WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
Coden USA: WJPRAP Impact Factor 8.63
Volume 15, Issue 4, 1457-1482. Review Article ISSN 2277–7105

LISSENCEPHALY (SMOOTH BRAIN): A COMPREHENSIVE REVIEW ASSOCIATED WITH CYTOMEGALOVIRUS (CMV)

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Article Received on 20 Jan. 2026,
Article Revised on 10 Feb. 2026,
Article Published on 15 Feb. 2026,

https://doi.org/10.5281/zenodo.18697991

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How to cite this Article: *Mrs. M. Anitha, K. Elavarasan, T. Madhan kumar, R. Nigila Sri, S. Ramadevi. (2026). Lissencephaly (Smooth Brain): A Comprehensive Review Associated With Cytomegalovirus (Cmv). World Journal of Pharmaceutical Research, 15(4), 1457–1482.

ABSTRACT

A rare congenital cortical abnormality called lissencephaly is characterized by decreased or missing cerebral gyri as a result of poor neuronal migration in the early stages of pregnancy. It is linked to severe neurodevelopmental damage and manifests as a spectrum between Agyria and Pachygyria. Although a significant percentage of cases are caused by genetic abnormalities involving genes including LIS1, DCX, TUBA1A, and RELN, non-genetic causes—particularly congenital infections—play an important and frequently overlooked role. Congenital cytomegalovirus (CMV) infection is the most important viral etiology because of its great preference for brain progenitor cells and the germinal matrix. Particularly in the first and early second trimesters, maternal CMV infection can interfere with neuronal migration and proliferation, resulting in lissencephaly and related symptoms like microcephaly, seizures, sensorineural hearing loss, and global developmental delay. Prenatal and postnatal neuroimaging, laboratory confirmation of CMV infection, and genetic testing to distinguish infectious from inherited causes are used in the diagnosis process. Early detection of CMV-associated disease allows for prompt antiviral medication and specialized supportive care, which may improve certain outcomes even though lissencephaly is still incurable. To lower the burden of disease, preventive approaches such as genetic counselling, prenatal screening, and maternal hygiene practices are crucial.

KEYWORDS: Lissencephaly, Neuronal migration, Congenital cytomegalovirus [CMV], Cortical malformation, Antiviral therapy.

AIM AND OBJECTIVES

AIM

To provide a thorough analysis of lissencephaly, with a particular emphasis on congenital cytomegalovirus (CMV) infection, emphasizing its involvement in aberrant neuronal migration, clinical presentations, diagnostic methods, treatment approaches, and preventive measures.

OBJECTIVES

1. To explain lissencephaly's genesis, classification, and epidemiology.
2. To distinguish between congenital cytomegalovirus (CMV) infection and other genetic and non-genetic causes of lissencephaly.
3. To describe the pathophysiology of lissencephaly linked to CMV and how it affects neuronal migration.
4. To describe the clinical characteristics and methods of diagnosis, including laboratory tests and imaging.
5. To talk about lissencephaly prevention and management techniques.

INTRODUCTION

Originally, the term "lissencephaly" was taken from the Ancient Greek words for smooth [Lissos] and brain [Enkephalos]. A group of uncommon brain conditions known as lissencephaly causes the entire or a portion of the brain's surface to be smooth. It is brought on by abnormal neuronal migration between weeks 12 and 24 of pregnancy, which prevents the development of brain folds (gyri) and grooves (sulci). The first pathological descriptions of human brains with an unusually smooth cerebral cortex occurred in 1914, and the word "lissencephaly" was subsequently used in clinical reports to designate the range of brain abnormalities. In severe lissencephaly the cortex lacks surface folds [agyria], while milder symptoms contain excessively broad folds [pachygyria].[1]

In 1983 Dambska originally used the labels ‘type I’ and ‘type II’ lissencephaly. Type I lissencephaly was used to refer to the ‘classical agyria syndrome’ in which the cortex Type II lissencephaly was used to refer to cortical malformations in which the brain was severely disorganized, and the individuals also had abnormalities of muscle and eyes, as part of a

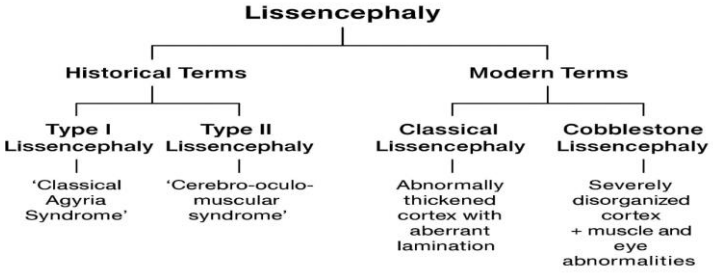
'cerebro–oculo–muscular syndrome'. Type I lissencephaly is now typically referred to as 'classical lissencephaly' and type II lissencephaly as 'cobblestone lissencephaly' [or 'cobblestone dysplasia' or 'cobblestone complex].[2]

A member of the Herpesviridae family, cytomegalovirus [CMV] has the ability to create a sequela of congenital defects when transferred from the mother to the fetus during pregnancy.[3] Acute onset of CMV infection might present with ambiguous indications, such as fever, sore throat, and exhaustion, or may present asymptomatically. Thus, the pregnant mother may present as fully asymptomatic, yet congenital CMV has various repercussions on the foetus, including hearing loss, seizures, and cognitive developmental delay. Although there is no clear cure for CMV infection, there are drugs available to reduce the replication of virus.

Globally, congenital CMV is thought to impact 0.2–2.2% of live births.[4] In a 17-year study, Bristow et al. Analysed an astounding total of 777 newborn deaths in the United States attributable to CMV infection symptoms, with 557 being under the age of one year old.[5]

According to current guidelines, individuals with severe, life-threatening symptoms should switch to oral VGCV after receiving IV ganciclovir for two to six weeks. Oral VGCV is administered for six weeks to patients who do not exhibit life-threatening symptoms. In this treatment several tests are taken to prevent the multiorgan damage.[6] Features of the "lissencephaly syndrome" presents with severe developmental delay, microcephaly, periventricular calcifications, peculiar facies, with a high forehead, slight anteversion of nostrils, minor upward palpebral slant, widely spaced eyes, micrognathia, and abnormal low-set ears.[7]

Therefore, lissencephaly is a deformity of the brain in which the surface of the brain is devoid of gyri and sulci. Among the different causes of lissencephaly, gestational insults by infection during pregnancy play a crucial role, particularly CMV. Lissencephaly is a congenital abnormality in neural migration that arises between 12 and 16 weeks of gestation.[8]



In this infection, it triggers various stages such as direct cytopathic effects, inflammation-mediated injury, and impaired neuronal migrations. Infants with CMV-associated disease may present with microcephaly, epileptic seizures, hypotonia, feeding difficulty, global developmental delay, sensorineural hearing loss, and visual impairment.[9] Neuronal imaging—prenatal ultrasound, laboratory confirmations of CMV infection testing via amniotic fluid PCR [polymerase chain reaction], other testing from urine, saliva, or blood, and targeted diagnostic testing like placental pathology, serologic testing, neonatal evaluation, and foetal MRI followed by neonatal MRI—plays a central role in identifying the cortical malformation, migrational abnormality, and other supportive signs of intrauterine infection. These are the most widely used diagnosis methods currently in use for lissencephaly caused by cytomegaloviral infections. The management mainly focuses on symptomatic and supportive care such as prenatal counselling, antiviral therapy [ganciclovir/valganciclovir], antiepileptic drugs for seizure control, and nutritional and feeding support, including gastrostomy when required. Also Physical, occupational, and developmental therapies, Hearing and vision monitoring methods.[10]

The goal of this review is to synthesize knowledge on differentiating CMV-associated lissencephaly from genetic forms, which has important implications for prenatal counselling, summarizing imaging features and neuropathologic findings, and discussing challenges and considerations for diagnosis and long terms management of lissencephaly by CMV.[10]

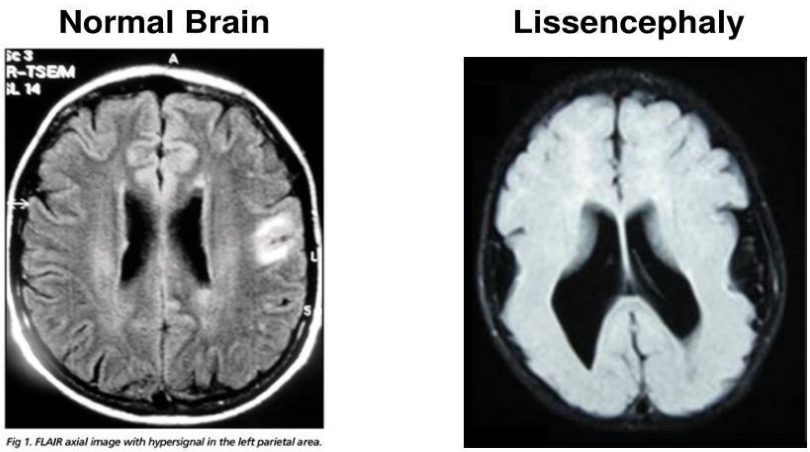


Fig 1. FLAIR axial image with hypersignal in the left parietal area.

EPIDEMIOLOGY

According to a study, the prevalence of lissencephaly in the Netherlands is approximately 1.2 per 100,000 births. As imaging technology advances, the diagnosis and prevalence of lissencephaly will rise.[11]

Data from other regional observations, such as Atlanta from 1968 to 1993, revealed rates in the same order of magnitude [4–11 per million births]. According to broader estimates, the prevalence of all types of lissencephaly [Type I] is approximately 1 in 100,000 live births. A broader range of 1 in 20,000 to 1 in 30,000 live births of lissencephaly is suggested by certain sources.[12,13]

- **Genetic Reasons**

About 40% of cases are caused by a mutation or deletion in **LIS1 [PAFAH1B1]**[14]
DCX [Doublecortin]: Mutations account for about 23% of instances, frequently with X-linked inheritance [subcortical band heterotopia in females, lissencephaly in males].[15]
TUBA1A: In about 5% of cases, mutations are caused.
DYNC1H1: In about 3% of cases, this gene is mutated.
RELN and others: Contributes to lissencephaly as well.[16]

- **Non-Genetic Reasons**

Viral Infections: During the first trimester [weeks 1-12 of gestation], infections such as Cytomegalovirus [CMV] in the mother are major offenders that reduce blood flow to fetal brain and Toxoplasmosis an another infection linked to disrupt the development of the fetus's brain.[8]

Fetal Hypoxia/Ischemia: Another significant non-genetic risk is inadequate oxygen delivery to the growing fetal brain.

Additional Factors: Prematurity and pregnancy-related trauma may also play a role and exposure to harmful substances like alcohol or certain medications during pregnancy.

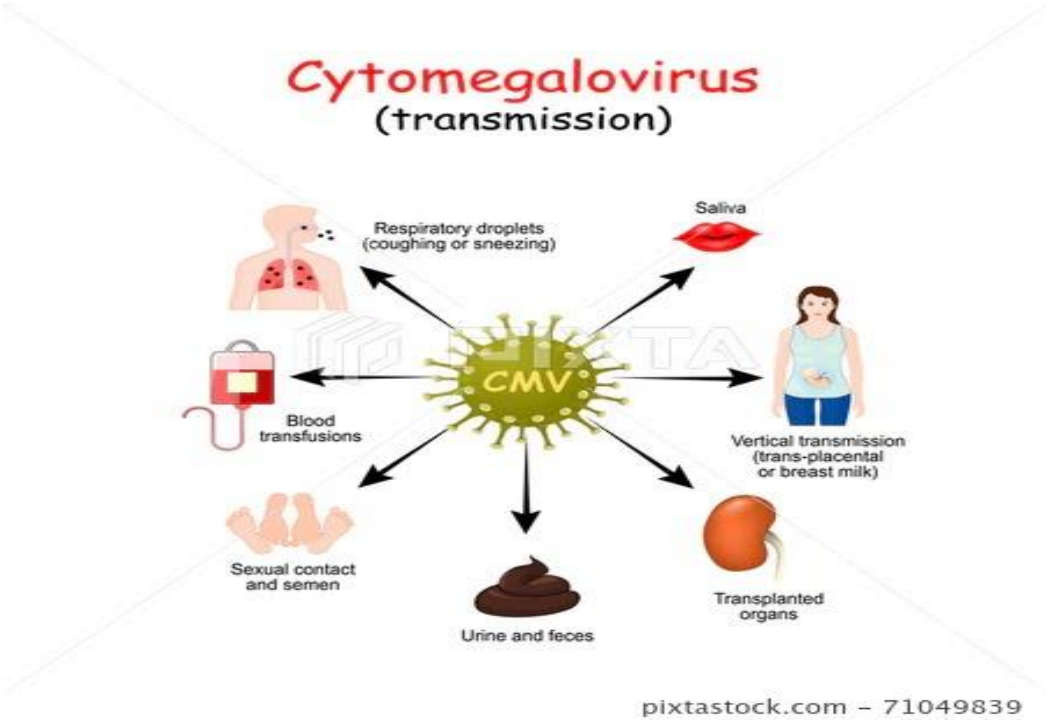
The percentage of cases to these non-genetic causes is still largely unknown in large-scale epidemiological reports due to the difficulties in accurate diagnosis and classification [particularly distinguishing lissencephaly from other cortical malformations].[17]

TRANSMISSION

The most common way of lissencephaly occurs by CMV is through spreading by transplacental transmission, which affects roughly one-third of mothers who have a primary CMV infection. About half of these infections in pregnancy cause a symptomatic clinical condition.[18]

Nearly every bodily fluid, including tears, urine, saliva, sexual secretions, and transplanted organs, might expose a person to CMV. Maternal transmission of CMV can occur during pregnancy or following postnatal exposure. The fetus has a 40% chance of contracting a primary maternal infection during pregnancy. It is believed that the transplacental pathway is how this transmission takes place. Maternally infected leukocytes travel to the placenta when there is maternal viremia. After a congenital infection, the virus can be isolated from the placenta; placental pathologic investigation shows placentitis. Following contact with human milk, blood products, or transplanted organs, postnatal infection may develop. Due to passively acquired maternal antibodies, human milk-associated CMV infections in term newborns usually show no symptoms.[19] On the other hand, because of their undeveloped immune systems and lack of maternal antibodies, extremely preterm newborns are more susceptible to symptomatic CMV infection via human milk. Hepatomegaly, thrombocytopenia, neutropenia, lymphocytosis, respiratory symptoms [pneumonitis], and other sepsis-like symptoms can all be signs of postnatal CMV disease in this population.[20]

One typical primary cause of infection for pregnant women is exposure to children infected with CMV, sometimes her own children who had contracted the virus while attending group day care.[18] Young children have long-term viral shedding on their mucosal surfaces. Both symptomatic and asymptomatic newborns are known to discharge viruses in their urine and saliva for many years after birth. Urine virus shedding is typically detected up to the age of ten, with a mean shedding interval of four years.[22] Furthermore, 15–70% of kids get infected with CMV in group day care centre and they keep shedding the virus for 6–48 months [mean ~18 months] following their initial infection.[18]



When a seronegative recipient receives an organ from a seropositive donor, CMV is usually transmitted during solid organ transplantation.[23] Apart from in utero transmission, exposure to vaginal fluids during delivery can also result in infection during the perinatal period. Toddlers in daycare facilities may shed up to 70% of their CMV. When caring for small children, standard precautions and excellent hand hygiene should be regularly followed, as they are sufficient to avoid transmission.[19] The rise in viral genomes in the amniotic fluid may indicate the extent of the fetus's viral burden, show up as viral replication in the fetal kidney, and be eliminated through the fetal urine.[24]

ETIOLOGY

It is brought on by abnormal neuronal migration between weeks 12 and 24 of pregnancy, which prevents the development of brain grooves [sulci] and folds [gyri]. Lissencephaly may result from inadequate blood flow to the foetal brain in the early stages of pregnancy or from viral infections of the uterus or the foetus during the first trimester.

GENETIC CAUSES

Category	Causes
Classic [or Type 1] lissencephaly	LIS1: lissencephaly due to PAFAH1B1 gene mutation, which subdivides into: type 1 isolated lissencephaly Miller–Dieker syndrome

	LISX1: lissencephaly due to doublecortin [DCX)] gene mutation lissencephaly, type 1, isolated, without other known genetic defects
Cobblestone [or Type 2] lissencephaly	Walker–Warburg syndrome also called HARD[E] syndrome Fukuyama syndrome Muscle–eye–brain disease [MEB]
Other types	LIS2: Norman–Roberts syndrome [mutation of reelin gene] LIS3: TUBA1A, 611603 LISX2: ARX, 300215 Microlissencephaly [microcephaly and lissencephaly]

These are the genes that cause lissencephaly by undergoing genetic mutation.[25]

NONGENETIC CAUSES

Lissencephaly has been linked to both inadequate blood flow to the developing fetal brain and viruses. Congenital abnormalities can be caused by the cytomegalovirus [CMV], a virus linked to herpes. The brain's growing germinal matrix is highly attractive to CMV. The length of gestation during which the fetus contracted the virus determines how severe it is. The cause of lissencephaly is early infection. This is because early infection interferes with neuron growth and migration.[8]

The lissencephaly can be caused by

- Intra-uterine viral infection
- Insufficient blood supply to the fetal brain
- Genetic disorders

A key viral cause is CMV, which

- Has a strong affinity for the germinal matrix of the developing brain.
- Can also infect other organs.
- Causes characteristic cytoplasmic or nuclear inclusion bodies.
- The severity of brain changes depends on gestational age at infection:
- Early infection → severe migrational and developmental anomalies
- Early 2nd trimester → complete lissencephaly
- Late 2nd trimester → polymicrogyria

Other infectious agents include

- Toxoplasmosis
- Rubella
- Herpes simplex

- HIV
- Syphilis

CMV may also lead to multifocal brain necrosis, especially in ependymal and subependymal areas.[8]

PATHOPHYSIOLOGY

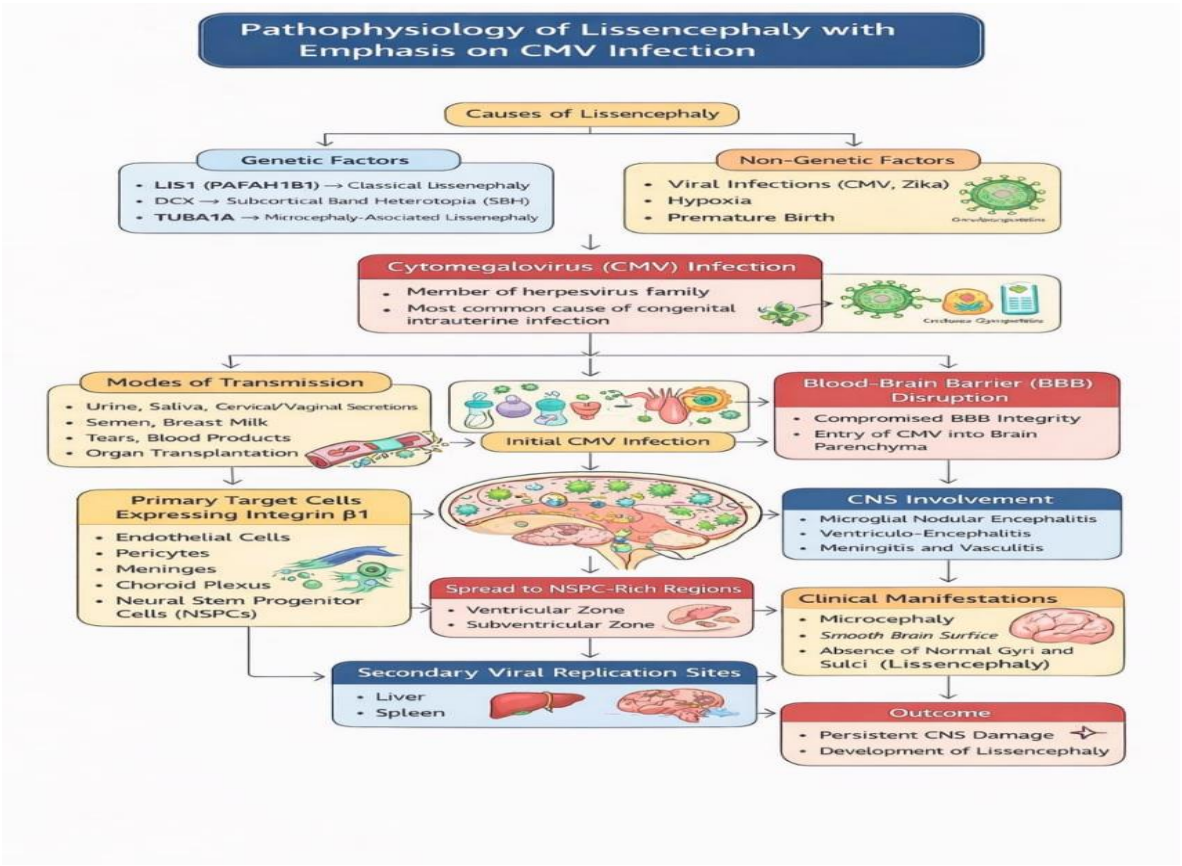
Genetic mutations, particularly in the LIS1 [PAFAH1B1] gene for classical lissencephaly, the doublecortin [DCX] gene for subcortical band heterotopia [SBH], and the TUBA1A gene for microcephaly, are the causes of lissencephaly. Other non-genetic contributors include viral infections such as CMV or Zika viruses, hypoxia, and premature birth.[26]

Cytomegalovirus [CMV], a member of the herpes virus family, is the most common mediator of congenital defects caused by intrauterine infections in humans. One distinctive sign of CMV infection is central nervous system [CNS] dysfunction, which is typified by microglial nodular encephalitis and ventriculo-encephalitis. There are few reports on the first distribution of CMV particles and their receptors on the blood-brain barrier [BBB]. However, a number of factors are proposed to influence the etiology of CMV. Urine, oropharyngeal, cervical, and vaginal secretions, semen, milk, tears, blood products, or organ transplants are examples of direct or indirect person-to-person contact that can result in transmission. The expression of integrin beta 1 in endothelial cells, pericytes, meninges, choroid plexus, and neural stem progenitor cells [NSPCs], which are the main targets of CMV infection.

After the initial infection, CMV compromises the structural integrity of the blood-brain barrier to allow viral particles to move into parenchyma and shows a protracted period of viral shedding. The virus goes through a replication phase before starting its cell-mediated dissemination. Monocytes, macrophages, endothelial cells, and other cell types are the primary host cells that are infected with CMV.

The initial meningitis and vasculitis then gradually spread to NSPC-dense regions like the ventricular zone and subventricular zone, where viral infection prevents neural cell growth and differentiation, leading to the loss of neuronal stem progenitor cells [NSPCs]. The liver and spleen are the primary secondary host replication sites. Clinically, these cellular processes show up as brain abnormalities, including microcephaly [micro-small size and cephaly-lissencephaly].[27,28] Following the infection, CMV can remain latent mostly in the monocytes, and host protection does not fully control replication and dissemination.

Furthermore, there is little defense against infection and the viral genome is quite diverse. Consequently, both the reactivation of endogen dormant strains and reinfection with distinct strains are resulted to seropositive hosts where the brain lacks its normal folds and convolutions, the lissencephaly development.[27]



SIGNS AND SYMPTOMS

Developmental Delays

- Sitting
- Walking
- Talking.[29]

Intellectual Disability

Severe to profound cognitive impairment.

Seizure

Commonly as infantile spasms [West Syndrome]

Muscle tone abnormalities

- Poor tone [Hypotonia]

- Spasticity [Stiffness]
- Muscle spasms.[30]

Poor head control

Difficulty holding the head up.

Poor psychomotor skills

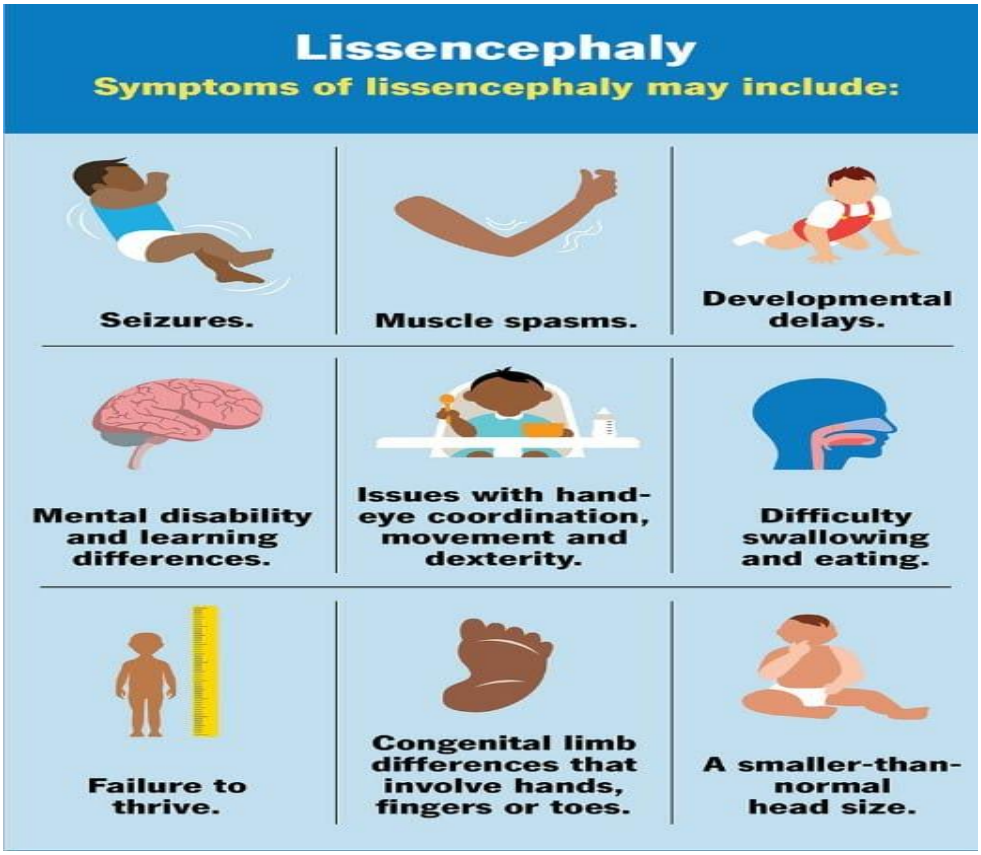
- Coordination
- Movement
- Drug-resistant epilepsy

Feeding difficulties

- Trouble swallowing [Dysphagia]
- Poor sucking.[31]

Failure to thrive

Slow or poor growth



Microcephaly

Smaller head size than typical.[32]

Unusual Facial Features

- Forehead
- Small jaw or Shortnose
- Facial dysmorphism

Limb Differences

Deformities in hands, fingers, toes or feet.

Vision and Hearing

Poor visual tracking and response to sounds.[33]

DIAGNOSIS

Lissencephaly is often diagnosed at birth or shortly using magnetic resonance imaging [MRI], computed tomography [CT], or ultrasound.[34] These findings should be read with caution, due to even skilled radiologists may mistakenly identify lissencephaly as polymicrogyria. Complex ultrasounds that are routinely performed during pregnancy may reveal the existence of a cerebral abnormality prior to birth, but this method of diagnosis should be supplemented by other methods, such as genetic studies and NMR.

Although ultrasound exams between weeks 25 and 30 are more typical, aberrant growth of the brain surface can be seen as early as week 20 of pregnancy.[36] The foetal brain often appears smooth up until this point. Chorionic villus sampling can detect some lissencephaly variations if lissencephaly is suspected, but only those with a known genetic mutation.[37]

Magnetic Resonance Imaging [MRI]

For identifying and verifying aberrant cortical development, MR imaging is quite helpful. MR scans also clearly show associated anomalies of the brainstem, cerebellum, and corpus callosum. MR scans may make it easier to identify less severe cases of lissencephaly.[38]

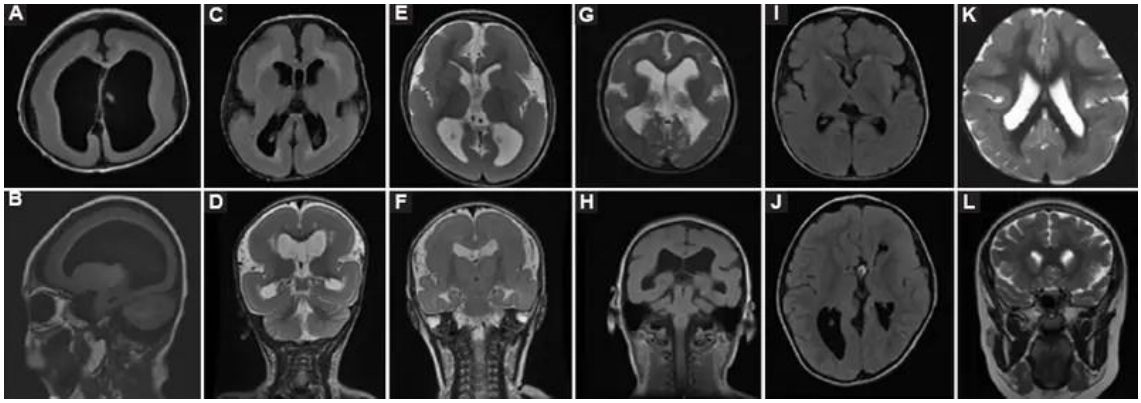


Figure: 1 Brain MRI results on figs.1 A and B: diffuse agyria. C–F: diffuse agyria on the frontal and temporal poles with a few surface undulations. G-H: frontal pachygyria, parieto-occipital agyria, and mixed agyria and pachygyria. I–J: anterior pachygyria that is more severe. K: partial pachygyria posterior, more severe. L: heterotopia inside the subcortical band.[29]

Genes Associated with Type I Lissencephaly

Condition	genes	locus
Isolated lissencephaly sequence	LIS1 or PAFAH1B1	17p13.3
Miller-Dieker syndrome	LIS1, YWHAE, CRK	17p13.3
X-linked lissencephaly	DCX	Xq22.3-q23
Lissencephaly with cerebellar abnormalities	RELN	7q22
Lissencephaly with ambiguous genitalia	ARX	Xp22.13

Genes Associated with Type II Lissencephaly or Cobblestone Complex

Condition	Gene	Locus
Walker-Warburg syndrome	POMT1	9q34.1
Muscle-eye-brain disease	POMGnT1	1p32
Fukuyama-type congenital muscular dystrophy	Fukitin	9q31
MDC1C muscular dystrophy	FKRP	19q13.3

A deletion at the 17p13.3 gene is linked to Miller-Dieker syndrome. Miller-Dieker syndrome, which includes facial dysmorphism, the most severe type of lissencephaly, and other abnormalities, is caused by deletions of LIS1, YWHAE, CRK, and likely other genes. Miller-Dieker syndrome can be verified by fluorescence in situ hybridization analysis utilizing a

DNA probe specific for the LIS1 gene to find a deletion at chromosome 17p13.3 when agyria is found during fetal MR imaging. The genetic composition of the mother and MR imaging can be utilized to determine if the mutation is inherited when a proband is diagnosed with X-linked lissencephaly. A DNA study can be used to make an early prenatal diagnosis if a mutation is known to exist.[39]

Computed Tomography [CT]

Mostly the diagnosis by CT scan is not advised during pregnancy but if medically necessary, it can be done in any trimester, especially in the second and third trimester. Agyria can be seen on CT [figs. 2-4] with a smooth cerebral surface and no white-gray interdigitations. The latter are replaced by smooth subsurface lines that are located immediately above the ventricles [indicating the abnormal white-gray interface, best seen in figures 3 and 4] and just beneath the surface [representing an abnormal cortical layer, seen in fig. 2]. Similar to the foetal arrangement, the ventricles are more expanded posteriorly. Although none of the individuals had hydrocephalus, ventricular size varies significantly between them. [Figure:2&3].

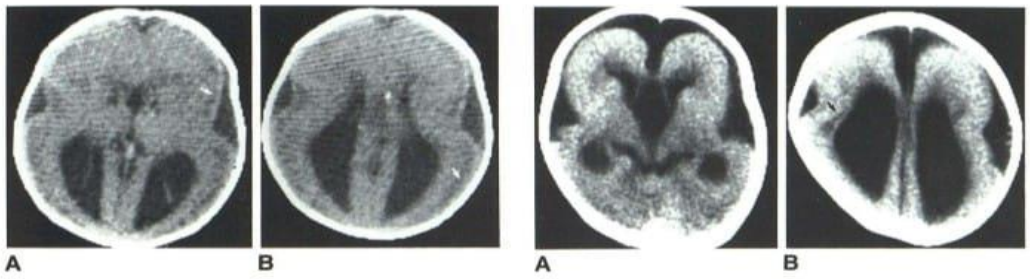
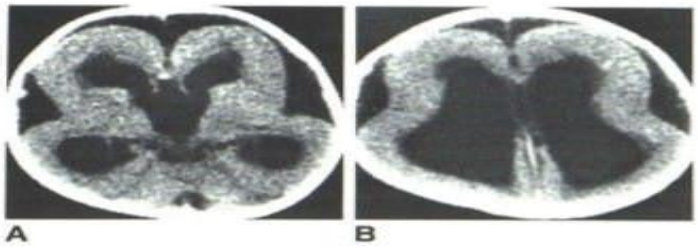


Figure 2: MDS with Type I lissencephaly. A CT scan after a month. B: A higher cut.

Figure 3: Type I lissencephaly in MDS. A, CT scans (A and higher cut, B) resemble Figure 2 with the exception of the absence of midline calcification.



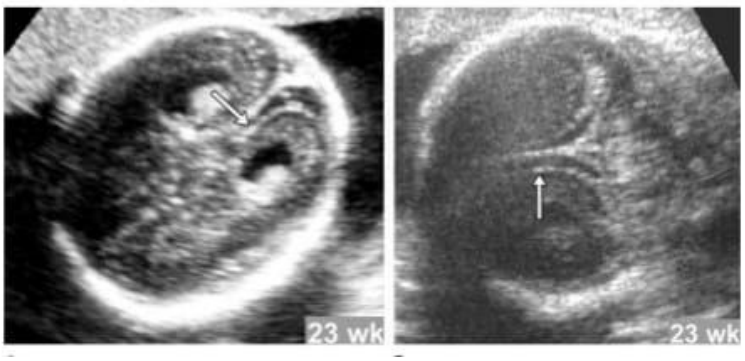
(Figure:4)

Figure 4: Type I lissencephaly in MDS, higher cut, CT image B. larger ventricles and midline calcification compared to Figures 2 and 3.

Additional anomalies that are suggestive of corpus callosum agenesis or hypoplasia include abnormal rostral extension of the third ventricle, abnormal separation of the frontal horns of the lateral ventricles, and a smaller distance between the third ventricle and the anterior interhemispheric fissure. The two patients with deletion of band 17p13.3 had small midline calcifications in the septum pellucidum or gene of the corpus callosum (figs. 2B and 4).[40]

Ultrasonographic imaging [US]

Sonography, another name for ultrasound, is a non-invasive imaging test used for diagnosis. It generates real-time images or films of internal organs or other tissues, using high-frequency sound waves. The ultrasound imaging tests are usually carried out during the period of all three trimesters for detecting the early abnormalities. The discovery of a smooth brain surface in two fetuses at 31 and 31.5 weeks of gestation led to the first documented diagnosis of lissencephaly linked to Miller-Dieker syndrome in the United States. It was recently revealed that certain abnormalities on prenatal US scans taken at 23 weeks of gestation may indicate lissencephaly associated with Miller-Dieker syndrome. These observations include the Sylvian fissure and insula appearing abnormally, the parieto-occipital fissure [fig 5] being absent, and the calcarine fissure [fig 6] being absent. The most common syndrome found at prenatal US is Walker-Warburg syndrome, which is linked to type II lissencephaly. Early prenatal diagnosis may be made possible by imaging findings of ventriculomegaly, anomalies of the posterior fossa, encephalocele, and ocular abnormalities (cataract, retinal dysplasia).



(Figure: 5, 6)

Figures 5 and 6. Miller-Dieker syndrome in a 23-week-old fetus with abnormal parieto-occipital and calcarine fissure development. On the medial hemisphere surface, an axial US picture reveals that the parieto-occipital fissure is absent from the anticipated site (arrow). On the medial hemispheric surface, the coronal US picture reveals the lack of the calcarine fissure from the anticipated location (arrow).[41]

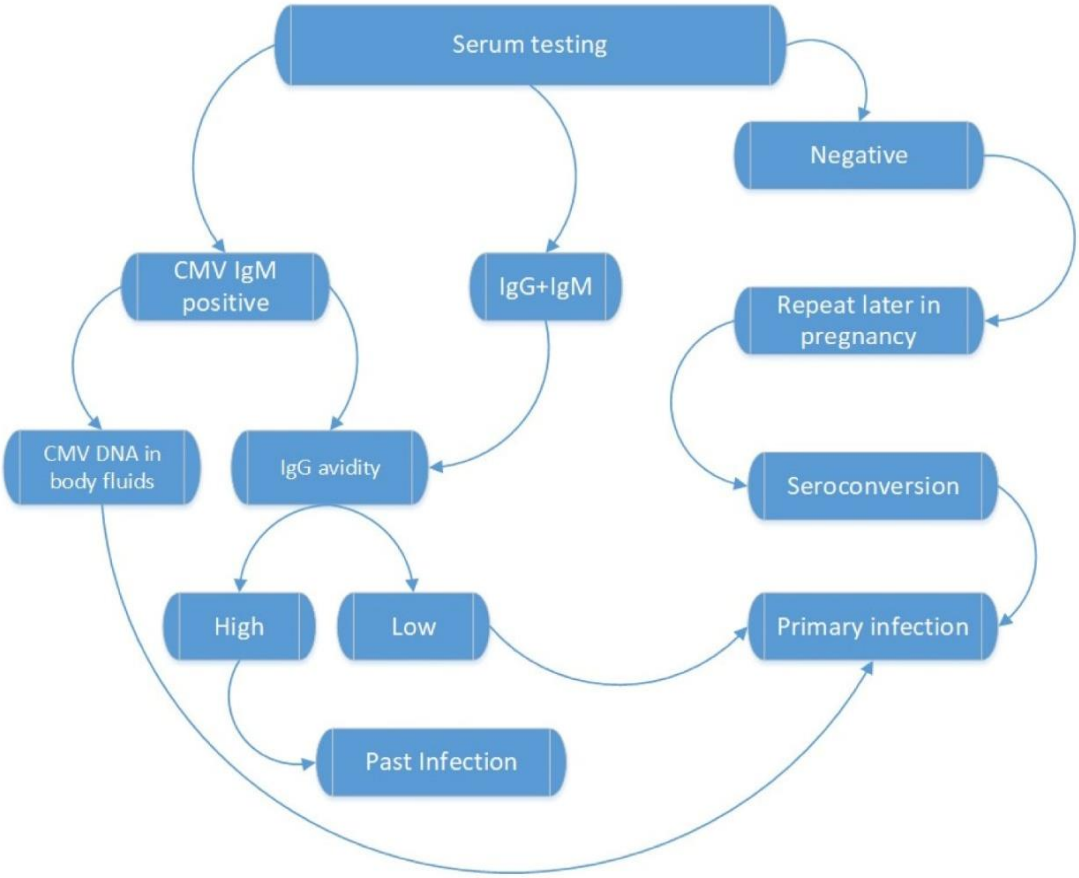
Detection of CMV in biological fluids

- Biological specimens required for CMV diagnosis
- Direct isolation of CMV
- Molecular methods for CMV diagnosis

Biological specimens required for CMV diagnosis

Many biological materials, such as blood, urine, saliva, semen, vaginal secretions, and amniotic fluid, can be used to isolate CMV. Urine testing enhances the likelihood of finding an ongoing infection because CMV shedding in urine is known to remain intermittently for a long time following an initial infection. Samples should be collected, kept at 4°C, and sent right away to the laboratory for testing. The majority of pregnant women who have a primary infection are confirmed to have blood viruses.

Maternal diagnosis of CMV infection



Direct isolation of CMV

The gold standard for detecting CMV infection is still viral isolation in cell culture since it shows that the virus is actively multiplying.

Molecular methods for CMV diagnosis

Numerous systems are available, such as qualitative PCR, which is now hardly used, and quantitative tests (PCR, hybrid capture assay, and nucleic acid sequence-based amplification [NASBA]). Because of its superior sensitivity and specificity, as well as the availability of commercial kits and automated platforms, real-time PCR is the most widely used technique for the molecular diagnosis of CMV infections.[42]

Management and treatment

Children with lissencephaly are treated symptomatically and it depends upon the disease complexity. The treatment mainly focuses on taking measures against the symptoms.

Symptomatic conservative treatment

- Seizures
- Stiffness
- Abnormal movements
- Problems in breathing
- Behavioural difficulties
- Sleep difficulties
- Constipation
- Urinary tract infections
- Hormonal imbalances

Surgery

Surgery is constantly recommended for cases with lissencephaly. Surgery is generally used for

- Feeding tube placement
- Muscle miserliness
- Hydrocephalus [a buildup of fluid in the brain]
- Seizures not responsive to drug [i.e., epilepsy surgery to remove the seizure focus]

Physical and Occupational remedy

- Motor development
- Muscle stiffness
- Inflexibility
- Motor chops

Speech and Swallowing remedy

These curatives can help with

- Safe eating
- Communication

Wheelchairs, trampers and other mobility outfit

Specialized outfit can help children

- Gain strength
- Ameliorate posture
- Move better

Feeding outfit and technical diets

Feeding outfit and technical diets numerous children profit from a tube that allows caregivers to give them nutrition and specifics. Special diets may be specified to maximize nutrition. Diets can also help treating seizures.

Communication aids and tools

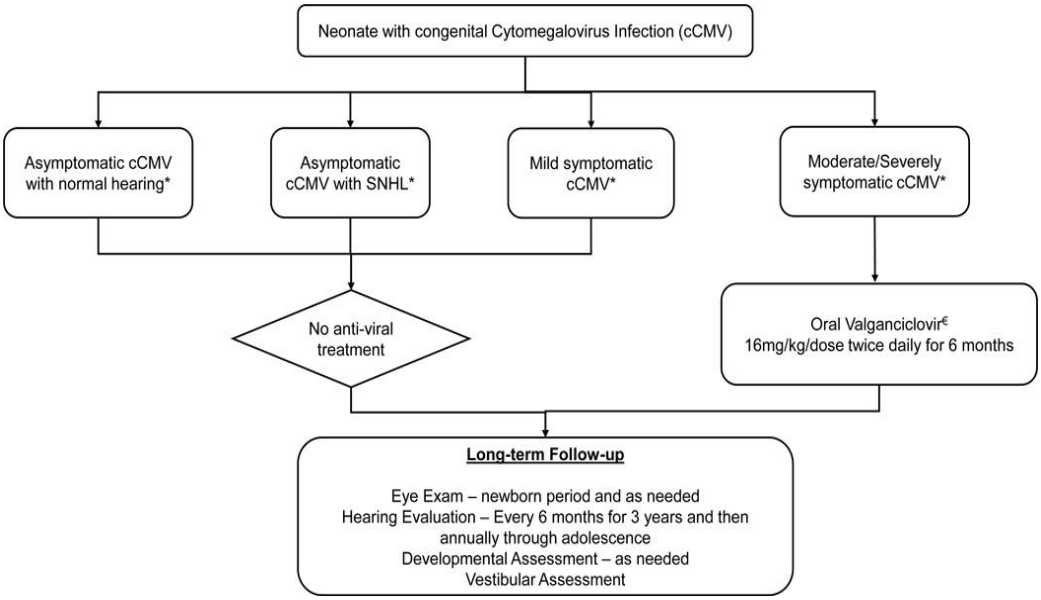
Tools and technologies are available to help children with this complaint more express their requirements.

Antiviral Therapy for Congenital CMV

Targeting the underlying viral illness, antiviral therapy can enhance more general neurologic outcomes:

Valganciclovir and Ganciclovir

- Ganciclovir (IV) or valganciclovir (oral) are used to treat symptomatic infants with congenital CMV (e.g., with CNS involvement).
- For about six months, valganciclovir can prevent hearing loss, lessen viral shedding, and somewhat improve neurodevelopmental outcomes in infants with symptoms.
- If GI absorption is inconsistent, ganciclovir may be administered.



Prenatal/Perinatal Considerations

- Lissencephaly and other established brain abnormalities caused by CMV cannot be reversed by prenatal therapy.
- There is little and inconclusive evidence that oral valacyclovir taken by the mother early in pregnancy may lessen fetal symptomatic illness.

Long-Term Follow-Up and Monitoring

- Children need long-term monitoring since congenital CMV and lissencephaly
- To detect delayed hearing loss, audiologic follow-up may be necessary for several years, neurodevelopmental evaluation to customize treatment and education programs, surveillance of CNS imaging and vision as required.[43]

Prevention

The prevention of lissencephaly by **genetic cause:**

Genetic counselling

➢ Prenatal genetic counselling should be provided to families with a history of lissencephaly or associated cortical abnormalities.

Carrier screening

➢ Carrier testing is advised for parents who have a child who was previously affected by neuronal migratory genes with known pathogenic mutations, especially crucial for X-linked disorders like lissencephaly caused by DCX.

Prenatal genetic diagnosis

- Chorionic villus sampling or amniocentesis are used to detect known pathogenic mutations.[44]

The prevention of lissencephaly by **non-genetic cause**

Congenital Infection Prevention Preventing cytomegalovirus (CMV)

Strict hand hygiene, particularly for expectant mothers who are around little children steer clear of exchanging toothbrushes, saliva, or utensils.

Avoiding Hypoxic-Ischemic Damage and providing appropriate treatment of

- Maternal hypertension
- Diabetes
- Prompt obstetric care to avoid fetal hypoxia.

Preventing Teratogens

- During pregnancy avoid alcohol
- Needless medications
- Prevent exposure to environmental pollutants and radiation.

Nutrition and Health of Mothers

- Sufficient consumption of folic acid,
- Iron and nutrient supplements.[45]

CONCLUSION

Lissencephaly is a severe cortical developmental condition that results from imperfect or absent cerebral gyri and sulci due to impaired neuronal migration during early gestation. Although well-characterized genetic abnormalities involving genes like LIS1, DCX, TUBA1A, and RELN account for a significant share of cases, non-genetic causes especially congenital infections remain crucial and frequently overlooked contributors. The most important infectious cause of these is congenital cytomegalovirus (CMV) infection, which has a special affinity for developing germinal matrix and neural progenitor cells and causes severe anatomical and functional abnormalities in the brain. Even while lissencephaly is still incurable, early detection of CMV infection allows for prompt antiviral treatment in infants with symptoms, which may lessen hearing loss and somewhat enhance neurodevelopmental outcomes. The majority of long-term care is still supportive and interdisciplinary, treating

developmental delays, motor impairment, feeding issues, seizures, and sensory deficiencies. Pregnancy-related preventive measures and the identification of CMV as a clinically unique and avoidable cause of lissencephaly are crucial. To maximize outcomes for impacted children and lessen the worldwide effect of this catastrophic neurodevelopmental disorder, more research, better screening methods, and increased clinician awareness are required.

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