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

Neurodevelopmental outcome

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Abstract

Objectives: Pediatric series of children with isolated posterior fossa anomalies are biased by the fact that only symptomatic patients come to the attention and affected by the adoption of different nomenclature, diagnostic criteria, outcome measures, duration of follow-up and neurodevelopmental tools adopted. The aim of this systematic review was to explore the neurodevelopmental outcome in 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 for "posterior fossa", and "outcome. Studies assessing the neurodevelopmental outcome in children with a prenatal diagnosis of isolated posterior fossa malformations. The posterior fossa anomalies analysed were: 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 (NOS) for cohort studies. Meta-analyses of proportions were used to combine data. Between-study heterogeneity was explored using the I^2 statistic.

Results: A total of 1640 articles were identified, 95 were assessed with respect to their eligibility for inclusion and total of 16 studies were included in the systematic review. The overall rate of abnormal neurodevelopmental status in children with a prenatal diagnosis of DWM was 49,2% (95% CI 17,9-80,8) and varied from 0% to 100%. In fetuses with MCM, the rate of abnormal neurodevelopmental outcome was 15% (95% CI 8,4-23,1; range 0%-50%). There was not significant association between BPC and the occurrence of abnormal neurodevelopmental delay (PP: 4,7%, 95% 0,1-12,1; range 0%-5%). Finally, 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 (PP: 30,7%, 95% CI 0,6-79,1; range 0%-33%).

Conclusions: Fetuses diagnosed with isolated DWM are at high risk of abnormal neurodevelopmental outcome, while isolated MCM or BPC have a generally favourable outcome. The risk of abnormal developmental delay in cases with isolated VH need to be further ascertained. 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.

Introduction

Advances in prenatal brain imaging allow detailed assessment of the anatomy of the posterior fossa; however, when an abnormality is found in this area of the fetal brain, parental counselling is particularly challenging. This is because the terminology is often confusing and because there are many small studies making 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. On the other hand, 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 negative diagnoses[5]. Likewise, pathological confirmation of posterior fossa anomalies has a low level of concordance with prenatal imaging[6]. In addition, many published studies do not differentiate between cases diagnosed before and after birth. Post-natal 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 in different 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 cognition functions[7]. Therefore, the use of different targeted neurodevelopmental tests in order to accurately assess the neurocognitive status of these patients might be necessary. The adoption of different periods of follow-up among the different studies means the rate of abnormal neurocognitive outcome remains uncertain, because some developmental anomalies may be evident only later on in life, while others, labelled as abnormal early in life, are mild and may have only a small effect on the overall quality of life[8].

The adoption of different nomenclature, different diagnostic criteria, outcome measures, duration of follow-up and neurodevelopmental tools means that there remains significant controversy regarding neurodevelopmental outcome in children with posterior fossa abnormalities. The aim of this systematic review was to explore the neurodevelopmental outcome 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-analysis[9-11]; PRISMA guidelines were followed during the conduct of this review[12].

Medline and Embase were searched electronically on the 15th February 2014 utilizing combinations of the relevant medical subject heading (MeSH) terms, key words, and word variants for "posterior fossa", "Dandy Walker", "Blake's pouch cyst", "mega cisterna magna", "vermian hypoplasia" or "agenesis" and "outcome" (Supplementary Material 1). The search was then updated on 14th July 2014. The search and selection criteria were restricted to 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 posterior fossa.

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

Quality assessment of the included studies was performed using the Newcastle-Ottawa Scale (NOS) for cohort studies. Each study was judged on three broad perspectives: the selection of the study groups; the comparability of the groups; and the ascertainment outcome of interest[13]. Assessment of the selection of a study included the evaluation of the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure and the demonstration that the outcome of interest was not present at start of study. Assessment of the comparability of the study includes the evaluation of the comparability of cohorts on the basis of the design or analysis. Finally, the ascertainment of the outcome of interest includes the evaluation of the type of the assessment of the outcome of interest, length and adequacy of follow-up. According to the 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 comparability[13].

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 the inclusion; case reports, conference abstracts and case series with fewer than 3 cases were excluded in order to avoid publication bias. In addition, we excluded from the analysis post-natal studies, or studies from which cases diagnosed pre-natally 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. Finally, studies published before 2000 were not included in the current systematic review for two, related, reasons: firstly, advances in prenatal imaging techniques are likely to have led to improvements in diagnosis and characterisation of CNS anomalies and therefore studies before this time are of relevance to modern day imaging; and secondly because older studies suffered from greater heterogeneity in definitions and nomenclature of the anomalies.

Risk of bias, summary measures and synthesis of the results

The posterior fossa anomalies considered in this systematic were defined on the basis of the morphological approach proposed by Tortori-Donati and were[14]:

- Dandy Walker malformation was defined by the classic triad of complete or partial agenesis of the cerebellar vermis; cystic dilatation of the 4th ventricle; and enlarged posterior fossa with the upward displacement of the tentorium, torcula and transverse sinuses.
- Mega-cisterna magna was defined as a large cisterna magna measuring >10 mm in the transverse cerebellar plane, and a normal cerebellar vermis.
- Blake's pouch cyst was defined by the presence of an upwardly displaced normal cerebellar vermis, normal appearing fastigium, tentorium and size of the cisterna magna.
- Vermian hypoplasia 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 with normal karyotype and no other associated major CNS or extra-CNS anomalies detected either pre- or post-natally. 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 malformation[14].

Abnormal neurodevelopmental outcome was defined as the overall presence of neurological, motor, cognitive, language and developmental deficits. A sub-analysis considering the different type of neurodevelopmental abnormalities was performed whenever possible. Furthermore, the occurrence of ventriculomegaly either before or after birth and the need for post-natal shunting procedure was computed.

We used meta-analyses of proportions to combine data[16,17]. Unfortunately, the small 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 age at follow-up, we also decided to provide the rate of abnormal outcomes for each study singularly.

Assessment of the potential publication bias was also problematic, both because of the outcome nature (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 versus their precision (1/standard error) were carried out 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 ten. In this case, the power of the tests is too low to distinguish chance from real asymmetry[18,19].

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 studies included, a random effect model was used.

All proportion meta-analyses were carried out using StatsDirect 2.7.9 (StatsDirect Ltd, Altrincham) and MetaDisc (Meta-DiSc Statistical Methods, 2006)

(ftp://ftp.hrc.es/pub/programas/metadisc/MetaDisc_StatisticalMethods.pdf).

Results

Study selection and characteristics

A total of 1640 articles were identified, 95 were assessed with respect to their eligibility for inclusion (Supplementary Material 2) and a total of 16 studies included in the systematic review (Figure 1). These 16 studies included 155 infants with isolated posterior fossa anomalies.

Quality assessment of the included studies was performed using Newcastle-Ottawa Scale (NOS) for cohort studies. 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 ta allow assessment of cognitive, affective and language anomalies, as well as motor dysfunction (Table 2). Finally, in view of the different imaging protocols and type of post-natal confirmation of the anomaly, it might be possible that infants with additional anomalies were included in the study population, thus affecting the overall figures of abnormal neurodevelopmental outcome reported in this systematic review.

Synthesis of the results

Dandy Walker Malformation (DWM)

Five studies including 13 infants with DWM with normal karyotype and no other associated CNS and extra-CNS anomalies were included in this systematic review. All, except one, used a basic neurological examination to assess the neurocognitive status of these patients[15]. The overall rate of abnormal neurodevelopmental status was 49.2% (95% CI 17.9-80.8) and varied from 0% to 100% (Table 3; Figure 2). A meta-analysis of the different neurodevelopmental abnormalities was possible only for the occurrence of abnormal motor outcome and showed a 30.4% (95% CI 8.1-59.3) incidence of motor delay.

The study by Guibaud et al included 6 fetuses with isolated DWM with normal standard karyotype[15]. After having excluded 3 fetuses with chromosomal micro deletions, detected using high resolution cytogenetic analysis; and 1 further fetus with a false positive diagnosis, the 2 remaining fetuses were included in the analysis. These two infants showed a normal motor outcome but exhibited mild expressive language delay, although verbal reasoning was good. Both of the fetuses developed hydrocephaly requiring a ventriculo-peritoneal shunt to decompress the raised intra-cranial pressure[15]. Has et al. included 3 patients with a prenatal diagnosis of isolated DWM, all of them showing severe delay in motor control although specific test to extensively assess the cerebellar function were not performed. Two of these three infants developed hydrocephaly after birth, requiring surgery[16]. This finding highlights the common occurrence of hydrocephaly in fetuses with DWM. The development of hydrocephaly is probably related to dynamic changes of cerebrospinal fluid, secondary to the mass effect of the cystic malformation[15]. In the study by Gandolfi-Colleoni[21], two children were evaluated at 2 years of age both showing severe motor retardation, while a third child had a post-natal diagnosis of Ritscher-Schinzel syndrome presenting with mild language and psychomotor impairment. Finally, the study by Ozkan and Ecker included only one patient with a limited period of follow-up and non-standardised assessment of the outcome measures[23,24] (Table 4).

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

Mega-cisterna magna (MCM)

Eight studies (81 infants) were included in the current systematic review. Only two studies used specific tools to assess the cerebellar function[24,25]. The rate of abnormal neurodevelopmental outcome was 15% (95% CI 8.4-23.1) and ranged from 0% to 50% (Table 3; Figure 2). A meta-analysis of the different neurodevelopmental abnormalities was possible only for the occurrence of abnormal motor outcome and showed an incidence of motor delay of 10.9% (95% CI 4.6-19.5).

In the largest study[25], Dror et al 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 follow-up ranged from 1.8 to 1.9 years. After having excluded fetuses with additional anomalies, 17 patients were included in the analysis. Two children exhibited abnormal neurodevelopmental outcome, consisting of a generalised delay in all developmental aspects (case 1 and 2) and abnormal language and communication skills (case 2) (Table 5). Children with a prenatal diagnosis of isolated MCM had significantly worse scores in general developmental quotient, social interaction and in visual-motor perception subtests; in contrast there were no differences between children with a normal posterior fossa and those with MCM in motor performance.

In the study by Vatansaver et al[24], the authors assessed the growth trajectories of the posterior fossa using semi-automatic segmentation of reconstructed fetal brain MR images. Six fetuses with isolated MCM were included in the study and Griffith Mental Development Scale and Bailey Scales of Infant Development were used to ascertain the neurodevelopmental outcome of these children. Half of the included patients showed some degrees of neurodevelopmental delay, including visuo-spatial perception and attention problems. Abnormal motor development was found in 1/11 infants in the study by Long et al.[26] and in 3/9 in that by Leitner et al.[27]. Both studies did not use specific tests to assess cerebellar function, while in the study by Leitner et al, the neurodevelopmental status was assessed by telephone interview conducted by paediatric neurologists[26,27]. In the study by Gandolfi-Colleoni 20 fetuses with isolated MCM were analysed and 2 children were were found to have mild language disorder at around 3 years of age[21].

All the other studies have not reported any significant neurological anomaly in children with a prenatal diagnosis of isolated MCM, although no specific neurodevelopmental tool was used (Table 5)[28-30].

Overall, ventriculomegaly before or after birth occurred in 2.3% (95% CI 0.1-12.3) of cases of MCM with no associated structural anomalies and normal karyotype, but in none of the cases included in this review a ventriculo-peritoneal shunt was needed (PP: 0%, 95% CI 0-8.2).

Blake's pouch cyst (BPC)

Five studies including 46 infants with a prenatal diagnosis of isolated BPC were included in this review. None used a specific neurodevelopmental test to assess the cerebellar function. The age of follow-up varied from 6 months to 7.5 years.

There was not significant association between BPC and the occurrence of abnormal neurodevelopmental delay (PP: 4.7%, 95% 0.1-12.1; range 0% to 5%). None of the fetuses tested for motor control showed an abnormal outcome (PP: 0%, 95% CI 0-13.2) (Table 3; Figure 2).

In the study by Gandolfi-Colleoni, the authors included 20 infants with a prenatal diagnosis of BPC, out of which only 1 child showed mild psychomotor disorder at 3 years[21]. In the other included studies, no case of abnormal neurodevelopmental outcome was found, although no specific neurodevelopmental tool was used (Table 6)[2,29,31,32].

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 (VH)

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 6 years.

There was high heterogeneity among the included studies which reported a non-significant occurrence of abnormal neurodevelopmental delay in these children (PP: 30.7%, 95% CI 0.6-79.1) wide range (0% to 33%) (Table 3; Figure 2). Among the included fetuses, none had abnormal motor outcome at assessments done at a variety of ages (PP: 0%, 95% CI 0-18.5).

In the largest series, Tarui et al prospectively followed 20 children with a prenatal diagnosis of VH at MRI with targeted neurodevelopmental tests including the assessment of cognitive, affective, language and behavioural measures at school age (Supplementary Table 7)[33]. When considering only cases with isolated VH and confirmed postnatal diagnosis, all children had normal neurodevelopmental outcome (Table 7).

None of the fetuses with VH included in this review required a ventriculo-peritoneal shunt (PP: 0%, 95% CI 0-24.7).

Discussion

Summary of evidence

The findings form this systematic review showed 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. 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 extrapolated for VH.

Limitations

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 represents 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 behavioural functions are needed in order to ascertain the actual rate of abnormal developmental. Furthermore, cases labelled as isolated may have had subtle undiagnosed associated chromosomal or structural anomalies[36].

Post-natal confirmation of posterior fossa anomalies could also be challenging with high rates of false positive diagnoses reported in the literature[5]. The lack of a standardized protocol for post-natal assessment in most of the included studies did not allow a precise estimation of the exact number of diagnoses confirmed after birth. Moreover, confirmation of the diagnosis using post-natal 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.

Implication for clinical practice

Prenatal counselling 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[34,35]; multiplanar assessment of the posterior fossa using axial, sagittal and coronal planes is necessary in order to precisely define these conditions, especially because anomalies with 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 the length of follow-up, neurodevelopmental tool adopted, age at assessment, presence of additional anomalies and choice of an appropriate control group preclude are all relevant. The term neurodevelopmental outcome can also be misleading and inappropriate when dealing with 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 highlights the need for new research aiming at finding reliable prognostic imaging markers: in this study the authors retrospectively reviewed the charts of 26 patients with a diagnosis of DWM[3]. They found that none of the patients in the group with a normal vermis

morphology had associated brain malformations and the majority had normal outcome; while all those with a dysplastic vermis 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 independently associated with a better outcome[3]. The feasibility of detailed evaluation of vermian anatomy during pre-natal life and its independent role in predicting the neurodevelopmental outcome have yet to be established[15].

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 completely elucidated 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 suggested that children with isolated MCM had lower developmental, visual motor and social performance compared to controls[25]. However, all the mean values for the neurodevelopmental

Failure of fenestration of posterior membranous area leads to the persistence of the Blake's pouch[37]. On imaging, BPC is characterised by the presence of an upward displacement of a normal cerebellar vermis, normal fastigium, tentorium and the size of the cisterna magna. Tetra-ventricular hydrocephaly is an associated finding commonly reported post-natally. Although none of the included studies used specific tools to ascertain the cerebellar function, the findings from this review suggest a generally favourable outcome.

The data from this systematic review on the prognosis of children with isolated VH are debatable. In view of the very small number of cases included, no robust evidence can really be extrapolated. The results from this meta-analysis are surprising and disagree with what is observed after birth, where vermian hypoplasia, 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 vermian hypoplasia before birth - many cases labeled as hypoplasia during the prenatal period may actually corresponded to a normal vermis, theoretically explaining the reason why the outcome reported in this meta-analysis was favorable. In the collective author's experience, prenatal diagnosis of VH is affected by high rates of false positive cases, with most of the cases found to be BPC at birth[5].

Implication for research

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

Conclusions

Isolated DWM is associated with increased risk of abnormal neurodevelopmental outcome, while isolated MCM and BPC have a generally favourable 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 need to be further ascertained. 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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Table 1. General characteristics of the included studies.

Author	Year	Country	Study design	Pre-natal imaging	Anomalies analysed	Neurodevelopmental tool	Age at follow up[Ω]
Tarui[*33]	2014	United States	Prospective	MRI	VH	Wechsler Preschool and Primary scale of intelligence for Children (3rd or 4th ed), Vineland Adaptive Behaviour Scale-II, Behavior Rating Inventory of Executive function, Child Behavior Checklist, Social Communication Questionnaire	6.1y (mean)
Zhao[31]	2013	China	Prospective	US, MRI	BPC	Basic neurological examination	1-3y
Vatansaver[24]	2013	United Kingdom	Prospective	MRI	MCM	Griffith Mental Developmental Scale (revised), Bayley Scales of Infant Development (3rd edition)	1-2.1y
Guibaud[*15]	2012	France	Retrospective	US, MRI	DWM	Clinical examination and early development scale	1.9-4y
Gandolfi-Colleoni[*21]	2012	Italy	Retrospective	US, MRI	DWM, BPC, MCM, VH	Standard neurological examination	1-5y
Paladini[*2]	2012	Italy	Retrospective	US, MRI	BPC	Standard neurological examination	1-42m
Patek[*28]	2012	USA	Retrospective	US, MRI	DWM, MCM, VH	Parental assessment, healthcare assessment	2m-4.5y
Bertucci[*29]	2011	Italy-Israel	Prospective	US, MRI	DWM, BPC, MCM, VH	Standard neurological examination	2y
Ozkan[*22]	2011	Turkey	Retrospective	US	DWM	Standard neurological examination	NS
Dror[*25]	2009	Israel	Prospective	US, MRI	MCM	Gessell developmental schedules and Peabody developmental motor scale	16-57m
Forzano[*30]	2007	United Kingdom	Retrospective	US, MRI	MCM	Semi-structured questionnaire (psychomotor developmental milestones, seizures)	2d-3m
Long[*26]	2006	United Kingdom	Retrospective	US	MCM	Basic neurological examination	4y
Zalel[32]	2006	Israel	Retrospective	US, MRI	BPC	Standard neurological examination	1-7.5y

Has[*20]	2004	Turkey	Retrospective	US, MRI	DW	Basic neurological examination	3-5.5y
Leitner[*27]	2004	Israel	Retrospective	US	MCM	Telephone interview, parental report	1.5-2y
Ecker[*23]	2000	United States	Retrospective	US	DWM	Standard neurological examination	6w

a: DWM: Dandy Walker malformation, MCM: mega-cisterna magna, BPC: Blakes' pouch cyst, VH: vermian hypoplasia. Ω: range. NS: not stated

*: Additional information provided by the authors.

Table 2. Quality assessment of the included studies according to Newcastle-Ottawa Scale (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 Comparability.

38.

Author	Year	Selection	Comparability	Outcome
Tarui[33]	2014	★★★★	★★	★★★
Zhao[31]	2013	★★	★	★
Vatansaver[24]	2013	★★★	★	★★
Guibaud[15]	2012	★★★	★	★★★
Gandolfi-Colleoni[21]	2012	★★★	★	★★
Paladini[2]	2012	★★★	★	★★
Patek[28]	2012	★★★	★	★★
Bertucci[29]	2011	★★	★	★
Ozkan[23]	2011	★	★	★
Dror[25]	2009	★★★	★★	★★★
Forzano[30]	2007	★★	★	★★
Long[26]	2006	★★	★	★
Zalel[32]	2006	★★	★	★★
Has[20]	2004	★★★	★	★★
Leitner[27]	2003	★	★	★
Ecker[22]	2000	★★	★	★

Table 3. Pooled proportions for the occurrence of abnormal neurodevelopmental outcome in children with a prenatal diagnosis of posterior fossa anomalies.

Anomaly	Studies (n)	Fetuses (n/N)	Raw % (95% CI)	I^2 (%)	Pooled proportion (95% CI)
DWM	6	7/13	53,84 (25,1-80,8)	53,8	49,18 (17,9-80,8)
MCM	81	12/81	14,81 (7,9-24,4)	41,6	14,98 (8,4-23,1)
BPC	46	1/46	2,17 (0,1-11,5)	0	4,7% (0,1-12,1)
VH	4	3/18	16,67 (3,6-41,4)	77,7	30,74 (0,6-79,1)

Table 4. Studies reporting the rate of abnormal neurodevelopmental outcome in fetuses with isolated Dandy Walker malformation.

Study	Patients tested	Abnormal neurodevelopmental outcome	Age at follow-up	Neurodevelopmental tool	Outcome description
Guibaud[15] (2012)	2	100% (2)	2.7-4y	Clinical examination and early development scale	Case 1: Walk at 15 months; last visit, 32 months: two- word sentences, clumsy left-hand grip, upgaze impairment. Hydrocephaly at 1 month and ventriculo-peritoneal shunting Case 2: Walk at 13 months; last visit, 4 years old: good non-verbal reasoning (visuospatialIQ109); verbalIQ78, good receptive and weak expressive language (under speech therapy). Hydrocephaly at 4 months and ventriculo-peritoneal shunting.
Gandolfi-Colleoni[*21] (2012)	5	60% (3)		Basic neurological examination	Case 1: Severe intellectual and motor retardation at 2 years (cerebral heterotopia diagnosed post-natally) Case 2: Severe neurological (mostly psychomotor) retardation at 2 years Case 3: Mild language and psychomotor impairment (postnatal diagnosis of Ritscher-Schinzel syndrome)
Ozkan[*22] (2011)	2	0% (0)	Not stated	Basic neurological examination	-
Has[*20] (2004)	3	100% (3)	3-5.5y	Basic neurological examination	Case 1: 3.5 years old with neuro-motor retardation and abnormal EEG findings; under anticonvulsive therapy. Case 2: 3.0 years old with neuro-motor retardation and cysto-peritoneal shunt at 7 months; under anticonvulsive therapy. Case 3: 5.5 years old with neuro-motor retardation and cysto- peritoneal shunt at 2 months.
Ecker[*23] (2000)	1	0% (0)	6w	Basic neurological examination	-

*: additional information provided by the authors

Table 5. Studies reporting the rate of abnormal neurodevelopmental outcome in fetuses with isolated mega-cisterna magna.

Study	Patients tested	Abnormal neurodevelopmental outcome	Age at follow-up	Neurodevelopmental tool	Outcome description
Vatansaver (2013)[24]	6	50% (3)	1-2.1y	Griffith Mental Developmental Scale (revised), Bailey Scales of Infant Development (3rd edition)	Visuo-spatial perception and attention problems
Gandolfi-Colleoni* (2012)[21]	16	12.5% (2)		Basic neurological examination	Case 1: Mild language disorder at 2 years 10 months years Case 2: Mild language and motor disorder at 3 years (facial dimorphism, no specific genetic diagnosis)
Patek*[28] (2012)	5	0% (0)	1.4-3.3	Basic neurological examination and parental report	-
Bertucci*[29] (2011)	1	0% (0)	6m	Basic neurological examination	-
Dror*[25] (2009)	17	11.8% (2)	1.8-1.9y	Gessell developmental schedules and Peabody developmental motor scale	Case 1: (cisterna magna: 12 mm during pregnancy) 23 months of age; 4- to 5-month general delay in all developmental aspects. 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 his development are language and communication. Currently under evaluation for autistic spectrum disorder.
Forzano*[30] (2007)	13	0% (0)	2d-3m	Basic neurological examination	-
Long*[26] (2006)	11	9.1% (1)	4y	Basic neurological examination	Case 1: Delayed motor development (poor feeding and delayed walking at 29 months).
Leitner[27] (2004)	9	33.3% (3)	3m-3y	Telephone interview	Case 1: Delayed motor development Case 2: Delayed motor development Case 3: Delayed motor development and language deficits.

*: additional information provided by the authors

Table 6. Studies reporting the rate of abnormal neurodevelopmental outcome in fetuses with isolated Blakes' pouch cyst.

Study	Patients tested	Abnormal neurodevelopmental outcome	Age at follow-up	Neurodevelopmental tool	Outcome description
Zhao[31] (2013)	8	0% (0)	1-3y	Basic neurological examination	-
Paladini[*2] (2012)	8	0% (0)	1m-3.5y	Basic neurological examination	-
Gandolfi-Colleoni[*21] (2012)	20	5% (1)		Basic neurological examination	Mild psychomotor disorder at 3 years, normal intellectual and language function
Bertucci[*29] (2011)	3	0% (0)	6m	Basic neurological examination	-
Zalel[32] (2007)	7	0% (0)	1-7.5y	Basic neurological examination	-

*: additional information provided by the authors

Table 7. Studies reporting the rate of abnormal neurodevelopmental outcome in fetuses with isolated vermian hypoplasia.

Study	Patients tested	Abnormal neurodevelopmental outcome	Age at follow-up	Neurodevelopmental tool	Outcome description
Tarui* (2014)[33]	12	0% (0)	6.1y (mean)	Wechsler Preschool and Primary scale of intelligence for Children (3rd or 4th ed), Vineland Adaptive Behaviour Scale-II, Behavior Rating Inventory of Executive function, Child Behavior Checklist, Social Communication Questionnaire	-
Patek*[28] (2012)	2	100% (2)	2.2-5.5y	Basic neurological examination and parental report	Case 1: Seizures and developmental delay based on parental report. Case 2: Developmental delay based on parental report
Gandolfi-Colleoni*[21] (2012)	3	33.3% (1)		Basic neurological examination	Not stated
Bertucci*[29] (2011)	1	0% (0)	6m	Basic neurological examination	-

*: additional information provided by the authors

FIGURE LEGEND

Figure 1. Systematic review flowchart

Figure 2. Pooled proportions for the occurrence of abnormal overall neurodevelopmental outcome in foetuses with different posterior fossa anomalies.