

# 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<sup>1</sup>
  - 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](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<sup>2</sup>
  - 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<sup>3</sup>
  - 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<sup>4</sup>

### **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, illicit, 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<sup>5</sup>

## **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<sup>6</sup>
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 abstinence rates during pregnancy<sup>7</sup>
2. Identify women who use alcohol in pregnancy and counsel regarding cessation<sup>8</sup>
3. Ensure needed immunizations in women prenatally

## Patient Education

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

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