Hong Kong J Gynaecol Obstet Midwifery 2023;23(1):54-62 | https://doi.org/10.12809/hkjgom.23.1.09

Fetal neurosonographic phenotyping of inborn errors of metabolism

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Fetal central nervous system malformations are commonly encountered during routine fetal morphology scans. Fetal ventriculomegaly is among the most common prenatal neuroimaging findings including midline abnormalities, posterior fossa abnormalities, and cortical malformation. Their imaging features are often symptoms or part of the phenotypic features of the underlying disease. Collective information from targeted fetal neurosonography, magnetic resonance imaging, and genetic testing can help clinicians to make the diagnosis. We review various common and essential fetal neuroimaging features and highlight their association with inborn errors of metabolism.

Keywords: Brain; Genetic testing; Magnetic resonance imaging; Metabolism, inborn errors; Prenatal diagnosis; Ultrasonography, prenatal

Introduction

Fetal central nervous system malformations are commonly identified during routine fetal morphology scans. Fetal ventriculomegaly is among the most common prenatal neuroimaging findings including midline, posterior fossa, and cortical malformations. Their imaging features are often symptoms or part of the phenotypic features of the underlying disease. Collective information from targeted fetal neurosonography, magnetic resonance imaging (MRI), and laboratory testing can help clinicians to make the diagnosis. In this review, we discuss various common fetal central nervous system abnormalities and their linked to inborn errors of metabolism (IEM).

IEM is broadly defined as a congenital defect of metabolism including catabolism (breakdown of molecules) and anabolism (synthesis of molecules) in our body. Early identification of IEM can be life-saving and prevent irreversible damage to the body. The first screening of IEM was invented by Dr Robert Guthrie in the early 1960s who collected a capillary blood sample from a newborn heel prick on a card (the Guthrie card) to screen for phenylketonuria (PKU). PKU is characterised by abnormally elevated blood phenylalanine levels. Untreated or poorly controlled maternal PKU can cause fetal microcephaly, congenital heart disease, structural anomalies, and fetal growth restriction[1]. To date, the definition of IEM is further defined as any condition leading to the dysfunction of specific enzymes or disruption of biochemical pathways intrinsic to the pathomechanism[2,3]. Although IEM is rare individually, it is not uncommon collectively, with an estimated incidence ranging from one in every 800 to 2500 newborns[4]. Nevertheless, the true prevalence of IEM is difficult to estimate owing to various confounding factors and underdiagnosis.

The Society for the Study of Inborn Errors of Metabolism has described >600 different IEMs under 15 categories based on the affected biochemical pathways. IEMs are caused by genetic mutations that alter metabolism. However, the significance of genetic variants in their phenotypes remains uncertain. With the advancement of genomics and metabolomics technology, a combined metabolomics and genomics approach has been proposed[5]. There are 217 920 metabolites from 114 100 entries in the Human Metabolome Database (version 5.0). This information covers 132 335 metabolic pathways, 136 878 metabolites or xenobiotics, and 2153 proteins[6]. In-depth knowledge for interpreting genomics and metabolomics information and understanding the role of IEMs in different fetal neurodevelopmental disorders is essential to prenatal diagnostics, which may enable early intervention and immediate postnatal management.

Holoprosencephaly

Holoprosencephaly (HPE) is a common structural anomaly of the forebrain[7]. The prosencephalon (the most anterior brain vesicle) is the precursor of the forebrain. It divides into the telencephalon (ie, the cerebral hemisphere, commissural fibres, and basal ganglia) and the diencephalon

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(ie, the thalamus, posterior commissural fibres, and hypothalamus)[8]. Failure or incomplete separation of the prosencephalon by 8 weeks of gestation results in HPE and associated facial dysmorphism, neurological impairment, and endocrine abnormalities[9]. Four classical types have been proposed based on the degree of forebrain non-separation[10,11]. Alobar HPE, the most severe form, is readily seen on the first trimester ultrasound. It is characterised by loss of the midline falx and the absence of two distinct choroid plexuses (Figure 1)[12]. The less severe form involves non-separation of the frontal lobes in semi-lobar HPE (Figure 2), the basal aspect of the frontal lobes in

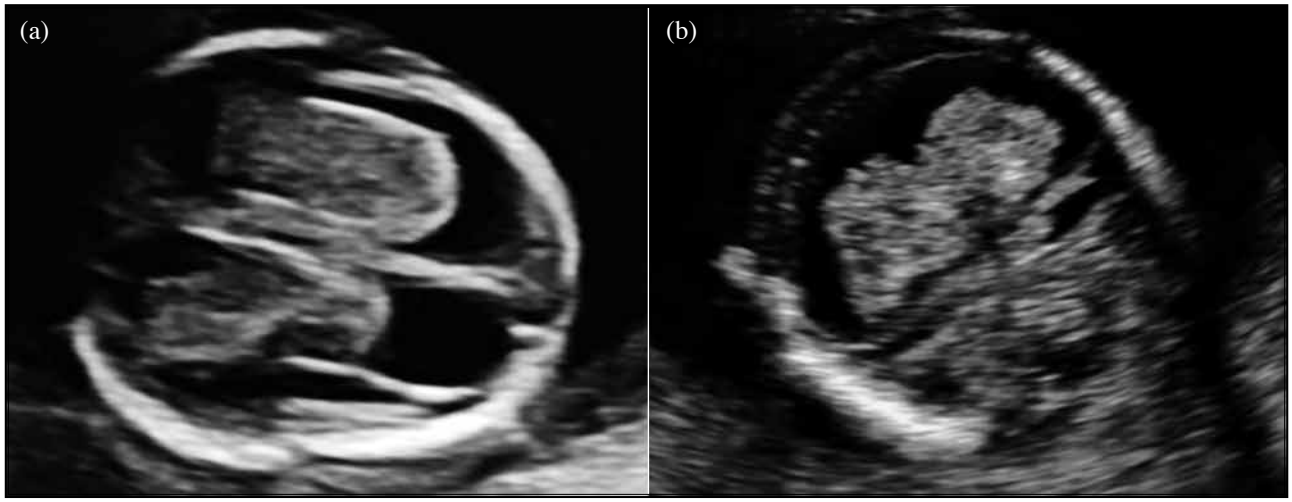

Figure 1. Fetal brain at 12 weeks of gestation: (a) a normal fetal brain showing a complete midline falx and each choroid plexus surrounded by fluid-filled cerebral ventricles, and (b) a fetal brain with alobar holoprosencephaly showing loss of the midline falx with a mono-ventricle and a fused choroid plexus at the coronal plane.

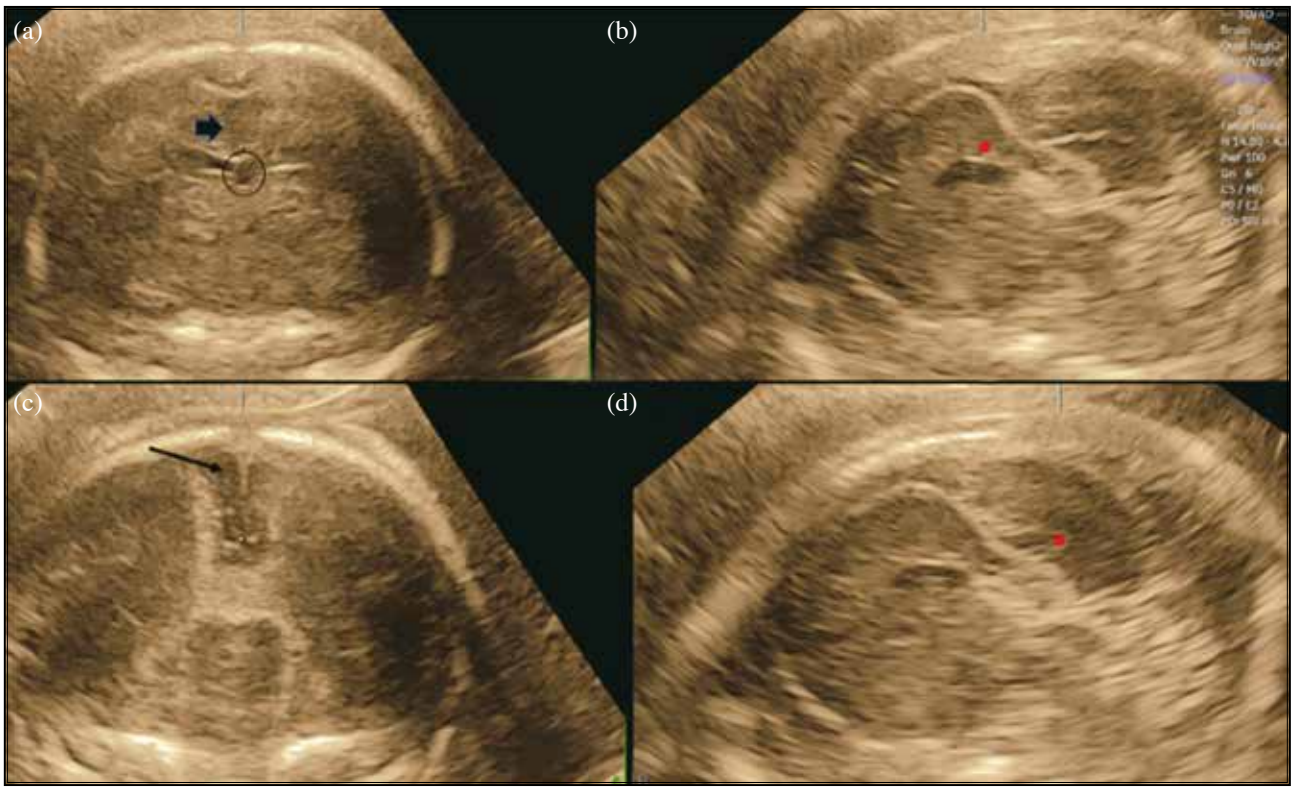

Figure 2. Three-dimensional neurosonography in the second trimester of a fetus affected by semi-lobar holoprosencephaly: the anterior (a) coronal and (b) sagittal planes showing a fused frontal lobe (arrow and dot) and the lack of a cavum septum pellucidum (circle). The posterior (c) coronal and (d) sagittal planes showing the presence of the midline falx (arrow and dot) indicating separation of the cerebral hemisphere at the parietal lobes.

lobar HPE, and the posterior frontal and parietal lobes in middle interhemispheric variant HPE.

Common neurosonography and/or MRI indications are absent in the cavum septum pellucidum during the second or third trimester. Common trisomies, namely 13 and 18, other chromosomal aberrations, and genetic abnormalities have been reported[13-16]. Smith-Lemli-Opitz syndrome (SLOS), a sterol metabolism disorder, is a known cause of HPE. Abnormalities such as microcephaly, corpus callosal agenesis, poly/syndactyly, polymicrogyria, ambiguous genitalia, and fetal growth restriction may be found in affected fetuses. In SLOS, the disease-causing variants in the *DHCR7* gene affect the enzyme 7-dehydrocholesterol reductase[17]. This enzyme is responsible for converting 7-dehydrocholesterol (7DHC) to cholesterol; thus, affected subjects have elevated circulating 7DHC (8-dehydrocholesterol) levels but low total cholesterol levels. 7DHC levels in the amniotic fluid were elevated among affected fetuses[18,19]. It remains unclear how this condition leads to fetal brain malformations. Nevertheless, myelin is rich in cholesterol, and the abnormal accumulation of 7DHC and a low-cholesterol environment may interfere with myelin synthesis[20].

In addition, Sonic Hedgehog (Shh) signalling defects are often associated with HPE. The Shh protein requires cholesterol as a modulator by covalently bonding with cholesterol and palmitic acid. Low-circulating cholesterol levels impact Shh signalling and causes HPE[17]. HPE is also observed in lathosterolosis (another IEM of cholesterol biosynthesis), which impairs the conversion of lathosterol to 7DHC. Interestingly, simvastatin, an HMG-CoA reductase inhibitor, has been reported to improve the biochemical phenotypes and various clinical features in some patients with lathosterolosis and SLOS[21-23]. However, more studies are required to substantiate the clinical significance of the finding[24].

Microcephaly

Fetal microcephaly is defined as a head circumference that is three standard deviations below the mean after correcting for gestational age[25-28]. Neuronal proliferative disorders causing reduced proliferation or excessive apoptosis of neuronal-glial progenitors can manifest early in the first and second trimesters of pregnancy. Migrational or post-migrational disorders affecting glial multiplication only manifest in the third trimester or become apparent after birth. The aetiology of autosomal recessive primary microcephaly is complex; at least 28 related genes are reportedly disease-causing or associated with severe microcephaly[29-31]. The causes of acquired microcephaly are beyond the context of the current review. Other factors that disrupt neuronal proliferation and migration (congenital infections, toxin exposure, ischaemic insults, and IEM) must be considered. Amino acid disorders (such as 3-phosphoglycerate dehydrogenase deficiency[32,33], asparagine synthetase deficiency[34], and maternal PKU[1]) have been described in cases of congenital and progressive microcephaly. Other IEMs linked to congenital microcephaly include SLOS[35] and pyruvate dehydrogenase deficiency[36]. High phenylalanine levels have potentially toxic effect on fetal neurodevelopment in maternal PKU. High phenylalanine levels compete with other neutral amino acids to facilitate transport across the blood-brain barrier. Relative depletion of non-phenylalanine neutral amino acids hinders cerebral enzyme activity or protein synthesis[37].

Macrocephaly

Macrocephaly was defined as head circumference that is two standard deviations above the mean after correcting for gestational age. Most cases are familial with normal developmental outcomes[38]. Macrocephaly secondary to underlying hydrocephalus or brain tumour and syndromic macrocephaly may result in abnormal neuropsychological development[39]. IEM cause prenatal macrocephaly and germinolysis cysts have been reported in glutaric aciduria type I[40,41], which is included in the current newborn screening in Hong Kong by analysing C5-DC carnitine in whole blood. Early metabolic treatment of newborns can prevent acute decompensation and irreversible neuronal damage[42,43]. Canavan disease, D-2-hydroxyglutaric aciduria, Hunter syndrome, Hurler syndrome, and Sly syndrome are often present as postnatal macrocephaly[44], which is beyond the scope of the current review.

Migrational disorder

Cortical development involves cerebral expansion and folding in three overlapping stages: neuronal proliferation, migration, and organisation. This highly complex fetal neurodevelopment is tightly regulated by cellular and molecular mechanisms that involve multiple genes and pathways[45]. The exact mechanisms of fetal brain development and neural migration are unclear. Nonetheless, *LIS1*, *DCX*, and *TUBA1A* were found in approximately 80% of patients with migrational disorders[46]. Neuronal migrational disorders are a spectrum of disease; the most severe form is schizencephaly and the agyria-pachygyria

Table. Brain disorders in different brain development phases[48]

Brain disorders in different brain development phases
Neuronal proliferation
Microcephaly
Megalencephaly
Neuronal migration
Heterotopia
Lissencephaly
Cobblestone malformation
Hemimegalencephaly
Neuronal organisation
Polymicrogyria
Schizencephaly

spectrum, whereas the milder form includes polymicrogyria and periventricular or subcortical heterotopia[47]. The Table shows brain disorders in different developmental phases[48].

Antenatal diagnosis of cortical development malformation is challenging. Standard screening in the second trimester includes assessments of fetal head size (by biparietal diameter), head circumference, and atrial width of the lateral ventricles[49]. Maturation of the Sylvian fissure is among the most readily identifiable hallmarks of cortical brain development. MRI can demonstrate continuous changes in the gyri and sulci that occur throughout gestation[8], with the Sylvian fissures being identified as early as 16 weeks of gestation. On ultrasound, the Sylvian fissure can be recognised at approximately 18 weeks of gestation, and the maturation of Sylvian fissure pattern is based on its shape[50-54].

Advances in high-resolution transvaginal fetal neurosonography have enhanced the precision of Sylvian fissure pattern evaluation[55-57]. Poon et al[58] pioneered a gestational age-specific reference chart of Sylvian fissure angle (SFA) development across 18 to 30 weeks of gestation based on 422 ultrasonographic data points from normal fetuses. The measurements were performed under a stringent and standardised protocol (Figure 3) that aims to minimise inter- and intra-observer variability. The SFA with respective to the gestational age and head circumference are expressed in a biometric chart to serve as a screening tool for fetal cortical malformations and enables early referral for further assessment.

Delayed cortical development

Classic lissencephaly (type 1), cobblestone lissencephaly (type 2), and lissencephaly secondary to tubulinopathy (type 3, also known as microlissencephaly) commonly present with ventriculomegaly and delayed or abnormal operculisation of the Sylvian fissure. In classic lissencephaly, the brain has broad or absent gyri and an abnormally thick cortex (Figure 4). Antenatal diagnosis of lissencephaly is largely made in the third trimester, with presentation of a slow-growing head circumference and ventriculomegaly. Clinical suspicion of lissencephaly in the second trimester is possible if the bilateral SFA is grossly delayed.

IEM-related lissencephaly mainly involves cobblestone lissencephaly. Cobblestone lissencephaly is characterised by over-migration of the neuroglial cell causing 'protrusions' of neurones over the brain surface that give rise to a cobblestone appearance on MRI. Cobblestone lissencephaly has been well reported in congenital glycosylation disorders. This category includes Walker-Warburg syndrome, muscle-eye-brain disease, and Fukuyama congenital muscular dystrophy, all of which share the clinical features of congenital muscular dystrophy. The presence of cobblestone lissencephaly together with cerebellar abnormalities (Z-shaped appearance of the brainstem), meningocele, and microphthalmia are pathognomonic of Walker-Warburg syndrome[59].

Microlissencephaly (type 3 lissencephaly) is characterised by microcephaly, lissencephaly, fetal growth restriction, polyhydramnios, micrognathia, and subcutaneous oedema secondary to fetal akinesia[60,61]. It is often associated with hypoplasia of the cerebellar vermis, with the anterior portion more severely affected. This subtype of lissencephaly encompasses genetic disorders that affect tubulin protein[62].

Polymicrogyria and heterotopia

Polymicrogyria is characterised by abnormal cortical migration. Many small plications are noted on the cortical surface that give rise to a wrinkled chestnut appearance over part or all the brain surface. Polymicrogyria primarily occurs during late neuronal migration or the early post-migrational period; therefore, it is often undetectable on second-trimester ultrasound. Heterotopia is characterised by arrested neuronal migration in the periventricular region (Figure 5) or subcortical white matter. Prenatally, heterotopia can present with an abnormally shaped Sylvian fissure, prominent subarachnoid space overlying the affected brain cortex, and ventricular wall irregularity.

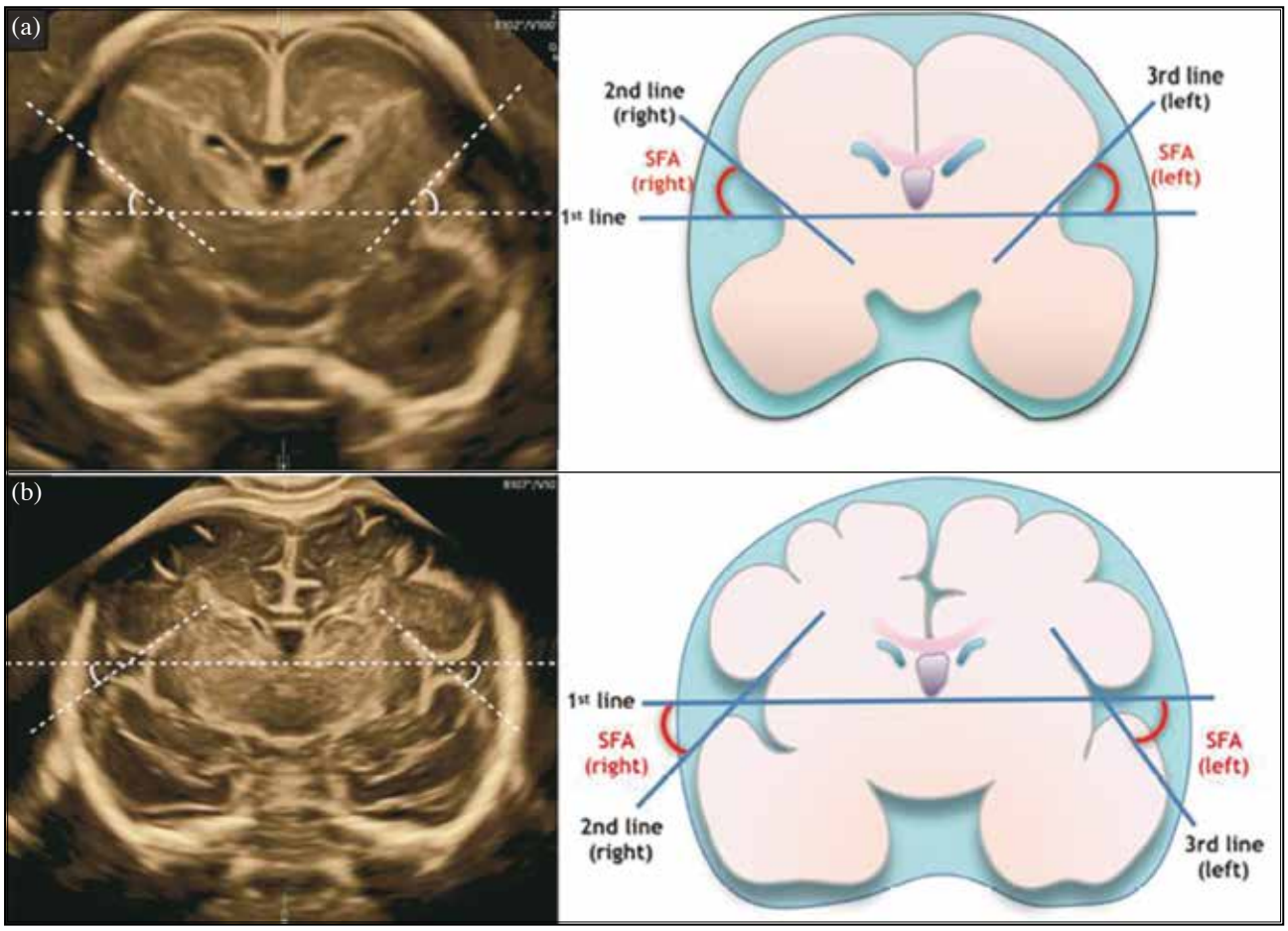

Figure 3. Measurement of (a) positive and (b) negative Sylvian fissure angle (SFA) on ultrasound images and corresponding schematic diagrams: the first line is drawn along the horizontal line and then the second and third lines are drawn along the upper sides of the right and left Sylvian fissures, respectively. The right and left SFA formed by these three lines are measured using the horizontal line as reference (0°). The angle above the horizontal line is deemed positive, whereas that below the horizontal line is deemed negative (adapted with permission from Poon LC, Sahota DS, Chaemsaithong P, et al. Transvaginal three-dimensional ultrasound assessment of Sylvian fissures at 18-30 weeks' gestation. Ultrasound Obstet Gynecol 2019;54:190-8.)

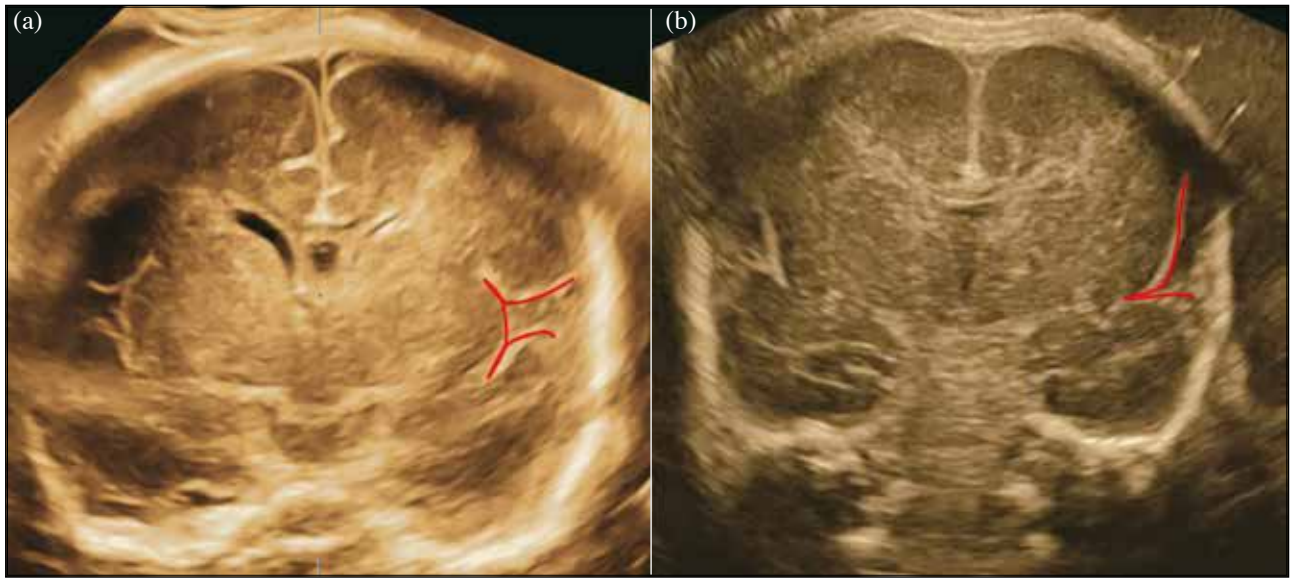

Figure 4. Fetal brains in coronal view at 30 weeks of gestation: (a) a normal fetal brain showing a normal quadrangular shape of the Sylvian fissure and (b) a fetal brain with Miller-Dieker lissencephaly showing abnormal development of the Sylvian fissure.

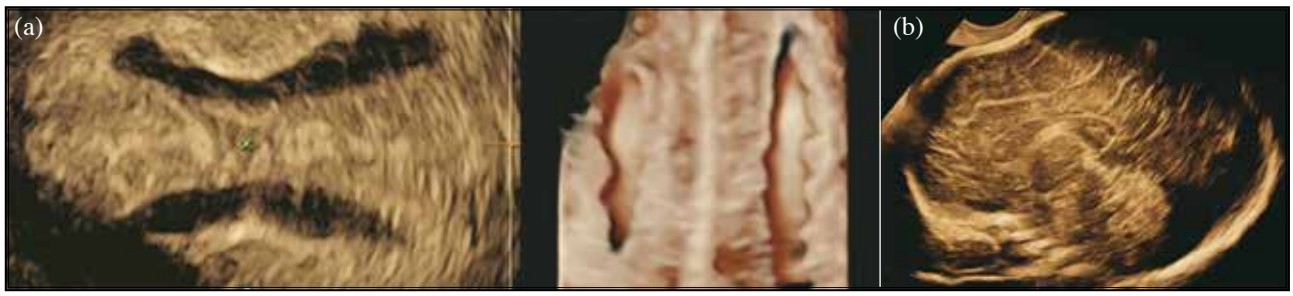

Figure 5. Ultrasound images of the fetal brain at 30 weeks of gestation showing (a) nodular irregularities at the ventricular wall in the ventricular view and (b) mega cisterna magna in the sagittal view.

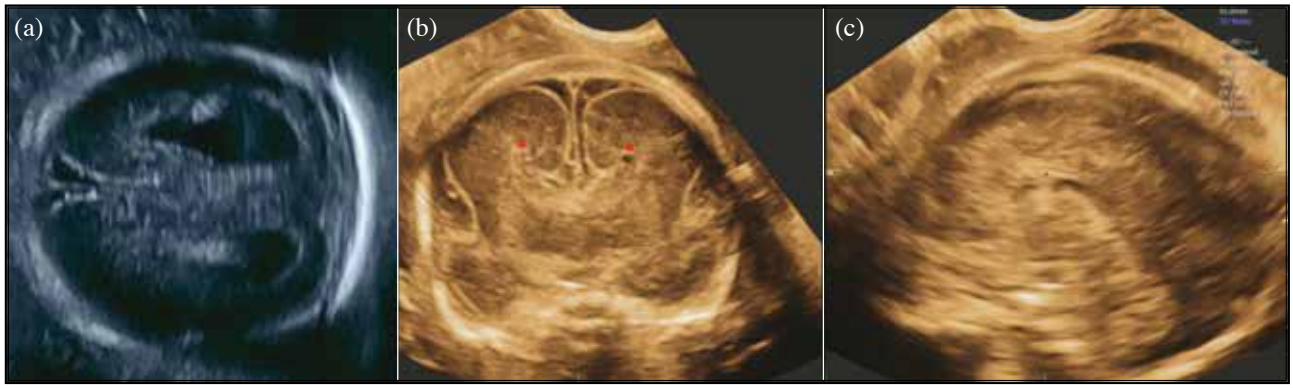

Figure 6. Ultrasound images of a 22-week fetal brain with complete agenesis of the corpus callosum: (a) axial plane showing tear drop–shaped lateral ventricles and (b) coronal and (c) midsagittal planes showing separation of the interhemispheric fissure and wide separation of the anterior frontal horns (asterisks) as well as complete absence of the corpus callosum.

These sonographic features are sometimes detectable on transvaginal ultrasonography[63]. Subcortical band heterotopia (double cortex) is essentially diagnosed by MRI.

Metabolic defects (such as the infantile form of pyruvate dehydrogenase deficiency, Zellweger syndrome, and SLOS) have been reported in cases of polymicrogyria and/or heterotopia. Pyruvate dehydrogenase deficiency is a potentially life-threatening mitochondrial disorder that can present with pachygyria, polymicrogyria, periventricular nodular heterotopias, and cerebellar and brainstem hypoplasia[36,64]. Zellweger spectrum disorder can present with migrational disorder and extracranial features such as renal cysts and bony stippling of the patella and long bones[65].

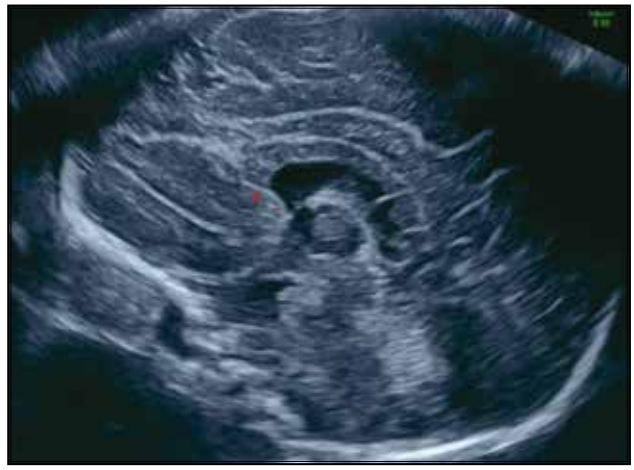

Figure 7. Ultrasound image of the sagittal plane of a fetal brain at 34 weeks of gestation showing a shortened and thickened corpus callosum with absence of the rostrum (asterisk).

Corpus callosum agenesis/ dysgenesis

The absence of the cavum septum pellucidum and the presence of a teardrop configuration of the lateral ventricle are common presentations of corpus callosum abnormalities (Figures 6 and 7). Complete agenesis of the corpus callosum is usually apparent on a second-trimester morphology scan. The mechanism of partial or complete agenesis of the corpus callosum is not entirely clear. Features of corpus callosum agenesis include midline axonal misguidance, decreased cortical neuron

numbers, a lack of long-range interhemispheric neurones, and a modified number of callosal axons[66,67]. The process is extremely dynamic, making the diagnosis of partial agenesis or dysgenesis extremely difficult, especially before the third trimester.

Corpus callosum abnormalities have been reported in various IEMs through neuroimaging and/or autopsy findings including pyridoxine-dependent epilepsy, 2,4-dienoyl-CoA reductase deficiency, argininosuccinate lyase deficiency, combined oxidative phosphorylation deficiency 12, complex I deficiency, cytochrome oxidase deficiency, fumaric aciduria, glutaric aciduria types I and II, Menkes disease, nonketotic hyperglycinaemia, pyruvate carboxylase deficiency, pyruvate dehydrogenase deficiency, and sulfite oxidase deficiency[67].

Anomalies of posterior fossa

The posterior fossa develops rapidly from the first to second trimester. The persistence of embryonic brain flexures after 15 weeks of gestation (ie, a Z-shaped appearance of the brainstem) is suggestive of severe cerebellar dysgenesis. This finding, together with cobblestone lissencephaly, is pathognomonic of Walker-Warburg syndrome[59].

Isolated cerebellar hypoplasia and, more commonly, progressive cerebellar and pons atrophy have been reported in congenital disorders of glycosylation such as PMM2 deficiency[68].

Conclusions

Prenatal ultrasound should be better be described as 'fetal sonographic phenotyping', which is a process of interpreting morphological findings with knowledge of physiology and pathomechanism. Because abnormal fetal neurosonographic features are usually a sign of an underlying disease, collective genomics and metabolomics information can supplement and substantiate sonographic phenotypes by providing a more specific and accurate aetiological diagnosis including IEM. Prenatal identification of IEM can improve antenatal and postnatal care through a multidisciplinary approach. We envision that making a diagnosis is not the end. Rather, it better prepares the family for the possible outcome and management. Novel therapeutic strategies are evolving with ongoing clinical trials to revitalise the defective biochemical pathways. These will shed light on the patients and their family regarding these previously unmanageable conditions.

Contributors

All authors designed the study, acquired the data, analysed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

Funding/support

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability

All data generated or analysed during the present study are available from the corresponding author on reasonable request.

References

1. Rohde C, Thiele AG, Baerwald C, et al. Preventing maternal phenylketonuria (PKU) syndrome: important factors to achieve good metabolic control throughout pregnancy. Orphanet J Rare Dis 2021;16:477. Crossref
2. Jeanmonod R, Asuka E, Jeanmonod D. Inborn Errors of Metabolism. Treasure Island, Florida: StatPearls Publishing; 2022.
3. Morava E, Rahman S, Peters V, Baumgartner MR, Patterson M, Zschocke J. Quo vadis: the re-definition of "inborn metabolic diseases". J Inherit Metab Dis 2015;38:1003-6. Crossref
4. Schuck PF, Ferreira GC, McKenna MC. Recent advances in the pathophysiology of inherited metabolic diseases. Int J Dev Neurosci 2020;80:50-1. Crossref
5. Law CY. Combined metabolomics and genomics approach for the diagnosis of inherited metabolic disorders (IMD). Topical Update — The Hong Kong College of Pathologists 2021.
6. Wishart DS, Guo A, Oler E, et al. HMDB 5.0: the Human Metabolome Database for 2022. Nucleic Acids Res 2022;50:D622-D631. Crossref
7. Raam MS, Solomon BD, Muenke M. Holoprosencephaly: a

guide to diagnosis and clinical management. Indian Pediatr 2011;48:457-66. Crossref
8. Stiles J, Jernigan TL. The basics of brain development. Neuropsychol Rev 2010;20:327-48. Crossref
9. Demyer W, Zeman W, Palmer CG. The face predicts the brain: diagnostic significance of median facial anomalies for holoprosencephaly (arhinencephaly). Pediatrics 1964;34:256-63. Crossref
10. Society for Maternal-Fetal Medicine (SMFM); Monteagudo A. Holoprosencephaly. Am J Obstet Gynecol 2020;223:B13-B16. Crossref
11. Weiss K, Kruszka PS, Levey E, Muenke M. Holoprosencephaly from conception to adulthood. Am J Med Genet C Semin Med Genet 2018;178:122-7. Crossref
12. Engels AC, Joyeux L, Brantner C, et al. Sonographic detection of central nervous system defects in the first trimester of pregnancy. Prenat Diagn 2016;36:266-73. Crossref
13. Chen CP, Wang TH, Lin CC, Tsai FJ, Hsieh LJ, Wang W. Prenatal diagnosis of partial trisomy 3p (3p21-->pter) and partial monosomy 11q (11q23-->qter) associated with abnormal sonographic findings of holoprosencephaly, orofacial clefts, pyelectasis and a unilateral duplex renal system. J Formos Med Assoc 2008;107:822-6. Crossref
14. Kanafani S, Aboura A, Pipiras E, et al. Semilobar holoprosencephaly prenatal diagnosis: an unexpected complex rearrangement in a de novo apparently balanced reciprocal translocation on karyotype. Prenat Diagn 2007;27:279-84. Crossref
15. Campeau PM, Ah Mew N, Cartier L, et al. Prenatal diagnosis of monosomy 1p36: a focus on brain abnormalities and a review of the literature. Am J Med Genet A 2008;146A:3062-9. Crossref
16. Roessler E, Muenke M. The molecular genetics of holoprosencephaly. Am J Med Genet C Semin Med Genet 2010;154C:52-61. Crossref
17. Haas D, Muenke M. Abnormal sterol metabolism in holoprosencephaly. Am J Med Genet C Semin Med Genet 2010;154C:102-8. Crossref
18. Mills K, Mandel H, Montemagno R, Soothill P, Gershoni-Baruch R, Clayton PT. First trimester prenatal diagnosis of Smith-Lemli-Opitz syndrome (7-dehydrocholesterol reductase deficiency). Pediatr Res 1996;39:816-9. Crossref
19. Kratz LE, Kelley RI. Prenatal diagnosis of the RSH/Smith-Lemli-Opitz syndrome. Am J Med Genet 1999;82:376-81. Crossref
20. Lee RW, Conley SK, Gropman A, Porter FD, Baker EH. Brain magnetic resonance imaging findings in Smith-Lemli-Opitz syndrome. Am J Med Genet A 2013;161A:2407-19. Crossref
21. Yaplito-Lee J, Pai G, Hardikar W, et al. Successful treatment of lathosterolosis: a rare defect in cholesterol biosynthesis: a case report and review of literature. JIMD Rep 2020;56:14-9. Crossref
22. Ho AC, Fung CW, Siu TS, et al. Lathosterolosis: a disorder of cholesterol biosynthesis resembling Smith-Lemli-Opitz syndrome. JIMD Rep 2014;12:129-34. Crossref
23. Wassif CA, Kratz L, Sparks SE, et al. A placebo-controlled trial of simvastatin therapy in Smith-Lemli-Opitz syndrome. Genet Med 2017;19:297-305. Crossref
24. Ballout RA, Bianconi S, Livinski A, Fu YP, Remaley AT, Porter FD. Statins for Smith-Lemli-Opitz syndrome. Cochrane Database Syst Rev 2020;2020:CD013521. Crossref
25. Opitz JM, Holt MC. Microcephaly: general considerations and aids to nosology. J Craniofac Genet Dev Biol 1990;10:175-204.
26. von der Hagen M, Pivarcsi M, Liebe J, et al. Diagnostic approach to microcephaly in childhood: a two-center study and review of the literature. Dev Med Child Neurol 2014;56:732-41. Crossref
27. Chervenak FA, Jeanty P, Cantraine F, et al. The diagnosis of fetal microcephaly. Am J Obstet Gynecol 1984;149:512-7. Crossref
28. Chervenak FA, Rosenberg J, Brightman RC, Chitkara U, Jeanty P. A prospective study of the accuracy of ultrasound in predicting fetal microcephaly. Obstet Gynecol 1987;69:908-10.
29. Zaqout S, Kaindl AM. Autosomal recessive primary microcephaly: not just a small brain. Front Cell Dev Biol 2021;9:784700. Crossref
30. Shaheen R, Maddirevula S, Ewida N, et al. Genomic and phenotypic delineation of congenital microcephaly. Genet Med 2019;21:545-52. Crossref
31. Martin AR, Williams E, Foulger RE, et al. PanelApp crowdsources expert knowledge to establish consensus diagnostic gene panels. Nat Genet 2019;51:1560-5. Crossref
32. De Koning TJ, Duran M, Van Maldergem L, et al. Congenital microcephaly and seizures due to 3-phosphoglycerate dehydrogenase deficiency: outcome of treatment with amino acids. J Inherit Metab Dis 2002;25:119-25. Crossref
33. de Koning TJ. Amino acid synthesis deficiencies. Handb Clin Neurol 2013;113:1775-83. Crossref
34. Alfadhel M, Alrifai MT, Trujillano D, et al. Asparagine synthetase deficiency: new inborn errors of metabolism. JIMD Rep 2015;22:11-6. Crossref
35. Nowaczyk MJM, Wassif CA. Smith-Lemli-Opitz syndrome. In: Adam MP, Everman DB, Mirzaa GM, et al, editors. GeneReviews. Seattle, Washington: University of Washington, Seattle: 1993-2023.
36. Pirot N, Crahes M, Adle-Biassette H, et al. Phenotypic and neuropathological characterization of fetal pyruvate dehydrogenase deficiency. J Neuropathol Exp Neurol 2016;75:227-38. Crossref
37. van Spronsen FJ, Hoeksma M, Reijngoud DJ. Brain dysfunction in phenylketonuria: is phenylalanine toxicity the only possible cause? J Inherit Metab Dis 2009;32:46-51. Crossref
38. Biran-Gol Y, Malinger G, Cohen H, et al. Developmental outcome of isolated fetal macrocephaly. Ultrasound Obstet Gynecol 2010;36:147-53. Crossref
39. Tan AP, Mankad K, Goncalves FG, Talenti G, Alexia E. Macrocephaly: solving the diagnostic dilemma. Top Magn Reson Imaging 2018;27:197-217. Crossref
40. Mellerio C, Marignier S, Roth P, et al. Prenatal cerebral ultrasound and MRI findings in glutaric aciduria type 1: a de novo case. Ultrasound Obstet Gynecol 2008;31:712-4. Crossref

41. Lin SK, Hsu SG, Ho ES, et al. Glutaric aciduria (type I): prenatal ultrasonographic findings. Ultrasound Obstet Gynecol 2002;20:305-7. Crossref
42. Kolker S, Christensen E, Leonard JV, et al. Diagnosis and management of glutaric aciduria type I: revised recommendations. J Inherit Metab Dis 2011;34:677-94. Crossref
43. Strauss KA, Williams KB, Carson VJ, et al. Glutaric acidemia type 1: treatment and outcome of 168 patients over three decades. Mol Genet Metab 2020;131:325-40. Crossref
44. Saudubray JM, Garcia-Cazorla A. An overview of inborn errors of metabolism affecting the brain: from neurodevelopment to neurodegenerative disorders. Dialogues Clin Neurosci 2018;20:301-25. Crossref
45. Barkovich AJ, Guerrini R, Kuzniecky RI, Jackson GD, Dobyns WB. A developmental and genetic classification for malformations of cortical development: update 2012. Brain 2012;135:1348-69. Crossref
46. Huang J, Wah IY, Pooh RK, Choy KW. Molecular genetics in fetal neurology. Semin Fetal Neonatal Med 2012;17:341-6. Crossref
47. Volpe JJ, Inder TE, Darras BT, et al. Volpe's Neurology of the Newborn. 6th Edition; 2017.
48. Murthy BSR. Imaging of Fetal Brain and Spine: an Atlas and Guide; 2019.
49. Paladini D, Malinger G, Birnbaum R, et al. ISUOG Practice Guidelines (updated): sonographic examination of the fetal central nervous system. Part 2: performance of targeted neurosonography. Ultrasound Obstet Gynecol 2021;57:661-71. Crossref
50. Glenn OA. Normal development of the fetal brain by MRI. Semin Perinatol 2009;33:208-19. Crossref
51. Cohen-Sacher B, Lerman-Sagie T, Lev D, Malinger G. Sonographic developmental milestones of the fetal cerebral cortex: a longitudinal study. Ultrasound Obstet Gynecol 2006;27:494-502. Crossref
52. Pooh RK, Nakagawa Y, Nishida S, Ohno Y. Fetal neuroimaging of neural migration disorder. Ultrasound Clin 2008;3:541-52. Crossref
53. Mittal P, Goncalves LF, Kusanovic JP, et al. Objective evaluation of sylvian fissure development by multiplanar 3-dimensional ultrasonography. J Ultrasound Med 2007;26:347-53. Crossref
54. Quarello E, Stirnemann J, Ville Y, Guibaud L. Assessment of fetal Sylvian fissure operculization between 22 and 32 weeks: a subjective approach. Ultrasound Obstet Gynecol 2008;32:44-9. Crossref
55. Cater SW, Boyd BK, Ghate SV. Abnormalities of the fetal central nervous system: prenatal US diagnosis with postnatal correlation. Radiographics 2020;40:1458-72. Crossref
56. Malinger G, Paladini D, Haratz KK, Monteagudo A, Pilu GL, Timor-Tritsch IE. ISUOG Practice Guidelines (updated): sonographic examination of the fetal central nervous system. Part 1: performance of screening examination and indications for targeted neurosonography. Ultrasound Obstet Gynecol 2020;56:476-84. Crossref
57. Malinger G, Paladini D, Pilu G, Timor-Tritsch IE. Fetal cerebral magnetic resonance imaging, neurosonography and the brave new world of fetal medicine. Ultrasound Obstet Gynecol 2017;50:679-80. Crossref
58. Poon LC, Sahota DS, Chaemsaithong P, et al. Transvaginal three-dimensional ultrasound assessment of Sylvian fissures at 18-30 weeks' gestation. Ultrasound Obstet Gynecol 2019;54:190-8. Crossref
59. Lacalm A, Nadaud B, Massoud M, Putoux A, Gaucherand P, Guibaud L. Prenatal diagnosis of cobblestone lissencephaly associated with Walker-Warburg syndrome based on a specific sonographic pattern. Ultrasound Obstet Gynecol 2016;47:117-22. Crossref
60. Allias F, Buenerd A, Bouvier R, et al. The spectrum of type III lissencephaly: a clinicopathological update. Fetal Pediatr Pathol 2004;23:305-17. Crossref
61. Di Donato N, Chiari S, Mirzaa GM, et al. Lissencephaly: expanded imaging and clinical classification. Am J Med Genet A 2017;173:1473-88. Crossref
62. Bahi-Buisson N, Maillard C. Tubulinopathies overview. In: Adam MP, Everman DB, Mirzaa GM, et al, editors. GeneReviews. Seattle, Washington: University of Washington, Seattle; 1993-2023.
63. Lerman-Sagie T, Pogledic I, Leibovitz Z, Malinger G. A practical approach to prenatal diagnosis of malformations of cortical development. Eur J Paediatr Neurol 2021;34:50-61. Crossref
64. Natarajan N, Tully HM, Chapman T. Prenatal presentation of pyruvate dehydrogenase complex deficiency. Pediatr Radiol 2016;46:1354-7. Crossref
65. Steinberg SJ, Raymond GV, Braverman NE, et al. Zellweger spectrum disorder. In: Adam MP, Everman DB, Mirzaa GM, et al, editors. GeneReviews. Seattle, Washington: University of Washington, Seattle; 1993-2023.
66. Wegiel J, Flory M, Kaczmarski W, et al. Partial agenesis and hypoplasia of the corpus callosum in idiopathic autism. J Neuropathol Exp Neurol 2017;76:225-37. Crossref
67. Hofman J, Hutny M, Sztuba K, Paprocka J. Corpus callosum agenesis: an insight into the etiology and spectrum of symptoms. Brain Sci 2020;10:625. Crossref
68. Accogli A, Addour-Boudrahem N, Srour M. Diagnostic approach to cerebellar hypoplasia. Cerebellum 2021;20:631-58. Crossref