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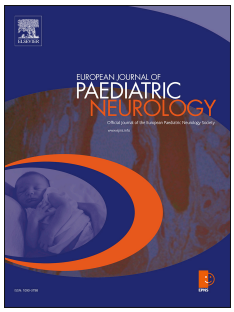

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Fetal midline anomalies: diagnosis and counselling

Part 1: Corpus callosum anomalies

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INTRODUCTION

Midline anomalies encompasses a heterogeneous group of conditions caused by an abnormal process of ventral induction after the end of primary neurulation[1] (Table 1). Classification systems for brain midline anomalies are varied and continuously improving as the underlying embryology and genetics are still partially uncovered. A relatively simple and robust classification system is based on the location of abnormalities, assuming that the large majorities of such anomalies involved different part of fetal brain. These anomalies are among the most common central nervous system (CNS) malformations diagnosed on prenatal ultrasound. Advances in prenatal imaging techniques have led to an increase in the detection rate of such anomalies since the first trimester of pregnancy although a significant proportion of them remain undiagnosed until birth. Although the most severe anomalies involving the midline, such as holoprosencephaly, can be detected on a basic examination of the fetal brain, others require a detailed assessment of cerebral structures through axial, sagittal and coronal views of the brain, thus explaining the relatively low detection rate reported in the published literature. Ultrasound is the primary technique in detecting such anomalies while fetal magnetic resonance imaging (MRI) is commonly performed to confirm the diagnosis and detect additional anomalies, especially those involving the cortical surface of the brain, which may potentially impact post-natal outcome. Neurodevelopmental outcome of cerebral anomalies involving the midline is directly related to the type of anomaly, cause and presence of associated anomalies. However, even in case of isolated anomalies prenatal counselling is challenging.

The aim of this review is to provide an up to date on the diagnosis, counselling and management of the most common supra-tentorial anomalies involving the midline and diagnosed on prenatal ultrasound.

EMBRIOLOGY

Development of midline structures begins at the end of prosencephalic maturation after primary neurulation, a series of inductive events that result in the formation of the brain and spinal cord. Prosencephalic development is characterized by three sequential events: prosencephalic formation (at the rostral end of the neural tube), cleavage and midline development[1-2]. In particular, during prosencephalic cleavage, three main splitting events occurs: horizontal, to form the paired optic vescicles, olfactory bulbs and tracts, transverse, in which telencephalon separates from diecephalon and sagittal, to form the cerebral hemispheres, lateral ventricles and basal ganglia. Prosencephalic development is characterized by appearance of three plates of tissue: the commissural, the chiasmatic and the hypothalamic plates. These structures are fundamental in the development of the corpus callosum (CC), cavum septum pellucidi (CSP), optic nerve chiasm and hypothalamic

structures[1]. Formation of the main cerebral commissures, including CC, anterior and the hippocampal commissures, involves multiple steps[3]. The CC development is not completed in utero but continues during neonatal period and infancy[4].

ASSESSMENT OF SUPRATENTORIAL MIDLINE STRUCTURES IN THE FETUS

Ultrasound assessment of fetal CNS is feasible since the first trimester of pregnancy although a precise assessment of intra-cranial structures is possible only from the second trimester onwards, at the time of the anomaly scan. Transabdominal sonography is usually the technique of choice to perform a basic examination of fetal CNS, while transvaginal ultrasound is commonly used to acquire coronal and sagittal views of the brain which can help in the differential diagnosis, but which are not easy to obtain with a trans-abdominal approach.

According to the International Society of Ultrasound in Obstetrics and Gynecology, a basic examination of supra-tentorial brain structures should include the visualization of two axial planes, trans-ventricular and trans-thalamic[5]. The structures that should be noted in the routine examination include the interhemispheric fissure, frontal horns of the lateral ventricles, CPS, thalami and posterior horn of the ventricles. Interhemispheric fissure appears as an echogenic line starting from the frontal part of the calvarium and it commonly visible since 8-9 weeks of gestation. Frontal horns of the lateral ventricles appear as two comma-shaped fluid filled structures, a well defined lateral wall, and medially are separated by the CSP. CSP is a fluid filled cavity between two thin membranes which undergoes obliteration in late pregnancy or in the early neonatal period. CSP can be detected since 16 weeks of gestation and should be always visible between 18 and 37 weeks (Figure 1). Visualization of the CSP is fundamental to assess the integrity of CC, which cannot be identifies on axial views of the brain but require acquisition of sagittal and coronal planes. Recently, ultrasound assessment of the anterior complex, defined as the group of all the anatomical structures visible in a routine trans-ventricular plane of the fetal brain, has been proposed to improve the detection rate of supra-tentorial midline anomalies[6].

ANOMALIES OF THE CORPUS CALLOSUM: COMPLETE AND PARTIAL AGENESIS

1. Diagnostic features and prevalence

The corpus callosum (CC) is the largest white matter commissure of the human brain; it contains about 200 million axons connecting the left and the right cerebral hemispheres with a fundamental role in the integration of sensory, motor, visuomotor, and cognitive processes[7-8].

CC has four segments: the rostrum, genu, body and splenium; the narrowing between the body and splenium is called the isthmus. The corpus callosum develops between 8 and 20 weeks' gestation with a cranio-caudally progression with the exception of the most anterior part called the rostrum that develops later[9], although other studies suggest that CC development progresses bidirectionally[10-13].

There is wide variation in the terminology used to describe CC abnormalities, and such differences should be considered when assessing previous reports of outcomes in these conditions.

The most common anomalies involving the CC are:

- Agenesis (ACC), either complete (cACC) or partial (pACC)
- Hypoplasia, characterized by the presence of a fully formed but thinner CC
- Hyperplasia, characterized by the presence of a fully formed but tick CC
- Dysplasia, defined as a CC with a hump shape

Hypo-, hyper- and dysplasia of the CC are rarely diagnosed before birth, and most of the available series focus upon cACC or pACC.

ACC is a rare clinical condition in which the main commissural pathway connecting the two homologous cortical hemispheres is partially (pACC) o completely (cACC) absent[14].

ACC is one of the most common congenital brain anomalies with an estimated incidence ranging from 1.8 per 10000 in the general population and 230-600 per 10000 in children with neurodevelopmental disabilities[15-17]. However, the actual incidence of ACC is difficult to estimate because of selection bias in reported series. The best available data probably come from the California Birth Monitoring Defect Program and suggest a prevalence of about 1.4 and 0.4 per 10,000 live births for ACC and hypoplasia of corpus callosum respectively[16]. This figure may however be an underestimate of the real incidence as it is likely that in this study a large proportion of asymptomatic individuals escaped detection.

ACC is associated with a large spectrum of CNS and extra-CNS anomalies in about 45% of cases, including neuronal migration disorders, interhemispheric cysts, posterior fossa malformations,

hypertelorism, cleft/lip palate, musculoskeletal, genitourinary, gastrointestinal disorders and congenital heart[14,18].

2. Etiology and pathophysiology

ACC can be determined by a large variety of conditions, such as genetic, infectious, vascular or toxic.

Chromosomal anomalies are commonly associated ACC, either complete or partial[14,19]. The most common chromosomal anomalies associated with ACC include trisomy 18, trisomy 13, and mosaic 8.The risk of abnormal karyotype is higher in fetuses presenting with ACC associated with other CNS and extra-CNS anomalies and has been reported to be around 18%[14].

In isolated cases, abnormal karyotype occurs in 4.8% (95% CI 2.2–8.4) of cACC and in 7.5% (95% CI 2.0–15.9) of pACC respectively, thus highlighting the need for prenatal assessment of fetal karyotype also in these cases.

Chromosomal microarray analysis (CMA) is a DNA-based method of genetic analysis, which can identify clinically significant chromosome abnormalities (gain and losses of DNA) that are below the resolution of conventional chromosome analysis, known as copy number variations (CNV)[20-21]. Fetuses with central nervous system (CNS) anomalies and normal karyotype have been shown to have a significantly higher risk of genetic anomalies at CMA analysis; furthermore, a higher incidence of CMA anomalies has been reported in children presenting with neuropsychological disabilities. In fetuses with isolated ACC, the rate of significant CNVs in fetuses with isolated ACC (either cACC or pACC) and normal karyotype has been reported to be 5.7% (95% CI, 1.3–13.1), thus highlighting the need for CMA even in case of isolated ACC on ultrasound. A recent joint committee opinion of the American College of Obstetricians and Gynecologists (ACOG) and the Society of Maternal-Fetal Medicine (SMFM) recommended that CMA analysis should be performed in fetuses undergoing invasive procedures for major structural anomalies detected on ultrasound[20].

Genetic factors are among the most common causes of ACC with more than 200 syndromes reported to be associated with this anomaly, involving either autosomal dominant, recessive and X-linked mode of inheritance. The most common genetic syndromes associated with ACC are Aicardi (ACC, chorioretinal abnormalities, infantile seizures and mental retardation), Anderman (ACC, progressive motor-sensory neuropathy and mental retardation) and Acrocallosal (ACC, polydactyly, craniofacial anomalies, mental retardation) syndromes[22-24].

Tubulinopathies, Smith-Lempli-Optiz syndrome, L1 syndrome can also be associated with ACC[25].

ACC has been also associated with mutation of FOXG-1 gene on chromosome 1 which leads to a peculiar phenotype characterized by callosal agenesis and delayed myelinization[26-27]. Children with this rare autosomal dominant disorder (also known as "atypical Rett syndrome") show neurodevelopmental delay and Rett-like features (hypotonia, motor disorders, gastroesophageal reflux disease and microcephaly)[28]. ACC is also among the most frequent CNS malformation in children with Papilllon-Leage-Psaume syndrome, an oral-facial-digital syndrome caused by OFD1 mutations[29].

Advances in genetic diagnostic techniques, such as Next-Generation Sequencing (NGS) like Whole-Exome (WES) and Whole-Genome Sequencing (WGS)[20,30], may help in determining the underlying cause of ACC especially in those cases not presenting with the classical clinical features of a syndromic condition [31] and in fetus with normal karyotype and CMA. WES allows examination of nucleotide sequence of expressed genes in the genome. Compound heterozygous variants in the CDK5RAP2 gene (also known as MCPH3, a causative gene for autosomal recessive primary microcephaly), ZBTB20, C12ofr57 and other gene mutations[30,32] have been described in patients with ACC[33-36]. These techniques, because ACC genetic heterogeneity, may play an important role in identifying cases affected by ACC at higher risk of intellectual disability. Despite this, identification of the underlying cause of ACC is achieved in less than 50% of the cases.

Finally, ACC had been reported to occur in in association with congenital infections, such as Cytomegalovirus[37-39], Toxoplasmosis[40], Rubella[38] and Influenza virus[41] but they are commonly associated with other CNS and extra CNS anomalies, while the incidence of infection in isolated ACC is negligible.

3. Prenatal diagnosis: ultrasound and fetal MRI

On ultrasound, the CC can be identified in a median sagittal view of the fetal brain as a hypoechoic structure located between the cavum septi pellucidi (CSP) and the cingulate gyrus, demarcated by two echogenic lines[42] (Figure 1). The peri-callosal artery, which develops in close association with the CC, can also act as a useful marker on 2D ultrasound imaging.

Prenatal diagnosis of ACC on ultrasound is challenging and it is based upon the complete (cACC) or partial (pACC) non-visualization of the CC on midsagittal view of the fetal head[14,43-44]. Despite its importance, a direct visualization of the CC is not required on the standard examination of the fetal CNS performed at the time of the routine scan[14], thus explaining the relatively low detection rate for ACC, in particular for pACC, reported in the recently published literature.

Trans-vaginal ultrasound is commonly the technique of choice when assessing a fetus with suspected ACC in vertex position, as it allows acquisition of sagittal and coronal planes of the brain which are fundamental to diagnose the anomaly (Table 2). Abnormal course of the pericallosal artery on midsagittal views fetal brain may also help in detecting ACC (Figure 2). In cACC, the semicircular loop of the pericallosal artery is lost and the branches of the anterior cerebral artery ascend linearly, while in pACC the pericallosal artery follows the anterior part of the corpus callosum but then loses its normal course where the corpus callosum disappears posteriorly and takes an upward posterior oblique direction [9,42,45] (Figure 2). A radial disposition of the sulci on the internal aspects of the hemispheres could be also be present on mid-sagittal views of the brain.

ACC can be also suspected on axial views of the brain although most of the reported signs are not specific and are present almost exclusively in case of complete rather than partial agenesis. Absent visualization of the CSP from 18 weeks of gestation is the most common indirect sign which can raise the suspicion of ACC; it is observed only in case of cACC but is not specific for this condition as it is observed in other CNS anomalies such as holoprosencephaly, hydrocephalus, septo-optic dysplasia, schizencephaly, porencephaly and hydranencephaly[46]. When assessing the fetal brain on axial views it is important not to misinterpret the columns of the fornix, which lie at a more basal level, with CSP. Because the embryologic development of the fornix is not directly associated with that of the CC, its identification does not rule out ACC[47]. Such misinterpretation may be responsible of the higher rate of false negative diagnoses for ACC reported in the published literature.

ACC causes a peculiar rearrangement of the midline supra-tentorial cerebral structures which can be detected on ultrasound. Lack of the CC induce a widening of the interemispheric fissure and the elevation of the third ventricle. Frontal horns of the lateral ventricles are usually displaced from the midline by a paired aberrant bundle of fibers (Bundle of Probst) that fail to cross the hemispheres and run parallel to the midline assuming the shape of a bull's horn. The absence of the posterior part of the CC in complete agenesis induces a dilatation of the atria and occipital horns of the lateral ventricles known as colpocephaly, which can on the standard axial view at the trans-ventricular level (Figure 2).

These signs are observed in case of cACC, while in partial agenesis, assessment of fetal brain on axial view can be unremarkable.

3D ultrasound has recently shown to provide several advantages in the evaluation of the anatomy of intracranial structures such us the CC allowing a multiplanar assessment of the fetal brain starting from an axial view of the fetal head[48-55].

The presence of associated anomalies is one of the major determinants of the prognosis of fetuses affected by ACC. These may include abnormalities of cortical development, which can only be

assessed with advancing gestation. Serial follow-up scan during pregnancy are therefore warranted to search for cerebral and extra-cerebral abnormalities that may not be evident during the second-trimester examination. However, there is no agreement in the literature regarding the timing and frequency of such follow-up scan in fetuses with ACC.

A list of the ultrasound signs of ACC in the different imaging plane is shown in Table 2.

When assessing fetuses with suspected callosal agenesis, it is important to state that ultrasound signs suggestive of ACC can change with gestation.

In a retrospective series of 54 cases affected by complete and partial ACC, colpocephaly was present in 20.6% of fetuses scanned before weeks and in 68.6% of those after 24 weeks of gestation, while the corresponding figures for an atrial width >10 mm were 73.5% and 25.7% of cases respectively.

CSP was present and visible in 63% of cases affected by pACC, while in 33.3% there was neither ventriculomegaly nor absence of CSP[43].

Fetal MRI is commonly performed in fetuses with suspected CNS anomalies and has been reported to add additional information compared to ultrasound which may significantly impact prognosis. Although the actual contribution of MRI compared to ultrasound in fetal CNS anomalies is difficult to quantify due to the large heterogeneity among the previously published studies, MRI is routinely used in clinical practice to confirm diagnosis and to look for associated anomalies in case of ACC. In a recent systematic review including only fetuses with isolated ACC, associated anomalies not detected on ultrasound were diagnosed on fetal MRI in 7.83% (95% CI, 1.2–19.6) and in 11.86% (95% CI, 3.2–24.9) of cACC and pACC. The large majority of such additional anomalies included neuronal migration disorders, which can be detected preferentially from the third trimester of pregnancy. In this scenario, it might be reasonable to arrange a fetal MRI in the third trimester of pregnancy to confirm that ACC is truly isolated, even in case MRI was performed earlier in gestation to confirm the diagnosis.

More recently, a secondary analysis of the Meridian Study, a multicenter prospective cohort study involving over 800 pregnancies with a fetal brain abnormality undergoing ultrasound and MRI within 14 days, the diagnostic accuracy for detecting ACC was 40.0% for ultrasound and 92.7% for MRI. More importantly, prognostic information given to the women changed in 45.6% cases after MRI and its overall effect on clinical management was 'significant', 'major' or 'decisive' in 44.3%[56]. Although affected by the small sample size and lack of accurate description on how ultrasound assessment of the brain was performed, this data suggests a potential contribution of fetal MRI in

the diagnostic algorithm of fetuses affected by ACC, but it requires confirmation in larger and appropriately designed series.

As reported from Paladini et al, the MERIDIAN trial does not describe the ultrasound approach whose diagnostic accuracy was compared to fetal MRI. It is underlined that MRI should represent a second-line resource to be employed in selected cases, and only after expert neurosonography[57].

However, even in cases of a prenatal diagnosis of isolated anomaly, the risk of ACC being not truly isolated is relatively high, with additional anomalies detected only at postnatal imaging and/or clinical examination reported to occur in 5.5% (95% CI 2.4–9.7) and 15.0% (95% CI 6.7-24.6) respectively, thus highlighting the need for a thorough post-natal assessment of these children.

4. Neurodevelopmental outcome

Assessing neurodevelopmental outcome in children affected by ACC is challenging. The main determinant of adverse outcome in children with ACC is the presence of associated CNS anomalies which can occur in about 45% of cases. However, even in case of a prenatal diagnosis of isolated ACC, the risk of additional anomalies detected only after birth is about 5% in cACC and 15% in pACC.

The wide heterogeneity in inclusion criteria, antenatal imaging protocol adopted, neurodevelopmental tool used and time of follow up among the include studies does not allow to extrapolate an objective evidence on the actual burden of neurodevelopmental disabilities affecting fetuses with isolated ACC. Post-natal studies reports a high rate of abnormal neuropsychological outcome in children with ACC, such as intellectual abilities, difficulties in pragmatic language skills and impaired mathematics, expressive and receptive language, visual and spatial reasoning, and attentional skills. However, they are biased by the inclusion of mainly symptomatic cases, thus potentially overestimating the figures for intellectual disabilities reported. The term neurodevelopmental outcome is also misleading and inappropriate when dealing with brain anomalies, because it includes a wide spectrum of signs that are not always easily measured and that represent a continuous interaction between pathological, environmental, and adaptive factors. Time at assessment represent another potential confounder, early neuropsychological examination may not accurately predict neurodevelopmental outcomes during later life[58], while late assessment may be biased by the influence of socio- economic, parenting, environmental, and educational factors, which may significantly affect developmental measures, especially when looking for subtle differences[59]. Finally, assessment of a control population may represent another considerable source of bias when assessing the diagnostic performance of children affected by brain anomalies. The risk for a given abnormal neurodevelopmental measure is commonly computed upon a control

population which should theoretically include "health" individuals, free from the anomaly and implies the knowledge of how this measure is abnormal in the cohort not affected by the anomaly. However, some series reported rates of abnormal neurodevelopmental outcome as high as 10%[60], thus questioning whether different populations should be compared to estimate the risk of a given neuropsychological measure.

A recent systematic review reported that 76.0% (95% CI 64.3–86.1) of children with a prenatal diagnosis of isolated cACC confirmed at birth had a normal neurodevelopmental outcome, 16.0% (95% CI 7.6–26.8) showed borderline to moderate impairment while 8.2% (95% CI 2.5–16.8) severe disabilities (Table 3). When looking at the different neurodevelopmental abilities, gross and fine motor skills were abnormal in 4.4% (95% CI 0.6-11.3) and 11.0% (95% CI 4.1-20.6) of cases, while cognitive anomalies in 15.2% (95% CI 6.9–25.9). Epilepsy occurred in 6.8% (95% CI 1.7–14.9) of isolated cACC, while the corresponding figures for abnormal sensory, visual and coordination skills were 0% (95% CI 0-9.2), 15.8% (95% CI 4.3-32.9) and 9.5% (95% CI 3.2-18.7). Finally, abnormal language was detected in 8.0% (95% CI 2.1-17.3) of cases.

In children with a prenatal diagnosis of isolated pACC confirmed at birth, a normal neurodevelopmental outcome was observed in 71.4% (95% CI 53.1–86.7) of cases, a mild to moderate impairment in 14.9% (95% CI 4.2–30.7) while severe disabilities in 12.5% (95% CI 2.9–27.5). When looking at the individual component neurodevelopmental outcome, gross and fine motor skills were abnormal in 0% (95% CI 0-23.0) and 11.7% (95% CI 0.9-32.1), while cognitive skills in 17.3% (95% CI 3.0-39.7). Epilepsy occurred in 16.1% (95% CI 2.0-53.2) of cases with isolated pACC while there was no case of impaired sensory or visual skills although the number of cases included was very small. Finally, coordination and language were abnormal in 11.7% (95% CI 0.9-32.2) and 17.3% (95% CI 3.0-39.7) of cases.

However, these figures should be interpreted with caution; differences in type of assessment, length of follow-up and neurodevelopmental test used may have represented a considerable source of bias in estimating such figures. Furthermore, although cases included in that systematic review were considered to be isolated on the basis of standard karyotype and normal pre and post-natal imaging, it may be entirely possible that children carrying chromosomal anomalies identifiable only at CMA analysis or those with genetic syndrome not showing clear phenotypic anomalies were included in this cohort, thus potentially biasing the figures for abnormal neurodevelopmental measures reported.

These results are in contrast those reported in individuals undergoing commissurotomy which show a disconnection syndrome[61], with complete lack of interhemispheric integration of sensory and motor information. Children with ACC usually show a normal ability to make comparison in particular of simple and familiar information. One theory to explain this preserved capacity is that this information could be transferred via others connecting pathways, such as the anterior commissure[3], although this capacity may be limited by task complexity. Regarding language abilities, children with ACC have intact general naming[62-63], receptive language[63-64] and lexical reading skills[65], while they could be impaired in the comprehension of syntax and linguistic pragmatics (such as idioms, proverbs, and narrative humor)[66-67]. They could also show difficulty in expressive language, in particular in the verbal expression of emotional experiences. Parents of children affected by ACC describe poor personal insight, social judgement and planning deficit, with poor communication of emotions that interfere with the daily lives of these children[68-70], leading to an overlap with the diagnostic criteria for autism. ACC has also been linked with schizophrenia[71-73], and individuals with this condition have been reported to have major morphological anomalies or microstructural changes in the CC on MRI[74].

5. Pre- and post-natal management

Fetuses suspected to be affected by ACC on ultrasound should be referred to centers with high expertise in the diagnosis and management of this anomaly for a detailed neurosonogram, to confirm the diagnosis and look for associated CSN and extra CNS anomalies, which can occur in almost half of cases and which significantly impact the prognosis of these children (Fig. 4). Prenatal invasive diagnosis to rule out chromosomal anomalies should be offered to parents in view of the high risk of aneuploidies even in fetuses presenting with isolated ACC on the scan. CMA should be also performed to rule out significant CNVs which can be associated with ACC in about 6% of fetuses with isolated ACC and normal standard karyotype.

NGS “panels”, exome and whole genome sequencing have an important role in this diagnostic iter.

Serial follow up scans during pregnancy are warranted in order to look for associated anomalies which can become evident only later on in gestation. Fetal MRI should be performed, if not at the time of the diagnosis, in the third trimester of pregnancy in order to detect anomalies of the cortical surface which are usually not easily detected on ultrasound. However, parents should be counselled that prenatal imaging is not completely able to rule out all anomalies and that a significant proportion of these may become evident only after birth.

Post-natal assessment should include a MRI scan and a thorough examination by a pediatric dismorphologist in order to rule out genetic syndromes which are common in case of ACC.

Children should be undergo a strict follow-up in order to early identify neuropsychological disorders which can be amenable of supportive therapy. Treatment in symptomatic children include antiepileptic drug in those presenting epilepsy, psycho and speech therapy.

OTHER DEVELOPEMNTAL ANOMALIES OF THE CORPUS CALLOSUM

1. Corpus callosum hypoplasia

CC hypoplasia is defined as complete thinning of the CC with intact morpphology[15,75].

CC hypoplasia is a rare developmental disorder, which can recognize different etiologies such as radiations, alcohol, teratogens, infection, compression due to intra-cranial masses, ischemia and metabolic disorders[76]. CC hypoplasia is commonly associated with other CNS and extra-CNS anomalies while isolated cases have been rarely reported in the published literature.

Prenatal diagnosis of CC hypoplasia is challenging and can be suspected when the length of the CC, measured in the midsagittal plane of the fetal brain, is below the 10th centile for the gestational age[45,77,78]. Neurodevelopmental outcome of children presenting with CC hypoplasia is variable and strictly dependent upon the presence of co-existing CNS anomalies, especially microcephaly. Although asymptomatic cases have been sporadically reported, mental and psychomotor delay are common in children affected by CC hypoplasia especially when associated with other CNS anomalies[79-80]. Moreover, literature reports a straight correlation of this finding with autism. Casanova et al. in a series of 17 autistic adolescents report a smaller CC in autistic individuals when examined against controls [81].

2. Corpus callosum dysgenesis and dysplasia

CC dysgenesis and dysplasia refer to rare developmental anomalies of the CC characterized by an abnormal shape and structure, which can co-exist with callosal hypoplasia and other CNS and extra-CNS anomalies. It may be due to genetic, infective, metabolic, environmental or extrinsic causes such lipoma, interhemispheric cyst or disorders of neuronal migration[82,83]. In clinical practice, it is also used as a synonym of ACC either complete or partial although they represent separate entities with different etiology and prognosis

CC dysplasia is a common finding in children with Piridoxine-dependent epilepsy (PDE), a rare autosomal recessive epileptic encephalopathy[84] characterized by seizures starting in the neonatal period, resistant to common antiepileptic drugs and controlled by a daily administration of pyridoxine.

Prenatal diagnosis of CC dysplasia and dysgenesis is not commonly reported in the published literature and it is commonly detected when other CNS and extra-CNS anomalies co-exist. Abnormal shape usually associated with hypoplasia of the CC are the most common ultrasound findings.

2. Hyperplasia of the corpus callosum (thick CC)

Increased thickness of the CC is a rare developmental anomaly rarely reported on pediatric brain imaging. Although it can present as an isolated finding, it is usually part of complex developmental anomalies involving different organ systems and has been described in children with Cohen Syndrome[85] in association with microcephaly and in cases affected by neurofibromatosis together with macrocephaly and white matter abnormalities[86].

Neurodevelopmental outcome of children with a tick CC is challenging. The anomaly has been only sporadically reported prenatally and the large majority of diagnosed cases presents with associated major CNS anomalies which significantly impact the prognosis In a recent series of 9 cases presenting with tick CC on prenatal imaging, CC thickness normalized during the third trimester of pregnancy and neurodevelopmental outcome (available for 6 patients) was normal[87].

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Table 1. Disorders of prosencephalic development[1]

Prosencephalic Formation	Aprosencephaly Atelencephaly
Prosencephalic Cleavage	Holoprosencephaly Holotelencephaly
Midline prosencephalic development	Agenesis of corpus callosum Agenesis of septum pellucidum (± cerebral clefts) Septooptic dysplasia Septooptic hypothalamic dysplasia

Table 2. Ultrasound diagnosis of cACC in the different imaging planes

US plane	Complete ACC
Mid sagittal view	***Primary sign*** ✓ Non-visualization of CC ***Secondary signs*** ✓ Visualization on abnormal course of pericallosal artery ✓ Radial disposition of the sulci on the internal aspecs of the hemisphere
Axial view	***Primary sign*** ✓ Non-visualization of CSP from 18 weeks of gestation ***Secondary signs*** ✓ Frontal horns displaced from the midline ✓ Colpocephaly
Coronal view	**Primary sign** ✓ *Non-visualization of CSP* **Secondary signs** ✓ *Frontal horns displaced from the midline*
	Partial ACC
Mid sagittal view	***Primary sign*** ✓ Partial visualization of the CC (missing splenium) ***Secondary signs*** ✓ Shorten course of pericallosal artery
Axial view	***Primary sign*** ✓ Abnormal shape of the CSP ✓ Absent CSP (not common)
Coronal view	***Primary sign*** ✓ Partial visualization of the CC (missing splenium)

Table 3. Incidence of abnormal neurodevelopmental outcome in children with isolated ACC (adapted from D'Antonio *et al.)*

Neurodevelopmental outcome	Pooled proportions (95% CI)
Complete ACC	
Normal	76.04 (64.3-86.1)
Borderline/Moderate	16.04 (7.6-26.8)
Severe	8.15 (2.5-16.8)
Gross motor	4.40 (0.6-11.3)
Fine motor	10.98 (4.1-20.6)
Cognitive	19.51 (10.1-31.1)
Epilepsy	6.80 (1.7-14.9)
Intelligence	21.30 (11.5-33.2)
Sensory	0 (0-9.2)
Visual	15.84 (4.3-32.9)
Coordination	9.50 (3.2-18.7)
Language	8.02 (2.1-17.3)
Partial ACC	
Normal	71.42 (53.1-86.7)
Borderline/Moderate	14.92 (4.2-30.7)
Severe	12.52 (2.9-27.5)
Gross motor	0 (0-23.0)
Fine motor	11.74 (0.9-32.1)
Cognitive	17.25 (3.0-39.7)
Epilepsy	16.11 (2.53.2)
Intelligence	12.40 (1.1-33.1)
Sensory	0 (0-23.0)
Visual	0 (0-23.0)
Coordination	11.74 (0.9-32.1)
Language	17.25 (3.0-39.7)

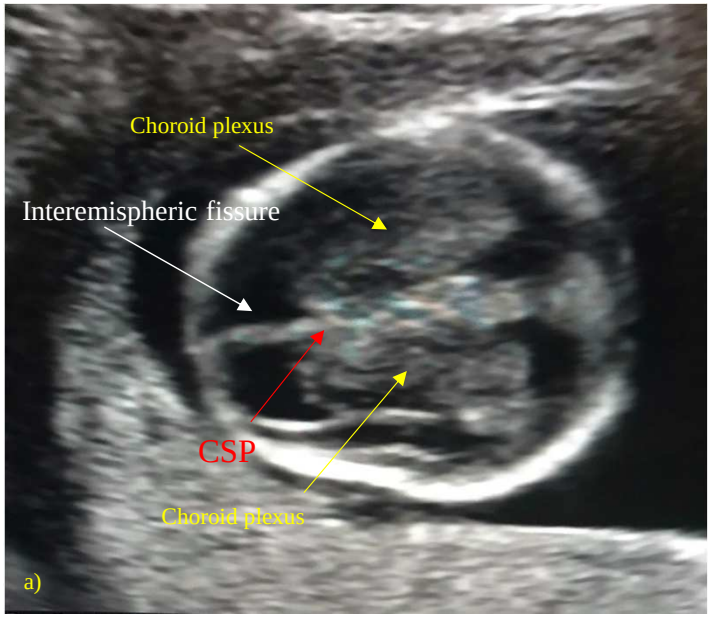
Figure legend

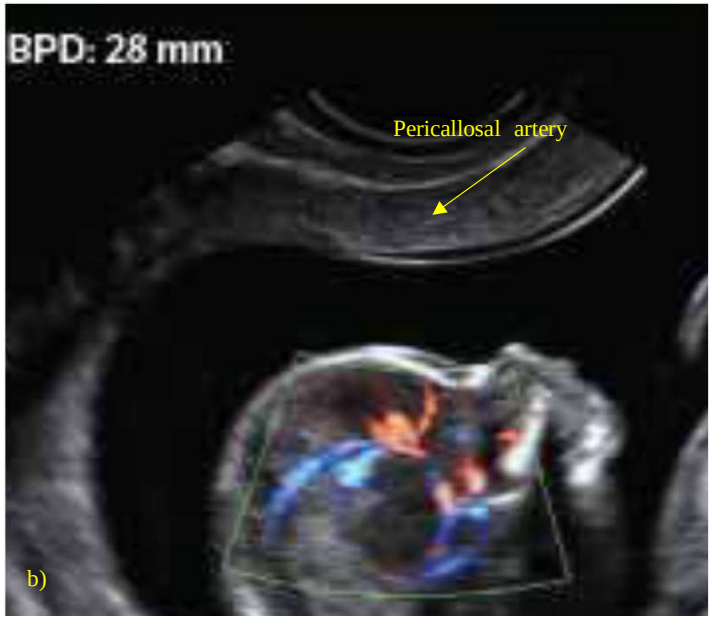
Figure 1. Normal brain anatomy in the first (a,b) and second (c,d,e) trimester of pregnancy.

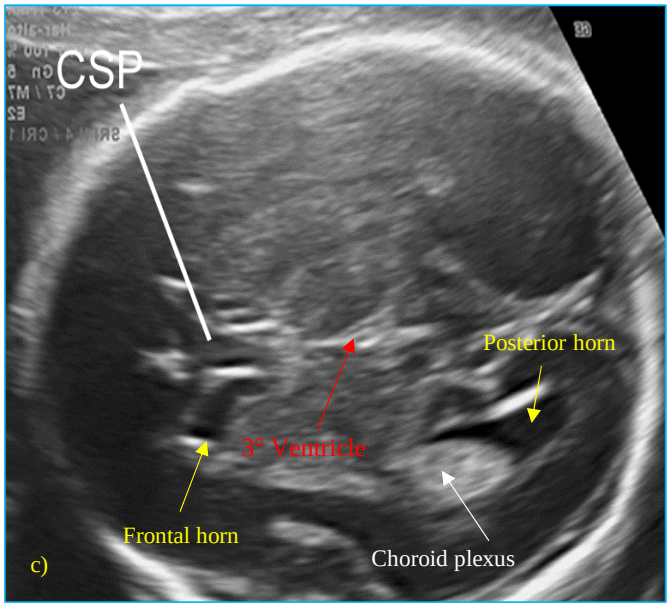
Figure 2. Sonography of a normal brain (a,b,c,d,e) and of a fetus affected by complete ACC (f,g,h,i) at the time of the anomaly scan (21 weeks of gestation) in axial, sagittal and coronal views. With complete agenesis, the anatomical complex formed by CC and CSP is completely absent, the inter-hemispheric fissure is enlarged, and the frontal horns (FH) are more separated than normal.

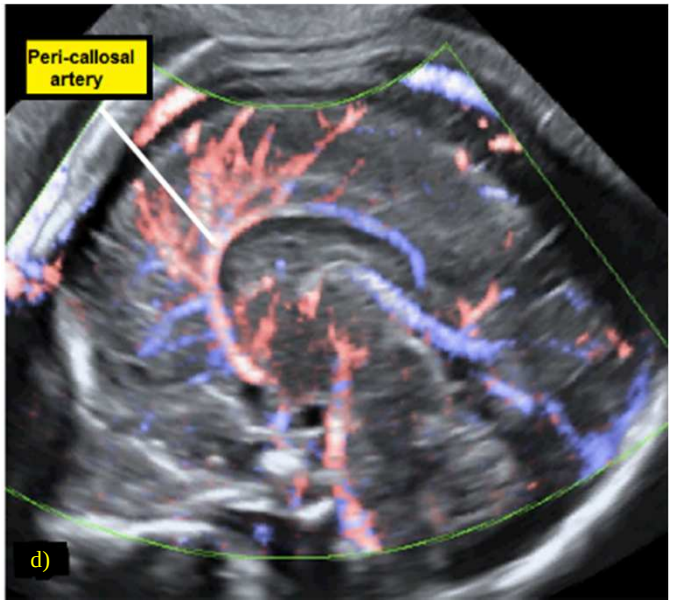
Figure 3. Sonography of a normal brain (a,b,c,d,e) and of a fetus affected by partial ACC at the time of the anomaly scan (21 weeks of gestation) in axial, sagittal and coronal views. In pACC, the findings are subtler compared to cACC, and the CC and CSP are present but shortened (3v = third ventricle). In sagittal view, a small portion of the CC can be identified. Please note the abnormal shape of the CSP with its antero-posterior and transverse diameters almost equal in size.

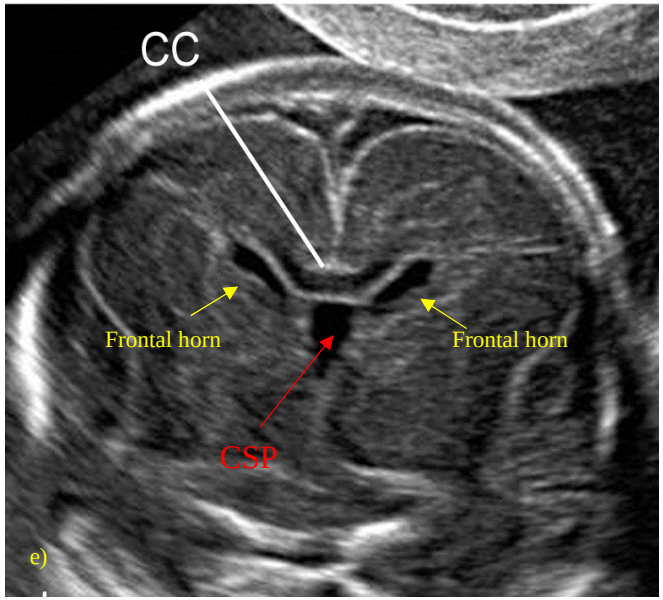
Figure 4. Pre-natal management of fetuses suspected to be affected by ACC

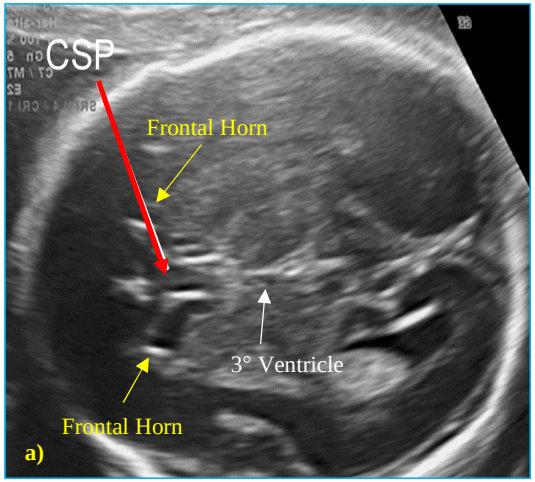

Choroid plexus
Interemispheric fissure
CSP
Choroid plexus
a)

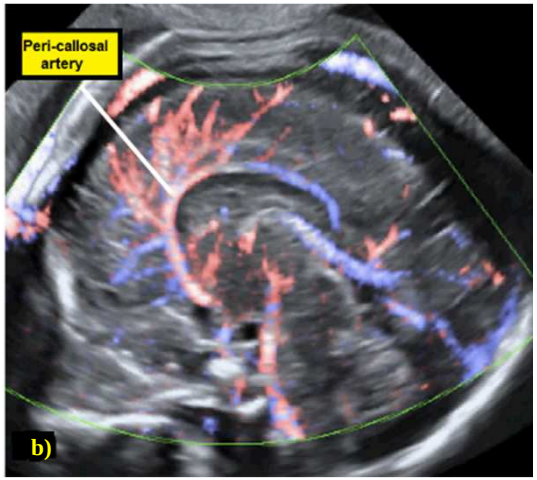

BPD: 28 mm
Pericallosal artery
b)

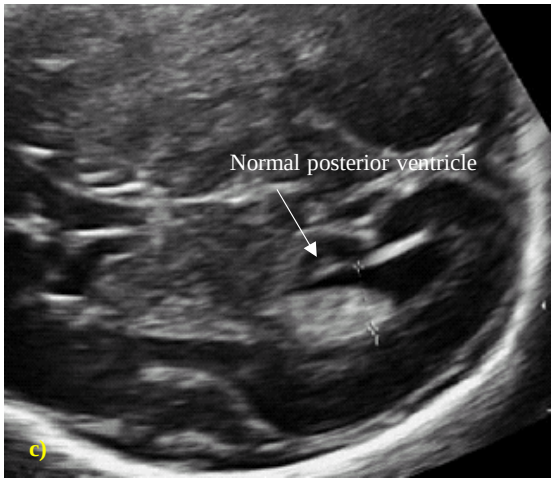

CSP
Posterior horn
3° Ventricle
Frontal horn
Choroid plexus
c)

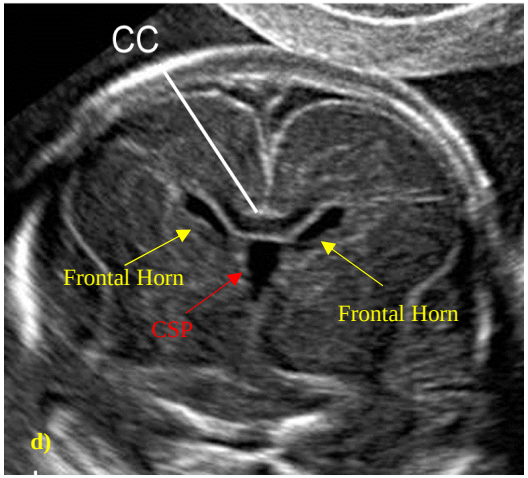

Peri-callosal artery
d)

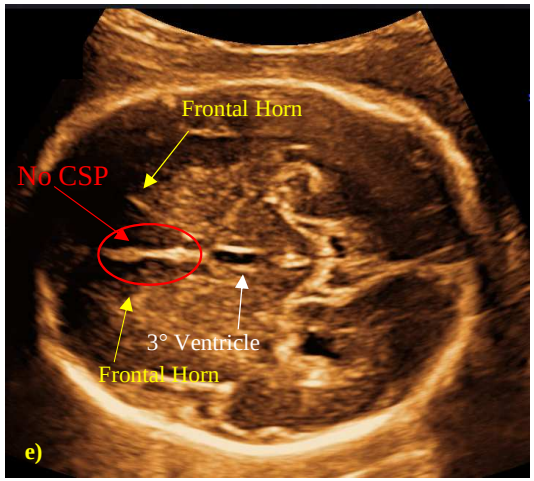

CC
Frontal horn
Frontal horn
CSP
e)

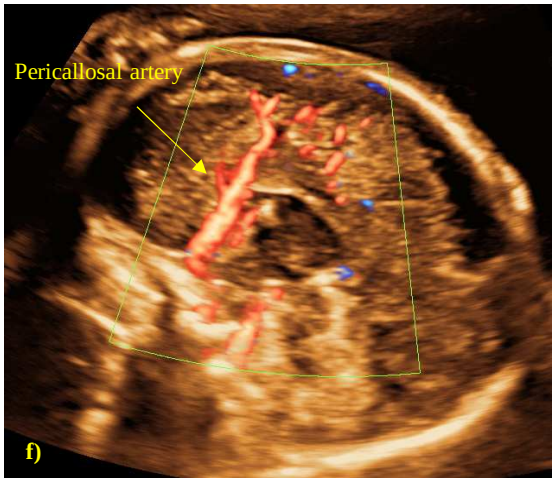

CSP
Frontal Horn
3° Ventricle
Frontal Horn
a)

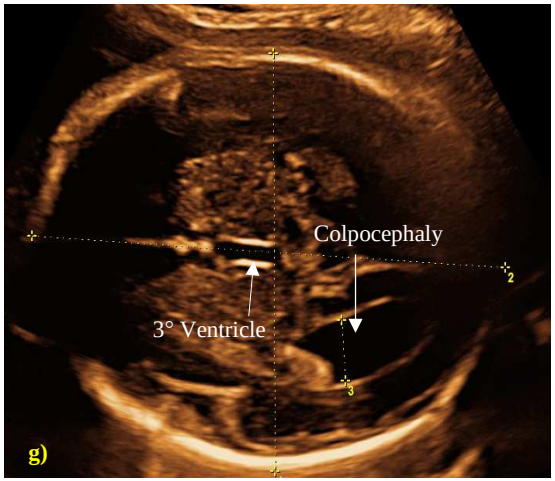

Peri-callosal artery
b)

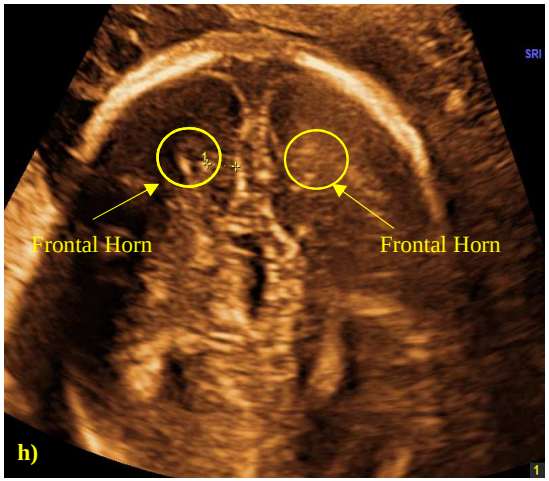

Normal posterior ventricle
c)

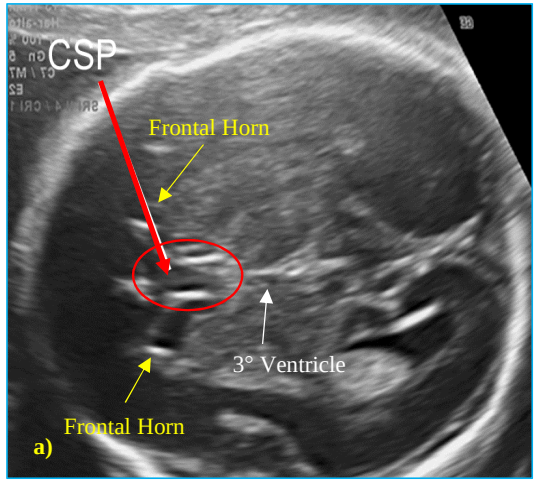

CC
Frontal Horn
CSP
Frontal Horn
d)

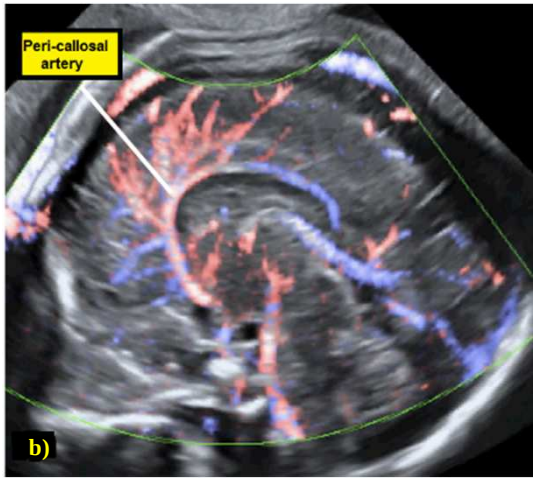

Frontal Horn
No CSP
3° Ventricle
Frontal Horn
e)

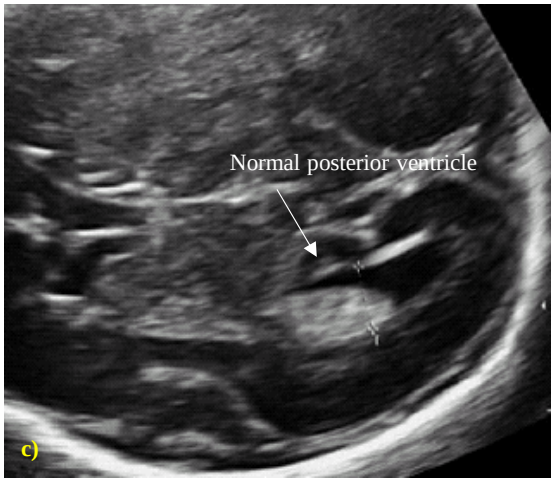

Pericallosal artery
f)

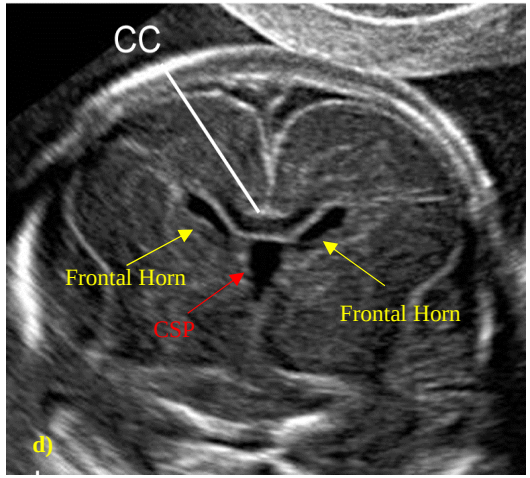

Colpocephaly
3° Ventricle
g)

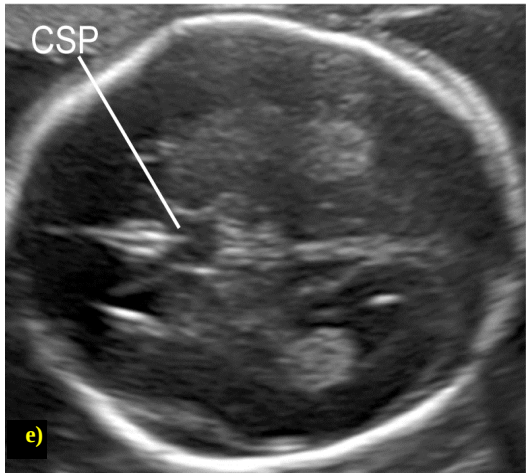

Frontal Horn
Frontal Horn
h)

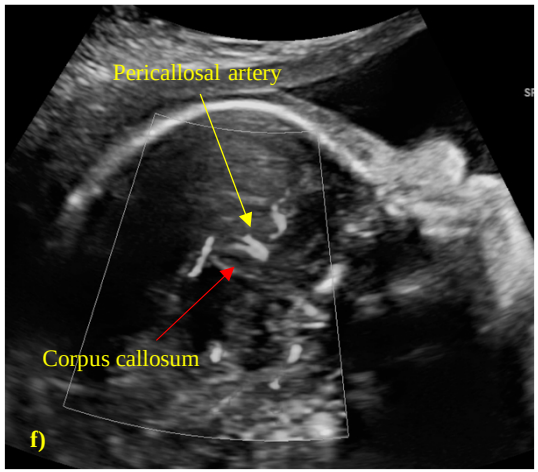

CSP
Frontal Horn
3° Ventricle
Frontal Horn
a)

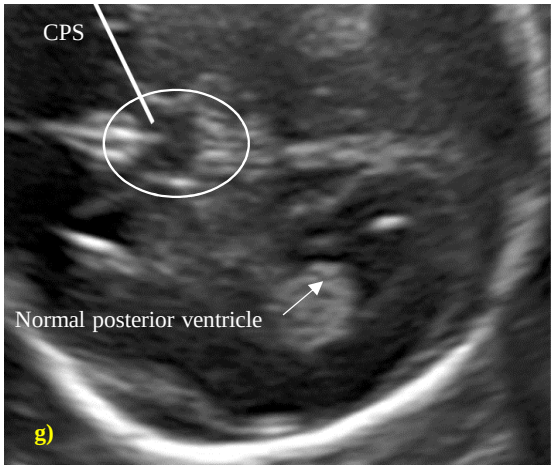

Peri-callosal artery
b)

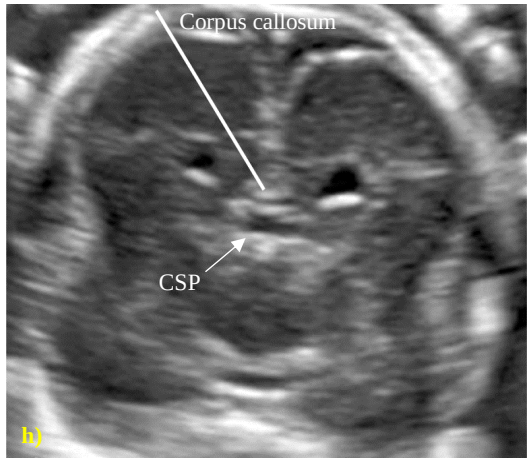

Normal posterior ventricle
c)

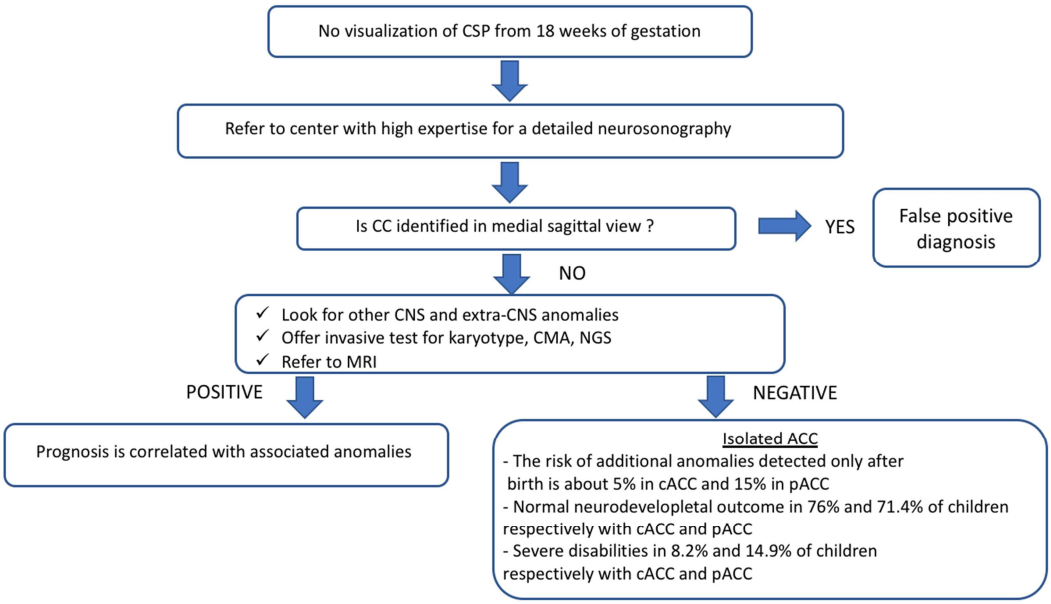

CC
Frontal Horn
CSP
Frontal Horn
d)


CSP
e)


Pericallosal artery
Corpus callosum
f)


CPS
Normal posterior ventricle
g)


Corpus callosum
CSP
h)



Highlights

- Midline anomalies are conditions caused by an abnormal process of ventral induction.
- These anomalies could be diagnosed on prenatal ultrasound.
- Neurodevelopmental outcome is directly related to the type and cause of anomaly.
- Neurodevelopmental outcome is related to associated anomalies.