ASK THE EXPERT

Primary CNS Vasculitis in Children

Primary angiitis of the central nervous system in children, which encompasses a spectrum of progressive and nonprogressive large- and small-vessel inflammatory brain diseases, has been linked in recent years to a range of neurologic conditions, such as refractory status epilepticus, movement disorders, severe cognitive dysfunction, optic neuritis, and psychiatric symptoms in previously healthy children, according to Dr. Susanne Benseler, director of the Childhood CNS Vasculitis Program at the Hospital for Sick Children in Toronto.

Although an accurate, timely diagnosis is essential for optimizing neurologic outcomes in this reversible disease, overlapping clinical features with noninflammatory brain conditions can complicate the diagnosis and lead to treatment delays, as well as potentially devastating consequences, Dr. Benseler said at the joint annual meeting of the Canadian Rheumatology Association and the Mexican Congress of Rheumatology.

In this column, Dr. Benseler discusses the management of primary angiitis of the central nervous system in children (cPACNS) and offers a diagnostic algorithm that allows for rapid evaluation and initiation of targeted therapy.

RHEUMATOLOGY NEWS: What is the incidence of cPACNS?

Dr. Benseler: Primary central nervous system vasculitis in children includes progressive and nonprogressive, angiography-positive, large-vessel vasculitis, small-vessel vasculitis, and most recently, primary CNS venulitis. Because it has only recently been described in case reports and case series, the true incidence of cPACNS remains unknown, but as recognition of the condition increases, so does the number of cases that are diagnosed and treated appropriately. For example, we currently have no idea how many kids presenting with status epilepticus have CNS vasculitis. We can assume that the number is large, however, because once we began looking for vasculitis in these children, we have been diagnosing it in case after case.

RN: What are some of the risk factors for the development of the disease?

Dr. Benseler: Primary childhood CNS vasculitis develops in heretofore perfectly healthy children. Preceding viral illness may play a role. However, no true risk factors have been identified so far. It does not run in families, and it does not reflect any "weakness" of the immune system. It is the exact opposite.

RN: How is cPACNS diagnosed, and what are some of the more pressing diagnostic challenges?

Dr. Benseler: The diagnosis is based on an algorithm of clinical features, including the presence of newly acquired neurologic deficits and/or psychiatric symptoms; such serum inflammatory markers as C-reactive protein, erythrocyte sedimentation rate, and von Willebrand's factor antigen; the absence of neuronal autoantibodies in the cerebrospinal fluid; evidence of ischemic or inflammatory parenchymal disease on MRI; and evidence of CNS vascular disease on angiography or brain biopsy (Curr. Opin. Rheumatol. 2010;22: 590-7). At the same time, causes of secondary vasculitis, noninflammatory vasculopathies, and nonvasculitic inflammatory brain diseases have to be excluded.

RN: Should elective brain biopsies be done routinely in patients with suspected cPACNS, or is there a specific subgroup of children in whom the procedure is most appropriate?

Dr. Benseler: Following the diagnostic algorithm, brain biopsies should be considered in children in whom the treating physician has a strong clinical suspicion of an inflammatory brain disease in the absence of vasculitis on angiography.

RN: You have noted that the spectrum of the disease in children comprises progressive and nonprogressive forms. Are there differences that are apparent at diagnosis that might help clinicians distinguish between the two forms, and how would this affect management?

Dr. Benseler: We have reported the clinical, laboratory, and imaging characteristics of both subtypes. Children with nonprogressive disease present with strokes in the absence of significant inflammatory markers. The vascular wall of the distal internal carotid artery and/or proximal middle cerebral artery and/or anterior cerebral artery are inflamed and thickened on gadolinium-enhanced MRI angiography. The lumen is narrowed, causing ischemic strokes in the vascular territory, which typically includes the basal ganglia. These kids are started on antithrombotic therapy in addition to a 3-month course of high-dose corticosteroids.

In contrast, children with progressive CNS vasculitis present with additional diffuse deficits, and have evidence of inflammatory markers and angiographic abnormalities affecting multiple vessel segments, including the distal vessels. Children are diagnosed based on their angiographic appearance and are treated with the same protocol that we have reported for small-vessel vasculitis, which includes 6 months of cyclophosphamide, monthly pulses plus high-dose steroids, followed by 18 months of mycophenolate maintenance therapy with tapering doses of steroids (Lancet Neurol. 2010;9:1078-84).

RN: What are some of the key management considerations for cPACNS?

Dr. Benseler: The management of CNS vasculitis has multiple components, including drug theory for inflammation; symptom therapy, such as antiseizure medications, selective serotonin reuptake inhibitors, and other drugs; supportive medications, such as vitamin D and pneumocystis jiroveci pneumonia prophylaxis; rehabilitation; family support; and school-adjustment counseling.

–Interview by Diana Mahoney

DR. BENSELER is also associate professor of pediatrics in the division of rheumatology and an associate scientist in Child Health Evaluative Sciences in the Research Institute at the University of Toronto. She had no conflicts of interest to disclose.

Serum Protein May Predict Response to Methotrexate

BY SARA FREEMAN

FROM THE ANNUAL MEETING OF THE BRITISH SOCIETY FOR RHEUMATOLOGY

BRIGHTON, ENGLAND – The pretreatment measurement of a serum protein could help determine if young children with juvenile idiopathic arthritis are likely to respond to methotrexate.

Data from the ongoing SPARKS–Childhood Arthritis Response to Medication Study (CHARMS) show that the pretreatment serum levels of myeloid-related protein (MRP) 8/14 are higher in children who will respond well to treatment with the disease-modifying antirheumatic drug, but levels are lower in those who are less likely to benefit.

The finding holds promise for the development of a simple predictive test that could be used to avoid giving unnecessary and prolonged methotrexate treatment to the estimated 30% of children who are unlikely to respond to the DMARD.

"Essentially what we are trying to do is give effective treatment at clinical presentation," said Halima Moncrieffe, Ph.D., a research fellow at University College of London (UCL) Institute of Child Health. Dr. Moncrieffe noted that giving methotrexate to all children at diagnosis possibly represents a missed opportunity, as children who are unlikely to respond face worsening arthritis before it is recognized that the disease-modifying antirheumatic drug has no great effect.

Giving methotrexate to all children at diagnosis possibly represents a missed opportunity.

DR. MONCRIEFFE

SPARKS-CHARMS thus is looking for biologic, genetic, or psychological factors that could help predict and explain the response to treatments for JIA. The overall study involves more than 800 children who are being treated at the Great Ormond Street Hospital in London. At enrollment, and before any treatment, standard assessments are made and a blood sample is taken for analysis. Assessments are then repeated 6 months after treatment.

Dr. Moncrieffe presented findings on 109 study participants who had been treated with methotrexate from a mean age of 5.2 years and had a mean disease duration of 0.9 years before treatment initiation; 70% were female.

After the researchers excluded children with systemic disease because they had higher inflammatory protein levels than did other JIA subtypes, the results showed higher pretreatment concentrations of MRP8/14, also known as calprotectin or S100A8/A9, in the blood samples of children who achieved an ACR70 response to methotrexate at 6 months than in those who did not respond.

The difference was not initially significant, but a comparison of samples from children who achieved an ACR50 or an ACR70 response with those who had an ACR30 or no response did show a statistical benefit ($P = .008$).

"MRP8/14 is a very stable protein," Dr. Moncrieffe said. It can be measured in a simple serum sample, left on a bench, and even sent through the post before being analyzed at a later date. It could therefore lend itself to the development of a routine predictive test and, together with the genetic findings from SPARKS-CHARMS, help physicians make clinical decisions based on a child's likelihood of responding to treatment.

Dr. Lucy Wedderburn, professor of pediatric rheumatology at UCL Institute of Child Health and an honorary consultant in rheumatology at Great Ormond Street Hospital, said, "MRP8/14 is a protein we already knew to be important."

Dr. Wedderburn, lead investigator of the study, added: "Levels of this protein are very high in the serum of children with JIA and in those who respond well to treatment. Higher levels have also been found in children who are in remission when compared to children without JIA."

The study was funded by SPARKS UK, The Big Lottery Fund, Arthritis Research UK, and Great Ormond Street Hospital Children's Charity. Dr. Moncrieffe and Dr. Wedderburn declared that they had no conflicts of interest. ■