Clinical Management Guidelines for M-CM (MCAP)

August 1, 2012

These guidelines have been excerpted with permission from a supplement to the following article: *De novo germline and postzygotic mutations in AKT3, PIK3R2 and PIK3CA cause a spectrum of related megalencephaly syndromes.* Nature Genetics 44, 934–940 (2012)
Short link: http://j.mp/mcmgene

The entire supplement can be downloaded directly from the bottom of the article page. The original text contains footnotes that have been removed in this excerpt. Note that the authors refer to M-CM as MCAP.

Clinical management

The most frequent medical complications requiring medical management for MCAP and MPPH involve the brain, and include delayed development, seizures, hydrocephalus, cerebellar tonsillar ectopia (including Chiari malformation type 1), and syringomyelia. The spectrum of reported symptoms is wide, and the risk for cancer is probably increased.
Based on our collective experience to date, we propose provisional management guidelines with the expectation that these will change. At this time, we suggest:

1. Clinic evaluations no less than every 6 months for the first ~6 years of life, and at least yearly thereafter. At each visit, a general medical history should be elicited with attention to the probable increased risk for childhood cancers. In addition, a history of breathing or sleep problems, seizures or other undefined spells, headaches, and behavior changes should be elicited, along with a detailed neurological evaluation. Any positive history or exam finding should be pursued with appropriate testing, for example sleep studies in individuals with apnea or sleep problems.
2. Baseline brain and spinal cord imaging in all patients with MCAP or MPPH at the time of diagnosis. Based on the limited retrospective data available to date, the risk of hydrocephalus, cerebellar tonsillar ectopia or both with low brainstem or high spinal cord compression appears to be highest in the first 2-4 years of life. The risk for brain tumors extends over a longer time period, possibly throughout life (for example, medulloblastoma in young children, and meningiomas in older children and adults). We therefore suggest repeat brain MRI every 6 months from 0-2 years and every year from 2-6 years. In older patients, repeat scans should be performed based on prior brain imaging results and the clinical course, with particular attention to apnea or other abnormal patterns of respiration, headaches, changes in gait or other neurologic problems. Prospective studies are needed to determine appropriate neurosurgical management.

3. Screening for Wilms tumor consisting of renal ultrasounds every 3 months to age 8 years following guidelines for Beckwith-Wiedemann syndrome. Note that AFP is not indicated at this time as this test is directed at early detection of hepatoblastoma, which has not been reported in MCAP or MPPH.
4. Evaluation by a pediatric cardiologist with baseline echocardiogram and electrocardiogram to evaluate for cardiovascular malformations and rhythm abnormalities for all children with MCAP. This suggestion is based on several reports of cardiovascular malformations and rare reports of cardiac rhythm abnormalities, and supported by reports of cardiovascular malformations and rhythm abnormalities in other overgrowth or RASopathy syndromes including Smith-Golabi-Behmel and Costello syndromes. Data is insufficient to characterize the natural history of arrhythmia in MCAP and care should be individualized.
5. Baseline thrombophilia evaluation may be warranted as dural sinus stasis and enlargement is common, and thrombosis has been reported in several individuals.