MACROCEPHALY AND MICROCEPHALY

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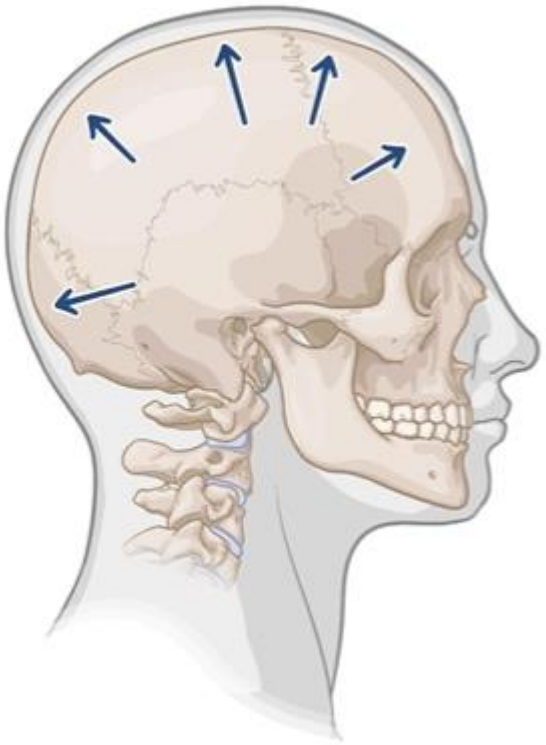
HEAD GROWTH

- Head growth is **affected by growth and alterations in the contents of the cranium** (**brain**, **blood**, **CSF** and **bone**) and the timing of these changes in relation to closure of the fontanelles and sutures.

- Head circumference **should be measured in all children at health maintenance visits between birth and three years of age**.

- Head circumference should also be measured at each visit **in children of all ages with neurologic or developmental disorders**.

- **Deviations from normal** head growth may be the **first indication of an underlying genetic, or acquired problem.**



HOW TO MEASURE HEAD CIRCUMFERENCE

The measuring tape passes just above the eyebrows and around the prominent posterior aspect of the head.

PITTFALLS

- Measurement of head circumference in the newborn may be unreliable **until the third or fourth day of life** since it may be affected by molding, caput succedaneum or cephalohematoma.

- In older infants, the accuracy of the measurement may be affected by thick hair and deformation or hypertrophy of the cranial bones.

NORMAL HEAD GROWTH

- **The average head circumference at birth is 34 - 35 cm**
- Head circumference usually is 1 to 2 cm larger than chest circumference at birth
- Head circumference increases approximately 1 cm per month during the first year of life, with the most rapid growth occurring during the first six months, with an increase of 2 cm in the first month and 6 cm in the first four months
- **Brain weight doubles by four to six months of age and triples by one year of age**
- Most head growth is complete by four years of age

NORMAL HEAD GROWTH: A MNEMONIC

Boys at term: **35 cm**

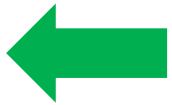
Girls at term: **34 cm**

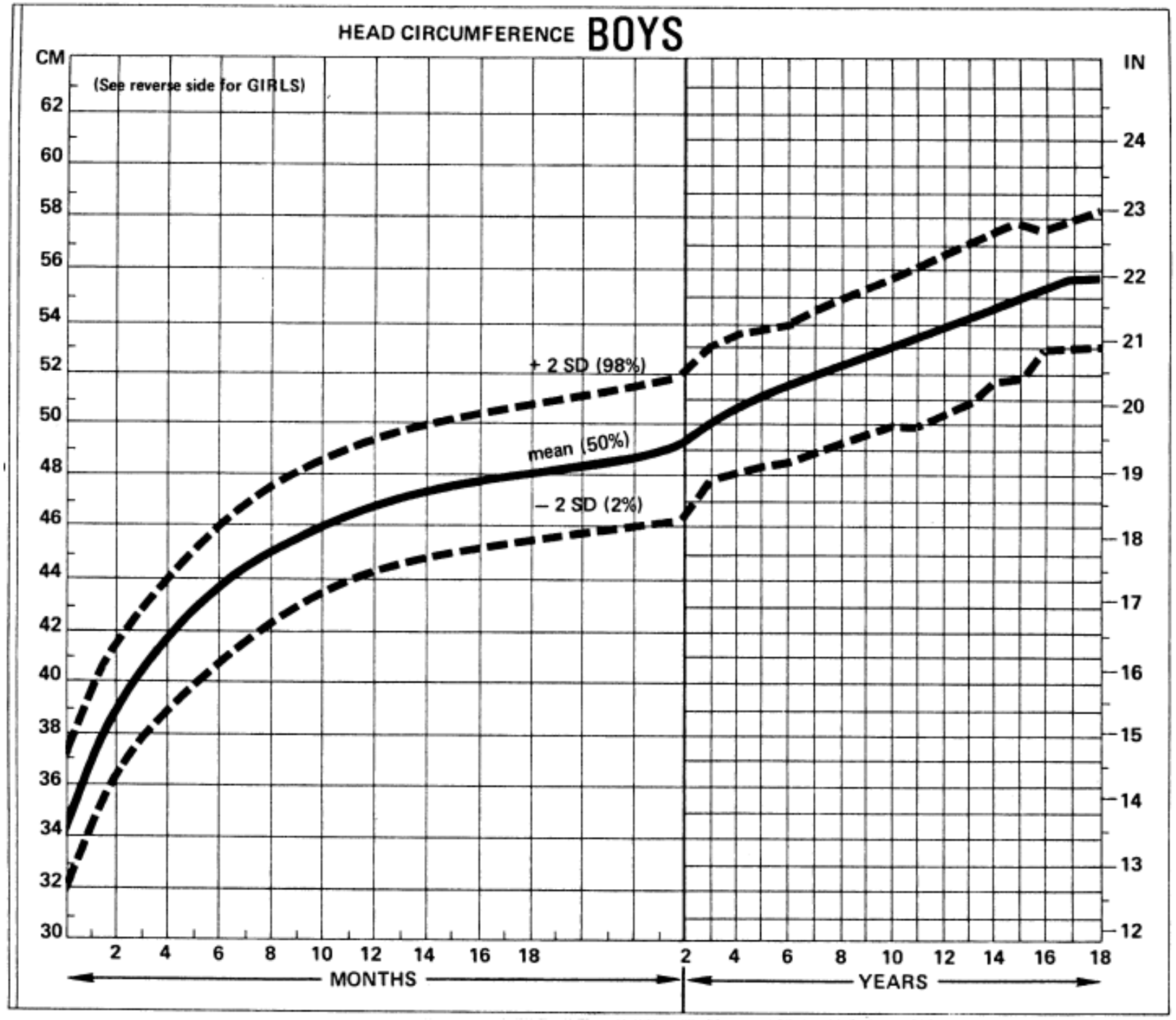
MONTHS	1	2	3	4	5	6	7	8	9	10	11	12
CM	**+ 2**	**+ 2**	**+ 2**	**+ 1**	**+ 1**	**+ 1**	**+ 0.5**	**+ 0.5**	**+ 0.5**	**+ 0.5**	**+ 0.5**	**+ 0.5**

MONTHS	13	14	15	16	17	18	19	20	21	22	23	24
CM	**+ 0.25**	**+ 0.25**	**+ 0.25**	**+ 0.25**	**+ 0.25**	**+ 0.25**	**+ 0.25**	**+ 0.25**	**+ 0.25**	**+ 0.25**	**+ 0.25**	**+ 0.25**

HEAD CIRCUMFERENCE GROWTH CHARTS

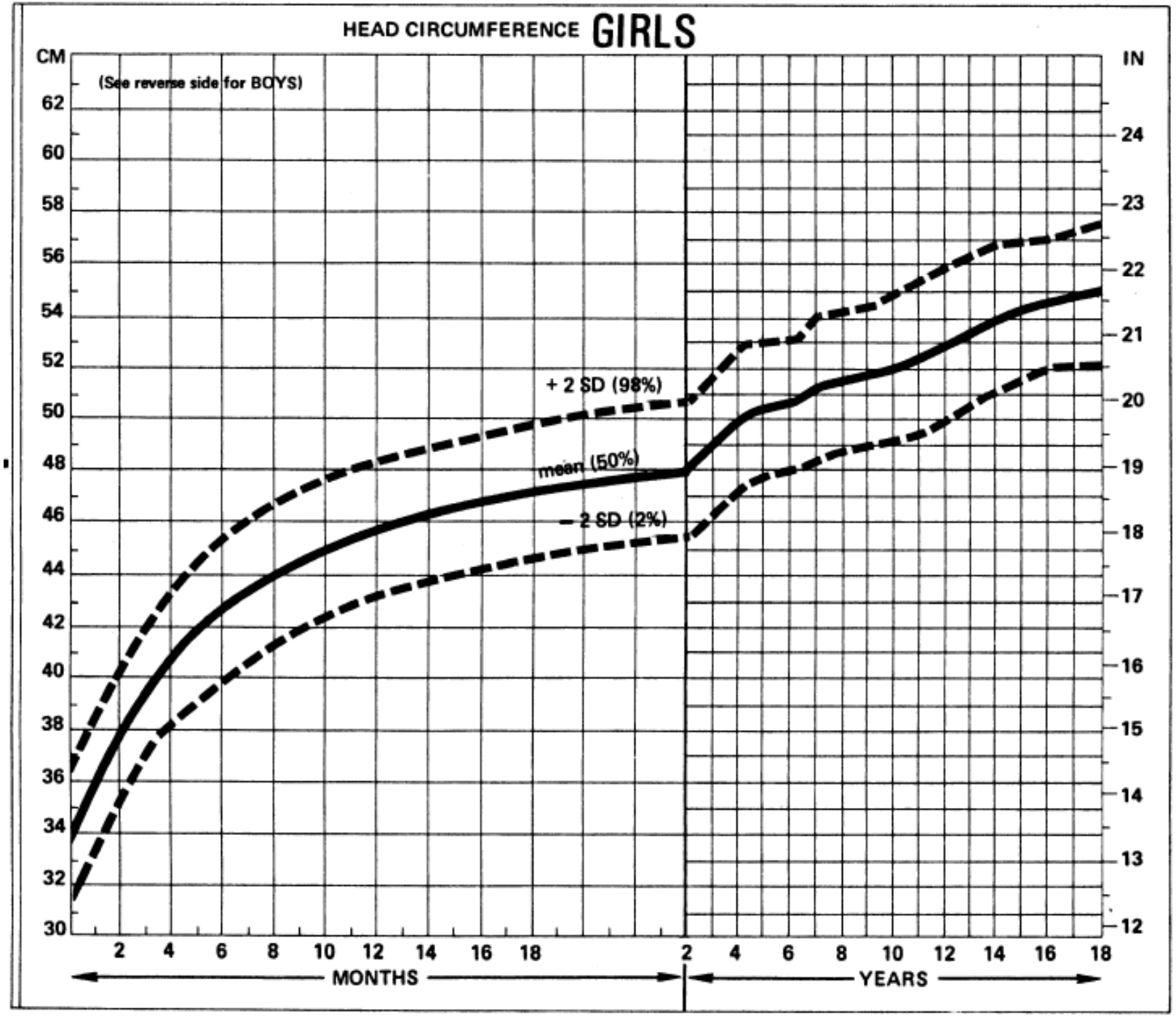
- **WHO growth charts**: recommended for children 0 to 2 years
- **CDC growth charts**: recommended for children 2 to 3 years
- For individuals older than 3 years, the following reference standards are available:
  - **Nellhaus head circumference charts** (0 to 18 years)
  - Fels head circumference charts (0 to 18 years)
  - United States Head Circumference Growth charts (0 to 21 years)
  - Bushby charts (adults)





Ref: NELLHAUS, G., Composite International & Interracial Graphs, Pediatrics 41:106, 1968

BOYS


HEAD CIRCUMFERENCE GIRLS
(See reverse side for BOYS)
CM
62
60
58
56
54
52
50
48
46
44
42
40
38
36
34
32
30
IN
24
23
22
21
20
19
18
17
16
15
14
13
12
+ 2 SD (98%)
mean (50%)
– 2 SD (2%)
2 4 6 8 10 12 14 16 18
MONTHS
2 4 6 8 10 12 14 16 18
YEARS

GIRLS

GROWTH CHARTS: PITTFALS

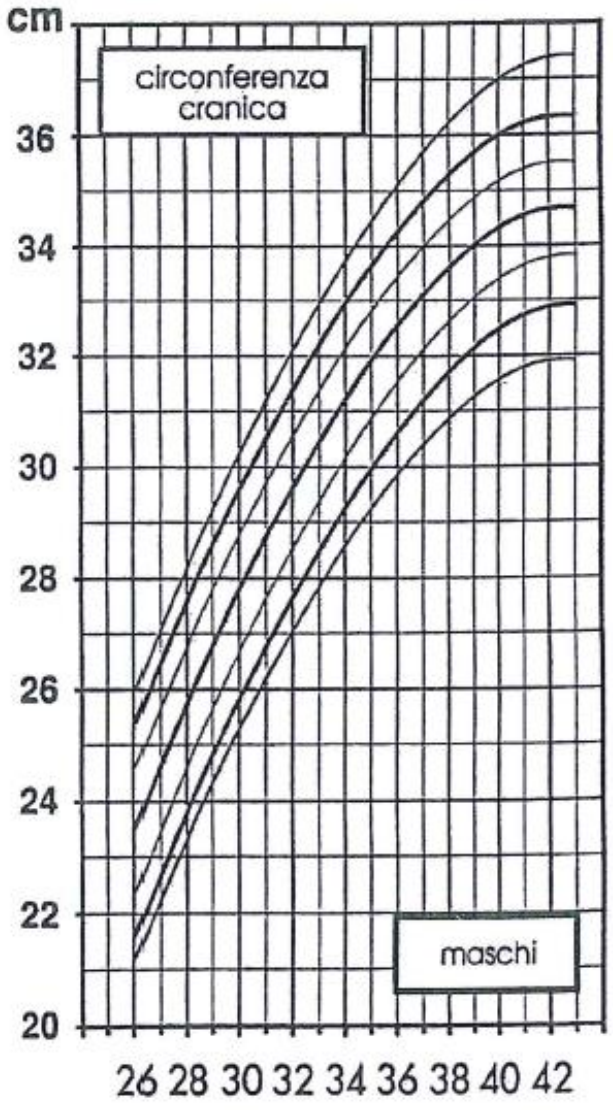
It may be inappropriate to use a single head circumference standard for children in all countries or **ethnic groups**: mean head circumferences in certain national or ethnic groups are sufficiently different from the WHO means to affect diagnosis of microcephaly or macrocephaly.

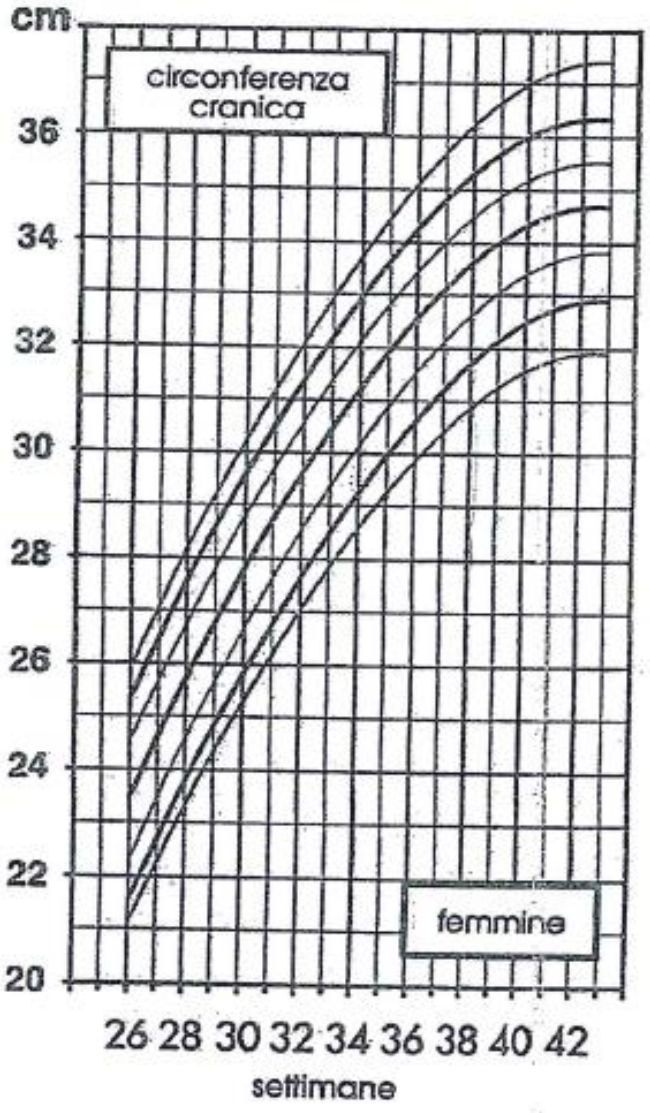
GROWTH CHARTS: SPECIAL POPULATIONS

- **Premature infants**
  Specific foetal head circumference growth charts
  Corrected age should be used until 18 - 24 months

- Down Syndrome
- Achondroplasia (macrocephaly)
- Neurofibromatosis (macrocephaly)
- Williams-Beuren syndrome (microcephaly)

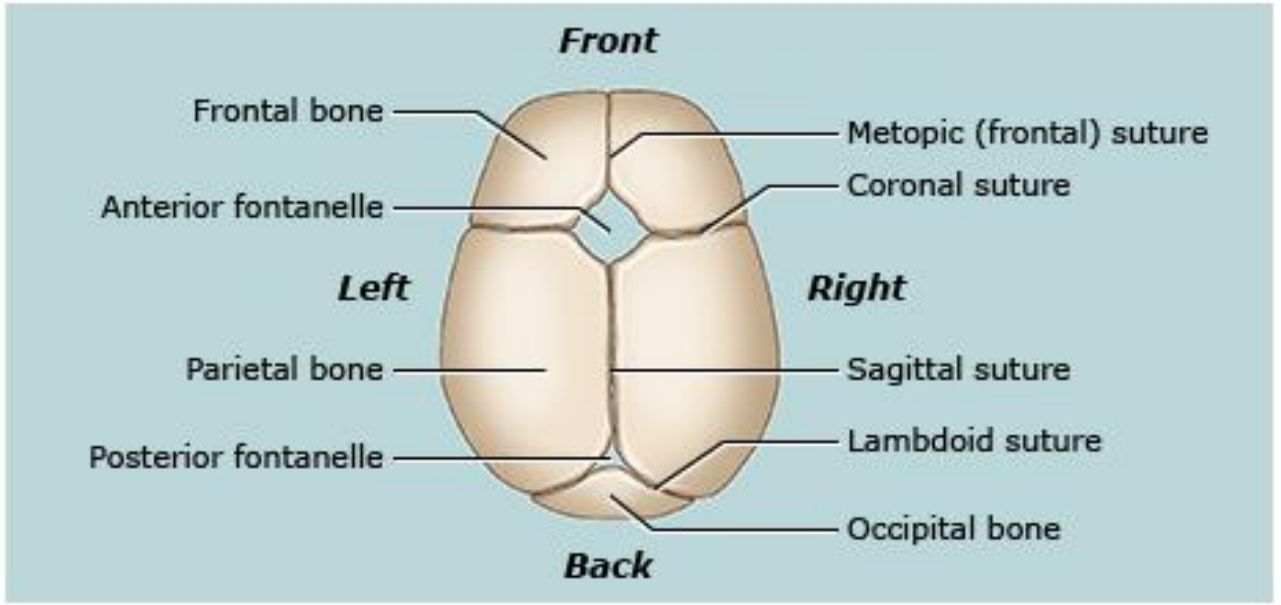
PREMATURE INFANTS





L. Gagliardi, RIP 1999; 25: 159-169

HEAD EXAMINATION



- Anterior fontanelle (3-6 cm diameter) → closes **between 10 and 24 months** of age

- Posterior fontanelle (1-1.5 cm diameter) → closes **before 2 months of age**

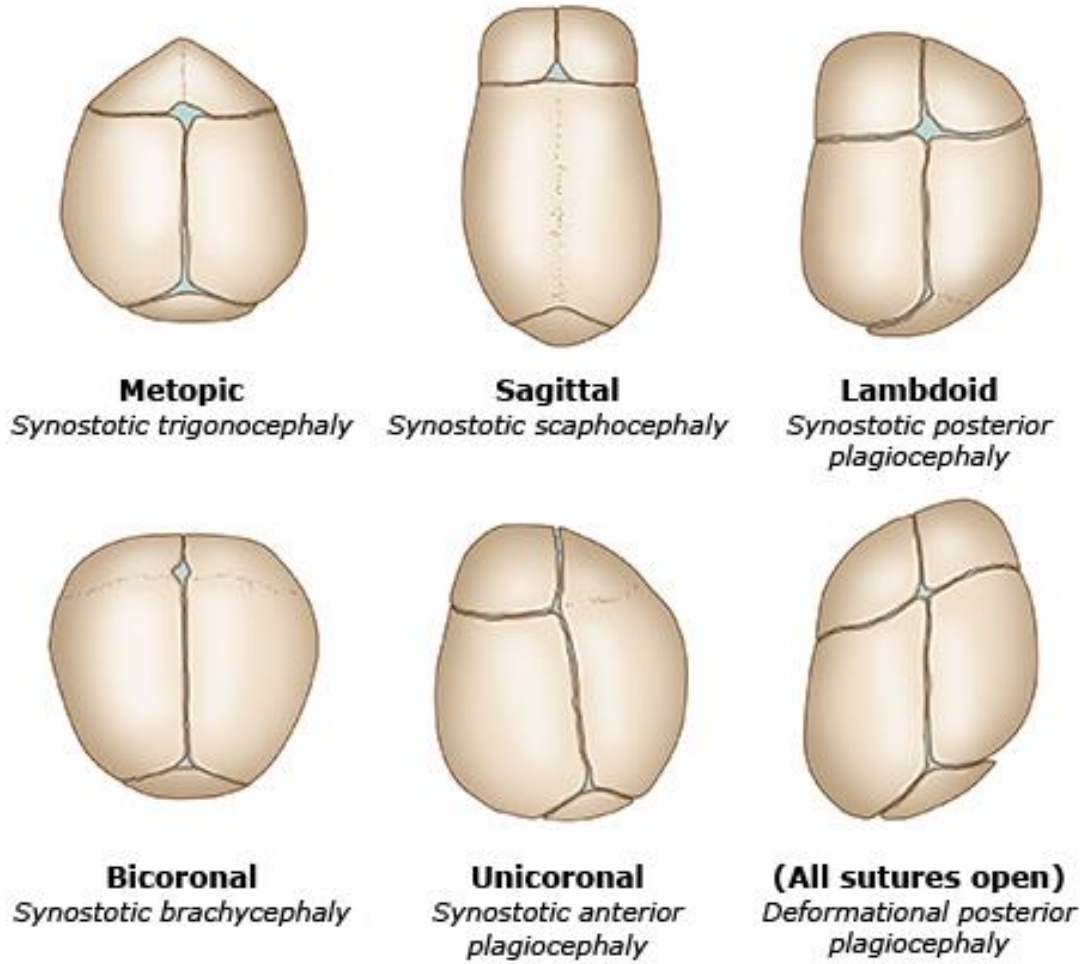
ANTERIOR FONTANELLE: EARLY CLOSURE

- **Normal variant**

- **Craniosynostosis**
- Hyperthyroidism
- Hypophosphatasia
- Hyperparathyroidism

OR

- **Developing microcephaly**



ANTERIOR FONTANELLE: DELAYED CLOSURE

Common causes
Normal variation
Congenital hypothyroidism
Primary megalencephaly
Increased intracranial pressure (of any etiology)
Down syndrome
Rickets
Skeletal disorders
Achondroplasia*
Osteogenesis imperfecta*
Cleidocranial dysostosis*
Apert syndrome*
Campomelic dysplasia
Otopalatodigital syndrome, Type II
Achondrogenesis-hypochondrogenesis, Type II
Acrocallosal syndrome
Antley-Bixler syndrome
Hypophosphatasia*
Pycnodysostosis*
Schinzel-Giedion syndrome
Kenny syndrome*
Lenz-Majewski hyperostosis*
Stanesco dysostosis
Chromosomal abnormalities
Down syndrome*
Trisomy 13*
Trisomy 18*

Endocrine disorders
Hypothyroidism*
Rickets*
Drugs/toxins
Fetal hydantoin syndrome
Aminopterin-induced malformation
Aluminum toxicity
Dysmorphogenetic syndromes
Russell-Silver syndrome*
Rubinstein-Taybi syndrome*
Hallermann-Streiff syndrome* (Oculomandibulofacial syndrome)
Zellweger syndrome* (cerebrohepatorenal syndrome)
Robinow syndrome*
Cutis laxa*
Progeria
VATER association*
Aase syndrome
Melnick-Needles syndrome
Conradi-Hunermann syndrome
Otopalatodigital syndrome
Saethre-Chotzen syndrome
Miscellaneous
Primary megalencephaly
Malnutrition*
Congenital syphilis*

* Also associated with an enlarged fontanelle.

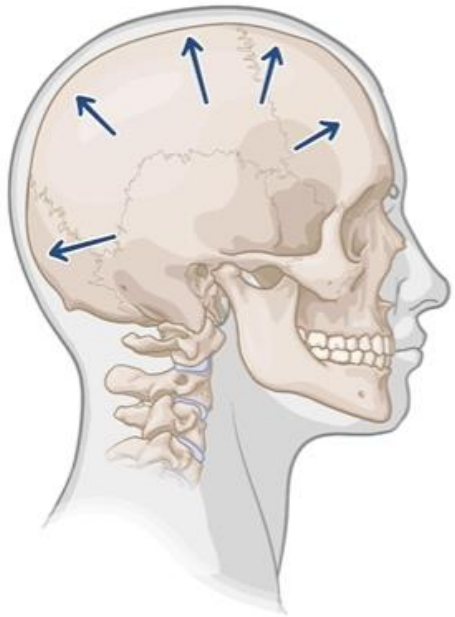
MACROCEPHALY

Uptodate 2023

MACROCEPHALY

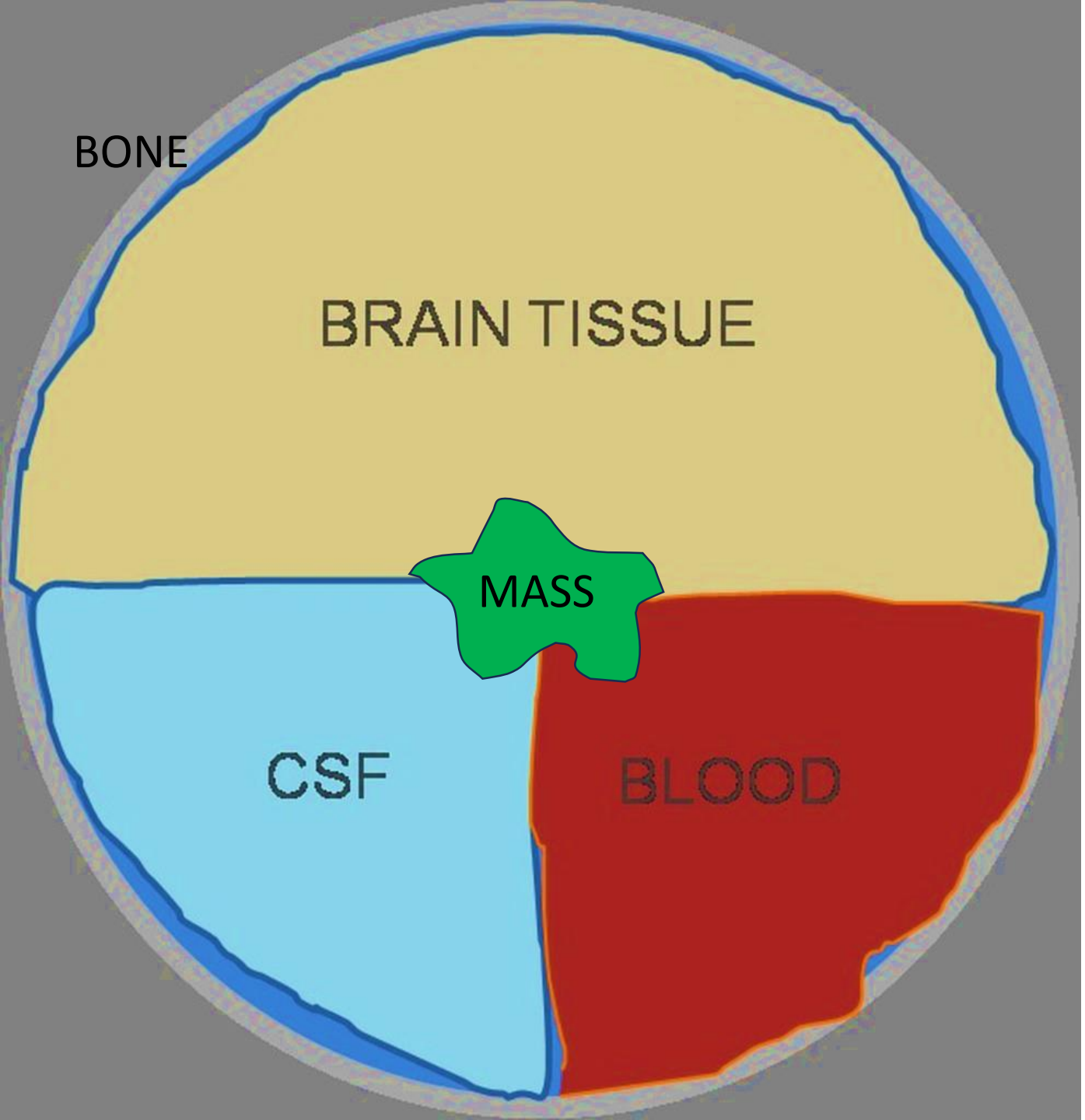
- **Macrocephaly** is defined as an occipitofrontal circumference greater than 2 SDs above the mean for a given age, sex, and gestation (ie, ≥97th percentile)

  ≠ Megalencephaly (or macrencephaly): enlargement of the brain parenchyma



- Macrocephaly is caused by an increase in size of any of the components of the cranium (brain, CSF, blood, or bone) or can be attributable to increased intracranial pressure (ICP)

- An **acceleration in head growth rate** must be followed and evaluated as "possible macrocephaly"



Increased brain (megalencephaly)
Anatomic
Familial megalencephaly
Neurocutaneous disorders (eg, neurofibromatosis, tuberous sclerosis, linear sebaceous nevus syndrome, Sturge-Weber syndrome, Klippel-Trenaunay-Weber syndrome, basal cell nevus syndrome syndrome])
Autism spectrum disorder
Achondroplasia
Cerebral gigantism (Sotos syndrome)
Fragile X syndrome
PTEN hamartoma syndromes (eg, Cowden/Bannayan-Riley-Ruvalcaba syndrome)
Metabolic
Leukodystrophies (eg, Alexander disease, Canavan disease, megalencephalic leukoencephalopathy)
Lysosomal storage disorders (eg, Tay-Sachs, mucopolysaccharidosis, gangliosidosis)
Organic acid disorders (eg, glutaric aciduria)

Increased cerebrospinal fluid
Hydrocephalus*
Benign enlargement of the subarachnoid space
Hydranencephaly
Choroid plexus papilloma

Increased blood
Hemorrhage (intraventricular, subdural, epidural, subarachnoid)
Arteriovenous malformation

Increased bone
Bone marrow expansion (eg, thalassemia major)
Primary bone disorders (eg, skeletal and cranial dysplasias such as achondroplasia, osteogenesis imperfecta, cleidocranial dysostosis, metaphyseal dysplasia, osteopetrosis, hyperphosphatasia)

Mass lesions
Intracranial cyst
Intracranial tumor
Intracranial abscess

Increased intracranial pressure
Idiopathic (pseudotumor cerebri)
Infection or inflammation (eg, meningitis)
Toxins (eg, lead)
Metabolic abnormalities (eg, vitamin A deficiency or excess, galactosemia)

INCREASED BRAIN PARENCHIMA (MEGALENCEPHALY)

ANATOMIC: increase in the size or number of brain cells in the absence of metabolic disease or acute encephalopathy

- Usually present at birth
- E.g. benign familial megalencephaly, neurocutaneous disorders, ASD, achondroplasia, Sotos, Fragile X, Cowden, Gorlin syndromes

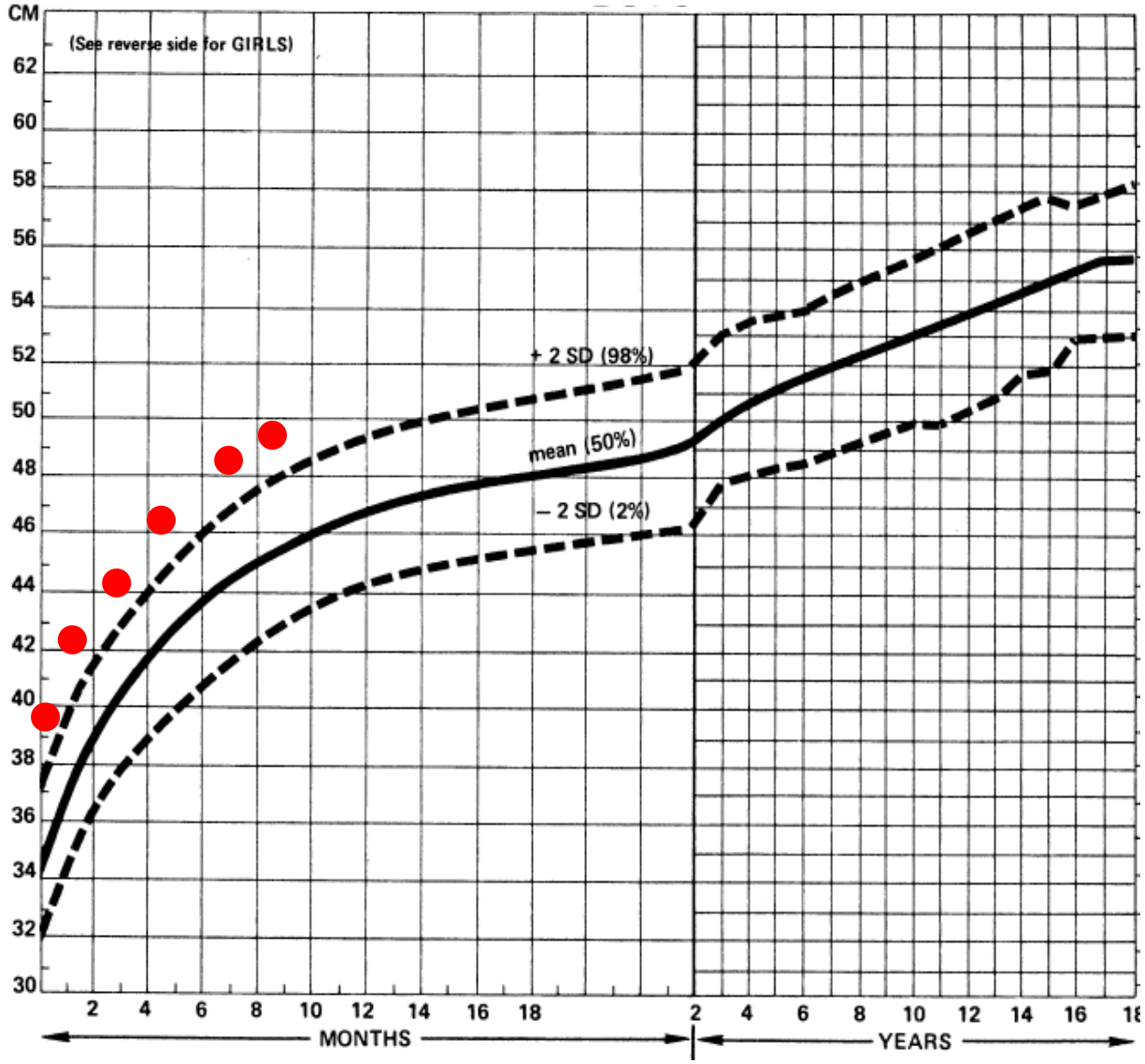
METABOLIC: deposition of metabolic products in the brain tissue

- Head circumference usually normal at birth, increases during neonatal period
- E.g. leukodystrophies, lysosomal storage disorders, organic acid disorders

BENIGN FAMILIAL MEGALENCEPHALY

- Most common type of anatomic megalencephaly
- Children are born with large heads and normal body size
- During infancy, head circumference increases to greater than the 90th percentile, typically 2 to 4 cm above, but **parallel to the 98th percentile**.
- Head growth velocity slows to a normal rate by approximately six months of age
- **Normal neurologic examination**, normal development, no clinical features suggestive of a specific syndrome, no family history of abnormal neurologic or developmental problems
- Familial megalencephaly can be confirmed by measuring the **patient's parents' head circumferences** and by using Weaver curves
- If the child’s head circumference falls within the normal ranges as estimated using the Weaver curves, neuroimaging is not necessary

EXAMPLE 1: child with normal development, normal neurological examination, no syndromic features



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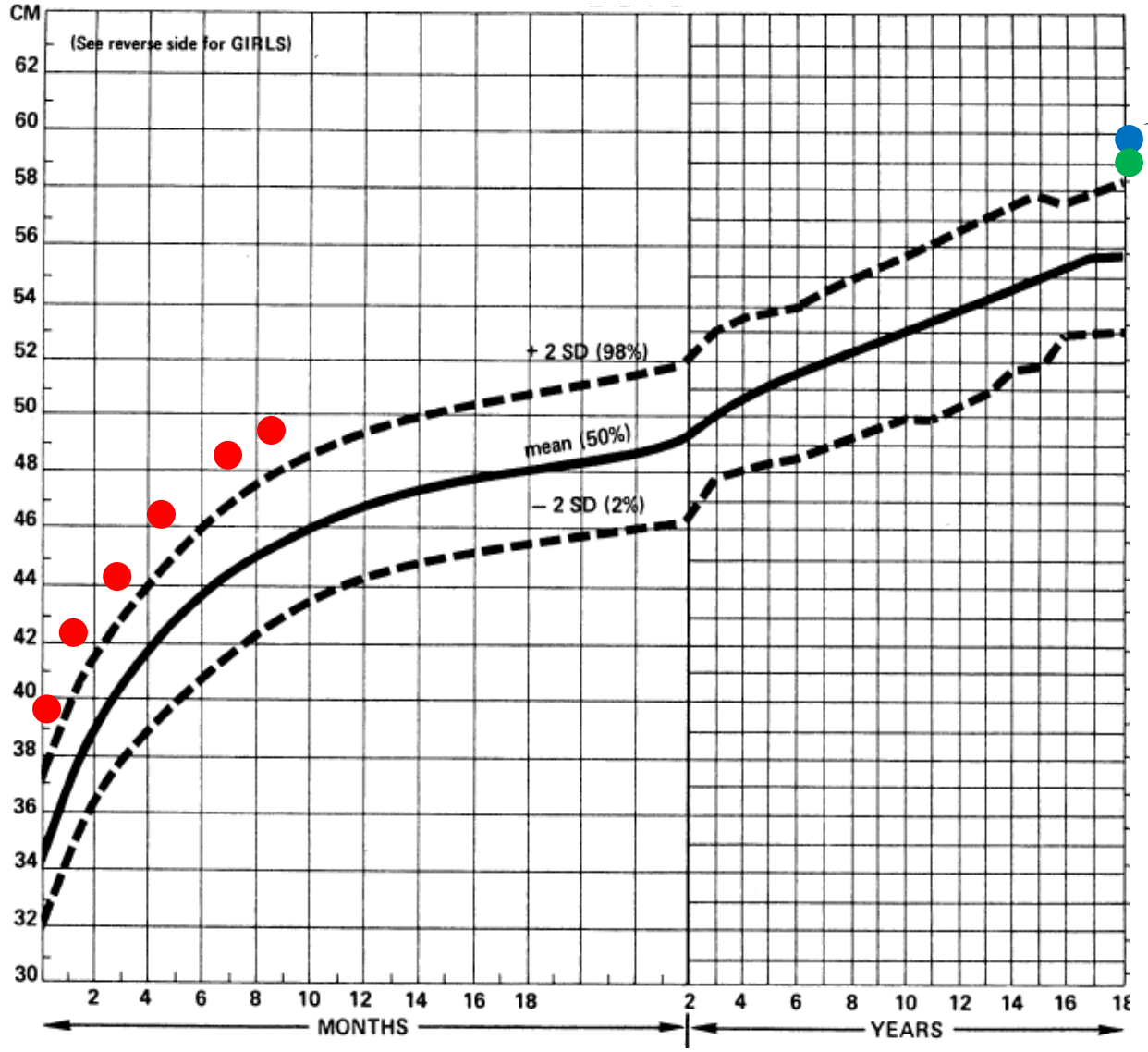


Father
59.5 cm

Mother
59 cm

WEAVER CURVES

Weaver curves determine the genetic contribution to macrocephaly

1. Obtain the parents' head circumference (OFC)

2. Calculate a standard score (SS) for the child and each of the parents using the following formula:

   Standard score (SS) = (OFC - mean value)/standard deviation (SD)

   (Use Nellhaus chart to calculate the mean values and SD for age and sex)
   (Use the mean value and SD for an 18-year-old to calculate the parents' SD)

3. Plot the average of the parents' SS and the child's SS on the Weaver curve

3. A genetic contribution to macrocephaly is suggested if the child's SS is within the range determined by the average parental score

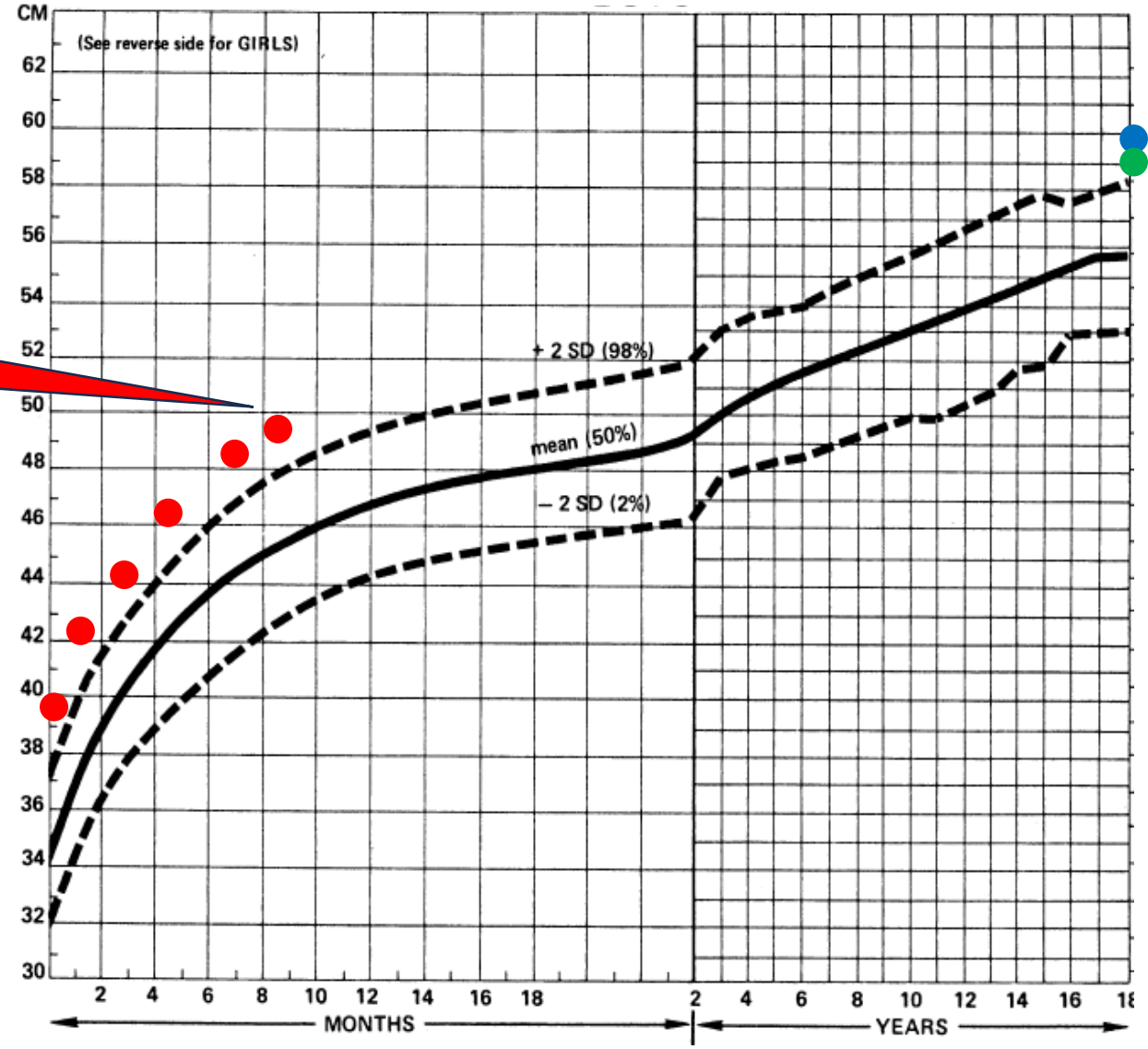
Age	Males		Females	
	Mean (cm)	1 SD	Mean (cm)	1 SD
Birth	34.74	1.33	34.02	1.22
1 mo	37.30	1.30	36.43	1.22
3 mo	40.62	1.23	39.71	1.20
6 mo	43.76	1.29	42.68	1.38
9 mo	45.75	1.28	44.69	1.30
12 mo	47.00	1.31	45.81	1.29
18 mo	48.31	1.36	47.27	1.36
2 yr	49.19	1.39	48.02	1.29
3 yr	50.63	1.38	49.25	1.36
4 yr	50.91	1.39	50.10	1.37
5 yr	51.41	1.37	50.55	1.32
6 yr	51.40	1.41	50.52	1.31
7 yr	52.24	1.52	51.46	1.35
8 yr	52.35	1.40	51.64	1.44
9 yr	52.58	1.44	51.87	1.33
10 yr	53.16	1.41	52.15	1.50
11 yr	53.25	1.53	52.64	1.39
12 vr	53.71	1.52	53.01	1.50
13 yr	54.14	1.57	53.70	1.37
14 yr	54.59	1.30	54.04	1.39
15 yr	54.95	1.51	54.39	1.34
16 yr	55.37	1.11	54.64	1.16
17 yr	55.77	1.32	54.78	1.35
18 yrs and older	55.95	1.34	54.94	1.40

EXAMPLE 1: child with normal development, normal neurological examination, no syndromic features

SS = (OFC - mean value) / SD

Child
49.5 cm
SS = +2.93

SS = (49.5-45.75) / 1.28



Father
59.5 cm
SS = +2.65

SS = (59.5-55.95) / 1.34

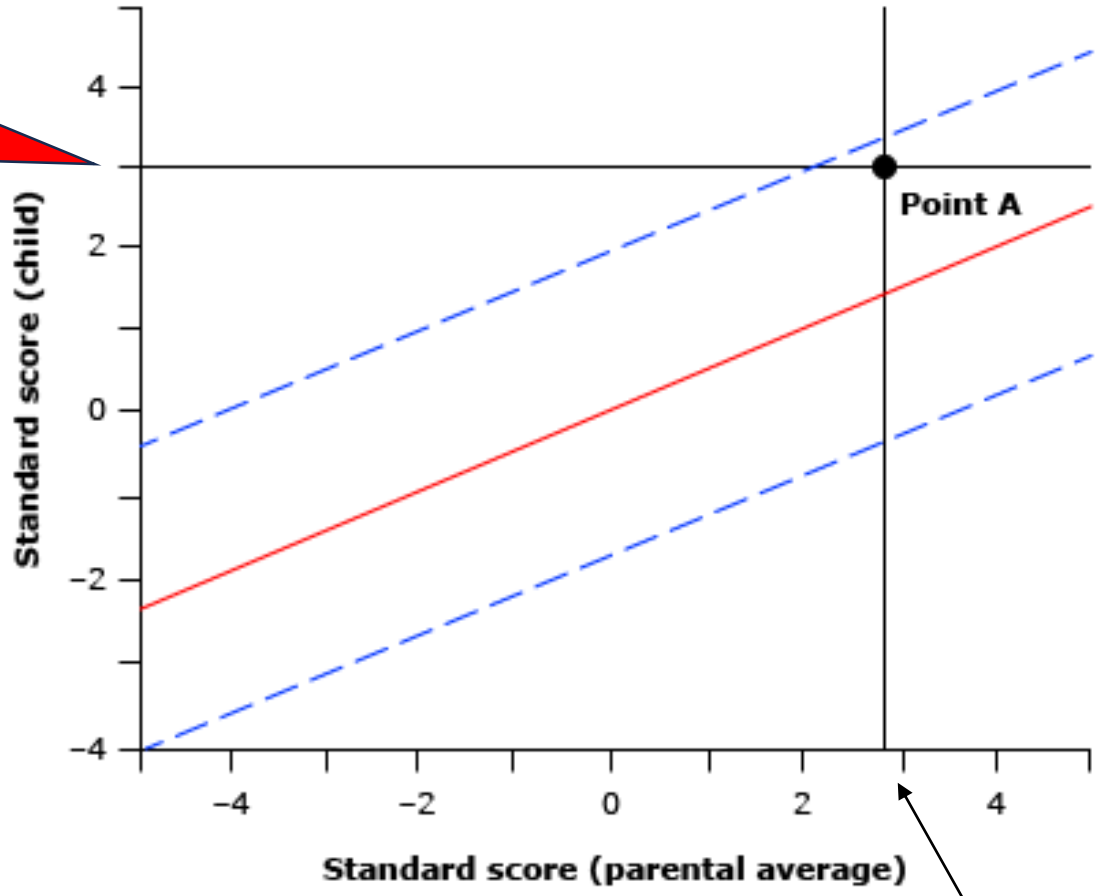
Mother
59 cm
SS = +2.90

SS = (59-54.94) / 1.40

Average parental SS: +2.78

EXAMPLE 1: child with normal development, normal neurological examination, no syndromic features

Child
49.5 cm
(SS +2.93)



Average parental SS: +2.78

When plotted, the intercept (point A) of lines from the SS falls below the +2 SD regression line.

Thus, the child's head size in relationship to that of his parents is judged to be normal.

INCREASED CEREBROSPINAL FLUID

HYDROCEFALUS

- Increased pressure and dilatation due to an excessive amount of CSF in the cerebral ventricular system
- It may be caused by increased production, decreased absorption, or obstruction to CSF flow
- Increased head circumference is frequently the presenting sign of hydrocephalus

BENIGN ENLARGEMENT OF THE SUBARACHNOID SPACE

- Also called benign extra-axial fluid, idiopathic external hydrocephalus, extraventricular hydrocephalus, or benign subdural effusion

HYDROCEFALUS

- **Obstructive** (noncommunicating) hydrocephalus:
  excess accumulation of CSF due to structural blockage of CSF flow within the ventricular system. This is the most common form of hydrocephalus in children and is almost always associated with increased ICP.

- **Communicating** hydrocephalus:
  CSF accumulation due to impaired absorption that occurs in the subarachnoid spaces. Rarely, CSF accumulates because of excessive production. It is also typically associated with increased ICP.

HYDROCEFALUS

- Hydrocephalus that begins in infancy before fusion of the cranial sutures, if untreated, typically results in marked **macrocephaly** and in **less compromise of brain tissue**, compared with hydrocephalus that develops acutely.

- If hydrocephalus occurs acutely or occurs after fusion of the cranial sutures, the head does not enlarge. This results in significantly increased ICP and in more rapid destruction of brain tissue.

HYDROCEFALUS: CAUSES

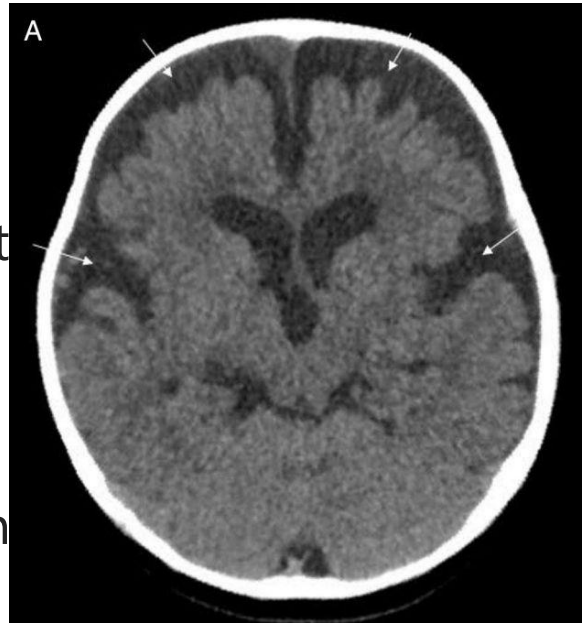
Communicating hydrocephalus
Permanent impaired absorption:
Primary congenital hydrocephalus
Malformed brain
Developmental/genetic association
Secondary prenatal hydrocephalus
Posthemorrhagic
Postinfectious
Secondary postnatal hydrocephalus
Prematurity-related
Posthemorrhagic
Postinfectious
Venous congestion: craniosynostosis, achondroplasia
Venous thrombosis: superior vena cava obstruction after cardiac surgery
Increased secretion: Choroid plexus papilloma/carcinoma
Communicating hydrocephalus with an obstructive component
Tumors
Intraventricular hemorrhage resulting in a clot at aqueduct or fibrosis of aqueduct (acute phase)*
Intraventricular hemorrhage resulting in intracranial cysts (acute phase)*
Infection resulting in intracranial cysts
Meningitis/encephalitis resulting in secondary obstruction*
Chiari 2 malformation
Dandy Walker malformation
Holoprosencephaly: lobar, semilobar, alobar
Encephalocele
Lissencephaly
Hydranencephaly

Obstructive hydrocephalus with a transient minor communicating component
Subacute or late phase (at least several months from the primary insult) of disorders due to hemorrhage or infection as listed above under "Communicating hydrocephalus with an obstructive component"*
Large arachnoid cysts
Chromosomal abnormalities, syndromic, genetic:
X-linked hydrocephalus (mostly aqueductal stenosis)
Osteogenesis imperfecta
Craniofacial syndromic disorders
Part of metabolic inherited disease:
Hurler's disease (MPS T1)
Achondroplasia
Obstructive hydrocephalus (pure)
Intracranial cysts with no evidence of bleed at diagnosis
Triventricular hydrocephalus due to radiologically apparent aqueductal stenosis
Membranous obstruction of aqueduct
Asymmetrical hydrocephalus, due to atresia of the foramen of Monro
Obstruction of fourth ventricle outlets

* In these disorders, the communicating component is initially prominent but tends to decrease over time so that the obstructive component predominates in the later phases.

BENIGN ENLARGEMENT OF THE SUBARACHNOID SPACE

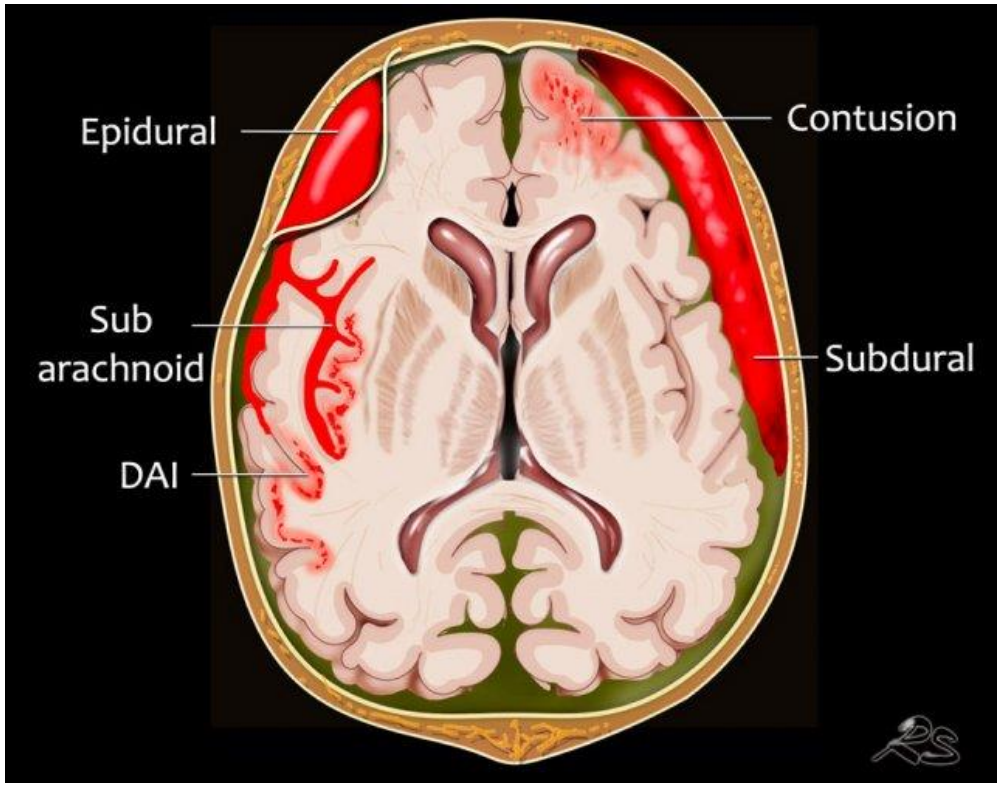
- **16%** of infants with macrocephaly, 0.4 per 1000 live births
- M>F, frequently occurs in other family members
- **Macrocephaly may or may not be present at birth**; if not, head circumference rapidly increases to greater than the 95th percentile and then tends to parallel the curve. Head growth velocity typically slows to normal by six months of age
- **Weaver curves outside genetic potential**
- Imaging is necessary to make the diagnosis: it shows **enlargement of the subarachnoid space in the frontal or frontoparietal areas** with a prominent interhemispheric fissure and normal ventricles.
- **Normal development** and normal neurologic examinations (with exceptions)
- Children may be at **increased risk for subdural hematoma** with minimal or n trauma



INCREASED BLOOD

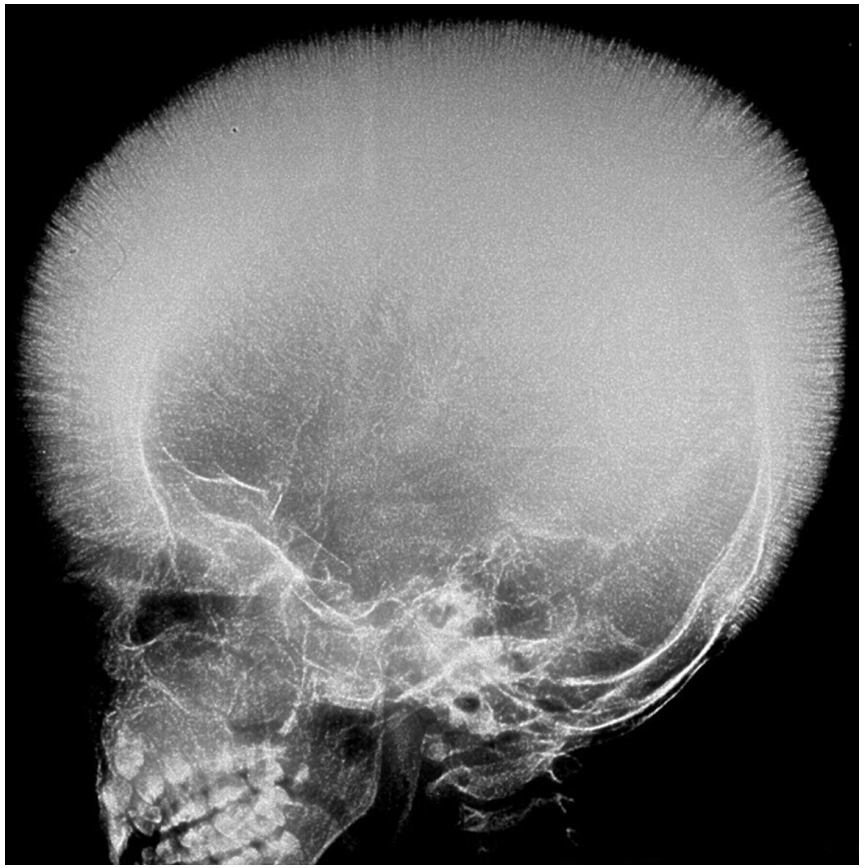
- Increased intracranial blood volume may be caused by **hemorrhage** (intraventricular, subdural, epidural) or **arteriovenous malformation**.

- Increased head circumference is rarely the sole manifestation of intracranial hemorrhage.



INCREASED BONE

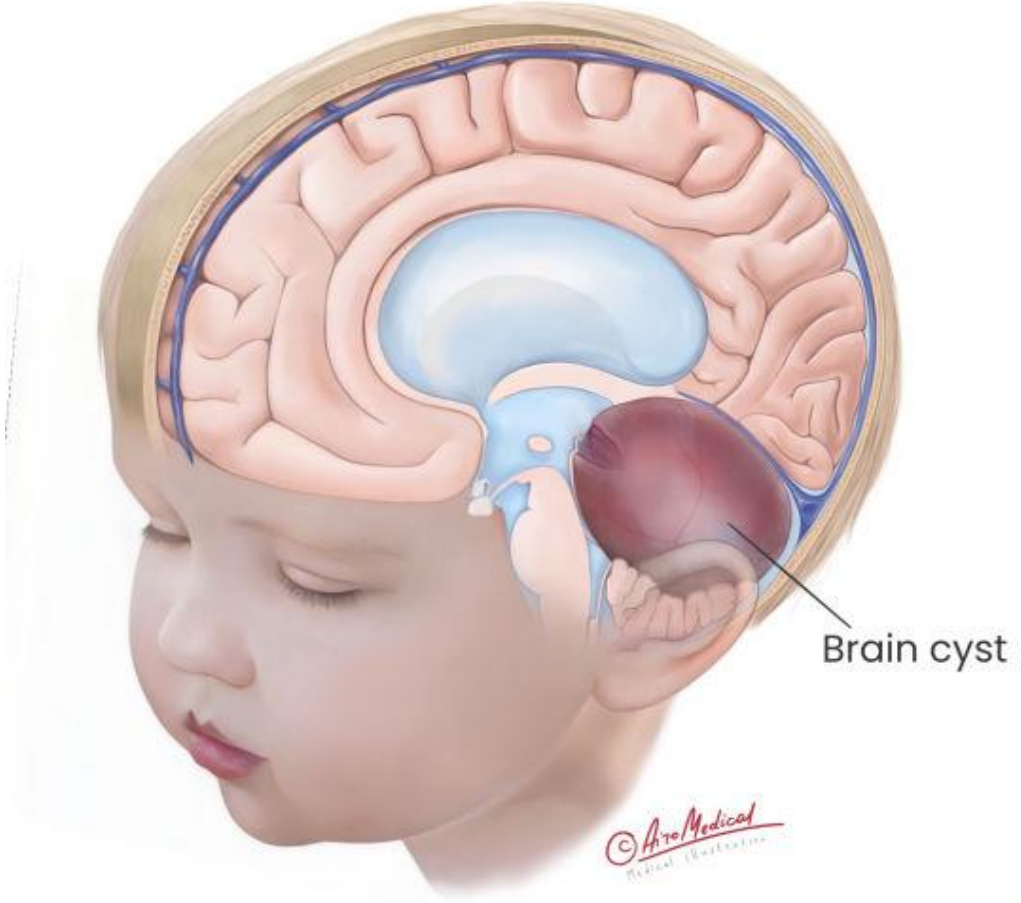
Bone thickening, a rare cause of macrocephaly, can occur from bone marrow expansion, as seen in **thalassemia major**, or **primary bone disorders** (eg, skeletal and cranial dysplasias).



MASS LESIONS

- Intracranial mass lesions include intracranial **cysts**, **tumors**, or **abscesses**.

- Increased head circumference is rarely the sole manifestation of intracranial tumor but may be a frequent presenting sign of intracranial cysts.



OTHER CAUSES of INCREASED INTRACRANIAL PRESSURE and AQUIRED MACROCEPHALY or INCREASING HEAD GROWTH RATE

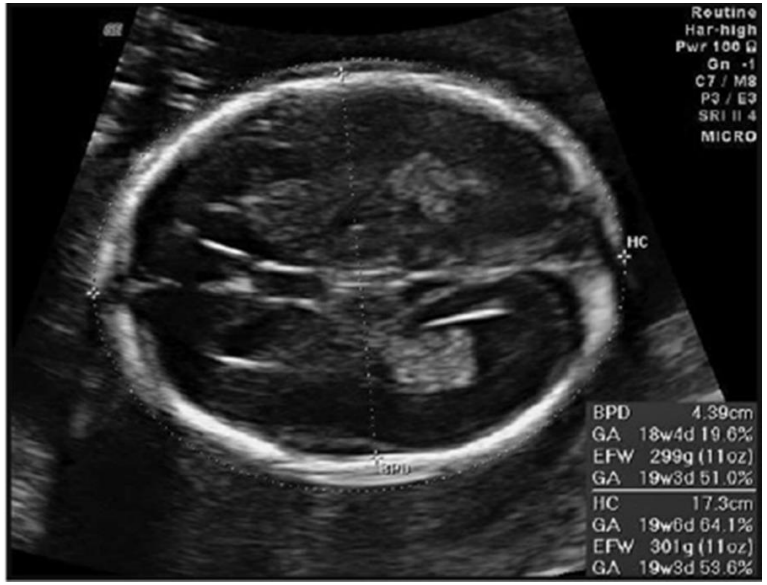
- Infection
- Inflammation
- Toxic or metabolic abnormalities (eg, lead poisoning, vitamin A deficiency or excess, galactosemia)
- Idiopathic (ie, *pseudotumor cerebri*)

MACROCEPHALY: CLINICAL CLASSIFICATION

- CONGENITAL (or PRENATAL)
- POSTNATAL

CONGENITAL MACROCEPHALY

- Defined as head circumference >2 SD above the mean or above the 98th percentile for gestational age



- The diagnosis is complicated by **limitations** in accuracy of head circumference measurements and inconsistency between prenatal and postnatal head circumference growth curves

CONGENITAL MACROCEPHALY

The approach varies according to **associated ultrasonographic anomalies**, appropriateness of **other fetal biometric parameters** in relation to gestational age, **family history** and head circumference measurements of parents and siblings:

- associated ultrasonographic anomalies (eg, callosal dysgenesis, malformations of cortical development, hypertelorism, enlarged kidneys, polydactyly, hypoplastic long bones) may indicate **syndromic macrocephaly**

- head circumference, abdominal circumference, and long-bone length that are greater than expected for gestational age may indicate an **overgrowth syndrome** (eg, Sotos syndrome, Weaver syndrome)

- fetal head circumference between 2 and 2.5 SD above the mean for gestational age and family members with macrocephaly but no stigmata of autosomal dominant conditions that include macrocephaly may indicate **familial macrocephaly**, although it is unusual for this to present prenatally

CONGENITAL MACROCEPHALY

- Additional evaluation (eg, karyotype, fetal brain MRI) may be obtained in case of:
    - parental consanguinity
    - family members with macrocephaly and stigmata of autosomal dominant conditions that include macrocephaly
    - otherwise unexplained fetal macrocephaly (eg, family members with normal head circumference and fetal biometric parameters other than head circumference appropriate for gestational age)
- Cesarean delivery is indicated in cases in which the head circumference is increased and vaginal delivery is thought not to be possible

CONGENITAL AND EARLY INFANTILE MACROCEPHALY

Early infantile (birth to 6 mo of age)	Hydrocephalus (progressive or "arrested")	
	Induction disorders	Spina bifida cystica, cranium bifidum, Chiari malformations (types I, II, and III), aqueductal stenosis, holoprosencephaly
	Mass lesions	Neoplasms, atrioventricular malformations, congenital cysts
	Intrauterine infections	Toxoplasmosis, cytomegalic inclusion disease, syphilis, rubella
	Perinatal or postnatal infections	Bacterial, granulomatous, parasitic
	Perinatal or postnatal hemorrhage	Hypoxia, vascular malformation, trauma
	Hydranencephaly	
	Subdural effusion	
	Hemorrhagic, infectious, cystic hygroma	
	Normal variant (often familial)	

Late infantile (6 mo to 2 yr of age)	Hydrocephalus (progressive or "arrested")	
	Space-occupying lesions	Tumors, cysts, abscess
	Postbacterial or granulomatous meningitis	
	Posthemorrhagic	Trauma or vascular malformation
	Dandy-Walker syndrome	
	Subdural effusion	
	Increased intracranial pressure syndrome	
	Pseudotumor cerebri	Lead, tetracycline, hypoparathyroidism, corticosteroids, excess or deficiency of vitamin A, cyanotic congenital heart disease
	Primary skeletal cranial dysplasias (thickened or enlarged skull)	
	Osteogenesis imperfecta, hyperphosphatemia, osteopetrosis, rickets	
	Megalencephaly (increase in brain substance)	
	Metabolic central nervous system diseases	Leukodystrophies (eg, Canavan, Alexander), lipidoses (Tay-Sachs), histiocytosis, mucopolysaccharidoses
	Proliferative neurocutaneous syndromes	von Recklinghausen tuberous sclerosis, hemangiomatosis, Sturge-Weber
	Cerebral gigantism	Sotos syndrome
	Achondroplasia	
	Primary megalencephaly	May be familial and unassociated with abnormalities of cellular architecture, or associated with abnormalities of cellular architecture

Early to late childhood (older than 2 yr of age)	Hydrocephalus (progressive or "arrested")	
	Space-occupying lesions	
	Preexisting induction disorder	Aqueductal stenosis
	Postinfectious	
	Hemorrhagic	
	Chiari type I malformation	
	Megalencephaly	
	Proliferative neurocutaneous syndromes	
	Familial	
	Pseudotumor cerebri	
	Normal variant	

POSTNATAL MACROCEPHALY: EVALUATION

WHEN TO BEGIN EVALUATION

- A **single** head circumference measurement is abnormal (+2 SDs), or
- Serial measurements reveal **progressive enlargement** (ie, crossing of one or more major percentile lines [eg, 10th, 25th, 50th, 75th, 90th] between health supervision visits, or
- For infants age <6 months, there is **an increase in head circumference of >2 cm per month**

It is important to verify the measurement:
isolated deviant measurements often are due to technical error!!!

POSTNATAL MACROCEPHALY: EVALUATION

URGENT EVALUATION

- Other symptoms or signs of **increased ICP** (eg, headache, vomiting, altered mental status, bulging fontanelle, papilledema)
- CNS **infection** (eg, fever, meningismus, lethargy, irritability)
- CNS **trauma**
- **Suspect physical abuse**

POSTNATAL MACROCEPHALY: HISTORY

- Birth weight, length, head circumference and **growth trajectory**
- Rate of attainment and/or loss of **milestones**
- History of **seizures**
- History of predisposing factors for **hydrocephalus** (eg, meningitis, prematurity with intraventricular hemorrhage)
- **Family history** of consanguinity, large OFC, neurocutaneous disorders, metabolic disorders, and malignancies (eg *PTEN* syndromes associated with breast and thyroid cancers)

POSTNATAL MACROCEPHALY: PHYSICAL EXAMINATION

- Weight and stature **trajectories**
- **Dysmorphic features**, abnormal head shapes
- Assessment of the **fontanelles** and auscultation for intracranial bruits
- The **eyes** should be examined for papilledema, cataracts, and retinal abnormalities
- Examination of the **skin** for hypopigmented or hyperpigmented macules, angiomas, shagreen patches, telangiectasia, subcutaneous nodules, lipomas, papillomata
- Signs of **congenital heart disease** or heart failure (suggestive of a neuro-cardio-facio-cutaneous syndrome)
- **Hepatosplenomegaly** (suggestive of a metabolic or storage disorder)
- Evidence of **skeletal dysplasia** (eg, short limbs, absent or hypoplastic clavicles)
- **Complete neurologic assessment**: hypotonia is a common feature of overgrowth syndromes; spasticity may be a feature of leukodystrophy

CLINICAL FEATURES OF SELECTED SYNDROMES ASSOCIATED WITH MACROCEPHALY

Syndrome	Clinical features (in addition to macrocephaly)
Predominantly cutaneous syndromes	
Tuberous sclerosis 1* MIM #191100	Facial angiofibromas, shagreen patch, hypopigmented macules, periungual fibromas, gingival fibromas
Neurofibromatosis type 1* MIM #162200	Café-au-lait spots, axillary freckling, dermal neurofibroma, short stature, Lisch nodules
Linear epidermal nevus syndrome MIM #163200	Asymmetric overgrowth, coloboma (eyelids, iris, choroid), linear nevus sebaceous; associated with basal cell carcinoma
Klippel-Trenaunay-Weber MIM %149000	Large cutaneous hemangioma with hypertrophy of related bones and soft tissues; syndactyly; polydactyly
Proteus MIM #176920	Asymmetric, disproportionate overgrowth of body parts, epidermal nevi, hypertrophy of skin of soles, hemangioma (thorax, upper abdomen)
Megalencephaly-capillary malformation-polymicrogyria syndrome MIM #602501	Vascular mottling of the skin; congenital telangiectasias, syndactyly of second and third toes; polydactyly; asymmetry of the head, face, or body; nevus flammeus of the lip and/or philtrum; overgrowth with prenatal onset
Nevoid basal cell carcinoma syndrome* (Gorlin syndrome) MIM #109400	Frontoparietal bossing, broad nasal bridge, coarse facial features, highly arched eyebrows, pouting lower lip; odontogenic keratocysts of the mandible and maxilla; increased risk of basal cell carcinoma
PTEN hamartoma tumor syndromes	
Cowden syndrome* (including Lhermitte-Duclos syndrome and Bannayan-Riley-Ruvalcaba syndrome) MIM #158350	Birdlike facies; hypoplastic mandible and maxilla; cataract; microstomia; high-arched palate; pectus excavatum; genitourinary anomalies; skin tags; lipomas; subcutaneous nodules
Predominantly overgrowth syndromes	
Sotos MIM #117550	High prominent forehead, down-slanting palpebral fissures, long pointed chin, high-arched palate; tall stature and advanced bone age; normal adult height
Weaver* MIM #277590	Accelerated growth with prenatal onset, advanced bone age, broad forehead, flat occiput, long philtrum, camptodactyly, broad thumbs, loose skin, deep-set nails; deep palmar and plantar creases
Simpson-Golabi-Behmel MIM #312870	Accelerated growth with prenatal onset (weight more affected than height), coarse facial features, down-slanting palpebral fissures, thickened lips, wide mouth, large tongue, high-arched palate, prominent jaw, short neck, supernumerary nipples, hepatomegaly
Beckwith-Wiedemann* MIM #130650	Omphalocele (or other umbilical abnormalities), hemihypertrophy, coarse facial features, macroglossia, neonatal macrosomia, neonatal hypoglycemia, increased risk of certain tumors (eg, Wilms tumor, hepatoblastoma)
Neuro-cardiofaciocutaneous syndromes¶	
Noonan* MIM #163950	Short stature (postnatal onset), congenital heart defects (atrial septal defect, ventricular septal defect, pulmonic stenosis), webbed neck, abnormal chest, hypertelorism, down-slanting palpebral fissures, epicanthal folds, deafness (sensorineural); deeply grooved philtrum
LEOPARD* MIM #151100	Lentigines, ECG conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, deafness (sensorineural)
Costello* MIM #218040	Poor weight gain, short stature, developmental delay, coarse facial features, deep palmar and plantar creases, papillomata, cardiac abnormalities, risk for tumors
Cardiofaciocutaneous MIM #115150	Cardiac abnormalities (atrial septal defect, pulmonic stenosis, hypertrophic cardiomyopathy), cutaneous abnormalities (ichthyosis, hyperkeratosis, hemangioma), postnatal short stature, prominent forehead, bitemporal narrowing, coarse facial features, prominent philtrum, down-slanting palpebral fissures, short upturned nose

PTEN: phosphate and tensin homolog deleted on chromosome gene; ECG: electrocardiogram.

* Autosomal dominant inheritance.

¶ Associated with mutations in the Ras/mitogen-activated protein (MAP) kinase signaling pathway genes.

POSTNATAL MACROCEPHALY: INVESTIGATIONS

- **Ophthalmologic evaluation**
- **Neurologic evaluation**
- Neurosurgical evaluation (if other signs and symptoms of ICP in the setting of ER, or in case of syndromic/isolated craniosynostoses in outpatient setting)

- (Genetic evaluation)
- (Metabolic evaluation)
- (Neuropsychologic evaluation)

- Skeletal survey in young children in whom physical abuse is suspected (eg, those with subdural hematoma)

POSTNATAL MACROCEPHALY: NEUROIMAGING

WHEN

- Alarming signs and symptoms
- Increase in head circumference across several major percentiles
- Neurologic or developmental symptoms

POSTNATAL MACROCEPHALY: NEUROIMAGING

Ultrasonography

- when anterior fontanelle is open
- in infants with macrocephaly, normal neurodevelopment, no evidence of increased ICP
- it may identify ventricular or subarachnoid space enlargement

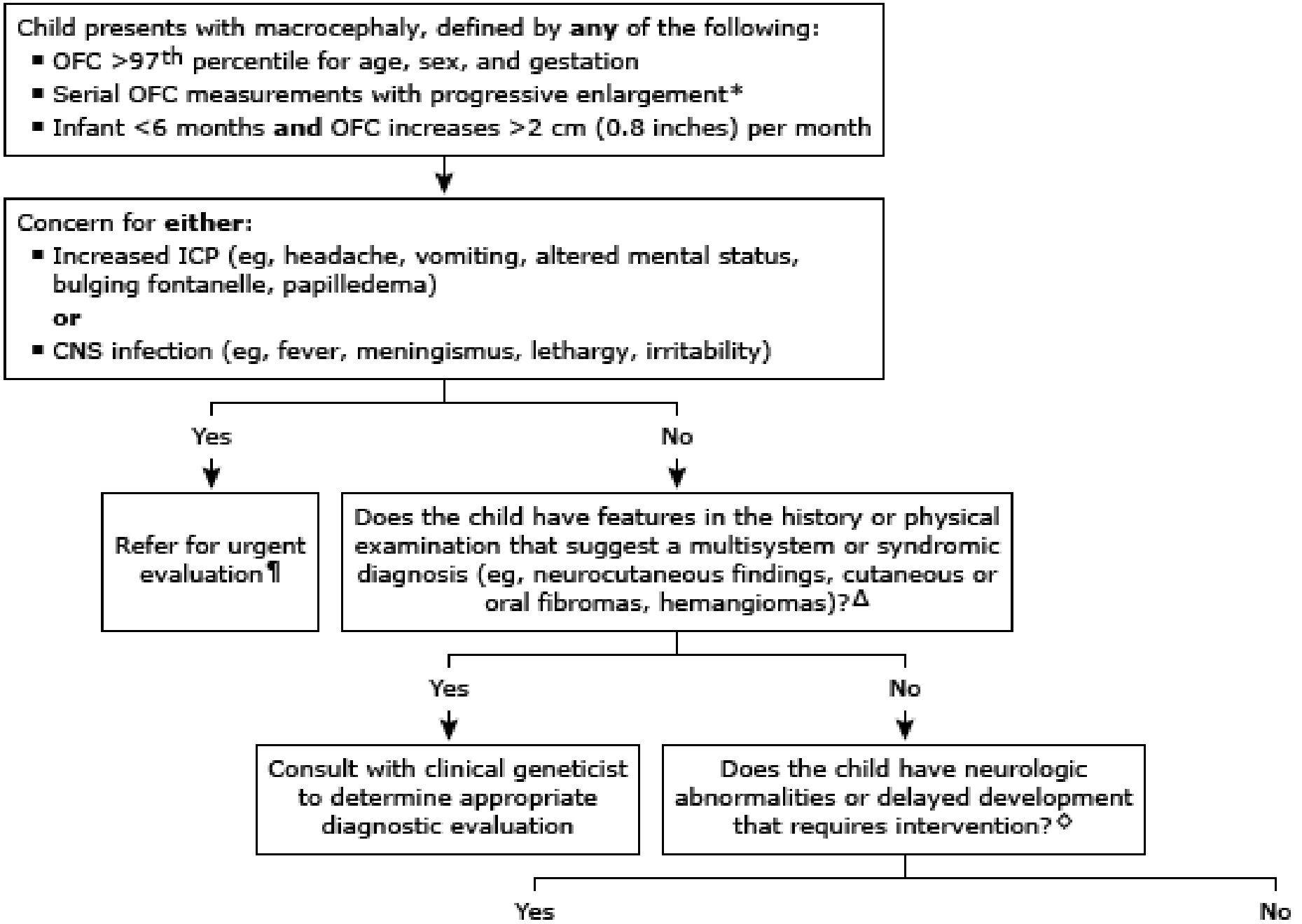
MRI

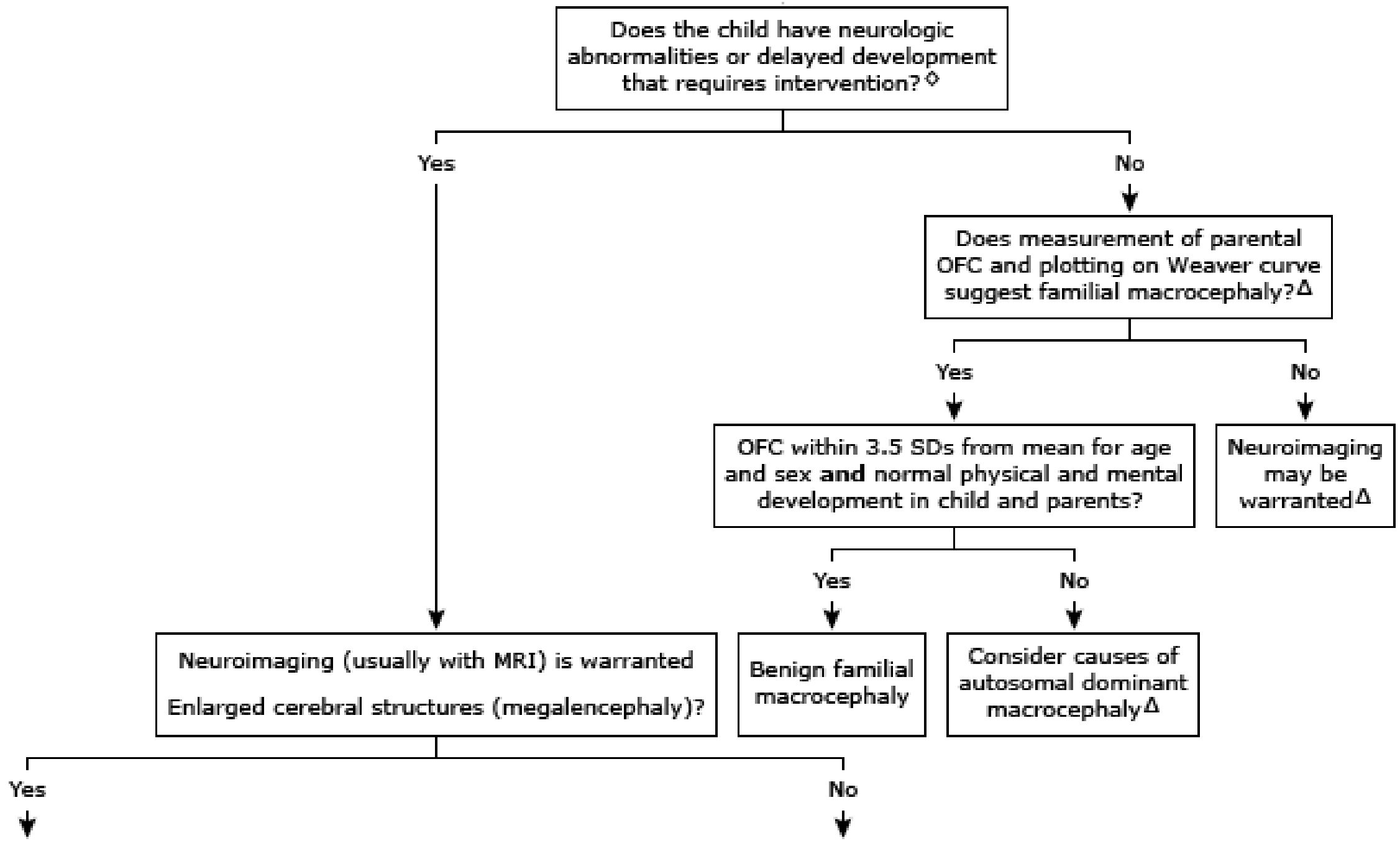
- infants with neurologic abnormalities, and/or progressively enlarging head circumference (without evidence of benign familial megalencephaly) or increased ICP
- determines size and position of the ventricles and width of the subarachnoid space; distinguishes communicating from noncommunicating hydrocephalus; identifies white matter changes, mass lesions, vascular malformations, subdural fluid collections, and porencephalic cysts; MRI with contrast or angiography may be performed to evaluate vascular abnormalities

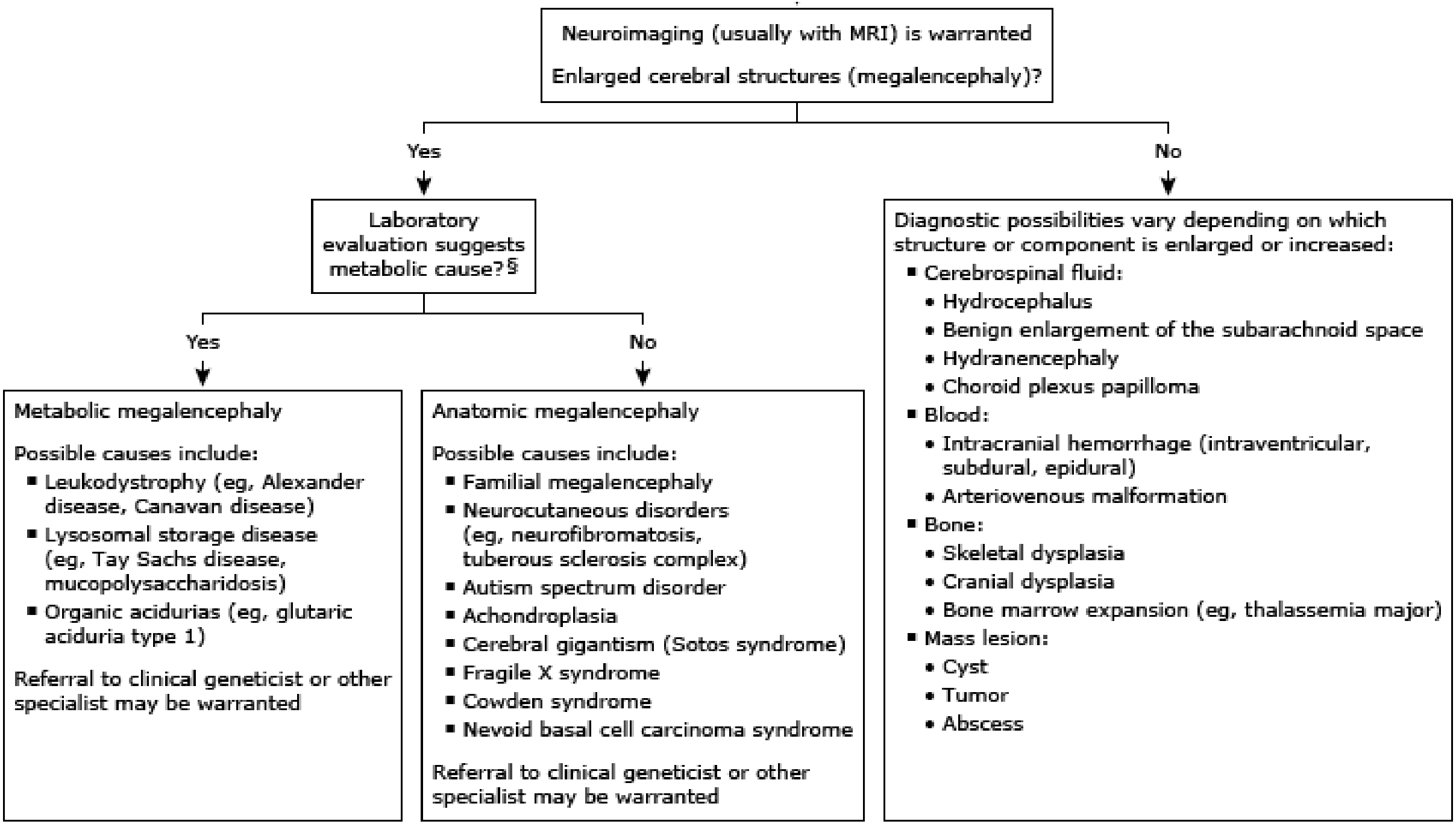
CT

- used in the acute setting
- identifies intracranial calcification and tubers

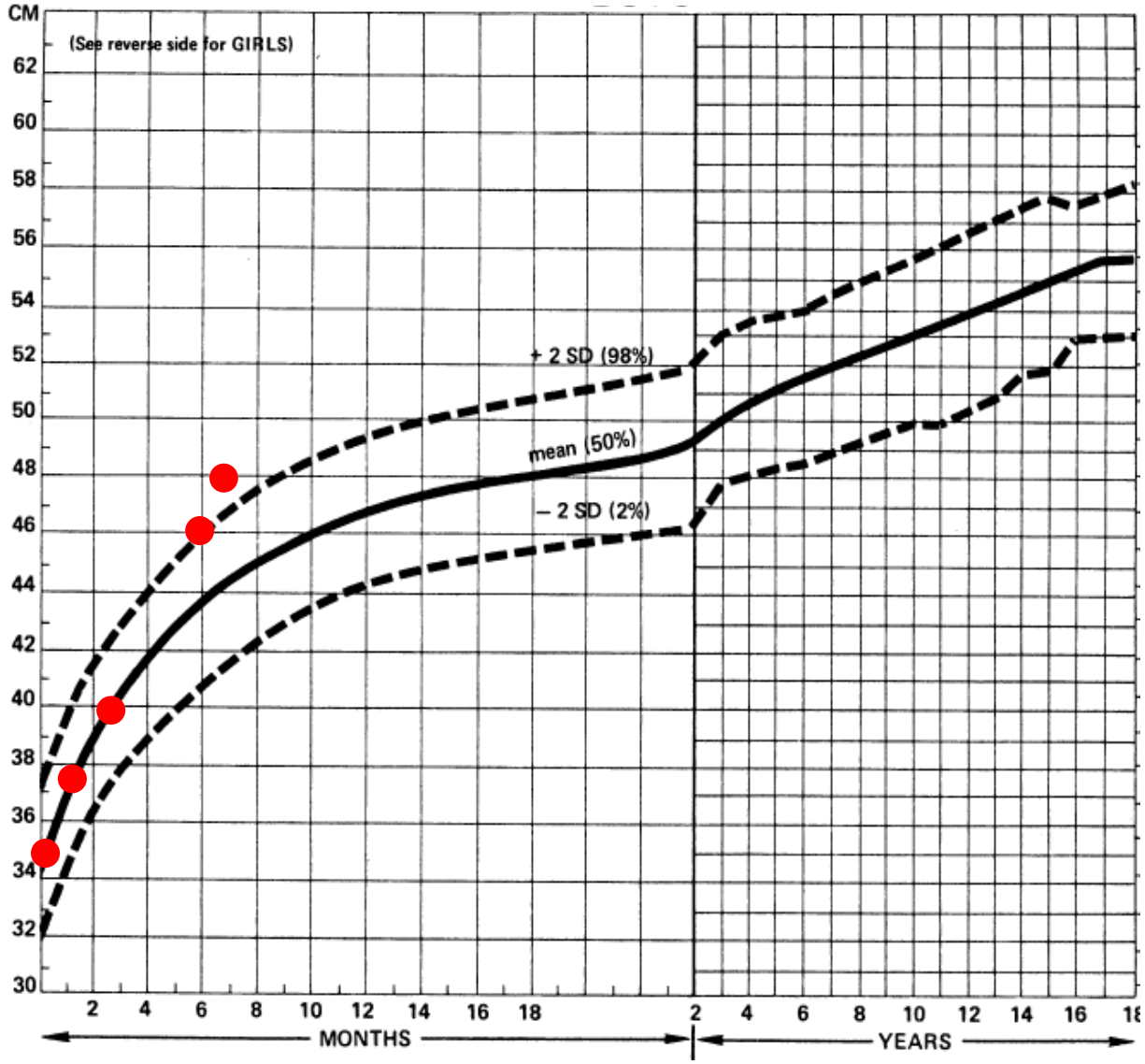
POSTNATAL MACROCEPHALY EVALUATION APPROACH



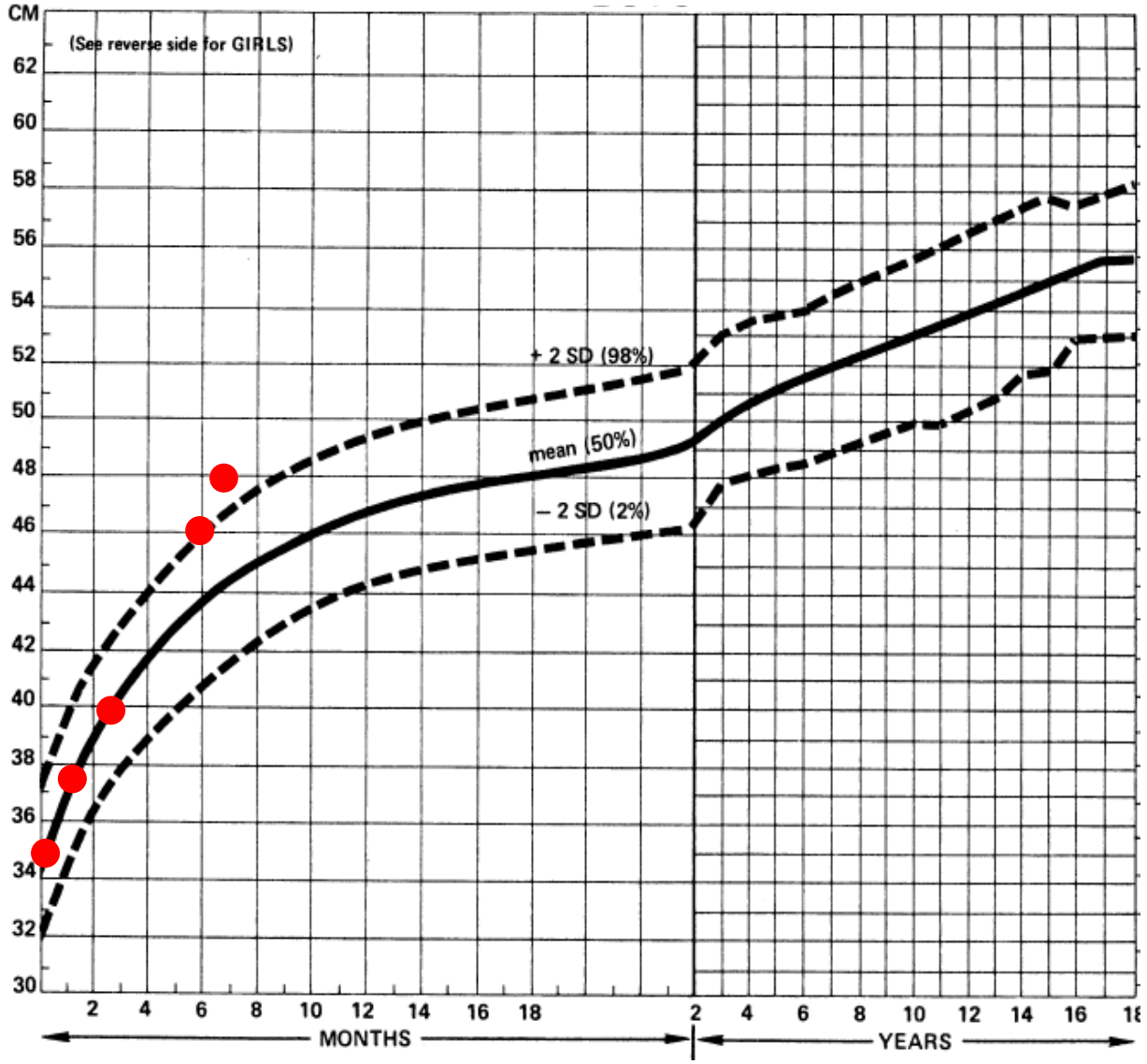

Does the child have neurologic abnormalities or delayed development that requires intervention?◇
Yes
No
Does measurement of parental OFC and plotting on Weaver curve suggest familial macrocephaly?Δ
Yes
No
OFC within 3.5 SDs from mean for age and sex and normal physical and mental development in child and parents?
Neuroimaging may be warrantedΔ
Yes
No
Neuroimaging (usually with MRI) is warranted
Enlarged cerebral structures (megalencephaly)?
Benign familial macrocephaly
Consider causes of autosomal dominant macrocephalyΔ
Yes
No


Neuroimaging (usually with MRI) is warranted
Enlarged cerebral structures (megalencephaly)?
Yes
No
Laboratory evaluation suggests metabolic cause?§
Yes
No
Metabolic megalencephaly
Possible causes include:
Leukodystrophy (eg, Alexander disease, Canavan disease)
Lysosomal storage disease (eg, Tay Sachs disease, mucopolysaccharidosis)
Organic acidurias (eg, glutaric aciduria type 1)
Referral to clinical geneticist or other specialist may be warranted
Anatomic megalencephaly
Possible causes include:
Familial megalencephaly
Neurocutaneous disorders (eg, neurofibromatosis, tuberous sclerosis complex)
Autism spectrum disorder
Achondroplasia
Cerebral gigantism (Sotos syndrome)
Fragile X syndrome
Cowden syndrome
Nevoid basal cell carcinoma syndrome
Referral to clinical geneticist or other specialist may be warranted
Diagnostic possibilities vary depending on which structure or component is enlarged or increased:
Cerebrospinal fluid:
Hydrocephalus
Benign enlargement of the subarachnoid space
Hydranencephaly
Choroid plexus papilloma
Blood:
Intracranial hemorrhage (intraventricular, subdural, epidural)
Arteriovenous malformation
Bone:
Skeletal dysplasia
Cranial dysplasia
Bone marrow expansion (eg, thalassemia major)
Mass lesion:
Cyst
Tumor
Abscess

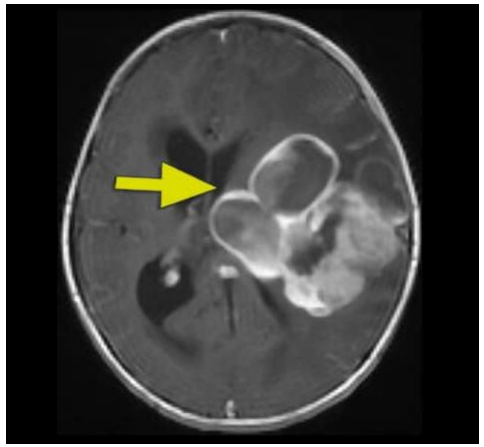
EXAMPLE 2: child with headache a vomiting



EXAMPLE 2: child with headache a vomiting



Brain tumor



MICROCEPHALY

AAN, 2009
Becerra-Solano, 2021
Uptodate, 2023

MICROCEPHALY

2% of the population!

- Defined as head circumference **more than 2 SDs below the mean** (<3rd percentile) for age, sex, and gestation

- It can be distinguished in:
  - **Borderline** microcephaly – head circumference between 2 and 3 SD below the mean
  - **Moderate** microcephaly – head circumference between 3 and 5 SD below the mean
  - **Severe** microcephaly – head circumference ≥5 SD below the mean

  ≠ Microencephaly: abnormally small brain

  Although microcephaly always implies microencephaly, microencephaly may be present in children with normal head circumference

- A **deceleration in head growth rate** must be followed and evaluated as "possible microcephaly"

MICROCEPHALY: CLASSIFICATIONS

- **CONGENITAL (or PRENATAL)**
- **POSTNATAL**

- GENETIC
- ENVIRONMENTAL (or ACQUIRED)

- SYMMETRIC (or PROPORTIONATE)
- ASYMMETRIC (or DISPROPORTIONATE)

- ISOLATED (or PURE)
- SYNDROMIC (or COMPLEX)

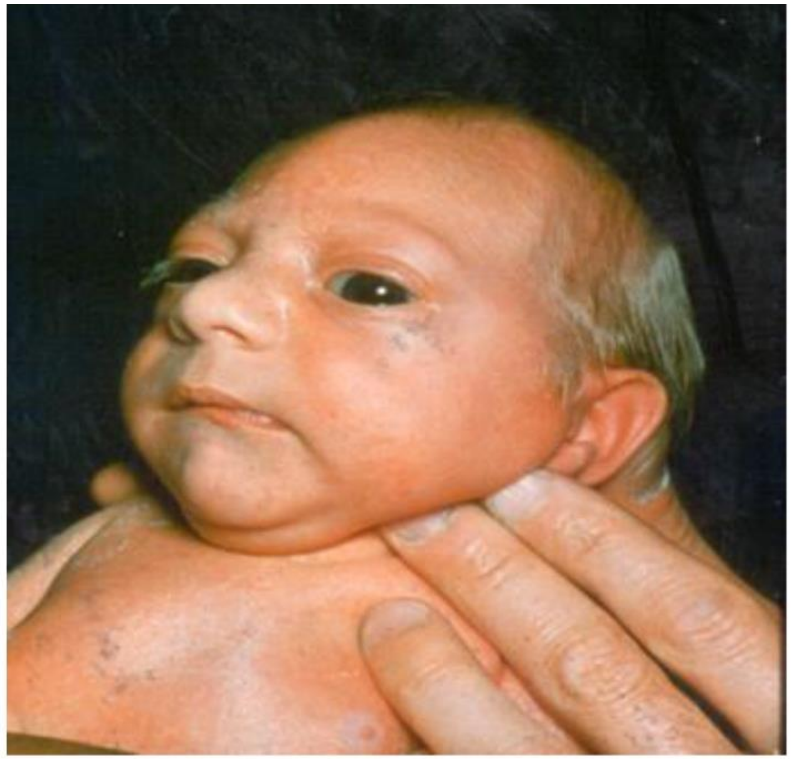
CONGENITAL AND POSTNATAL MICROCEPHALY: CAUSES

Congenital	Postnatal onset
Genetic	**Genetic**
Isolated	***Inborn errors of metabolism***
Autosomal recessive microcephaly	Congenital disorders of glycosylation
Autosomal dominant microcephaly	Mitochondrial disorders
X-linked microcephaly	Peroxisomal disorders
Chromosomal (rare: "apparently" balanced rearrangements and ring chromosomes)	Menkes disease
	Amino acidopathies and organic acidurias
	Glucose transporter defect
Syndromic	***Syndromic***
Chromosomal	
Trisomy 21, 13, 18	
Unbalanced rearrangements	
Contiguous gene deletion	*Contiguous gene deletion*
4p deletion (Wolf-Hirschhorn syndrome)	17p13.3 deletion (Miller-Dieker syndrome)
5p deletion (cri-du-chat syndrome)	
7q11.23 deletion (Williams syndrome)	
22q11 deletion (velocardiofacial syndrome)	
Single gene defects	*Single gene defects*
Cornelia de Lange syndrome	Rett syndrome
Holoprosencephaly (isolated or syndromic)	Nijmegen breakage syndrome
Smith-Lemli-Opitz syndrome	Ataxia-telangiectasia
Seckel syndrome	Cockayne syndrome
	Aicardi-Goutieres syndrome
	XLAG syndrome
	Cohen syndrome

Congenital Acquired	Postnatal onset Acquired
Disruptive injuries	*Disruptive injuries*
Death of a monozygous twin	Traumatic brain injury
Ischemic stroke	Hypoxic-ischemic encephalopathy
Hemorrhagic stroke	Hemorrhagic and ischemic stroke
Infections	*Infections*
TORCHES (toxoplasmosis, rubella, cytomegalovirus, herpes simplex, syphilis) and HIV	Meningitis and encephalitis
	Congenital HIV encephalopathy
Teratogens	*Toxins*
Alcohol, hydantoin, radiation	Lead poisoning
Maternal phenylketonuria	Chronic renal failure
Poorly controlled maternal diabetes	
Deprivation	*Deprivation*
Maternal hypothyroidism	Hypothyroidism
Maternal folate deficiency	Anemia
Maternal malnutrition	Malnutrition
Placental insufficiency	Congenital heart disease

CONGENITAL MICROCEPHALY

- Head circumference **<3 SD below the mean** (<2 SD according to other authors) or below the 2nd percentile for gestational age
- **The majority of cases of microcephaly are congenital**
- The (prental) diagnosis is complicated by **limitations** in accuracy of head circumference measurements and inconsistency between prenatal and postnatal head circumference growth curves.



CONGENITAL MICROCEPHALY: GENETIC CAUSES

- May be **isolated** or **syndromic**

- Isolated microcephaly usually has autosomal **recessive** inheritance (MCPH syndromes)

Isolated
Autosomal recessive microcephaly
Autosomal dominant microcephaly
X-linked microcephaly
Chromosomal (rare: "apparently" balanced rearrangements and ring chromosomes)

Syndromic
Chromosomal
Trisomy 21, 13, 18
Unbalanced rearrangements
Contiguous gene deletion
4p deletion (Wolf-Hirschhorn syndrome)
5p deletion (cri-du-chat syndrome)
7q11.23 deletion (Williams syndrome)
22q11 deletion (velocardiofacial syndrome)
Single gene defects
Cornelia de Lange syndrome
Holoprosencephaly (isolated or syndromic)
Smith-Lemli-Opitz syndrome
Seckel syndrome

CONGENITAL MICROCEPHALY: ACQUIRED CAUSES

- Mainly **TORCH** infections + **Zika** virus
- Maternal exposure to **teratogens**

Disruptive injuries
Death of a monozygous twin
Ischemic stroke
Hemorrhagic stroke
Infections
TORCHES (toxoplasmosis, rubella, cytomegalovirus, herpes simplex, syphilis) and HIV

Teratogens
Alcohol, hydantoin, radiation
Maternal phenylketonuria
Poorly controlled maternal diabetes
Deprivation
Maternal hypothyroidism
Maternal folate deficiency
Maternal malnutrition
Placental insufficiency

CONGENITAL MICROCEPHALY: ACQUIRED CAUSES

Agent, factor or disease	Brain abnormalities	Presence of brain calcifications	Other anomalies
Cytomegalovirus	Ventriculomegaly, subependymal cysts and neuronal migration disorders	Yes	Chorioretinitis, hearing loss, hyperechogenic bowel, intrauterine growth restriction (IUGR) and oligohydramnios
Herpes simplex virus	Hydrocephalus, porencephalic cyst and subependymal cysts	Yes	Chorioretinitis and microphthalmia
Rubella	Subependymal cysts	Yes	Hearing loss, cataracts, retinopathy, cardiac abnormalities and IUGR
Toxoplasmosis	Hydrocephalus (aqueductal stenosis)	Yes	Chorioretinitis and optic atrophy
Syphilis	Hydrocephalus and pseudoparalysis	Yes	Hearing loss, dental anomalies and pulmonary hemorrhage
Varicella zoster	Hydrocephalus and cortical atrophy	No	Microphthalmia, cataracts, chorioretinitis, skeletal abnormalities, limb hypoplasia, IUGR and scars
Acquired immunodeficiency syndrome	Cerebral atrophy, ventriculomegaly and white matter abnormalities	Yes	Long palpebral fissures, hypertelorism, blue sclera, depressed nasal bridge, deep philtrum, prominent vermilion border and IUGR
Zika virus	Cortical atrophy, ventriculomegaly, malformations of cortical development, corpus callosum abnormalities, enlargement of subarachnoid space, cerebellar hypoplasia, brain stem hypoplasia, mega cisterna magna and delayed myelination	Yes	Hypertonia/spasticity, hyperreflexia, epileptogenic activity, neurodevelopmental delay, arthrogryposis, hearing loss and visual disturbances

CONGENITAL MICROCEPHALY: ACQUIRED CAUSES

Prenatal exposure to drugs or toxic substances			
Alcohol	Agenesis of the corpus callosum and abnormal cortical gyration	No	Dysmorphic facial features, hearing loss, cardiac abnormalities, renal anomalies, scoliosis and IUGR
Cocaine	Intracranial hemorrhage and encephalocele	No	Craniofacial abnormalities and cardiac abnormalities
Anti-epileptic drugs (carbamazepine, phenytoin, barbiturates and sodium valproate)	Spina bifida	No	Dysmorphic facial features, facial cleft, cardiac abnormalities, digital anomalies and IUGR
Maternal diseases and perinatal factors			
Phenylketonuria	Abnormal cortical gyration	No	Small for gestational age, epileptogenic activity, neurodevelopmental delay, dysmorphic facial features, esophageal atresia, cardiac abnormalities, vertebral defects, renal anomalies, bladder exstrophy, digital anomalies and IUGR
Placental insufficiency, malnutrition, anemia and systemic disease	Impaired cortical axonal cytoarchitecture, neurodegeneration, porencephaly, periventricular leukomalacia and neural tube defects	No	Acute encephalopathy, epileptogenic activity, hypotonia, neurodevelopmental delay, microphthalmia, sensorineural hearing loss, cardiac abnormalities, anemia, and IUGR
Hypoxic-ischemic lesions (pre or postnatal)/Intraventricular hemorrhage	Basal ganglia, thalamus, white matter and cerebral cortex abnormalities, hypoplasia of the corpus callosum, ventricular dilatation and diffuse gray matter abnormalities	Yes	Epileptogenic activity, hypotonia or hypertonia, hearing loss, hemiplegia, diplegia or quadriplegia, neurodevelopmental delay and behavioral disorders

POSTNATAL MICROCEPHALY: GENETIC CAUSES

- Metabolic (Eg, **PKU**, **GLUT1** deficiency)
- Syndromic (Eg, **Rett** and **Angelman** syndromes)

Inborn errors of metabolism
Congenital disorders of glycosylation
Mitochondrial disorders
Peroxisomal disorders
Menkes disease
Amino acidopathies and organic acidurias
Glucose transporter defect

Syndromic
Contiguous gene deletion
17p13.3 deletion (Miller-Dieker syndrome)
Single gene defects
Rett syndrome
Nijmegen breakage syndrome
Ataxia-telangiectasia
Cockayne syndrome
Aicardi-Goutieres syndrome
XLAG syndrome
Cohen syndrome

POSTNATAL MICROCEPHALY: ACQUIRED CAUSES

- Mainly **hypoxic-ischemic encephalopathy** and **infections**

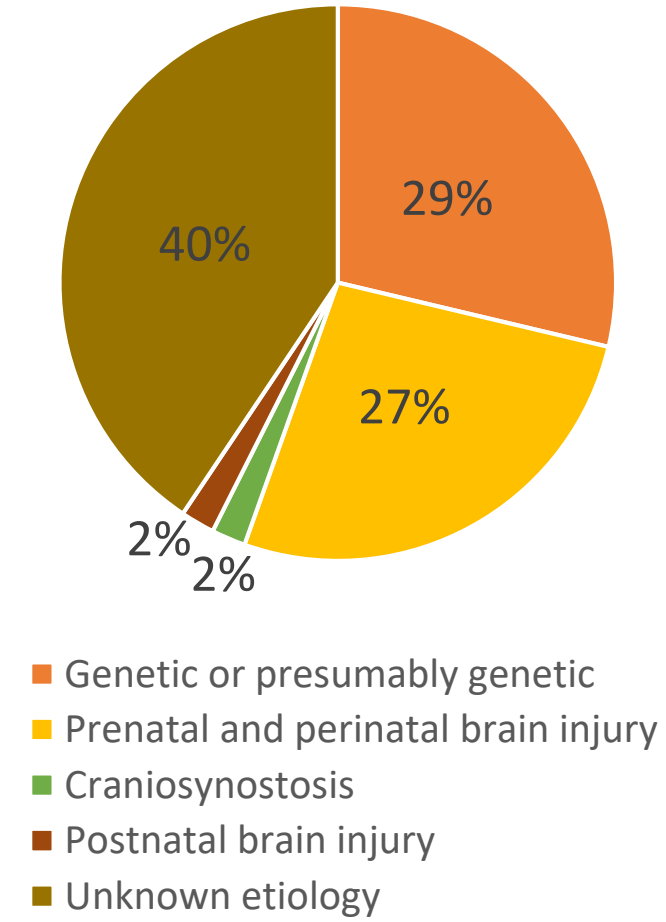
Disruptive injuries
Traumatic brain injury
Hypoxic-ischemic encephalopathy
Hemorrhagic and ischemic stroke
Infections
Meningitis and encephalitis
Congenital HIV encephalopathy

Toxins
Lead poisoning
Chronic renal failure
Deprivation
Hypothyroidism
Anemia
Malnutrition
Congenital heart disease

CONGENITAL AND POSTNATAL MICROCEPHALY: CAUSES

- In the majority of cases, the cause of microcephaly remains **unknown**

- In a retrospective series of 680 children with microcephaly who presented for pediatric neurology evaluation at two centers in Germany, the etiologic distribution was as illustrated in the pie chart: **40%** of the cases remained of unknown etiology



MICROCEPHALY: EVALUATION

WHEN TO BEGIN EVALUATION

- **Single** head circumference measurement more than 2 to 3 SD below the mean

or

- **Progressive decrease** in head size (ie, crossing of ≥2 major percentile lines [eg, 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th}] between health supervision visits

MICROCEPHALY: HISTORY

- **Prenatal** history, particularly maternal medical problems (eg, diabetes, epilepsy, PKU, medications, infections, tobacco, alcohol, or substance use, radiation exposure), findings of antenatal ultrasonography
- **Birth** history (eg, perinatal complications, infections, metabolic issues)
- Weight, length, and head circumference **at birth** and **trajectory**
- History of **seizures**
- **Developmental** history (regression of milestones may indicate metabolic disease)
- **Parents' and siblings' head circumference**
- **Family history** of consanguinity or similarly affected individuals.

  The family history should include three generations to detect recessive disorders, which may skip a generation

MICROCEPHALY: PHYSICAL EXAMINATION

- Weight, length and head circumference **trajectories**
- **Dysmorphic** features
- Head shape, **fontanelles** and cranial sutures
- Examination of the **eyes** (eg, chorioretinitis, cataract suggestive of intrauterine infection or metabolic disease)
- Examination of the **oropharynx** (eg, single maxillary incisor and cleft palate in holoprosencephaly)
- Examination of the **skin** (eg, petechiae and/or jaundice suggestive of intrauterine infection)
- Hepatomegaly or splenomegaly suggestive of congenital infection
- **Complete neurologic evaluation**: children with microcephaly are at risk for cerebral palsy and intellectual/developmental disability

SYNDROMIC MICROCEPHALY: ASSOCIATED FEATURES

Syndrome	Clinical features
Down syndrome MIM #190685	Brachycephaly, upslanting palpebral fissures, epicanthal folds, short neck, transverse palmar crease, space between first and second toes, hypotonia
Trisomy 18	Prominent occiput, narrow bifrontal diameter, hypoplastic supraorbital ridge, short palpebral fissures, micrognathia, structural cardiac lesions (VSD, ASD, PDA)
Trisomy 13	Holoprosencephaly, wide sagittal suture, cleft lip, cleft palate, loose skin, transverse palmar crease, polydactyly, posterior prominence of heel; structural cardiac lesions (VSD, PDA, ASD, dextrocardia)
Fetal alcohol syndrome	Pre- and postnatal growth retardation, short palpebral fissures, flat philtrum, thin upper lip
Seckel syndrome MIM #210600	Pre- and postnatal growth retardation, average birth weight approximately 1540 g, proportionate short stature; micrognathia, facial asymmetry, downslanting palpebral fissures, prominent beaked nose; limb hypoplasia; gap between first and second toes
Smith-Lemli-Opitz syndrome MIM #270400	Ptosis, broad nasal tip, anteverted nostrils, cleft palate, micrognathia, congenital heart defects, syndactyly of second and third toes, postaxial polydactyly, hypospadias or cryptorchidism (in males)
Williams-Beuren (7q11.23 deletion) MIM #194050	Cardiovascular disease (supravalvular aortic stenosis), idiopathic hypercalcemia, periorbital fullness, short upturned nose, long philtrum, wide mouth, full lips
Cornelia de Lange syndrome MIM 122470, 300590, 610759	Pre- and postnatal growth retardation, generalized hirsutism, fusion of eyebrows (synophrys), arched brows, long eyelashes, small upturned nose, thin lips, midline beaking of the upper lip; limb reduction defects, missing fingers, syndactyly of second and third toes
Miller-Dieker lissencephaly (17p13.3 deletion) MIM #247200	Bitemporal narrowing, upturned nose, small jaw, vertical furrowing of forehead, micrognathia, genitourinary anomalies
Wolf-Hirschhorn (4p deletion) MIM #194190	CHD, hearing loss, prominent glabella, hypertelorism, wide nasal bridge, beaked nose, short philtrum, down-turned upper lip
Cri-du-chat (5p15.2 deletion) MIM #123450	Round face, hypertelorism, micrognathia, epicanthal folds, hypotonia, high-pitched cry
Monosomy 1p36 deletion MIM #607872	Brachycephaly, large fontanelle, pointed chin, hearing loss, flat nasal bridge, flat nose, cleft lip, cleft palate, short fifth finger
Mowat-Wilson syndrome MIM #235730	Pre- or postnatal microcephaly, short stature, hypertelorism, iris coloboma, deep-set eyes, downslanting palpebral fissures, cupped ears, pointed chin, seizures, hypospadias (in males), Hirschsprung disease, CHD
Rubinstein-Taybi syndrome MIM #180849	Postnatal short stature, low anterior hairline, hypoplastic maxilla, micrognathia, heavy eyebrows, long eyelashes, broad thumbs, and big toes
Aicardi-Goutières syndrome MIM #225750	Congenital microcephaly, abnormal eye movements, hepatosplenomegaly, cerebral calcification, thrombocytopenia, spasticity, seizures

MICROCEPHALY: ASSOCIATED NEUROLOGIC DISORDERS

- **Developmental disabilities** (**50%**, >severe microcephaly [<3 SDs])
- **Epilepsy** (**40 - 50%**, >postnatal microcephaly)
- Cerebral palsy (21%, >postnatal microcephaly)
- Ophthalmologic disorders (6%, > severe microcephaly)

MICROCEPHALY and SEVERE EPILEPSY GENETIC SYNDROMES

Disorder	Gene(s)	
Structural malformations		
Classic lissencephaly (isolated LIS sequence)	*Lis1, DCX, TUBA1A*	
Lissencephaly: X-linked with abnormal genitalia	*ARX*	
Lissencephaly: autosomal recessive with cerebellar hypoplasia	*RELN*	
Bilateral frontoparietal polymicrogyria (COB)	*GPR56*	
Periventricular heterotopia with microcephaly	*ARFGEF2*	
Schizencephaly	*EMX2 (rare)*	
Holoprosencephaly	*HPE1 21q22.3*	*HPE 6 2q37.1*
	HPE2 2p21	*HPE7 9q22.3*
	HPE3 7q36	*HPE 8 14q13*
	HPE4 18p11.3	*HPE9 2q14*
	HPE5 13q32	
Syndromes		
Wolf-Hirschhorn syndrome	*4p–*	
Angelman syndrome	*UBE3A,15q11-q13*	
Rett syndrome	*Xp22, Xq28*	
MEHMO (mental retardation, epilepsy, hypogonadism, microcephaly, obesity)	*Xp22.13-p21.1*	
Mowat-Wilson syndrome (microcephaly, mental retardation, distinct facial features with/without Hirschsprung disease)	*ZFHX1B, 2q22*	

MICROCEPHALY: INVESTIGATIONS

- Ophthalmologic examination
- Neurologic evaluation

- (Genetic evaluation)
- (Metabolic evaluation)
- (Paediatric infectious disease evaluation)
- (Audiologic examination)

MICROCEPHALY: NEUROIMAGING

WHEN

- Abnormal development
- Syndromic features
- History of CNS trauma or infection
- Associated symptoms
- Family history

MICROCEPHALY: NEUROIMAGING

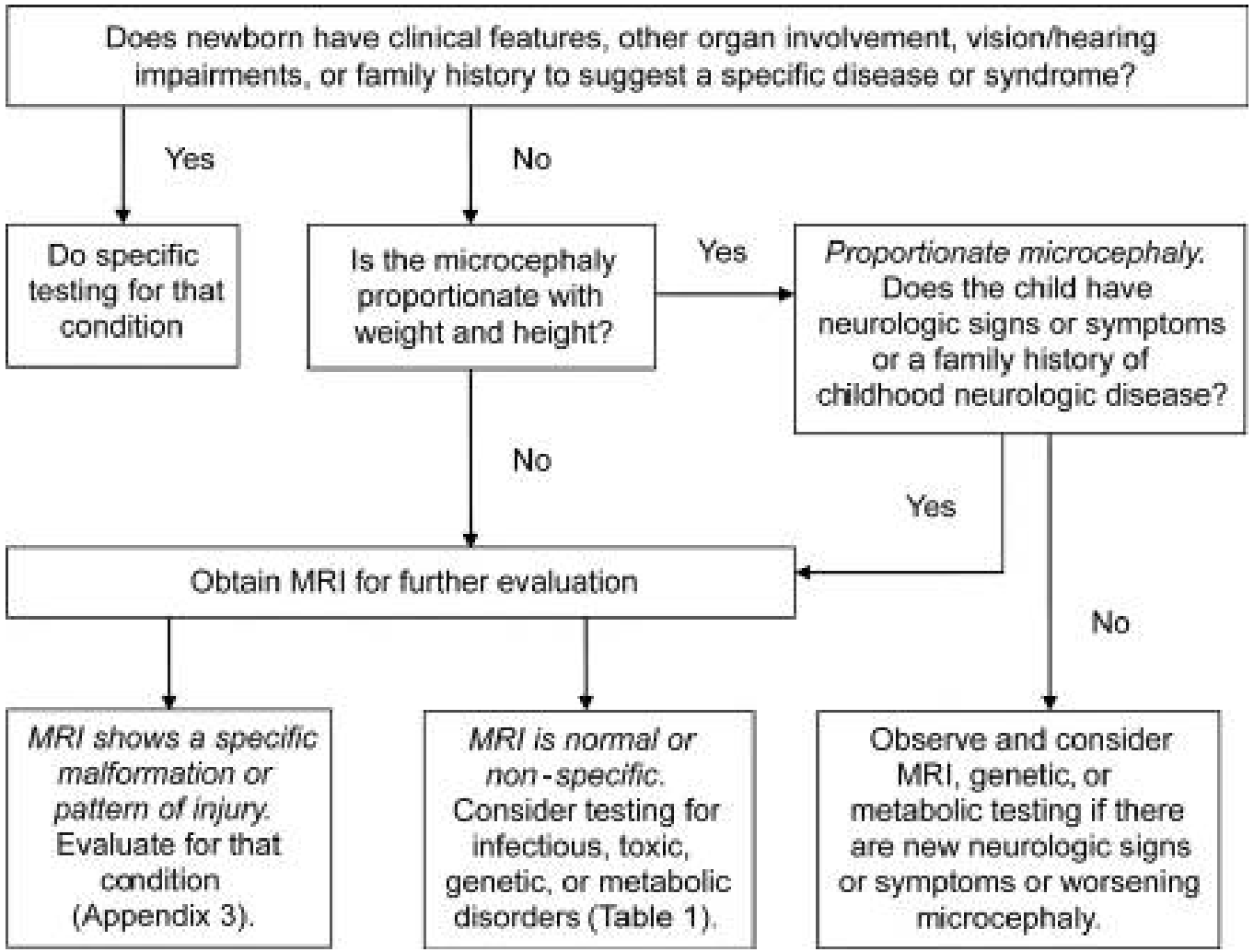
MRI

- Preferred imaging modality
- Repeated MRI after two years of age is recommended given complete myelination at this age

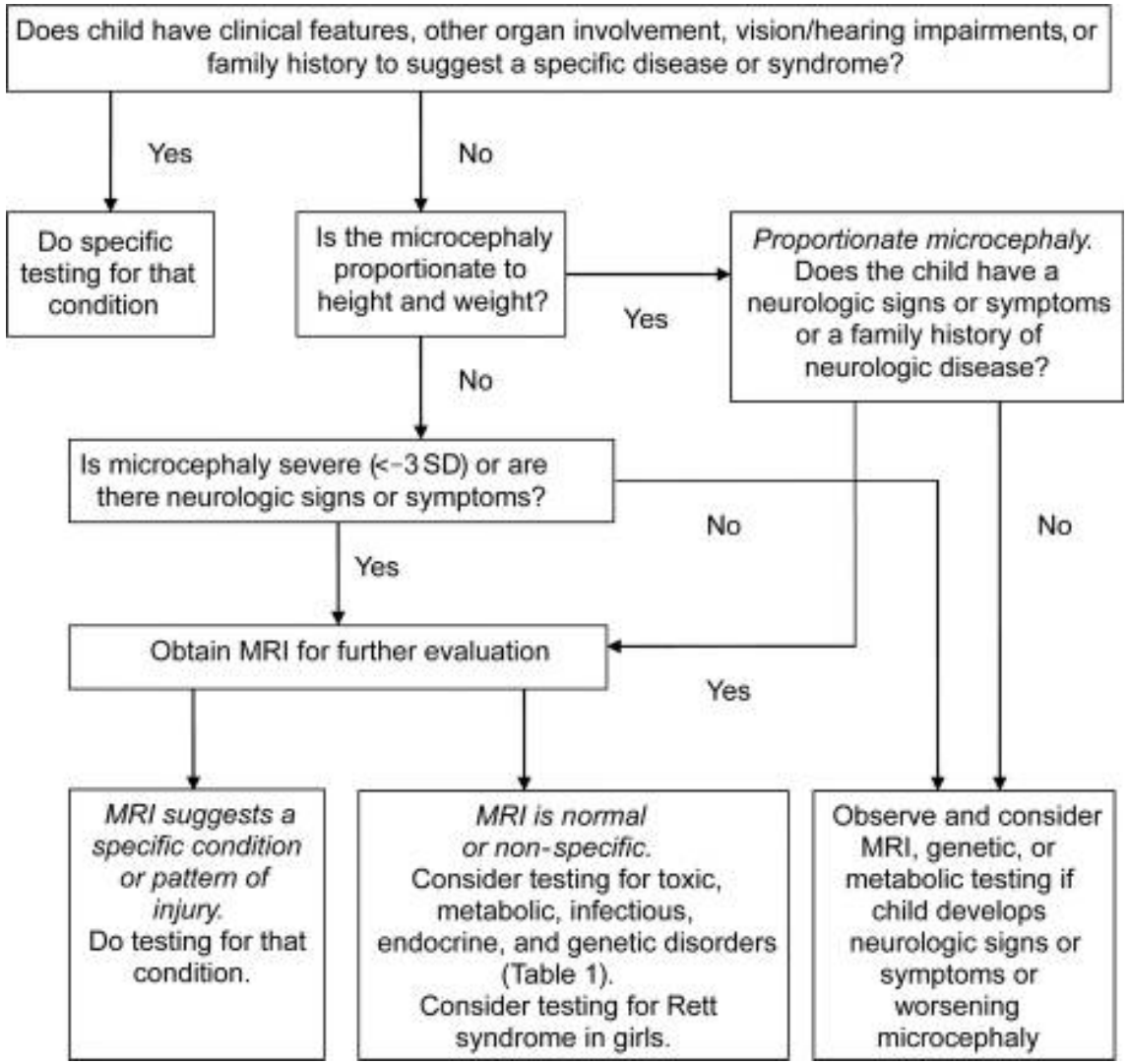
CT

- Better choice in non-acquired craniosynostoses
- TORCH or Zika virus infection (microcalcifications)

CONGENITAL MICROCEPHALY: EVALUATION



POSTNATAL MICROCEPHALY: EVALUATION



FAMILIAL MICROCEPHALY

- Familial microcephaly may reflect:
  - **Familial variation**
  - **Autosomal dominant microcephaly** (normal stature, normal intelligence, no dysmorphic features)

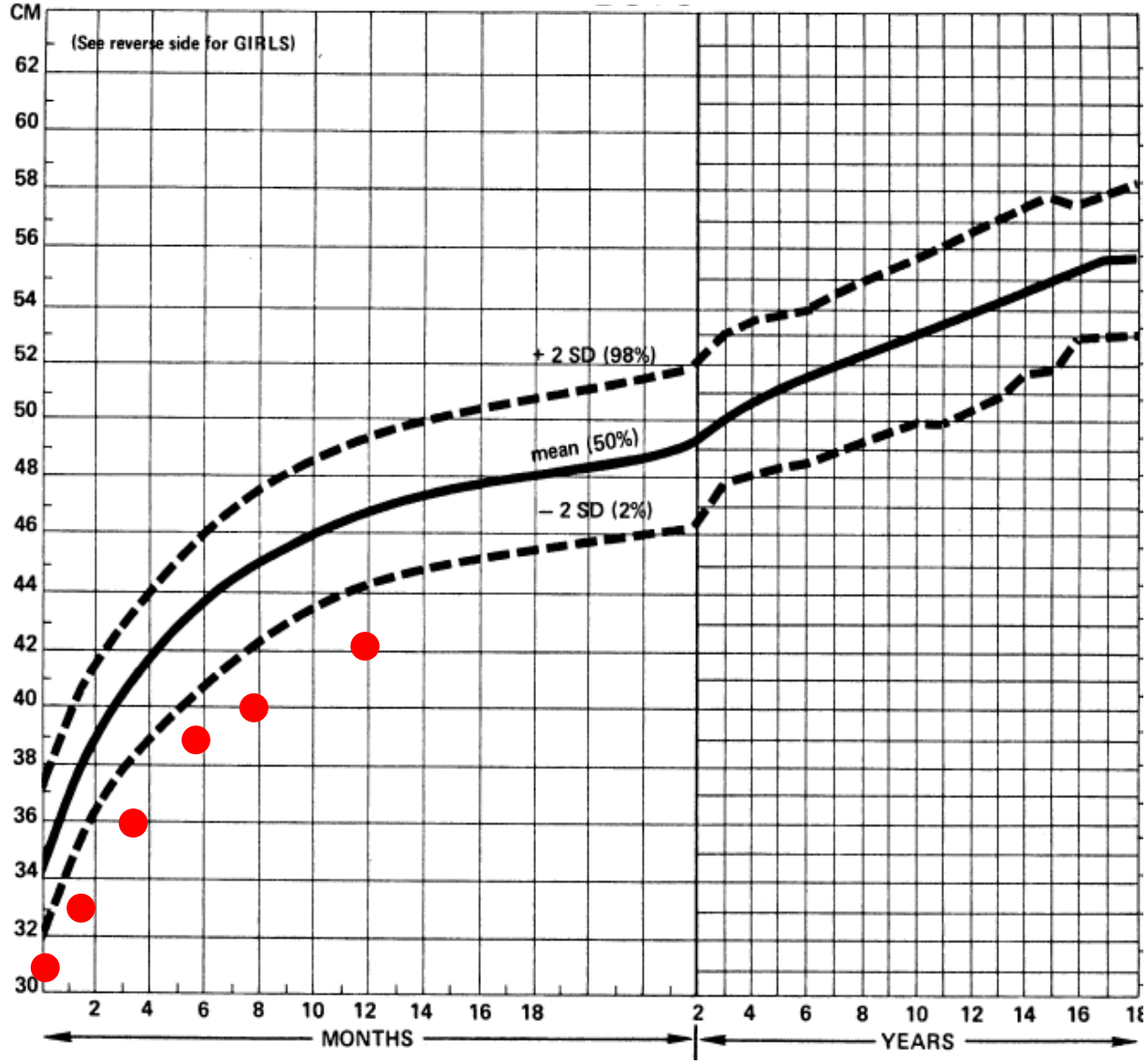
FAMILIAL MICROCEPHALY

- Weaver curves should be used in children without syndromic features, with normal development and whose parents have normal development without syndromic features.

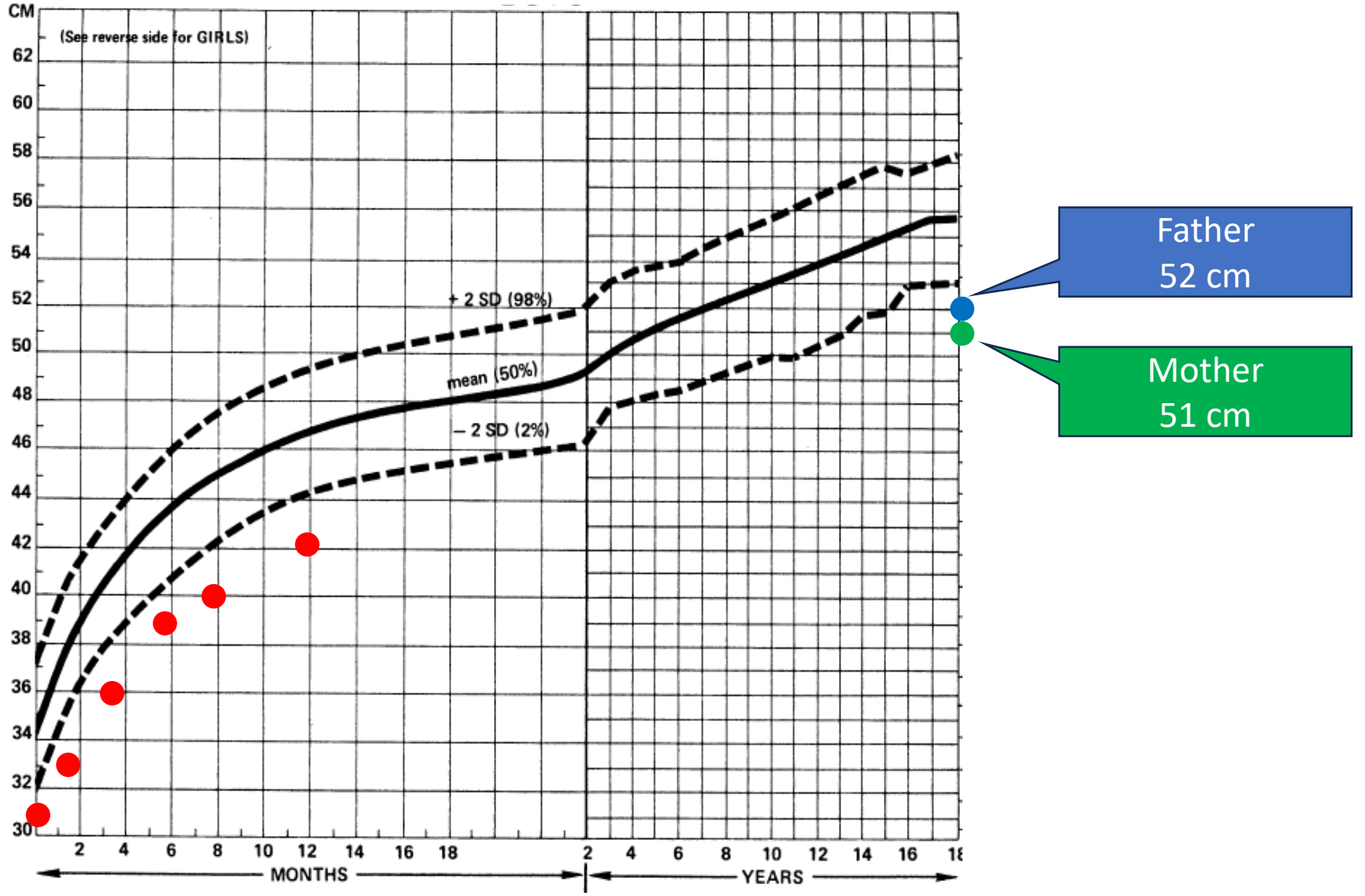
- Familial microcephaly is suggested if the child's SS is within the range determined by the average parental SS. In these cases, particularly if the child's head circumference is **2 to 3 SDs** below the mean for age and sex, additional evaluation may be deferred unless the child develops neurologic findings or the microcephaly worsens.

- Familial microcephaly is unlikely if the child's SS is below the range determined by the average parental SS score; additional evaluation may be warranted, particularly if the child's OFC is **>3 SDs** below the mean for age and sex.

EXAMPLE 1: child with normal development, normal neurologic examination, no syndromic features



EXAMPLE 1: child with normal development, normal neurologic examination, no syndromic features



WEAVER CURVES

Weaver curves determine the genetic contribution to microcephaly

1. Obtain the parents' head circumference

2. Calculate a standard score (SS) for the child and each of the parents using the following formula:

   Standard score (SS) = (OFC - mean value)/standard deviation (SD)

   (Use Nellhaus chart to calculate the mean values and SD for age and sex)
   (Use the mean value and SD for an 18-year-old to calculate the parents' SD)

3. Plot the average of the parents' SS and the child's SS on the Weaver curve

4. A genetic contribution to microcephaly is suggested if the child's SS is within the range determined by the average parental score

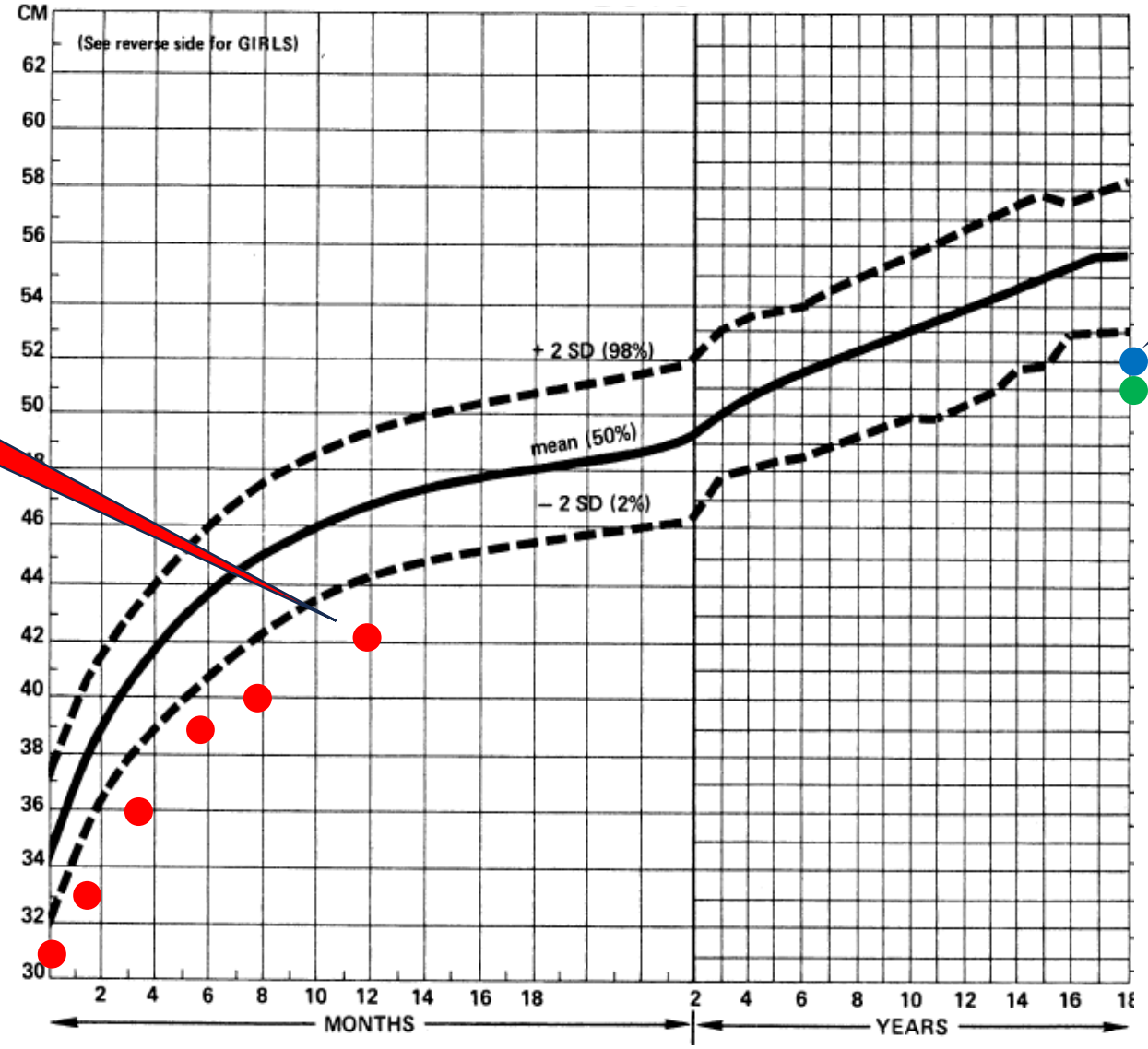
Age	Males		Females	
	Mean (cm)	1 SD	Mean (cm)	1 SD
Birth	34.74	1.33	34.02	1.22
1 mo	37.30	1.30	36.43	1.22
3 mo	40.62	1.23	39.71	1.20
6 mo	43.76	1.29	42.68	1.38
9 mo	45.75	1.28	44.69	1.30
12 mo	47.00	1.31	45.81	1.29
18 mo	48.31	1.36	47.27	1.36
2 yr	49.19	1.39	48.02	1.29
3 yr	50.63	1.38	49.25	1.36
4 yr	50.91	1.39	50.10	1.37
5 yr	51.41	1.37	50.55	1.32
6 yr	51.40	1.41	50.52	1.31
7 yr	52.24	1.52	51.46	1.35
8 yr	52.35	1.40	51.64	1.44
9 yr	52.58	1.44	51.87	1.33
10 yr	53.16	1.41	52.15	1.50
11 yr	53.25	1.53	52.64	1.39
12 vr	53.71	1.52	53.01	1.50
13 yr	54.14	1.57	53.70	1.37
14 yr	54.59	1.30	54.04	1.39
15 yr	54.95	1.51	54.39	1.34
16 yr	55.37	1.11	54.64	1.16
17 yr	55.77	1.32	54.78	1.35
18 yrs and older	55.95	1.34	54.94	1.40

EXAMPLE 1: child with normal development, normal neurologic examination, no syndromic features

SS = (OFC - mean value) / SD

Child
42 cm
SS = -2.95

SS = (42-45.81) / 1.29



Father
52 cm
SS = -2.95

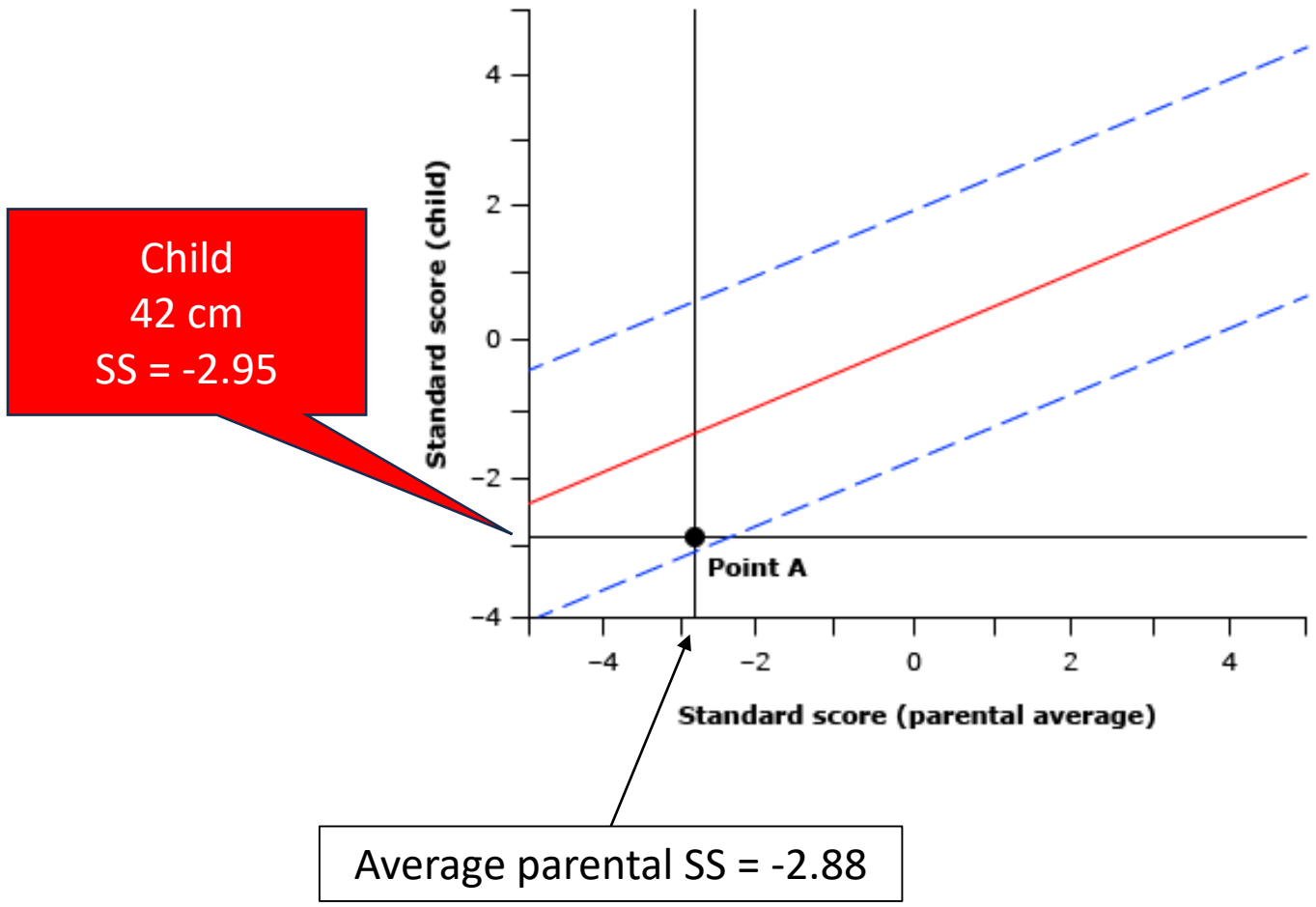
SS = (52-55.95) / 1.34

Mother
51 cm
SS = -2.81

SS = (51-54.94) / 1.40

Average parental SS: -2.88

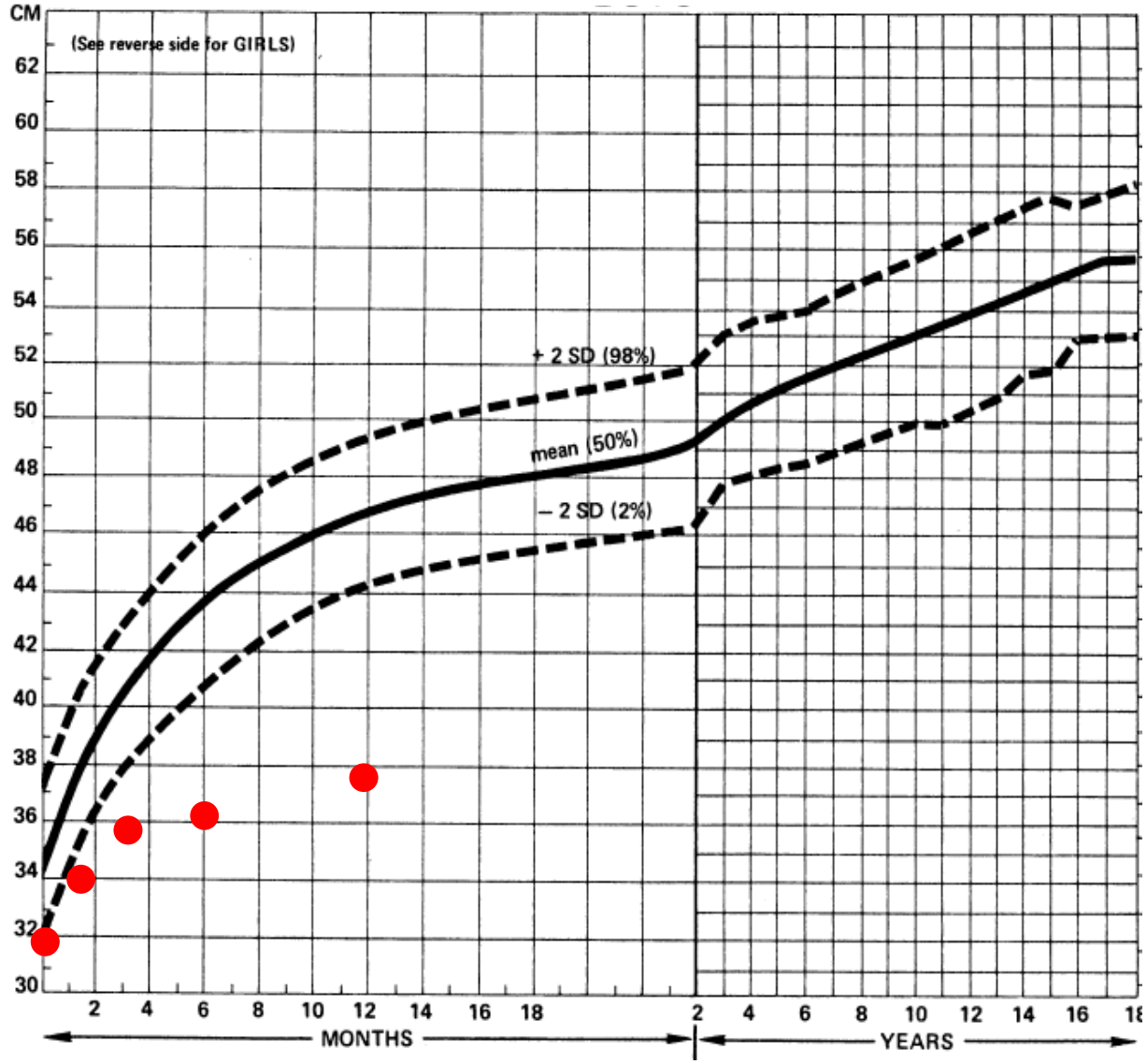
EXAMPLE 1: child with normal development, normal neurologic examination, no syndromic features



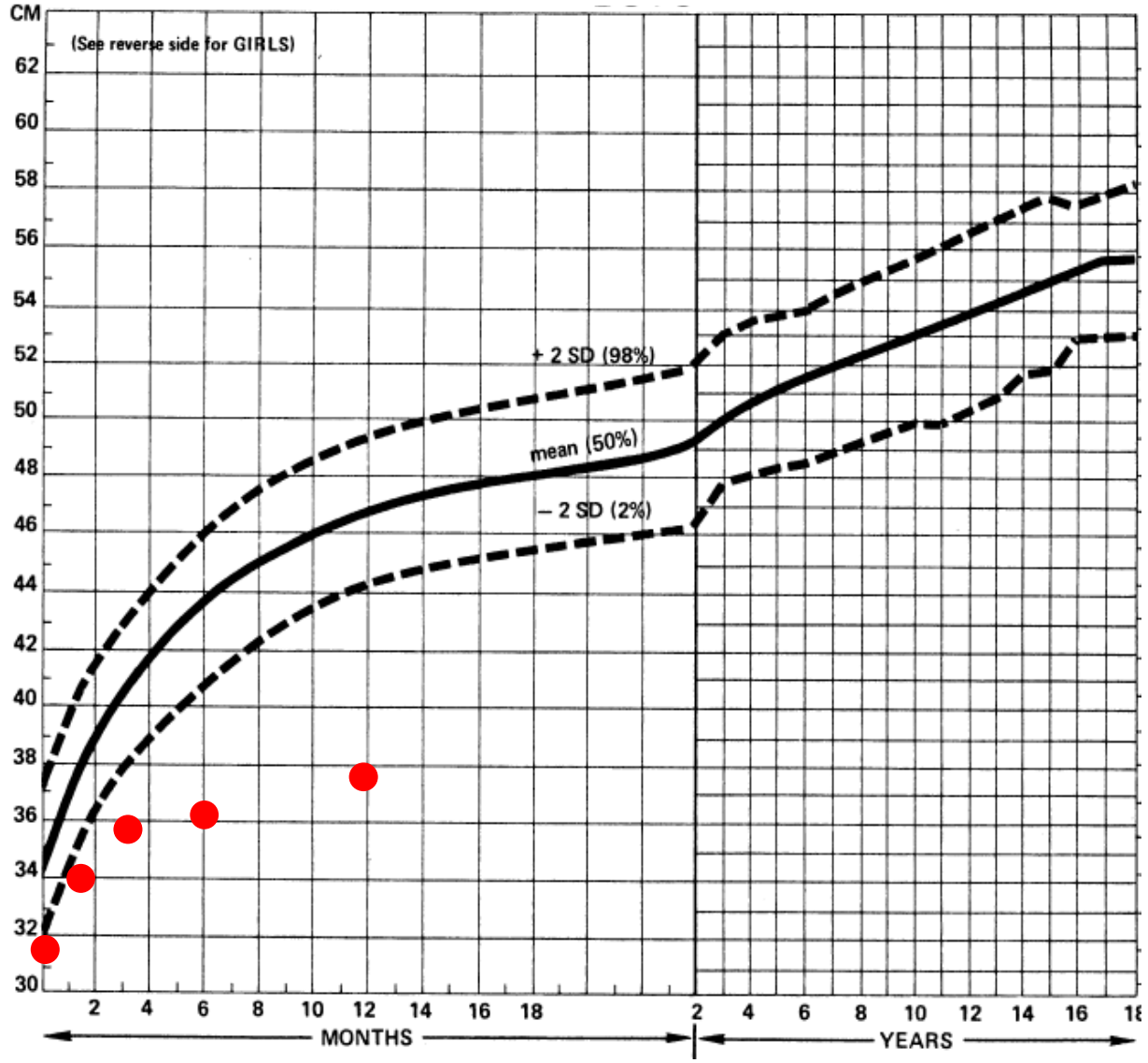
When plotted in the Weaver curve, the intercept (point A) of lines from the SS falls within 2 SD of the regression line.

Thus, the child's head size in relationship to that of his parents is judged to be normal.

EXAMPLE 2: child with microcephaly and hearing loss

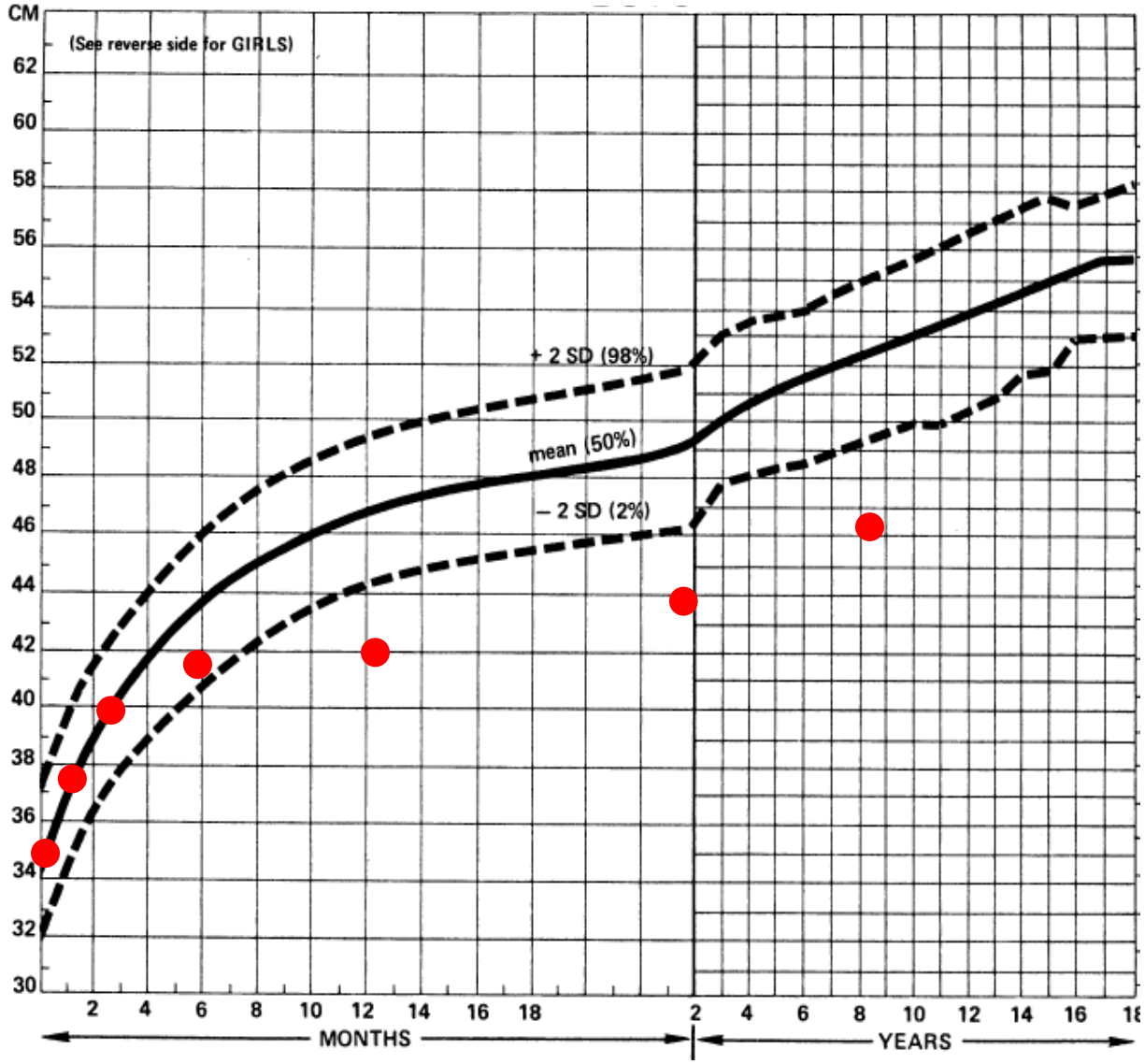


EXAMPLE 2: child with microcephaly and hearing loss

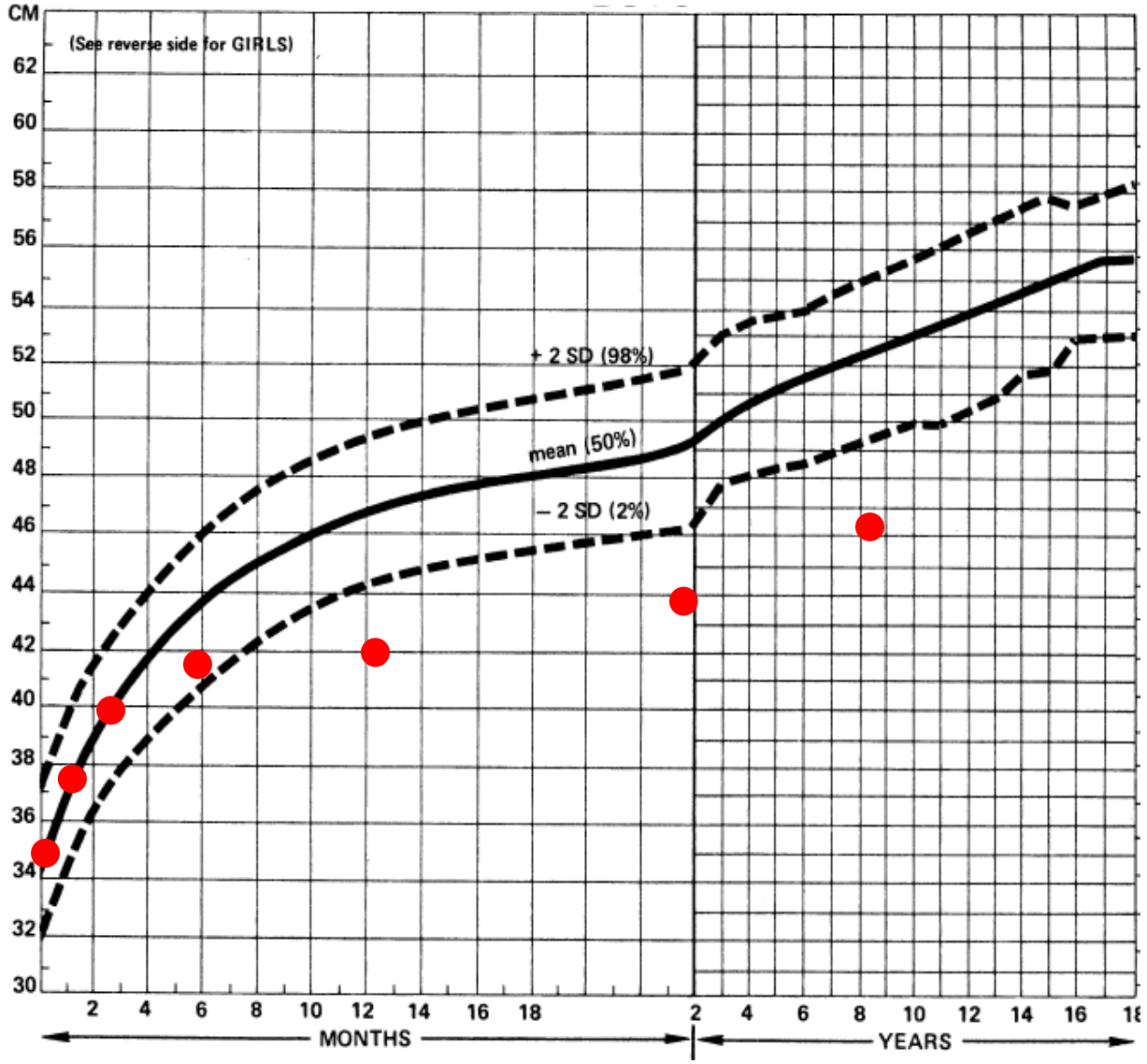


Congenital CMV infection

EXAMPLE 3: girl with deceleration in head growth rate and stagnation



EXAMPLE 3: girl with deceleration in head growth rate and stagnation



Rett syndrome


THANK
YOU
FOR
YOUR
ATTENTION


POSO
SESSO
RENDE
MIOPI
Seplicemente
Super