Enlarged posterior fossa on prenatal imaging: differential diagnosis, associated anomalies and postnatal outcome

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Abstract
Introduction. The primary aim of this study was to ascertain the prevalence of the individual conditions and of associated anomalies in fetuses with the prenatal diagnosis of enlarged posterior fossa (PF) and to explore the diagnostic accuracy of ultrasound in these anomalies. The secondary aim was to evaluate the postnatal outcome of children affected by PF anomalies. Material and methods. All fetuses with enlarged PF detected by prenatal sonography at a referral center from 2001 to 2015 were analyzed retrospectively. Some were also studied by fetal magnetic resonance imaging (MRI) or volume ultrasound examinations. Fetal sonographic and MRI were compared using following classification: Dandy–Walker malformation (DWM); megacisterna magna (MCM); Blake's pouch cyst; isolated vermian hypoplasia; vermian agenesis; PF arachnoid cyst (AC); and cerebellar hypoplasia (CH). Results. The ultrasound diagnoses of the 69 fetuses were as follows: MCM (n = 29; of these isolated n = 15), DWM (n = 28, isolated n = 4), vermian hypoplasia (n = 5, isolated n = 4), Blake's pouch cyst (n = 4, isolated n = 1), CH (n = 2; none isolated) and AC in the PF (n = 1, isolated). Thirteen of the 41 karyotyped fetuses were aneuploid, including seven with DWM. Associated malformations were found in 37/69 cases. There were 39 live births, including 11 with confirmed DWM, six of whom show a normal development. There were eight false-positive prenatal diagnoses (or resolution until birth) of “enlarged PF”: three with Blake's pouch cyst, two with MCM and one with vermian hypoplasia. Conclusions. An enlarged PF requires specific diagnoses for the best possible counseling. The term “Dandy–Walker variant” should not be used anymore. Isolated MCM and Blake’s pouch cyst can either resolve or be normal variants, but may also indicate the presence of a more severe anomaly or associated malformations.

Abbreviations: AC, arachnoid cyst; BPC, Blake’s pouch cyst; BV, brainstem-vermis; CH, cerebellar hypoplasia; DWM, Dandy–Walker malformation; MCM, megacisterna magna; MRI, magnetic resonance imaging; PCH, ponto-cerebellar hypoplasia; PF, posterior fossa; VH, vermian hypoplasia.

Introduction
Posterior fossa malformations encompass a heterogeneous spectrum of conditions characterized by abnormal development of the posterior and anterior membranous areas. Prenatal ultrasound imaging can reveal posterior fossa (PF) malformations relatively easily. However, antenatal counseling is still challenging due to different nomenclatures, diagnostic criteria and outcome measures.
Some published studies do not differentiate cases with and without associated anomalies, but postnatal outcome of children with PF malformations is largely influenced by the presence of such anomalies. Accurate prenatal diagnosis of PF anomalies is required to assess the risk for long-term disabilities.

PF anomalies are usually suspected when an enlarged cisterna magna is detected at the scan. However, the standard axial plane used for second trimester screening may be insufficient when dealing with these conditions, and anomalies with different postnatal outcomes may share the same sonographic appearance. Fetal magnetic resonance imaging (MRI) is often carried out once an anomaly in the PF is diagnosed by ultrasound, but its real contribution in the case of isolated PF malformations is still under debate.

Two recent systematic reviews suggested that the risk of associated chromosomal or structural anomalies and abnormal postnatal outcome was high in fetuses with isolated Dandy–Walker malformation (DWM), but low in isolated megacisterna magna (MCM) and Blake’s pouch cyst (BPC) (1, 2).

The primary aim of this study was to ascertain the prevalence of the individual conditions and of associated anomalies in fetuses with a prenatal diagnosis of enlarged PF and to explore the diagnostic accuracy of ultrasound to correctly identify these anomalies. The secondary aim was to evaluate the postnatal outcome of children affected by PF anomalies.

Material and methods

A fetal imaging and diagnostic database at a tertiary referral center for fetal-maternal medicine was searched for fetuses with enlarged PF to identify all cases diagnosed between 2001 and 2015. This unit has a catchment population of about 2.5 million inhabitants and about 20,000 births annually. The cases included referrals and cases from our own screening population, comprising about 4500 pregnant women examined per year.

The PF anomalies included in this studies were defined on the basis of a proposed morphological approach (3):

(1) Mega-cisterna magna was defined as a large cisterna magna measuring >10 mm in the transverse cerebellar plane, and a normal cerebellar vermis.

(2) DWM was defined by the classic triad of complete or partial agenesis of the cerebellar vermis; cystic dilation of the 4th ventricle; and enlarged PF with the upward displacement of the tentorium, torcular and transverse sinuses.

(3) BPC was defined by the presence of an upwardly displaced normal cerebellar vermis, normal-appearing fastigium, tentorium and size of the cisterna magna.

(4) Vermian hypoplasia was defined as a normally formed vermis but of smaller size, with the PF otherwise of normal size and anatomy.

(5) Vermian agenesis was defined as complete absence of the cerebellar vermis.

(6) PF arachnoid cyst (AC): normal-sized cerebellum and vermis, but displacement by a cystic structure different from a persisting BPC.

(7) Cerebellar hypoplasia (CH): intact cerebellar vermis but transverse cerebellar diameter below the fifth centile.

Prenatal sonograms were acquired transabdominally using the standard axial views for screening exam, from 2008 onwards by detailed formal fetal neurosonography, according to published guidelines (4). In all cases before 2008, at least two axial scanning planes were documented as still images: the transventricular and the transcerebellar plane. From 2008 onward, formal volume (3D) ultrasound was also performed, as described previously (5). The cerebellar size on the axial transcerebellar view was assessed according to published normal ranges (6). Vermian hypoplasia (small but detectable vermis) and vermian agenesis (no detectable vermis) were diagnosed qualitatively in the mid-sagittal section.

During the study period, different diagnostic ultrasound systems equipped for fetal studies with their respective abdominal and transvaginal probes were used (Acuson Sequoia; Toshiba Aplio; GE Voluson 730 and E8).

Fetal MRI was requested when the managing obstetrician required more diagnostic certainty or the sonographic imaging was judged suboptimal. MRI exams were performed with a Siemens Magnetom Sonata or Avanto 1.5 T system (Siemens Medical Systems, Erlangen, Germany) using a four-channel body phased array coil combined with channels from the spine array coil adjacent to the fetus. Depending on which was more comfortable for the pregnant women, they were positioned supine or on the left lateral side. Intravenous contrast or sedative premedication was not used. The standard protocol included T1-weighted fast-low angle shot (FLASH;
TR = 85 ms, TE = 4.76 ms, flip angle = 70°), T2-weighted half-Fourier acquired single-shot turbo-spin echo (HASTE; TR = 1260 ms, TE = 84 ms), T1-weighted inversion recovery (TR = 9470 ms, TE = 17 ms) and T2-weighted true fast imaging with steady procession (FISP, TR = 4.3 ms, TE = 1.86 ms; all three gradients refocused) sequences with a slice thickness of 3 mm and one acquisition. For all sequences, the field of view (320–400 mm) and acquisition matrix (256–448 mm) were adapted to the size of the mother to gain an in-plane resolution of 1.25 × 1.25 mm or less. In all cases, axial and coronal images were acquired by HASTE sequences, which were evaluated for the purposes of this study. The number of slices varied according to slice orientation and size of the fetus. Mean scanning duration was about 40 min. For the detection of PF anomalies we included contiguous orthogonal slices in the axial, coronal and sagittal plane with a slice thickness of 3 mm.

From the early 1990s, in prenatal ultrasound cases with dysgenesis of the cerebellar vermis were categorized as DWM, or “Dandy–Walker variants” (7). Different entities with enlarged PF, some associated with a hypoplasic vermis, but distinct from DWM, may have been classified as “Dandy–Walker variants.” Since then, the classification has changed to describe the different entities more distinctly, which may eventually improve prognostic accuracy. At the time of the analysis, the authors agreed on the current terminology and diagnostic criteria.

We analyzed all cases according to the first diagnostic ultrasound examination in our center as documented in the initial report. These diagnoses had been obtained by a fetal-medicine specialist, typically using real-time cross-sectional B-mode sonography and at the time of the individual woman’s care. At the analysis, the authors (A.W., B.T.) reviewed all charts and images and classified them. Analogously, a review of fetal MRI studies was done by two of the authors (R.W., M.S.).

We reviewed the pediatric records for the latest survivors’ neurological findings, seizures, karyotype (if available) and additional malformations. Short-term outcome was defined as survival to hospital discharge or intrauterine fetal death (IUFD), perinatal death or elective termination of pregnancy. Where available, autopsy reports including microscopic description were evaluated, and postmortem and postnatal imaging diagnosis was compared with the prenatal sonographic findings. Long-term outcome information was obtained from pediatric records. The outcome was designated normal if the child passed the normal, routine pediatric developmental examination.

Approval of an ethics committee was not required according to local regulations in effect at the time of initiation of the study. The study was executed in accordance with the “WMA Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects.”

Results

Sixty-nine fetuses with a prenatal diagnosis of enlarged PF were included in the analysis.

Median gestational age at diagnosis was 21 weeks (range 15–37), and median gestational age at live birth was 37 weeks (range 26–40 weeks’ gestation). The male-to-female ratio was 1.1 to 1. Of the cases included in the present study, 64 were singleton gestations, and five were twin pregnancies (three monochorionic diamniotic and two dichorionic gestations), in which only one twin was affected.

The prenatal sonographic diagnoses comprised MCM (n = 29), DWM (n = 28), BPC (n = 4), vermian hypoplasia (VH) (n = 5), CH (n = 2) and PF AC (n = 1). The review of all imaging material at the time of writing of the study had led to re-classification of seven cases with the initial sonographic diagnosis “Dandy–Walker variant”; as DWM (n = 4), CH (n = 1), VH (n = 1) and BPC (n = 1).

The prevalence of associated intracranial anomalies diagnosed at the first diagnostic ultrasound examination in fetuses with DWM was 39% (11/28), with MCM 21% (6/29), with BPC 0/4, with VH 40% (2/5), with CH 1/2 and with PF AC 0/1.

There were eight false-positive prenatal diagnoses or resolution until birth of “enlarged PF”: three with BPC, three MCM and two with VH. For the purpose of the analysis, these cases were considered correct prenatal diagnoses.

Overall, the number of anomalies with enlarged PF confirmed at birth or at autopsy was as follows: 14 DWM, 15 MCM, one BPC, one VH, three CH and one PF AC.

Fetal karyotype was performed in 41 cases, providing 13 abnormal karyotypes: 32% (7/22) in fetuses with DWM, 31% (4/13) in those with MCM, 0/3 of those with BPC, and 1/2 of those. When considering only cases of isolated PF anomalies, all fetuses were euploid.

Fetal MRI was obtained in 22 cases at gestational ages between 20 and 34 weeks. The MRI diagnoses were MCM (n = 8), DWM (n = 7), BPC (n = 2), VH (n = 1) and normal PF (n = 4). In six cases, other or additional brain malformations were detected by MRI: hypoplastic corpus callosum (n = 3) and neuronal migration disorders (lissencephaly; n = 2) and Walker Warburg syndrome (n = 2).

Among the cases with both fetal sonography and MRI, there were five with diagnostic discordances:
In one case the ultrasound diagnosis of DWM was made at 20 weeks, but MRI diagnosis was vermian hypoplasia (at 22 weeks); autopsy confirmed DWM.

In one case the ultrasound diagnosis was DWM (22 weeks) but was revised by MRI as BPC (23 weeks); autopsy showed CH.

In one case the ultrasound diagnosis was MCM (30 weeks) but was revised by MRI as BPC (31 weeks), which was also confirmed postnatally.

In one case the ultrasound diagnosis of BPC (at 23 weeks) was revised by MRI (also at 23 weeks) as DWM; the neonatal brain sonogram showed normal anatomy.

In one case the ultrasound diagnosis was DWM (27 weeks), but was revised by MRI as Walker Warburg syndrome.

In 7/69 cases with enlarged PF intrauterine fetal deaths occurred. Termination of pregnancy at the request of the parents was performed in 23 cases (between 15 and 30 weeks’ gestation).

Five perinatal deaths occurred: two neonates with DWM and an abnormal karyotype (trisomy 13 and partial trisomy 6q); one neonate that was diagnosed postnatally with VACTERL association; one death due to prematurity; and one neonate with Walker Warburg syndrome.

The length of follow up of the 34 survivors lasted up to seven years. Four cases were lost to follow up. Ten affected neonates showed genetic syndromes or additional relevant malformations. In the DWM group there were 11 live births: so far, six infants with isolated DWM show a normal development, two only mild language impairment, two motor- and neuro-developmental delay, and one atactic cerebral paresis, muscular hypotonia and developmental delay. All children with DWM and developmental delay have additional malformations.

Discussion

Our study showed that MCM and DWM each accounted for about 45% of fetuses with enlarged PF. In MCM and DWM there were 21 and 39% associated intracranial anomalies, respectively. About a third of the fetuses with MCM or DWM that were karyotyped were aneuploid.

Anomalies of the PF include multiple entities. Those with enlarged cisterna magna are easily detectable by antenatal sonography, however, the correct prenatal classification remains challenging. The accuracy of the initial diagnoses in our study reflects this, mainly by being affected by diagnostic criteria and terminology used at the time of pregnancy management. In the final analysis we avoided the term “Dandy–Walker variant” because prognoses of the individual entities summarized under it may differ significantly (8–11). Inhomogeneous classification and the frequent association with other cerebral or extra-cerebral anomalies cause the prognostic differences in follow-up studies of infants with enlarged PF (12,13).

Guibaud et al. (12) indicate the importance of the displacement of the tentorium cerebelli to distinguish the different diagnoses of PF abnormalities. In DWM it is entirely displaced upwards; however, there may be a focal displacement of the tentorium in BPC or AC due to a mass effect (12). In one case we misdiagnosed DWM as BPC prenatally, probably due to poor imaging of the tentorium.

Another sonographic feature to discriminate BPC from DWM is the brainstem-vermis (BV) angle (14): after 20 weeks’ gestation a measurement of the BV angle >45° favors the diagnosis of DWM, in contrast to an BV angle <30°, which is indicative of a BPC. This important sign was only proposed after initiation of our study. Post-hoc review of the images from our study cases for this parameter confirmed its utility (data not shown).

Intrauterine resolution of a PF fluid collection is not infrequent in cases with BPC and MCM, leading to six of the eight “false-positive” ultrasound diagnoses in our study.

Lomax et al. (15) estimated the agreement between prenatal ultrasonography and fetal autopsy findings in pregnancies terminated because of fetal anomalies. They found a sensitivity of ultrasound for brain malformations of 100%; however, the specificity was low. In our study, the fetal ultrasound diagnoses were discordant with the final diagnoses in 13 cases; eight of them had a normal PF postnatally. Among the remaining mismatches, two suspected cases of MCM turned out to be ponto-cerebellar hypoplasia.

The majority of cases with DWM appear to be sporadic, with recurrence rates for siblings quoted at about 1–5%, but there are a few reports indicating X-linked or autosomal recessive inheritance, obviously with higher recurrence risk (16–18). In our cohort, there was one consanguineous couple with three affected pregnancies; unfortunately, the couple declined genetic testing. Termination of pregnancy was requested in all three cases diagnosed as DWM by sonography.

We included two cases with DWM diagnosed before 18 weeks’ gestational age. Sonographically, the posterior-inferior part of the vermis may be undersized until 18 weeks of gestation: At 14 weeks’ gestation, 56% of fetuses had a wide open fourth ventricle, decreasing to 23% at 15 weeks and 6% at 17 weeks (19). It was proposed that the diagnosis of the different forms of vermian hypoplasia should not be made before 24 weeks’ gestation.
(8). Recently, however, abnormal structures in the PF have been found as early as 12–13 weeks in fetuses that (later) exhibit DWM (20–23).

Cerebellar atrophy may be difficult to detect during pregnancy, and it may progress after birth. In ponto-cerebellar hypoplasia (PCH), with its poor prognosis, the progressive cerebellar degeneration continues after birth. There were two siblings in our study with a false antenatal diagnosis (MCM) that turned out to be a PCH. The only chance for antenatal diagnosis may be the depiction of a small cerebellum and an abnormal development of the ventral pons during late pregnancy (8). For couples with a family history of PCH or in the case of suspicion, genetic prenatal diagnosis is possible for certain types of PCH (24–26).

The primary technique for prenatal diagnosis of the fetal brain in general and PF anomalies in particular is ultrasound, but sonographic imaging also has its limitations: Gyration, dural, and tentorial anomalies that can accompany DWM are not easily to detect by ultrasound. Maternal and other factors such as oligohydramnios, persistent unfavorable fetal position or advanced gestational age may also impair ultrasound imaging. Prenatal MR imaging is increasingly being used for these anomalies (11,27,28). Fetal MRI is an important adjunct when there is a sonographic suspicion of a complex brain anomaly. Fetal MRI also has limitations in sensitivity and specificity compared with postnatal MRI: in one study, only 60% of prenatal fetal MRI diagnoses were confirmed postnatally, stressing the need for postnatal MRI after an abnormal fetal MRI (27), which is also confirmed in our cohort. On the other hand, additional information was obtained from fetal MRI in several cases, mainly in corpus callosum anomalies and migration disorders. The appropriate time proposed for performing fetal MRI is after 24–26 weeks, which may limit its use (11).

We can speculate about the reasons for discordant ultrasound and MRI diagnoses. The structures in the PF evolve in the sense that (i) the cerebellum is a relatively late-appearing structure and (ii) the communication between the fourth ventricle and the cisterna magna, if used as an indirect marker for the size of the cerebellar vermis, can be misleading. BPC and MCM can regress during gestation, and a seemingly small vermis, if imaged only in the standard planes, can later appear normal in size. On the other hand, PCH may mimic MCM on prenatal ultrasound, as the brain stem is difficult to visualize.

The main limitation of our study is the retrospective review of case data: multiple fetal images from either MRI or ultrasound were available for all fetuses, but from different examiners. Additional sections could not be obtained. In a few cases the available stored image material was limited for a comprehensive retrospective analysis. From 2008 onwards we collected all cases prospectively, adhering to the standardized guidelines for obtaining diagnostic sections and using volumetric ultrasound, often permitting reconstruction of additional and potentially diagnostic planes that had not been acquired during the real-time examination. At least two advantages of 3D ultrasound have been reported: (i) the offline navigation of the volume, which allows a fine calibration of the slice to be used for morphometric measurements of the cerebellar vermis and PF; (ii) the possibility of selecting different rendering filters which improve the visibility of the important anatomical landmarks, such as the tentorium cerebelli (29).

Recently, the often-held belief that the normal cerebellar vermis develops “top-down” has been challenged. Phylogeny suggests cerebellar vermis growth from ventral to dorsal or from the inside, placing phylogenetically older regions further from the center (the vermar equator). With higher resolution diagnostic systems, it may be possible with both ultrasound and MRI to distinguish the individual segments of the cerebellum. These data may ultimately improve diagnosis and prognosis in affected pregnancies (30). It was not possible to obtain this level of detail was in our present study, which includes cases from 2001 onwards.

Another limitation of this study is the sample size, making conclusions from homogeneous, but small subgroups difficult; this problem also is highlighted in a recent meta-analysis (1). We estimated the incidence of serious anomalies with enlarged PF and, assuming a 50% prenatal screening detection rate, the number of cases included seems representative for our population. Further prospective studies with sufficient sample sizes and standardized diagnostic and follow-up protocols are needed to identify the prognoses in children with isolated PF anomalies (2).

In conclusion, correct and standardized prenatal categorization and a multi-disciplinary approach are of paramount importance in fetuses with enlarged PF to assess appropriately long-term prognosis when counseling the affected pregnant women. Karyotyping should be offered for affected fetuses (31,32). Prognostic information is still limited for some of the entities encountered, contributing to the challenge of counseling. MCM and BPC can mimic DWM, but may either resolve in utero or indicate associated anomalies. Diagnostic abilities (volume ultrasound, MRI) have improved, but ultrasound and MRI may be discordant.

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References


