Neurodevelopmental outcomes in children with cerebellar malformations: a systematic review

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PUBLICATION DATA
Accepted for publication 12th October 2008.
Published online 3rd February 2009.

LIST OF ABBREVIATIONS

DWM	Dandy–Walker malformation
DWV	Dandy–Walker variant
IVH	Inferior vermis hypoplasia
MCM	Mega cisterna magna
PCH	Pontocerebellar hypoplasia

ACKNOWLEDGEMENTS
Marie-Eve Bolduc is supported by a McGill University Health Center Studentship award for her graduate studies. Dr Limperopoulos is supported by the Canadian Research Chairs Program.

Cerebellar malformations are increasingly diagnosed in the fetal period. Consequently, their consideration requires stressful and often critical decisions from both clinicians and families. This has resulted in an emergent need to understand better the impact of these early life lesions on child development. We performed a comprehensive literature search of studies describing neurodevelopmental outcomes of cerebellar malformations between January 1997 and December 2007. Overall, the data suggested that children with isolated inferior vermis hypoplasia (IVH) and mega cisterna magna (MCM) have a good developmental outcome, whereas children with molar tooth sign/Joubert syndrome, vermis hypoplasia, pontocerebellar hypoplasia (PCH) type II, and cerebellar agenesis experience moderate to severe global developmental delays. Reports for Dandy–Walker malformation (DWM) were conflicting; however, the presence of a normally lobulated vermis and the absence of associated brain anomalies were associated with a more favourable outcome. Finally, children with isolated cerebellar hypoplasia experienced fewer impairments. Important methodological limitations highlighted include a lack of standardized outcome measure use in 79% of studies and the predominant use of retrospective study designs (85%), with 40% limited to case reports or case-series. In summary, rigorous outcome studies describing the spectrum of disabilities in survivors are urgently needed to accurately delineate the long-term neurodevelopmental consequences of cerebellar malformations.

Recent advances in neonatal intensive care and neuroimaging techniques, in particular magnetic resonance imaging, have greatly enhanced our ability to detect structural anomalies of the brain. This is particularly true for lesions in the posterior fossa.[1,2] The incidence of posterior fossa malformations diagnosed in the newborn period is estimated to be 1 out of every 5000 live births.[3] Fetal posterior fossa malformations on imaging are now among the most commonly diagnosed brain malformations in utero, though the actual prevalence is unknown. Advances in our ability to diagnose accurately cerebellar malformations have increased the need for a greater understanding of the impact of these early-life lesions on child function. Despite these advances, the long-term neurodevelopmental consequences of cerebellar malformations in children remain poorly defined. However, their consideration requires stressful and often critical decisions from both clinicians and families. This is particularly important in view of the fact that studies are now showing that up to 80% of parents choose to terminate their pregnancy after a prenatal diagnosis of a cerebellar malformation, even in the absence of rigorous outcomes data.[4,5]

In recent years, the traditional role of the cerebellum has been repeatedly challenged. The cerebellum, once underestimated as a simple centre for motor coordination and execution, is now increasingly recognized as a centre for higher cognitive functions as well. There is growing evidence in primate and adult literature to support an important role for the cerebellum in perceptual, linguistic, cognitive, and affective functions.[1,6–9] In fact, Schmahmann and Sherman[10] and Schmahmann[11] have described the cerebellar cognitive affective syndrome in adults with

 DOI: 10.1111/j.1469-8749.2008.03224.x

lesions or malformations confined to the cerebellum. These patients were found to have a constellation of symptoms including cognitive, affective, and behavioural deficits.[12] It has been hypothesized that the cerebellum acts as a modulator for all the cerebrocerebellar subsystems that control motor, sensory, cognitive, affective, and autonomic domains.[10] Moreover, the cerebellum has been associated with deficits in spatial navigation, autism, and mutism, and with impaired ability to learn music.[13]

Despite this accumulating evidence, it is unclear whether these higher-order cognitive functions have been systematically evaluated in children with cerebellar malformations. Therefore, the objective of this paper was to summarize our current knowledge of the neurodevelopmental outcomes in children with cerebellar malformations. Studies describing cognitive, language, socialization, behavioural, or neuromotor outcomes published over the past decade were systematically reviewed.

METHOD

To delineate better the current impact of cerebellar malformations on child development, we performed a systematic review of the literature on neurodevelopmental outcomes in children with cerebellar malformations limited to studies published in the past 10 years (January 1997 to December 2007). Our systematic search was performed using PubMed, Medline, and CINAHL using the following keywords: cerebellar malformation; cerebellar dysgenesis; posterior fossa malformation; posterior fossa dysgenesis; cerebellar hypoplasia, cerebellar dysplasia, cerebellar agenesis; DWM; Dandy–Walker variant (DWV); Dandy–Walker complex; Dandy–Walker syndrome; vermis hypoplasia; rhombencephalosynapsis; pontocerebellar atrophy; pontocerebellar hypoplasia, (PCH); Joubert syndrome, molar tooth sign, development, and outcome. English-language studies describing neurodevelopmental outcomes in children (0–18y) were retained for this review. The reference list of selected articles was also searched.

RESULTS

The spectrum of dysgenetic abnormalities of the cerebellum is broad, ranging from subtle to very significant malformations. The most commonly described entity of cerebellar malformations is often referred to as the Dandy–Walker complex or continuum, a term used to characterize the different degrees of malformations of the cerebellar vermis and which includes DWM, DWV, or inferior vermis hypoplasia, (IVH), and mega-cisterna magna (described below).[14,15] Other malformations that are summarized in the current review include the molar tooth sign, rhombencephalosynapsis, cerebellar hypoplasia/dysplasia, vermis hypoplasia, PCH, and vermis hypoplasia. A total of 46 studies were reviewed based on our search strategy that specifically described neurodevelopmental outcomes in children with cerebellar malformations, and are summarized in Table I. An overall summary of the prevalence of developmental, cognitive, language, behavioural, and motor disabilities, as well as neurological abnormalities over our 10-year review period are provided in Table II. The frequency of occurrence of central nervous system (CNS) and extra-CNS findings are presented in Table III.

Dandy–Walker malformation

The most common and striking of these cerebellar malformations is known as the Dandy–Walker malformation (DWM).[16] DWM is characterized by partial or complete agenesis of the cerebellar vermis, cystic dilation of the fourth ventricle, and an enlarged posterior fossa combined with a superior displacement of the cerebellar hemisphere[17] (Fig. 1). However, variations in the definition of DWM were evident over our 10-year review period. For instance, some authors included features such as the presence of hydrocephalus[18,19] or the presence of communication between the posterior fossa cyst and the fourth ventricle as a fundamental criterion for the diagnosis of DWM.[20] Conversely, some studies used the term Dandy–Walker complex to describe what most define as DWM. As a result, the generalizability of the data is limited and the importance of a universally accepted classification scheme for cerebellar malformation is a priority.

Overall, reports on the outcome of DWM were conflicting. Although one study reported that all children with DWM experienced some degree of cognitive impairment,[19] other studies have reported a more favourable outcome.[17,20] Overall, up to one-third of survivors were reported to be developing normally.[4,21,22] Specifically, Boddaert et al.[17] compared the IQ of 21 children with DWM with and without normal vermis lobulation and showed that 82% of children in the former group had a normal IQ as opposed to none in the latter. Furthermore, among the subgroup with normal vermis lobulation and abnormal IQ, all children had associated CNS and extra-CNS abnormalities. Similarly, Klein et al.[20] divided 26 children into two groups, one with partial agenesis of the vermis with normal lobulation, and a second with severe vermis malformations. In the former group the majority (90%) had a normal IQ and developmental quotients as opposed to none in the latter group. However, it is important to note that one of the two children with partial agenesis of the vermis who scored in the impaired range had fragile X, and the other, severe periventricular leukomalacia resulting from being born preterm. It is also

Table I: Summary of articles describing neurodevelopmental outcomes of children with cerebellar malformations over the 10-year review period

Author	Year	Diagnosis	Study design	*n*	Age range (mean/median)	Standardized outcome measures
Dandy–Walker complex (DWC)						
Forzano et al.[5]	2007	DWC, MCM	Chart review	56	2d–5mo (1mo)	No
Poot et al.[23]	2007	DWM	Case report	1	10y (n/a)	No
Limperopoulos et al.[26]	2006	IVH	Cross-sectional	19	Range not specified (19.2mo)	Yes
Abdel-Salam et al.[24]	2006	DWM	Case report	2	6–8y (7y)	No
Long et al.[25]	2006	DWM, DWV, MCM	Chart review	86	Range not specified (96mo)	No
Has et al.[22]	2004	DWM, DWV	Chart review	78	3mo–5y 6mo (n/a)	No
Boddaert et al.[17]	2003	DWM	Chart review	21	9mo–34y	Yes[a]
Klein et al.[20]	2003	DWM	Chart review	26	Not specified (10y 6mo)	Yes[a]
Kumar et al.[18]	2001	DWS	Chart review	42	9mo–12y (3y 10mo)	No
Ecker et al.[4]	2000	DWC, DWV	Chart review	99	6wk (n/a)	No
Kölble et al.[21]	2000	DWM	Chart review	10	4wk–21mo (n/a)	No
Aletebi et al.[19]	1999	DWM, MCM	Chart review	15	23–50mo (n/a)	Yes[a]
Haimovici et al.[27]	1997	MCM	Chart review	15	0d–9mo (n/a)	No
Molar-tooth sign/Joubert syndrome						
Kumar et al.[36]	2007	Joubert	Case report	1	1y	No
Ray et al.[39]	2007	Joubert	Case report	1	7mo	No
Braddock et al.[41]	2006	Joubert	Cross-sectional	21	32mo–19y (10y 5mo)	Yes
Romano et al.[34]	2006	Molar tooth	Chart review	13	2–16y (n/a)	No
Hodgkins et al.[37]	2004	Joubert	Chart review	18	3mo–21y (10y 11mo)	Yes[a]
Kumandas et al.[30]	2004	Joubert	Cross-sectional	7	4d–8y (n/a)	No
Torres et al.[38]	2001	Joubert	Case report	1	40mo	Yes[a]
Fennell et al.[32]	1999	Joubert	Cross-sectional	51	11mo–17y (n/a)	Yes
Maria et al.[33]	1999	Joubert	Cross-sectional	61	1y 4mo–17y (7y 6mo)	No
Gitten et al.[35]	1998	Joubert	Cross-sectional	32	14–204mo (68.7mo)	Yes
Steinlin et al.[40]	1997	Joubert	Chart review	19	1y 6mo–37y (n/a)	No
Rhombencephalosynapsis (RCS)						
Chemli et al.[42]	2007	RCS	Case report	1	3y 6mo	No
Odemis et al.[48]	2003	RCS	Case report	1	8mo	No
Jellinger[47]	2002	RCS	Case report	1	7y	No
Toelle et al.[43]	2002	RCS	Cross-sectional	9	1y 6mo–6y (n/a)	No
Danon et al.[46]	2000	RCS	Case report	1	5y	No
Utsunomiya et al.[44]	1998	RCS	Case report	2	Infancy–4y	No
Aydingoz et al.[45]	1997	RCS	Case report	1	17mo	No
Cerebellar hypoplasia/dysplasia						
Tavano et al.[54]	2007	Hypoplasia, dysplasia	Cross-sectional	27	3–34y (11y 1mo)	Yes
Tavano et al.[57]	2007	Dysgenesis	Chart review	5	2–11y (n/a)	Yes[a]
Ventura et al.[56]	2006	Hypoplasia	Chart review	14	4–20y (n/a)	Yes[a]
Yapici et al.[53]	2005	Hypoplasia	Chart review	2	5–12y	No
McCollom et al.[55]	2003	Hypoplasia	Case report	1	6mo	No
Wassmer et al.[52]	2003	Hypoplasia	Chart review	45	Not specified (children)	No
Soto-Ares et al.[51]	2000	Dysplasia	Chart review	46	10d–14y (n/a)	No
Vermis hypoplasia						
Bruck et al.[58]	2000	Hypoplasia	Case report	2	2y and 9y	No
Koutsouraki et al.[59]	2007	Hypoplasia	Case report	1	15y	No
Pontocerebellar hypoplasia type II (PCH)						
Steinlin et al.[60]	2007	PCH	Chart review	21	4mo–11y 2mo (49mo)	No
Dilber et al.[63]	2002	PCH	Case report	2	30mo and 17y	No
Sans-Fito et al.[65]	2002	PCH	Case report	1	3y	No
Coppola et al.[64]	2000	PCH	Case report	2	18mo and 5y	No

Table I: Continued

Author	Year	Diagnosis	Study design	*n*	Age range (mean/median)	Standardized outcome measures
Cerebellar agenesis						
Titomanlio et al.[67]	2005	Agenesis	Case report	1	17y	No
Gardner et al.[68]	2001	Agenesis	Chart review	5	2–17y (n/a)	No

[a]Standardized outcome measures extracted from chart review. DWC, Dandy-Walker complex; DWM, Dandy–Walker malformation; DWS, Dandy–Walker syndrome; DWV, Dandy–Walker variant; IVH, inferior vermis hypoplasia; MCM, mega cisterna magna; PCH, pontocerebellar hypoplasia; RCS, rhombencephalosynapsis; n/a, not available.

Table II: Summary of developmental/cognitive delays, language, behavioural deficits, and neurological abnormalities in children with cerebellar malformations

Diagnostic group	Developmental/ cognitive delay (%)	Language deficits (%)	Social/behavioural deficits (%)	Neurological abnormalities (%)
Molar tooth sign/Joubert syndrome	100	100	100	100
Vermis hypoplasia	100	100	100	20–100
Pontocerebellar hypoplasia type II	100	n/a	n/a	100
Cerebellar agenesis	100	100	n/a	80
Dandy–Walker malformation	67–100	50	n/a	50–100
Cerebellar hypoplasia/dysplasia	53–87	6–100	14–71	67–100
Rhombencephalosynapsis	56	25	61	94
Dandy–Walker variant	46	n/a	n/a	100
Isolated inferior vermis hypoplasia	23	23	23	23
Mega cisterna magna	0–8	n/a	n/a	0

n/a, not available.

Table III: Summary of central nervous system (CNS) and non-CNS anomalies in children with cerebellar malformations

Diagnostic group	Associated CNS anomalies (%)	Associated non-CNS anomalies (%)
Cerebellar hypoplasia/dysplasia	20–88	29–47
Rhombencephalosynapsis	56	25
Dandy–Walker malformation	43–67	9–75
Dandy–Walker variant	35–71	64–65
Pontocerebellar hypoplasia type II	55	n/a
Mega cisterna magna	36–66	18–62
Molar tooth sign/Joubert syndrome	0–38	2–71
Cerebellar agenesis	20	n/a
Vermis hypoplasia	n/a	n/a

n/a, not available.

worthy of mention that all children with severe vermis malformations had associated cerebral anomalies, three of which had agenesis of the corpus callosum.

Language and communication abilities in survivors of DWM have not been well described. In fact, language deficits were only described in a single chart review and two case reports.[19,23,24] Conversely, neurological abnormalities have been reported in up to 50% of survivors[4,18,21,22] and included hypotonia (50%),[21,23,24] signs of cerebellar dysfunction (not further described; 42%),[18] and hemiparesis (5%).[18]

Associated anomalies in both the CNS and other systems have been reported in up to 86% of children.[4] Specifically, CNS abnormalities have been described in 13 to 67% of cases,[17–22] with the most common anomaly being ventriculomegaly, observed in 36 to 67% of children.[4,17,21,22] Other common CNS malformations included agenesis of corpus callosum, reported in 5 to 50% of children.[5,18,21,23] Interestingly, agenesis of the corpus callosum was observed in 60 to100% of the children with abnormal vermis lobulation.[17,20] In studies where comparison of children with isolated DWM and those who had associated CNS anomalies was possible, we found that all children with DWM who were developing normally had no associated CNS malformations.[17,20,21] Conversely, all but one with developmental delays had associated CNS anomalies or epilepsy.[17,19–21] However, many studies clustered those with and without concurrent CNS findings, and therefore further analysis was not possible. Extra-CNS

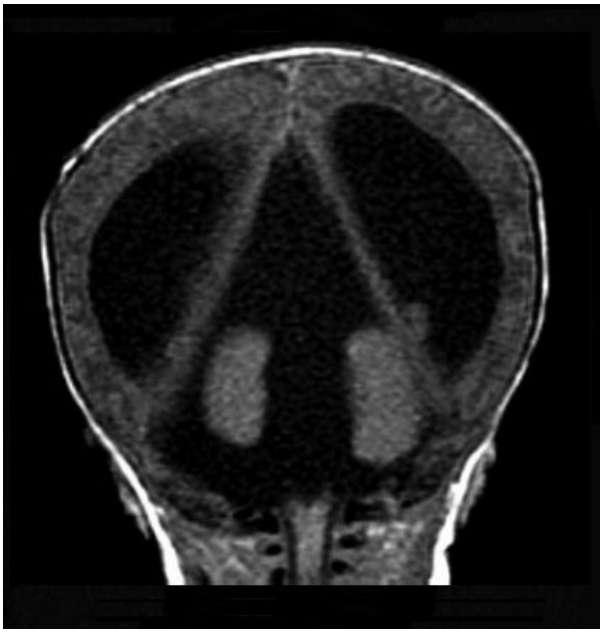

Figure 1: T1-weighted coronal magnetic resonance image of a term infant with Dandy–Walker malformation, characterized by hypoplasia of the cerebellar vermis, massive cystic dilation of the fourth ventricle, and elevated tentorium.

anomalies were less common, and were reported in 9 to 44% of children[18,22] and included structural heart defects, renal, extremity and facial anomalies, and single umbilical artery. [4,17,18,21–24]

Two studies in the literature have collectively described the outcome of children with DWM and DWV without differentiating between the two diagnostic groups. Forzano et al.[5] compared the outcome in 34 children with isolated and non-isolated DWM and DWV diagnosed prenatally. Interestingly, 68% of parents elected to terminate the pregnancy. Among survivors, 40% were developing normally, of which half were diagnosed with associated syndromes[5] including occipital encephalocoele. In a second study[25] all children with atypical development had associated anomalies, however, the presence of CNS anomalies did not predict a poorer outcome. Associated (CNS and non-CNS) anomalies were reported in 83% of cases.[25]

In summary, available evidence on the outcome of DWM suggests a more favourable neurodevelopmental outcome in children with no associated supratentorial findings and in those with a normally lobulated vermis.

Dandy–Walker variant

DWV has been used to describe a combination of cystic dilation of the fourth ventricle and hypoplastic cerebellar vermis in the absence of an enlargement of the posterior fossa.[14] However, in recent years, it has been strongly advocated that the term DWV be abandoned altogether, given its multiple and variable definitions.[14] To date, these inconsistencies have prevented the meaningful comparison of diagnosis and outcome among published series, thereby compromising accurate prognostication. As such, it is now strongly recommended that the term DWV be abandoned altogether. However, for the purposes of this review, we have summarized the literature that has described the outcome of DWV to date. Some reports indicate that more than half of children with DWV were developing normally.[4] On the other hand, in a study by Has et al.,[22] all children with DWV experienced neurological sequelae, including microcephaly in 21%. Associated anomalies (CNS and non-CNS) have been described in up to 71% of children with DWV, with the most common being ventriculomegaly (27–71%)[4,22] and agenesis of corpus callosum (14%).[4,22] Extra-CNS anomalies have also been reported in up to 65%,[4,22] with cardiac, renal, extremity, and facial anomalies occurring most frequently.[4,22]

Inferior vermis hypoplasia

IVH is characterized by partial absence of the inferior portion of the cerebellar vermis with normal- or near normal-shaped cerebellar hemispheres, a normal-sized posterior fossa without obvious cystic lesions, and normal supratentorial structures[26] (Fig. 2). IVH represents an arrested, incomplete downward growth of the vermis, leaving an enlarged midline cerebrospinal-fluid space, which may be mistaken for a cystic lesion. It is important to note that the diagnostic entity of IVH continues to be inconsistently used. For example, some investigators consider this lesion a normal variant, whereas others have used the term DWV interchangeably, even in the absence of a cystic fourth ventricle and with a normal-sized posterior fossa.

Normal development was reported in 77% of children with isolated IVH.[26] In the subgroup of children (23%) with isolated IVH who had delayed development, gross and fine motor disabilities, as well as social and communication deficits, were reported. Furthermore, 15% of these children were found to have behavioural problems, particularly symptoms of disruptive behaviour.[26] Moreover, 23% of the children with IVH were found to be hypotonic on neurological examination.

Mega cisterna magna

MCM is characterized by an enlarged cisterna magna with a normal fourth ventricle and cerebellar hemispheres and vermis[14] (Fig. 3). The developmental outcome of children with MCM was generally described as favourable, with the majority of children (92–100%) with isolated MCM

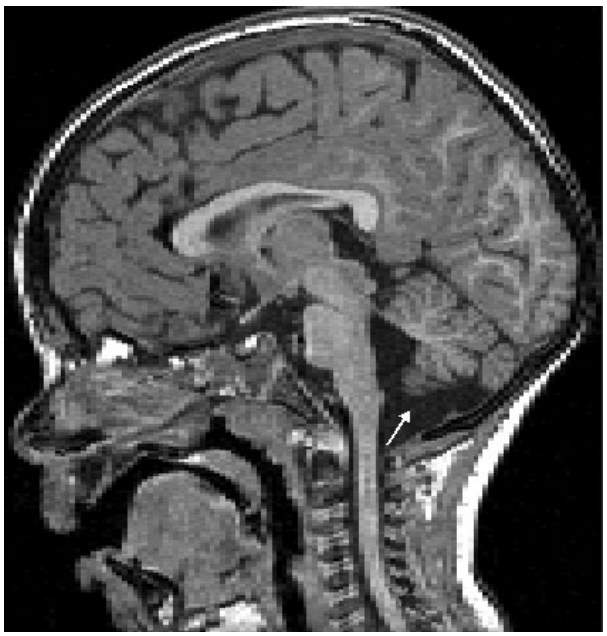

Figure 2: T1-weighted magnetic resonance image of the midline sagittal view illustrating incomplete downgrowth of the vermis (arrow) in a 18-month-old child with inferior vermian hypoplasia.

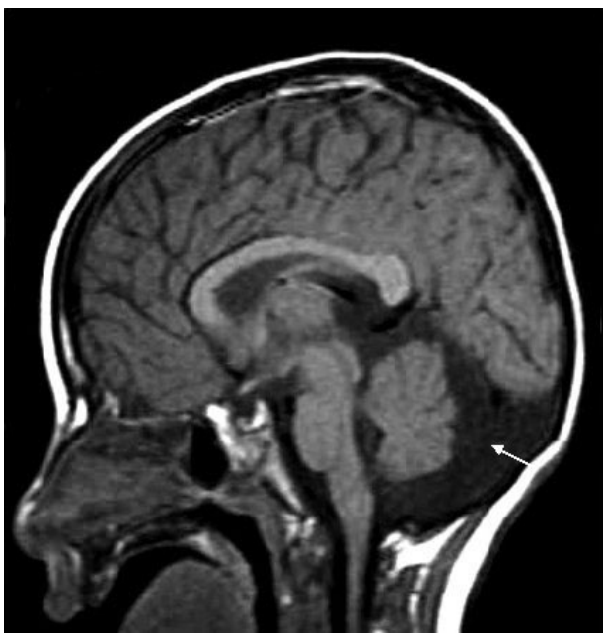

Figure 3: T1-weighted sagittal magnetic resonance image showing an enlarged cisterna magna (arrow) and normal fourth ventricle and cerebellar hemispheres and vermis in a 2-year-old child with mega cisterna magna.

developing normally.[5,25,27] In fact, on the basis of medical record reviews only one patient was presenting with delayed motor development.[25] However, available data in adults with MCM suggest that higher cognitive functions and language abilities, such as verbal memory and fluency, executive functions and semantic fluency, may be impaired in this population.[28] It is possible that more subtle deficits may be undiagnosed because of the lack of in-depth neuropsychological testing performed in the paediatric studies that were reviewed, or that some of these higher cognitive deficits present in later life.

More than two-thirds of children with MCM and associated CNS (e.g. ventriculomegaly) and non-CNS anomalies (e.g. orthopaedic malformations)[5] were reported to be developing normally[5,25] on the basis of medical chart reviews. In the remaining one-third, the spectrum of disability included cognitive and language delay as well as delayed motor development and neurological abnormalities (e.g. cerebellar ataxia).[25] Only one patient had severe cognitive impairment; however, this patient was also diagnosed with cytomegalovirus infection and therefore deficits cannot be directly linked to the cerebellar malformation. Ventriculomegaly was the most common CNS finding associated with MCM, reported in 46 to 66% of children,[5,25] whereas a renal defect was the most frequent non-CNS anomaly described in approximately one-third.[5,25] Agenesis of the corpus callosum and cardiac and liver anomalies were also reported but these were less frequent (4%).[25]

In summary, the presence of concomitant CNS anomalies in children with MCM was associated with a poorer prognosis albeit most children were developing normally and impairments were found to be mild in severity.

Molar tooth sign/Joubert syndrome

The molar tooth sign is characterized by an abnormally deep interpeduncular fossa, enlarged superior cerebellar peduncles that are more horizontally oriented, and a hypoplastic cerebellar vermis[29] (Fig. 4). Joubert syndrome is the most known syndrome typified and is associated with developmental delays, hypotonia, breathing anomalies, abnormal eye movement, and facial dysmorphia.[30] More than eight different types of Joubert syndrome-related disorders have been identified and were found to have various genotypes and phenotypes.[31] Although the different types of Joubert syndrome-related disorders may have diverse outcomes, it was not possible in the context of the literature reviewed to identify the specific impact of each type of Joubert syndrome on neurodevelopmental outcome.

Nevertheless, available evidence suggests that impaired cognitive function or developmental delay was present in all children, with the majority experiencing severe

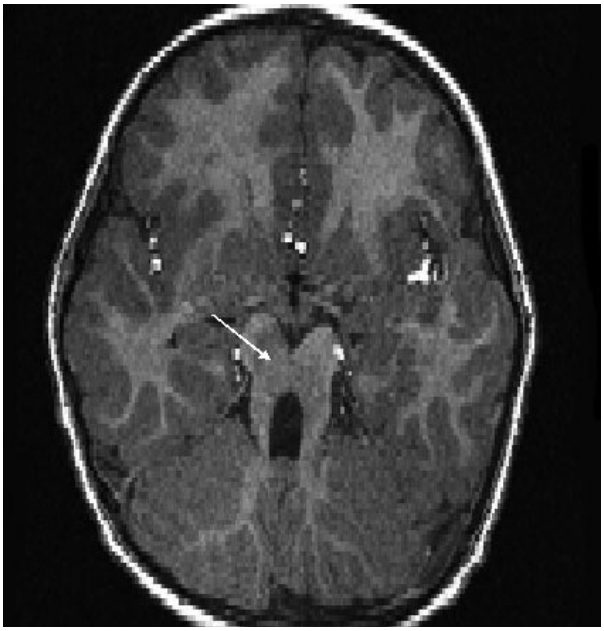

Figure 4: T1-weighted axial magnetic resonance image at the level of the brainstem showing deep interpeduncular cistern (as a result of reduced pyramidal decussation (arrow)), thick superior cerebellar peduncles, and enlarged fourth ventricle representing the molar tooth sign in a 3-year old with child Joubert syndrome.

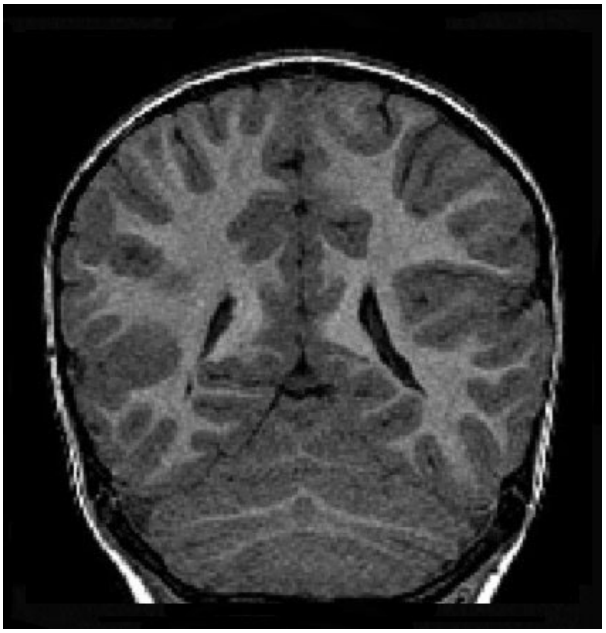

Figure 5: T1-weighted coronal magnetic resonance image of a 3-year-old child with rhombencephalosynapsis, demonstrating a complete absence of the vermis and fusion of the cerebellar hemispheres.

disability.[30,32–39] Moreover, in addition to delayed developmental milestones and impaired developmental quotients, immediate and delayed memory, conceptual development, perceptual discrimination, and daily living skills were reported to be impaired.[32,33,38,40] Language abilities were also affected in all children with molar tooth sign or Joubert syndrome.[9,32,34,37,38,40,41] In particular, deficits in expressive language,[38] verbal fluency,[33] and vocabulary were noted.[32,34] Furthermore, approximately half of children with Joubert syndrome were found to have impaired concept development, as evaluated by the Bracken Basic Concept Scale.[32] Behavioural and social problems were also found to be prevalent in two studies.[32,38] In fact, 100% of parents reported their children as being demanding or strong-willed the children were also described as hyperactive (50%) or aggressive (25%). Additionally, in a case report a child was reported to have significant social deficits,[39] and two other children had behavioural difficulties (tendency to aggression).[40] Moreover, significant motor delays were frequently reported.[30,32,34,37,38,40,41]

Neurological impairments were present in all cases,[30,32,34,40] and were characterized by ataxia (100%),[30,32] hypotonia (97–100%),[30,33,34,36–40] and oculomotor disturbances (42–77%).[30,33,34,36,38,40] In addition, visuomotor deficits were also found to be prevalent.[32] Associated CNS anomalies were less prevalent, with the most common CNS abnormality being dysgenesis of the corpus callosum in 5 to 29% of children.[30,33,37] Atrophy of the cerebrum,[33] anomalies of the mesencephalon[30] and of the pontomesencephalic junction,[33] brainstem hypoplasia,[37] dilation of the ventricular system,[37] as well as delayed myelination[33] and white-matter lesions[37] were also reported. The most common extra-CNS anomalies included breathing abnormalities (38–86%),[30,33,34,37] facial dysmorphism (71%),[30,38] and extremity malformations (8–43%).[30,33,34,37]

Rhombencephalosynapsis

Rhombencephalosynapsis is considered a rare cerebellar malformation that includes agenesis of the cerebellar vermis and fusion of the cerebellar hemispheres[14] (Fig. 5). Data describing cognitive development in this population have been conflicting: some have reported normal cognitive abilities[42,43] whereas others have reported severe learning disability* and developmental delay.[44–47] Neuromotor impairments were reported in all case reports of rhombencephalosynapsis,[42–48] including delayed motor development,[44,48] hypotonia,[44,48] cerebral palsy,[43] decreased balance,[46] and oculomotor disturbances.[44,46] Language deficits were reported in a single case report.[44] Irritability was reported in one child.[45]

*North American usage: mental retardation.

Importantly, CNS abnormalities have also been reported in the majority of cases with rhombencephalosynapsis,[42–44,46,47] including agenesis or thinning of the corpus callosum, hydrocephalus, and ventriculomegaly. Non-CNS malformations included facial dysmorphism[42,45] as well as extremity[45] anomalies. Interestingly, the presence of CNS or extra-CNS malformations was not found to be predictive of a poorer outcome in this population. However, it is important to note that the majority of studies did not use standardized outcome measures.

Cerebellar hypoplasia and dysplasia

Cerebellar hypoplasia is characterized by incomplete or underdevelopment of the cerebellum[49] whereas cerebellar dysplasia is characterized by an abnormality in maturation of tissue cells.[50] The studies presented herein described the outcome of children with focal cerebellar hemispheric hypoplasia and global cerebellar hypoplasia. Children with vermis hypoplasia were also included if the study design did not allow separate analysis. It is important to note that the clustering of children with various types of cerebellar hypoplasias is a recurrent limitation in the available literature. Consequently, this affects our ability to characterize reliably the outcome of the different types of hypoplasias or dysplasias. For example, unilateral hypoplasias are believed to be the result of a prenatal lesion rather than being true malformations.[1] However, whenever possible, we present a summary of the outcome of children with unilateral and bilateral hypoplasia separately.

Available evidence showed that well over half of children (53–87%)[51–54] were found to have developmental delay or cognitive impairments, among whom over one-third (38%) had severe deficits.[54] Although one case report described a child with 'normal neural development' at 6-month follow-up, no information was provided.[55] Overall, language deficits were found to be prevalent in the majority of studies but were reported as infrequent by others (6–95%),[51–54,56] and the levels of disability ranged from mild impairment (76%) to severe impairment or total absence of language development (19%).[54] Furthermore, 5 to 20% were reported to present with autistic features,[52,54] 81% were found to have an impaired affect,[55] and 71% social or behavioural difficulties. Delayed motor development was variable, observed in 18 to 90% of children.[51–54,56]

Neurological abnormalities were described in up to 100%.[53] They included increased tone (58%),[52] ataxia and/or decreased coordination (12–49%),[51,52,54] hypotonia (49-93%),[51,52,54,56] oculomotor disturbances (35–57%),[51,52,56] and abnormal movements such as tremor, dysdiadochokinesis, or head titubation (9–100%).[52,54] It is noteworthy that all reported cases had associated cerebral anomalies in one of the larger studies:[52] 22% suffered from cerebral atrophy or periventricular leukomalacia; 20% were microcephalic; 16% had neuronal migrational defects; and 11% had anomalies of corpus callosum. Moreover, 20% of cases had associated syndromes or disorders.[52] Associated non-CNS anomalies included facial dysmorphism[51,56] and skeletal[52] and kidney malformations.[51]

In two chart reviews of children with isolated cerebellar dysgeneses,[56,57] 40 to 71% were described to have normal cognitive development, 40% showed mild impairment, and 20% moderate impairment.[57] Moreover, language skills were affected in all children, with 80% being mildly impaired and 20% moderately impaired.[57] Affect was reported to be normal in 60%, whereas 20% had a mild impairment and 20% a moderate impairment.[57] In addition, 14 to 80% of the children were reported to have emotional, social, or behavioural difficulties.[56,57] Finally, 71 to 100% had motor impairments as well.[56,57]

In the subset of articles in which we were able to distinguish between unilateral and bilateral hypoplasia/dysplasia, bilateral cerebellar lesions were found to be associated with a poorer outcome. Specifically, children with bilateral cerebellar hypoplasia experienced a high prevalence of cognitive/developmental delay (60–100%) compared with those children with unilateral cerebellar lesions (17–50%).[51,54,56,57] Similarly, language impairments were reported in 44 to 89% in the former group versus 17 to 100% in the latter group,[51,54,56,57] Behavioural difficulties, neurological deficits, and associated CNS anomalies were also reported more frequently in children with bilateral cerebellar hypoplasia and dysplasia.[51,54–57]

In summary, outcome data on children with hypoplasia and dysplasia of the cerebellum are inconsistent. The presence of a large and variable spectrum of disability among survivors described in the present studies could be explained by the important differences in the topography and severity of the lesions. However, children with isolated hypoplasia of the cerebellar hemispheres appear to have a more favourable prognosis.[57]

Vermis hypoplasia

Vermis hypoplasia is characterized by incomplete development or underdevelopment of the cerebellar vermis. A subgroup of five children with partial or complete hypoplasia of the cerebellar vermis was reported by Tavano et al.[54] All children presented with developmental delays: 80% with severe delay and 20% with moderate deficits. Moreover, language skills were affected in all children, with 80% presenting with severe deficits and 20% with complete absence of language skills. In addition, all children showed impairment in behaviour modulation. Motor development was found to be delayed

in all children but to a lesser degree, with 80% displaying a moderate deficit and 20% a severe deficit. Neurological abnormalities included hypotonia (100%), ataxia (80%), and intention tremor (20%).

Additionally, Bruck et al.[58] reported a case of two siblings with vermis hypoplasia, one of whom was described as having normal cognitive skills. However, language and motor skills were impaired in both children and both presented with hypotonia. Furthermore, severe cognitive and language impairments as well as motor disabilities were described in a case report of a 15-year-old male with cerebellar vermis hypoplasia.[59] Neurological findings included hypotonia, oculomotor dysfunction, and ataxia. The presence of CNS (megalocephaly) and extra-CNS (e.g. micrognathy and syndactyly) abnormalities were also reported.

Finally, three patients with vermis hypoplasia were described by Ventura et al.,[56] of which two were found to have impaired cognition and one was reported to have motor delay and anxiety.

In summary, available data suggest that the majority of children with partial or near-complete hypoplasia of the vermis present with global developmental delay, as well as language, motor, and neurological disabilities.

Pontocerebellar hypoplasia

PCH is a heterogeneous group of conditions characterized by hypoplasia of the cerebellum and the ventral pons.[60] It can be divided into type I and type II.[61] Type I is characterized by spinal anterior horn involvement and death in infancy, and consequently will not be addressed in this review.[61] Type II pontocerebellar atrophy is characterized by progressive microcephaly and severe cognitive and motor delays, in addition to dyskinesia and dystonia.[61] It is noteworthy that some authors classify PCH as a degenerative disorder rather than a true malformation.[62]

In a chart review of 24 children with PCH type II, significant developmental and language delays were reported in all children.[60] A series of case reports have also been published[63–65] in which all four children presented with developmental delay and two were reported to have language deficits.[63] Neurological findings included microcephaly in all children,[60,63–65] seizures (25%),[60] respiratory abnormalities (46%),[60] hypotonia (16%),[60,65] hypertonia (13%),[60,63,64] oculomotor anomalies,[63] ataxia (8%),[60] and dyskinetic and choreic movements (58%).[60,64,65]

Associated CNS malformations including ventriculomegaly and reduced white matter were present in about half of the children described from chart review,[60] ventricular and sulci widening and myelination delay in two children in a case report,[64] and thinning of the corpus callosum in one.[64] Facial dysmorphism and orthopaedic anomalies were described in one child.[63]

Overall, PCH type II is associated with significant global developmental delays and neurological deficits.

Cerebellar agenesis

Cerebellar agenesis is characterized by a complete or near-complete absence of the cerebellum[66] (Fig. 6). Very few studies have described the outcome of children with cerebellar agenesis. Titomanlio et al.[67] presented a case of a 17-year-old male with isolated cerebellar agenesis. Mild cognitive impairment, ataxia, and dysmetria were documented. However, no standardized outcome measures were used. On the other hand, near-total absence of the cerebellum was reported in five children.[68] All children had developmental delay, including one with severe developmental delay. Moreover, 100% of children had delayed language development. Only one case was reported to have associated cerebral malformations, however they were not further described.[68]

DISCUSSION

Cerebellar malformations are now diagnosed with increasing frequency in the fetal and neonatal period.[69,70] As such, the importance of accurate prognostic information to guide parental decision making has become essential. However, despite recent advances in neuroimaging and the growing interest in the role of the cerebellum in higher-order cognitive functions, our review of the literature

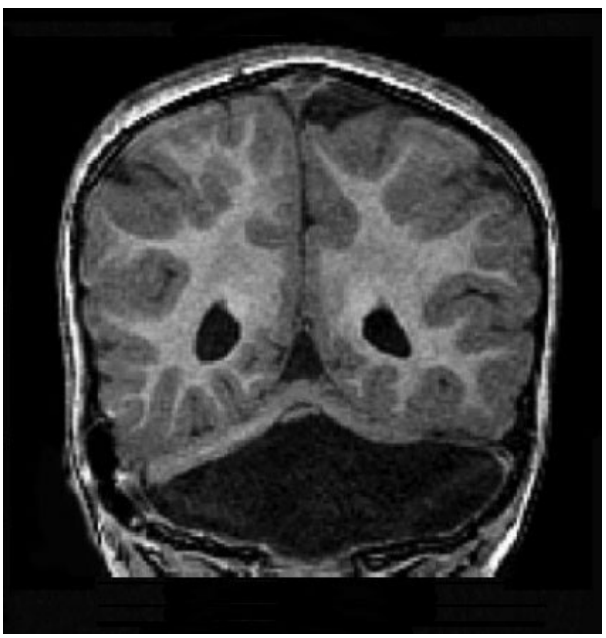

Figure 6: T1-weighted coronal magnetic resonance image representing near-complete absence of the cerebellum in an 18-month-old child.

suggests that the neurodevelopmental and functional outcome of children with cerebellar malformations remains poorly defined. Important inconsistencies in the outcomes reported are frequent, and the spectrum of disability is often broad, ranging from normal or near-normal to profound disability for a given malformation. Furthermore, the results of this comprehensive review show that clear diagnostic criteria for the different types of cerebellar malformations are lacking, resulting in the description of heterogeneous study populations with results that are not easily generalizable.

However, certain global trends in the neurodevelopmental outcome in survivors of cerebellar malformations were evident. Overall, children with MCM and isolated IVH show good developmental progress, whereas children with molar tooth sign/Joubert syndrome, vermis hypoplasia, PCH type II, and cerebellar agenesis are likely to experience moderate to severe global developmental delay. Outcome data remain conflicting in children with DWM; however, the presence of a normally lobulated vermis and the absence of associated CNS anomalies appear to be associated with a better neurodevelopmental outcome. Finally, patients with isolated cerebellar hypoplasia (not including the vermis) appear to have a more favourable prognosis.

Our review over the 10-year period underscored wide-ranging outcomes in children with cerebellar malformations. These inconsistencies can be partly explained by the lack of a widely accepted classification scheme for cerebellar malformations. For example, several studies collapsed different diagnostic groups and described the developmental outcome of survivors collectively. Consequently, children with different types of cerebellar malformations were often clustered together, which further impeded our understanding of the relative contribution of individual cerebellar diagnostic groups on subsequent neurodevelopmental disabilities. Furthermore, the reported wide-ranging outcomes identified in the current review may also be attributed to the overall lack of rigorous study designs and standardized outcome measures, where a prominent 83% of the reviewed studies were conducted retrospectively. Consequently, children with normal development or mild impairments may be underrepresented. Moreover, just under half (39%) of the reviewed studies were case reports or case series. The complete absence of any longitudinal data over this 10-year review period is quite striking. Longitudinal studies are essential, particularly in assessing and monitoring children's progress during important developmental transitions through the lifespan. Furthermore, the wide age range at testing introduced a lot of noise in the studies, and consequently the appreciation of specific outcome information at key intervals in child development was limited.

It is noteworthy that the lack of standardized assessment tools in 74% of the studies reviewed was also an important limitation of the current literature. Furthermore, the studies focused primarily on mortality and morbidities such as IQ, neurological impairments, and other biomedical markers. Cognitive, language, social, and behavioural disabilities were seldom investigated. Given the growing evidence supporting an important role of the cerebellum in cognitive function, including language, perception, and social skills, outcome measures used to date prove to be largely insufficient in this population.[10] Additionally, measures of quality of life and parental burden were completely absent in our 10-year review. These are essential in capturing the added impact of these malformations in the child and their family.

LIMITATIONS

Several limitations of our review should be highlighted. First, it was limited to English-language literature, and therefore studies published in other languages were not included. Second, given that there is no universally accepted classification scheme for posterior fossa malformations, the diagnostic categories proposed by the different studies in this review often varied from one study to another. Moreover, cerebellar diagnostic groups were at times collapsed by some authors because of a small sample size. Consequently, it is likely that certain aspects of the outcome data described in this review may not reflect accurately the developmental outcome of survivors of cerebellar malformations. Finally, given that our review extended over a 10-year study period, recent advances in genetics and neuroimaging studies that have permitted a more accurate identification of cerebellar malformations and their associated chromosomal anomalies are not necessarily reflected in the current paper.

CONCLUSION

Rigorous longitudinal outcome studies that incorporate advanced neuroimaging techniques and genetic testing are urgently needed to delineate better the long-term significance of cerebellar malformations. Furthermore, more holistic measures that assess a larger number of functional domains are required in order to capture the entire spectrum of disability in children with cerebellar malformations that extends far beyond the motor and cognitive domains. These measures must not be limited to evaluating impairments but extended to their functional impact on daily activities, school performance, and societal roles. Collectively, such studies will assist in the development of a rational and clinically useful classification and ultimately improve our understanding of the functional consequences of cerebellar malformations at key intervals across the lifespan.

Finally, a better understanding of the developmental and functional consequences of cerebellar malformations on the developing child will allow earlier and possibly more effective therapeutic interventions, since cerebellar development is not fully completed before the end of the first postnatal years.[49] Additionally, given the greater plasticity of the younger brain coupled with the highly plastic properties of the cerebellum,[71] early targeted intervention could potentially translate into reorganization of the cerebellar circuitry and result in improved outcome.

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