WHAT IS YOUR CALL?

Meningeal signs and facial edema in a child with sickle cell disease

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A five-year-old girl with sickle cell disease presented with a two-day history of left frontal headache and mild fever. There were no signs of toxicity, and the patient was hemodynamically stable. Her rectal temperature was 39.5°C. Marked nuchal rigidity was noted. Palpation of the dorsal vertebrae caused mild pain. There were no focal neurologic signs. The patient had been admitted to hospital several times for episodes of fever associated with pneumonia and urinary tract infections, but she had no history of vaso-occlusive crisis.

Laboratory tests showed a hemoglobin level of 51 (normal 115–135) g/L, a leukocyte count of 19.4 (normal 5.5–15.5) $\times 10^9/L$, and a neutrophil count of 13.9 (normal 1.5–7.1) $\times 10^9/L$. Cerebrospinal fluid obtained by lumbar puncture yielded a leukocyte count of 2.0, a erythrocyte count of 1.0 $\times 10^6/L$ and normal levels of glucose and protein.

Figure 1: Computerized tomography scan of the brain in a five-year-old girl with sickle cell disease showing infiltration of the subcutaneous fat of the left hemiface extending into the left occipital and parietal regions (arrow).

Morphine was prescribed and, despite the absence of a specific cause of the fever, treatment with intravenous ceftriaxone was started, pending results of cultures. Over the next four to six hours, a nonpainful pitting edema was seen in the left palpebral and frontoparietal regions. There was no proptosis, and the ocular movements were normal. The skin was not red or warm over the edematous zone.

What is the next step?

- Computed tomography scan of the brain
- Diagnostic puncture of the swollen region
- Radiography of the sinuses
- Doppler ultrasonography of the cervical vessels
- Bone scintigraphy

Tests (a) and (e) were performed. A computerized tomography scan of the brain showed normal parenchyma, but there was an infiltration of the subcutaneous fat of the left hemiface extending into the subcutaneous tissue of the left occipital and parietal regions (Figure 1). Bone scintigraphy of the cranial vault showed areas of decreased activity in the frontal and parietal bones compatible with infarcts (Figure 2). Bone scintigraphy of the spine showed decreased activity in the region of T5 and possibly T8.

What is your diagnosis?

- Cervical spine osteomyelitis
- Peri-orbital cellulitis
- Cerebral sinovenous thrombosis
- Bacterial meningitis
- Vaso-occlusive crisis of the cranial vault and dorsal spine

The diagnosis is (e), vaso-occlusive crisis of the cranial vault and dorsal spine. The child received a transfusion of packed red blood cells. Narcotics were given to control pain, and ceftriaxone was continued until the fever disappeared. Bacterial cultures of cerebrospinal fluid and blood gave negative results. The nuchal rigidity and fever resolved gradually over

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Figure 2: Bone scintigraphy of the cranial vault showing decreased activity in the frontal and parietal bones compatible with infarcts.

seven days. The swelling of the left side of the face had disappeared by the patient's eighth day in hospital. On the ninth day, radiography of the skull showed thickening of the cranial vault related to sickle cell disease but was otherwise normal. The child was discharged from hospital 10 days after admission.

Discussion

Sickle cell disease results from the presence of abnormal β chains in hemoglobin. It is one of the most common autosomal recessive diseases, affecting millions of people in West and Central Africa, South America, Central America, India and Mediterranean countries. The gene that causes the disease is particularly prevalent in people of African origin. Approximately 8% of African-American people are heterozygous and 1 in 600 is homozygous for the gene. Although reliable data for Canada are scarce, it is estimated that 2000 to 3000 children in this country have sickle cell disease.

Acute painful episodes from vaso-occlusive crises are the most common manifestations of sickle cell disease; they occur most frequently in the lumbar spine, abdomen, femur, knees and sternum¹ but can affect any bone with active marrow. Dactylitis, often referred to as hand-foot syndrome, is often the first manifestation of vaso-occlusive crisis in children with sickle cell disease, occurring in 50% of children before two years of age. The vulnerability of the bone marrow to microvascular occlusion may be due to the anatomically confined space and hypercellularity of the marrow. Flat bones are less commonly infarcted, probably because of their many nutrient vessels.²

Box 1: Differential diagnosis of nuchal rigidity in children with sickle cell anemia*

Bacterial meningitis

- The two predominant clinical patterns are sudden onset with rapidly progressive manifestations of shock and reduced level of consciousness over a few hours; more often, increased lethargy, fever and irritability develop over a few days.
- Diagnosis is based on analysis of cerebrospinal fluid. Positive results of blood culture are found in 80%–90% of children with meningitis.

Retro- or parapharyngeal cellulitis or abscess

- Condition is more common in early childhood (< 3–4 years of age).
- Generally accompanied by abrupt onset of fever, difficulty swallowing and refusal to eat.
- Lateral radiograph of the neck shows retropharyngeal mass; computed tomography scan may confirm diagnosis.

Acute tonsillitis

- Symptoms include odynophagia, fever, dysphagia, referred otalgia and headache; nuchal rigidity uncommon.
- Most episodes are caused by viruses; group A *B-hemolytic streptococcus* is the most common cause of bacterial tonsillitis.

Acute cervical adenitis

- Uni- or bilateral infection is frequent in children.
- Bilateral cervical adenitis is most commonly caused by systemic viral infection; acute unilateral cervical adenitis is most commonly caused by infection with *Staphylococcus aureus* or group A streptococcus. Acutely infected nodes are usually tender, and local erythema is seen often.
- Diagnosis is clinical.

Cervical spine osteomyelitis

- Condition is very uncommon.
- Children with sickle cell disease are more susceptible than healthy children.

Infarction of cervical spine or cranial vault

- Condition is very uncommon and is almost specific to sickle cell disease and seen in the context of a vaso-occlusive crisis.

*Also includes viral meningoencephalitis, subarachnoid hemorrhage, fracture of the cervical spine, torticollis and myositis. Children with sickle cell disease are at no higher risk of these disorders than the healthy population.

Acute infarction of the skull bone (calvarial infarction) is an uncommon complication of sickle cell disease. It could involve the cranial vault, as in our patient, but also the facial bones and orbits.³ Headache related to calvarial infarction may originate from pain-sensitive structures such as the skull, dura, periosteum and extracranial arteries.⁴ Local meningeal inflammation can cause meningismus. The infarction may also be associated with pitting scalp edema.⁴ In our patient, the infiltration of the subcutaneous fat over the left hemiface was found to be edema of the subcutaneous tissue caused by the infarction. Bone infarction is self-limiting, and only conservative treatment is usually required. However, infarctions at these sites may cause subperiosteal or epidural hematomas or even abscesses,³ complications that can be life- or sight-threatening and may require urgent decompression.³

Box 2: Management of acute febrile illness in a child with sickle cell disease*

- Assess patient in hospital if temperature > 38.5°C (rectal) or > 38°C (oral); give oxygen as needed.
- Proceed to:
 - rapid triage and physical examination
 - standard blood work (complete blood count, reticulocyte count, blood cultures), urinalysis and culture, and chest radiograph as soon as possible
 - analysis of cerebrospinal fluid and other cultures according to clinical manifestations
- Exclude septic arthritis, osteomyelitis, cholecystitis if signs and symptoms are relevant.
- Immediately prescribe broad-spectrum parenteral antibiotics.

*This aggressive approach is usually not indicated in patients without sickle cell disease, except in critically ill children or in those with immune deficiency (e.g., severe neutropenia).

The spine is the area most commonly involved in vaso-occlusive crisis.⁵ The lumbosacral level is affected in two-thirds of patients, and the thoracic level in approximately 20%.⁵ Signs of spinal vaso-occlusive crisis — mostly local tenderness and a decreased range of motion in the spine — have been reported only in small series.⁵ That infarctions of the cranial vault and the thoracic spine were observed simultaneously in our patient is not surprising; in the classic description of vaso-occlusive crisis by Serjeant and colleagues, multiple sites of bone infarction occur in 79% of patients.¹ Indeed, in a patient with sickle cell disease, the presence of many sites of pain reinforces the possibility of vaso-occlusive crisis rather than a primary infectious process.

Diagnostic testing

Radiologic techniques may be helpful in patients for whom the diagnosis is in question or when it seems necessary to exclude infectious processes. A bone scan may show the three-stage process that occurs in infarction.⁶ Variability of the scan images depends on the interval between the onset of symptoms and the time of the scan.⁶ Stage 1 (about 48 hours after onset of symptoms), shows decreased tracer activity in the area of the infarction; stage 2 (about 1 week after onset) shows normal uptake; and stage 3 (2–4 weeks after onset) shows increased uptake. A bone marrow scan or magnetic resonance imaging may be more sensitive in identifying bone infarction,⁶ but in most instances a bone scan is sufficient.

Differential diagnosis

The two prominent clinical manifestations in our patient were marked nuchal rigidity and facial edema.

In a child with fever, nuchal rigidity is of concern, and meningitis must be ruled out. However, stiffness of the neck is not necessarily the result of meningeal infection, as was the case in our patient. Some extrameningeal infections (e.g., tonsillopharyngitis, cervical adenitis, retropharyngeal abscess and cervical spine osteomyelitis) may also cause neck stiffness (Box 1). In a child with fever, sickle cell disease, neck stiffness and normal cerebrospinal fluid, these infections must be excluded promptly. Indeed, children with sickle cell dis-

Box 3: Differential diagnosis of facial edema in children with sickle cell anemia***Cerebral sinovenous thrombosis**

- In infants older than neonates, the main neurologic manifestations are decreased level of consciousness, headache, focal signs and cranial nerve palsy; dilated veins in the scalp and swelling of the eyelids have also been seen in infants.
- Risk factors depend on the child's age (e.g., dehydration in neonates, infection and hematologic disorders in older infants or children).

Periorbital cellulitis

- Inflammation occurs in the structures superficial to the orbital septum.
- Three common causes are skin infection (i.e., caused by trauma or insect bite), bacteremia and sinusitis; periorbital cellulitis caused by bacteremia is very uncommon in young children as a result of pneumococcal and *Haemophilus influenzae* vaccination.
- Depending on the mechanism involved, the patient may or may not show systematic symptoms.
- Swelling of the eyelids is seen in all patients and is mostly unilateral with skin erythema.

Orbital cellulitis

- Inflammation occurs in the structures deep to the orbital septum; the disorder almost always occurs as a complication of sinusitis.
- A red, swollen eye, proptosis, ophthalmoplegia and pain on movement of the eye are classic manifestations.
- The diagnosis is confirmed by results of computed tomography.
- The infection can result in serious complications, including blindness, meningitis, cavernous sinus thrombosis, subdural empyema and brain abscess.

Acute bacterial sinusitis

- The disorder may occur at any age.
- It typically follows a viral infection in the upper respiratory tract. Patients usually present with nonspecific complaints, including headache, nasal congestion and fever; less common symptoms include a decreased sense of smell and periorbital edema.
- Diagnosis is based mostly on history. Radiography of the sinuses or computed tomography can confirm inflammation but cannot differentiate between its causes (viral or bacterial infection, allergy).

Infarction of skull bones (cranial vault, facial bones and orbit)

- Very uncommon condition that is almost specific to sickle cell disease and seen in the context of a vaso-occlusive crisis.
- Clinical manifestations may differ depending on the site of the infarct (e.g., common presentation for orbital infarction includes prodromal headache, proptosis and edema of the eyelids in a patient who shows no signs of toxicity).

*Also includes trauma and angioneurotic edema; children with sickle cell disease are at no higher risk of these disorders than the healthy population.

ease, mostly those under five years of age, are at higher risk of bacterial infection, which is one of the major causes of illness and death in this population.⁷ All patients with fever and sickle cell disease require rapid triage, urgent blood cultures,

and analysis of cerebrospinal fluid and other cultures as required (Box 2).⁸

In our patient, physical examination showed no evidence of tonsillopharyngitis or cervical adenitis. She was not complaining of sore throat or difficulty in swallowing, which suggested that a retro- or parapharyngeal infection was unlikely. Cervical spine osteomyelitis could not explain the facial edema, and the bone scan images did not support this diagnosis.

Local trauma to the orbits, the facial bones or the skull is a major cause of facial edema (Box 3); in almost all instances, the traumatic nature of the lesions is obvious. There was no history of trauma in our patient. The child was an unlikely candidate for periorbital or orbital cellulitis; she presented with hemiface edema, predominantly on the scalp and not in the periorbital region, and the results of ocular examination were normal. Acute sinusitis can cause periorbital edema, but not edema in the parietal region, as in our patient. Hemiface edema is not a usual clinical manifestation of cerebral sinovenous thrombosis. Angioneurotic edema is usually bilateral and symmetric, and typically involves sites other than the face: the arms, legs, hands, tongue, larynx, genitalia and trunk.

In our patient, the diagnosis was infarction of the cranial vault associated with vaso-occlusive crisis. Bone infarction of the cranial vault is a specific manifestation of sickle cell disease and may lead to an uncommon clinical presentation characterized by fever, neck stiffness and hemiface edema. In retrospect, the fact that our patient showed no signs of toxicity and was hemodynamically stable, despite the fever and nuchal rigidity, could have been an element in favour of a vaso-occlusive crisis. Nonetheless, it is important for clinicians to remember that vaso-occlusive crisis of the cranial vault is very uncommon. It is always a priority to exclude meningitis or other serious extrameningeal infections in a child with fever and nuchal rigidity.

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