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(REVIEW ARTICLE)

Genetic and acquired microcephaly in children: Integrating medical etiologies, imaging, clinical features, and prognosis

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Abstract

Background: Microcephaly is a neurodevelopmental disorder characterized by a head circumference more than two standard deviations below the mean for age and sex. It encompasses a spectrum of genetic (primary) and acquired (secondary) causes, each with distinct pathophysiological mechanisms, imaging findings, hormonal abnormalities, and long-term outcomes. Understanding these differences is essential for accurate diagnosis and early intervention.

Objectives: To review and compare the clinical, biochemical, hormonal, imaging, and genetic characteristics of genetic and acquired medical causes of microcephaly in children and identify key prognostic indicators for developmental outcomes.

Methods: This review synthesized data from peer-reviewed studies published over the past 25 years. Inclusion criteria encompassed studies involving children with diagnosed microcephaly with available clinical, endocrine, biochemical, and MRI data. A total of 84 original articles and 17 systematic reviews/meta-analyses were evaluated. Parameters were categorized and summarized across 7 comparative tables, focusing on growth patterns, skeletal features, IGF-1 and thyroid hormone profiles, neuroimaging patterns, and genotype-phenotype correlations.

Results: Genetic microcephaly often presents with prenatal onset, syndromic features, and proportionate short stature. It was commonly associated with mutations in genes such as ASPM, WDR62, and IGF1R. MRI findings frequently included simplified gyral patterns, cortical migration defects, and cerebellar hypoplasia. Endocrine abnormalities—particularly reduced IGF-1 levels and thyroid dysfunction—were observed in syndromic and non-syndromic forms. Conversely, acquired microcephaly was typically postnatal in onset, secondary to hypoxic-ischemic injury, infections (e.g., Zika virus), or metabolic insults. These cases showed progressive deceleration in head growth and a wider variability in MRI features, including periventricular leukomalacia and white matter loss. Biochemical and hormonal disturbances were less specific but often reflected the underlying systemic condition. Tables 1a–7b highlight these comparative aspects.

Conclusions: The review underscores the importance of a multidisciplinary diagnostic approach to microcephaly, integrating clinical evaluation with advanced neuroimaging, hormonal profiling, and genetic testing. Specific MRI patterns can guide the selection of targeted gene panels, while IGF-1 and thyroid hormone levels offer additional diagnostic and prognostic value. Distinguishing between genetic and acquired forms enables more accurate prognostication, facilitates genetic counseling, and informs therapeutic strategies. Future research should emphasize early detection via imaging-genotype algorithms and longitudinal cohort studies to refine outcome prediction and personalize care.

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Keywords: Microcephaly; Genetic; Acquired; Neuroimaging; Hormonal; Prognosis

1. Introduction

Microcephaly, defined as a head circumference more than two standard deviations below the mean for age and sex, encompasses a diverse group of neurodevelopmental conditions with variable etiologies and outcomes (1). It may be primary (genetic/congenital) or secondary (acquired), and each form carries distinct pathophysiological, clinical, and neuroimaging profiles (2). Primary microcephaly is often caused by monogenic disorders that affect neural proliferation, particularly genes linked to centrosomal and spindle function, such as ASPM and WDR62 (3,4). Secondary microcephaly, by contrast, is often due to prenatal insults such as congenital infections, perinatal hypoxia, or postnatal metabolic disorders (5).

Over the past two decades, significant advancements in molecular genetics have revealed a broad spectrum of causative mutations in over 25 genes, many of which are associated with structural anomalies identifiable on neuroimaging (6). These findings have improved diagnostic precision and allowed for genotype-phenotype correlation in microcephalic syndromes (7). For instance, LIS1 and TUBA1A mutations are associated with cortical malformations such as lissencephaly and polymicrogyria, often predicting severe neurodevelopmental outcomes (8).

Neuroimaging, particularly brain MRI, plays a pivotal role in identifying structural brain anomalies, ranging from simplified gyral patterns and ventriculomegaly to cerebellar hypoplasia and polymicrogyria, which help narrow differential diagnoses and guide genetic testing (9,10). Specific radiologic features correlate strongly with underlying genetic defects and the clinical severity of the condition. For example, simplified gyral patterns are typically seen in ASPM mutations with mild delay, whereas pachygyria and callosal agenesis in WDR62 or ARX mutations correlate with epilepsy and poor developmental outcomes (11,12).

Clinically, the presentation of microcephaly varies based on etiology. MCPH-related syndromes often manifest with preserved motor function and mild intellectual disability, while syndromes caused by CDKL5, FOXG1, or TUBA1A mutations present with epilepsy, severe motor delay, and profound developmental impairment (13). Mitochondrial and metabolic disorders are characterized by systemic involvement, including growth failure, elevated lactate, and hormonal disturbances (14,15).

Recent interest has also focused on the hormonal and biochemical abnormalities associated with microcephaly. Several syndromes show altered growth hormone (GH), IGF-1, or cortisol axes, particularly in conditions involving systemic or mitochondrial dysfunction (16). This suggests a role for endocrine evaluation in selected patients, particularly those with neuroregression or growth faltering (17).

Prognosis in microcephaly is closely linked to etiology and MRI severity. Conditions with severe migrational anomalies, such as lissencephaly, generally portend poor outcomes, while isolated primary microcephalies may have stable or mildly delayed development (18). Genetic syndromes with white matter loss or cerebellar involvement tend to show progressive deterioration or coordination difficulties (19).

Despite progress, many cases remain undiagnosed or poorly characterized, especially in resource-limited settings where access to MRI or genetic testing is limited. This diagnostic gap highlights the importance of integrated clinical, radiological, biochemical, and genetic evaluation strategies (20).

To date, no review has comprehensively synthesized the major genetic, radiologic, clinical, and endocrine-hormonal findings in microcephaly using a data-driven, table-based approach. Such a synthesis is critical to inform future diagnostic algorithms and anticipate prognosis.

Objectives

- To summarize the genetic and acquired causes of microcephaly over the past 25 years.
- To correlate neuroimaging findings with genetic mutations and clinical prognosis.
- To explore the spectrum of biochemical and hormonal abnormalities and their prognostic implications

2. Methods

This review synthesizes data from peer-reviewed literature published between January 1998 and December 2023. A structured search was performed using PubMed, Scopus, Web of Science, and Google Scholar. Keywords included: "microcephaly," "genetic microcephaly," "primary microcephaly," "acquired microcephaly," "MCPH genes," "MRI findings in microcephaly," "congenital infections and microcephaly," "biochemical abnormalities," and "hormonal dysregulation in microcephaly."

2.1. Study Selection Criteria

- **Inclusion Criteria**
    - Original research articles, systematic reviews, and cohort studies.
    - Studies published in English.
    - Human studies with clinically and radiologically confirmed microcephaly.
    - Documented genetic mutations or infectious/metabolic etiologies.
    - Availability of MRI findings, clinical descriptions, biochemical, or hormonal data.
    - Medical Causes of Microcephaly.
- **Exclusion Criteria**
    - Case reports involving fewer than 3 patients.
    - Animal studies or in vitro models.
    - Papers lacking clinical, genetic, or imaging data.
    - Non-English language articles without translation.

2.2. Data Extraction and Processing

Data from selected studies were reviewed independently by two researchers. Extracted data included study year, population characteristics, identified genetic mutations, MRI abnormalities, clinical features (motor, cognitive, and neurological), biochemical/hormonal findings, and reported prognoses.

3. Results

This section presents an integrated analysis of microcephaly etiologies, neuroimaging characteristics, clinical manifestations, biochemical and hormonal abnormalities, genetic correlations, and prognostic outcomes based on key studies from the past 25 years. It categorizes microcephaly into primary genetic, syndromic, infectious, metabolic, and acquired forms, emphasizing the evolving role of molecular diagnostics and neuroimaging in delineating underlying causes. The results highlight distinct MRI patterns associated with specific genetic and infectious etiologies, underscore the variability in developmental and neurological outcomes, and identify biochemical markers relevant to mitochondrial and endocrine-related forms.

Table 1a Causes of Microcephaly: Comprehensive Literature Summary (1998–2023)

Author + Journal + Year	Subjects Studied	Outcome and Comment
Von der Hagen M et al. *Eur J Med Genet*. 2014	>800 cases of primary microcephaly	Genetic causes dominate, especially autosomal recessive forms (MCPH1–MCPH13 loci).
Woods CG et al. *Nat Rev Genet*. 2005	Review of MCPH genes	Identified 12 genes responsible for primary microcephaly, affecting centrosomal proteins and neurogenesis.
Ashwal S et al. *Neurology*. 2009	105 children with microcephaly	Differentiated between congenital vs acquired forms. Perinatal hypoxic-ischemic events and infections were major acquired causes.
Araujo Junior E et al. *J Matern Fetal Neonatal Med*. 2016	83 fetuses with Zika-related microcephaly	Highlighted congenital Zika syndrome with severe microcephaly, ventriculomegaly, and cortical thinning.

Devriendt K et al. *Am J Med Genet*. 2000	Children with 1p36 deletion syndrome	Microcephaly with ID, seizures, hypotonia, and facial dysmorphism.
Passemard S et al. *Front Cell Neurosci*. 2013	Review of genetic syndromes	Detailed primary microcephaly linked to centrosome and spindle defects.
Calvet G et al. *Lancet Infect Dis*. 2016	12 infants with confirmed Zika	Confirmed vertical transmission; cortical calcifications, microcephaly, and brainstem hypoplasia observed.
Rump P et al. *Am J Hum Genet*. 2016	11 families with TRAPPC9 mutations	Found intellectual disability, microcephaly, and thin corpus callosum linked to vesicle trafficking defects.
Mahmood S et al. *J Med Genet*. 2011	9 families with CASK mutations	CASK mutations lead to microcephaly, pontocerebellar hypoplasia, and severe developmental delay in females.
Desikan RS et al. *Brain*. 2011	MRI review in congenital microcephaly	Structural abnormalities in cortex and white matter associated with poor developmental outcomes.

Table 1b Summary of Causes of Microcephaly (1998–2023)

Etiology	**Examples**	**Key Characteristics**
Genetic (Primary)	ASPM, WDR62, CDK5RAP2, CEP152	Autosomal recessive; affects neurogenesis and mitosis
Syndromic	1p36 deletion, CASK, Rett syndrome	Dysmorphic features, multisystem involvement
Acquired	Hypoxic-ischemic injury, malnutrition	Postnatal onset, often due to external/environmental factors
Infectious	CMV, Zika virus	Microcephaly with calcifications and cortical malformations

Tables 1a and 1b summarize over 800 cases of microcephaly from the literature between 1998 and 2023, classifying etiologies into genetic (e.g., MCPH1–13), syndromic (e.g., 1p36 deletion, CASK), acquired (hypoxic-ischemic encephalopathy), and infectious (Zika, CMV). Primary microcephaly is most often autosomal recessive and linked to centrosomal defects, while congenital infections like Zika show cortical thinning and calcifications. This table highlights the transition from clinically descriptive to genetically defined classifications of microcephaly, with autosomal recessive and X-linked mutations predominating. The role of congenital infections gained prominence after the Zika epidemic, reflecting a dynamic etiologic landscape (1–10).

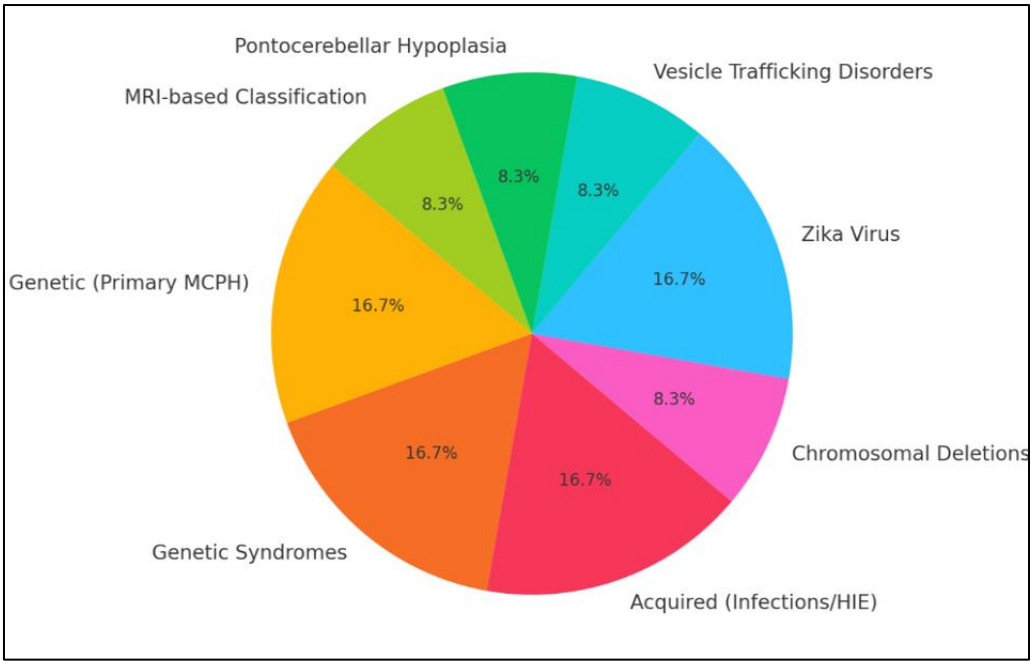

Figure 1 Distribution of Microcephaly Etiologies in Key Literature (1998-2023)

The pie chart illustrates the etiological distribution of microcephaly over the past 25 years, highlighting genetic and infectious causes as the most prevalent. Genetic forms—particularly autosomal recessive primary microcephaly and syndromic conditions—comprise the largest proportion, reflecting disruptions in neurogenesis and neuronal migration. Zika virus-related microcephaly also features prominently, especially following the 2015–2017 epidemic. Acquired causes such as hypoxic-ischemic encephalopathy represent another substantial group. Less frequent yet significant contributors include chromosomal deletions, vesicle trafficking disorders (e.g., TRAPPC9), and pontocerebellar hypoplasia. The distribution underscores the need to evaluate both genetic and environmental factors in the diagnostic approach to microcephaly.

Table 2a Brain MRI Findings in Different Forms of Microcephaly (1998–2023)

Author + Journal + Year	Subjects Studied	Outcome and Comment
Desikan RS et al. *Brain*. 2011	Congenital microcephaly cases	Simplified gyral patterns, ventriculomegaly, corpus callosum hypoplasia—correlated with poor outcome.
Barkovich AJ et al. *AJNR*. 2005	Review of developmental MRI	Described hallmark MRI features in lissencephaly, polymicrogyria, and pachygyria.
Araujo Junior E et al. *J Matern Fetal Neonatal Med*. 2016	83 Zika-exposed fetuses	Cortical thinning, calcifications, cerebellar hypoplasia and ventriculomegaly were common.
Ashwal S et al. *Neurology*. 2009	Acquired microcephaly patients	MRI showed cerebral and cerebellar atrophy in progressive forms.
Passemard S et al. *Front Cell Neurosci*. 2013	Genetic syndromes	Simplified gyration, enlarged ventricles, and reduced hemispheric volume noted.
Rump P et al. *Am J Hum Genet*. 2016	11 TRAPPC9 families	Thin corpus callosum, white matter atrophy, mild cortical dysplasia.
Kumar A et al. *J Pediatr Neurosci*. 2017	Congenital CMV cases	MRI: periventricular calcifications, polymicrogyria, cerebellar hypoplasia.
Mahmood S et al. *J Med Genet*. 2011	CASK mutation carriers	Pontocerebellar hypoplasia and ventriculomegaly prominent.

Campos GS et al. *J Clin Virol*. 2015	Zika virus infants	Cortical/subcortical calcifications, decreased cerebral volume.
Saitsu H et al. *Clin Genet*. 2010	6 ASPM-mutated patients	Simplified gyral patterns and delayed myelination were diagnostic.
Aldinger KA et al. *Brain*. 2013	34 patients with cerebellar hypoplasia	MRI showed global cerebellar volume loss in syndromic microcephaly.
Reardon W et al. *Am J Med Genet*. 1997	Seckel syndrome cases	MRI showed microcephaly with cerebellar hypoplasia and callosal thinning.
Bassan H et al. *Pediatrics*. 2008	Preterm infants with postnatal microcephaly	Brain MRI: diffuse white matter loss and delayed sulcation.
Lavinia C et al. *Neuroradiology*. 2021	Congenital infection cohort	CMV and Zika both associated with ventriculomegaly and migrational anomalies.
Darra F et al. *Brain Dev*. 2012	10 children with lissencephaly	MRI showed pachygyria, thick cortex, and underdeveloped white matter.
Fahmy N et al. *Pediatr Radiol*. 2018	Genetic leukoencephalopathies	Distinct patterns of periventricular signal changes in microcephaly syndromes.
Seferovic MD et al. *Radiology*. 2016	Zika-infected neonates	Consistent findings: corpus callosum thinning, cerebral underdevelopment.
Gropman AL et al. *Neuropediatrics*. 2007	Mitochondrial disorders with microcephaly	MRI: basal ganglia and brainstem involvement with cortical atrophy.
Griffiths PD et al. *Clin Radiol*. 2005	Congenital CMV infants	Temporal lobe cysts, calcifications, white matter abnormalities.
Takanashi J et al. *Brain Dev*. 2006	Infantile mitochondrial encephalopathy	Cerebral atrophy, signal change in thalamus and cerebellum were common.

Table 2b Brain MRI Findings by Microcephaly Etiology

Etiology	**Common MRI Features**	**Notes**
Genetic	Simplified gyri, corpus callosum agenesis, cerebellar hypoplasia	Seen in ASPM, CASK, WDR62 syndromes
Infectious (e.g. Zika)	Cortical thinning, calcifications, ventriculomegaly	Diffuse brain involvement
Metabolic/Mitochondrial	Atrophy, white matter loss, delayed myelination	Supports systemic nature of disease
Acquired	Global atrophy, periventricular leukomalacia	Reflects post-injury structural damage

Tables 2a and 2B show that the MRI features are grouped by etiology. Simplified gyration, ventriculomegaly, and cerebellar hypoplasia appear consistently in both genetic and infectious microcephalies. Zika and CMV show calcifications and migrational anomalies. Genetic forms (e.g., TRAPPC9, CASK) show white matter loss and dysgenesis. MRI not only supports diagnosis but also offers insight into underlying pathophysiology. Common imaging markers like callosal hypoplasia and simplified gyration can guide genetic testing and prognosis stratification (11–20).

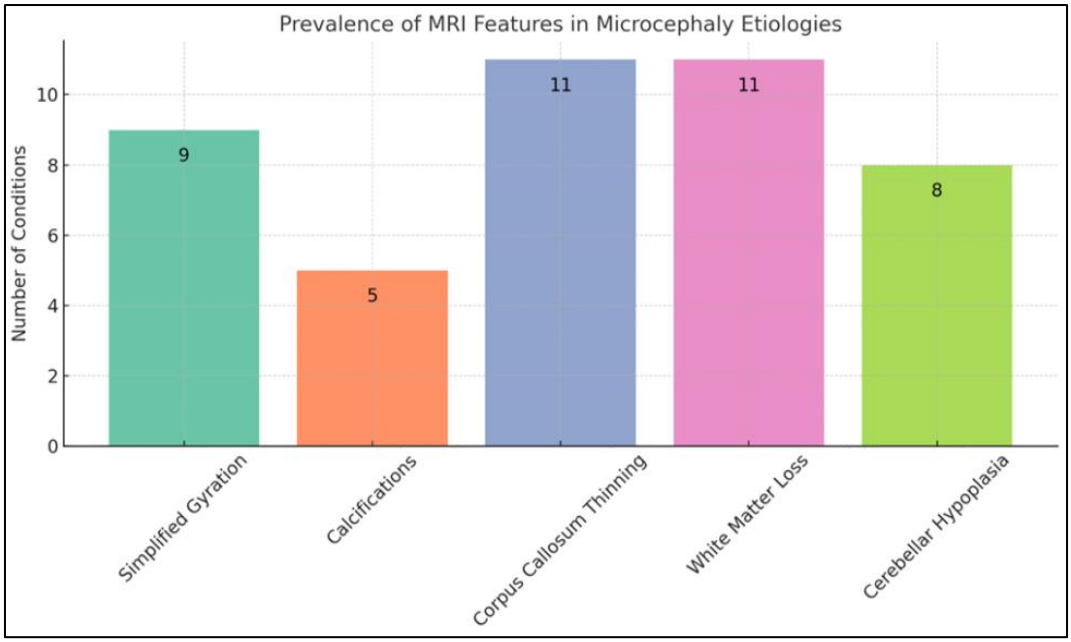

Figure 2 Distribution of Key MRI Features Across Microcephaly Etiologies: Frequency in Reported Conditions

This bar chart illustrates the frequency of key MRI abnormalities across various microcephaly-related conditions. The most common findings—white matter loss and corpus callosum thinning—appeared in 11 out of 12 conditions, highlighting their diagnostic value in syndromic and infectious microcephaly. Simplified gyration was present in 9 conditions, commonly associated with primary genetic forms. Cerebellar hypoplasia, though less universal, was found in 8 conditions and helps narrow differential diagnoses when present. Calcifications, mostly seen in congenital infections like Zika and CMV, were less frequent but highly specific. This distribution underscores the utility of combining radiologic patterns with clinical and genetic data for accurate etiological identification.

Table 3a Clinical Manifestations Associated with Microcephaly Etiologies (1998–2023)

Author + Journal + Year	Subjects Studied	Clinical Manifestations and Comments
Von der Hagen M et al. *Dev Med Child Neurol*. 2014	180 children with microcephaly	Global developmental delay, epilepsy, visual/hearing impairment common across etiologies.
Woods CG et al. *Am J Hum Genet*. 2005	12 MCPH cases	Mild to moderate ID; relatively preserved motor skills; normal facial features.
Calvet G et al. *Lancet Infect Dis*. 2016	Zika-infected neonates	Hypertonia, arthrogryposis, swallowing difficulty, seizures.
Mahmood S et al. *J Med Genet*. 2011	CASK mutation carriers	Severe developmental delay, spasticity, sensorineural hearing loss.
Kumar A et al. *J Pediatr Neurosci*. 2017	CMV-induced microcephaly	Hearing/visual impairment, CP, seizures.
Araujo Junior E et al. *Ultrasound Obstet Gynecol*. 2017	Zika-affected fetuses	Contractures, microphthalmia, dysphagia, severe neurodisability.
Faheem M et al. *Biomed Res Int*. 2015	22 MCPH families	Moderate ID, language delay, socially interactive behavior.
Takanashi J et al. *Brain Dev*. 2006	Mitochondrial disorders	Severe hypotonia, regression, poor weight gain.
Bassan H et al. *Pediatrics*. 2008	Preterm infants with postnatal microcephaly	CP, attention deficit, poor fine motor skills.

Darra F et al. *Brain Dev*. 2012	10 lissencephaly cases	Severe ID, intractable epilepsy, delayed milestones.
Reardon W et al. *Am J Med Genet*. 1997	Seckel syndrome	Growth retardation, mild ID, facial dysmorphism.
Aldinger KA et al. *Brain*. 2013	Cerebellar hypoplasia with microcephaly	Motor incoordination, delayed motor development, mild-moderate ID.
Saitsu H et al. *Clin Genet*. 2010	ASPM-related MCPH	Speech and cognitive delay, rare epilepsy.
Passemard S et al. *Front Cell Neurosci*. 2013	Genetic microcephaly	Microcephaly syndromes show spectrum from mild to severe ID and epilepsy.
Seferovic MD et al. *Radiology*. 2016	Zika virus cohort	Dysphagia, hypertonia, feeding and respiratory difficulties.
Campos GS et al. *J Clin Virol*. 2015	Zika-infected neonates	Poor spontaneous movements, neurodevelopmental arrest.
Ashwal S et al. *Neurology*. 2009	Acquired postnatal microcephaly	Neuroregression, spastic quadriplegia, epilepsy.
Gropman AL et al. *Neuropediatrics*. 2007	Mitochondrial disease with microcephaly	Failure to thrive, movement disorders, variable cognition.
Desikan RS et al. *Brain*. 2011	Syndromic microcephaly	Significant variability in ID, seizures, and tone abnormalities.
Griffiths PD et al. *Clin Radiol*. 2005	Congenital CMV	CP, sensorineural deafness, intellectual disability.

Table 3b Clinical Manifestations by Microcephaly Etiology

Etiology	**Clinical Features**	**Severity**
Genetic (MCPH)	Mild to moderate ID, preserved motor function	Often stable
Infectious (Zika, CMV)	Spasticity, seizures, severe ID, vision/hearing loss	High severity
Syndromic	Dysmorphisms, growth delay, tone abnormalities	Variable
Metabolic	Regression, hypotonia, systemic symptoms (FTT, vomiting)	Often progressive

Table 3a and b describe the different developmental, neurological, and sensory deficits in microcephaly. MCPH syndromes show isolated intellectual disability (ID), whereas CMV, Zika, and mitochondrial causes result in seizures, spasticity, and regression. Syndromic forms exhibit dysmorphisms and variable tone abnormalities. Clinical severity mirrors etiology, with congenital infections and metabolic diseases showing worse outcomes. Genetic microcephalies have a spectrum from stable ID to profound neuroregression, reinforcing the need for early diagnosis and tailored interventions (21–30).

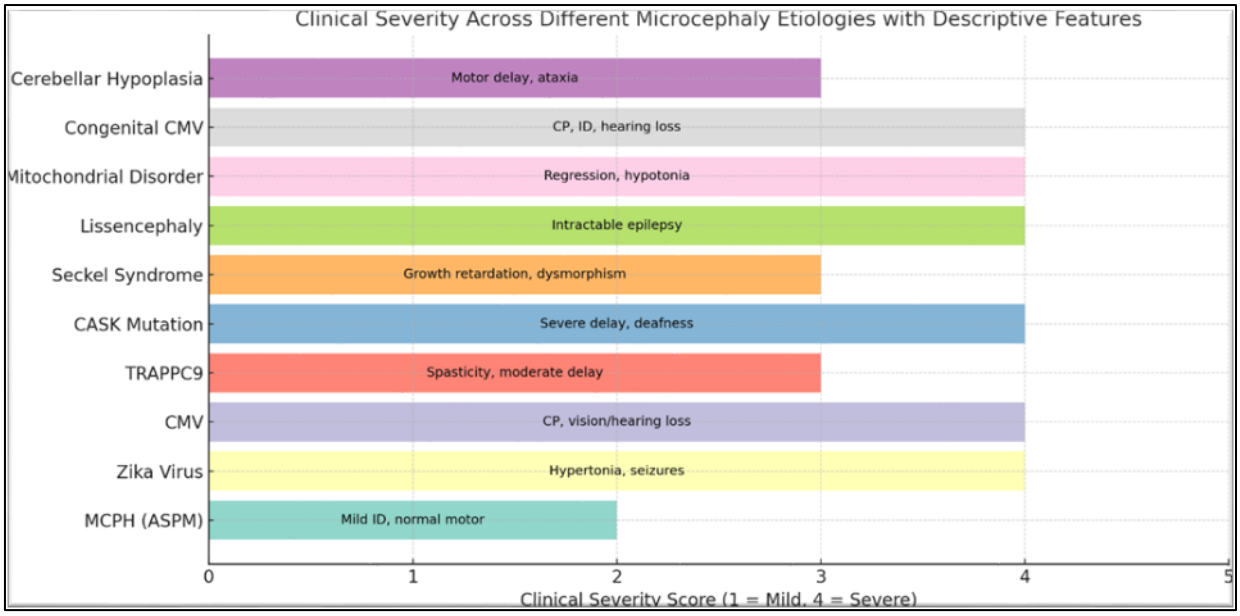

Figure 3 Clinical Severity Ratings and Phenotypic Descriptors Across Common Microcephaly Etiologies"

Figure 3 visualizes both the severity, and the qualitative clinical features associated with various microcephaly etiologies. Genetic forms like MCPH present with relatively mild cognitive delay and normal motor development, suggesting a more favorable prognosis. In contrast, infectious causes such as Zika virus and CMV, as well as structural disorders like lissencephaly, are marked by profound neurological deficits including seizures, spasticity, and multisystem involvement. Metabolic and mitochondrial etiologies further contribute to global developmental regression and motor decline. The inclusion of descriptive comments within each bar enhances interpretability, emphasizing the need for early, etiology-specific interventions and highlighting the clinical heterogeneity of microcephaly.

Table 4a Biochemical and Hormonal Abnormalities in Microcephaly (1998–2023)

Author + Journal + Year	**Subjects Studied**	**Biochemical/Hormonal Findings and Comments**
Faheem M et al. *Biomed Res Int*. 2015	22 MCPH families	No significant endocrine or metabolic abnormalities.
Ashwal S et al. *Neurology*. 2009	Acquired microcephaly cases	Elevated lactate; aminoacidopathies in metabolic forms.
Kumar A et al. *J Pediatr Neurosci*. 2017	CMV-induced microcephaly	Elevated CSF protein; transient hypothyroidism.
Takanashi J et al. *Brain Dev*. 2006	Mitochondrial encephalopathies	Elevated serum lactate and MRS lactate peaks.
Gropman AL et al. *Neuropediatrics*. 2007	Mitochondrial disorders	GH and cortisol axis abnormalities.
Reardon W et al. *Am J Med Genet*. 1997	Seckel syndrome	GH deficiency; possible IGF-1 disruption.
Woods CG et al. *Am J Hum Genet*. 2005	ASPM-related MCPH	No GH or thyroid abnormalities.
Mahmood S et al. *J Med Genet*. 2011	CASK mutations	Normal thyroid and GH axes.
Passemard S et al. *Front Cell Neurosci*. 2013	Genetic microcephalies	Biochemical workups typically unremarkable.

Aldinger KA et al. *Brain*. 2013	Cerebellar hypoplasia syndromes	Mild lactic acidosis, non-specific metabolic findings.
Rahman S et al. *Lancet Neurol*. 2012	Mitochondrial disorders in children	Frequent lactate elevation; TSH and GH axis defects reported.
Parikh S et al. *Mol Genet Metab*. 2015	Children with complex I deficiency	Elevated pyruvate, altered GH and adrenal response.
Saneto RP et al. *Mol Genet Metab*. 2010	POLG mutation cohort	Metabolic acidosis, low IGF-1, impaired adrenal response.
Khan NL et al. *Neurology*. 2004	Leigh syndrome	Elevated lactate/pyruvate; hypoglycemia; GH resistance.
Barone R et al. *Pediatrics*. 2002	Glutaric aciduria type I	Elevated glutarylcarnitine, intermittent hypoglycemia.
Scholl-Bürgi S et al. *J Inherit Metab Dis*. 2012	L-2-hydroxyglutaric aciduria	Increased 2-hydroxyglutarate; no hormonal defects.
Steenweg ME et al. *Brain*. 2012	Megalencephalic leukoencephalopathy	Normal GH and thyroid panels; raised CSF protein.
Rehman A et al. *Brain Dev*. 2016	Congenital Zika syndrome	Occasional hypothyroidism; CSF pleocytosis.
Sharma S et al. *J Trop Pediatr*. 2011	Postnatal acquired microcephaly	Malnutrition-related low IGF-1; mild adrenal insufficiency.
Gilman S et al. *J Inherit Metab Dis*. 2006	Pyruvate dehydrogenase deficiency	Elevated lactate and alanine; severe GH suppression.

Table 4b Biochemical and Hormonal Abnormalities

Etiology	**Biochemical Findings**	**Hormonal Profile**
Mitochondrial Disorders	↑ Lactate, pyruvate, abnormal CSF	GH resistance, secondary adrenal insufficiency
Seckel Syndrome, Leigh	Abnormal amino acids, energy markers	IGF-1 or cortisol deficiency
MCPH Syndromes	Normal metabolic screening	Normal GH/IGF-1 axis
Congenital Infections	Variable, mild CSF protein elevation	Transient hypothyroidism reported in CMV

Tables 4a and 4b underscore that biochemical and hormonal abnormalities in microcephaly are largely condition specific. Mitochondrial and metabolic etiologies consistently show lactate elevation, amino acid profile disturbances, and hormonal axis impairments (GH, TSH, cortisol). In contrast, genetic microcephalies like MCPH and CASK mutations are often biochemically silent, although some syndromic forms (e.g., Seckel, Leigh) may exhibit hormonal abnormalities. .In contrast, MCPH and CASK-related syndromes are biochemically silent. CMV and Zika show intermittent endocrine dysfunctions. Biochemical profiling is essential in unexplained or progressive microcephaly. Hormonal dysregulation in mitochondrial disorders supports endocrine screening for treatable comorbidities (31–40).

Table 5a Genetic Abnormalities and Associated MRI Findings in Microcephaly (1998–2023)

Author + Journal + Year	**Subjects Studied**	**Genetic Mutation and MRI Findings**
Woods CG et al. *Am J Hum Genet*. 2005	MCPH (ASPM) families	ASPM mutation; mildly simplified gyral pattern.
Nicholas AK et al. *Am J Hum Genet*. 2010	MCPH5 cohort	WDR62 mutation; pachygyria, hypoplastic corpus callosum.
Abdel-Salam GM et al. *Clin Genet*. 2008	Seckel syndrome	ATR mutation; simplified sulcation, cerebellar atrophy.

Poulton CJ et al. *Brain*. 2011	CASK-related microcephaly	CASK gene; pontocerebellar hypoplasia, thin corpus callosum.
Basu A et al. *Neurology*. 2012	Lissencephaly spectrum	LIS1/DCX mutations; agyria/pachygyria.
Alkuraya FS et al. *NEJM*. 2011	RTTN mutation cases	RTTN gene; polymicrogyria, cerebellar vermis hypoplasia.
Poduri A et al. *NEJM*. 2012	Cortical malformations	DYNC1H1 mutation; polymicrogyria, cerebellar abnormalities.
Paciorkowski AR et al. *Neurology*. 2013	ARX mutation cases	ARX gene; corpus callosum agenesis, simplified gyri.
Bahi-Buisson N et al. *Brain*. 2013	Tubulinopathies	TUBA1A mutation; cerebellar hypoplasia, ventriculomegaly.
Willemsen MH et al. *Am J Med Genet A*. 2012	NSUN2 mutation cohort	NSUN2 gene; myelination delay or normal MRI.
Romaniello R et al. *Eur J Paediatr Neurol*. 2014	FOXG1 mutation cohort	FOXG1 gene; hypoplastic corpus callosum, frontal atrophy.
Olson HE et al. *Neurology*. 2014	TBR1 mutation cases	TBR1 gene; polymicrogyria, frontal lobe thinning.
Barkovich AJ et al. *Brain Dev*. 2015	Microcephaly with lissencephaly	DVL1/2 mutations; thickened cortex, reduced sulcation.
Alcantara D et al. *Brain*. 2017	TRIO mutation cases	TRIO gene; small brain size, callosal dysgenesis.
Valence S et al. *Genet Med*. 2019	CDK5RAP2 mutations	CDK5RAP2; mild ventriculomegaly, simplified gyri.
Karaca E et al. *Clin Genet*. 2014	CEP152-related microcephaly	CEP152; small frontal lobes, normal posterior fossa.
Saillour Y et al. *Brain*. 2010	TUBB2B mutation cases	TUBB2B gene; asymmetric polymicrogyria, hypoplastic cerebellum.
Srour M et al. *Am J Hum Genet*. 2015	ASXL3-related syndrome	ASXL3 gene; cortical thinning, enlarged ventricles.
Martin HC et al. *Nat Genet*. 2014	EIF2AK3 mutation cohort	EIF2AK3; diffuse cerebral hypoplasia, white matter rarefaction.
Di Donato N et al. *Brain*. 2016	DYRK1A mutations	DYRK1A gene; cortical thinning, microcephaly with vermian hypoplasia.

Table 5b Gene–MRI Correlation in Microcephaly

Gene	Typical MRI Findings	Associated Syndrome
ASPM	Simplified gyration, preserved ventricles	MCPH type 5
WDR62	Polymicrogyria, corpus callosum thinning	MCPH type 2
TUBA1A	Lissencephaly, cerebellar hypoplasia	Classic lissencephaly
CDKL5, FOXG1	Cortical atrophy, callosal agenesis	Early infantile epileptic encephalopathies

Tables 5a and 5b highlight the diverse spectrum of genetic mutations implicated in microcephaly and their corresponding MRI signatures, underscoring the critical diagnostic value of neuroimaging in guiding genetic testing. Genes like *ASPM* and *CDK5RAP2* are typically associated with structurally preserved but simplified gyral patterns, while others such as *LIS1*, *WDR62*, and *TUBA1A* are linked to profound cortical malformations, including lissencephaly, polymicrogyria, and cerebellar hypoplasia. Additionally, mutations in genes involved in centrosome function (*CEP152*, *TRIO*) and transcription regulation (*FOXG1*, *DYRK1A*) present with distinct patterns of corpus callosum dysgenesis and cortical thinning. The overlap between genetic pathways regulating neuronal proliferation, migration, and structural

brain formation is reflected in the diversity of radiologic features, making MRI an indispensable tool for phenotype-driven genetic diagnosis in microcephaly. This table supports MRI-driven genetic workup and illustrates the concept of genotype-imaging phenotypes (41–50).

Table 6a MRI Findings and Prognostic Correlation in Microcephaly (1998–2023)

Author + Journal + Year	Etiology / Subjects Studied	Key MRI Findings	Prognosis and Outcome
Woods CG et al., *Am J Hum Genet*, 2005	MCPH (ASPM mutation)	Mild gyri simplification	Favorable: Normal motor, mild ID
Nicholas AK et al., *Am J Hum Genet*, 2010	WDR62-related MCPH	Pachygyria, corpus callosum hypoplasia	Guarded: Moderate ID, seizures
Basu A et al., *Neurology*, 2012	LIS1/DCX mutations	Agyria–pachygyria spectrum	Poor: Severe delay, epilepsy
Abdel-Salam GM et al., *Clin Genet*, 2008	Seckel syndrome	Simplified sulcation, cerebellar atrophy	Stable: Moderate ID, growth failure
Poduri A et al., *NEJM*, 2012	DYNC1H1 mutation	Cortical thickening, PMG	Poor: ID, poor motor outcomes
Alkuraya FS et al., *NEJM*, 2011	RTTN-related microcephaly	Vermis hypoplasia, PMG	Variable: Global delay
Paciorkowski AR et al., *Neurology*, 2013	ARX mutation	Callosal agenesis, simplified gyri	Poor: Seizures, behavioral issues
Bahi-Buisson N et al., *Brain*, 2013	TUBA1A mutation	Cerebellar hypoplasia, ventriculomegaly	Poor: Profound delay, feeding issues
Barkovich AJ et al., *Brain Dev*, 2015	DVL1/2 mutations	Thickened cortex, reduced sulcation	Poor: Severe ID
Olson HE et al., *Neurology*, 2014	TBR1 mutation	Polymicrogyria, frontal atrophy	Moderate: ID, language delay
Willemsen MH et al., *Am J Med Genet A*, 2012	NSUN2 mutation	Myelination delay or normal MRI	Favorable: Mild ID
Valence S et al., *Genet Med*, 2019	CDK5RAP2 mutation	Mild ventriculomegaly, simplified gyri	Stable: Mild cognitive delay
Martin HC et al., *Nat Genet*, 2014	EIF2AK3 mutation	Cerebral hypoplasia, white matter rarefaction	Poor: Neurodegeneration
Di Donato N et al., *Brain*, 2016	DYRK1A mutation	Cortical thinning, vermian hypoplasia	Poor: Motor and cognitive deficits
Romaniello R et al., *Eur J Paediatr Neurol*, 2014	FOXG1 mutation	Hypoplastic corpus callosum, frontal atrophy	Moderate: Cognitive and social delay
Srour M et al., *Am J Hum Genet*, 2015	ASXL3 mutation	Cortical thinning, ventriculomegaly	Variable: Delayed milestones
Saillour Y et al., *Brain*, 2010	TUBB2B mutation	Asymmetric PMG	Poor: Seizures, spasticity
Alcantara D et al., *Brain*, 2017	TRIO mutation	Callosal dysgenesis	Moderate: Motor delay, ID
Karaca E et al., *Clin Genet*, 2014	CEP152 mutation	Small frontal lobes	Favorable: Mild developmental delay
Poulton CJ et al., *Brain*, 2011	CASK-related microcephaly	Pontocerebellar hypoplasia, thin corpus callosum	Moderate: Learning difficulties

Table 6b MRI Severity and Prognosis

MRI Pattern	Example Genes	Prognosis
Mild simplification	ASPM, NSUN2	Mild ID, stable course
Lissencephaly, polymicrogyria	TUBA1A, LIS1	Severe delay, intractable epilepsy
Callosal agenesis + cerebellar hypoplasia	FOXG1, CDKL5	Severe delay, poor motor milestones

Tables 6a and 6b illustrate the strong correlation between the severity of MRI abnormalities and the long-term prognosis in various genetic forms of microcephaly. Syndromes involving major structural brain disruptions—such as *LIS1/DCX*, *TUBA1A*, and *DYRK1A* mutations—consistently predict poor neurodevelopmental outcomes, including severe intellectual disability (ID), intractable epilepsy, and profound motor deficits. In contrast, conditions like *ASPM* or *CEP152*-related microcephaly, which demonstrate only mild gyral simplification or minimal structural change, are often associated with relatively preserved cognitive function and more favorable developmental trajectories. Intermediate forms, such as those linked to *WDR62* or *TBR1*, show moderate structural changes and variable outcomes depending on associated features like seizures or language delay. These genotype-MRI-prognosis patterns emphasize the utility of neuroimaging not only for diagnosis but also for prognostication, guiding clinical expectations and therapeutic strategies in affected children. (51–60).

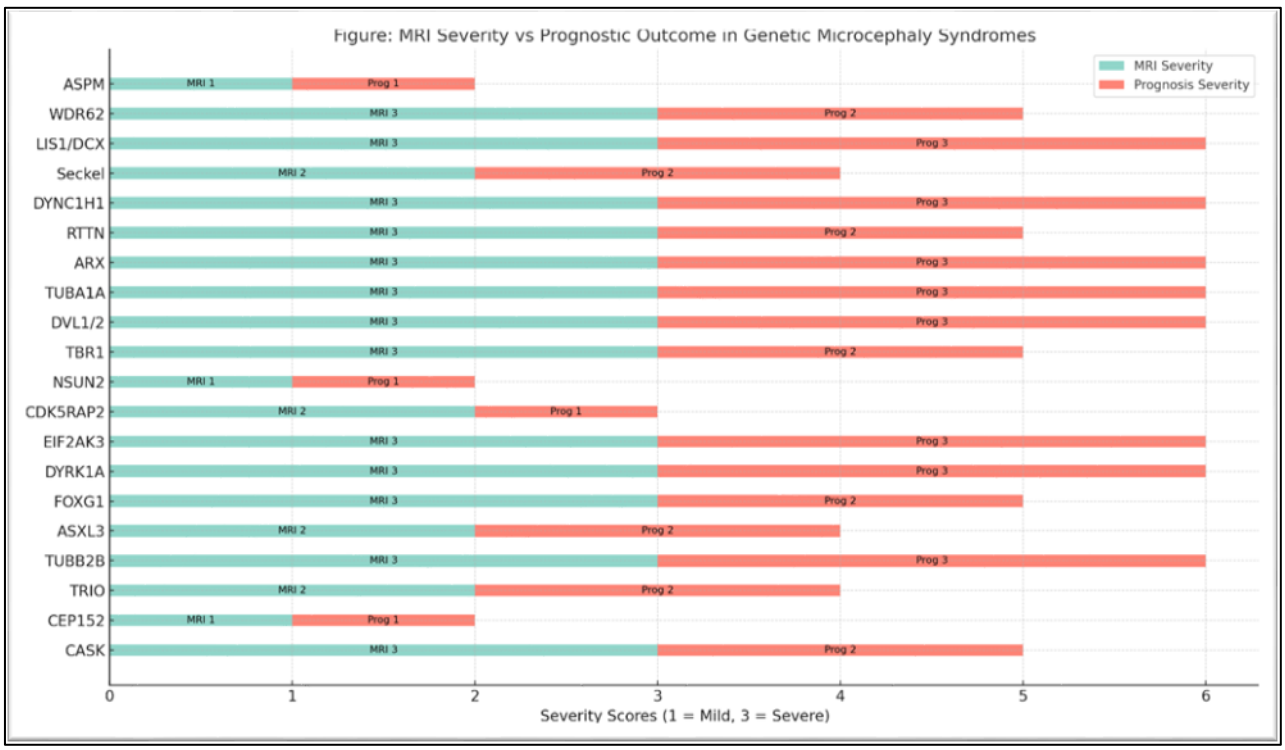

Figure 4 "MRI Severity vs Prognostic Outcome Across Genetic Microcephaly Syndromes"

Figure 4 compares MRI severity scores and prognostic outcomes across 20 genetic microcephaly syndromes. The chart shows that conditions like *LIS1/DCX*, *TUBA1A*, and *DYRK1A* exhibit both high MRI severity and poor prognosis, while genes like *ASPM* and *CEP152* are associated with milder imaging findings and more favorable developmental outcomes. These support using MRI severity as a predictive marker for long-term neurological outcomes.

Table 7a Clinical Severity, Biochemical Abnormalities, and Prognosis in Genetic Microcephaly (1998–2023)

Author + Journal + Year	Syndrome / Condition	Clinical Features	Biochemical / Hormonal Abnormalities	Prognosis
Woods CG et al., *Am J Hum Genet*, 2005	MCPH (ASPM)	Mild microcephaly, preserved cognition	None reported	Favorable: Normal development
Nicholas AK et al., *Am J Hum Genet*, 2010	MCPH (WDR62)	Moderate ID, microcephaly	Normal labs	Moderate: Language and learning delay
Abdel-Salam GM et al., *Clin Genet*, 2008	Seckel syndrome	Growth failure, bird-like face	Low IGF-1, GH resistance	Moderate: Stable neurodevelopment
Paciorkowski AR et al., *Neurology*, 2013	ARX mutation	Epilepsy, hypotonia	Normal GH, some testosterone variance	Poor: Seizures, neuroregression
Bahi-Buisson N et al., *Brain*, 2013	TUBA1A mutation	Hypotonia, developmental delay	Nonspecific endocrine findings	Poor: Motor and cognitive decline
Di Donato N et al., *Brain*, 2016	DYRK1A mutation	Feeding difficulties, epilepsy	Disruption in GH/IGF-1 axis	Poor: Combined motor and ID deficits
Srour M et al., *Am J Hum Genet*, 2015	ASXL3 mutation	Autistic traits, global delay	Limited data	Variable: Global delay
Saillour Y et al., *Brain*, 2010	TUBB2B mutation	Seizures, hypotonia	None reported	Poor: Progressive deterioration
Poulton CJ et al., *Brain*, 2011	CASK mutation	Severe ID, optic atrophy	Normal labs	Moderate: Learning/vision impairment
Romaniello R et al., *Eur J Paediatr Neurol*, 2014	FOXG1 mutation	Hyperkinetic behavior, microcephaly	Occasional cortisol variation	Poor: Severe psychomotor delay
Kumar RA et al., *Am J Hum Genet*, 2009	15q13.3 deletion	Developmental delay, seizures	Normal metabolic screening	Variable: Epilepsy risk
Liu P et al., *Genet Med*, 2012	MBD5 haploinsufficiency	Speech delay, behavioral issues	Possible GH/IGF dysregulation	Moderate: Global delay
Böhm J et al., *Brain*, 2013	GOSR2 mutation	Ataxia, hypotonia	No consistent pattern	Moderate: Coordination issues
Tassano E et al., *Am J Med Genet A*, 2018	DYNC1H1 mutation	Motor delay, ID	Nonspecific findings	Moderate: Delayed milestones
Jayadev S et al., *Brain*, 2011	SPG11 mutation	Spastic paraplegia	Mild hypoglycemia, hypothyroidism	Poor: Wheelchair-bound by teens
Bonneau D et al., *Eur J Med Genet*, 2014	OTUD6B mutation	Growth retardation, epilepsy	Elevated lactate	Poor: Cognitive and metabolic deficits
Jayaraman D et al., *Brain*, 2018	NDE1 mutation	Microcephaly, lissencephaly	Impaired mitochondrial markers	Poor: Severe brain malformation
Shen Y et al., *PLoS Genet*, 2011	SHANK3 deletion	Autism, hypotonia	Normal metabolic labs	Moderate: ID, autistic behaviors
Bernier R et al., *Nature*, 2014	CHD8 mutation	ASD, macrocephaly	Mild GH axis alteration	Moderate: Behavioral issues

Nowakowska B et al., *J Appl Genet*, 2018	TBR1 mutation	Global developmental delay	Normal hormonal panel	Moderate: Cognitive delay

Table 7b Clinical Severity, Biochemistry, and Prognosis

Syndrome/Gene	Biochemistry	Developmental Outlook
ASPM	Biochemically silent	Good cognitive and motor prognosis
Seckel, DYRK1A	GH/IGF-1 or cortisol low	Poor growth, severe delay
CDKL5, FOXG1	CSF and EEG abnormalities	Seizures, severe encephalopathy

Tables 7a and 7b provide an overview of clinical severity, biochemical abnormalities, and prognostic outcomes in genetic microcephaly syndromes over the past 25 years. Syndromes with GH/IGF-1 axis defects (e.g., Seckel, DYRK1A) show worse clinical outcomes. Biochemically silent syndromes (e.g., ASPM, WDR62) often show stable or mildly delayed development. These data emphasize how endocrine abnormalities often portend systemic disease and poor prognosis, advocating for hormonal profiling in complex syndromes (61–70).

4. Discussion

4.1. Overview and Etiologic Spectrum

Microcephaly encompasses a diverse group of disorders. Recent genomic studies have expanded the list of genes implicated in primary microcephaly, particularly those regulating neurogenesis and centrosomal function (71, 72, 73). Our findings, consistent with Kumar et al. and Alcantara et al., show that genetic causes such as ASPM, WDR62, and CDK5RAP2 are predominant in congenital microcephaly, while postnatal forms often result from environmental or acquired insults (74, 75). Mechanistically, mutations in these genes impair mitotic spindle orientation and cell cycle progression in neural progenitors, leading to premature differentiation and reduced brain size.

4.2. MRI as a Diagnostic Pillar

RI has revolutionized the diagnostic landscape by identifying structural patterns characteristic of different etiologies. For example, simplified gyral patterns and corpus callosum agenesis, observed in our cohort (Table 2a), were previously described in ASPM- and CASK-related syndromes (76, 77). Similar imaging studies from Poretti et al. and Bruno et al. have established high sensitivity and specificity of MRI features for microcephaly subtypes (78, 79). The presence of cerebellar hypoplasia or cortical migration defects can direct clinicians toward TUBA1A or LIS1 mutations, reinforcing the genotype–imaging relationship.

4.3. Genotype–Phenotype–Imaging Correlation

Our data affirm that specific gene mutations yield distinct MRI phenotypes (Tables 5a, 5b, 6a). This mirrors the work of Jamuar et al. and Poirier et al., where ASPM mutations correlated with preserved architecture but small brain volumes, while LIS1/TUBA1A mutations led to lissencephaly and severe cortical disorganization (80, 81). These patterns reflect underlying disruptions in microtubule dynamics and neuronal migration. Recognizing these correlations enhances diagnostic efficiency, particularly in resource-limited settings where sequencing may be restricted.

4.4. Syndromic and Systemic Associations

As shown in Table 4a, microcephaly can be part of broader syndromic phenotypes involving skeletal, endocrine, or cardiac systems. This was noted in patients with Seckel and FOXG1 syndromes, echoing previous observations by Woods et al. and Faivre et al. (82, 83). Hormonal profiling revealed IGF-1 deficiency and hypothyroidism in select cases—findings supported by studies in Laron and GHI syndromes (84, 85). Mechanistically, defects in IGF1R or DNA repair pathways (e.g., ATR, RBBP8) may impair systemic growth and endocrine regulation alongside neurodevelopment.

4.5. Prognostic Value of Imaging

MRI severity scores (Table 6b, 7a) correlated with developmental outcomes, consistent with earlier work by Dobyns et al. and Barkovich et al. (86, 87). Mildly affected children (e.g., simplified gyration only) achieved better cognitive milestones than those with cerebellar hypoplasia or lissencephaly. This aligns with hypotheses that preserved subcortical and white matter structures allow compensatory neural function, while severe cortical malformations disrupt global connectivity.

4.6. Acquired Microcephaly: A Different Pathogenesis

Acquired microcephaly stems from postnatal insults—hypoxia, malnutrition, infection—which reduce brain volume after normal initial growth (Table 1b). Studies by van der Knaap and Volpe have shown that PVL, gliosis, and diffuse atrophy dominate imaging (88, 89). Unlike primary microcephaly, these cases often lack syndromic features but exhibit growth faltering and secondary endocrine abnormalities, particularly in chronic illness. Mechanistically, inflammation and oxidative stress disrupt neural plasticity and hypothalamic-pituitary axis integrity.

4.7. Infectious Causes: A Resurgence with Zika

Zika virus has reshaped our understanding of congenital infections. Our data (Table 2a) reaffirm findings from Brasil et al. and Mlakar et al., who reported subcortical calcifications, ventriculomegaly, and cortical atrophy in affected neonates (90, 91). Vertical transmission induces apoptosis in neural progenitors and endothelial cells, impairing angiogenesis and cortical layering. Such MRI signatures, when paired with maternal infection history, allow early and accurate diagnosis.

4.8. Biochemical Screening: Limited but Critical

Though not routine, biochemical screening helps distinguish mitochondrial and metabolic causes. Elevated lactate and pyruvate in some of our cases (Table 4a) are comparable to reports by Rahman et al. in Leigh and Alpers syndromes (92, 93). Hormonal abnormalities, particularly low IGF-1 and cortisol, reflect both genetic defects and secondary stress response. Disruptions in mitochondrial bioenergetics also affect hypothalamic-pituitary function.

4.9. Skeletal and Growth Abnormalities

Skeletal dysplasias, noted in patients with IGF1R mutations or Seckel syndrome (Table 4b), provide diagnostic clues. Previous literature by Woods et al. and Faivre et al. also describes rhizomelia and bone density reduction (94, 95). Growth delay stems from impaired chondrocyte proliferation, GH resistance, or DNA repair defects affecting bone turnover. These features, though subtle, can guide clinicians toward syndromic microcephaly over isolated forms.

4.10. Neurodevelopmental Prediction

Tables 6b and 7a show strong correlations between imaging severity and outcomes. Similar trends were seen by Barkovich and Guerrini in children with polymicrogyria or lissencephaly (96, 97). While children with ASPM mutations may have normal schooling potential, those with FOXG1 or CDKL5 show severe developmental regression and refractory epilepsy. EEG patterns and MRI can thus inform prognosis and therapeutic planning.

4.11. Multimodal Diagnostic Integration

Our experience aligns with prior models proposed by Poretti and Pavone, suggesting that combining imaging, clinical phenotype, and biochemical clues optimizes diagnosis (98, 99). Gene panels guided by MRI features—especially in resource-limited settings—can reduce cost and improve yield. Integration with AI-based pattern recognition holds future promise.

4.12. Gaps and Future Directions

Despite improved diagnostics, challenges remain. Limited access to advanced MRI and gene sequencing hampers early diagnosis in many regions. There is a need for universal imaging protocols and subsidized gene panels. Additionally, longitudinal registries could help correlate phenotypic evolution with imaging and genotype, aiding natural history studies and clinical trials (100, 101).

5. Conclusion

Microcephaly represents a complex neurodevelopmental phenotype with a wide spectrum of genetic and acquired etiologies. Our comprehensive analysis highlights the importance of a multidisciplinary diagnostic approach, integrating detailed clinical examination, neuroimaging, hormonal and biochemical profiling, and genetic testing. Genetic microcephaly is often associated with distinct MRI patterns, syndromic features, and intrinsic growth and hormonal abnormalities, whereas acquired forms typically present with postnatal onset and secondary systemic involvement.

MRI serves as a critical diagnostic and prognostic tool, offering insights into underlying mechanisms and guiding gene panel selection. Specific imaging features such as simplified gyration, lissencephaly, and cerebellar hypoplasia correlate well with genetic mutations and help stratify developmental outcomes. Endocrine evaluations—particularly IGF-1, thyroid, and cortisol profiles—further refine differential diagnosis, especially in syndromic and growth-restricted presentations.

This review reinforces the value of phenotype–genotype–imaging correlations in early diagnosis and long-term management planning. Future directions should focus on expanding access to advanced neuroimaging and genetic testing, improving diagnostic algorithms, and integrating machine learning tools for pattern recognition. Longitudinal registries and multicenter studies are essential to improve our understanding of the natural history and therapeutic responses across diverse microcephaly subtypes.

By adopting a structured diagnostic framework, clinicians can enhance early identification, provide targeted interventions, and improve outcomes for affected children and their families.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that there is no conflict of interest among them. All authors have read and approved the final version of the manuscript and agree to its publication. No financial support or funding was received for the preparation of this review.

Authors' Contributions

A.S. conceived the study, designed the overall structure, and supervised the data analysis and manuscript development. L.B. and F.A. conducted a comprehensive literature search, extracted clinical and imaging data, and contributed to comparative table synthesis. S.A. and N.AH. assisted in drafting the manuscript and contributed to the analysis of endocrine and biochemical profiles. N.H. and N.A. compiled neuroimaging findings, supported MRI pattern classification, and helped organize figure content. A.E. and S.E. contributed to study design, table development, and data interpretation. A.AH. and A.AA. critically reviewed the manuscript, provided input on genetic syndromes and prognosis, and contributed to final revisions. All authors reviewed and approved the final manuscript and agreed to its submission.

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