New Insights into the Anterior Complex

Article *in* Fetal Diagnosis and Therapy · January 2020

DOI: 10.1159/000504980

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Fetal Diagnosis and Therapy

Fetal Diagn Ther
DOI: 10.1159/000504980

Received: September 10, 2019
Accepted after revision: November 25, 2019
Published online: January 13, 2020

New Insights into the Anterior Complex

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Established Facts

- Anterior complex (AC) evaluation has proven to be a valuable tool in the diagnosis of midline and cortical malformations during the performance of a basic ultrasound study of the fetal brain.
- Peri-intraventricular hemorrhage, subependymal/connatal cysts, and white matter lesions are pathological conditions that are clearly underdiagnosed in the fetus.

Novel Insights

- Inclusion of the germinal matrix area, external angle of the frontal horn, and periventricular white matter into AC structures can significantly improve the prenatal diagnosis of hemorrhagic/cystic/hypoxic-ischemic pathologies.

Keywords
Peri-intraventricular hemorrhage · Subependymal cyst · White matter lesion · Central nervous system · Prenatal diagnosis

Abstract
Objective: To introduce visualization of the germinal matrix (GM), external angle of the frontal horn, and periventricular white matter while evaluating the anterior complex (AC) during basic ultrasound assessment of the fetal brain. ***Case Presentations:*** This is a retrospective observational study of healthy women with singleton pregnancies, with no increased risk of fetal central nervous system anomalies, attending routine ultrasound screening at 20–32 weeks' gestation. Seventeen cases are presented in which an abnormal aspect of the GM or external angle of the frontal horn or periventricular white matter on AC evaluation has allowed a pre-

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natal diagnosis of peri-intraventricular hemorrhage, subependymal cysts, connatal cysts, periventricular venous hemorrhagic infarction, and white matter injury. ***Conclusion:*** An extended AC evaluation could significantly improve the diagnosis of hemorrhagic/cystic/hypoxic-ischemic lesions during the performance of a basic ultrasound study of the fetal brain.

Introduction

Visualization of the anterior complex (AC) on routine transventricular axial planes has been proposed as a tool to improve the diagnosis of fetal midline anomalies [1, 2] (Fig. 1a, b). Integrating visualization of AC structures as part of routine fetal cerebral sonographic analysis should serve to improve the diagnosis not only of midline anomalies but also of other lesions across a broader spectrum. Certainly, we found that at least 50% of fetuses with cortical anomalies had an abnormal AC, suggesting that morphological abnormalities of the AC are not exclusive markers of midline defects [2].

After incorporating AC visualization into our daily practice, further observation has enabled us to visualize additional structures to those initially described [1]. These include the germinal matrix (GM), the external angle of the frontal horns, and the periventricular white matter [3]. We present a series of cases in which including the visualization of these brain structures into the AC assessment has further broadened the spectrum of pathological conditions diagnosable during a standard ultrasound screening of the fetal brain, such as GM hemorrhage and periventricular hemorrhagic infarction, subependymal and connatal cysts, and white matter lesions.

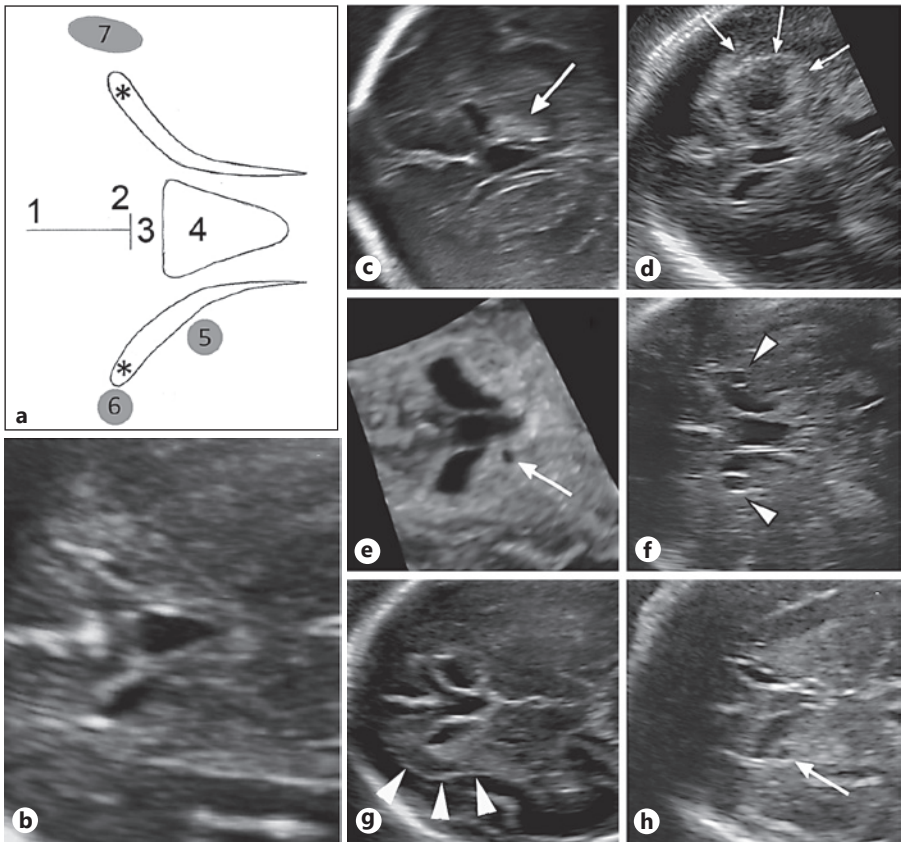

Fig. 1. a, **b** Diagram (**a**) and ultrasound image (**b**) of the normal anterior complex indicating the interhemispheric fissure (1), callosal sulcus (2), genu of the corpus callosum (3), cavum septi pellucidi (4), anterior horns of the lateral ventricles (*), germinal matrix (5), external angle of the frontal horns (6), and periventricular white matter (7). **b–h** Axial transventricular plane showing an abnormal anterior complex. **c** Ultrasound image of a fetus at 26 weeks' gestation showing a unilateral peri-intraventricular hemorrhage at the level of the germinal matrix (arrow). **d** Ultrasound image of a fetus at 24 weeks' gestation showing a heterogeneous area of increased echogenicity and a frontoparietal cavitation (arrows). The diagnosis was periventricular hemorrhagic infarction. **e** Ultrasound image of a germinal matrix cyst (arrow) in a fetus at 26 weeks' gestation. **f** Bilateral connatal cyst (arrowheads) in a fetus at 32 weeks' gestation affected by in utero ileal obstruction. **g** Ultrasound image of a fetus at 24 weeks' gestation affected by cytomegalovirus infection. An extended, mainly homogeneously increased periventricular echogenicity (arrowheads) suggested periventricular white matter injury, confirmed by in utero MRI. **h** Germinal matrix cyst (arrow) in a fetus at 24 weeks' gestation. Ultrasound follow-up demonstrated also a connatal cyst at the level of the body of the lateral ventricles and suspected white matter disease on in utero MRI.

Case Presentation

This was a retrospective observational multicenter study of healthy women with low-risk singleton pregnancies undergoing routine ultrasound examination at 20–32 weeks' gestation. Following standard scanning planes, the transabdominal axial transventricular plane was scanned in all cases. At this level and in both the proximal and the distal cerebral hemisphere, visualization of the posterior and lateral areas of the anterior horns of the lateral ventricles provided diagnoses of cystic structures or abnormalities of the periventricular echogenicity pattern in 17 fetuses. All of these were subsequently assessed with 2D transvaginal neurosonography (Fig. 1). Pre- and/or postnatal MRI was performed in 11 of the 17 cases (Fig. 2), and neonatal cranial ultrasound in 15 of the 17 cases (there was 1 stillbirth and 1 termination of pregnancy).

The gestational age at diagnosis, imaging findings, final diagnosis, and length of the follow-up period are displayed in Table 1. Six fetuses showed hemorrhagic pathologies: 3 had GM hemorrhage, 1 of them having an ipsilateral connatal cyst and all of them having a normal neonatal outcome; 2 fetuses were affected by peri-intraventricular hemorrhage, one having a normal neonatal outcome and the other having hemiparetic cerebral palsy; and the remaining fetus showed periventricular venous hemorrhagic infarction and was diagnosed after birth with unilateral spastic cerebral palsy.

Of the cases with connatal cysts, 3 were unilateral, all with a normal neonatal outcome, and 5 were bilateral. Of these, 2 had a normal neonatal outcome and the remaining cases were associated with central nervous system or extra-central nervous system anomalies, one of them being concomitantly affected by bilateral GM cysts. Another fetus with bilateral GM cysts had pontocerebellar hypoplasia. A single case with a unilateral GM cyst had a normal neonatal outcome. Finally, 2 fetuses had increased echogenicity of the periventricular area, one associated with a GM cyst and cytomegalovirus infection and the other affected by fetal supraventricular tachycardia with hydrops.

Discussion

The GM, located in the caudothalamic groove, extends from the external side of the frontal horns, below their external angle, towards the midline. Knowing its location is of great importance because, due to the fragility of its vessels, the GM is the site of origin of peri-intraventricular hemorrhage in the fetal and neonatal population. Bleeding appears echogenic in its acute and subacute phases, and cystic during its resolution (Fig. 1c, d). A cyst located in the GM area is called a subependymal cyst (Fig. 1d), and it can occur not only as a result of a hemorrhage but also in association with TORCH infections, asphyxia, chromosomal abnormalities, twin-to-twin transfusion, metabolism disorders, congenital heart disease, and other less frequent pathological conditions such as peroxisomal disorders, Zellweger syndrome, and bilateral striatal necrosis [4].

Awareness of the location of the external angle of the frontal horns is also advisable because cysts at this location (Fig. 1e) seem to have a better prognosis than subependymal cysts (or GM cyst). These cysts are known as "connatal cysts" (also as frontal horn cysts or coarctation of the lateral ventricles). Previously, this type of cyst was believed to be secondary to in utero ischemic or hemorrhagic events, but it is now assumed that in many cases it represents a normal variant due to approximation of the walls of the frontal horns of the lateral ventricles proximal to their external angles [5].

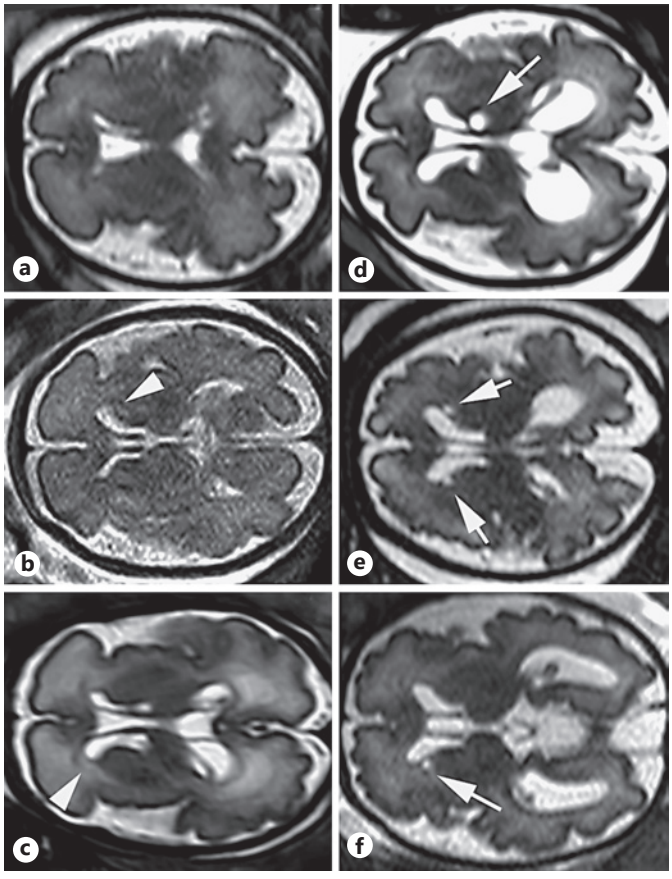

Fig. 2. Axial T2-weighted MR images at the level of the anterior complex. **a** Normal fetus at 28 weeks' gestation. **b** Peri-intraventricular hemorrhage (arrowhead) at 32 weeks' gestation. **c** Periventricular white matter hyperintensities (arrowhead) reflecting edema, gliosis, or demyelination in a fetus at 32 weeks' gestation affected by congenital cytomegalovirus leukoencephalopathy. **d** Isolated germinal matrix cyst (arrow) at 32 weeks. The long-term outcome demonstrated sensorineural hearing loss. **e** Image of bilateral germinal matrix cysts (arrows) obtained at 32 weeks' gestation in a fetus affected by pontocerebellar hypoplasia. **f** Connatal cyst (arrow) associated with mega cisterna magna in a fetus at 32 weeks' gestation. The final diagnosis was glutaric acidemia type 2.

Table 1. Summary of the 17 cases with abnormalities of the GM, external angle of the FH of the LV, or periventricular white matter at the level of the anterior complex

Case No.	GA, weeks	Ultrasound findings	Final diagnosis	MRI	NNU	Outcome	Follow-up, years
1	24	Heterogeneous area of increased echogenicity and frontoparietal cavitation at the level of the external side of the frontal horns of the LV	Frontoparietal hemorrhagic infarction	Y	Y	Unilateral spastic cerebral palsy	8
2	32	GM hemorrhage and intraventricular hemorrhage grade 3	Peri-intraventricular hemorrhage	Y	Y	Hemiparetic cerebral palsy	6
3	26	GM hemorrhage and intraventricular hemorrhage grade 2	Peri-intraventricular hemorrhage	N	Y	Normal neurological outcome	7
4	32	Bilateral connatal cysts; proximal fetal bowel obstruction	Bilateral connatal cysts; ileal atresia	N	Y	Ileoileostomy; normal neurological outcome	4
5	31	Bilateral connatal cysts	Isolated bilateral connatal cysts	N	Y	Normal neurological outcome	6
6	28	Bilateral GM cysts; pontocerebellar hypoplasia	Bilateral GM cysts; pontocerebellar hypoplasia	Y	Y	Neonatal death	–
7	31	Unilateral GM cyst	Isolated GM cyst	Y	Y	Sensorineural hearing loss	10
8	32	Connatal cyst; mega cisterna magna; quadrangular aspect of the FH of the LV	Glutaric acidemia type 2	Y	Y	Infant death	–
9	28	Hydrops fetalis; ventriculomegaly; increased echogenicity of the periventricular area	Noncystic form of periventricular white matter injury	N	–	Intrauterine death; PM examination	–
10	26	Unilateral GM hemorrhage	Unilateral GM hemorrhage	Y	Y	Normal neurological outcome	4
11	26	Unilateral GM hemorrhage	Unilateral GM hemorrhage	Y	Y	Normal neurological outcome	2
12	24	Bilateral connatal cysts; persistent left superior vena cava; cerebellar hypoplasia	Bilateral connatal cysts; persistent left superior vena cava; fetal alcohol syndrome	N	Y	Developmental delay; spastic diplegia	1
13	29	Unilateral connatal cysts; aberrant right subclavian artery	Unilateral connatal cysts; aberrant right subclavian artery	Y	Y	Normal neurological outcome	4
14	27	Unilateral connatal cyst	Isolated connatal cyst	N	Y	Normal neurological outcome	5
15	30	Unilateral GM hemorrhage and connatal cyst	GM hemorrhage and ipsilateral connatal cysts	Y	Y	Normal neurological outcome	3
16	24	Increased echogenicity of the periventricular area; unilateral GM cyst	Congenital CMV leukoencephalopathy; GM cyst	Y	Y	Developmental delay	1
17	20	Bilateral connatal and GM cyst	Bilateral connatal and GM cyst; white matter disease	Y	–	TOP; PM examination	–

GA, gestational age; FH, frontal horn; LV, lateral ventricle; MRI, magnetic resonance imaging; NNU, neonatal cranial ultrasound; CMV, cytomegalovirus; GM, germinal matrix; Y, yes; N, no; TOP, termination of pregnancy; PM, postmortem.

Furthermore, periventricular venous hemorrhagic infarction is also frequently located laterally and/or inferiorly to the external angle of the frontal horns. This lesion was formerly named "grade IV cerebral hemorrhage," since the primary factor is the local subependymal venous damage which results in GM hemorrhage and, by obstructing the bleeding vein, in an upstream thrombosis and hemorrhagic infarction in the territory of the afferent tributaries [6, 7]. The venous infarct can occur from a few hours up to a few days after an initial venous infarction, and it can initially be identified as a parenchymal echogenic lesion while later presenting heterogeneous echogenicity [8].

Finally, the periventricular white matter, located above and lateral to the external angle of the frontal horns (Fig. 1f), is the focus of the most frequent form of hypoxic-ischemic lesion in the preterm infant. Recently, white matter injury (previously more commonly referred to as "periventricular leukomalacia") has been increasingly associated with the prenatal period [9, 10]. Both in the fetal and in the neonatal population, the pathogenesis of white matter injury is multifactorial and can be divided into three mechanisms: ischemia, inflammation, and excitotoxity/free radical attack [9, 11–13]. Abnormal peritrigonal hyperechogenicity caused by white matter lesions is usually heterogeneous, asymmetrical, and with sharp margins and/or a nodular aspect [14]. A relatively recent concept is that the noncystic form of white matter lesion is much more frequent than the cystic one; thus, it is not necessary to wait for the appearance of cysts to make this diagnosis [15].

In conclusion, extended routine examination of the fetal brain adding the AC to the standard axial planes may be helpful for detecting not only cortical and midline brain defects but also hemorrhagic, cystic, and/or hypoxic-ischemic anomalies.

Acknowledgements

The authors would like to thank the study participants, since without their involvement this study would not have been possible.

Statement of Ethics

Written consent was obtained for publication of the case report.

Disclosure Statement

All authors declare that they have no conflicts of interest to disclose.

Founding Sources

There was no sponsorship or funding arranged for this case report.

Author Contributions

All authors mentioned contributed substantially to the conception, case contribution, and design of the present study.

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