



# Postnatal Imaging of the Microcephalic Pediatric Patient

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## Abstract

The purpose of this article is to review the clinical and imaging manifestations of microcephaly, with an emphasis on syndromic causes. Defined as a head circumference greater than 2 standard deviations below the mean, microcephaly can manifest from primary causes during fetal development, or can occur postnatally from postnatal injury or genetic syndromes. Imaging plays an integral role in the evaluation of microcephaly and can hint at contributory gene or external causes; most importantly, imaging can help detect signs of nonaccidental trauma. While ultrasound remains the primary diagnostic tool for prenatal evaluation, Magnetic Resonance Imaging is the preferred imaging modality following birth.

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**Keywords:** TORCH: Toxoplasmosis; Other (Syphilis, Varicella-Zoster, Parvovirus B19), Rubella, Cytomegalovirus (CMV), And Herpes Infections, CNS: Central Nervous System; DTI: Diffusion Tensor Imaging; SWI: Susceptibility Weighted Imaging; HIE: Hypoxic Ischemic Encephalopathy; PVL: Periventricular Leukomalacia; IQ: Intelligence Quotient.

## Introduction

Microcephaly is a result of abnormal brain development and is defined as a head circumference greater than 2 standard deviations below the mean. The term "severe microcephaly" is reserved for head circumference exceeding 3 standard deviations [1]. The abnormal development can result from either prenatal or postnatal injury, and the time of clinical presentation divides microcephaly into primary or secondary (acquired) categories [2]. The majority of neurogenesis occurs by week 21 of fetal de-

velopment, whereas the majority of dendritic connections and myelination occur after birth [2]. Therefore, prenatal injuries result in a failure of neurogenesis, whereas postnatal injuries result in abnormal development of previously-normal neurons.

The etiologies for microcephaly can also be categorized based on extent of the disease manifestation, whether the anomalies are limited to cerebral development, or occur in con-



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junction with other extracerebral anomalies as part of a syndrome. The non-syndromic causes are relatively common, and are typically limited to cerebral development [1]. The syndromic causes are relatively rare and are associated with extracerebral involvement including visceral malformations, skeletal malformations, and/or facial dysmorphisms. Syndromic and nonsyndromic causes may also co-exist in some etiologies such as fanconi anemia [3]. For the purpose of this review, we will discuss microcephaly with respect to syndromic and non-syndromic causes, with an emphasis on select syndromes. Furthermore, we will concentrate on postnatal patients, for whom MRI is the primary modality.

### Clinical and imaging assessment

The evaluation of microcephaly relies on both clinical and imaging assessment, and is initiated when a head circumference measurement is greater than 2 standard deviations below the mean. Careful history, including maternal factors, is crucial in the workup of primary microcephaly. Etiologies, including a maternal history of diabetes, phenylketonuria, medication use, alcohol or substance use, radiation exposure, and prenatal infections such as the TORCH infections or fetal alcohol syndrome are important considerations. Therefore, the history and the clinical assessment of the parents as well as the infant is invaluable in the assessment of the microcephalic infant [4]. Genetic testing with microcephaly panels are also a valuable component in the assessment of a microcephalic patient with a suspected syndrome.

Clinically, the prognosis of microcephaly varies, with some of the worst outcomes seen in syndromic cases such as Trisomy 13, which is nearly fatal by the first year of life. Another important clinical association is cognitive and developmental delay, the severity of which has been directly linked to the severity of microcephaly. In a study of 212 patients, decreasing head circumference directly correlated to decreasing IQ, with the highest IQs documented in conditions typically arising after the first trimester, and the lowest IQs documented in children with chromosomal abnormalities, inborn errors of metabolism, or multiple congenital anomalies. Other predictors of poor cognitive performance include atrophy, cortical dysplasia, and myelination abnormalities [4,5,45].

Similarly, imaging plays an integral role in the evaluation of microcephaly and can hint at contributory gene or external causes. Imaging can help to assess for the sequela of non accidental injury by demonstrating subdural hematoma accompanied by post traumatic encephalomalacia. MR imaging is used to identify gyral, migrational, or myelination abnormalities, while CT is generally restricted to confirming calcifications, which may be present in the TORCH syndromes, our institution MR protocol will include T1, T2, and Inversion Recovery sequences in multiple planes on a high field magnet. Gradient echo and susceptibility weighted imaging is performed to assess for calcifications and can preclude the need for CT evaluation. We note that the *fluid attenuated inversion recovery (FLAIR)* sequence may be a limited value in the unmyelinated brain. Furthermore, intravenous contrast agent is not generally administered. MR spectroscopy is utilized, especially if metabolic disease is suspected.

### Syndromic microcephaly

Syndromic microcephaly presents with cerebral and extracerebral anomalies including visceral malformations, skeletal mal-

formations, and/or facial dysmorphism. Causes include chromosomal abnormalities and gene deletion syndromes. Utilizing the "Online Mendelian Inheritance In Man", a comprehensive online database categorizing human genes and genetic phenotypes, a database search for "microcephaly [clinical synopsis]" yields 795 genetic phenotypes with a component of microcephaly [5]. For the purpose of this review, however, we will discuss select syndromes including, Cri-du-chat Syndrome, mitochondrial abnormalities, such as Leigh's syndrome and Wilsons disease, Craniosynostosis in a patient with Aperts syndrome, Sturge Weber Encephalotrigeminal Angiomatosis, Trisomy 13, Cockayne Syndrome and Pelizaeus-Merzbacher Disease.

### Cri-du-chat syndrome

After the discovery of the normal human chromosome number in 1956, Cri du chat syndrome was first recognized by Lejeune in 1963 [6]. This karyotype contains the normal number of chromosomes, but results from deletions of the short arm of chromosome 5p. A cat-like cry, facial dysmorphism, microcephaly, and severe psychomotor and mental retardation are clinically evident [7]. Additional findings such as congenital heart disease and renal anomalies are present. Characteristic radiographic findings initially described include microcephaly and hypertelorism [7]. Further assessment of brain morphometry utilizing MRI revealed a characteristic brainstem atrophy, predominantly at the pontine level, with associated small cerebellum, cerebellar peduncles, and cerebellar white matter (Figure 1) [8,9]. In addition, the literature suggests a lack of myelination in the anterior limbs of the internal capsule in this disease entity [10,11].

### Mitochondrial chromosomal abnormalities

Mitochondrial diseases are an established etiology for microcephaly. These are a myriad of disease processes that result from abnormal oxidative phosphorylation, and can be inherited in germline mutations or acquired from environmental factors such as infections. They are categorized as primary when directly involving mutations in the electron transport chain proteins, such as in Leigh's Syndrome (Figure 2). Mitochondrial disease are termed secondary when accompanying another pathologic process that affects mitochondrial function, such as in Wilson's disease or hepatocellular degeneration (Figure 3) [12].

Due to the pervasive nature of oxidative phosphorylation, a defect can affect any tissue, leading to progressive multi-organ system involvement, typically beginning with the central and/or peripheral nervous system. Progressive myopathy, nephropathy, hepatic dysfunction, and cardiomyopathy are often demonstrated [11]. Patients can present either in childhood or adulthood, but approximately 45% of childhood presentations begin with neuromuscular symptoms of weakness, atrophy, hypotonia, peripheral neuropathy, cerebellar ataxia, and leukodystrophy [13].

Neuroimaging findings include cerebral and cerebellar atrophy, white matter changes, and signal abnormality involving the basal ganglia and thalami which are believed to represent necrosis in a pattern resembling hypoxic-ischemic encephalopathy, but without a history of birth asphyxia [14,15]. MR Spectroscopy has proven to be a useful adjunct in diagnosis and can demonstrate decrease in NAA, representing neuronal loss as well as elevation of the lactate doublet, suggesting necrosis, in the affected areas, as noted in Leigh's Syndrome (Figure 2) [16,17].

## Craniosynostosis – Apert syndrome

Apert syndrome is an autosomal dominant mutation in the FGFR2 gene. Characteristic clinical features include craniosynostosis, facial dysmorphism, abnormal skull development, and syndactyly [17]. The CNS anomalies in Apert are a result of either primary malformations, or secondary to the osseous deformity.

In a review of 30 patients with Apert syndrome, Quintero-Rivera et al. documented the most common intracranial findings as ventriculomegaly with cerebral volume loss (87% of patients), partial or complete absence of the septum pellucidum (40%), malformations of the septum pellucidum (23%), and progressive hydrocephalus (13%) (Figure 4) [18]. The cranial malformation can subsequently lead to tonsillar herniation, temporal lobe deformity, hydrocephalus, and encephaloceles [19]. Though not known to be associated with microcephaly, the submitted patient was noted to have the diagnoses. Microcephaly is associated with craniosynostosis in the MCPH1 mutation [20].

## Sturge Weber angiomatosis

Sturge Weber is a neurocutaneous disorder characterized by facial port-wine stains, ocular choroidal hemangiomas, and pial angiomas, with clinical manifestations of glaucoma, seizures, and possible hemiparesis. Facial port-wine stains are not specific for Sturge Weber, and are most often an isolated uncomplicated finding. The underlying mechanism is impaired cortical venous drainage due to an anomalous venous plexus over the cerebral surface, leading to venous stasis and progressive venous outflow obstruction. Collaterals form in the deep venous system to help provide cortical drainage, but are inadequate. CT and MRI will demonstrate abnormal intracranial calcifications, enlarged choroid plexus, cortical enhancement due to disruption of the blood brain barrier, and abnormal deep venous system (Figure 5) [21]. Characteristic white matter signal abnormality and atrophy are best noted on the T2 weighted and Fluid Attenuated Inversion Recovery (FLAIR) images.

Susceptibility Weighted Imaging (SWI) and Diffusion Tensor Imaging (DTI) also offer an additional benefit of assessing microstructural abnormalities in the early stages of Sturge Weber, allowing for earlier interventions. SWI can detect transmedullary collateral veins in patients that have not yet developed cortical functional abnormality, as assessed by PET imaging. DTI in these patients can demonstrate abnormal diffusion in the white matter tracts surrounding these transmedullary veins which drain the functionally normal cortex. Therefore, while the cortical integrity may not yet be compromised in this early stage, the presence of transmedullary veins and the loss of integrity of the surrounding white matter surrounding veins may lead to future cognitive impairment [22].

## Trisomy 13 with holoprosencephaly

Trisomy 13 (Patau syndrome) is a chromosomal abnormality associated with CNS, facial/ocular, renal, and cardiac anomalies, as well as polydactyly, rocker-bottom feet, and a single umbilical artery. It is nearly always fatal within the first year, therefore postnatal imaging is sparse and the documented findings are predominantly based on prenatal ultrasound.

Based on a prenatal ultrasound study of 33 fetuses with Trisomy 13, the CNS abnormalities include holoprosencephaly, lateral ventricular dilatation, enlarged cisterna magna, and microcephaly (Figure 6). Facial anomalies include cleft lip/pal-

ate, cyclopia, hypoplastic face, and microphthalmia. Of the CNS anomalies, holoprosencephaly is the most prevalent (39%), but the absence of holoprosencephaly does not exclude Trisomy 13 [23]. Few case reports of cross sectional imaging in postnatal infants over the age of 1 have documented milder morphological CNS manifestations of trisomy 13, which may be an indicator for better outcomes [24-26].

## Additional syndromes with microcephaly

Two additional rare syndromes which have as a main feature microcephaly are Cockayne's Syndrome and Pelizaeus-Merzbacher disease. Cockayne's Syndrome is a rare autosomal recessive condition comprising microcephaly, photosensitivity, cachectic dwarfism, progeria, and progressive neurological degeneration. Imaging findings include diffuse cerebral atrophy and basal ganglia calcifications (Figure 7) [27,28].

Pelizaeus-Merzbacher is an X linked autosomal recessive syndrome presenting with microcephaly and a near complete lack of myelin. The disease can be categorized into three types; classical, connatal, and transitional, which differ in their time of onset and clinical severity. The classical form is noted at infancy with lack of control of the head and nystagmus. Patients experience cognitive decline by age 5 or 6 with death in most patients in late adolescence or young adulthood (Figure 8) [29].

## Non-syndromic microcephaly

Differential concerns for non-syndromic microcephaly include intracranial malformations, environmental factors such as fetal alcohol syndrome, hypoxic ischemic encephalopathy (HIE), intrauterine infections, teratogens, as well as maternal disease, such as phenylketonuria and poorly controlled maternal diabetes [1]. It is important to recognize that microcephaly can be the sequelae of non accidental injury.

The environmental causes have been extensively described in other reviews, therefore we will focus primarily on HIE, a potentially devastating condition, and its manifestations. Following this, microcephaly as the result TORCH infections will be illustrated, with examples of HIV and Pneumococcus as well as Herpes Simplex Two. Finally microcephaly, seen in non-accidental injury, will be briefly discussed.

## Hypoxic ischemic encephalopathy

The pattern of brain injury by a perinatal ischemic event depends on the severity and duration of the ischemic event, as well as the stage of brain development during the event. A mild to moderate hypoxic-ischemic event can result in periventricular leukomalacia or germinal matrix hemorrhage in preterm neonates. On the other hand, watershed infarcts can be expected in full-term neonates.

Cranial ultrasound is the initial imaging of choice and is highly sensitive for detecting intracranial hemorrhage, hydrocephalus, and cystic Periventricular Leukomalacia (PVL). However, ultrasound has lower sensitivity for detecting cortical involvement, and has marked inter observer and operator variability [30]. MRI offers the most sensitive and specific evaluation of HIE. Diffusion weighted imaging is excellent for detecting white matter injury, while MR spectroscopy has shown high sensitivity for predicting the severity of brain injury in full term infants, performed within 24 hours after birth. An elevated lactate/creatine ratio on day 1 predicts a poor neurological outcome, whereas the absence of lactate on day 1 predicts a normal outcome. MR spectroscopy is unfortunately not recommended in preterm

neonates as they show elevated lactate peaks [31,32]. CT can also be useful since it does not require sedation, but offers less sensitivity and specificity than MRI, with the adverse effect of radiation exposure [33,34].

### Periventricular leukomalacia

The periventricular white matter is the most vulnerable to injury in preterm neonates with an immature brain, and mild to moderate hypoxia-ischemia will lead to periventricular leukomalacia (PVL) [34]. Studies have demonstrated the distribution of watershed infarcts differs in preterm and term neonates as the watershed regions of the brain change as the fetus matures. Therefore, in preterm infants, watershed infarcts occur in the periventricular regions, specifically adjacent to the trigone and frontal horns of the lateral ventricles. As the gestational age increases, watershed ischemia move peripherally to lie in the cortical and subcortical areas, in an adult like pattern [35].

The predominant neuroimaging finding is loss of periventricular white matter with cerebral volume loss. (Figure 9) [36]. Increased T2 and FLAIR signal is typical in those fetus which are able to mount a gliotic response (Figure 10) [37]. Impairment of cerebral cortical gray matter development in premature infants with PVL has also been documented [38]. Periventricular cavitation and cyst formation is seen in end-stage PVL, and cysts >3mm often carry a poorer prognosis [35].

### Watershed infarcts in term neonates

Watershed infarcts are typically due to a perinatal acute cerebral hypoperfusion event, leading to bilateral infarcts and subsequent brain atrophy [38]. As cerebral blood flow declines, circulation is shunted from the anterior to the posterior circulation, to maintain supply to the vital structures such as the brainstem, basal ganglia, and cerebellum. This leads to two predominant imaging patterns: A peripheral pattern (also known as parasagittal, watershed, or borderzone), which is more common and occurs with mild to moderate hypoxia, and a basal ganglia-thalamus pattern, which is less common and occurs with more severe hypoxic episodes [39].

The peripheral pattern demonstrates restricted diffusion in

the cortex and subcortical white matter, with parieto-occipital and posterior temporal lobes typically more affected than the anterior regions. As the area of ischemia becomes infarcted, cortical thinning with laminar necrosis and diminutive subcortical white matter is demonstrated, with resultant ex vacuo dilatation of the adjacent lateral ventricles (Figure 11).

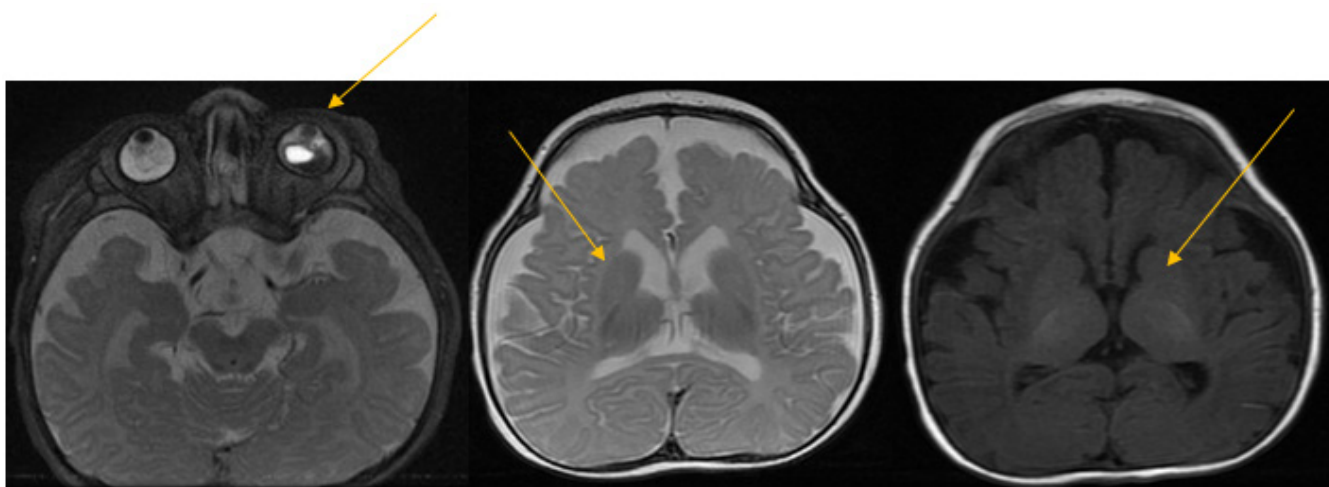
The basal ganglia-thalamus pattern occurs due to inadequate shunting to the vital structures, and is seen with severe hypoxia or cardiopulmonary arrest. Signal abnormality is present in the ventrolateral thalami, posterior putamina, corticospinal tracts, and hippocampi. An additional finding is the loss of the normal hyperintense focus seen in the posterior limb of the internal capsule on T1-weighted images, called the absent posterior limb sign. It is important to note that this sign is useful after 72 hours from the onset of a severe ischemic event, as the normal signal may not be lost within the first 72 hours [40,41].

### TORCH infections

The sequelae of neonatal infection and the effect on the developing brain is well documented. Furthermore, the age of the fetus is the greatest predictor of insult type and degree. For example, if the fetus is exposed to the pathogen during the first and second trimester, there will be a propensity to develop congenital malformations. If the exposure is during the 3<sup>rd</sup> trimester and at birth, the result will be brain destruction with calcification and leukoencephalomalacia. For example, in neonatal Herpes Simplex Encephalitis, the fetal exposure occurs during birth with symptoms manifesting within the first month of life (Figure 12). Babies born with HIV can have additional infections, such as Pneumococcus (Figure 13). Since 2015, Zika infection has been a well documented etiology for microcephaly [42,43].

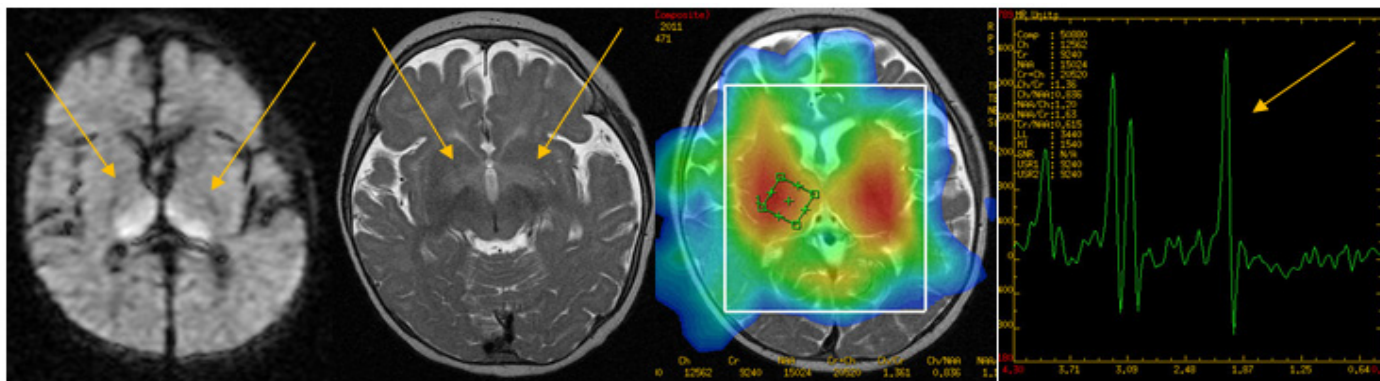
### Non accidental injury

Children who have sustained non accidental injury can have a myriad of intracranial manifestations. Classically, the complex subdural hematoma is the hallmark, although neglect, resulting in brain shrinkage can result in microcephaly as well (Figure 14). The prevalence of microcephaly following abusive head trauma was noted to be 93% in a study of 15 children who sustained abusive head injury and subsequently developed microcephaly [44].

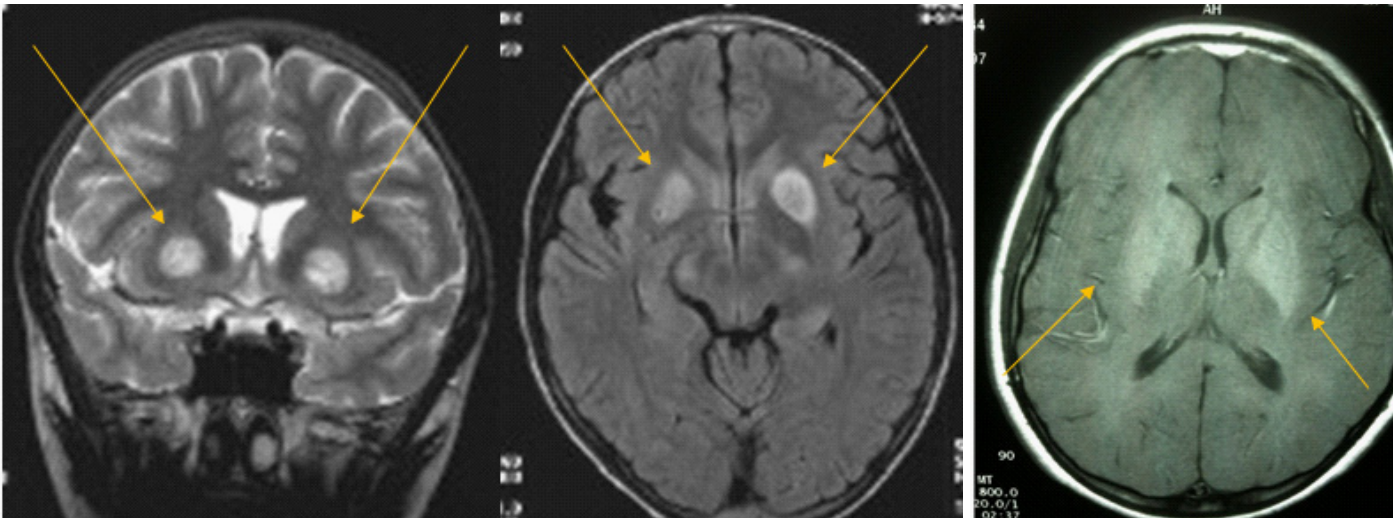


**Figure 1:** Cri-du-chat:

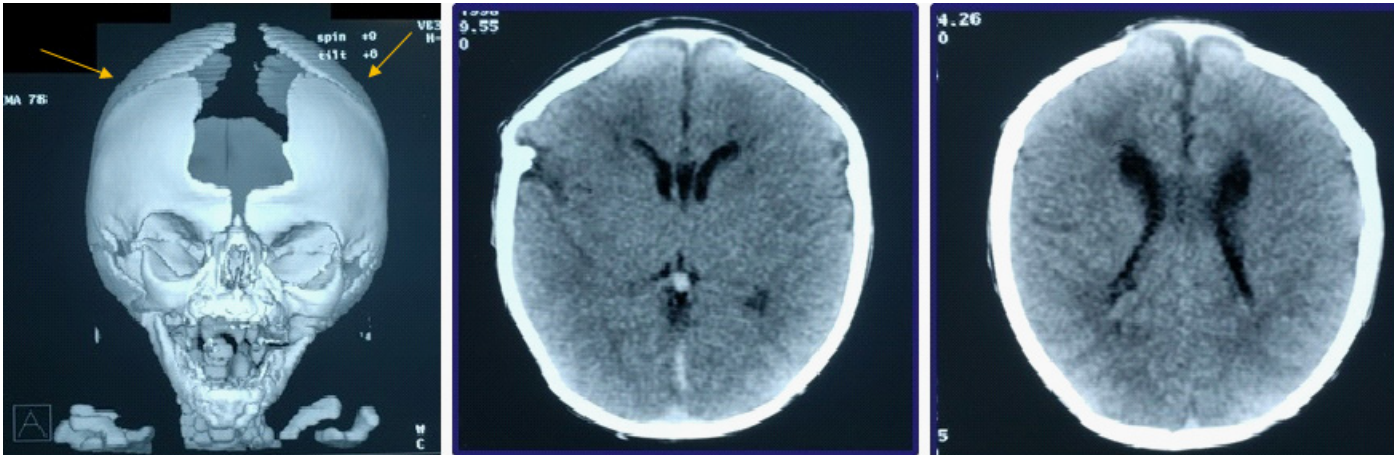
Serial axial images demonstrate cerebral volume loss and left orbital retinal detachment. There is brain stem hypoplasia and a lack of myelination of the anterior limbs of the internal capsules (arrows).



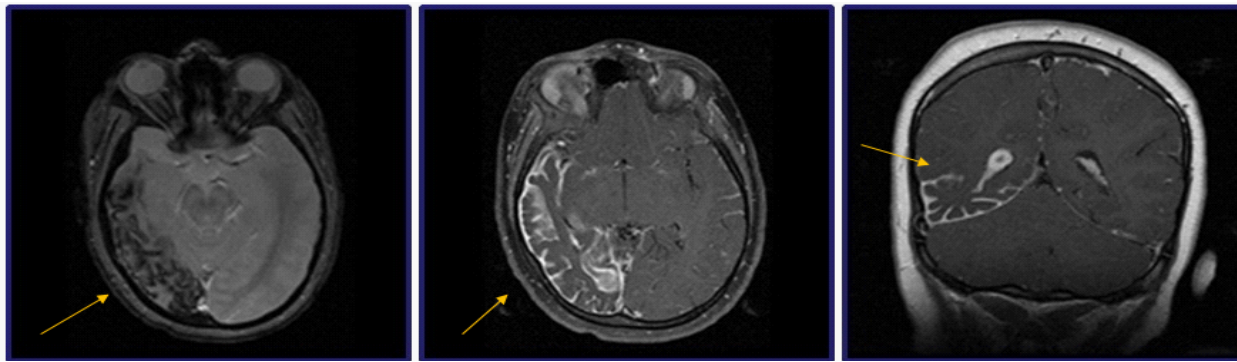
**Figure 2:** Mitochondrial chromosomal abnormalities-Leigh's Syndrome: Axial Diffusion, T2 weighted, and MR spectroscopy images demonstrate cortical atrophy, restricted diffusion in the thalamus (arrow), and a broad elevated lactate peak (arrow).



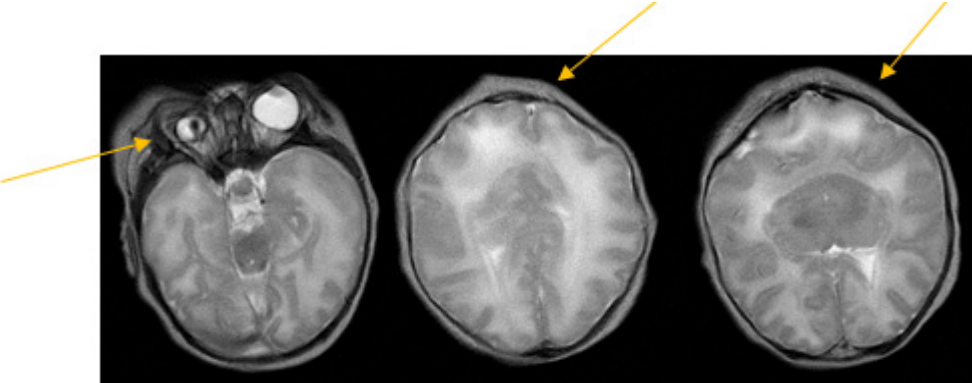
**Figure 3:** Mitochondrial chromosomal abnormalities-Wilson's Disease: Patient 1: Coronal T2 and axial flair images demonstrate bilateral symmetric increased signal in the putamen, globus pallidus and midbrain (arrow). Patient 2: Axial T1 weighted image reveals increased T1 signal in the basal ganglia (arrow).



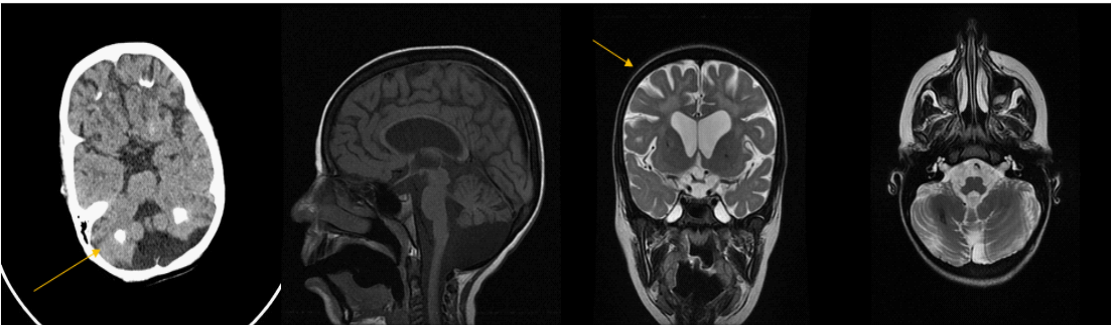
**Figure 4:** Craniosynostosis – Aperts Syndrome: Three dimensional reconstructed and axial images demonstrate bilateral coronal synostosis and microcephaly. There is ridging of the coronal sutures (arrow).



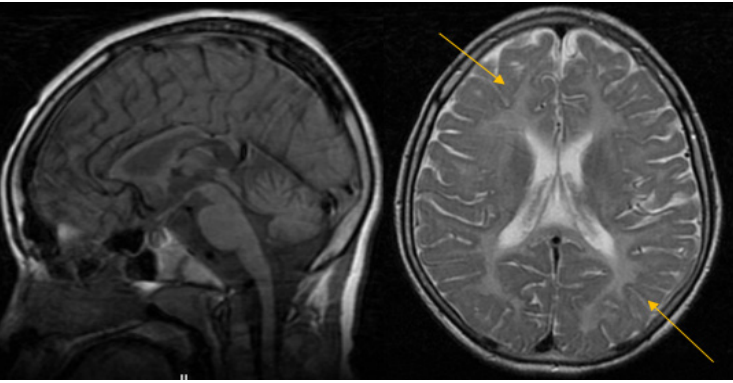
**Figure 5:** Sturge Weber Angiomas:  
Axial Gradient echo and axial and coronal post-gadolinium T1 images demonstrate calcifications and associated pial enhancement typical of Sturge Weber encephalotrigeminal angiomas (arrows).



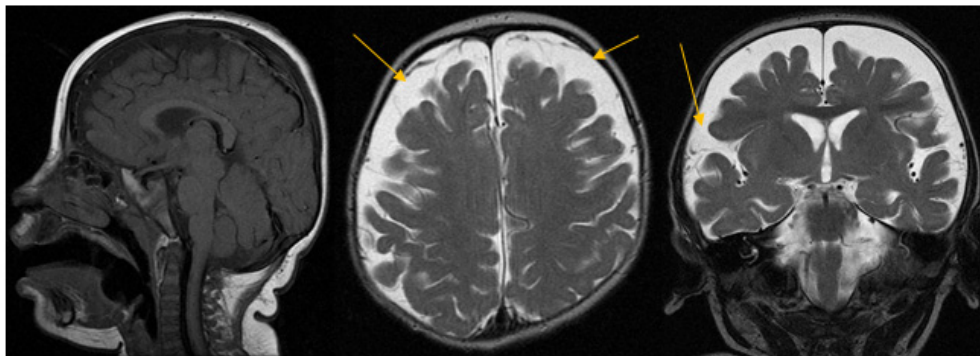
**Figure 6:** Trisomy 13 with Holoprosencephaly:  
Axial and coronal T2 weighted images demonstrating forebrain fusion anomaly in this patient with trisomy 13 (arrows). There is microphthalmia on the first image (arrow).



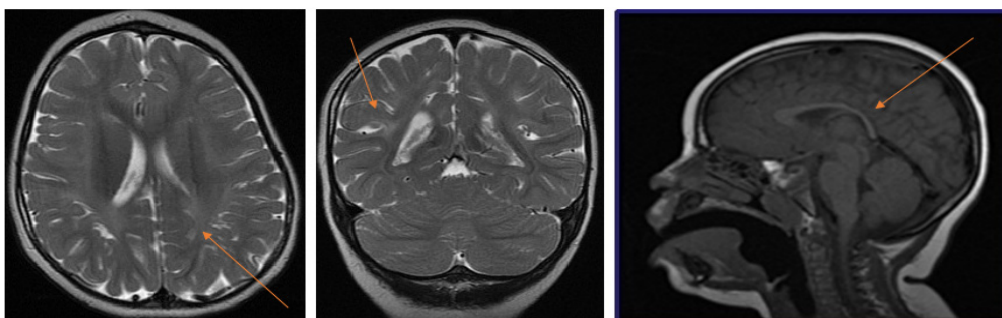
**Figure 7:** Cockayne Syndrome:  
CT: arrows demonstrate calcification in the cerebellum. Calcification is present in the frontal lobes as well. sagittal T1, coronal T2 and axial T2 reveal cerebral atrophy in this microcephalic patient (arrow).



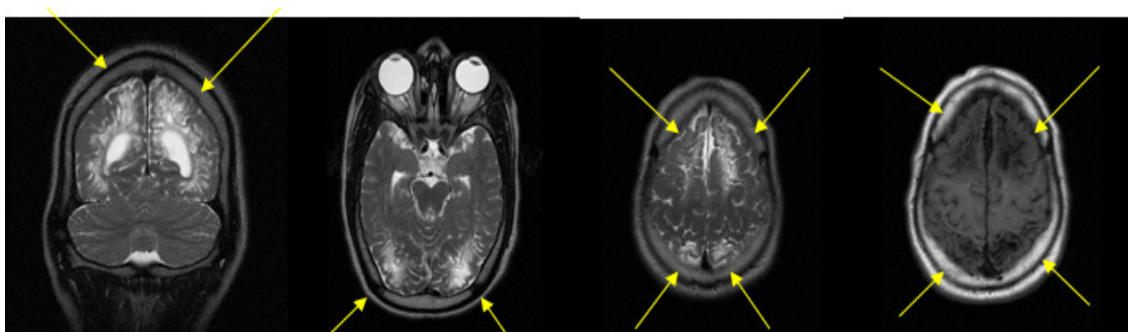
**Figure 8:** Pelizaeus-Merzbacher Disease:  
Sagittal T1 and axial T2 weighted images reveal a reduction in cerebral white matter which is not myelinated in a 9 year old patient (arrow demonstrates unmyelinated white matter in the right forceps minor and left forceps major).



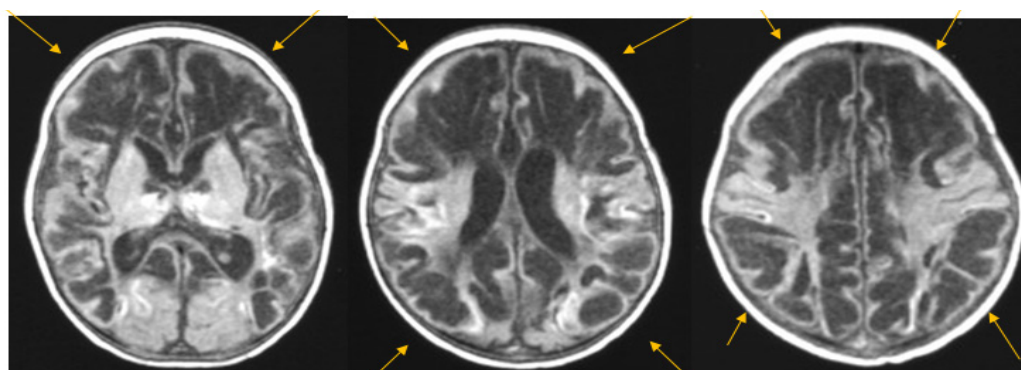
**Figure 9:** Non gliotic periventricular leukomalacia: Sagittal T1, axial T2 and coronal T2 weighted images reveal cerebral volume loss and reduction of white matter volume (arrows), including the corpus callosum in this 9 month preterm patient with microcephaly, developmental delay and hypertonicity.



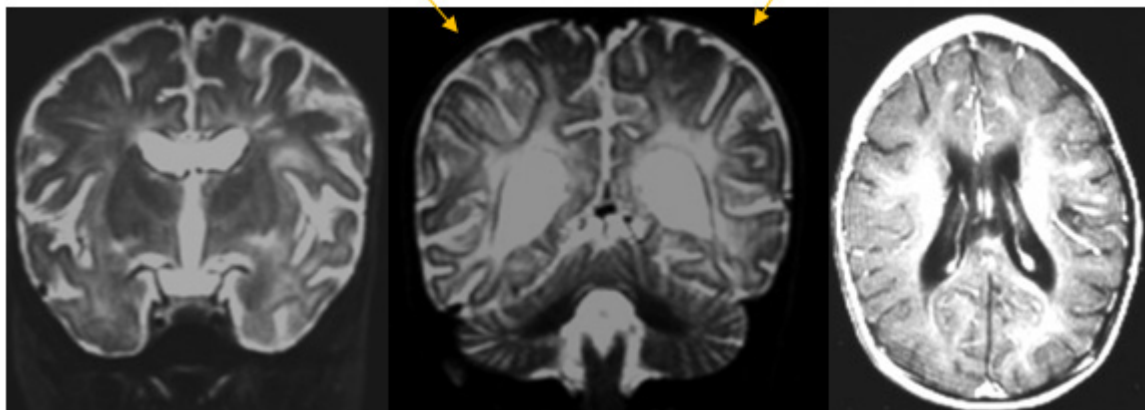
**Figure 10:** Periventricular Leukomalacia: Axial T2, coronal T2 and sagittal T1 images demonstrate hypoplasia of the splenium corpus callosum as well as gliosis in the coronal radiata (arrows).



**Figure 11:** Watershed Infarcts: Coronal T2, axial T2, and axial T1 weighted images demonstrate sulcal and ventricular enlargement with leukoencephalomalacia involving the cerebral hemispheres in this patient with chronic watershed infarcts (arrows). The coronal T2 weighted image demonstrates severe atrophy of the cerebrum with relative preservation of cerebellar volume.

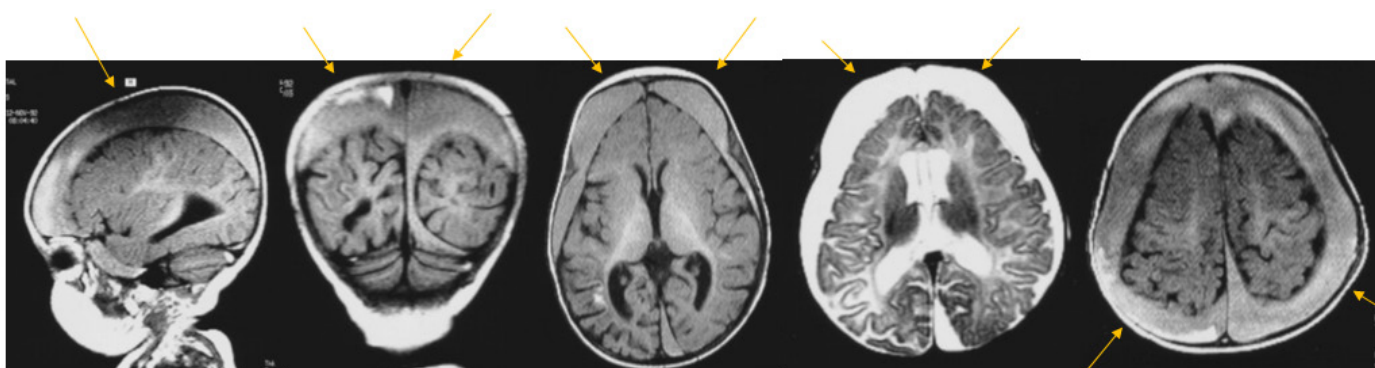


**Figure 12:** Herpes Simplex Two: Serial axial T1 weighted images demonstrate extensive cerebral atrophy, cystic encephalomalacia and laminar necrosis, as represented as intrinsic increase T1 signal (arrow).



**Figure 13:** HIV and Pneumococcus:

Coronal T2 weighted images (left, center) and contrast enhanced axial t1 weighted images demonstrate extensive cerebral atrophy and cerebral white matter gliosis (arrows).



**Figure 14:** Non accidental trauma:

Sagittal, coronal and axial T1 weighted, axial T2 and axial T1 weighted images demonstrate complex subdural hematomas containing different ages of blood products (arrows) seen in conjunction with cerebral atrophy.

## Conclusion

Assessment of microcephaly requires a multidisciplinary approach with important clinical and imaging components. Careful history taking can help exclude common environmental factors such as fetal alcohol syndrome or TORCH infections, and imaging can help detect important causes such as non-accidental injury. Imaging also offers clues to diagnosing syndromic causes of microcephaly, and is integral to the evaluation of the microcephalic pediatric patient.

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