



Systematic review and meta-analysis of isolated posterior fossa malformations on prenatal imaging (part 2): neurodevelopmental outcome

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KEYWORDS: Blake's pouch cyst; Dandy–Walker malformation; mega cisterna magna; meta-analysis; neurodevelopmental outcome; posterior fossa anomaly; vermian hypoplasia

ABSTRACT

Objectives Diagnosis of isolated posterior fossa anomalies in children is biased by the fact that only those that are symptomatic are brought to the attention of the appropriate clinical personnel, and the reported rate is often affected by the adoption of different nomenclature, diagnostic criteria, outcome measures, duration of follow-up and neurodevelopmental tools. The aim of this systematic review was to explore the neurodevelopmental outcome of fetuses with a prenatal diagnosis of isolated posterior fossa anomalies.

Methods MEDLINE and EMBASE were searched electronically, utilizing combinations of the relevant medical subject heading terms for 'posterior fossa' and 'outcome'. Studies assessing the neurodevelopmental outcome in children with a prenatal diagnosis of isolated posterior fossa malformations were considered eligible. The posterior fossa anomalies analyzed included Dandy–Walker malformation (DWM), mega cisterna magna (MCM), Blake's pouch cyst (BPC) and vermian hypoplasia (VH). Two authors reviewed all abstracts independently. Quality assessment of the included studies was performed using the Newcastle–Ottawa Scale for cohort studies. Meta-analyses of proportions were used to combine data, and between-study heterogeneity was explored using the I^2 statistic.

Results A total of 1640 articles were identified; 95 were assessed for eligibility and a total of 16 studies were

included in the systematic review. The overall rate of abnormal neurodevelopmental outcome in children with a prenatal diagnosis of DWM was 58.2% (95% CI, 21.8–90.0%) and varied from 0–100%. In those with a prenatal diagnosis of MCM, the rate of abnormal neurodevelopmental outcome was 13.8% (95% CI, 7.3–21.9%), with a range of 0–50%. There was no significant association between BPC and the occurrence of abnormal neurodevelopmental delay, with a rate of 4.7% (95% CI, 0.7–12.1%) and range of 0–5%. Although affected by the very small number of studies, there was a non-significant occurrence of abnormal neurodevelopmental delay in children with a prenatal diagnosis of VH, with a rate of 30.7% (95% CI, 0.6–79.1%) and range of 0–100%.

Conclusions Fetuses diagnosed with isolated DWM are at high risk of abnormal neurodevelopmental outcome, while isolated MCM or BPC have a generally favorable outcome. The risk of abnormal developmental delay in cases with isolated VH needs to be further assessed. In view of the wide heterogeneity in study design, time of follow-up, neurodevelopmental tests used and the very small number of included cases, further future large prospective studies with standardized and objective protocols for diagnosis and follow-up are needed in order to ascertain the rate of abnormal neurodevelopmental outcome in children with isolated posterior fossa anomalies. Copyright © 2015 ISUOG. Published by John Wiley & Sons Ltd.

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INTRODUCTION

Advances in prenatal brain imaging have allowed detailed assessment of the anatomy of the posterior fossa; however, when an abnormality is found in this area of the fetal brain, parental counseling is particularly challenging because the terminology is often confusing and there are many small studies that make it difficult to reach firm conclusions regarding the long-term outcome of an individual fetus or infant. For instance, mega cisterna magna (MCM) and Blake's pouch cyst (BPC) have been reported to have a favorable outcome when isolated. Conversely, anomalies such as Dandy–Walker malformation (DWM) are commonly considered to have a poor prognosis^{1–4}.

The lack of an objective reference standard to confirm the diagnosis after birth represents another challenge. Magnetic resonance imaging (MRI) interpretation is hampered by high rates of both false-positive and false-negative diagnoses⁵. Likewise, pathological confirmation of posterior fossa anomalies has a low level of concordance with prenatal imaging⁶. In addition, many published studies do not differentiate between cases diagnosed before and after birth. Postnatal series might be biased by the fact that only symptomatic patients come to the attention of medical practitioners, meaning that they do not reflect the natural history of the disease.

Finally, how the neurodevelopmental outcome is assessed differs between studies. This is of particular relevance because the traditional role of the cerebellum as a mere center for motor control has been reconsidered in view of recent evidence, highlighting its influence on language, socialization and cognitive functions⁷. Therefore, the use of different targeted neurodevelopmental tests in order to assess accurately the neurocognitive status of these patients might be necessary. The adoption of different periods of follow-up among the studies means that the rate of abnormal neurocognitive outcome remains uncertain, because some developmental anomalies may be evident only later in life, while others, labeled as abnormal early in life, are mild and may have only a small effect on the overall quality of life⁸.

The adoption of different nomenclature, diagnostic criteria, outcome measures, duration of follow-up and neurodevelopmental tools means that there remains significant controversy regarding neurodevelopmental outcomes in children with posterior fossa abnormalities. The aim of this systematic review was to explore the neurodevelopmental outcomes in children diagnosed *in utero* with isolated posterior fossa anomalies.

METHODS

Protocol, eligibility criteria, information sources and search

This review was performed according to an *a-priori* designed protocol and based on recommended methods for systematic reviews and meta-analyses^{9–11}; PRISMA guidelines were followed during the conduct of this review¹².

MEDLINE and EMBASE were searched electronically on 15 February 2014, utilizing combinations of the relevant medical subject heading (MeSH) terms, keywords and word variants for 'posterior fossa', 'Dandy–Walker', 'Blake's pouch cyst', 'mega cisterna magna', 'vermian hypoplasia' or 'agenesis' and 'outcome' (Table S1). The search was then updated on 14 July 2014. The search and selection criteria were restricted to the English language. Reference lists of relevant articles and reviews were hand-searched for additional reports.

Study selection, data collection and data items

Studies were assessed according to the following criteria: population, outcome, gestational age at examination and type of imaging assessment of the posterior fossa.

Two authors (F.D., A.K.) reviewed all abstracts independently. Full-text copies of relevant papers were then obtained and relevant data regarding study characteristics and pregnancy outcome were extracted independently. Agreement regarding inclusion of studies and relevance of data was reached by consensus or by discussion with a third author (A.T.P.). If more than one study was published on the same patient cohort with identical endpoints, the report containing the most comprehensive information was included to avoid overlapping populations. For those articles in which information was not reported, but the methodology suggested that this information would have been recorded initially, the authors of the articles were contacted.

Quality assessment of the included studies was performed using the Newcastle–Ottawa Scale (NOS) for cohort studies. According to the NOS, each study was judged on three broad perspectives: selection of the study groups; comparability of the groups; and ascertainment of outcome of interest¹³. Assessment of the selection of a study includes evaluation of the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure and demonstration that the outcome of interest was not present at the start of the study. Assessment of the comparability of the study includes evaluation of the comparability of cohorts on the basis of the design or analysis. Finally, ascertainment of the outcome of interest includes evaluation of the type of assessment of the outcome of interest, and the length and adequacy of follow-up. According to NOS, a study can be awarded a maximum of one star for each numbered item within the selection and outcome categories. A maximum of two stars can be given for comparability¹³.

Risk of bias, summary measures and synthesis of results

The posterior fossa anomalies considered in this systematic review were defined on the basis of the morphological approach proposed by Tortori-Donati *et al.*¹⁴ and were: (1) DWM was defined by the classic triad of complete or partial agenesis of the cerebellar vermis, cystic dilatation of the fourth ventricle and enlarged posterior fossa with upward displacement of the tentorium, torcula and

transverse sinuses; (2) MCM was defined as a cisterna magna measuring > 10 mm in the transverse cerebellar plane, and a normal cerebellar vermis; (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 (VH) was defined as a normally formed vermis but of smaller size, with the posterior fossa otherwise of normal size and anatomy.

Isolated abnormalities were defined as those posterior fossa abnormalities occurring with normal karyotype and no other associated major central nervous system (CNS) or extra-CNS anomalies detected either pre- or postnatally. In the case of DWM, ventriculomegaly was not included as an associated CNS anomaly because its development is related to dynamic changes in cerebrospinal fluid secondary to the mass effect of the cystic malformation¹⁴.

Abnormal neurodevelopmental outcome was defined as the overall presence of neurological, motor, cognitive, language or developmental deficits. A subanalysis considering the different types of neurodevelopmental abnormalities was performed whenever possible. Furthermore, the occurrence of ventriculomegaly, either before or after birth, and the need for any postnatal shunting procedure were assessed.

Only studies reporting a prenatal diagnosis of clearly defined isolated posterior fossa anomalies were considered suitable for inclusion in this systematic review. Only full-text articles were considered eligible for inclusion; case reports, conference abstracts and case series with fewer than three cases were excluded in order to avoid publication bias. In addition, we excluded from the analysis postnatal studies or studies from which cases diagnosed prenatally could not be extracted, cases of Dandy–Walker variant and those with a lack of a clear definition of the anomaly, and studies with non-isolated cases of posterior fossa anomalies. Studies published before the year 2000 were not included in the current systematic review for two related reasons: first, advances in prenatal imaging techniques are likely to have led to improvements in the diagnosis and characterization of CNS anomalies and therefore studies before this time are of little relevance to modern-day imaging; and second, older studies suffer from greater heterogeneity in definitions and nomenclature of the anomalies.

We used meta-analyses of proportions to combine data^{15,16}. Unfortunately, the low number of studies did not permit meaningful stratified meta-analyses to explore the test performance in subgroups of patients that may be less or more susceptible to bias. Furthermore, in view of the multitude of definitions, neurodevelopmental tests used and different ages at follow-up, we also decided to provide the rate of abnormal outcome for each study individually.

Assessment of the potential publication bias was also problematic, both because of the nature of the outcome (rates with the left side limited to the value zero), which limits the reliability of funnel plots, and because of the scarce number of individual studies, which strongly limits

the reliability of formal tests. Funnel plots displaying the outcome rate from individual studies *vs* their precision ($1/\text{standard error}$) were constructed with an exploratory aim. Tests for funnel-plot asymmetry were not used when the total number of publications included for each outcome was less than 10. In this case, the power of the tests is too low to distinguish chance from real asymmetry^{17,18}.

Between-study heterogeneity was explored using the I^2 statistic, which represents the percentage of between-study variation that is due to heterogeneity rather than chance. A value of 0% indicates no observed heterogeneity, whereas I^2 values of $\geq 50\%$ indicate a substantial level of heterogeneity. A fixed-effects model was used if substantial statistical heterogeneity was not present. In contrast, if there was evidence of significant heterogeneity between included studies, a random-effects model was used.

All proportion meta-analyses were carried out using StatsDirect 2.7.9 (StatsDirect Ltd, Altrincham, UK) and Meta-DiSc (Meta-DiSc Statistical Methods, 2006: [ftp://ftp.hrc.es/pub/programas/metadisc/Meta-DiSc StatisticalMethods.pdf](ftp://ftp.hrc.es/pub/programas/metadisc/Meta-DiSc%20StatisticalMethods.pdf)).

RESULTS

Study selection and characteristics

A total of 1640 articles were identified; 95 were assessed with respect to their eligibility for inclusion (Table S2) and a total of 16 studies were included in the systematic review (Figure 1 and Table 1). These 16 studies included 158 infants with isolated posterior fossa anomalies.

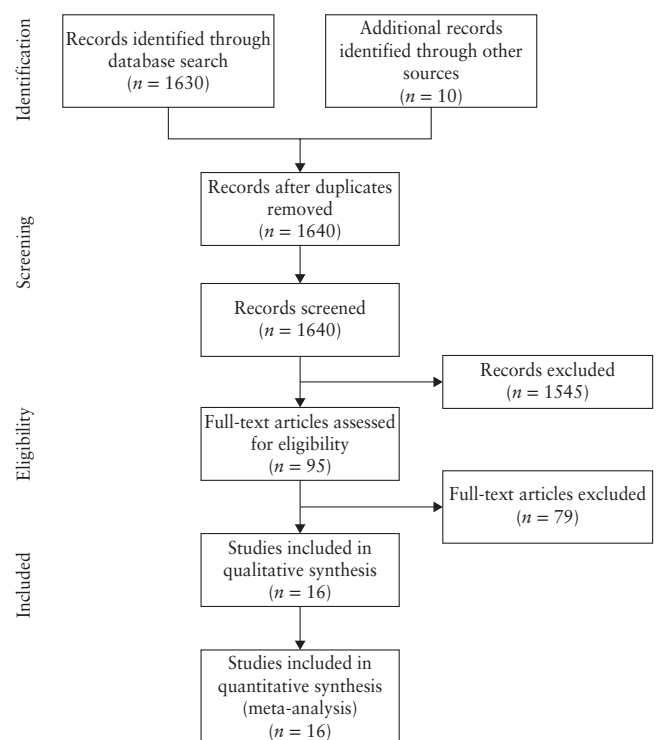


Figure 1 Flowchart summarizing selection of studies reporting on neurodevelopmental outcome of children with isolated posterior fossa anomalies diagnosed prenatally.

Table 1 General characteristics of 16 studies reporting on neurodevelopmental outcome of children with isolated posterior fossa malformations diagnosed prenatally

Study	Country	Study design	Prenatal imaging	Anomalies analyzed	Neurodevelopmental tool	Age at follow-up
Tarui (2014) ^{33*}	USA	Prosp.	MRI	VH	Wechsler Preschool and Primary Scale of Intelligence (3 rd or 4 th edn), Vineland Adaptive Behaviour Scale-II, Behavior Rating Inventory of Executive function, Child Behavior Checklist, Social Communication Questionnaire	Mean 6.1 years
Zhao (2013) ³¹	China	Prosp.	US, MRI	BPC	Basic neurological examination	1–3 years
Vatansever (2013) ²⁴	UK	Prosp.	MRI	MCM	Griffith Mental Developmental Scale (revised), Bayley Scales of Infant Development (3 rd edn)	1–2.1 years
Guibaud (2012) ^{19*}	France	Retro.	US, MRI	DWM	Clinical examination and early development scale	1.9–4 years
Gandolfi Colleoni (2012) ^{21*}	Italy	Retro.	US, MRI	DWM, BPC, MCM, VH	Basic neurological examination	1–5 years
Paladini (2012) ^{2*}	Italy	Retro.	US, MRI	BPC	Basic neurological examination	1 month to 3.5 years
Patek (2012) ^{28*}	USA	Retro.	US, MRI	MCM, VH	Parental assessment, healthcare assessment	2 months to 5.5 years
Bertucci (2011) ^{29*}	Italy/Israel	Prosp.	US, MRI	BPC, MCM, VH	Basic neurological examination	Mean 2 years
Ozkan (2011) ^{22*}	Turkey	Retro.	US	DWM	Basic neurological examination	NS
Dror (2009) ^{25*}	Israel	Prosp.	US, MRI	MCM	Gessell Developmental Schedules and Peabody Developmental Motor Scale	16–57 months
Forzano (2007) ^{30*}	UK	Retro.	US, MRI	MCM	Semi-structured questionnaire (psychomotor developmental milestones, seizures)	2 days to 3 months
Long (2006) ^{26*}	UK	Retro.	US	MCM	Basic neurological examination	4 years
Zalel (2006) ³²	Israel	Retro.	US, MRI	BPC	Basic neurological examination	1–7.5 years
Has (2004) ^{20*}	Turkey	Retro.	US, MRI	DWM	Basic neurological examination	3–5.5 years
Leitner (2004) ^{27*}	Israel	Retro.	US	MCM	Telephone interview, parental report	3 months to 3 years
Ecker (2000) ^{23*}	USA	Retro.	US	DWM	Basic neurological examination	6 weeks

Only first author of each study is given. *Additional information provided by the authors. BPC, Blake's pouch cyst; DWM, Dandy–Walker malformation; edn, edition; MCM, mega cisterna magna; MRI, magnetic resonance imaging; NS, not stated; Prosp., prospective; Retro., retrospective; US, ultrasound examination; VH, vermian hypoplasia.

Quality assessment of the included studies was performed using NOS for cohort studies (Table 2). All studies included a relatively small number of patients and had different periods of follow-up. Furthermore, most of the included studies did not use neurodevelopmental tests for the assessment of cognitive, affective and language anomalies and motor dysfunction. Finally, in view of the different imaging protocols used and types of postnatal confirmation of the anomaly, it is possible that infants with additional anomalies were included in the study population, thus affecting the overall values of abnormal neurodevelopmental outcome reported in this systematic review.

Synthesis of the results

Dandy–Walker malformation

Five studies including 13 infants with DWM, normal karyotype and no other associated CNS or extra-CNS anomalies were included in this systematic review. All studies except one¹⁹ used a basic neurological examination to assess the neurocognitive status of the patients. The overall rate of abnormal neurodevelopmental status

was 58.2% (95% CI, 21.8–90.0%) and varied from 0–100% (Table 3 and Figure 2a). A meta-analysis of the different neurodevelopmental abnormalities was possible only for the occurrence of abnormal motor outcome, which showed a 30.4% (95% CI, 8.1–59.3%) incidence of motor delay.

The study by Guibaud *et al.*¹⁹ included six fetuses with isolated DWM and normal standard karyotype. After excluding three fetuses with chromosomal microdeletions, detected using high-resolution cytogenetic analysis, and one further fetus with a false-positive diagnosis, the two remaining fetuses were included in the analysis. These two cases showed normal motor outcome but exhibited mild expressive language delay, although verbal reasoning was good, on postnatal assessment. Both infants developed hydrocephaly requiring a ventriculoperitoneal shunt to decompress the raised intracranial pressure¹⁹. Has *et al.*²⁰ included three cases with a prenatal diagnosis of isolated DWM, all of which showed severe delay in motor control, although specific tests to assess extensively the cerebellar function were not performed. Two of these three infants developed hydrocephaly after birth, requiring surgery²⁰. This finding highlights the common

Table 2 Quality assessment of the 16 included studies according to Newcastle–Ottawa Scale

Study	Selection	Comparability	Outcome
Tarui (2014) ³³	★★★★	★★	★★★★
Zhao (2013) ³¹	★★	★	★
Vatansever (2013) ²⁴	★★★	★	★★
Guibaud (2012) ¹⁹	★★★	★	★★★★
Gandolfi Colleoni (2012) ²¹	★★★	★	★★
Paladini (2012) ²	★★★	★	★★
Patek (2012) ²⁸	★★★	★	★★
Bertucci (2011) ²⁹	★★★	★	★
Ozkan (2011) ²²	★★	★	★
Dror (2009) ²⁵	★★★	★★	★★★★
Forzano (2007) ³⁰	★★	★	★★
Long (2006) ²⁶	★★★	★	★
Zalel (2006) ³²	★★★	★	★★
Has (2004) ²⁰	★★★	★	★★
Leitner (2003) ²⁷	★★	★	★
Ecker (2000) ²²	★★★	★	★

Only first author of each study is given. A study can be awarded a maximum of one star for each numbered item within the selection and outcome categories. A maximum of two stars can be given for comparability.

occurrence of hydrocephaly in cases of DWM. The development of hydrocephaly is probably related to dynamic changes in the cerebrospinal fluid, secondary to the mass effect of the cystic malformation¹⁹. In the study by Gandolfi Colleoni *et al.*²¹, two children were evaluated at 2 years of age, both showing severe motor impairment, while a third child had a postnatal diagnosis of Ritscher–Schinzel syndrome, presenting with mild language and psychomotor impairment. Finally, the studies by Ozkan *et al.*²² and Ecker *et al.*²³ had limited periods of follow-up and non-standardized assessment of the outcome measures (Table 4).

Overall, ventriculomegaly before or after birth occurred in 68.0% (95% CI, 32.3–94.5%) of fetuses with DWM despite no associated structural anomalies and normal karyotype. Ventriculomegaly requiring a ventriculoperitoneal shunt to reduce raised intracranial pressure occurred in 62.7% (95% CI, 27.9–91.3%) of the cases.

Mega cisterna magna

Eight studies including 81 infants with MCM were included in the systematic review. Only two studies

used specific tools to assess cerebellar function^{24,25}. The rate of abnormal neurodevelopmental outcome was 13.8% (95% CI, 7.3–21.9%) and ranged from 0–50% (Table 3 and Figure 2b). A meta-analysis of the different neurodevelopmental abnormalities was possible only for the occurrence of abnormal motor outcome, which showed an incidence of motor delay of 10.9% (95% CI, 4.6–19.5%).

In the largest of the studies, Dror *et al.*²⁵ included children with a prenatal diagnosis of isolated MCM with normal karyotype, evaluated by the Gesell Developmental Schedules and the Peabody Developmental Motor Scale. The age of postnatal follow-up ranged from 16 to 57 months. After excluding fetuses with additional anomalies, 17 patients were included in the analysis. Two children exhibited abnormal neurodevelopmental outcome, consisting of a generalized delay in all developmental aspects (Cases 1 and 2) and abnormal language and communication skills (Case 2) (Table 4). Children with a prenatal diagnosis of isolated MCM had significantly worse scores in their general developmental quotient, and in social interaction and visual–motor perception subtests; in contrast there was no difference in motor performance between children with a normal posterior fossa and those with MCM.

In the study by Vatansever *et al.*²⁴, the authors assessed the growth trajectories of the posterior fossa using semi-automatic segmentation of reconstructed fetal brain MRI. Six fetuses with isolated MCM were included in the study and the Griffith Mental Development Scale and Bailey Scales of Infant Development were used to ascertain the neurodevelopmental outcome of these children. Half of the included cases showed some degree of neurodevelopmental delay, including visuospatial perception and attention problems. Abnormal motor development was found in 1/13 infants in the study by Long *et al.*²⁶ and in 3/9 in that by Leitner *et al.*²⁷. Neither study used specific tests to assess cerebellar function, and in the study by Leitner *et al.*, the neurodevelopmental status was assessed by telephone interview conducted by pediatric neurologists²⁷. In the study by Gandolfi Colleoni *et al.*²¹, 16 cases with isolated MCM were analyzed and two children were found to have mild language disorder at around 3 years of age.

All other studies did not report any significant neurological anomaly in children with a prenatal diagnosis of isolated MCM, although no specific neurodevelopmental tool was used (Table 4)^{28–30}.

Overall, ventriculomegaly before or after birth occurred in 2.3% (95% CI, 0.1–12.3%) of cases of MCM

Table 3 Pooled proportions (PP) for occurrence of abnormal neurodevelopmental outcome in infants with prenatal diagnosis of posterior fossa anomaly

Anomaly	Studies (n)	Fetuses (n/N)	Raw (95% CI) (%)	I ² (%)	PP (95% CI) (%)
DWM	5	8/13	61.54 (31.6–86.1)	54.2	58.15 (21.8–90.0)
MCM	8	11/81	13.58 (7.0–23.0)	36.2	13.8 (7.3–21.9)
BPC	5	1/46	2.17 (0.1–11.5)	0.0	4.7 (0.7–12.1)
VH	4	3/18	16.67 (3.6–41.4)	77.7	30.7 (0.6–79.1)

BPC, Blake's pouch cyst; DWM, Dandy–Walker malformation; MCM, mega cisterna magna; VH, vermian hypoplasia.

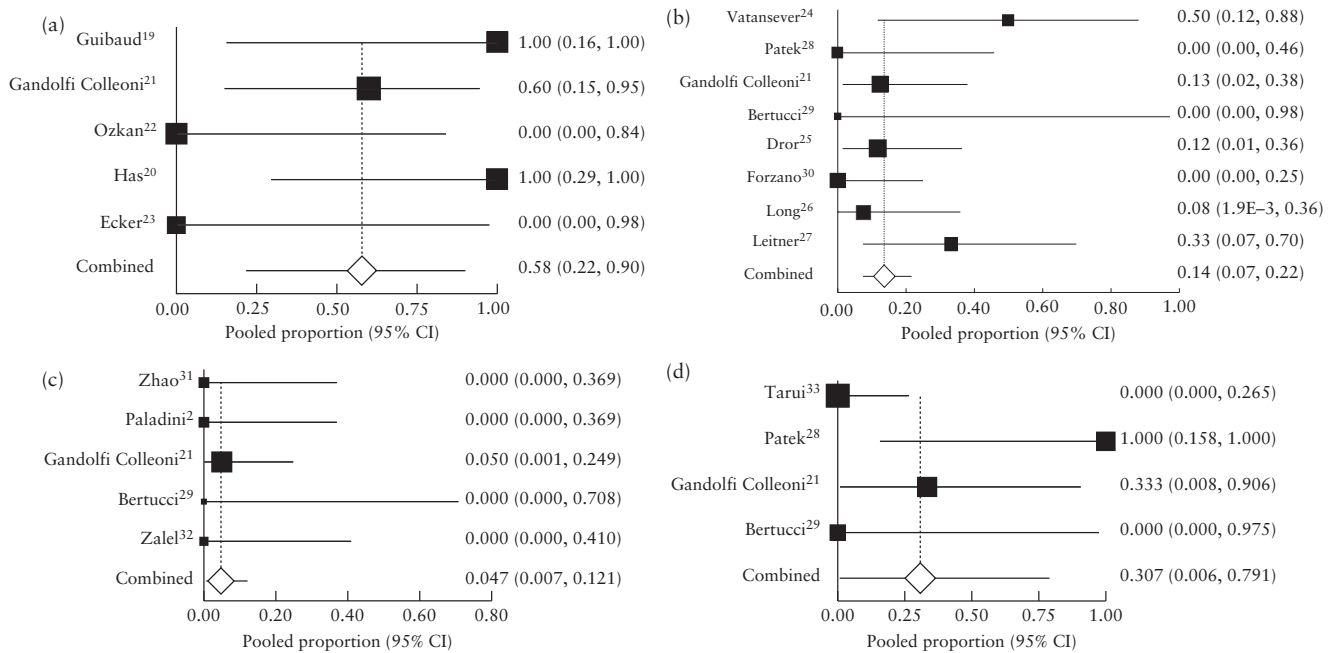


Figure 2 Pooled proportions of occurrence of abnormal overall neurodevelopmental outcome in infants with prenatal diagnosis of isolated posterior fossa malformations: (a) Dandy–Walker malformation; (b) mega cisterna magna; (c) Blake’s pouch cyst; (d) vermian hypoplasia. Only first author of each study is given.

with no associated structural anomalies and normal karyotype, but in no case included in this review was a ventriculoperitoneal shunt needed (pooled proportion (PP), 0% (95% CI, 0–8.2%)).

Blake’s pouch cyst

Five studies including 46 infants with a prenatal diagnosis of isolated BPC were included in this review. No study used a specific neurodevelopmental test to assess cerebellar function. The age of follow-up varied from 1 month to 10 years. There was no significant association between BPC and the occurrence of abnormal neurodevelopmental delay (PP, 4.7% (95% CI, 0.7–12.1%); range, 0–5%; Table 3 and Figure 2c). No fetus tested for motor control showed an abnormal outcome (PP, 0% (95% CI, 0–13.2%)).

In the study by Gandolfi Colleoni *et al.*²¹, the authors included 20 infants with a prenatal diagnosis of BPC, of which only one showed mild psychomotor disorder at 3 years. In the other included studies, no case of abnormal neurodevelopmental outcome was found^{2,29,31,32}, although no specific neurodevelopmental tool was used (Table 4).

The rate of ventriculomegaly occurring either before or after birth was 12.4% (95% CI, 2.9–27.1%) but it did not require shunting in any of the cases (PP, 0% (95% CI, 0–15.4%)).

Vermian hypoplasia

Four studies including 18 infants with a prenatal diagnosis of VH were included in this review. The duration of follow-up ranged from 6 months to 10 years.

There was high heterogeneity among the included studies, which reported a non-significant occurrence of abnormal neurodevelopmental delay among these children (PP, 30.7% (95% CI, 0.6–79.1%); range, 0–33%; Table 3 and Figure 2d). Of the included fetuses, none had abnormal motor outcome at assessment, performed at a variety of ages (PP, 0% (95% CI, 0–18.5%)).

In the largest series in this review, Tarui *et al.*³³ prospectively followed 20 children with a prenatal diagnosis of VH on MRI, with targeted neurodevelopmental tests including the assessment of cognitive, affective, language and behavioral measures at school age (Table 4). When considering only cases with isolated VH and a confirmed postnatal diagnosis, all 12 children had normal neurodevelopmental outcome.

No fetus with VH included in this review required a ventriculoperitoneal shunt (PP, 0% (95% CI, 0–24.7%)).

DISCUSSION

Summary of evidence

The findings of this systematic review show that children with a prenatal diagnosis of isolated DWM are at increased risk of abnormal neurodevelopmental outcome. Isolated MCM has a generally good outcome, although a small proportion of children may exhibit variable degrees of developmental delay. Isolated BPC is a benign condition and the rate of abnormal neurodevelopmental delay seems to be low. In view of the very small number of included studies, no clear evidence can be extracted for isolated VH.

Table 4 Summary of studies reporting on the rate of abnormal neurodevelopmental outcome in infants with prenatal diagnosis of isolated Dandy–Walker malformation ($n = 5$), mega cisterna magna ($n = 8$), Blake's pouch cyst ($n = 5$) or vermian hypoplasia ($n = 4$)

Study	Patients assessed (n)	Ab neurodev outcome (n (%))	Age at follow-up	Neurodevelopmental tool	Outcome in cases of abnormal development
<i>Dandy–Walker malformation</i>					
Guibaud (2012) ¹⁹	2	2 (100)	1.9–4 years	Clinical exam and early development scale	Case 1: Walking at 15 months; last visit at 32 months: two-word sentences, clumsy left-hand grip, upgaze impairment. Hydrocephaly at 1 month and ventriculoperitoneal shunting Case 2: Walking at 13 months; last visit at 4 years: good non-verbal reasoning (visuospatial IQ, 109; verbal IQ, 78), good receptive and weak expressive language (under speech therapy). Hydrocephaly at 4 months and ventriculoperitoneal shunting
Gandolfi Colleoni (2012) ^{21*}	5	3 (60)	2–10 years	Basic neurological exam	Case 1: Severe intellectual and motor impairment at 2 years (cerebral heterotopia diagnosed postnatally) Case 2: Severe neurological (mostly psychomotor) impairment at 2 years Case 3: Mild language and psychomotor impairment, postnatal diagnosis of Ritscher–Schinzel syndrome
Ozkan (2011) ^{22*}	2	—	NS	Basic neurological exam	Case 1: 3.5 years old with neuromotor impairment and abnormal electroencephalography findings, under anticonvulsive therapy
Has (2004) ^{20*}	3	3 (100)	3–5.5 years	Basic neurological exam	Case 2: 3.0 years old with neuromotor impairment and cystoperitoneal shunt at 7 months, under anticonvulsive therapy Case 3: 5.5 years old with neuromotor impairment and cystoperitoneal shunt at 2 months
Ecker (2000) ^{23*}	1	—	6 weeks	Basic neurological exam	
<i>Mega cisterna magna</i>					
Vatansever (2013) ²⁴	6	3 (50.0)	1–2.1 years	Griffith Mental Developmental Scale (revised), Bailey Scales of Infant Development (3 rd edn) Basic neurological exam	Visuospatial perception and attention problems
Gandolfi Colleoni (2012) ^{21*}	16	2 (12.5)	2–10 years	Basic neurological exam	Case 1: Mild language disorder at 2 years 10 months Case 2: Mild language and motor disorder at 3 years (facial dysmorphism, no specific genetic diagnosis)
Patek (2012) ^{28*}	6	—	1.4–3.3 years	Basic neurological exam and parental report	
Bertucci (2011) ^{29*}	1	—	6 months	Basic neurological exam	Case 1: (cisterna magna: 12 mm during pregnancy) 23 months of age; 4–5-month general delay in all developmental aspects
Dror (2009) ^{25*}	17	2 (11.8)	16–57 months	Gessell Developmental Schedules and Peabody Developmental Motor Scale	Case 2: (cisterna magna: 14 mm during pregnancy) 22 months of age; all developmental milestones delayed. Achieved independent walking at 20 months. The most affected aspects of development were language and communication. Currently under evaluation for autistic spectrum disorder
Forzano (2007) ^{30*}	13	—	2 days to 3 months	Basic neurological exam	Delayed motor development (poor feeding and delayed walking at 29 months)
Long (2006) ^{26*}	13	1 (7.7)	4 years	Basic neurological exam	Case 1: Delayed motor development Case 2: Delayed motor development
Leitner (2004) ²⁷	9	3 (33.3)	3 months to 3 years	Telephone interview	Case 3: Delayed motor development and language deficits

Table 4 Continued

Study	Patients assessed (n)	Ab neurodev outcome (n (%))	Age at follow-up	Neurodevelopmental tool	Outcome in cases of abnormal development
<i>Blake's pouch cyst</i>					
Zhao (2013) ³¹	8	—	1–3 years	Basic neurological exam	
Paladini (2012) ^{2*}	8	—	1 month to 3.5 years	Basic neurological exam	
Gandolfi Colleoni (2012) ^{21*}	20	1 (5)	2–10 years	Basic neurological exam	Mild psychomotor disorder at 3 years, normal intellectual and language function
Bertucci (2011) ^{29*}	3	—	6 months	Basic neurological exam	
Zalel (2006) ³²	7	—	1–7.5 years	Basic neurological exam	
<i>Vermian hypoplasia</i>					
Taruı (2014) ^{33*}	12	—	Mean 6.1 years	Wechsler Preschool and Primary Scale of Intelligence (3 rd or 4 th edn), Vineland Adaptive Behaviour Scale-II, Behavior Rating Inventory of Executive Function, Child Behavior Checklist, Social Communication Questionnaire	
Patek (2012) ^{28*}	2	2 (100)	2.2–5.5 years	Basic neurological exam and parental report	Case 1: Seizures and developmental delay based on parental report Case 2: Developmental delay based on parental report
Gandolfi Colleoni (2012) ^{21*}	3	1 (33.3)	2–10 years	Basic neurological exam	NS
Bertucci (2011) ^{29*}	1	—	6 months	Basic neurological exam	NS

Only first author of each study is given. *Additional information provided by the authors. Ab neurodev, abnormal neurodevelopmental; IQ, intelligence quotient; NS, not stated.

Limitations of the study

The small sample size of the included studies, high degree of variability in the definition of the different posterior fossa anomalies and differences in age at follow-up represent the major limitations of this review. A basic neurological examination, as carried out in most of the published studies, may not be sufficient to determine the neurodevelopmental status of these children and more accurate tests investigating cognitive, affective and behavioral functions are needed in order to ascertain the actual rate of abnormal development. Furthermore, cases labeled as isolated may have had subtle undiagnosed associated chromosomal or structural anomalies³⁴. Postnatal confirmation of posterior fossa anomalies can also be challenging, with high rates of false-positive diagnoses reported in the literature⁵. The lack of a standardized protocol for postnatal assessment in most of the included studies did not enable a precise estimation of the exact number of diagnoses confirmed after birth. Moreover, confirmation of the diagnosis using postnatal imaging was not performed in some of the included cases. It is therefore plausible that limitations in study design, sample size, data extraction and outcomes observed might bias the findings of the current review.

Implications for clinical practice

Prenatal counseling when a fetus is diagnosed with a posterior fossa anomaly is challenging. Correctly defining posterior fossa anomalies is the first step in an optimal diagnostic approach^{35,36}; multiplanar assessment of the posterior fossa using axial, sagittal and coronal planes is necessary in order to define precisely these conditions, especially because anomalies with a similar appearance in the axial plane may have different appearances in other planes, and may be associated with different outcomes.

The factors already outlined, such as length of follow-up, neurodevelopmental tool adopted, age at assessment, presence of additional anomalies and choice of an appropriate control group are all relevant. The term ‘neurodevelopmental outcome’ can also be misleading and inappropriate when considering brain anomalies because it encompasses a wide spectrum of signs with different underlying disorders and pathological processes, which are not always easily measured and which represent a continuous interaction between pathological, environmental and adaptive factors.

The study by Klein *et al.*³ highlights the need for new research aimed at finding reliable prognostic imaging markers; the authors reviewed retrospectively the charts of 26 patients with a diagnosis of DWM. They found that no patient in the group with normal vermian morphology had associated brain malformations and the majority had normal outcome, while all those with a dysplastic vermian had associated brain anomalies and abnormal outcome. As all patients in the second group had associated brain anomalies, it was not possible to assess whether the presence of the normal vermian anatomy was associated independently with a better outcome³.

The feasibility of detailed evaluation of vermian anatomy during prenatal life and its independent role in predicting neurodevelopmental outcome have yet to be established¹⁹.

Isolated MCM is a relatively common finding. The rate of chromosomal abnormalities and additional CNS and extra-CNS structural anomalies that are not detected on ultrasound is low³⁷. In the current review, most of the included studies reported a normal or borderline neurodevelopmental outcome in the majority of children with isolated MCM. The pathophysiology of isolated MCM has not been elucidated completely yet and it is not clear whether expansion of the posterior fossa by fluid is a pathological development or represents a normal variant. Dror *et al.*²⁵ suggested that children with isolated MCM had lower developmental, visual motor and social performance than did controls. However, all the mean values for the neurodevelopmental measures observed were within normal range, suggesting a generally favorable outcome.

Failure of fenestration of the posterior membranous area leads to the persistence of Blake's pouch³⁸. On imaging, BPC is characterized by the presence of an upward displacement of a normal cerebellar vermis, normal fastigium, tentorium and size of the cisterna magna. Tetraventricular hydrocephaly is an associated finding commonly reported postnatally. Although none of the included studies used specific tools to assess cerebellar function, the findings of this review suggest a generally favorable outcome.

Data on the prognosis of children with isolated VH in this review are debatable. In view of the very small number of cases included, no robust evidence can be confidently extrapolated. The results from this meta-analysis are surprising and disagree with what is observed after birth, where VH, even if isolated, has been reported to be associated with developmental delay. We might speculate that the main bias is due to the definition of VH before birth – many cases labeled as hypoplasia during the prenatal period may actually correspond to a normal vermis, theoretically explaining the reason behind the favorable outcome reported in this meta-analysis. In the collective authors' experience, prenatal diagnosis of VH is affected by high rates of false-positive cases, with most of the cases found to be BPC at birth⁵.

Implications for research

The wide heterogeneity in diagnostic criteria, nomenclature and outcome definitions highlights the urgent need for prospective studies that standardize objectively the classification and prognosis of these anomalies. Future research should aim at describing objectively the different posterior fossa anomalies and correlating them with robust long-term neurodevelopmental measures.

Conclusions

Isolated DWM is associated with an increased risk of abnormal neurodevelopmental outcome, while isolated

MCM and BPC have a generally favorable outcome. In view of the very small number of patients tested and lack of an objective prenatal definition, the risk of abnormal developmental delay in cases with isolated VH needs to be further assessed. Future large prospective studies with standardized and objective protocols for diagnosis and follow-up are needed in order to ascertain the rate of abnormal neurodevelopmental outcome in children with isolated posterior fossa anomalies.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:



Table S1 Search strategy – PRISMA 2009 checklist

Table S2 Excluded studies and reason for exclusion



RESUMEN

Objetivos El diagnóstico de anomalías aisladas de la fosa posterior en niños/as está sesgado por el hecho de que sólo se notifica al personal clínico apropiado cuando presentan síntomas, y la tasa reportada se ve a menudo afectada por la adopción de nomenclatura diferente, los criterios de diagnóstico, las medidas del resultado, la duración del seguimiento y las herramientas de desarrollo neurológico. El objetivo de esta revisión sistemática fue explorar el resultado del desarrollo neurológico de los fetos con diagnóstico prenatal de anomalías aisladas de la fosa posterior.

Métodos Se hicieron búsquedas electrónicas en MEDLINE y EMBASE, utilizando combinaciones de los términos médicos más relevantes para ‘fosa posterior’ y ‘resultado’. Se consideraron adecuados los estudios que evaluaron el resultado del desarrollo neurológico en niños/as con un diagnóstico prenatal de malformaciones aisladas de la fosa posterior. Entre las anomalías de la fosa posterior analizadas están el síndrome de Dandy-Walker (SDW), la megacisterna magna (MCM), el quiste de la Bolsa de Blake (BPC, por sus siglas en inglés) y la hipoplasia vermiana (VH, por sus siglas en inglés). Todos los resúmenes fueron revisados de forma independiente por dos de los autores. La evaluación de calidad de los estudios incluidos se realizó mediante la escala Newcastle-Ottawa para estudios de cohortes. Se utilizaron metaanálisis de proporciones para la combinación de datos, y la heterogeneidad entre estudios se examinó mediante el estadístico I^2 .

Resultados Se identificaron un total de 1640 artículos, de los cuales se evaluó la elegibilidad de 95 y se incluyó un total de 16 estudios en la revisión sistemática. La tasa global de resultado de desarrollo neurológico anormal en niños/as con un diagnóstico prenatal de SDW fue del 58,2% (IC del 95%, 21,8–90,0%), con un rango de 0–100%. En niños/as con un diagnóstico prenatal de MCM, la tasa de resultado de desarrollo neurológico anormal fue del 13,8% (IC del 95%, 7,3–21,9%), con un rango de 0–50%. No se encontró una asociación significativa entre el BPC y la presencia de retraso de desarrollo neurológico anormal, con una tasa del 4,7% (IC del 95%, 0,7–12,1%) y un rango de 0–5%. Se encontró un resultado no significativo de casos con retraso del desarrollo neurológico anormal en niños/as con un diagnóstico prenatal de VH, con una tasa del 30,7% (IC del 95%, 0,6–79,1%) y un rango de 0–100%. Aunque afectado por el escaso número de estudios

Conclusiones Los fetos diagnosticados con SWD aislado poseen un alto riesgo de resultado de desarrollo neurológico anormal, mientras que el MCM o BPC aislados tienen, en general, un resultado favorable. El riesgo de retraso en el desarrollo anormal en casos con VH aislada debe estudiarse más todavía. En vista de la gran heterogeneidad en el diseño de los estudios, el tiempo de seguimiento, las pruebas de desarrollo neurológico empleadas y el pequeño número de casos incluidos, será necesario realizar en el futuro estudios prospectivos más amplios con protocolos objetivos y estandarizados para el diagnóstico y el seguimiento, con el fin de determinar la tasa de resultados de desarrollo neurológico anormal en niños/as con anomalías aisladas de la fosa posterior.

Objetivo: Debido a que sólo los niños con síntomas atraerían la atención de los médicos clínicos, la tasa reportada de diagnóstico de anomalías aisladas de la fosa posterior en niños/as está sesgado. Además, la tasa reportada puede verse afectada por la adopción de nomenclatura diferente, los criterios de diagnóstico, las medidas del resultado, la duración del seguimiento y las herramientas de desarrollo neurológico. El objetivo de esta revisión sistemática fue explorar el resultado del desarrollo neurológico de los fetos con diagnóstico prenatal de anomalías aisladas de la fosa posterior.

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Conclusiones: Los fetos diagnosticados con SWD aislado poseen un alto riesgo de resultado de desarrollo neurológico anormal, mientras que el MCM o BPC aislados tienen, en general, un resultado favorable. El riesgo de retraso en el desarrollo anormal en casos con VH aislada debe estudiarse más todavía. En vista de la gran heterogeneidad en el diseño de los estudios, el tiempo de seguimiento, las pruebas de desarrollo neurológico empleadas y el pequeño número de casos incluidos, será necesario realizar en el futuro estudios prospectivos más amplios con protocolos objetivos y estandarizados para el diagnóstico y el seguimiento, con el fin de determinar la tasa de resultados de desarrollo neurológico anormal en niños/as con anomalías aisladas de la fosa posterior.