Microcephaly

Background

1. Definition varies
    - Head circumference [occipito-frontal circumference (OFC)]
        - <2 standard deviations (SD) below mean for age (<3rd percentile)
        - <3 SD (<1st percentile) = severe microcephaly[1]
    - Actual growth charts
        - http://www.cdc.gov/growthcharts/charts.htm#set1
    - Some definitions adjust for prematurity and parental head size
2. General information
    - May require serial measurements (crossing several percentile lines); in utero antenatal diagnosis requires multiple measures less than 3 or 4 SD
3. CDC growth charts based on US population are slightly different than WHO charts
    - http://www.who.int/childgrowth/standards/hc_for_age/en/index.html

Pathophysiology

1. Pathology of disease
    - Lack of brain development from variety of causes or insult to a previously normal brain
2. Incidence, prevalence
    - By definition 1-3% of population; individual etiologies much less common
3. Risk factors / etiology
    - Genetic
        - Isolated vs. syndromic microcephaly
            - Several genes and multiple syndromes with associated anomalies
        - Microcephalia vera (MV) and microcephaly with simplified gyral pattern (MSG) are genetic forms of isolated congenital microcephaly with no extracerebral malformation
        - Well-known associated genetic syndromes
            - Down syndrome, Trisomy 18, Trisomy 13, Cri-du-chat
    - Neuroanatomic abnormalities
        - Neural tube defects, holoprosencephaly, others
        - See http://www.merck.com/mmpe/sec19/ch292/ch292b.html#sec19-ch292-ch292b-2567
    - Metabolic
        - Aminoacidurias, urea cycle disorders, organic acidurias, storage dz
    - Infection
        - TORCH
            - Toxoplasmosis
            - Hepatitis B
            - Syphilis
            - Herpes zoster
            - Rubella
            - Cytomegalovirus (CMV)
            - Herpes simplex virus

- Drug / toxin exposure in utero
  - Fetal alcohol syndrome, maternal opioid use
- Acquired brain injury
  - Hypoxic-ischemic insult, intraventricular hemorrhage
- Systemic disease
  - Renal failure, biliary atresia, etc
- Severe malnutrition
- Hyperthermia
  - Associated with significant fever in 1st trimester with seizures and facial anomalies
- Abnormal fusion of cranial sutures
  - Craniosynostosis

4. Morbidity / mortality
   - Most cases associated with some degree of mental retardation
   - Severity correlates with degree of microcephaly
   - Craniosynostosis morbidity depends on severity and if treated early (referred by 8-12 months)
   - Most conditions
     - Prognosis depends on cause, severity, and associated abnormalities

Diagnosis

1. History
   - Prenatal history
     - Maternal medical illness, medications, tobacco, substance abuse
     - Findings on prenatal lab tests and ultrasounds
   - Birth history
     - Infections, medications, complications
   - Family history
     - Similar conditions, consanguinity, syndromes
     - Parental head size
   - Developmental and neurologic history
     - Milestones, seizures
2. Physical examination
   - Technique of measurement
     - http://www.simulconsult.com/resources/ftemp20.html
   - Compare height, weight, OFC percentiles
   - Genetic influences
     - Weaver curve compares child's OFC to that expected based on parental OFC[2]
   - OFC trajectory; height and weight trajectories
   - General appearance
     - Dysmorphic features
   - Head
     - Sutures and fontanelles
     - Head symmetry
   - Eyes
     - Chorioretinitis, cataracts

- Mouth
  - Midline defects with holoprosencephaly and related conditions
- Skin
  - Petechiae, jaundice, eczema (infection, metabolic or systemic dz)
- Abdomen
  - Hepatosplenomegaly with infection, metabolic dz
- Neurologic
  - Reflexes, symmetry, muscle tone

3. Diagnostic testing
   - Physical findings can be used to identify syndromes, for example entering findings into OMIM database
     - http://www.ncbi.nlm.nih.gov/omim/
   - Especially if dysmorphic features, short stature
     - Consider karyotype, genetic analysis
   - Maternal serum phenylalanine level
   - Fasting plasma and urine amino acids
   - Serum ammonia
   - Thyroid stimulating hormone
   - Infection
     - TORCH titers
     - Urine CMV culture
     - Maternal and infant HIV
   - Diagnostic imaging
     - MRI esp if abnormal development or neuro exam
     - CT or cephalometric radiography if craniosynostosis suspected
4. Diagnostic criteria
   - OFC
     - <2 SD from mean for age
     - <3 SD severe; or
     - Decreasing head growth, crossing 2 or 3 major percentile lines on growth curve
5. Recommendations
   - Neuroimaging is recommended in a child with global developmental delay
     - As presence of physical findings (e.g., microcephaly, focal motor findings) increases, the yield of making a specific diagnosis increases, and scan has higher yield[3]
   - Every child (birth through 24 months of age) found to have microcephaly should be followed and periodically screened for late-onset congenital or acquired hearing loss[4]

Differential Diagnosis

1. Key DDx
   - Craniosynostosis
2. Extensive DDx
   - Primary
     - Genetic
       - Isolated Microcephaly: present at birth, no other anomalies

        - Receding forehead, normal-sized face, and relatively large-appearing ears
      - Autosomal dominant: normal stature, normal intelligence or mild MR
      - X-Linked: severe MR
    - Syndromic
      - Trisomy 13
      - Trisomy 18 syndrome
      - Cornelia de Lange's syndrome
      - Rubinstein-Taybi syndrome
      - Prader-Willi syndrome
    - Neuroanatomic
      - Neural tube defects
      - Holoprosencephaly
        - Incomplete development and septation of midline CNS structures
      - Varying degrees of brain separation, hypotelorism, facial clefts, and nasal malformations
      - Atelencephaly
        - Absence of cerebrum and associated structures
      - Lissencephaly
        - Surface of the brain appears completely or partially smooth with loss or reduction of sulci
      - Schizencephaly
        - Asymmetric infolding of cortical gray matter
      - Polymicrogyria
        - Excessive gyri on surface of brain
      - Macrogyria
        - Reduction in number of sulci of cerebrum and is often seen in lissencephaly
      - Fetal brain disruption sequence
        - Severe microcephaly of prenatal onset (average OFC 5.8 SD below the mean), overlapping cranial sutures, prominence of the occipital bone, and scalp rugae
  - Secondary
    - Metabolic disorders
      - PKU
        - Part of Newborn screen in all 50 states, District of Columbia, Puerto Rico, US Virgin Islands and Guam
      - Methylmalonic aciduria
        - Typically have severe metabolic acidosis with an increased anion gap, ketosis, and hyperammonemia
      - Citrullinemia
        - Quantitative plasma amino acid analysis
    - Environmental factors
      - TORCH infections: Toxoplasmosis, Other (syphilis), Rubella, CMV, HSV
      - In utero toxin exposure (ie ETOH, illicits, solvents)

- Hypoxic-ischemic insults
- Intraventricular hemorrhage or stroke
- Malnutrition

Therapeutics

1. Acute treatment
    - Not an urgent condition unless associated metabolic or systemic illness present
2. Further management
    - If severe and congenital, evaluation and consultation indicated
    - If OFC is low-normal, can be followed serially
    - Management depends on etiology
        - Craniosynostosis
            - Referral to craniofacial team by age 8-12 months
        - Dietary modification for certain metabolic syndromes
        - Treatment if specific infection identified
        - Treat underlying medical illness, as appropriate (thyroid, renal, hepatic)
        - Neurosurgical referral for neural tube defects, neuroanatomic anomalies
        - Genetics, developmental pediatrics referral if genetic syndrome identified
3. Long-term care
    - Family and patient typically need long term psychological support
    - Medical social work involvement for support and resources[5]

Follow-Up

1. Return to office
    - Newborn
        - Depends on etiology and severity
    - Declining OFC in older child: repeat exam in 1-2 months if developmentally normal
    - Recommendations for earlier follow-up
        - Vomiting, delayed milestones, focal neurologic symptoms
2. Refer to specialist
    - Newborn
        - Genetics, developmental pediatrics, neurosurgery as indicated
    - Older child
        - Depends on suspected cause, consider developmental pediatrics
    - Craniosynostosis
        - Craniofacial team (neurosurgery, plastic surgery, otolaryngology, speech therapy, audiology, radiology, orthodontics, etc.)
3. Admit to hospital
    - Concern regarding increased intracranial pressure (vomiting, altered awareness)

Prognosis

1. Poor postnatal head growth in preterm infants becomes more evident by 2 years and is strongly associated with poor neurodevelopmental outcome and cerebral palsy[6]
2. Otherwise prognosis depends on underlying cause

Prevention

1. Women who use heroin should be maintained on an opioid agonist other than heroin during pregnancy; use of long-acting morphine is superior to methadone in abstention rates during pregnancy[7]
2. Identify women who use alcohol in pregnancy and counsel regarding cessation[8]
3. Ensure needed immunizations in women prenatally

Patient Education

1. National Institute of Neurological Disorders and Stroke
    - http://www.ninds.nih.gov/disorders/microcephaly/microcephaly.htm
2. National Library of Medicine: Medline Plus
    - http://www.nlm.nih.gov/medlineplus/ency/article/003272.htm
3. Foundation for Children with Microcephaly
    - http://www.childrenwithmicro.org/

References

1. Kinsman SL, Johnston MV. Chapter 592: Congenital anomalies of the central nervous system. In: Kliegman RM, Behrman, RE, Jenson, HB, Stanton, BF. Kliegman: Nelson Textbook of Pediatrics, 18th ed. Philadelphia: Saunders-Elsevier 2007.
2. Weaver, DD, Christian, JC. Familial variation in head size and adjustment for parental head circumference. J Pediatr 1980; 96:990.
3. Shevell M, Ashwal S, Donley D, Flint J, Gingold M, Hirtz D, Majnemer A, Noetzel M, Sheth RD. Practice parameter: evaluation of the child with global developmental delay: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology 2003 Feb 11;60(3):367-80.
4. Cunningham M, Cox EO. Hearing assessment in infants and children: recommendations beyond neonatal screening. Pediatrics 2003 Feb;111(2):436-40.
5. Wise, PH. Chapter 38: Developmental disabilities and chronic disease. In: Kliegman RM, Behrman, RE, Jenson, HB, Stanton, BF. Kliegman: Nelson Textbook of Pediatrics, 18th ed. Philadelphia: Saunders-Elsevier 2007.
6. Cheong JL, Hunt RW, Anderson PJ, Howard K, Thompson DK, Wang HX, Bear MJ, Inder TE, Doyle LW. Head growth in preterm infants: correlation with magnetic resonance imaging and neurodevelopmental outcome. Pediatrics. 2008 Jun;121(6):e1534-40
7. Minozzi S, Amato L, Vecchi S, Davoli M. Maintenance agonist treatments for opiate dependent pregnant women. Cochrane Database of Systematic Reviews 2008, Issue 2.
8. May P. A multiple-level, comprehensive approach to the prevention of fetal alcohol syndrome (FAS) and other alcohol related birth defects (ARBD). Int J Addictions, 1995; 30(12): 1549-1602.

Authors: Thomas Michels, MD, Monica Morris, MD, & Tammy Myers, MD, *University of Colorado FMR, Denver, CO*

Editor: Vince WinklerPrins, MD, *Georgetown University-Providence Hospital, Washington DC*