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Neuroimaging of postoperative pediatric cerebellar mutism syndrome: a systematic review

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Abstract

Background. Postoperative pediatric cerebellar mutism syndrome (ppCMS) poses serious morbidity after posterior fossa tumor surgery. Neuroimaging studies aim to understand its pathophysiology, yet these vary in methodology and outcome measures. Therefore, we systematically reviewed the current literature to evaluate the evidence for differences in neuroimaging features between children with and without ppCMS.

Methods. Following PRISMA guidelines, a systematic review was conducted by searching for original articles on neuroimaging in children undergoing posterior fossa tumor surgery, comparing patients with and without ppCMS. Articles were selected based on predefined eligibility criteria. Data were systematically extracted, and risk of bias was evaluated.

Results. From the 866 articles identified, 50 studies fulfilled the inclusion criteria. Studies were categorized into 3 imaging domains: structural, diffusion, and functional imaging. Risk of bias assessment revealed a medium risk in most articles, predominantly due to unclear ppCMS definition and qualitative image analysis without blinding for ppCMS diagnosis. Preoperative structural imaging showed the association of ppCMS with midline tumor localization and involvement of the brainstem, superior cerebellar peduncle (SCP), or middle cerebellar peduncle. Postoperative structural and diffusion imaging highlighted SCP injury with reduced white matter integrity, while functional imaging demonstrated hypoperfusion in frontal lobes. Late follow-up showed T2-weighted hyperintensities in the inferior olivary nuclei of ppCMS patients.

Conclusion. Neuroimaging features suggest that ppCMS is associated with efferent cerebellar pathway injury and hypoperfusion in frontal lobes, with level 2 a/b evidence. Large-scale prospective longitudinal neuroimaging studies comparing pre- and postoperative imaging are needed to further elucidate the pathophysiological mechanism of ppCMS.

Keywords. postoperative pediatric cerebellar mutism syndrome (ppCMS) | posterior fossa syndrome | neuroimaging | radiology | pediatric brain tumor.

Key Points:

- ppCMS is associated with efferent cerebellar pathway injury and hypoperfusion in frontal lobes.
- Large-scale, prospective longitudinal studies using noninvasive MR techniques are needed to better understand the pathophysiological mechanisms of ppCMS.

Postoperative pediatric cerebellar mutism syndrome (ppCMS) is a devastating outcome after posterior fossa tumor surgery with up to 25% of children developing ppCMS.[1–3] Key symptoms of ppCMS include mutism or reduced speech, emotional lability, and behavioral changes.[4] Additionally, patients may have hypotonia and oropharyngeal dysfunction/dysphagia. The onset of symptoms typically occurs within the first 24-48 h after surgery.[4,5] Despite the transient nature of most symptoms, affected patients experience long-term sequelae such as cognitive impairment that significantly impact daily life.[6,7]

The currently accepted hypothesis of ppCMS is an injury to the dentato-rubro-thalamo-cortical tract (DRTCT) leading to cerebello-cerebral diaschisis.[8,9] This tract runs from the ipsilateral dentate nucleus through the superior cerebellar peduncle (SCP), crossing at the level of the mesencephalic tegmentum, and continues toward the contralateral red nucleus and ventrolateral thalamus.[8,10] The DRTCT has a key role in the connection between the cerebellar cortex and the cerebrum. Consequently, injury to this tract may result in changes in the functioning of distant cerebral cortical regions, known as cerebello-cerebral diaschisis.[8] Hypothetically, tumor characteristics affect the surgical resection and therefore the risk of surgical damage to the DRTCT. Commonly recognized tumor characteristics associated with ppCMS include the histopathological diagnosis of medulloblastoma, midline localization, and tumor size >5 cm.[11,12]

Neuroimaging studies such as structural MRI, diffusion MRI, and perfusion imaging (eg, single-photon-emission computerized tomography [SPECT] and arterial spin labeling [ASL]) have been performed to improve the understanding of the pathophysiology of ppCMS. These studies mainly focus on structural and morphological changes to the cerebellum and efferent cerebellar tracts (cerebello-thalamo-cerebral pathways) and changes in cerebral metabolism and/or perfusion. Various narrative reviews outline neuroimaging features of ppCMS.[13–15] However, there is a large heterogeneity among neuroimaging studies concerning the number of included patients (ie, typically small sample sizes), definition of ppCMS, timing of imaging, imaging measurements, and statistical analyses. Consequently, findings may vary greatly, causing extensive discussion in the field and posing challenges in extrapolating the neuroimaging findings of ppCMS to clinical practice.

The aim of this systematic review is to provide a structured overview of the current literature on neuroimaging in ppCMS and to evaluate the evidence supporting the hypothesis of damage to the DRTCT and cerebello-cerebral diaschisis. Therefore, we systematically reviewed if neuroimaging findings/features *(outcome)* are different in ppCMS patients *(exposure)* compared with non-ppCMS patients *(comparison)* in pediatric patients after posterior fossa tumor surgery *(population)*.

Methods

The systematic review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[16]

Search

A literature search was conducted across 3 electronic databases (Pubmed, Embase [Ovid], Cochrane) to identify relevant studies. Languages were limited to English and Dutch, and no date restrictions were applied.

The search intended to include all available literature on neuroimaging in children undergoing posterior fossa tumor surgery, comparing patients with and without postoperative cerebellar mutism syndrome. The search strategy encompassed a combination of keywords and synonyms within 4 domains: (1) anatomical location (posterior fossa), (2) population (children), (3) neurological and/or neuropsychological outcome, and (4) neuroimaging (as per August 9, 2023, Supplementary Table S1.1). Duplicate articles across databases were removed in EndNote[17] according to the deduplication method described by Bramer et al.[18] Additional articles were identified by cross-reference search of included articles. Eligible studies were included in the review if they met the following criteria:

1. Original research article.
2. Population: children and adolescents (0-21 years at diagnosis) who underwent posterior fossa tumor surgery (and overall sample included at least 10 patients).
3. Reported on patients with and without ppCMS.
4. Reported on neuroimaging findings, quantitatively, and/or qualitatively.

The protocol was registered in the international prospective register of systematic reviews (PROSPERO; CRD42023449276).

Study selection

All identified articles were independently screened for eligibility by 2 reviewers (I.V.O. and K.M.v.B.), initially based on title and abstract. Discrepancies between reviewers were resolved by reading full-text and discussion. The web-based software program Rayyan[19] was used to screen the literature. A final review of the eligible records was carried out by 2 reviewers (I.V.O. and M.P.) by reading the full text.

Data extraction

Data were systematically extracted from included studies, including variables such as year of publication, number of ppCMS patients and non-ppCMS patients, age at diagnosis, tumor pathology (grade and type), performed imaging (eg, imaging modality and in case of MRI, sequences, and field strength), and time interval between imaging and surgery. Details regarding neuroimaging findings were extracted, either qualitatively or quantitatively, depending upon the level of detail available within the studies.

Quality assessment

The quality of evidence was assessed by considering the risk of bias, study limitations, and consistency across different studies (generalizability).

The risk of bias in the included studies was assessed by 2 reviewers (I.V.O. and M.P.) using Cochrane's collaboration

tool (Quality in Prognosis Studies tool; QUIPS).[20] This tool evaluates risk across several key domains, including participation, prognostic factor measurement, confounding measurement and account, outcome measurement and analysis, and reporting. The QUIPS tool was modified to align with the diagnostic research design of studies included. Important study characteristics considered in assessing the risk of bias included: consecutive patient inclusion, description of ppCMS diagnosis criteria, inclusion of ≥10 ppCMS patients and ≥10 non-ppCMS patients, quantitative versus qualitative measures of neuroimaging features, and blinding of the image assessor for diagnosis of ppCMS. A detailed description of the adjusted QUIPS tool for the different key domains is given in Supplementary Table S2.1.

The overall risk of bias for each article was judged as low, moderate, or high based on the following criteria: (1) low if all key domains were classified as low risk of bias or only one key domain was rated as moderate risk of bias (green), (2) moderate if a maximum of 2 key domains were classified with moderate risk of bias (orange), and (3) high if ≥3 key domains were classified as moderate risk of bias or ≥1 key domain was rated as high risk of bias (red).[21]

Results

The search identified 866 articles in combined PubMed, Embase (Ovid), and Cochrane databases, of which 64 articles fulfilled the inclusion criteria based on title and abstract screening. Three articles were identified via conferences and/or meetings and 2 articles were identified via cross-reference checking. In total, 50 articles were included after full-text screening. Articles were split into 3 domains: structural imaging ($n = 37$), diffusion imaging ($n = 10$), and functional imaging ($n = 7$). Four articles in the diffusion imaging or functional imaging domain also reported structural imaging results. The PRISMA flow diagram is shown in Figure 1.

Baseline characteristics of all 50 included articles are presented in Supplementary 3. All studies were performed between 1995 and 2023. Most studies had a retrospective cohort design ($n = 31$), whereas others had a retrospective case-control design ($n = 9$) or a prospective cohort design ($n = 10$). Eight articles reported both preoperative and postoperative imaging, while most of the articles only reported either preoperative ($n = 19$) or postoperative ($n = 23$) imaging. The number of included patients ranged between 8 and 182 without ppCMS and between 3 and 71 with ppCMS. The age of participants ranged between 2 months and 22 years. In all studies, tumors were located in the posterior fossa, with a midline localization (ie, fourth ventricle and/or vermis) or more lateral localization (ie, cerebellar hemisphere). The main tumor types reported were pilocytic astrocytoma, ependymoma, and medulloblastoma. Fourteen articles included only medulloblastoma patients.

Risk of bias assessment

Risk of bias assessment showed a medium ($n = 21$) to high risk ($n = 17$) in most studies, while some studies had a low risk ($n = 12$). An overview of the overall risk of bias as well as the risk of bias per imaging domain for each key domain of the QUIPS tool are presented in Figure 2. Assessment of the risk of bias for each individual study is provided in Supplementary 4.

Across the 3 imaging domains, the outcome measurement domain presented the greatest risk of bias. This was primarily due to many studies relying on qualitative image analysis or quantitative assessment based on manually drawn regions of interest; therefore, these analyses were subject to investigator interpretation bias. Additionally, in many of these studies, investigators were not blinded to ppCMS diagnosis. Moreover, confounders specific to functional imaging studies, such as sedation, hemoglobin, and hematocrit levels, were often not accounted for in analyses, potentially affecting study results. Furthermore, many articles lacked a clear definition of ppCMS, failed to specify who diagnosed the patient with ppCMS, or included a limited number of patients with ppCMS. The key domains "study design" and "statistical analysis and reporting" generally exhibit a low risk of bias.

Imaging findings

A visual overview of imaging findings that were significantly different between patients with and without ppCMS and were consistent across the majority of the studies is highlighted in Figure 3. Detailed imaging findings specific to each imaging domain are presented below.

Structural imaging.—Thirty-seven studies investigated structural imaging. Most of the studies acquired T1-weighted, T2-weighted, and fluid-attenuation inversion recovery (FLAIR) MR images to investigate imaging features associated with ppCMS. In all studies, regions of interest were located in the posterior fossa and focused on lesion location and/or involvement, invasion, compression, or injury to anatomical structures, such as cerebellar nuclei or cerebellar peduncles (Table 1).

Preoperative imaging findings indicated that midline localization[24,26,27,29,30,33,35,37,40] of the tumor was associated with ppCMS, while tumor lateralization[24,27,29,30,35] within the cerebellar hemisphere was protective and less likely associated with ppCMS (Table 2). Furthermore, structural imaging features showed a significant increased involvement or compression of brainstem,[24,26,29,32,34–36,38,44] SCP,[24,26,28,29] and middle cerebellar peduncle (MCP)[24,28,29] in children with ppCMS versus without ppCMS. Early postoperative imaging (<9 months after diagnosis) demonstrated significant injury to bilateral SCP[25,33,52–57] in children with ppCMS (Supplementary Table S5.1). Furthermore, mapping of early postoperative lesions showed that patients with ppCMS frequently exhibited lesions in the inferior vermis,[53,57,58] a region connected to cerebellothalamocortical tracts.[53,58] T2-weighted imaging of the inferior olivary nuclei (ION) showed increased bilateral hypertrophic olivary degeneration (HOD)[22,54,59,60] during late follow-up (>9 months after diagnosis) in patients with ppCMS.

Diffusion imaging.—Ten studies performed diffusion tensor imaging (DTI) to explore damage to white matter tracts. Metrics mostly examined in these studies were fractional anisotropy (FA) and mean diffusivity (MD), serving

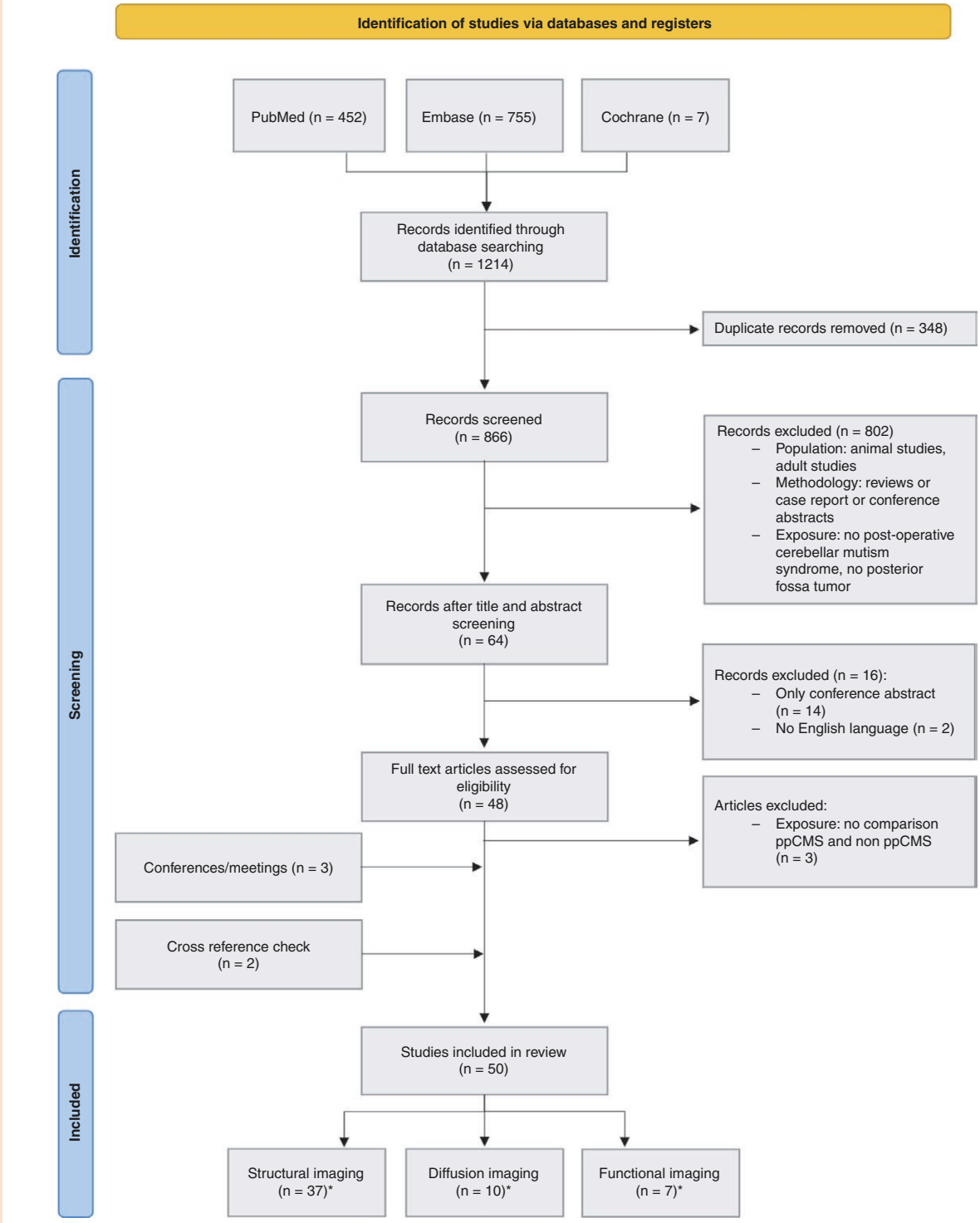

Figure 1. PRISMA Flow diagram, and *4 studies were categorized in multiple imaging domains.

as indicators of white matter integrity. Most studies examined white matter tracts connecting the cerebellum with the cerebrum, that is, SCP, MCP, and inferior cerebellar peduncle (ICP) on postoperative imaging (Table 2).

Preoperative imaging features indicated no significant difference in white matter integrity of SCP, MCP, and ICP between children with ppCMS and without ppCMS[31,45,50] (Supplementary Table S5.2). Meoded et al. highlighted preoperative alterations in white matter connectivity of bilateral corpus callosum and right corticothalamic pathway and corticostriatal pathway in patients with ppCMS.[61] Early postoperative imaging (<9 months after

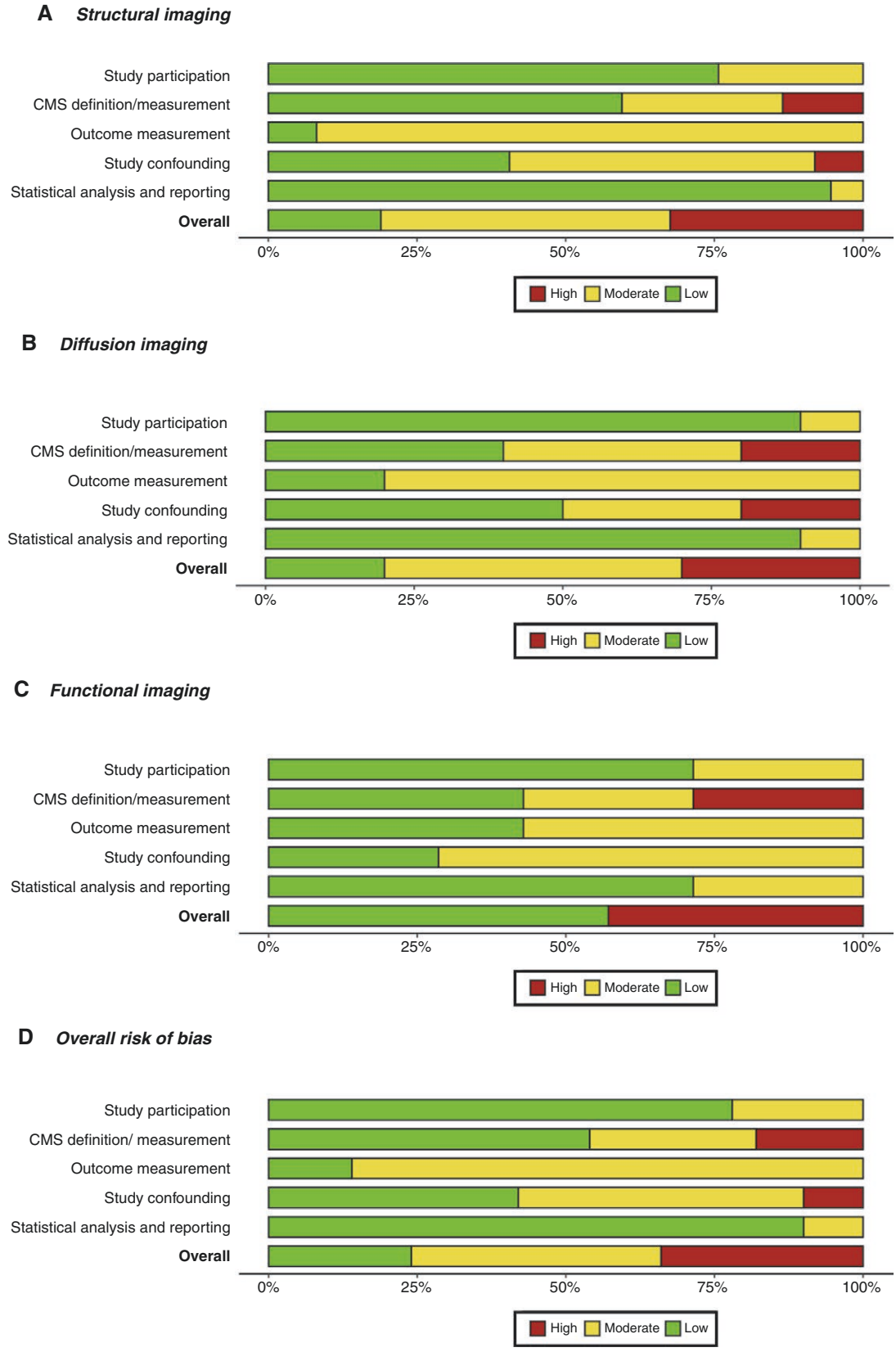

Figure 2. Risk of bias according to the QUIPS tool; (A) structural imaging studies; (B) diffusion imaging studies; (C) functional imaging studies; and (D) overall risk of bias including all studies.

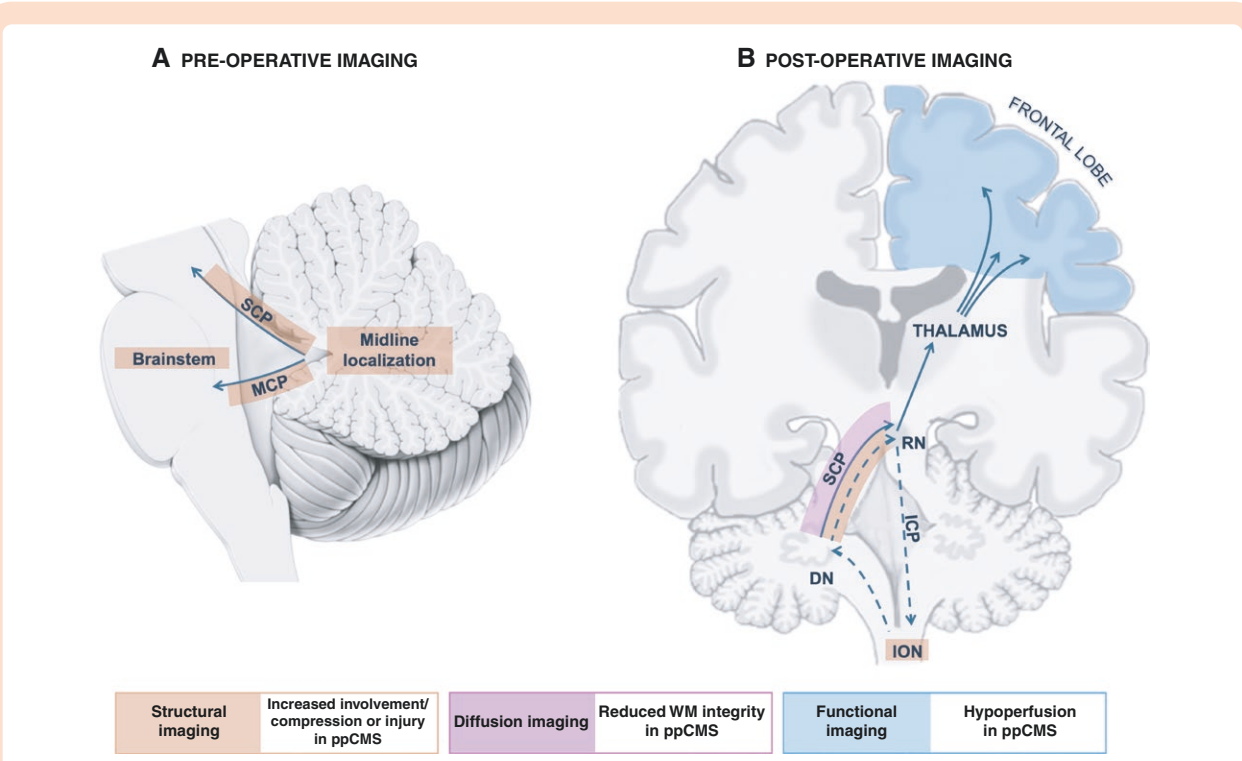

Figure 3. Overview of significant differences in imaging findings between ppCMS and non-ppCMS patients at pre-operative imaging (A) and post-operative imaging (B). Imaging domains are indicated by color: structural imaging, diffusion imaging, functional imaging. The arrows indicate white matter tracts, at pre-operative imaging (A) the solid arrows indicate the cerebellar peduncles (ie, superior (SCP) and middle (MCP)); and at post-operative imaging (B) the solid arrows indicate the DRTCT and the dashed arrow indicates the dentato-rubro-olivary pathway. Acronyms: SCP, superior cerebellar peduncle; MCP, middle cerebellar peduncle; ICP, inferior cerebellar peduncle, DN, dentate nucleus; RN, red nucleus; ION, inferior olivary nucleus. Image used under license from Kenhub GmbH. Illustrator: Paul Kim (Figure 3A) and adapted from Avula et al.[22] with permission from AME publishing Company (Figure 3B).

diagnosis) consistently revealed injury to bilateral SCP in all studies.[31,33,45,48,50,51] Conversely, white matter metrics in MCP showed no significant differences between children with and without ppCMS,[31,33,45,50,51] while ICP was rarely considered in the analyses. Three articles investigated several supratentorial white matter tracts and found significantly reduced white matter integrity in children with ppCMS.[33,46,49]

Functional imaging.—Seven studies performed functional imaging, including single-photon emission computed tomography (SPECT) ($n = 2$), arterial spin labeling (ASL) ($n = 3$), dynamic susceptibility contrast ($n = 1$), or blood-oxygen-level-dependent imaging (BOLD) ($n = 1$). Primarily, these studies examined the postoperative perfusion pattern of the frontal lobes, temporal lobes, parietal lobes, occipital lobes, and deep cerebral nuclei (including basal ganglia) (Table 3). One study investigated functional connectivity using BOLD imaging and is therefore not included in Table 3 but summarized below.[65]

Preoperatively, no perfusion differences were observed between children with ppCMS and without ppCMS[23,62] (Supplementary Table S5.3). On the other hand, there was a consistent significant association between ppCMS and hypoperfusion in the frontal lobes at postoperative scans.[6,23,56,63,64] Parietal, temporal, and occipital lobes did not show any significant perfusion differences between patients with and without ppCMS.[6,23,56,62,64] In contrast, there was one study that reported a significantly higher mean cortical cerebral blood flow (CBF) in children who developed ppCMS compared with non-ppCMS patients 1-year postsurgery.[62] McAfee et al. investigated supratentorial connectivity using BOLD imaging and showed altered functional connectivity between the periaqueductal grey and the medial frontal cortex, Broca's area, and left amygdala in patients with ppCMS.[65]

Discussion

This systematic review revealed significant differences in neuroimaging features between ppCMS patients and non-ppCMS patients. Preoperative structural imaging studies demonstrated the association between ppCMS and midline tumor localization as well as the involvement of brainstem, SCP, or MCP. Postoperatively, both structural and diffusion imaging studies highlighted SCP injury in ppCMS. Functional imaging studies indicated an association between ppCMS and frontal lobe hypoperfusion postoperatively. During late follow-up (>9 months after diagnosis), hyperintensities of the ION were noticed on T2-weighted images in ppCMS patients.

Table 1. Overview of Preoperative Structural Imaging Features in ppCMS Compared With Non-ppCMS Patients

Preoperative structural imaging—ppCMS compared with non-ppCMS patients										
Author	Year	Modality	Lesion localization		Involvement/ invasion/ compression/ injury					QUIPS Overall Risk of Bias
			CH	4V and/ or V	Brain-stem	SCP	MCP	Cerebellar nuclei	ION	
Boisgontier et al.[23]	2021	MRI (ASL/T2W)	ns	V ns	-	ns	ns	DN ns	-	Low Risk
Liu et al.[24]	2018	MRI (NM)	↓*	↑ 4V*	↑ns	↑L ↑R ns	↑BI*	DN ↑L* ↑R*	-	Low Risk
Toescu et al.[25]	2018	MRI (T1W/T2W/ FLAIR/DWI)	-	-	-	ns	-	DN & RN ns	-	Low Risk
Yang et al.[26]	2023	MRI (T1w/T2W/ FLAIR)	↑L* ↑R* superior	↑V*	↑*	↑R* > ↑L*	-	-	-	Low Risk
Catsman-Berrevoets et al.[27]	1999	CT & MRI *(NM)*	↓*	↑4V/V*	-	-	-	-	-	Moderate Risk
de Laurentis et al.[28]	2022	MRI *(NM)*		↑4V* ↑V ns	↑ ns	↑R*	↑R*	-	-	Moderate Risk
Dhaenens et al.[29]	2020	MRI *(NM)*	↓*	↑4V*	↑*	↑R* > ↑L*	↑R* > ↑L*	-	-	Moderate Risk
Kotil et al.[30]	2008	CT & MRI *(NM)*	↓*	↑4V/V*	-	-	-	-	-	Moderate Risk
McEvoy et al.[31]	2016	MRI *(DTI/ MPRAGE (T1W))*	-	-	ns	-	-	-	-	Moderate Risk
McMillan et al.[32]	2009	MRI *(T1W/T2W)*	-	-	↑*	-	-	-	-	Moderate Risk
Morris et al.[33]	2009	MRI *(DTI/T2W)*		↑4V (rostal)*	ns	ns	ns	DN ns	-	Moderate Risk
Pols et al.[34]	2017	MRI *(T1W/T1W-C/T2W/FLAIR)*	-	-	↑*	-	-	-	-	Moderate Risk
Ruella et al.[35]	2023	MRI *(NM)*	↓ *	↑ 4V/ V*	↑*	-	-	-	-	Moderate Risk
Wells et al.[36]	2010	MRI *(T1W/T2W/ T1W-C)*	-	-	↑*	-	-	-	-	Moderate Risk
Yang et al.[37]	2023	T1W/T2W/ FLAIR/DWI	-	↑4V/V*	-	-	-	-	-	Moderate Risk
Doxey et al.[38]	1999	MRI *(NM)*	-	-	↑*	-	-	-	-	High Risk
Gora et al.[39]	2017	CT &MRI *(NM)*	-	-	ns	ns	ns		-	High Risk
Ma et al.[40]	2019	MRI *(NM)*	-	↑4V*	-	-	-	-	-	High Risk
Renne et al.[3]	2020	MRI *(NM)*	-	-	↑*	-	-	-	-	High Risk
Schmidt et al.[41]	2023	MRI *(NM)*	↓ns	↑4V/V ns	ns	-	-	-	-	High Risk
Sergeant et al.[42]	2017	MRI *(T1w/T1w-C/ T2W/DWI/ FLAIR)*	-	↑4V ns	-	-	-	-	-	High Risk
Siffert et al.[43]	2000	CT & MRI *(NM)*	↑edema ns	-	↑edema ns	-	-	DN ns	-	High Risk
Zhang et al.[44]	2019	CT & MRI *(NM)*	↑com-pression*	-	↑*	-	-	-	-	High Risk

↑More involvement of the region in ppCMS compared with non-ppCMS patients;
↓Less involvement of the region in ppCMS compared with non-ppCMS patients.
*Significant results; ns, nonsignificant; -, not measured.
4V, 4th ventricle; ASL, arterial spin labeling; BI, bilateral; CH, cerebellar hemisphere; DN, dentate nucleus; DTI, diffusion tensor imaging; DWI, diffusion weighted imaging; FLAIR, fluid attenuation inversion recovery; ION, inferior olivary nucleus; MCP, middle cerebellar peduncle; NM, not mentioned; PD, proton density; RN, red nucleus; SCP, superior cerebellar peduncle; T1W-C, T1-weighted imaging with contrast; T1W, T1-weighted imaging; T2W, T2-weighted imaging; UNI, unilateral; V, vermis.

The observed structural, morphological, and functional alterations evident in neuroimaging studies provide supporting evidence for the hypothesis of injury to the DRTCT and cerebello-cerebral diaschisis in patients with ppCMS. Additionally, alongside diminished white matter integrity within the DRTCT and decreased perfusion in the frontal

Table 2. Overview of Postoperative Diffusion Imaging Features in ppCMS Compared With Non-ppCMS Patients

Postoperative fractional anisotropy (FA)—ppCMS compared with non-ppCMS patients									
	Year	Modality	Cerebellar white matter°	SCP	MCP	ICP	ION	Supratentorial brain region	QUIPS Overall Risk of Bias
Toescu et al.[45]	2022	MRI *(DTI)*	-	↓L ns I ↓L* II,III	ns I,II,III	↓R ns II ns I,III	-	-	Low Risk
Law et al.[46]	2012	MRI *(DTI)*	ns III	-	-	-	-	L & R thalamus/ internal capsule nsIII L & R frontal ns III L & R midbrain/pons ns III	Moderate Risk
McEvoy et al.[31]	2016	MRI *(DTI/ MPRAGE (T1W))*	↓L*,I,III	↓L* ↓R* I,III	ns I,III	-	-	-	Moderate Risk
Morris et al.[33]	2009	MRI *(DTI/ T2W)*	ns I	↓L* ↓R* I	ns I	ns I	-	Fornices ↓L* ↓R* I WM promixate to angular gyrus ↓R* I WM region proximate to frontal gyrus ↓L* I	Moderate Risk
Yecies et al.[47]	2019	MRI *(DTI)*	-	-	-	-	↑L ↑R ns I	-	Moderate Risk
Ojemann et al.[48]	2013	MRI *(DTI)*	-	↓L ↓R? I	-	-	-	-	High Risk
Soelva et al.[49]	2013	MRI *(DTI)*	-	-	-	-	-	volume FCF ↓L ↓R III	High Risk
Vedantam et al.[50]	2019	MRI *(DTI)*	-	↓L*,I ns III	ns I,III	-	-	-	High Risk
Postoperative mean diffusivity (ADC/MD)—ppCMS compared with non-ppCMS patients									
Author	Year	Modality	Cerebellar white matter°	SCP	MCP	ICP	ION	Supratentorial brain region	QUIPS Overall Risk of Bias
Avula et al.[51]	2015	MRI *(DWI/ DTI)*	↓L* ↓R* I	↓L* ↓R* I	nsI	-	-		Moderate Risk
Law et al.[46]	2012	MRI *(DTI)*	↑ R* III	-	-	-	-	L & R thalamus/internal capsule ns III L & R frontal ns III L & R midbrain/pons ns III	Moderate Risk
McEvoy et al.[31]	2016	MRI *(DTI/ MPRAGE (T1W))*	-	ns I,III	-	-	-	-	Moderate Risk
Yecies et al.[47]	2019	MRI *(DTI)*	-	-	-	-	↑ L* I	-	Moderate Risk

↑Higher fractional anisotropy or mean diffusivity in ppCMS compared with non-ppCMS patients;
↓Lower fractional anisotropy or mean diffusivity in ppCMS compared with non-ppCMS patients.
*Significant results; ns, nonsignificant; ?, no statistics; -, not measured.
°Including abnormalities surrounding the surgical cavity.
I, immediate postoperative (≤72h); II, early follow-up (≤9-months after diagnosis); III, late follow-up.
ADC, apparent diffusion coefficient; DTI, diffusion tensor imaging; DWI, diffusion weighted imaging; FA, fractional anisotropy; FCF, fronto-cerebellar association fibers; ICP, inferior cerebellar peduncle; ION, inferior olivary nucleus; MCP, middle cerebellar peduncle; MD, mean diffusivity; SCP, superior cerebellar peduncle; T1W, T1-weighted imaging; WM, white matter.

lobes, the development of HOD in patients with ppCMS also suggests injury to the proximal efferent cerebellar pathway. The dentate nucleus is linked to the contralateral ION via the dentato-rubro-olivary pathway, also referred to as the triangle of Guillian–Mollaret.[66] Given the inhibitory role of the dentato-rubro-olivary pathway on the ION, any injury or lesion impacting this pathway results in stimulation of the ION, leading to hypertrophy over time.[66] These interrelated neural circuits point toward common anatomical substrates, thereby indicating injury to the white matter tract originating from the dentate nucleus and projecting toward the contralateral red nucleus and subsequently the cerebral lobes.

Furthermore, preoperative structural imaging studies highlighted the association between the tumor's proximity to eloquent anatomical structures, such as the dentate nuclei and SCP, and an increased risk for the development of ppCMS. The increased involvement and compression of these structures by the tumor prior to surgery may help explain the higher frequency of preoperative speech impairments observed in patients who later develop ppCMS.[67–69] This is supported by the meta-analysis of Petterson et al.,

Table 3. Overview of Postoperative Perfusion Imaging Features in ppCMS Compared With Non-ppCMS Patients

Postoperative perfusion—ppCMS compared with non-ppCMS patients										
Author	Year	Modality	Cerebellum	Frontal lobe	Parietal lobe	Temporal lobe	Occipital lobe	Deep cerebral nuclei**	Global	QUIPS Overall Risk of Bias
Boisgontier et al.[23]	2021	MRI *(ASL/T2W)*	-	↓L* I	ns I	ns I	ns I	↓L* I	-	Low Risk
Toescu et al.[62]	2022	MRI *(ASL)*	ns I,II	ns I,II	ns I,II	ns I,II	ns I,II	ns I,II	mean cortical CBF nsI ↑ mean cortical CBF* II	Low Risk
Yecies et al.[63]	2019	MRI *(ASL)*	-	↓L ↓R* I	-	-	-	-	difference in global perfusion ns I	Low Risk
Catsman-Berrevoets et al.[6]	2010	SPECT *(Tc-99m HMPAO)*	↓L ↓R? II	↓L ↓R? II	? II	↓L ↓R? II	↓L ↓R? II	? II	-	High Risk
Ersahin et al. [64]	2002	SPECT *(Tc-99m HMPAO)*	? II	↓L ↓R? II	↓L ↓R? II	? II	? II	? II	differences in all SPECT findings ns II	High Risk
Miller et al.[56]	2010	MRI (*DSC/T2W/DWI)*	-	↓L*↓R* II	↓R* II	↓R* II	↓L ↓R nsII	↓L ↓R nsII	-	High Risk

↑Increased perfusion in ppCMS compared with non-ppCMS patients;
↓Decreased perfusion in ppCMS compared with non-ppCMS patients.
*Significant results; ns, nonsignificant; ?, no statistics; -, not measured.
**Including thalamus and basal nuclei.
I, immediate postoperative (≤72h); II, early follow-up (≤9-months after diagnosis); III, late follow-up.
ASL, arterial spin labeling; CBF, cerebral blood flow; DSC, dynamic susceptibilty contrast; DWI, diffusion-weighted imaging; SPECT, single photon emission computed tomography; T2W, T2-weighted imaging; Tc-99m HMPAO, 99mTc HexaMethylPropyleneAmine Oxime.

which focused on clinical and surgical risk factors and identified midline localization and tumor invasion into the SCP as risk factors as well.[12]

As per classification outlined by the Oxford Centre for Evidence-Based Medicine,[70] this systematic review provided evidence classified as "Level 2a/b," regarding differences in neuroimaging features between patients with and without ppCMS. This level of evidence primarily draws from the numerous retrospective cohort studies with a single time point included in the review. Accordingly, the results of this systematic review warrant careful interpretation, given the presence of various limitations, which also highlight the need for further research.

Limitations and considerations

There are several limitations that need to be addressed to contextualize the interpretation and generalizability of our findings. First, the variability in the definition of ppCMS remains a persistent challenge within the field. This systematic review included articles published between 1995 and 2023, spanning a period during which the consensus definition of ppCMS evolved.[4] Consequently, there was significant heterogeneity in the definition of ppCMS across the included studies, with terminology such as (cerebellar) mutism and posterior fossa syndrome 1 and 2 being used. In recent years, several scoring scales have been introduced, aiming to standardize the severity assessment of ppCMS,[2,71] but these are not widely adopted in clinical practice yet. This heterogeneity in terminology may have introduced ambiguity in the definition of ppCMS and hindered the comparison of findings across the literature.

Second, discrepancies exist in imaging acquisition protocols which hindered the comparison of quantitative results, such as FA and CBF. This underscores the necessity of harmonizing and standardizing imaging acquisition protocols, particularly in the context of multicenter studies, which is also stressed by the European Society for Paediatric Oncology-Brain Tumor Imaging group.[72] Additionally, a significant portion of included studies relied on qualitative assessments of neuroimaging features and often lacked blinding for ppCMS diagnosis. These studies typically focused on structures directly linked to the DRTCT, rather than including broader brain regions. This tendency is also observed in postoperative analyses, which often prioritized the SCP over the MCP and ICP, despite all 3 cerebellar peduncles being pivotal in connectivity between the cerebrum and cerebellum.[73] To address these concerns and strengthen the evidence for the pathophysiological mechanisms underlying ppCMS, a transition toward standardized acquisition and analyses (eg, automated and/or atlas-based) is needed in both the preoperative and postoperative setting.[74]

Thirdly, there are several clinical and neuroimaging features, such as hydrocephalus and tumor size, that we did not take into account, as they are nonspecific with regard to the anatomical substrate of ppCMS. However, they may serve as important confounders in research analyses. For example, a correlation between hydrocephalus and reduced CBF has been reported.[55] Additionally,

clinical characteristics such as sedation, hemoglobin levels, and hematocrit were only sparsely mentioned and could not be included in our analyses, despite their possible confounding effects. Lower levels of hemoglobin and hematocrit are correlated with increased CBF in other populations.[75,76] Notably, in neuroimaging studies investigating the anatomical substrate of ppCMS, both clinical risk factors, and confounders potentially affecting imaging metrics, must be considered.

Lastly, publication bias may have influenced the findings of this review, potentially leading to an overrepresentation of certain outcomes.

The scope of this review was restricted to pediatric patients diagnosed with a posterior fossa tumor, since this population appears particularly susceptible to the onset of ppCMS. Hence, the conclusions drawn from this systematic review might not be extrapolated to the adult population and other medical conditions such as cerebellitis, arteriovenous malformation, and trauma.[77] Nevertheless, the development of ppCMS in these populations may share similarities in pathophysiological mechanism, which can be examined in future studies.

Future perspectives

In order to thoroughly understand the anatomical substrate and pathophysiology of ppCMS, a longitudinal study design is essential. Recent studies demonstrated the involvement of the efferent cerebellar pathways in ppCMS; however, this only confirms an association. It is paramount to understand whether this involvement was already present before surgery (thus implying a risk factor) or was caused by the surgery. Only a comparison of pre- and postoperative imaging can confirm a causal relationship between the involved anatomical structures and the origin of ppCMS. Similarly, this necessity also applies to the understanding of ppCMS recovery, which requires regular imaging from ppCMS onset until recovery. For example, hyperperfusion of mean CBF has been reported following clinical improvement 1-year postsurgery,[62] which potentially serves as a compensatory mechanism for previous hypoperfusion. The understanding of factors and mechanisms associated with ppCMS, alongside its onset and recovery, can facilitate better counseling of patients and families as well as establish an optimal time window for interventions.

Large prospective longitudinal cohort studies incorporating various noninvasive advanced MR techniques, such as diffusion imaging and ASL, are warranted in future research. The combined assessment of white matter integrity and perfusion shows potential in unraveling a causal relationship between structural and functional deficits observed on MR images and the spectrum of deficits present in ppCMS. Moreover, a comprehensive approach that examines structures beyond the DRTCT will be crucial in understanding the underlying mechanisms of ppCMS. Currently, the European CMS study, the largest study on ppCMS to date, includes children with posterior fossa tumors in an international prospective study (NCT02300766).[78] Additionally, the FASTigial study is an add-on to the European CMS study (ISRCTN70465429), which aims to investigate clinical and neuroradiological predictors of neuropsychological outcome, including ppCMS, and will start patient recruitment soon.

Conclusion

This systematic review showed structural and functional neuroanatomical alterations in patients with ppCMS compared with patients without ppCMS after posterior fossa tumor surgery. Neuroimaging studies demonstrated a significant association between ppCMS, efferent cerebellar pathway injury, and hypoperfusion in the frontal lobes. While the level of evidence is limited to a level 2 a/b, these findings support the hypothesis of involvement of the DRTCT as well as a functional disconnection between the cerebellum and cerebrum in ppCMS patients. To better understand the etiology and mechanisms of ppCMS, future research should involve large-scale prospective longitudinal cohort studies utilizing various noninvasive MR techniques, such as diffusion imaging and ASL, and broaden analyses by including anatomical structures beyond the DRTCT.

Supplementary material

Supplementary material is available online at *Neuro-Oncology Advances* (https://academic.oup.com/noa).

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Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflict of interest.

Authorship

Iris V. Obdeijn (Conceptualization, Methodology, Data curation, Formal analysis, Writing—original draft, Writing—review & editing, Visualization), Kirsten M. van Baarsen (Conceptualization, Methodology, Data Curation, Formal analysis, Writing—original

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Data Availability

All data generated or analyzed during this study are included in this published article, including its supplementary information files.

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