic resonance imaging of the brain showed a hyperintense signal involving the midbrain, hypothalamus, anterior commissure, thalami, caudate, and lenticular nuclei bilaterally on the fluid-attenuated inversion-recovery sequence, initially interpreted as an infiltrative glioma (Figure 1).

The patient was treated with acyclovir and intravenous antibiotics pending results of cultures, with no clinical improvement. A stereotactic brain biopsy showed hemorrhagic tissue with chronic inflammatory cell and microglia. No organisms were seen or cultured. A therapeutic trial with corticosteroids was associated with a significant improvement in mental status, level of arousal, and the patient's ability to care for herself. Her clinical course was marked by a mild left hemiparesis, choreiform movements, jerky motions (left more than right), restlessness, and difficulty concentrating and processing sequential commands but no difficulty with computations. Echolalia, preservative speech, and obsessive-compulsive features were present. She was discharged home on 40-mg prednisone a day with instructions for gradual taper of the medication. On discontinuation of corticosteroids, her behavior deteriorated dramatically, even though the MRI findings showed progressive resolution. She developed an increase in involuntary choreiform and jerky movements, severe agitation, auditory hallucinations, aggressive striking out behavior, poor judgment and insight, and hypersexuality requiring hospitalization in a psychiatric facility.

A therapeutic trial with intravenous IgG for 5 days showed no change in symptomatology. She was treated with risperidone. Clonazepam and guanfacine hydrochloride did not fully control her symptoms, prompting the restart of corticosteroids, which were eventually discontinued after 6 months.

Discussion

Acute necrotizing encephalopathy of childhood is a newly proposed disease entity characterized by symmetrically distributed brain

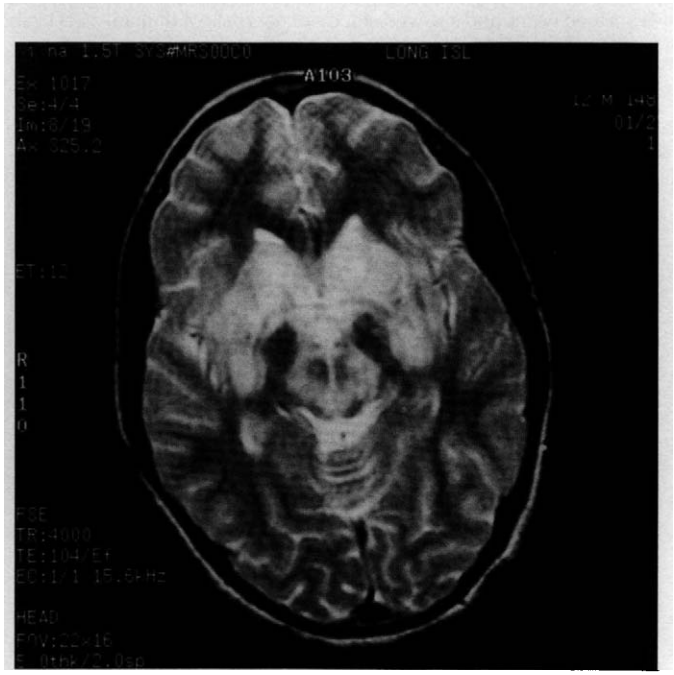

Figure 1. Axial fluid-attenuated inversion-recovery image from brain MRI revealing confluent hyperintense signal within the midbrain, hypothalamus, thalami, caudate, and lentiform nuclei bilaterally.