Joint pain is a common reason for children and adolescents to seek medical attention. A minority of these children will ultimately be diagnosed with a rheumatologic disease. Although the incidence of childhood rheumatic disease is rare, the long-term consequences of untreated disease are debilitating.

Pediatric rheumatologists understand the challenges for primary care providers to accomplish a comprehensive history and physical exam in a short timeframe. Guardians may not have an appreciation for key symptoms in different environments. Moreover, patients can be reluctant to report symptoms during the visit to avoid further blood tests.

The following three historical elements suggest an inflammatory disease and warrant further investigation:

**Morning stiffness**

Morning stiffness longer than 15 minutes is significant. Since it is not intuitive for families to distinguish stiffness from fatigue or weakness, it is important to recognize the telltale signs that suggest arthritis. For example, parents may say “she walks like an old lady” or “he's lazy until later in the day.” In general, preverbal children might be cranky after naps or prolonged sitting in the car.

**Pain improves with activity**

Pain alleviated by activity is often overlooked, as the guardian needs to observe the patient throughout the day. If the teacher or day-care provider can give input to the family about behavior outside the home, this can help us clarify the pattern of pain not appreciated in the clinic.

(Article continued on next page)
Self-restricting activities

This is a red flag! It is amazing how resilient children are and often modify their activity to avoid what they cannot do. Sometimes they may even do this subconsciously. While this is not specific for rheumatic disease, this detail warrants further inspection. Families may comment on strength or endurance changes, but not necessarily both.

What is PFAPA? by Christos Gabriel, MD

PFAPA is the acronym for a syndrome including recurrent fever with aphthous stomatitis, pharyngitis and cervical adenitis. It is one of the most common recurrent fever syndromes and generally begins between 2 to 5 years of age. Both sexes and all ethnic groups can develop PFAPA. What causes PFAPA is unknown but it is not related to infection or genetic defect. It is an inflammatory process with consistent clinical findings.

Features include abrupt onset of fever (generally ranging from 38.9 to 41.1 c) with associated irritability, sore throat and apthous ulcers. Ulcers occur in 40 to 70 % of patients and are found on the lips and inside the mouth. They can be small and missed and can occur the day before the fever begins. Patients develop sore throat with erythema and sometimes edematous and enlarged painful cervical lymph nodes. These children often complain of headache, abdominal pain, vomiting, diarrhea and generalized muscle and joint pain. The PFAPA episodes occur every 26 to 30 days and last on average 4 to 5 days. Episodes rarely last more than 7 days. Fever lasting 7 days or longer should prompt a search for another diagnosis. Children are completely normal in between episodes.

There are no laboratory tests to confirm the diagnosis. Patients will have elevated inflammatory markers during the acute episodes which result to normal when the child is well. If these markers are consistently elevated, other causes should be considered.

The diagnosis is made if all of the following are present (at any age):

• More than three documented episodes of fever lasting no more than five days and occurring at regular intervals for individual patients’ intervals between attacks are nearly identical within a range of three to six weeks and the symptoms with each episode usually identical
• Throat inflammation plus tender enlarged lymph nodes
• Normal growth and good health between episodes
• Prolongation of symptoms with prednisone

Other possible causes should be considered if there is a low white blood cell count either prior or during the episodes. Atypical symptoms, persistently elevated labs showing persistent inflammation, or a family history of recurrent fever.

The aim of treatment is to control symptoms during the episodes of fever, to shorten the duration of the episodes and to prevent episodes from recourecing. The PFAPA fever usually does not respond well to acetaminophen or nonsteroidal anti-inflammatory drugs. A single dose of steroids (usually prednisone), given when the symptoms first start, has been shown to shorten—and often even end—the episode. These recouercing episodes usually end during the second decade of life. Some patients seem to improve with removal of their tonsils. There is no long-term health danger to the child.

For more information on PFAPA, go to www.rheumatology.org.

Care Coordination: Keys to Success by Matthew Hollander, MD

Rheumatic diseases comprise a heterogeneous group of conditions, including juvenile idiopathic arthritis (JIA). Many of these conditions involve topics requiring communication between primary care physicians and rheumatologists. The following issues are helpful to keep in mind as we co-manage these children and adolescents:

Vaccination status

Our patients often receive immunosuppressive medications such as methotrexate. While on immunosuppressants, patients should not receive live virus vaccines, such as the oral flu vaccine. The immunocompromised child who develops a fever or is unwell should be examined by the pediatrician to exclude an underlying bacterial infection. It is important to note that children taking such agents, including the “biologic” class of anti-tumor necrosis factor (TNF) inhibitors may not run a particularly high fever despite active infection. However, if a patient does have an active infection, the immunosuppressive medications are routinely held until the infection has cleared. The current AAP Red Book is a great reference.

Routine eye exams

We stress routine ophthalmologic exams for disease surveillance and monitoring for medication toxicity. Particular conditions dictate the frequency of these exams. Children with JIA carry a greater risk than the general population for developing inflammation in the anterior chamber, termed uveitis or iritis. Appropriate screening is imperative as the inflammation can present without symptoms of pain, redness or vision changes. Children with the oligoarticular subtype of JIA and are ANA positive are at a particularly high risk, requiring routine eye surveillance every 3 months. Up to 20% of the children with this subtype may develop uveitis at some point in course. Without treatment, potential complications include cataracts, glaucoma, and vision loss. Positive outcomes require early diagnosis and treatment. If a patient followed in Rheumatology complains of “pink eye” have them see their ophthalmologist promptly.

Growth disturbances

Limb length discrepancies must be monitored in growing children with chronic arthritis. Prolonged active disease affecting a knee can result in accelerated growth of the affected leg; disease in the ankles, feet, wrists or hands usually results in local growth retardation.

Arthritis of the temporomandibular joint (TMJ) can be particularly devastating because of the growth plate’s close proximity to the joint space, resulting in micrognathia. TMJ arthritis can present with surprisingly innocuous complaints: adjusting their eating habits to not open their mouth wide as, pain with yawning, headache or ear pain. One quick physical exam feature is s/h should be able to fit fingers 2-4 stacked comfortably between their incisors. Professional secret is it is almost impossible to learn this fact and not test yourself.
Many CSG Divisions routinely see new patients within 2 weeks of referral, however all will work with you to get urgent patients in. For referral information please go to the desired specialty at: www.csgdocs.com/specialties. Click on the ‘Referral Information’ link. There you will find information that will help facilitate a successful referral for your patient.

Founding Partners
Pioneers that remain CSG practicing physicians
Complement Inhibition with PIC1 in Hypoxic-Ischemic Encephalopathy

by Tushar Shah, MD

Brain damage resulting from neonatal asphyxia (hypoxic-ischemic encephalopathy, HIE) has an incidence of 1-2 per 1000 live births, with up to 60% mortality and 25% of survivors left with a significant disability. Virginia has the 17th highest infant mortality rate in the country, with birth asphyxia being an important contributor. Risk of death or disability resulting from HIE is almost 50%, even after treatment with therapeutic hypothermia. Average lifetime costs per person with a significant disability resulting from HIE can exceed 1 million dollars. An adjuvant therapy to hypothermia for HIE could reduce some of these financial, emotional and societal costs of death and disability.

In HIE, there is hypoxic stress to the brain and some initial tissue damage directly from the hypoxia. Upon reperfusion, a much larger region of the brain is damaged (i.e. reperfusion injury). Reperfusion injury has not yet occurred at the time of neonatal resuscitation and can be modulated by hypothermia. Even though several clinical trials have demonstrated that hypothermia improves survival and neurodevelopment in newborns with HIE, it offers only an 11% reduction in risk of death or disability, a decrease from 58% to 47%. There have been multiple mechanisms postulated to contribute to the reperfusion injury and multiple mechanisms postulated for the benefits of hypothermia. However, a successful pharmacological intervention has not been found, yet.

The complement system, an extremely potent inflammatory cascade of the immune system (Fig. 1), which is critical for phagocytic cell recruitment and direct cell lysis, has been shown to play a major role in the pathogenesis of HIE in animal models and human studies. In HIE and other reperfusion injury diseases, complement-mediated inflammation is activated during reperfusion by ischemia neoantigens expressed on the endothelial cells lining blood vessels. Although hypothermia has a beneficial impact on HIE over all, in vitro data from our lab has shown that therapeutic hypothermia temperatures paradoxically increase pro-inflammatory complement activation potentially limiting the benefit, derived via other mechanisms, to the infant brain. These findings suggest that the addition of a complement inhibitory strategy to therapeutic hypothermia would likely further improve the modest benefits of hypothermia alone.

Our lab has developed a compound (Peptide inhibitor of C1, PIC1) that blocks the complement system and potentially reduces brain damage. Our experiments aim to demonstrate decreased brain damage. Our long-term goal is to develop PIC1 as an intervention to decrease mortality and improve neurological outcomes in infants with HIE.

The complement system, an extremely potent inflammatory cascade of the immune system (Fig. 1), which is critical for phagocytic cell recruitment and direct cell lysis, has been shown to play a major role in the pathogenesis of HIE in animal models and human studies. In HIE and other reperfusion injury diseases, complement-mediated inflammation is activated during reperfusion by ischemia neoantigens expressed on the endothelial cells lining blood vessels. Although hypothermia has a beneficial impact on HIE over all, in vitro data from our lab has shown that therapeutic hypothermia temperatures paradoxically increase pro-inflammatory complement activation potentially limiting the benefit, derived via other mechanisms, to the infant brain. These findings suggest that the addition of a complement inhibitory strategy to therapeutic hypothermia would likely further improve the modest benefits of hypothermia alone.

Our lab has developed a compound (Peptide inhibitor of C1, PIC1) that blocks the complement system and potentially reduces brain damage. Our experiments aim to demonstrate decreased brain damage. Our long-term goal is to develop PIC1 as an intervention to decrease mortality and improve neurological outcomes in infants with HIE.

Our lab has developed a compound (Peptide inhibitor of C1, PIC1) that blocks the complement system and potentially reduces brain damage. Our experiments aim to demonstrate decreased brain damage. Our long-term goal is to develop PIC1 as an intervention to decrease mortality and improve neurological outcomes in infants with HIE.

Fig. 1: Hypoxic insult induces expression of neoantigens on the surface of ischemic endothelial cells. These neoantigens are recognized by natural antibodies (IgM) initiating complement activation leading to downstream inflammatory effects. Therapeutic hypothermia temperatures were shown to increase C1 binding, increase opsonization with C4-fragments and C3-fragments, increase C3a and C5a anaphylatoxin generation, and increase eukaryotic cell lysis via membrane attack complex (MAC) formation. Increases in complement functions are shown in red. PIC1 inhibits complement activation at C1 preventing C4 activation and downstream complement effector action (eg. C5a, MAC formation).

Did You Know?

There are 6 Board Certified Pediatric Rheumatologists in the state of Virginia: Children's Specialty Group employs 2 of them right here in the Hampton Roads community!

www.rheumatology.org

Visit www.csgdocs.com for more CSG info!
Seventeen years ago, eight pediatric sub-specialists got together for dinner with the CEO of the pediatric medical practice group at EVMS. They discussed how the practice of medicine was shifting and had concerns regarding their ability to prepare for those changes and continue to grow their clinical practices within the traditional academic environment. While they valued their relationship with EVMS, they felt strongly that the business aspects of their clinical practices should be under their own control and management. They took a bold and innovative approach to radically change their relationship with the medical school. They were quickly joined by 55 other physicians who together created the practice group called Children's Specialty Group (CSG).

CSG, through an affiliation agreement, committed contractually to provide the pediatric subspecialty care to CHKD and also teaching and academic activities to EVMS's Department of Pediatrics, no longer as employees, but as partners. The progressive idea payed off and new and stronger bonds were formed with the medical school. Now 17 years later, CSG is among the largest and most successful multispecialty group practices in Virginia. The EVMS Department of Pediatrics is recognized for excellence in education. There are now more than 80 partners and 170 physicians and mid-level providers, all part of the team. Since its inception, CSG has had 2,852,856 patient encounters including inpatient and outpatient visits.

In the beginning, an executive committee was formed and Dr. Svinder Toor, Child Neurologist, took the helm as president. On June 11th, he was honored with the first CSG Excellence in Physician Leadership Award. This award was created and named after him for his years of dedication to CSG. Suzanne Lavin, CEO of CSG, said, “Dr. Toor embodies the qualities and characteristics of an effective and successful physician leader”. She said his stand out qualities included confidence, collaboration, vision and humility. “He has been an advocate for his colleagues, for his staff, for CHKD, for medical education and of course for his patients and children’s health in general. He’s had the humility to recognize and admit mistakes along the way and the vision to look beyond today and strategize for the future.”

The award was uniquely created by Robin Rogers of the Chrysler Museum of Art Glass Studio in his honor. Dr. Toor said he was very moved by the outpouring of respect and appreciation but added he had been the lucky one. It had been his honor and privilege to serve his colleagues in a leadership capacity. In April, Dr. Toor stepped down as president of CSG but elected to remain on the practice Management Committee as the representative for Neurology. Dr. Toor also serves on the Children’s Health System Board of Directors as a physician representative.