

# Prenatal Ultrasound and Magnetic Resonance Findings of Glutaric Acidemia Type 1 and Its Challenges in Prenatal Diagnosis

CME Credits

Jo-Ting Wang<sup>1</sup>, Han-Jui Lee<sup>2,3</sup>, Tung-Yao Chang<sup>1\*</sup><sup>1</sup>Department of Fetal Medicine, Taiji Clinic, Taipei, Taiwan, <sup>2</sup>Department of Radiology, Taipei Veterans General Hospital, Taipei, Taiwan, <sup>3</sup>School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan

## Abstract

Glutaric acidemia type 1 (GA1) presents unique challenges in prenatal diagnosis, especially in cases with no family history. This review article aims to review and present the prenatal ultrasound and magnetic resonance findings of GA1 and consolidate key insights into the difficulties associated with GA1 prenatal diagnosis and the neuroimaging features that require careful differentiation during the diagnostic process.

**Keywords:** Fetal magnetic resonance imaging, glutaric acidemia type 1, prenatal ultrasound, Sylvian fissure

## INTRODUCTION

Glutaric acidemia type 1 (GA1) is a rare autosomal recessive inborn error of metabolism characterized by a deficiency of the enzyme glutaryl-CoA dehydrogenase (GCDH). This deficiency leads to the accumulation of glutaric acid (GA) and its metabolites in the body. GA1 is a rare condition, with an estimated global incidence ranging from 1/90,000 to 1/120,000.<sup>[1-3]</sup>

The genetic basis of GA1 involves the presence of two pathogenic variants in the GCDH gene located on chromosome 19p13.13. Nearly 300 different mutations are identified in the GCDH gene, affecting the enzymatic function, stability, and formation of oligomers of GCDH.<sup>[4]</sup> These mutations result in abnormal metabolism of the amino acids lysine, hydroxylysine, and tryptophan, leading to the accumulation of toxic compounds, including GA and 3-hydroxyglutaric acid. These substances can cause damage to the brain, particularly the basal ganglia, which is responsible for controlling movement.<sup>[5]</sup> Variable neurological manifestations include dystonia, seizures, and cognitive impairment. However, early diagnosis and initiation of treatment, including dietary lysine restriction and carnitine supplementation, significantly improve outcomes.

## CLINICAL TYPES AND PRESENTATION

Clinical presentation and severity can vary among individuals with GA1. It can be classified into high excretor or low excretor types based on the concentration of GA in the urine.<sup>[6]</sup> High excretors typically have lower residual GCDH enzyme activity and exhibit a higher frequency of extraatrial abnormalities, elevated intracerebral levels of GA and 3-OH-GA (detected through 1H-MRS), larger head circumference, increased susceptibility to subdural hemorrhage, and poorer cognitive outcomes compared to low excretors.

The clinical manifestations can range from asymptomatic or mild chronic neurological symptoms to acute neurological crises, with the age of onset varying from infancy to adulthood. Early diagnosis and intervention are crucial for improving the prognosis of GA1, particularly when intervention occurs before the age of six, as it corresponds to a critical period of brain development, including myelination.

This review comprehensively summarizes key insights into prenatal diagnosis challenges and distinguishing

**Address for correspondence:** Dr. Tung-Yao Chang, Department of Fetal Medicine, Taiji Clinic, 2F, No. 210, Section 3, New Taipei Boulevard, Xinzhuang District, New Taipei City 242, Taiwan. E-mail: tychang@fetalmedicine.tw

Received: 03-06-2024 Accepted: 15-07-2024 Available Online: 28-08-2024

### Access this article online

#### Quick Response Code:



**Website:**  
<https://journals.lww.com/jmut>

**DOI:**  
10.4103/jmu.jmu\_63\_24

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

**For reprints contact:** WKHLRPMedknow\_reprints@wolterskluwer.com

**How to cite this article:** Wang JT, Lee HJ, Chang TY. Prenatal ultrasound and magnetic resonance findings of glutaric acidemia type 1 and its challenges in prenatal diagnosis. J Med Ultrasound 2024;32:202-8.

neuroimaging features of GA1 based on an in-depth literature analysis.

## POSTNATAL NEUROIMAGING FINDINGS

Based on the literature review of postnatally diagnosed cases of GA1, there are a few possible distinctive neuroimaging findings.<sup>[2,7-12]</sup> According to the guidelines, if distinctive neuroimaging features are observed, such as frontotemporal hypoplasia accompanied by the widening of anterior temporal cerebrospinal fluid (CSF) spaces and the Sylvian fissure (SF), it is advised to conduct a quantitative analysis of GA and 3-OH-GA levels in urine and/or blood.<sup>[3]</sup>

Postnatal imaging features of GA1 include macrocephaly. Among asymptomatic infants, a highly specific neuroimaging characteristic is the symmetric incomplete opercularization of the SF, co-occurring with normal cortical thickness and well-developed gyral patterns.<sup>[8,9]</sup> In addition, there can be focal enlargement of the temporal fossa with frontotemporal hypoplasia.<sup>[8,9,12]</sup> Some cases may also display nonspecific subependymal cysts on imaging.<sup>[13]</sup> On the other hand, in cases with neurological symptoms, magnetic resonance imaging often reveals abnormal signals in the basal ganglia, encompassing structures such as the caudate nucleus, putamen, and thalamus while showing high signal intensity on T2-weighted images.<sup>[2,10]</sup>

## PRENATAL NEUROIMAGING FINDINGS

Compared to postnatal cases, there are relatively few published articles on prenatal cases.<sup>[14-19]</sup> Prenatal genetic diagnosis is mainly based on past family medical histories.<sup>[14,15,17,19]</sup> The imaging findings of prenatal GA1 are mostly similar to those of asymptomatic patients postnatally. These imaging characteristics include symmetric widening of the SF, and incomplete opercularization, yet with normal cortical thickness and other gyral patterns. In addition, there are localized or diffused accumulations of CSF around the brain parenchyma (in the temporal fossa, mesencephalic cistern, and SF), along with the manifestation of macrocephaly in the third trimester of pregnancy or at birth.<sup>[15,18]</sup> In a limited number of prenatally detected cases of GA1, there are other imaging features such as subependymal cysts on ultrasound and abnormal T2 signals in the periventricular region on fetal magnetic resonance imaging (MRI).<sup>[15,18,20]</sup> These findings may indicate there is evidence of further stages of neurological degeneration. Next, we will break down the differentiation of different neuroimaging features.

## WIDE SYLVIAN FISSURE

The most distinctive imaging feature of GA1 is the formation of a wide SF due to frontotemporal hypoplasia and wide CSF space in the bilateral SF.<sup>[3]</sup>

A wide SF reflects an anomaly in the development of the insula. The development of the insula can be evaluated

during fetal ultrasound. Literature suggests a graded method for subjective assessment of the degree of insular morphogenesis.<sup>[20,21]</sup> Between weeks 22 and 32 of gestation, the overriding of the insula by the temporal lobe initiates earlier in gestation and maintains stability across gestational stages compared to the frontal lobes. Therefore, we can obtain axial images of the fetal brain to display the SF and classify the developmental stages of the SF into five grades, further subdivided into 10 levels.<sup>[20,21]</sup> In summary, imaging markers were established to characterize the insular opercularization process by considering the angle formed between the insula and temporal lobe, as well as the extent of insular coverage. At 24 weeks of gestational age, the angle between the insula and temporal lobe measures approximately 90°. By 28 weeks of gestation, the angle becomes acute, and insular coverage (opercularization) reaches around 50%, whereas at 30 weeks, the opercularization surpasses 50%.<sup>[21]</sup> The study supports that fetal SF maturation (the degree of opercularization) can be evaluated and scored using ultrasound imaging, providing a valuable tool for assessing normal fetal brain development during pregnancy.<sup>[22]</sup> The mentioned gestational ages (24, 28, and 30 weeks) serve as reference points for the expected progression of SF maturation in healthy fetuses.

On the other hand, we can assess the presence of a wide SF in the bilateral SF through measurements of the lateral craniocortical width.<sup>[23]</sup> In the clinical example below, at 24 weeks of gestation, the SF presented atypically and was accompanied by an increased lateral craniocortical width. In addition, localized or diffused accumulation of CSF around the brain parenchyma (temporal fossa, mesencephalic cistern, and Sylvian cistern) might be observed. Fetal MRI also showed increased pericerebral space, especially in the temporal fossa and Sylvian cistern. The differential diagnosis includes GA1 and opercular dysplasia. Despite this, no abnormalities were detected in the sulcation or brain volume.

## MACROCEPHALY

Macrocephaly, defined as an occipitofrontal head circumference exceeding the 98<sup>th</sup> percentile or >2 standard deviations (SDs) above the mean for gestational age, holds varying clinical implications. Macrocephaly is present in approximately 2% of all pregnancies and 0.9% of neonates, with most cases being familial.<sup>[24]</sup> Its significance escalates notably when fetal macrocephaly is more than 2.5 SD and associated with other anomalies, indicating a higher likelihood of syndromic and neurogenetic disorders.<sup>[25-28]</sup>

In postnatally diagnosed cases, macrocephaly emerges as a crucial hallmark of GA1.<sup>[7,8,29]</sup> However, the literature suggests varying rates of macrocephaly in confirmed GA1 cases at birth, ranging from around 45% to 100%.<sup>[2,7,30]</sup>

Metabolic disorders like GA1, contributing to macrocephaly, might arise due to metabolic substance accumulation in the brain, astrocyte swelling, or myelin vacuolization, whereas the neuronal cytoarchitecture remains relatively intact.<sup>[31]</sup>

Although initial presentations may feature macrocephaly, subsequent brain atrophy might occur later due to cell death or degeneration.

Macrocephaly induced by GA1 differs from hydrocephalus-linked macrocephaly as it lacks internal brain structural anomalies or elastic lesions, which cause severe ventriculomegaly.<sup>[26,32]</sup> In contrast to macrocephaly attributed to overgrowth syndromes, or skeletal dysplasias, GA1 typically does not present with extracranial anomalies.<sup>[26,28]</sup> Besides, distinguishing macrocephaly linked to CSF expansion in GA1 from benign enlargement of subarachnoid spaces (BESS) is crucial. BESS, more common in infancy, involves increased subarachnoid space along frontal convexities with minimal lateral ventricle enlargement.<sup>[33]</sup> Unlike BESS, GA1 tends to accumulate CSF focal in the temporal fossa and bilateral SF rather than the frontal interhemispheric fissure followed by frontal subarachnoid space expansion.<sup>[28]</sup>

In a pathological context, macrocephaly caused by GA1 is characterized by a gradual progression. This occurs due to a normal brain volume alongside the increased accumulation of CSF in areas such as the mesencephalic cistern, temporal fossa, and bilateral Sylvian cistern. As shown previously, the head circumference might not exceed 2 SDs during midpregnancy followed by a steep growth slope in the late second and third trimesters and then present postnatally.<sup>[15]</sup> Furthermore, varying mutations in the GCDH gene causing GCDH deficiency may lead to different toxin accumulations and phenotypic expressions, resulting in not all GA1 cases exhibiting macrocephaly at birth.<sup>[4]</sup>

## CEREBROSPINAL FLUID BUILDUP

One of the characteristic imaging features of GA1 is the localized or diffused accumulation of CSF around the brain parenchyma, which may occur in the temporal fossa, mesencephalic cistern, and Sylvian cistern. According to the literature review, the accumulation of CSF in the Sylvian cistern or temporal fossa could have been mistaken for an arachnoid cyst.<sup>[34]</sup> As in our clinical example, serial prenatal ultrasound and MRI identified enlarged spaces filled with CSF in the quadrigeminal cistern. CSF accumulation in the mesencephalic cistern may be mistaken for an arachnoid cyst in the quadrigeminal cistern, making it challenging to distinguish between the two. Therefore, when encountering localized CSF accumulation on neuroimaging, it becomes crucial to differentiate between normal arachnoid membrane and arachnoid cyst.

From the pathological structure of arachnoid cysts, two distinctive features stand out compared to normal arachnoid membranes: first, the cyst wall contains proliferative arachnoid cells, which may contribute to collagen synthesis and possess a thick layer of collagen; second, the absence of transverse trabeculations within the cyst.<sup>[35,36]</sup>

Reviewing the ultrasound images in the case of CSF buildup, one can observe some hyperechoic vague lines within the

hypoechoic cystic space [Figure 1]. Moreover, the boundary of the cystic space does not exhibit the strong and coarse echogenicity typically seen in arachnoid cysts.

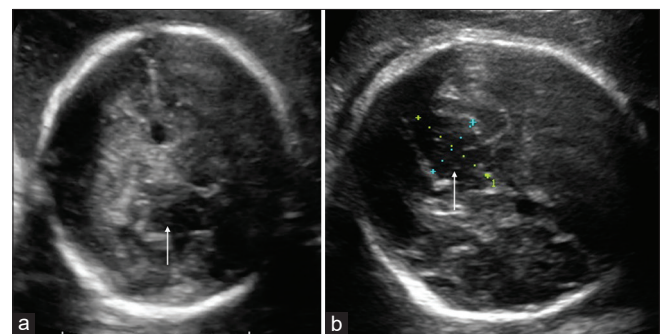
## CLINICAL EXAMPLE

A 33-year-old woman (gravida 1, para 0), with unremarkable medical history visited our clinic for a detailed ultrasound second-trimester anatomical screening at 23 weeks of gestation. The ultrasound showed no abnormalities except for the dilated ambient cistern and quadrigeminal cistern [Figure 2]. The woman returned for follow-up at 24 and 29 weeks of gestation. The ultrasound revealed the same dilatation of the ambient cistern and quadrigeminal cistern, the equivocal shape of bilateral SFs, and increased pericerebral space around the Sylvian cistern [Figure 3]. The fetal head circumference showed a significant increase in measurements from 23 weeks (34<sup>th</sup> percentile) to 24 weeks (82<sup>nd</sup> percentile) and further to 29 weeks (96<sup>th</sup> percentile). Fetal MRI arranged at 25 and 30 weeks of gestation showed the presence of cystic space in the quadrigeminal cistern [Figure 4] and mildly increased pericerebral CSF space, especially in the temporal fossa and Sylvian cistern with cerebral volume within the normal range [Figure 5]. The baby was delivered at 40 weeks by cesarean section, with a head circumference of 37.5 cm (Z-score = 3.1, 99.9<sup>th</sup> percentile).

The newborn was subsequently screened for metabolic disorders, including GA1, as a part of routine screening protocols. The results showed elevated GA levels in dried blood spots, leading to further confirmatory tests, including urine organic acid analysis and genetic testing. The results confirmed a diagnosis of GA1. Subsequent postnatal MRI demonstrated the specific neuroimaging pattern associated with GA1 [Figure 6].

## DISCUSSION

In cases of GA1 without a family history, prenatal diagnosis is challenging. This is primarily because the incidence of GA1 is relatively low compared to other conditions. In addition,



**Figure 1:** The cerebrospinal fluid buildup has a distinctive appearance on fetal ultrasound, (a) Coronal ultrasound image at 24 + 6 weeks of gestation reveals hyperechoic vague lines (arrow) within the hypoechoic cystic space, (b) Ultrasound image at 29 + 6 weeks of gestation shows persistent hyperechoic vague lines (arrow) within the hypoechoic cystic space



ultrasound and MRI features of GA1 can overlap with other conditions, leading to diagnostic uncertainties.

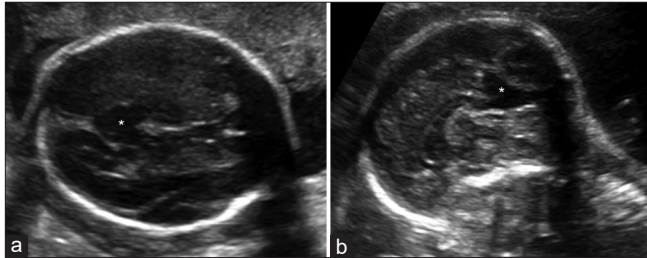
Unlike other congenital structural abnormalities, GA1 progresses slowly during fetal development due to the gradual accumulation of toxins. The imaging features become more evident over time, causing delays in diagnosis.

## PATHOPHYSIOLOGICAL INSIGHTS

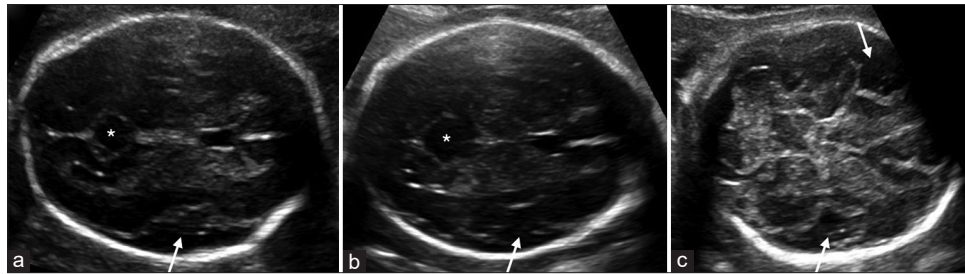
Based on our experience and considering the pathological mechanisms of GA1, we can infer that the accumulation of toxic substances may lead to the prenatal accumulation of CSF in specific regions of the fetal brain during midterm development. These regions may include the mesencephalic cistern, temporal fossa, and Sylvian cistern. Although the overall brain volume remains consistent with gestational age, the accumulation of CSF results in a steeper slope for the fetal head circumference growth curve.

In addition, abnormalities in the development of the frontal and temporal lobes may become more apparent after 30 weeks of gestation, leading to incomplete brain gyration (abnormal Sylvian operculization). When these three neurological imaging features become apparent simultaneously, prenatal sequencing of the GCDH gene can be conducted for a definitive diagnosis.

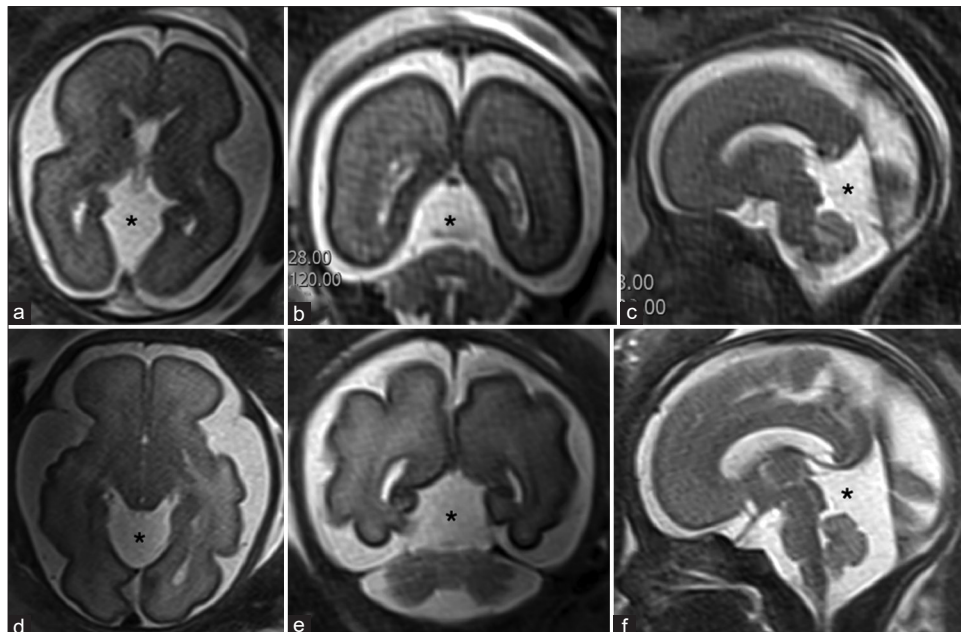
It is important to note that the variety of mutations in the GCDH gene can result in varying degrees of GCDH



**Figure 2:** (a and b) Depict axial and sagittal ultrasound images at 23 + 2 weeks of gestation, illustrating an overall normal fetal anatomy. Notably, there is observed dilatation in both the ambient cistern and quadrigeminal cistern (\*)

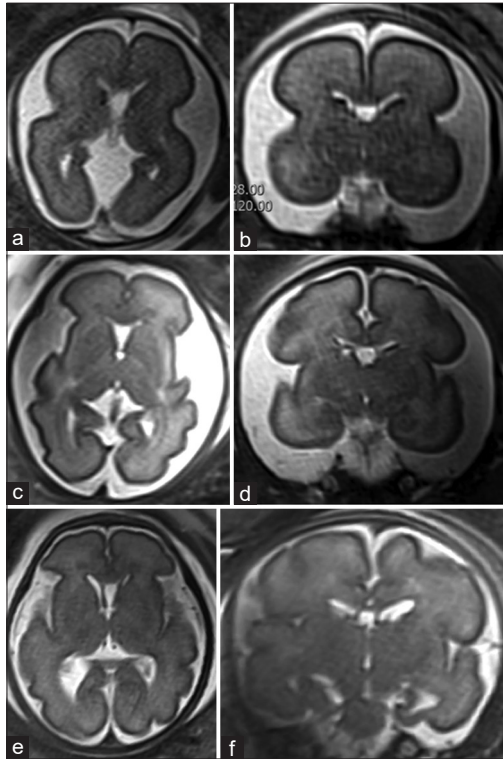


**Figure 3:** (a) Axial ultrasound image at 24 + 6 weeks of gestation shows the persistent dilatation of the ambient cistern (\*), along with an equivocal shape of the Sylvian fissure and dilation of the Sylvian cistern (arrow), (b) Axial ultrasound image at 29 + 6 weeks of gestation displays continued dilatation of the ambient cistern (\*), along with an equivocal shape of the Sylvian fissure and dilation of the Sylvian cistern (arrow), (c) Axial ultrasound image at 29 + 6 weeks of gestation reveals an equivocal shape of bilateral Sylvian fissures and dilation of the Sylvian cistern (arrow)



**Figure 4:** Fetal magnetic resonance imaging at 25 weeks of gestation in axial (a), coronal (b), and sagittal (c) planes and at 30 weeks of gestation in axial (d), coronal (e), and sagittal (f) views. Planes show persistent enlarged cystic space in the quadrigeminal cistern (\*)

activity deficiency, leading to differences in phenotypes. This includes a rare subset of cases that are missed by newborn screening and diagnosed at a later age due to the occurrence of acute encephalopathy.<sup>[37,38]</sup> Upon reviewing neuroimaging, different levels of CSF accumulation or abnormal opercularization may be observed, with the primary feature being abnormal basal ganglia signaling or subependymal cystic lesions.



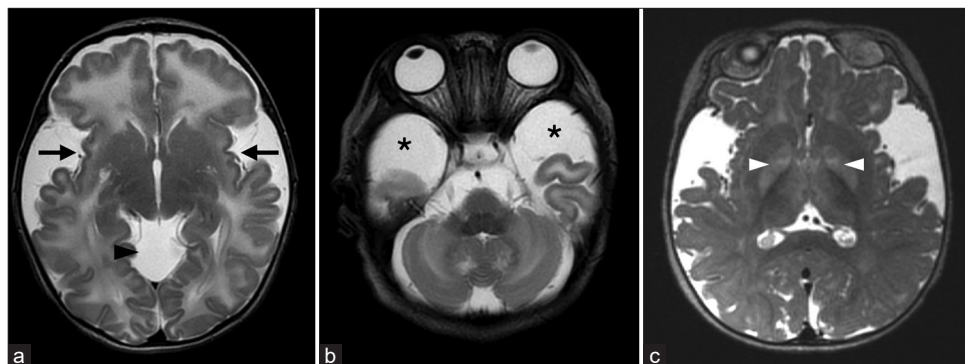
**Figure 5:** (a-d) Fetal magnetic resonance imaging (MRI) at 25 weeks of gestation in the axial plane (a), and coronal plane (b), and Fetal MRI at 30 weeks of gestation in the axial plane (c), and coronal plane (d), show mildly increased pericerebral cerebrospinal fluid (CSF) space, particularly notable in the temporal fossa and Sylvian fissures (e and f). Note normal pericerebral CSF space and Sylvian fissure in a fetus at 30 weeks of gestation in the MRI axial plane (e) and coronal plane (f)

## PRENATAL DIAGNOSIS TIMING

Prenatal diagnosis of GA1 is facilitated by recognizing the distinctive neuroimaging pattern associated with this disorder. Localized CSF accumulation appears the earliest among the fetal imaging features, typically evident after 20 weeks of gestation based on limited prenatal case reports.<sup>[15,18]</sup> Abnormal SF maturation grading and incomplete opercularization of the insula may be noted around 24 weeks and incomplete opercularization of the insula usually becomes apparent after 30 weeks.<sup>[15,16,18,20,22]</sup> Early prenatal MRI (as early as 22 weeks) can reveal characteristic findings suggestive of GA1, such as focal reduction of the anterior pole of the temporal lobes and widening of the liquor space.<sup>[18]</sup> Observations from limited prenatally diagnosed cases show that not all exhibit macrocephaly.<sup>[18]</sup> If macrocephaly was present, fetal head circumference was often below 2 SDs prenatally; instead, an accelerated growth rate was noted, leading to macrocephaly at birth.<sup>[15]</sup>

Employing a comprehensive systematic approach of fetal anatomical screening and both qualitative and quantitative evaluations of brain structure, sequential ultrasounds play a vital role in detecting the evolution of findings. This involves assessing midline structures, ventricles, brain sulcation, pericerebral space, and monitoring head circumference with growth rate. Fetal MRI provides additional information, particularly in the third trimester, which assists in differentiating and diagnosing brain abnormalities.<sup>[15,39]</sup> It is important to highlight that the spatial resolution of fetal MRI may be restricted by slice thickness.<sup>[40]</sup> Ultrasound, which provides better resolution, is crucial for discerning the arachnoid complex in the quadrigeminal cistern, aiding in the distinction between an arachnoid cyst and localized CSF accumulation in the quadrigeminal cistern.<sup>[41]</sup>

In summary, prenatal ultrasound and MRI can reveal characteristic findings of GA1 as early as the second trimester, with the earliest signs being localized CSF accumulation and abnormal SF maturation. Recognizing the distinctive neuroimaging pattern, particularly the temporal lobe findings, is essential for prompting genetic testing and enabling



**Figure 6:** Postnatal brain magnetic resonance imaging at 7 days old (a and b), and 14 months old (c). Axial T2-weighted images revealed the widening of the Sylvian fissure (arrows in a), dilatation of the subarachnoid space in the quadrigeminal cistern (arrowheads in a) and bilateral temporal fossa (asterisks in b). On the follow-up examination, an axial T2-weighted image showed persistence of the widening of the Sylvian fissure. Note the high signal changes in the bilateral lentiform nuclei (arrowheads in c) and thalami. These findings are compatible with glutaric acidemia type 1

timely prenatal diagnosis, which is crucial for appropriate management and counseling.

## CONCLUSION

Prenatal ultrasound findings indicative of GA1 can evoke concerns and prompt further examinations. However, ultrasound characteristics associated with GA1 can overlap with other conditions. Notably, distinct features such as wide SF and macrocephaly often become more evident in the third trimester of pregnancy, leading to diagnostic uncertainties. Understanding prenatal neuroimaging for GA1 allows for raising awareness during midterm pregnancy screenings, enabling follow-ups. When observing specific features, such as symmetric widening of the SF and focal accumulation of CSF in mesencephalic cistern or temporal fossa and Sylvian cistern, considering GA1 for differential diagnosis, especially in primiparous women or cases lacking a family history, can facilitate early detection through prenatal genetic sequencing of the GCDH gene. Newborn screening also plays a pivotal role in early and accurate confirmation, enabling immediate medical intervention and appropriate management.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

## Financial support and sponsorship

The study was funded by Taiwan Institute of Fetal Medicine (Taiwan Registered Non-profit Organization 1080280906).

## Conflicts of interest

Dr. Tung-Yao Chang, an editorial board member at *Journal of Medical Ultrasound*, had no role in the peer review process of or decision to publish this article. The other authors declared no conflicts of interest in writing this paper.

## REFERENCES

- Boy N, Mengler K, Thimm E, Schiergens KA, Marquardt T, Weinhold N, et al. Newborn screening: A disease-changing intervention for Glutaric aciduria type 1. *Ann Neurol* 2018;83:970-9.
- Tsai FC, Lee HJ, Wang AG, Hsieh SC, Lu YH, Lee MC, et al. Experiences during newborn screening for Glutaric aciduria type 1: Diagnosis, treatment, genotype, phenotype, and outcomes. *J Chin Med Assoc* 2017;80:253-61.
- Boy N, Mühlhausen C, Maier EM, Ballhausen D, Baumgartner MR, Beblo S, et al. Recommendations for diagnosing and managing individuals with Glutaric aciduria type 1: Third revision. *J Inherit Metab Dis* 2023;46:482-519.
- Schuurmans IM, Dimitrov B, Schröter J, Ribes A, de la Fuente RP, Zamora B, et al. Exploring genotype-phenotype correlations in Glutaric aciduria type 1. *J Inherit Metab Dis* 2023;46:371-90.
- Wajner M, Amaral AU, Leipnitz G, Seminotti B. Pathogenesis of brain damage in Glutaric acidemia type I: Lessons from the genetic mice model. *Int J Dev Neurosci* 2019;78:215-21.
- Baric I, Wagner L, Feyh P, Liesert M, Buckel W, Hoffmann GF. Sensitivity and specificity of free and total Glutaric acid and 3-hydroxyglutaric acid measurements by stable-isotope dilution assays for the diagnosis of Glutaric aciduria type I. *J Inherit Metab Dis* 1999;22:867-81.
- Forstner R, Hoffmann GF, Gassner I, Heideman P, De Klerk JB, Lawrenz-Wolf B, et al. Glutaric aciduria type I: Ultrasonographic demonstration of early signs. *Pediatr Radiol* 1999;29:138-43.
- Twomey EL, Naughten ER, Donoghue VB, Ryan S. Neuroimaging findings in Glutaric aciduria type 1. *Pediatr Radiol* 2003;33:823-30.
- Neumaier-Probst E, Harting I, Seitz A, Ding C, Kolker S. Neuroradiological findings in Glutaric aciduria type I (glutaryl-CoA dehydrogenase deficiency). *J Inherit Metab Dis* 2004;27:869-76.
- Harting I, Neumaier-Probst E, Seitz A, Maier EM, Assmann B, Baric I, et al. Dynamic changes of striatal and extra-striatal abnormalities in Glutaric aciduria type I. *Brain* 2009;132:1764-82.
- Nunes J, Loureiro S, Carvalho S, Pais RP, Alfaiate C, Faria A, et al. Brain MRI findings as an important diagnostic clue in Glutaric aciduria type 1. *Neuroradiol J* 2013;26:155-61.
- Mohammad SA, Abdelkhalik HS, Ahmed KA, Zaki OK. Glutaric aciduria type 1: Neuroimaging features with clinical correlation. *Pediatr Radiol* 2015;45:1696-705.
- Bats AS, Molho M, Senat MV, Paupe A, Bernard JP, Ville Y. Subependymal pseudocysts in the fetal brain: Prenatal diagnosis of two cases and review of the literature. *Ultrasound Obstet Gynecol* 2002;20:502-5.
- Goodman SI, Gallegos DA, Pullin CJ, Halpern B, Truscott RJ, Wise G, et al. Antenatal diagnosis of Glutaric acidemia. *Am J Hum Genet* 1980;32:695-9.
- Lin SK, Hsu SG, Ho ES, Tsai CR, Hsieh YT, Lo FC, et al. Novel mutation and prenatal sonographic findings of Glutaric aciduria (type I) in two Taiwanese families. *Prenat Diagn* 2002;22:725-9.
- Mellerio C, Marignier S, Roth P, Gaucherand P, des Portes V, Pracros JP, et al. Prenatal cerebral ultrasound and MRI findings in Glutaric aciduria Type 1: A *de novo* case. *Ultrasound Obstet Gynecol* 2008;31:712-4.
- Peng HH, Shaw SW, Huang KG. Prenatal diagnosis of fetal Glutaric aciduria type 1 with rare compound heterozygous mutations in GCDH gene. *Taiwan J Obstet Gynecol* 2018;57:137-40.
- Righini A, Fiori L, Parazzini C, Doneda C, Arrigoni F, Riva E, et al. Early prenatal magnetic resonance imaging of Glutaric aciduria type 1: Case report. *J Comput Assist Tomogr* 2010;34:446-8.
- Xiao B, Qiu W, Ye J, Zhang H, Zhu H, Wang L, et al. Prenatal diagnosis of Glutaric acidemia I based on amniotic fluid samples in 42 families using genetic and biochemical approaches. *Front Genet* 2020;11:496.
- Guibaud L, Selleret L, Larroche JC, Buenerd A, Alias F, Gaucherand P, et al. Abnormal sylvian fissure on prenatal cerebral imaging: Significance and correlation with neuropathological and postnatal data. *Ultrasound Obstet Gynecol* 2008;32:50-60.
- Pistorius LR, Stoutenbeek P, Groenendaal F, de Vries L, Manten G, Mulder E, et al. Grade and symmetry of normal fetal cortical development: A longitudinal two- and three-dimensional ultrasound study. *Ultrasound Obstet Gynecol* 2010;36:700-8.
- Rodriguez-Sibaja MJ, Villar J, Ohuma EO, Napolitano R, Heyl S, Carvalho M, et al. Fetal cerebellar growth and sylvian fissure maturation: International standards from Fetal Growth Longitudinal Study of INTERGROWTH-21<sup>st</sup> project. *Ultrasound Obstet Gynecol* 2021;57:614-23.
- Corbacioglu Esmer A, Yuksel A, Aksu Uzunhan T, Demir O, Sarac Sivriköz T, Aydinli N. Evaluation of fetal subarachnoid space using transabdominal ultrasonography and normal values during pregnancy. *Springerplus* 2016;5:1439.
- Yılmazbaş P, Gökçay G, Eren T, Karapınar E, Kural B. Macrocephaly diagnosed during well child visits. *Pediatr Int* 2018;60:474-7.
- Malinger G, Lev D, Ben-Sira L, Hoffmann C, Herrera M, Viñals F, et al. Can syndromic macrocephaly be diagnosed *in utero*? *Ultrasound Obstet Gynecol* 2011;37:72-81.
- Shinar S, Chitayat D, Shannon P, Blaser S. Fetal macrocephaly: Pathophysiology, prenatal diagnosis and management. *Prenat Diagn* 2023;43:1650-61.
- Pirozzi F, Nelson B, Mirzaa G. From microcephaly to megalencephaly: Determinants of brain size. *Dialogues Clin Neurosci* 2018;20:267-82.
- Accogli A, Geraldo AF, Piccolo G, Riva A, Scala M, Balagura G, et al. Diagnostic approach to macrocephaly in children. *Front Pediatr*



- 2021;9:794069.
29. Hoffmann GF, Trefz FK, Barth PG, Böhles HJ, Lehnert W, Christensen E, *et al.* Macrocephaly: An important indication for organic acid analysis. *J Inherit Metab Dis* 1991;14:329-32.
  30. Hoffmann GF, Trefz FK, Barth PG, Böhles HJ, Biggemann B, Bremer HJ, *et al.* Glutaryl-coenzyme A dehydrogenase deficiency: A distinct encephalopathy. *Pediatrics* 1991;88:1194-203.
  31. Renaud DL. Leukoencephalopathies associated with macrocephaly. *Semin Neurol* 2012;32:34-41.
  32. Giorgione V, Haratz KK, Constantini S, Birnbaum R, Malinger G. Fetal cerebral ventriculomegaly: What do we tell the prospective parents? *Prenat Diagn* 2022;42:1674-81.
  33. Zahl SM, Egge A, Helseth E, Wester K. Clinical, radiological, and demographic details of benign external hydrocephalus: A population-based study. *Pediatr Neurol* 2019;96:53-7.
  34. Martínez-Lage JF, Casas C, Fernández MA, Puche A, Rodríguez Costa T, Poza M. Macrocephaly, dystonia, and bilateral temporal arachnoid cysts: Glutaric aciduria type 1. *Childs Nerv Syst* 1994;10:198-203.
  35. Rengachary SS, Watanabe I. Ultrastructure and pathogenesis of intracranial arachnoid cysts. *J Neuropathol Exp Neurol* 1981;40:61-83.
  36. Ahmed AK, Cohen AR. Intracranial arachnoid cysts. *Childs Nerv Syst* 2023;39:2771-8.
  37. Boy N, Heringer J, Brackmann R, Bodamer O, Seitz A, Kölker S, *et al.* Extrastriatal changes in patients with late-onset Glutaric aciduria type I highlight the risk of long-term neurotoxicity. *Orphanet J Rare Dis* 2017;12:77.
  38. Gelener P, Severino M, Diker S, Terah K, Tuncel G, Tuzlali H, *et al.* Adult-onset Glutaric aciduria type I: Rare presentation of a treatable disorder. *Neurogenetics* 2020;21:179-86.
  39. Guibaud L. Contribution of fetal cerebral MRI for diagnosis of structural anomalies. *Prenat Diagn* 2009;29:420-33.
  40. Pugash D, Brugger PC, Bettelheim D, Prayer D. Prenatal ultrasound and fetal MRI: The comparative value of each modality in prenatal diagnosis. *Eur J Radiol* 2008;68:214-26.
  41. Zhang X, Qi S, Fan J, Huang G, Peng J. Arachnoid membranes in the posterior half of the incisural space: An inverted lilliequist membrane – Like arachnoid complex: Laboratory investigation. *J Neurosurg* 2014;121:390-6.