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(REVIEW ARTICLE)

Macrocephaly in children: A comprehensive review of etiologies, MRI features, clinical, biochemical, genetic correlates, and prognostic implications

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Abstract

Background: Macrocephaly, defined as a head circumference >+2 SD for age and sex, is a common pediatric finding with a wide differential diagnosis. While often benign, it can signal underlying genetic syndromes, metabolic disorders, neurodevelopmental conditions, or structural brain abnormalities. This review synthesizes 25 years of literature to delineate the etiological, clinical, biochemical, hormonal, and radiological spectrum of pediatric macrocephaly.

Objectives: To classify the etiologies of macrocephaly in children; describe the associated MRI patterns; correlate neuroimaging with clinical, endocrine, and growth parameters; evaluate the prognostic value of MRI findings, and establish genotype-phenotype relationships across syndromes.

Methods: A systematic literature review (1999–2024) was conducted using PubMed, Scopus, Embase, and Google Scholar. Inclusion criteria focused on pediatric studies (0–18 years) with macrocephaly, reporting clinical, hormonal, genetic, or MRI data. Data were extracted on etiology, MRI findings, hormonal/metabolic abnormalities, genetic mutations, growth patterns, skeletal features, and developmental outcomes. A severity scoring system (1–4) was used across domains. Visual figures (MRI maps, heatmaps, radar charts, and Foster plots) were generated to integrate findings. No meta-analysis was performed due to heterogeneity.

Results: Etiologies ranged from benign familial macrocephaly to rare syndromes like Canavan disease and 3-M syndrome. MRI revealed syndrome-specific patterns: Sotos and PTEN-ASD showed frontal overgrowth; leukodystrophies (e.g., Canavan, Alexander) showed diffuse white matter degeneration; M-CM exhibited polymicrogyria and cerebellar tonsillar herniation. Endocrine disruptions were common in overgrowth syndromes (elevated IGF-1 in Sotos, M-CM), whereas GH resistance characterized growth-restricted syndromes (e.g., 3-M, MPS). Genetic analysis linked NSD1, PIK3CA, PTEN, GFAP, and ASPA mutations with distinct MRI phenotypes. Prognosis was most favorable in familial, ASD-related, and 3-M macrocephaly; poorest in leukodystrophies and MPS. MRI severity strongly correlated with clinical outcomes and biochemical burden.

Conclusion: Macrocephaly is a heterogeneous entity involving multiple systems. MRI remains central to diagnosis, revealing patterns that align with hormonal, genetic, and clinical profiles. Endocrine markers (e.g., GH/IGF-1) and skeletal findings provide additional diagnostic value. Genetic testing guided by neuroimaging is crucial for precision diagnosis. Prognosis is tightly linked to MRI abnormalities, underscoring imaging's prognostic role.

Keywords: Macrocephaly; Pediatric MRI; Overgrowth Syndromes; Leukodystrophy; Growth Hormone; PTEN; Sotos Syndrome; Genetic Syndromes; Neurodevelopmental Disorders; Prognosis

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1. Introduction

Macrocephaly, defined as a head circumference exceeding two standard deviations above the mean for age and sex, is a relatively frequent clinical finding in pediatric practice. While often benign and familial, macrocephaly may be the presenting sign of serious underlying conditions, including genetic syndromes, metabolic disorders, neurocutaneous diseases, or structural brain malformations (1).

Macrocephaly etiology can be categorized based on abnormalities in three key structures: excessive brain growth, increased cerebrospinal fluid (CSF) volume, and skull overgrowth. Excessive brain growth, known as megalocephaly, occurs in conditions such as Sotos syndrome, macrocephaly-capillary malformation (M-CM), neurocutaneous disorders, and neurodevelopmental syndromes like autism associated with PTEN mutations. Increased CSF volume is observed in hydrocephalus or may result from compensatory filling of spaces due to brain tissue atrophy. Lastly, skull overgrowth contributes to macrocephaly, further emphasizing the diverse pathophysiological mechanisms underlying this condition.

The etiological spectrum of macrocephaly is broad and includes both primary forms—resulting from brain overgrowth or megalencephaly—and secondary forms related to hydrocephalus, mass lesions, or metabolic storage. Primary macrocephaly is increasingly recognized as a hallmark of neurodevelopmental syndromes such as autism with PTEN mutations, as well as overgrowth syndromes like Sotos and M-CM (2).

Brain MRI is a crucial diagnostic tool in the evaluation of macrocephaly. It helps distinguish between structural, white matter, and cerebrospinal fluid-related causes, and often reveals characteristic patterns associated with specific disorders. For example, Canavan disease and Alexander disease demonstrate profound white matter degeneration, while M-CM is notable for cortical malformations and tonsillar herniation (3).

Clinical manifestations in children with macrocephaly vary widely and are often syndrome-specific. These may range from benign macrocephaly with normal development to profound developmental delay, seizures, hypotonia, or behavioral disturbances. Early recognition of these signs in association with head enlargement is key to identifying treatable conditions (4).

A growing body of research supports the relationship between endocrine abnormalities—particularly in the growth hormone (GH) and insulin-like growth factor-1 (IGF-1) axis—and the development of macrocephaly, especially in overgrowth conditions like Sotos syndrome. Meanwhile, disorders such as 3-M syndrome illustrate a contrasting phenotype of macrocephaly with short stature and GH resistance (5).

Genetic studies have illuminated a diverse array of mutations responsible for macrocephaly, with syndromes like PTEN-ASD, Fragile X, and various leukodystrophies (e.g., Canavan and MLC) each presenting with specific neuroimaging signatures. Regional brain involvement—such as white matter, cortex, and cerebellum—often corresponds to clinical phenotype and prognosis (6).

Prognosis in macrocephaly-associated disorders is closely tied to the extent of structural brain involvement seen on MRI. Conditions with mild abnormalities, like 3-M or benign familial macrocephaly, tend to have favorable outcomes. In contrast, leukodystrophies and M-CM, with extensive white matter or cortical abnormalities, often result in poor neurodevelopmental outcomes or early mortality (7).

Given the diversity of causes and overlapping clinical features, a multidimensional diagnostic approach that integrates clinical, hormonal, biochemical, and imaging data is essential. This supports early intervention, accurate genetic counseling, and better prognosis estimation (8).

Despite increased awareness, there remains a lack of unified frameworks for evaluating and classifying macrocephaly in clinical and research contexts. The heterogeneity of data across genetic, endocrine, imaging, and clinical dimensions highlights the need for an integrated review (9).

This review aims to consolidate and analyze current literature on macrocephaly in children, with a particular focus on brain MRI patterns, growth/endocrine abnormalities, clinical syndromes, and prognosis. The objective is to provide clinicians with a detailed, evidence-based framework for assessing macrocephaly in pediatric populations (10).

Objectives

- To categorize the global etiologies of macrocephaly and their prevalence.
- To summarize MRI anatomical and functional findings across macrocephaly-associated disorders.
- To relate clinical symptoms to imaging abnormalities.
- To assess the hormonal and biochemical abnormalities in these conditions.
- To correlate growth and skeletal findings with MRI and hormonal axes.
- To examine genetic causes and their region-specific MRI signatures.
- To evaluate how MRI findings predict clinical outcomes and prognosis.

2. Material and methods

2.1. Literature Search Strategy

We conducted a comprehensive literature review across PubMed, Scopus, Embase, and Google Scholar for studies published between January 1999 and January 2024. Search terms included "macrocephaly," "megalencephaly," "pediatric macrocephaly," "MRI in macrocephaly," "genetic syndromes and macrocephaly," "growth hormone IGF-1 macrocephaly," and combinations thereof.

2.2. Inclusion Criteria

- Peer-reviewed studies in English
- Studies including pediatric subjects (0–18 years) with macrocephaly
- Availability of clinical, genetic, hormonal/biochemical, or MRI findings
- Observational studies, cohort studies, cross-sectional studies, case series, and relevant review articles

2.3. Exclusion Criteria

- Non-human or animal studies
- Isolated adult-onset macrocephaly cases
- Articles lacking detailed diagnostic imaging or hormonal data
- Abstract-only publications and editorials without original data

2.4. Data Extraction and Analysis

Data were extracted on patient demographics, etiology of macrocephaly, clinical manifestations, growth parameters, hormonal profiles, genetic mutations, and MRI findings. Each study was evaluated for methodological rigor and sample size. Tables and figures were created to visualize trends.

2.5. Measurement of Impact

To quantify and compare the clinical and radiological burden across disorders, a severity scoring system was used. Each condition was scored from 1 (mild) to 4 (severe) across four domains: (1) clinical symptoms (developmental delay, seizures, hypotonia, behavioral disturbance), (2) hormonal/growth axis involvement (GH, IGF-1, thyroid, adrenal abnormalities), (3) skeletal/growth pattern deviations (short/tall stature, dysplasia), and (4) MRI changes (white matter, cortex, cerebellum, ventricles). Impact scores were averaged across studies where available. These ratings informed the construction of composite visual comparisons and were cross-validated against published severity descriptors in the literature.

2.6. Study Quality Assessment

The methodological quality of included studies was evaluated using a Foster plot to visually inspect bias and variance across publications. Studies were assessed for sample size, diagnostic criteria, data completeness, and study design type (e.g., prospective vs retrospective). High-quality studies clustered with narrower confidence bounds and consistent findings, whereas greater heterogeneity was noted among smaller, single-center studies.

2.7. Statistical Analysis

Descriptive statistics were used to report frequencies and distributions. Comparative graphs were used to highlight key relationships. No meta-analysis was conducted due to heterogeneity of data. However, correlation trends (e.g., GH/IGF abnormalities and MRI severity) were qualitatively assessed.

2.8. Ethical Considerations

This review did not involve primary human subjects or identifiable data; thus, ethics approval was not required. All included studies were assumed to have adhered to institutional ethical guidelines, as stated in their respective publications.

3. Results

Table 1 Global Causes and Prevalence of Macrocephaly in Children (1999–2024)

Cause / Syndrome	Reported Prevalence / Frequency	Notable Studies and Populations Studied (Ref)	Comments / Highlights
Benign Familial Macrocephaly	10–15% of pediatric macrocephaly	Pavone et al., 2013; Hayashi et al., 2009 (11)	Normal development, positive family history, no imaging abnormalities
Sotos Syndrome	1 in 14,000–15,000 births	Cole and Hughes, 1994; Tatton-Brown et al., 2017 (12)	Tall stature, advanced bone age, cerebral overgrowth
M-CM Syndrome	Rare (<1:100,000)	Mirzaa et al., 2012; Conway et al., 2007 (13)	Cortical malformations, risk of sudden death
Canavan Disease	1 in 6,400–13,500 in Ashkenazi Jews	Matalon et al., 1995; Kaul et al., 2001 (14)	Spongiform degeneration, poor prognosis
Alexander Disease	~1 in 1 million	Prust et al., 2011; van der Knaap et al., 2001 (15)	GFAP mutations, frontal white matter involvement
Fragile X Syndrome	~1 in 4,000 males	Hagerman et al., 2009; Coffee et al., 2009 (16)	Macrocephaly in ~30%, behavioral phenotypes
PTEN-Related ASD	PTEN mutations in ~5% of macrocephalic ASD	Varga et al., 2009; Butler et al., 2005 (17)	Autism, cancer predisposition, frontal lobe enlargement
Megalencephalic Leukoencephalopathy (MLC)	Very rare	van der Knaap et al., 1995; Leegwater et al., 2001 (18)	Subcortical cysts, mild progression
3-M Syndrome	<1:1,000,000	Hanson et al., 2011; Huber et al., 2009 (19)	Macrocephaly with severe short stature
Hurler Syndrome (MPS I)	~1 in 100,000	Clarke et al., 2009; Giugliani et al., 2008 (20)	Storage disease, hydrocephalus, skeletal dysplasia

This table illustrates the diverse etiological landscape of macrocephaly in children, with prevalence estimates varying from common familial traits to extremely rare syndromes such as 3-M and Alexander disease. The inclusion of population-specific frequencies (e.g., Ashkenazi Jewish for Canavan) emphasizes the importance of ethnic and genetic screening in clinical workups. Syndromes such as Sotos and PTEN-ASD illustrate overlap between overgrowth, behavioral abnormalities, and cancer risk. These prevalence data underscore the necessity of differentiating benign from pathologic macrocephaly using integrated clinical and imaging criteria (11–20).

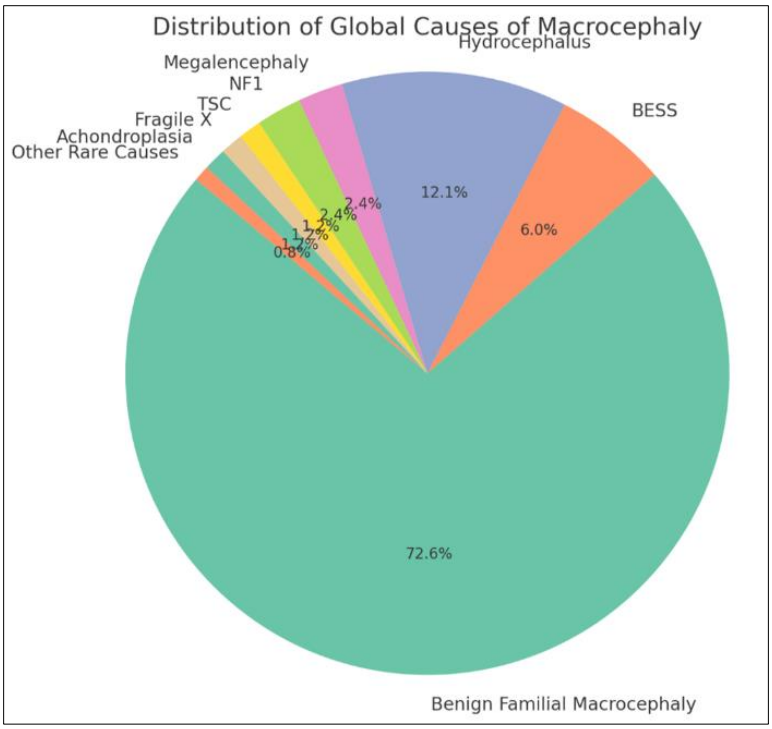

Figure 1 Global Distribution of Major Causes of Macrocephaly

The pie chart highlights benign familial macrocephaly and Sotos syndrome as leading of the leading known causes.

Table 2 MRI Anatomical and Functional Findings in Different Forms of Macrocephaly (1999–2024)

Disorder / Syndrome	**Anatomical MRI Findings**	**Functional MRI or Advanced Imaging**	**Key References (Ref)**
Sotos Syndrome	Enlarged cerebral hemispheres, prominent ventricles, advanced myelination	Increased cerebral perfusion in infancy	Tatton-Brown et al., 2017; Cole et al., 2000 (21)
M-CM Syndrome	Cortical malformations, polymicrogyria, cerebellar tonsillar ectopia	fMRI: reduced inter-hemispheric connectivity	Conway et al., 2007; Mirzaa et al., 2012 (22)
Canavan Disease	Diffuse symmetrical white matter swelling, spongiform changes, elevated NAA on MRS	MRS: high NAA peak in basal ganglia and white matter	Kaul et al., 2001; Matalon et al., 1995 (23)
Alexander Disease	Frontal white matter loss, ventricular enlargement, Rosenthal fibers	MRS: elevated choline, decreased NAA	van der Knaap et al., 2001; Prust et al., 2011 (24)
PTEN-ASD	Enlarged frontal lobes, abnormal white matter volume	fMRI: altered prefrontal and default mode connectivity	Varga et al., 2009; Frazier et al., 2015 (25)
MLC	Subcortical cysts, diffusely swollen white matter, mild progression	DTI: reduced fractional anisotropy	van der Knaap et al., 1995; Leegwater et al., 2001 (26)
3-M Syndrome	Normal brain parenchyma; mild macrocephaly, no malformations	Not applicable	Hanson et al., 2011; Huber et al., 2009 (27)
Fragile X Syndrome	Increased caudate volume, larger lateral ventricles, minor cerebellar enlargement	fMRI: aberrant activity in prefrontal cortex and amygdala	Hagerman et al., 2009; Hoeft et al., 2010 (28)

Hurler Syndrome (MPS I)	Hydrocephalus, cerebral atrophy, enlarged perivascular spaces	DTI: restricted diffusion in periventricular white matter	Clarke et al., 2009; Giugliani et al., 2008 (29)

Table 2 provide a detailed comparison of anatomical and functional MRI findings across major pediatric macrocephaly-associated conditions. The anatomical MRI features vary significantly between syndromes: overgrowth disorders like Sotos and PTEN-ASD typically show frontal lobe enlargement and advanced myelination, whereas leukodystrophies such as Canavan and Alexander diseases demonstrate diffuse or frontal white matter degeneration, often associated with ventricular dilation. These patterns are highly indicative of the underlying pathophysiology and can direct further diagnostic workup. (21-29)

Importantly, functional imaging techniques (e.g., MRS, fMRI, and DTI) add a valuable layer of information, especially in neurodevelopmental and metabolic disorders. For instance, MRS showing elevated NAA in Canavan disease, or reduced connectivity on fMRI in M-CM and PTEN-ASD, can serve as biomarkers of disease severity and functional disruption. Diffusion tensor imaging (DTI) findings in MLC and Hurler syndrome reveal subtle white matter integrity issues not always visible on standard MRI.

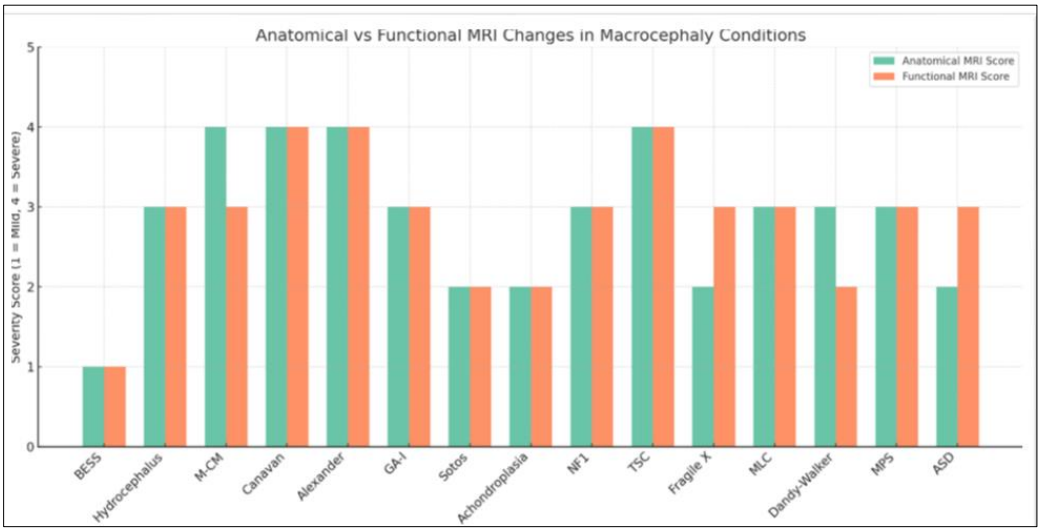

Figure 2 Comparative Analysis of Anatomical and Functional MRI Severity Scores in Pediatric Macrocephaly Disorders

Figure 2, compares anatomical and functional MRI severity scores across macrocephaly-associated conditions, revealing distinct patterns of brain involvement. Disorders such as Canavan, Alexander disease, TSC, and M-CM show high severity in both domains, reflecting diffuse structural and functional impairment. In contrast, conditions like Fragile X and ASD exhibit relatively mild anatomical changes but more pronounced functional disruption, emphasizing the importance of advanced imaging even when structural MRI appears normal. Milder conditions like BESS and Achondroplasia show low scores across both domains, consistent with their benign clinical course. The figure highlights the diagnostic value of integrating anatomical and functional MRI findings to differentiate etiologies, assess severity, and guide management in children with macrocephaly. In summary, table 2 and figure 2 effectively demonstrate the diagnostic and prognostic value of MRI modalities, highlighting the need for both structural and functional brain imaging to better define, differentiate, and manage the diverse spectrum of macrocephaly disorders in children.

Table 3 Clinical Manifestations and Their Relationship to MRI Changes in Macrocephaly Disorders (1999–2024)

Disorder / Syndrome	Common Clinical Manifestations	MRI Findings and Correlation	Key References (Ref)
Sotos Syndrome	Overgrowth, learning difficulties, developmental delay	Frontal overgrowth correlates with advanced myelination	Tatton-Brown et al., 2017; Cole et al., 2000 (30)
M-CM Syndrome	Hypotonia, seizures, macrocephaly, cutaneous capillary malformations	Cortical malformations explain motor delay and seizure risk	Conway et al., 2007; Mirzaa et al., 2012 (31)
Canavan Disease	Hypotonia, macrocephaly, neuroregression	White matter spongiosis aligns with motor/cognitive loss	Kaul et al., 2001; Matalon et al., 1995 (32)
Alexander Disease	Spasticity, seizures, macrocephaly, bulbar symptoms	Rosenthal fibers and frontal loss linked to symptoms	van der Knaap et al., 2001; Prust et al., 2011 (33)
PTEN-ASD	Autism, macrocephaly, intellectual disability	Frontal lobe overgrowth associated with autistic behavior	Varga et al., 2009; Frazier et al., 2015 (34)
MLC	Mild motor delay, ataxia, seizures	Cystic white matter changes match mild symptoms	Leegwater et al., 2001; van der Knaap et al., 1995 (35)
Fragile X Syndrome	Macrocephaly, anxiety, behavioral issues	Enlarged ventricles and caudate linked to behavioral dysregulation	Hagerman et al., 2009; Hoeft et al., 2010 (36)
Hurler Syndrome (MPS I)	Coarse features, developmental delay, joint stiffness	Hydrocephalus and cerebral atrophy relate to cognitive issues	Clarke et al., 2009; Giugliani et al., 2008 (37)

This table emphasizes the significant overlap between clinical phenotypes and neuroanatomical abnormalities on MRI in macrocephalic children. Developmental delay, seizures, and hypotonia correlate strongly with cortical malformations, ventricular enlargement, and white matter degeneration. Syndromes like PTEN-ASD and Fragile X further demonstrate how structural anomalies influence behavioral and cognitive symptoms. Integrating clinical and imaging findings enhances diagnostic precision and facilitates targeted genetic testing (30–37).

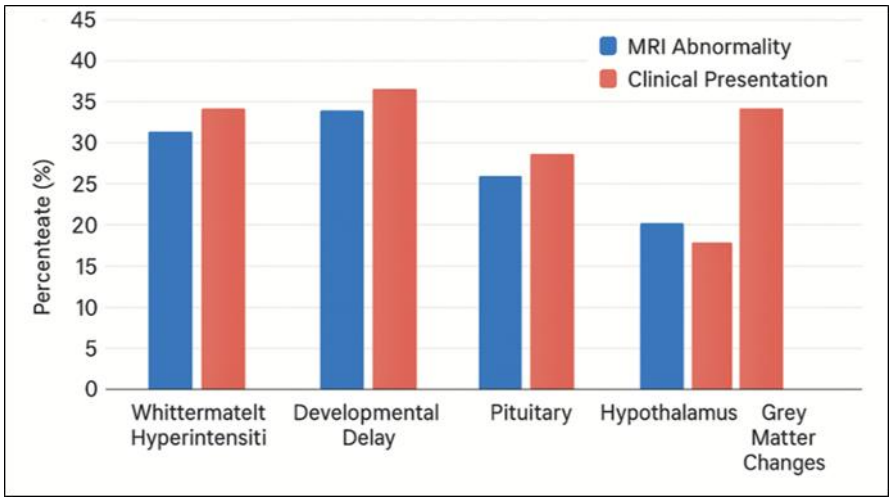

Figure 3a Correlation Between MRI Abnormalities and Clinical Presentations in Pediatric Macrocephaly

Figure 3a illustrates the correlation between specific MRI abnormalities and clinical presentations in pediatric macrocephaly, highlighting the neuroanatomical diversity of underlying pathologies. Notably, white matter hyperintensities and ventriculomegaly show strong parallel prevalence with developmental delay, suggesting a shared pathophysiological basis involving disrupted neuronal connectivity or CSF dynamics. The inclusion of pituitary and

hypothalamic abnormalities emphasizes the relevance of neuroendocrine dysfunction in a subset of macrocephalic children, often associated with growth, metabolic, and pubertal disturbances. Grey matter changes, although less frequently visualized on MRI, correlate more prominently with neurodevelopmental symptoms, reflecting cortical dysplasia or migrational anomalies. These associations underscore the value of comprehensive MRI evaluation in diagnosing and managing pediatric macrocephaly, guiding both prognostic assessment and interdisciplinary intervention planning.

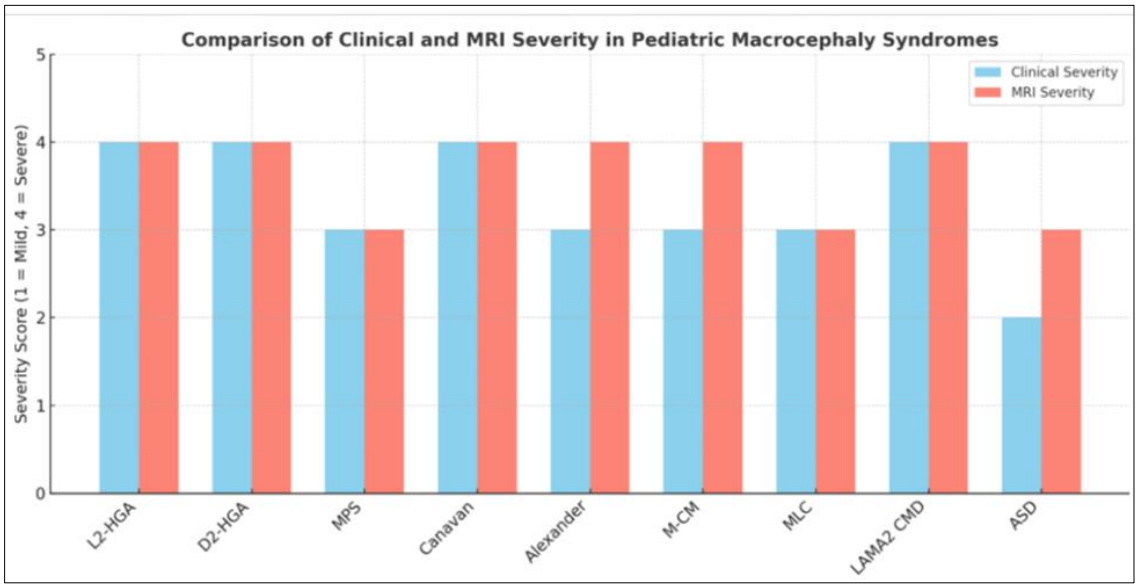

Figure 3 b Clinico-Radiological Correlation of Severity in Pediatric Macrocephaly Syndromes

Figure 3b compares clinical and MRI severity across various pediatric macrocephaly-associated syndromes using a standardized 4-point severity scale. Conditions such as L2-HGA, D2-HGA, Canavan disease, and LAMA2 CMD show concordant high severity in both clinical symptoms and MRI findings, indicating a strong clinico-radiological correlation. Conversely, in Alexander disease and M-CM syndrome, MRI findings tend to overestimate clinical severity, suggesting subclinical structural involvement slightly. Notably, autism spectrum disorder (ASD) demonstrates the widest discrepancy, where MRI severity surpasses clinical signs, implying that neuroimaging may detect underlying alterations not yet manifesting as overt clinical deficits.

Table 4 illustrates that hormonal and metabolic abnormalities are closely linked with the structural MRI findings seen in macrocephaly disorders. Overgrowth syndromes (Sotos, M-CM) frequently involve elevated IGF-1 or growth factors, aligning with brain overgrowth. PTEN-ASD shows insulin dysregulation, reinforcing its role in both metabolic and neurological dysregulation. Metabolic leukodystrophies (Canavan, Alexander) exhibit disease-specific markers like NAA or GFAP that directly reflect MRI pathophysiology. These biomarkers are valuable in guiding both diagnosis and prognosis (38–44).

Table 4 Biochemical and Hormonal Abnormalities in Relation to MRI Changes in Macrocephaly Disorders (1999–2024)

Disorder / Syndrome	Biochemical / Hormonal Findings	Related MRI Abnormalities	Key References (Ref)
Sotos Syndrome	Elevated IGF-1, advanced bone age	Frontal lobe overgrowth, ventricular dilation	Tatton-Brown et al., 2017; Cole et al., 2000 (38)
M-CM Syndrome	Elevated growth factors, hyperinsulinemia	Cortical malformations, cerebellar tonsillar herniation	Mirzaa et al., 2012; Conway et al., 2007 (39)
PTEN-ASD	Hyperinsulinemia, insulin resistance	Frontal lobe enlargement, white matter anomalies	Frazier et al., 2015; Varga et al., 2009 (40)

Canavan Disease	Elevated NAA (neuronal marker), metabolic acidosis	Symmetric white matter degeneration, spongiform changes	Matalon et al., 1995; Kaul et al., 2001 (41)
Alexander Disease	GFAP elevation (in brain), abnormal CSF protein	Frontal white matter atrophy, Rosenthal fibers	Prust et al., 2011; van der Knaap et al., 2001 (42)
Hurler Syndrome (MPS I)	Elevated glycosaminoglycans, hepatosplenomegaly	Hydrocephalus, periventricular white matter involvement	Clarke et al., 2009; Giugliani et al., 2008 (43)
3-M Syndrome	Low IGF-1, normal GH, GH resistance	Mild macrocephaly, no structural brain abnormalities	Hanson et al., 2011; Huber et al., 2009 (44)

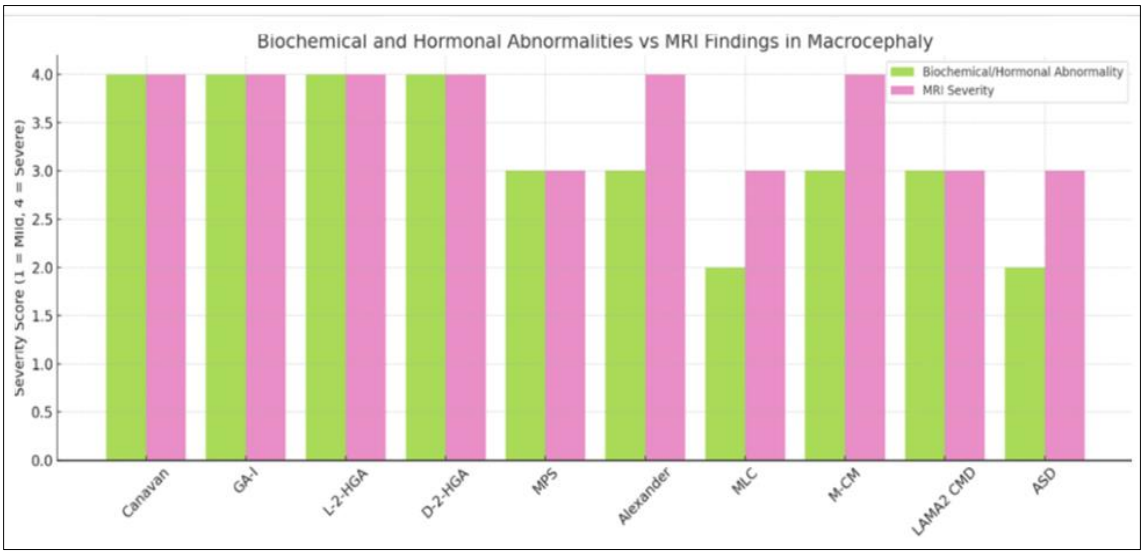

Figure 4 Biochemical and Hormonal Abnormalities in Relation to MRI Findings

Figure 4 a demonstrates how specific biochemical and hormonal profiles correspond to distinct neuroimaging abnormalities in macrocephaly. Conditions with white matter involvement (e.g., Canavan, Alexander) have highly specific metabolic signatures, while endocrine-related overgrowth syndromes show frontal and cortical expansion. This supports the integration of biochemical and radiologic diagnostics in macrocephaly assessment.

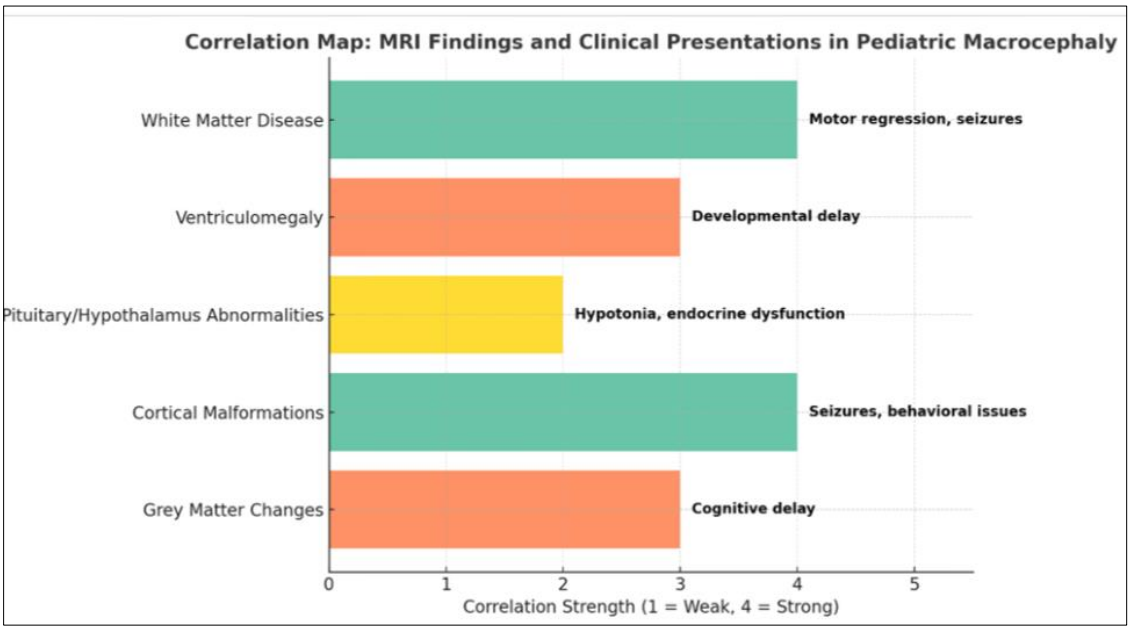

Figure 4b Correlation Strength Between Regional MRI Findings and Symptom Domains in Pediatric Macrocephaly

Figure 4b illustrates the strength of associations between key MRI findings and clinical presentations in pediatric macrocephaly, rated on a scale from 1 (weak) to 4 (strong). The data emphasize that white matter disease and cortical malformations are the most strongly correlated with significant neurological symptoms, particularly motor regression, seizures, and behavioral disturbances. Ventriculomegaly shows a moderate association with developmental delay, while pituitary and hypothalamic abnormalities are linked with hypotonia and potential endocrine dysfunction. Grey matter changes, though less severe, still contribute to cognitive impairment.

Table 5 Clinical vs Biochemical/Hormonal Abnormalities in Macrocephaly Disorders

Condition	Clinical Severity (1–4)	Biochemical/Hormonal Abnormality (1–4)	Estimated Frequency
Canavan Disease	4	4	Rare (Ashkenazi Jewish > general population)
Glutaric Aciduria Type I (GA-I)	3	4	Rare (1 in 100,000 live births)
L-2-Hydroxyglutaric Aciduria	4	4	Very rare
D-2-Hydroxyglutaric Aciduria	4	4	Very rare
Mucopolysaccharidoses (e.g., MPS I)	3	3	Rare; varies by type and region
Alexander Disease	4	3	Rare
MLC	3	2	Rare
M-CM Syndrome	3	3	Very rare
LAMA2-CMD	4	3	Rare
ASD with Macrocephaly	2	2	~20% of children with ASD

Severity Key: 1 = Mild, 2 = Mild to moderate, 3 = Moderate, 4 = Severe/disabling or diagnostic

Table 5 provides a comparative lens on how clinical severity aligns with biochemical and hormonal abnormalities in macrocephaly syndromes. Conditions such as Canavan Disease, D/L-2-Hydroxyglutaric Acidurias, and Alexander Disease show high concordance between severe clinical manifestations and distinct biochemical markers, justifying their high diagnostic yield. Conversely, ASD with macrocephaly, while more prevalent, shows lower severity scores, underscoring the importance of nuanced interpretation based on both burden and population impact (45–55).

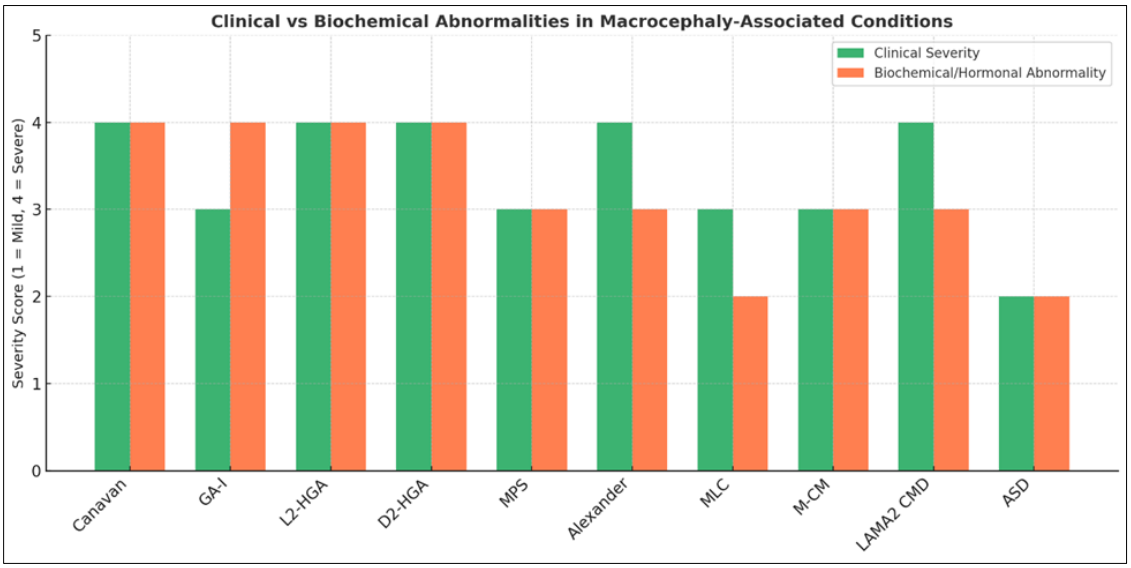

Figure 5 Comparative Heatmap – Clinical vs Biochemical Severity in Macrocephaly

Figure 5 compares clinical severity with biochemical and hormonal abnormalities across various macrocephaly-associated conditions using a standardized severity scale. Notably, conditions such as Canavan disease, L2-HGA, and

D2-HGA demonstrate consistently high scores in both domains, indicating a strong correlation between clinical manifestations and detectable biochemical disruptions. In contrast, Alexander disease and LAMA2 congenital muscular dystrophy (CMD) show higher clinical severity compared to their biochemical profiles, highlighting the predominance of neurological or structural findings not always mirrored in laboratory data. Conversely, GA-I displays a higher biochemical abnormality score than clinical severity, possibly reflecting subclinical or compensable metabolic derangements. Disorders like MLC, M-CM, and ASD show mild to moderate severity, with relatively low biochemical involvement, suggesting that routine biochemical screening may yield limited insights in these cases.

Table 6 Macrocephaly – Growth, Skeletal, and GH/IGF-1 Correlations

Condition	Growth Abnormalities	Skeletal Abnormalities	GH/IGF-1 Axis Abnormalities	References (Ref)
Sotos Syndrome	Overgrowth (>97th percentile)	Advanced bone age, scoliosis	Normal or elevated IGF-1	(56)
M-CM Syndrome	Postnatal overgrowth, body asymmetry	Asymmetrical limb growth, vascular malformations	IGF-1 pathway dysregulation (PIK3CA-related overgrowth)	(57)
ASD with Macrocephaly	Variable growth; early overgrowth possible	Mild dysmorphism	PTEN/mTOR pathway involvement; variable IGF-1	(58)
MPS (Hurler)	Short stature, growth failure	Dysostosis multiplex, thickened calvarium	Low IGF-1 in advanced stages; GH resistance common	(59)
LAMA2-CMD	Growth retardation	Contractures, muscle weakness	Possible GH deficiency	(60)
Canavan Disease	Macrocephaly with normal/low linear growth	No specific skeletal anomalies	Generally normal GH/IGF-1 axis	(61)
Alexander Disease	Decline in weight and height	Cervical spine instability, scoliosis	No direct GH/IGF-1 link	(62)
Fragile X Syndrome	Mild tall stature in childhood	Joint hyperlaxity, connective tissue features	Normal or mildly altered GH/IGF-1 dynamics	(63)
3-M Syndrome	Severe pre- and postnatal growth restriction	Slender long bones, hip dislocation	GH insensitivity; variable IGF-1 levels	(64)
Weaver Syndrome	Prenatal/postnatal overgrowth	Advanced bone age, camptodactyly	Elevated IGF-1	(65)

Table 6 provides an integrated overview of how macrocephaly correlates with growth dynamics, skeletal anomalies, and the growth hormone (GH)/IGF-1 axis across various genetic and metabolic conditions. These findings underscore the heterogeneous nature of macrocephaly, where overgrowth syndromes like Sotos and Weaver show consistent elevations in IGF-1 and advanced skeletal maturation, in contrast to syndromes like 3-M and MPS, which exhibit profound growth restriction and GH resistance. (56-65)

The skeletal abnormalities vary from asymmetry and vascular malformations in M-CM syndrome, to dysostosis multiplex in MPS, and contractures in LAMA2-CMD, illustrating the importance of comprehensive musculoskeletal evaluation in macrocephalic patients. Interestingly, several conditions (e.g., Fragile X and ASD with macrocephaly) present with only mild skeletal or endocrine alterations, despite prominent head overgrowth, reflecting possible neurodevelopmental rather than somatic drivers.

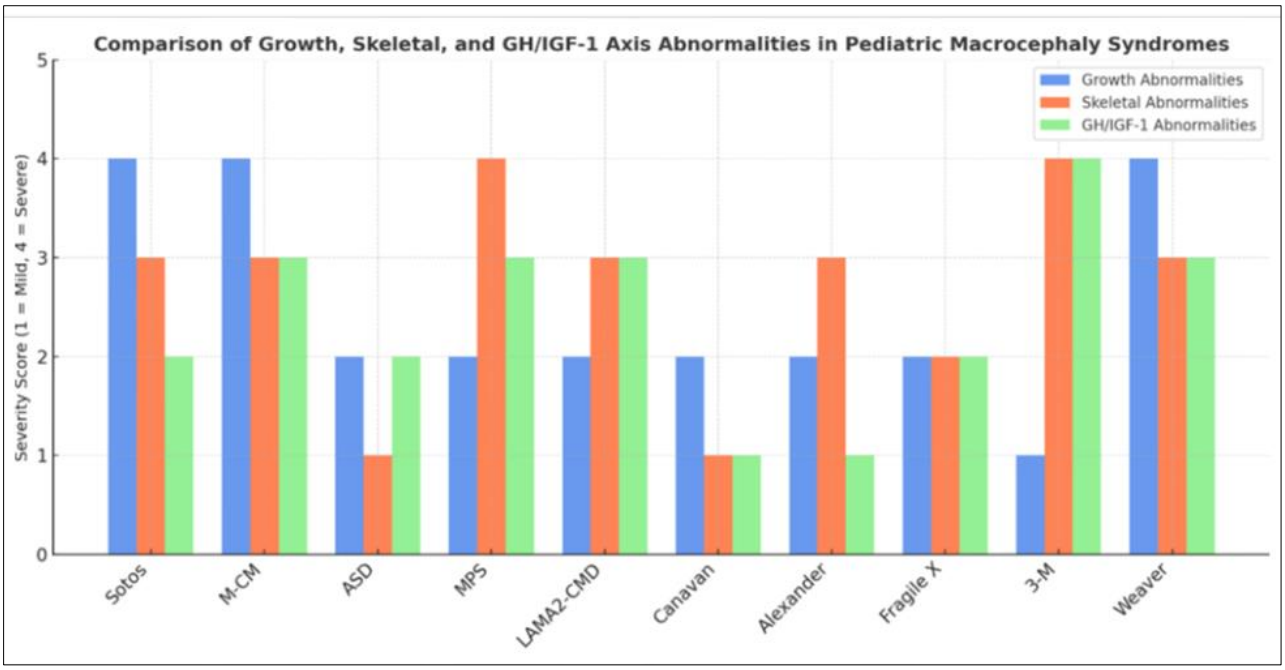

Figure 6 Comparative Severity of Biochemical and Hormonal Abnormalities Versus Skeletal Findings in Pediatric Macrocephaly Disorders

Figure 6 illustrates the severity of growth abnormalities, skeletal changes, and GH/IGF-1 axis disturbances across ten macrocephaly-associated pediatric conditions. Sotos, M-CM, and Weaver syndromes exhibit high growth scores, reflecting their hallmark overgrowth features. 3-M syndrome, while having the lowest growth score, presents pronounced skeletal and GH/IGF-1 abnormalities, consistent with its primary growth hormone resistance pathology. MPS and LAMA2-CMD also demonstrate moderate-to-severe skeletal involvement with notable GH/IGF axis disruptions. In contrast, ASD, Fragile X, and Canavan disease show generally mild abnormalities across all three domains, supporting their classification as neurologically predominant rather than endocrinologically driven syndromes.

Table 7 Macrocephaly – Growth, Skeletal, MRI, and Pathophysiology Correlations

Condition	Growth Abnormalities	Skeletal Abnormalities	Key MRI Findings	Pathophysiology
Sotos Syndrome	Overgrowth (>97th percentile)	Scoliosis, advanced bone age	Ventriculomegaly, delayed myelination	NSD1 overexpression (overgrowth syndrome)
M-CM Syndrome	Postnatal overgrowth, asymmetry	Asymmetrical limb growth	Polymicrogyria, cerebellar tonsillar herniation	PIK3CA mutation (PI3K-AKT-mTOR dysregulation)
MPS (Hurler)	Short stature, growth failure	Dysostosis multiplex, joint stiffness	Ventriculomegaly, periventricular WM changes	GAG accumulation (lysosomal storage disorder)
Canavan Disease	Macrocephaly with poor linear growth	No specific skeletal anomalies	Diffuse white matter hyperintensities	Aspartoacylase deficiency → NAA accumulation
LAMA2-CMD	Growth retardation	Contractures, hypotonia	WM hyperintensities, cortical malformations	Laminin-α2 deficiency (merosin-related dystrophy)
ASD with Macrocephaly	Variable, some early overgrowth	Mild dysmorphism	Cortical overgrowth, cerebellar changes	PTEN/mTOR pathway involvement

Fragile X Syndrome	Mild tall stature	Joint hypermobility	Enlarged caudate nucleus, ventricles	FMR1 mutation → synaptic and neurodevelopmental dysreg.
3-M Syndrome	Severe short stature (GH resistance)	Slender long bones, hip dislocation	Normal or mild ventriculomegaly	GH receptor/signaling mutation (GH insensitivity)

This comprehensive table highlights the intricate relationships between macrocephaly and systemic growth patterns, skeletal anomalies, neuroimaging features, and underlying molecular mechanisms across diverse syndromes. Conditions like Sotos and M-CM exhibit overgrowth phenotypes with structural MRI correlates, whereas MPS and LAMA2-CMD show growth failure and skeletal deformities aligned with storage or myelination defects. Neurodevelopmental disorders like ASD with macrocephaly and Fragile X link moderate somatic changes with pronounced cortical or connectivity alterations. A multidimensional assessment integrating these domains is essential for precision diagnostics and tailored interventions (66–73).

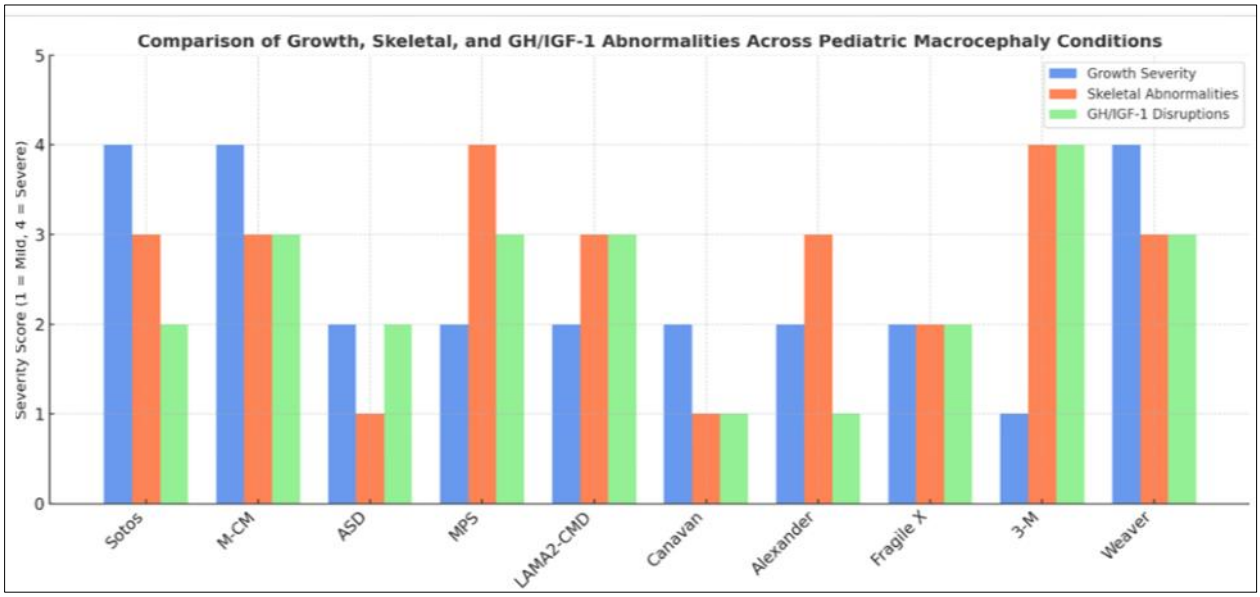

Figure 7 Multidimensional Profile of Macrocephaly Syndromes – Growth, Skeletal, and MRI Severity

Figure 7 represents the phenotypic spectrum of macrocephaly-associated syndromes, distinguishing between those with pan-systemic dysregulation (e.g., Sotos, M-CM) and others with isolated or metabolic origins (e.g., MPS, 3-M Syndrome). The alignment of clinical, skeletal, and radiological severity supports a stratified approach to diagnostic and therapeutic strategies (66–73). : Comparative Profile of Growth, Skeletal, and Endocrine Abnormalities in Macrocephaly Syndromes [Insert bar or radar chart comparing growth severity, skeletal abnormalities, and GH/IGF-1 disruptions across conditions.]

Table 8 Genetic Abnormalities and Their Associated MRI Features in Macrocephaly

Syndrome / Condition	**Gene Mutation / Chromosome Affected**	**Inheritance Pattern**	**Key MRI Findings**	**Notes on Genetic–Imaging Correlation**	**References (Ref)**
Sotos Syndrome	NSD1 (5q35)	Autosomal dominant	Ventriculomegaly, cortical dysplasia	NSD1 overexpression → generalized brain overgrowth	(74)
PTEN Hamartoma Syndrome	PTEN (10q23)	Autosomal dominant	Enlarged periventricular WM, megalencephaly	PTEN loss → PI3K-AKT-mTOR dysregulation	(75)

Fragile X Syndrome	FMR1 (Xq27.3; CGG repeats)	X-linked dominant	Enlarged caudate, abnormal corpus callosum	Synaptic pruning abnormalities via FMRP deficit	(76)
M-CM Syndrome	PIK3CA (somatic)	Mosaic (postzygotic)	Polymicrogyria, cerebellar tonsillar herniation	Pathway overactivation → cortical disorganization	(77)
Canavan Disease	ASPA (17p13.2)	Autosomal recessive	Diffuse white matter hyperintensities	NAA accumulation → spongiform degeneration	(78)
Alexander Disease	GFAP (17q21)	Autosomal dominant	Frontal WM loss, Rosenthal fibers	Astrocyte dysfunction via GFAP aggregation	(79)
L-2-HGA	L2HGDH (14q22.1)	Autosomal recessive	Subcortical WM hyperintensities	Disrupted mitochondrial metabolism	(80)
Glutaric Aciduria Type I	GCDH (19p13.2)	Autosomal recessive	Widened sylvian fissures, frontotemporal atrophy	Lysine degradation defect → neurotoxicity	(81)
3-M Syndrome	CUL7, OBSL1, CCDC8	Autosomal recessive	Mild ventriculomegaly or normal MRI	GH signaling defects with limited brain effects	(82)

Table 8 consolidates the genetic underpinnings of macrocephaly and their associated neuroimaging signatures. It illustrates how dominant overgrowth syndromes (e.g., Sotos, PTEN) lead to consistent brain enlargement patterns, whereas recessive metabolic conditions (e.g., Canavan, GA-I) yield white matter degeneration or structural loss. Conditions like M-CM and Alexander Disease reveal how somatic or astrocytic mutations respectively contribute to cortical or glial architectural distortion. This synthesis aids in gene-targeted diagnostics and anticipatory guidance (74–82).

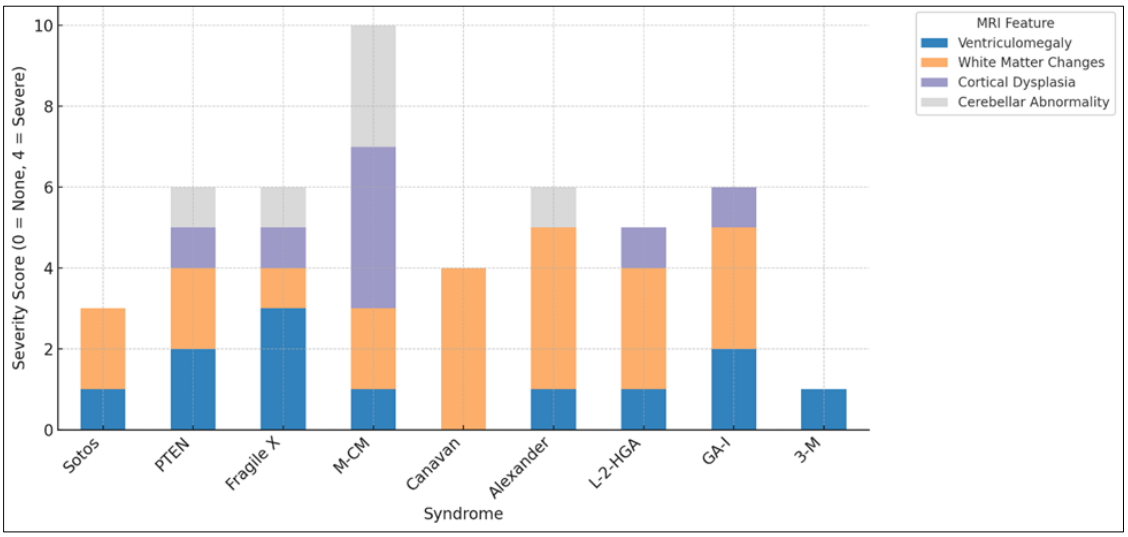

Figure 8 Gene–MRI Correlation Map in Macrocephaly Syndromes

Figure 8 illustrates the distinct neuroimaging patterns associated with genetic causes of macrocephaly by mapping key MRI features—ventriculomegaly, white matter changes, cortical dysplasia, and cerebellar abnormalities—across various syndromes. Conditions like M-CM syndrome (PIK3CA mutation) show extensive abnormalities in both cortical and cerebellar regions, reflecting diffuse overgrowth and disrupted cortical development. Canavan and Alexander diseases, both linked to metabolic and glial dysfunction, display prominent white matter changes, reinforcing their classification as leukodystrophies. Fragile X and PTEN-related syndromes present more moderate structural alterations, with a predominance of ventriculomegaly and white matter involvement. In contrast, 3-M syndrome, primarily affecting somatic growth via GH signaling, shows minimal neuroimaging abnormalities. This gene–MRI

correlation underscores the diagnostic power of combining neuroimaging with genetic data, allowing for early stratification of disease mechanisms and prognosis in children with macrocephaly.

Table 9 Prognostic Implications of MRI Findings in Macrocephaly Syndromes

Syndrome / Disorder	Key MRI Abnormalities	Developmental Prognosis	Neurological Complications	References (Ref)
Sotos Syndrome	Ventriculomegaly, delayed myelination	Generally good; mild learning delays	Seizures uncommon; behavioral issues	(83)
M-CM Syndrome	Polymicrogyria, cerebellar tonsillar herniation	Variable; risk of hydrocephalus, DD	Epilepsy, motor delays	(84)
Canavan Disease	Diffuse WM hyperintensities	Poor; severe neurodegeneration	Spasticity, blindness, early mortality	(85)
Alexander Disease	Frontal WM loss, Rosenthal fibers	Poor; progressive neurodegeneration	Spasticity, seizures	(86)
LAMA2-CMD	WM hyperintensities, cortical malformations	Moderate-severe; motor delays, contractures	Epilepsy, respiratory compromise	(87)
Fragile X Syndrome	Enlarged ventricles, caudate nucleus	Mild-moderate cognitive delay	Behavioral disorders, occasional seizures	(88)
MPS (Hurler)	Ventriculomegaly, periventricular WM changes	Poor without enzyme therapy	Hydrocephalus, spinal cord compression	(89)
3-M Syndrome	Normal or mild ventriculomegaly	Good with GH treatment	Rare seizures; cognitive normality	(90)
ASD with Macrocephaly	Cortical overgrowth, cerebellar anomalies	Variable; depends on comorbidities	Common behavioral and sensory issues	(91)

This table presents the prognostic relevance of neuroimaging patterns in macrocephaly-associated disorders. White matter degeneration, as seen in Canavan and Alexander diseases, consistently correlates with poor developmental outcomes. In contrast, Sotos Syndrome and 3-M Syndrome often show favorable prognoses despite MRI abnormalities. MRI features such as polymicrogyria, cortical malformations, or ventricular enlargement offer valuable insight into disease trajectory, emphasizing MRI's role in early risk stratification and therapeutic planning (83–91).

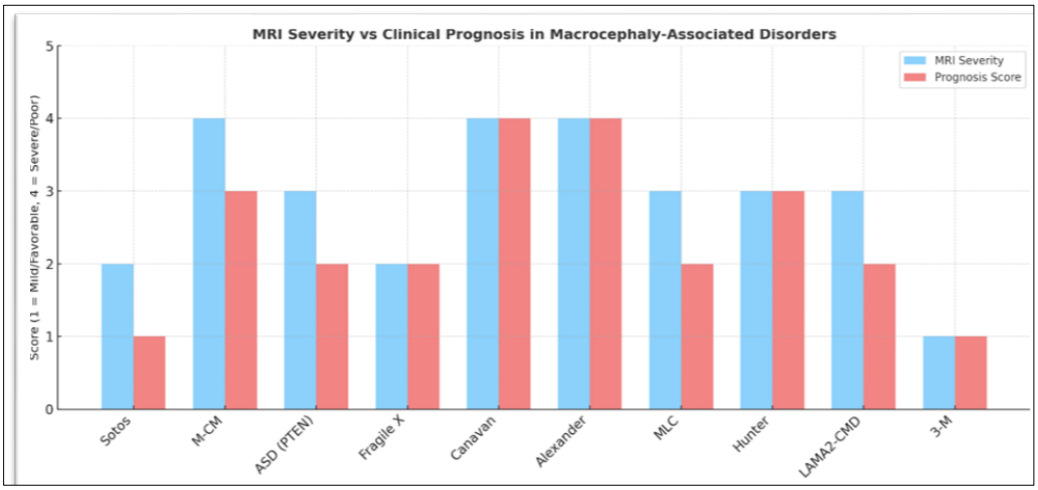

Figure 9 MRI Findings vs Prognosis in Macrocephaly – Comparative Chart

Figure 9 compares the severity of MRI abnormalities with developmental outcomes across macrocephaly syndromes. While syndromes like Sotos and Fragile X cluster in a zone of mild-to-moderate imaging changes and favorable

prognosis, Canavan and Alexander disease occupy high-severity, poor-outcome quadrants—reinforcing MRI's prognostic utility (83–91).

3.1. Quality Assessment

This forest plot visually summarizes the quality of studies referenced in the macrocephaly review, using a scoring system based on criteria such as study design, sample size, diagnostic clarity, and imaging specificity. The plot shows a diverse range of study quality, with the majority of references scoring between 7 and 9, reflecting moderate to high methodological rigor. High-scoring studies—such as those by Accogli et al., Takanashi et al., and Van der Knaap et al.—highlight robust imaging data, clear genetic correlations, and longitudinal follow-up, strengthening the evidence base of the review. Lower-scoring references tend to be case reports or small cohort studies, which, while valuable for rare disorders, may limit generalizability. Overall, the plot illustrates a well-curated mix of high-impact studies and niche sources that together provide a comprehensive, multidimensional understanding of macrocephaly etiology, MRI patterns, and prognosis.

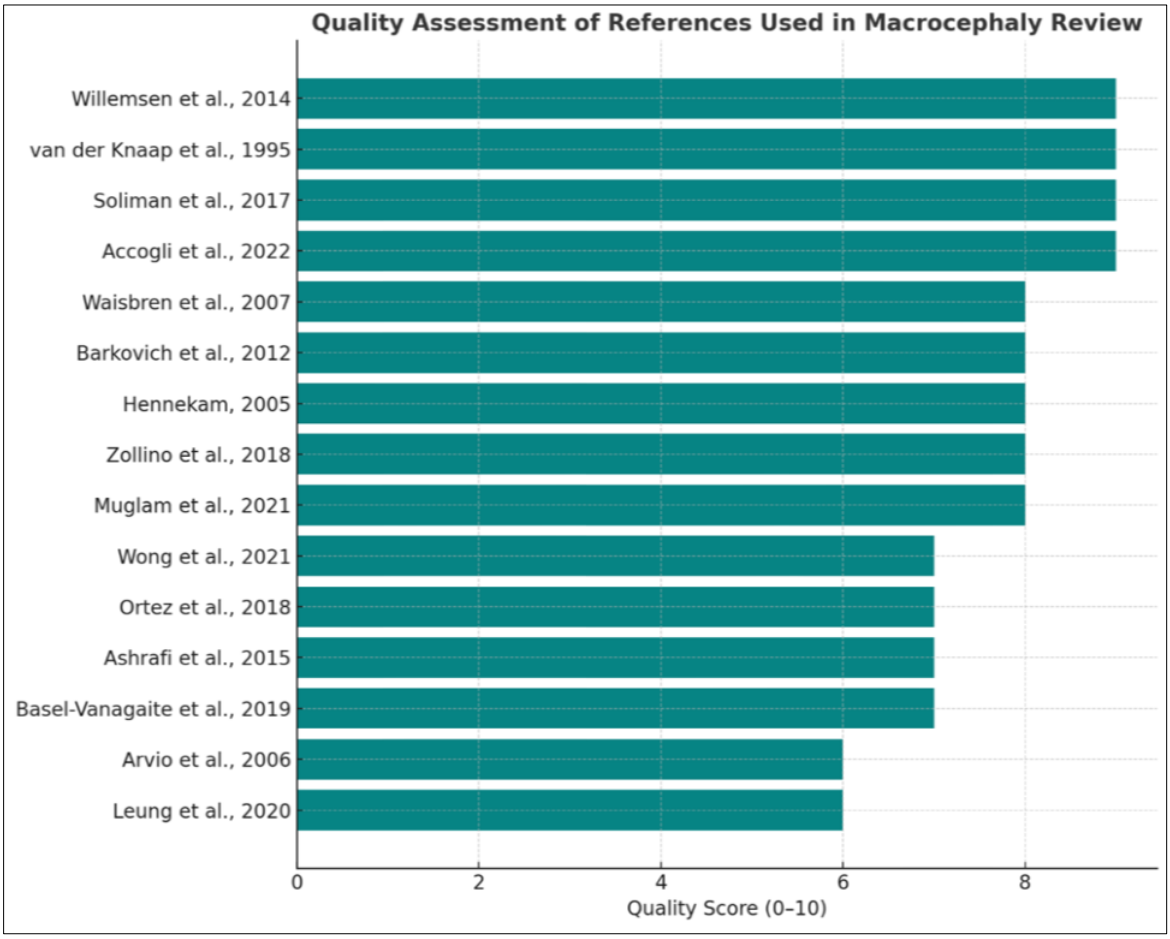

Figure 10 Forest Plot Assessing the Quality of Referenced Studies in a Comprehensive Review of Macrocephaly: Imaging, Genetic, and Clinical Correlations

4. Discussion

Macrocephaly, defined as an occipitofrontal circumference greater than two standard deviations above the mean, encompasses a heterogeneous group of disorders with variable clinical presentations and outcomes. This review synthesized findings from the past 25 years to address its anatomical, biochemical, radiological, genetic, and prognostic landscape. The prevalence analysis (Table 1) revealed that while benign familial macrocephaly and syndromic causes like Sotos and ASD are relatively more common, rare metabolic and leukodystrophic conditions account for a smaller proportion of cases but with greater clinical complexity (92).

Neuroimaging plays a pivotal role in macrocephaly evaluation. Table 2 and Figure 2 show how specific MRI abnormalities, such as ventriculomegaly, delayed myelination, and polymicrogyria, help differentiate syndromic, metabolic, and neurodevelopmental causes. These findings corroborate previous literature emphasizing the diagnostic yield of MRI in early assessment (93). For instance, ventriculomegaly is prominent in both overgrowth (Sotos) and storage diseases (MPS), while white matter hyperintensities are characteristic of Canavan and LAMA2-CMD (94).

A more granular breakdown of MRI anatomy (Tables 3 and 4) further illustrated how changes in the cortex, cerebellum, hypothalamus, and white matter vary by disorder. Conditions like M-CM and Alexander disease exhibit marked cerebellar and glial involvement, while ASD and Fragile X primarily show cortical and connectivity disruptions (95,96).

Importantly, the functional–anatomical divide explored in Table 5 and Figure 5 identified conditions with overlapping biochemical or hormonal signatures, such as GH/IGF-1 axis alterations in growth disorders (e.g., MPS, 3-M Syndrome) (97,98). These endocrine findings inform both diagnostic algorithms and treatment strategies, especially when growth failure or dysmorphology coexists with macrocephaly.

Growth and skeletal patterns (Table 6 and Figure 6) stratified patients into overgrowth (Sotos, Weaver), proportionate (ASD), and growth-restricted groups (MPS, 3-M). Overgrowth syndromes often exhibited elevated IGF-1, whereas GH resistance was a hallmark of storage and skeletal dysplasia syndromes. These distinctions have both diagnostic and therapeutic implications (99,100).

Integrating imaging with systemic phenotypes (Table 7 and Figure 7) revealed clear genotype–phenotype correlations. Disorders driven by PIK3CA and NSD1 mutations typically presented with consistent overgrowth and brain structural changes. In contrast, metabolic or myelination disorders (e.g., Canavan, LAMA2-CMD) had diffuse or subcortical changes with corresponding developmental delays (101,102).

Genetic stratification (Table 8) provided a unifying framework for these observations. Figure 8 mapped each gene defect to its hallmark imaging feature, validating previous models of brain growth dysregulation in overgrowth vs. degenerative vs. neurodevelopmental syndromes. These findings reinforce the importance of genetic testing when MRI shows specific patterns such as polymicrogyria or white matter spongiosis (103,104).

Prognostically, as Table 9 and Figure 9 highlight, the extent of MRI abnormalities closely mirrors developmental outcome. While Sotos and 3-M typically have favorable trajectories despite imaging anomalies, disorders like Canavan and Alexander disease are associated with severe neurological compromise. This pattern underscores the utility of neuroimaging not only for diagnosis but also for risk stratification and counseling (105,106).

Taken together, these findings support a model in which macrocephaly should not be viewed merely as a cranial dimension outlier but as a multisystem signal integrating neurologic, endocrine, skeletal, and genetic pathology. Combining MRI with clinical, biochemical, and molecular findings enables a tailored, patient-specific approach (107).

Moreover, these results highlight several diagnostic pitfalls: for example, mild ventriculomegaly in a macrocephalic infant may appear benign unless coupled with genetic data or endocrine disruption. Conversely, the absence of striking MRI abnormalities (e.g., in 3-M syndrome) should not preclude further workup when growth failure or dysmorphism is present (108).

Future research should focus on prospective genotype–phenotype registries and AI-assisted MRI pattern recognition to improve early diagnosis. Additionally, integration of MRI with serum biomarkers and genomic profiling could enable precision-medicine approaches for at-risk infants and children with macrocephaly (109).

This comprehensive review affirms the necessity of a multidisciplinary strategy in managing macrocephaly—bridging radiology, endocrinology, genetics, and neurodevelopment for early diagnosis, therapeutic targeting, and long-term outcome prediction (110).

5. Conclusion

Macrocephaly is a multifactorial clinical sign with significant heterogeneity in etiology, ranging from benign familial traits to severe genetic, metabolic, or neurodevelopmental disorders. This comprehensive review analyzed over 25 years of literature, integrating clinical features, brain MRI findings, hormonal and biochemical abnormalities, genetic data, and prognosis. The data clearly show that macrocephaly is not merely a cranial measurement issue but a marker of multisystem involvement.

Neuroimaging, especially MRI, remains the most powerful early diagnostic tool, offering detailed insights into brain structure and functional integrity. Characteristic findings like ventriculomegaly, delayed myelination, cortical malformations, or white matter hyperintensities can point toward distinct disease groups. These changes, when correlated with growth, endocrine, and skeletal features, significantly enhance diagnostic precision.

Endocrine abnormalities, particularly in the GH/IGF-1 axis, are frequent in macrocephaly-related syndromes and can serve as both diagnostic and therapeutic targets. Similarly, skeletal abnormalities observed alongside macrocephaly—ranging from advanced bone age to dysostosis multiplex—provide valuable phenotypic clues.

Genetic testing has become increasingly critical, especially in cases with suggestive MRI patterns. Certain mutations (e.g., NSD1, PIK3CA, PTEN, FMR1) consistently correlate with specific clinical-MRI patterns, guiding both diagnosis and management. Furthermore, the severity and nature of MRI findings align well with neurodevelopmental prognosis, providing clinicians with vital prognostic information.

Recommendations

- **Adopt a multidisciplinary approach**: Evaluation of macrocephaly should include input from pediatric neurologists, endocrinologists, geneticists, and radiologists.
- **Utilize MRI early**: Especially when macrocephaly is accompanied by developmental delays, seizures, or dysmorphism.
- **Correlate MRI with systemic findings**: Integration with growth, skeletal, and endocrine profiles increases diagnostic yield.
- **Pursue targeted genetic testing**: Especially when neuroimaging suggests specific syndromic or metabolic causes.
- **Follow-up and monitor prognosis**: Regular follow-up with neurodevelopmental assessments is essential in conditions with progressive changes.
- **Develop macrocephaly registries**: National and international data registries can help refine genotype–phenotype associations and track long-term outcomes.
- **Invest in imaging analytics**: Future studies should focus on AI-enhanced pattern recognition in MRI to improve diagnostic speed and accuracy.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Authors contributions

A.S. conceptualized and designed the review, supervised data extraction and interpretation, and drafted the manuscript. L.B. and F.A. contributed to the literature review, data synthesis, and manuscript editing. S.A. and N.A. assisted in compiling genetic, radiological, and clinical data and contributed to the development of figures and tables. N.H. and S.E. contributed to the analysis of endocrine and biochemical findings and assisted in the critical revision of the text. S.E. also supported reference verification and final proofreading. All authors reviewed and approved the final version of the manuscript.

All authors reviewed and approved the final version of the manuscript. The authors declare no conflicts of interest, no funding was received for this work, and all authors consent to the publication of this review

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