Clinical Factors Predict CNS Vasculitis Progression in Children

**Ask the Expert**

**ANCA-Associated Vasculitis Management**

**BY JOHN R. BELL**

**Associate Editor**

The likelihood of progression of primary angitis of the central nervous system in children can be predicted by using a high-risk profile comprising clinical features seen at diagnosis and on follow-up, according to new findings.

Dr. Susanne M. Benseler of the Hospital for Sick Children in Toronto and her colleagues found that in their study’s cohort of patients with childhood primary angitis of the central nervous system (cPACNS), progressive disease was associated with neurocognitive dysfunction, multifocal lesions as seen on MRI, and angiographic evidence of distal stenoses at presentation. Thus, they devised a high-risk profile encompassing those factors; the profile for their cohort had a high predictive value of disease progression (predicted \( P = 0.02; \) odds ratio 3.47; 95% confidence interval 2.11-8.24).

The investigators retrospectively assessed data from a consecutive cohort of children with cPACNS and followed patients who had been diagnosed with cPACNS over a 12-year period (1990-2002). Cases came from the institution’s rheumatology database, as well as the Pediatric Ischemic Chemic Stroke Registry (Arthritis Rheum. 2006;54:1291-7).

Criteria for having cPACNS were a clinical diagnosis of PACNS vasculitis and conventional CNS angiography and/or magnetic resonance angiography (MRA) findings of arterial stenosis that were not explained by other causes. The investigators excluded neonates and children with any various confounding conditions, such as systemic vasculitis. The study’s primary outcome was the presence or absence of stenosis progression more than 3 months after initial angiography. The researchers defined progression as “a decrease of at least 25% in the diameter at sites of initial stenosis or the appearance of new areas of stenosis.”

Specialists in stroke, neurology, and rheumatology followed up on all patients, collecting data on clinical presentation, underlying disease, stroke risk, and treatments from the databases.

Progressive disease was linked with neurocognitive dysfunction, multifocal lesions, and angiographic evidence of distal stenoses at presentation.

The researchers found that patients with progressive disease were noted to have a lower mean age at disease onset, had an out-of-hospital stroke, and were less likely to have autoimmune disease, seizures, headaches, and renal insufficiency.

In addition, laboratory tests were conducted, comprising an assessment of inflammatory markers, blood testing, prothrombotic testing, antibody profiling, and detection of abnormalities in cerebrospinal fluid. All children received MRI, MRA, or conventional cerebral angiography at diagnosis and follow-up, with results analyzed by blinded neuroradiologists.

There were three treatment categories: antiangiogenic therapy (bevacizumab, bevacizumab, or warfarin) alone; antiangiogenic therapy plus steroids; and antiangiogenic therapy with steroids and intravenous cyclophosphamide.

In all cases, the optimal cyclophosphamide treatment is 3-6 months, followed by maintenance treatment with azathioprine or methotrexate for 12-18 months.

**TNF:** Are there any other options for induction therapy?

**Dr. Guillevin:** At the moment, we have no best induction treatment other than immunosuppressants and steroids, but anti-CD20 therapy (rituximab) is promising and is currently under investigation in an international prospective trial (Rituximab in ANCA-Associated Vasculitis, sponsored by the National Institute of Allergy and Infectious Diseases and the Immune Tolerance Network).

**RN:** What is the optimal management strategy for patients who relapse during or after treatment?

**Dr. Guillevin:** This is certainly the major concern, because relapse rates are high—50% in Wegener’s, 33% in microscopic polyangiitis, and 25% in Churg-Strauss syndrome. When relapses occur, patients have sometimes already been heavily treated and the introduction of immunosuppressants increases the risk for side effects. Treatment strategies depend on the previous therapy administered and the time of occurrence of relapse, whether it’s during treatment or after previous treatments have stopped. When relapse occurs months or years after stopping treatment, a new conventional treatment can be started. When relapse occurs under treatment, new combinations of conventional drugs and new biotherapies should be tried. In such cases, however, effectiveness can be difficult to obtain and side effects are frequent.

**RN:** Are there any other treatment options available or on the horizon?

**Dr. Guillevin:** The immunosuppressant monoclonal antibody mogiliximab is currently being tested as an alternative to azathioprine as a maintenance therapy in a trial by the European Vasculitis Study Group. Plasma exchanges have shown their effectiveness in improving renal function in patients with an initial creatinine level of 500 \( \mu \)mol/l or higher. Intravenous immunoglobulin also has been shown to be effective in controlling relapses and could have an indication as a steroid-sparing agent. Anti-tumor necrosis factor antibodies have successfully been used in severe vasculitis that is refractory to conventional therapies, despite the risk of developing infectious side effects. The anti-TNF drug etanercept, however, has not shown effectiveness as a maintenance treatment in Wegener’s granulomatosis and was associated with an increased number of malignancies.

**Dr. Guillevin** is the head of the department of internal medicine at Hôpital Cochin in Paris, and is a member of the French Vasculitis Study Group.