Pseudotumor Cerebri in Children With Sickle Cell Disease: A Case Series

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ABSTRACT. Headache is a frequent symptom in sickle cell disease (SCD) that usually is attributable to anemia or cerebrovascular disease. We report 3 pediatric patients with SCD (1 patient with SCD-SC and 2 patients with SCD-SS) who presented with headache and were diagnosed with pseudotumor cerebri (PC). All 3 patients had elevated opening pressures during a lumbar puncture with normal cerebrospinal fluid studies. Magnetic resonance imaging revealed no evidence of hydrocephalus or arteriopathy in all 3 cases. Magnetic resonance venograms performed in 2 of the patients at diagnosis revealed no evidence of cerebral sinus thrombosis. Each patient received a thorough ophthalmologic examination. A diagnostic funduscopic examination revealed bilateral papilledema without signs of retinopathy in all 3 patients. There were no clinically significant changes in visual acuity or abnormalities of color vision in any patient. Goldmann or Humphrey visual-field assessment was abnormal only in patient 1, who demonstrated bilaterally enlarged blind spots at diagnosis and later developed reduced sensitivity in the inferomedial quadrant of the left eye in an arcuate pattern (which later resolved). The diagnosis of PC was made in all 3 patients, and acetazolamide treatment was started. Two of the patients' symptoms resolved completely with medical treatment, whereas the third patient's symptoms improved. None of these patients had permanent visual-field deficits as a result of their syndrome. PC has been reported in several other types of anemia including SCD-SC, but these cases are the first reported in conjunction with pediatric SCD. Early recognition of the signs and symptoms of PC in patients with SCD who present with headache can expedite proper diagnosis and treatment and prevent long-term neurologic sequelae. Pediatrics 2004;113:265–269. URL: http://www.pediatrics.org/cgi/content/full/113/3/265; pseudotumor cerebri, sickle cell disease, anemia, headache.

ABBREVIATIONS. SCD, sickle cell disease; MRI, magnetic resonance imaging; PC, pseudotumor cerebri; CSF, cerebrospinal fluid; SC, hemoglobin SC; TCD, transcranial Doppler ultrasonography; MRA, magnetic resonance angiography; SS, hemoglobin SS.

Sickle cell disease (SCD) is a hereditary disorder of hemoglobin affecting 1 in 400 African American births.1 Cerebrovascular disease is a common cause of morbidity and mortality in SCD.2–5 Approximately 10% of SCD patients will have a clinical stroke by the age of 20 years,6 and an additional 22% can have a clinically silent stroke detected by magnetic resonance imaging (MRI).7,8 Regardless of whether it is clinically evident, stroke in SCD can cause neurocognitive deficits and associated learning impairment.9

The most common ophthalmologic complications of SCD include retinopathy,10,11 vitreous hemorrhage,11 retinal artery occlusion,10,12,13 When considered together, ophthalmologic and neurologic complications comprise a large portion of the complications of SCD.

Pseudotumor cerebri (PC), or benign intracranial hypertension, is a rare syndrome defined by increased intracranial pressure in the absence of a space-occupying lesion or apparent obstruction to the cerebrospinal fluid (CSF) pathway. Patients with this syndrome have a normal CSF evaluation and a nonfocal neurologic examination.14–16 There are several case reports of the association of PC in children with medications17 and various systemic conditions including pregnancy,18 disorders of coagulation,19 collagen vascular disease,20 nutritional derangements,21 endocrinopathies,22 infection,23 cerebral sinus thrombosis,24 and a variety of other miscellaneous conditions.25 There also have been reports of PC in various forms of anemia including acquired aplastic anemia,26 iron-deficiency anemia,27,28 paroxysmal nocturnal hemoglobinuria,29 megaloblastic anemia,30 pernicious anemia,31 and SCD-SC.32 We discuss herein 3 children with SCD who were diagnosed with PC. To our knowledge, these cases are the first reported instances of PC in children with SCD in the absence of sagittal sinus thrombosis.

CASE REPORTS

Patient 1

An obese 9½-year-old girl with SCD-SC presented with worsening headache, blurred vision, and photophobia of 3 days' duration. She had no fever or signs or symptoms of head trauma. Her clinical course included frequent hospitalizations for vasoocclusive pain crises, pneumonia, acute chest syndrome, and multiple splenic sequestration episodes eventually requiring splenectomy. She began treatment with hydroxyurea at the age of 8½ years and developed headache a few months later. There was no family history of headaches or migraines. A neurology consultation diagnosed left frontal migraine. Neuroimaging, including transcranial Doppler ultrasonography (TCD), MRI, and magnetic resonance angiography (MRA), was negative for acute changes and/or arteriopathy. Her headaches were treated with varying degrees of success over the next several months with a combination of nonsteroidal and narcotic medications. Six months later, she presented to the sickle cell clinic with severe headache, blurred vision, and photophobia. Ophthalmologic examination revealed...
bilateral papilledema. Pupils were sluggish without an afferent pupil defect with a best-corrected vision of 20/30 (right) and 20/25 (left). Goldmann visual-field tests showed bilateral blind-spot enlargement. Computed tomographic head imaging, MRI, and MRA did not reveal hydrocephalus, stroke, or venous thrombosis. A lumbar puncture was performed. The CSF protein, glucose, and cell count were normal, but the opening pressure was 44.5 cm H2O (normal: ≤20 cm H2O). Her hemoglobin was 9.3 g/dL (baseline: 9–10 g/dL). A diagnosis of PC was made, and she was prescribed oral acetazolamide at a dose of 8 mg/kg per day. A few weeks later, her acetazolamide dose was increased to 10 mg/kg per day due to persistent complaints of headache. Once her eye examination returned to normal, the acetazolamide was discontinued on a taper schedule. Within a few weeks of discontinuation, the patient redeveloped headaches and papilledema. At this point, a Humphrey visual-field test showed bilateral enlarged blind spots with decreased central sensitivity of the right eye (Fig 1) and an inferior arcuate defect of the left eye (Fig 2). Visual acuity and pupils were normal. Her acetazolamide dose was titrated up to 20 mg/kg per day. She continues on a weaning dose of acetazolamide, and, at the time of this review, she has been treated for a total of 10 months (current dose: 8 mg/kg per day). Follow-up MRI, MRA, and noncontrast magnetic resonance venography (MRV) did not reveal any structural abnormality, arteriopathy, or venous thrombosis. Her hydroxyurea was discontinued recently after she presented with complaints of severe headache, and she was found to have papilledema on funduscoppy. Follow-up lumbar puncture revealed a significantly elevated opening pressure (45 cm H2O).

Patient 2
An 8½-year-old girl with SCD-SS disease presented with blurred vision and difficulty reading small print of 1 day’s duration. Her SCD history involved multiple hospitalizations for vasoocclusive pain crises, pneumonia, and acute chest syndrome. She also had a history of focal segmental glomerulonephropathy, presumably secondary to her underlying sickling syndrome. On funduscopic examination she had bilateral papilledema. Ophthalmologic examination confirmed papilledema, with normal retinal periphery and without features of sickle retinopathy. Visual acuity was best corrected to 20/20 in each eye with intact color vision and normal pupillary responses. Her hemoglobin was 8.4 g/dL (baseline: 8–9 g/dL). Computed tomographic imaging and MRI of her brain (including MRA and noncontrast MRV) were normal, with no signs of cavernous sinus thrombosis. A lumbar puncture was performed with an opening pressure of 29 cm H2O. Baseline blood pressure was 116/63 (high-normal for age and height). A diagnosis of PC was made, and she was started on acetazolamide at a dose of 15 mg/kg per day. Her headaches and visual complaints resolved. She was taken off the acetazolamide after 3 months of treatment. Follow-up eye examination 2 months later was normal without optic atrophy.

Patient 3
A 16-year-old girl with SCD-SS disease was admitted for extremity pain and severe headache. Her previous SCD history included numerous hospitalizations for vasoocclusive pain crises. For an abnormal TCD at the age of 9 years, she was enrolled in the stroke-prevention trial in SCD (STOP trial)5 with a randomization to the red blood cell transfusion arm. She was transfused monthly to maintain her hemoglobin S percentage <30% for 4½ years, and she required iron chelation therapy with deferoxamine. The transfusions were discontinued on the STOP II trial after normal TCD, MRI, and MRA examinations. Previous ophthalmologic examinations had been normal. At the time of her hospitalization, she had been having sporadic headaches over a period of several months. Her hemoglobin was 6.6 g/dL (baseline: 7–8 g/dL). Papilledema was noted bilaterally on funduscopic examination (Fig 3). Vision was 20/20 in each eye with intact color vision for 12/12 Ishihara color plates and intact pupillary responses. Subsequent MRI, MRA, and noncontrast MRV of her head were normal except for a small Arnold-Chiari I malformation, and there was no evidence of cavernous sinus thrombosis. The patient underwent lumbar puncture with an opening pressure elevated at 36 cm H2O. A diagnosis of PC was made. Acetazolamide treatment was initiated.

Fig 1. Patient 1: right eye. Automated Humphrey 30-2 visual-field test demonstrating an enlarged blind-spot size. The optic nerve is the area of the fundus without photoreceptors, and therefore the optic nerve appears as a "blind spot" on normal visual-field testing that increases in size with a swollen optic nerve from papilledema.

Fig 2. Patient 1: left eye. Automated Humphrey 30-2 visual-field test shows blind spot and reduced sensitivity in the inferomedial quadrant in an arcuate pattern, presumably secondary to increased retinal edema.

Fig 3. Patient 3: right eye. Moderate disk edema and hyperemia are present, as is typical in papilledema.
at a dose of 15 mg/kg per day, and the patient had rapid symptomatic relief from her headaches. After a few weeks of acetazolamide treatment, her dose was increased to 19 mg/kg per day. After ~9 months of medical treatment, she is maintained on her lower, original dose of 15 mg/kg per day.

**DISCUSSION**

PC is a rare condition characterized by increased intracranial pressure and normal CSF examination in the absence of a space-occupying lesion or obstruction to the CSF pathway. The most common presenting symptom is papilledema, but other frequent manifestations include headache, diplopia (from cranial nerve VI palsy), nausea and/or vomiting, altered light perception, and decreased visual acuity. Potential peripheral visual-field deficits or vision loss give significance to the early diagnosis of PC. Medical management with acetazolamide or furosemide is successful in most cases of PC. Symptoms occasionally can resolve spontaneously. Other medical treatments used with anecdotal success include corticosteroids and glycerol. Serial lumbar punctures are therapeutic but not a long-term option. With progressive visual changes, surgery is considered.

PC has been reported in several medical conditions and in various forms of anemia including acquired aplastic anemia, iron-deficiency anemia, paroxysmal nocturnal hemoglobinuria, megaloblastic anemia, pernicious anemia, SCD-SC, and now in SCD-SS. The mechanism of the development of idiopathic intracranial hypertension in the face of anemia is unclear, but several theories have been posited. It has been suggested that anemia itself causes the production of CSF to be increased, but that mechanism is unclear as yet. Other theories suggest the possibility of anemia and tissue hypoxia causing altered cerebral hemodynamics and increased brain capillary permeability, which could lead to papilledema and increased intracranial pressure. Any or all of these mechanisms could increase the risks for PC in SCD. Although the symptoms of PC abated with correction of the acquired anemias (ie, iron-deficiency anemia), the symptoms and eye examinations improved or resolved in the 3 patients we report regardless of the presence of their chronic anemia.

There is a known association between obesity and the development of PC, but the etiology of this relationship remains unclear. Two recent pediatric case series of PC report obesity in 59% to 70% of patients. Patient 1 in our case series is obese, with a body mass index of 26.6 kg/m² (95th percentile for age: 22.5 kg/m²). It is interesting to note that this patient has had the most difficulties in decreasing her dose of acetazolamide and has required 2 therapeutic lumbar punctures for treatment of her symptoms of PC.

One factor that could be contributing to the difficult clinical course of patient 1 is her hydroxyurea regimen, which was started 1 year before the onset of PC due to her unusually clinically severe medical course. Normally, hydroxyurea is not prescribed to patients with SCD-SC because of their milder disease course relative to that of SCD-SS. Hydroxyurea is used widely in patients with SCD to increase the percentage of fetal hemoglobin in the erythrocyte, thereby decreasing the percentage of hemoglobin S, and thus diminishing the degree of erythrocyte sickling and resultant end-organ damage. Hydroxyurea also increases a patient’s red blood cell mass by increasing the intracellular hemoglobin concentration. This process could lead to increased blood viscosity, because patients with SCD-SC are thought to have higher baseline blood viscosities than patients with SCD-SS. In the face of poor cerebral vessel autoregulation in SCD patients, such elevated blood viscosity feasibly could lead to decreased cerebral oxygenation and a perpetuation of the mechanisms that give rise to headache and PC in patients with SCD. Therefore, in a patient with SCD and PC who is taking hydroxyurea and is not symptomatically improving with respect to PC, decreasing or discontinuing the patient’s hydroxyurea should be considered as a possible therapeutic option, as was done in patient 1.

Acetazolamide, a carbonic anhydrase inhibitor, is the main medical modality used for the treatment of PC. The mechanism of action of carbonic anhydrase inhibitors is to block the dehydration of carbonic acid into water and carbon dioxide. As a result, H⁺ and bicarbonate ion are produced. The secretion of CSF is thought to be highly dependent on this process, and acetazolamide has been shown to decrease the production of CSF secondary to its inhibitory effect on the carbonic anhydrase reaction. Other studies have demonstrated that increased tissue partial pressure of carbon dioxide and a subsequent reduction in pH can increase retinal perfusion pressure, red cell velocity, and retinal vessel dilatation after the administration of acetazolamide. This process could serve to decrease papilledema and retinal artery occlusion in patients with ophthalmologic complications of various conditions including SCD.

It is worthwhile to note that carbonic anhydrase inhibitors also are used to enhance diuresis secondary to an amplified osmotic effect of increased sodium bicarbonate production in the renal tubules. Patients with SCD have an impaired ability to concentrate urine due to microvascular infarctions in the kidney and subsequent renal tubular dysfunction with increased excretion of sodium and retention of potassium. Therefore, carbonic anhydrase inhibitors should be used with caution in patients with SCD because of the deleterious effects of dehydration on sickle erythrocytes. Before starting patients with SCD on acetazolamide, baseline serum electrolytes should be obtained. Once treatment has been initiated, increased fluid intake is recommended, and serum electrolytes should be monitored. The 3 patients in our case series had normal baseline and follow-up serum electrolytes, and they did not incur problems with dehydration or excessive sickling crises.

Vision loss can be severe and permanent in PC when patients do not respond to acetazolamide. Regular ophthalmology examinations need to be scheduled to follow optic-disk swelling, visual acuity, color vision, pupillary responses, and serial vi-
sual-field tests to determine response to treatment. If progressive vision or visual-field loss occurs while on maximal medical treatment, optic nerve sheath fenestration or lumbar-peritoneal shunt may be required. The aforementioned 3 cases responded to medical treatment alone. It is noteworthy that papilledema returned in patient 1 after the acetazolamide taper, and she required 2 subsequent lumbar punctures to alleviate her symptoms.

In addition to being a common symptom of PC, headache is also a common complaint of SCD patients. It is unclear as to whether the headache is anemia-related, stress-related, or a consequence of an as-yet-unknown factor that predisposes this population of patients to headache. One model suggests that the anemia of SCD causes a compensatory cerebral hyperemia and hypervolemia. In the presence of poor cerebral vessel autoregulation seen in sickle cell patients, the cerebral vessels vasodilate but do not increase blood flow. Such cerebral vasodilatation is well known to cause headaches. In addition, abnormalities in cerebral perfusion, as measured by perfusion magnetic resonance studies, have been shown to be correlated with several neurologic sequelae of SCD, including headache. The abnormalities demonstrated on such perfusion imaging studies are irrespective of the TCD, MRI, MRA, and MRV results.

These 3 cases demonstrate that complaints of severe headache in patients with SCD who have normal neuroimaging studies can be related to the development of PC. Prompt evaluation of a patient PC by an ophthalmologist and a neurologist and with appropriate, emergent, cerebral imaging (such as MRI, MRA, MRV, and/or perfusion MRI) to rule out infarction or cerebral venous thrombosis can avoid long-term ophthalmologic deficits. PC responds well to carbonic anhydrase inhibitors, but these drugs should be used with caution in patients with SCD secondary to their diuretic effects.

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