Abstract

Post-operative paediatric cerebellar mutism syndrome (pCMS) occurs in around 25% of children undergoing surgery for cerebellar and fourth ventricular tumours. Reversible mutism is the hallmark of a syndrome which comprises severe motor, cognitive and linguistic deficits. Recent evidence from advanced neuroimaging studies has led to the current theoretical understanding of the condition as a form of diaschisis contingent on damage to efferent cerebellar circuitry. Tractography data derived from diffusion MRI studies have shown disruption of the dentato-rubro-thalamo-cortical tract in patients with pCMS, and perfusion studies have indicated widespread supratentorial regions which may give rise to the florid signs and symptoms of pCMS. Given the difficulties in predicting pCMS from standard structural MRI, this review discusses findings from quantitative MRI modalities which have contributed to our understanding of this debilitating syndrome, and considers the goals and challenges which lie ahead in the field.

Introduction

Post-operative paediatric cerebellar mutism syndrome (pCMS) is a well-recognised complication of resective surgery for brain tumours of the cerebellum and fourth ventricle region in children. It is characterised by a delayed onset of mutism and emotional lability, and can result in motoric and cognitive cerebellar deficits. These symptoms may be transient, but recovery occurs over a prolonged period, and is often incomplete. Similar syndromes have also been described following infective[1,2], traumatic[3,4] or vascular[5,6] brain pathologies, but the majority of cases of pCMS arise following craniotomy for infratentorial brain tumours in children, and it is this group which will be the focus of this review.

Nomenclature and semiology

The syndrome of pCMS as it relates to surgery of the posterior fossa has its first depiction in the medical literature in 1958 in a 14-year old boy following resection of a midline cerebellar low-grade astrocytoma in the sitting position via a trans-vermian route[7]. Post-operatively, the patient developed inhibition of voluntary movement, cerebellar motor signs, external ophthalmoplegia and mutism, the latter recovering by way of monosyllabic words at 34 days after the operation. Later surgical series reported “postoperative mutism”[8] and “emotional incontinence”[9], and in 1985,

Rekate and colleagues were the first to describe “muteness of cerebellar origin” in 6 patients following posterior fossa surgery[10]. “Posterior fossa syndrome”[11,12](PFS) is a broader term, again centred around cerebellar mutism, but which also includes cerebellar motor, cognitive, linguistic and behavioural abnormalities. Of late, the terms PFS and CMS have been used interchangeably in many reports. In an effort to standardise nomenclature, a 2016 consensus statement proposed a definition of ‘post-operative paediatric cerebellar mutism syndrome’ (pCMS)[13], which is the preferred terminology adopted here.

Typically, the patient will initially recover well from surgery of the posterior fossa, with normal speech immediately postoperatively. Mutism – that is, an inability to produce speech despite normally functioning vocal apparatus, and retained comprehension of spoken and written language – develops with a mean latency of 1.7 days and persists for an average of 6-8 weeks[3,14]. Longer periods of mutism have been described[14,15], and although the general tendency is for mutism to slowly improve by way of dysarthria[16], speech rarely returns to normal[15].

Many patients will exhibit deficits in other functional spheres. Motor features are not uncommon. These include the classical signs of cerebellar pathology: dysdiadochokinesis, ataxia, nystagmus, intention tremor, dysmetria and hypotonia. Oropharyngeal apraxia[17] can be so severe as to necessitate tracheostomy or gastrostomy formation[18]. Formal cranial neuropathies (of upper or lower motor neuron type) can also contribute to motor deficits. Urinary and faecal incontinence have also been reported[19], and these may be additionally interpreted as part of the wide spectrum of neurobehavioural abnormalities seen in pCMS[20], which includes an overlap with cerebellar cognitive affective syndrome[21].

pCMS is now recognised to be a heterogeneous condition – indeed symptoms of posterior fossa syndrome have been described in the absence of mutism[20,22,23] – and may be less likely to be diagnosed as pCMS in those who present only with subtle motoric or cognitive signs. There is currently a lack of standardised core descriptors for pCMS severity, hindering cross-study comparisons, although a large multi-centre prospective study is underway to address this[24]. The only published scoring scale[25] for pCMS, originally developed in 1993 by the Neurology

Committee of the Children's Cancer Group, is yet to be widely taken up in clinical practice.

Incidence and risk factors

The incidence of pCMS is broadly in the region of 25% in children undergoing posterior fossa craniotomy for tumour resection, although this varies from 8% in early studies[19,26] with no selection as to tumour type or cerebellar location, to 39-40%[20,27] in more recent cohorts comprised solely of medulloblastoma. The latter is a well-established risk factor for developing pCMS[20,28–32], along with brainstem infiltration or compression[25,27,28,33–36] (see Table 1).

Tumour location in the vermis has been shown to be associated with increased risk of pCMS[29,31,34] (despite conflicting reports[25,33]). There is some evidence that the transvermian approach to a fourth ventricular tumour is a risk factor for development of pCMS[30,33,37]; however the alternative telovelar approach – which avoids transgression of neural tissue – does not seem to mitigate against this risk[38]. There is also contradictory evidence with respect to tumour size[29,32,35,36] and younger age[32,34].

There are unconfirmed reports of raised mean body temperature post-operatively[36], left-handedness[32], a lower socioeconomic background[34] and pre-operative language impairment[39] as relevant risk factors. Factors which are now thought not to contribute to the risk of pCMS include gender[25,29], CSF leak or peri-operative meningitis (either infective or aseptic)[25,27,29], pre-operative hydrocephalus[27,29], neurosurgical specialisation (paediatric vs general)[25], and extent of resection[25,32]. Scoring tools have been developed in an attempt to predict development of pCMS based on combined clinical[32] and radiological[40] criteria, as pre-operative imaging alone is unable to predict development of pCMS[19,27,41].

Anatomy and pathophysiology

The efferent cerebellar pathway (ECP) – the dentate nucleus and the SCP as it decussates in the midbrain – occupies a central role in the most widely accepted hypothesis of the cause of pCMS. The primary surgical injury is to the proximal

dentato-rubro-thalamo-cortical tract (DRTC), which, after decussating in the pontomesecephalic tegmentum, passes via the red nucleus and subthalamus to the ventrolateral, interpositus and dorsomedial nuclei of the thalamus before projecting to widespread cortical regions, including primary motor, sensory and supplementary motor areas (SMA; Figure 1)[42]. This injury disturbs the finely balanced reciprocal cerebello-cerebral circuitry, with a resulting loss of function in supratentorial structures which are responsible for higher-order cognitive, motor and linguistic functions. It is this latter effect of supratentorial hypofunction which gives rise to the symptoms seen in pCMS. This constitutes a form of diaschisis[43], a phenomenon originally described in 1914 by von Monakow[44] as a “functional standstill” in a region of the brain remote to a causative lesion. In addition, the ECP contributes to the triangle of Guillain-Mollaret, a brainstem feedback loop initially recognised in the context of palatal myoclonus[45], now thought to play a role in pCMS. Interestingly, the phenomenon of mutism can result from damage at many points in the pathways described, from the dentate nucleus[46] to the SMA[47]. Indeed, clinical parallels between pCMS and ‘SMA syndrome’[47], particularly with regards to the transient mutism seen in both conditions, have recently been noted[48].

The aforementioned anatomical regions have been implicated in pCMS owing to converging evidence from a number of imaging modalities. However, the current hypothesis does not contain any indication as to the functional pathophysiological mechanism by which pCMS is mediated. A number of candidates have been proposed, including vasospasm, oedema, impaired venous drainage, direct axonal injury[35] leading to trans-synaptic neuronal dysfunction[41], and iatrogenic effects of intraoperative ultrasonic aspirators[49]. However, none of these models are currently supported by compelling experimental evidence.

Structural MRI

In recent years, magnetic resonance imaging (MRI) has been able to provide a window into the pathophysiology of pCMS. Almost all children suspected of harbouring an infratentorial brain tumour undergo structural MRI, including T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR) and T1-weighted post-Gadolinium sequences (Figure 2). Case series have been unable to consistently demonstrate any features on pre-operative MRI which reliably predict

the development of pCMS[19,27,41,50], though a seminal paper in the field reported that more rostrally located fourth ventricle tumours had a significant statistical association with pCMS[18]. Early post-operative structural MRI showing oedema in middle or superior cerebellar peduncles is likely to be associated with pCMS[19,27], and generalised atrophy of the brainstem and cerebellar structures on delayed follow up MRI has been shown to be significantly more likely in pCMS[27].

Post-operative structural MRI can be a sensitive tool for demonstrating hypertrophic olivary degeneration (HOD) in patients with pCMS. This is a form of trans-synaptic neurodegeneration affecting the triangle of Guillain-Mollaret (see Figure 1), leading to concomitant proliferation of glial elements in the inferior olivary nucleus (ION), seen as hypertrophy of the ION on MRI, particularly proton-density weighted images. Lesions of the contralateral dentate nucleus, contralateral SCP, or ipsilateral central tegmental tract give rise to degeneration of the ipsilateral olivary nucleus. Originally described in 1887 by Oppenheim[51], the natural history of HOD from a radiological[52] and histopathological[53] perspective have been well-described. Recently, both qualitative[54] and quantitative[55,56] structural MRI studies have confirmed its association with pCMS. However, due to its latency, at present HOD can only be noted as an *a posteriori* confirmation of pCMS, or a 'validation tool' in clinically equivocal cases.

Diffusion MRI

Diffusion-weighted MRI (dMRI) is sensitive to the random motion of water molecules under specialised MR sequences. Mathematical models of the measured signal can be interpreted to infer the underlying properties of brain tissue, such as orientation of white matter tracts and microstructural parameters. Reconstruction of streamlines based on voxel-wise principal directions of diffusion allows the non-invasive identification and reconstruction of white matter pathways *in vivo*, a computational process known as tractography (Figures 3 and 4). The most basic model of diffusion signal is the diffusion tensor[57]. The term diffusion tensor imaging (DTI) stems from this, although state-of-the-art dMRI has evolved both in terms of acquisition and analysis of data. A variety of metrics can be extracted from DTI, key amongst them fractional anisotropy (FA) – a measure of the coherence of diffusion directionality – and mean diffusivity (MD) – a measure of the magnitude of diffusion, which is

modulated by structures such as cell membranes that act as restrictions to water diffusion. As pCMS has been hypothesised to be associated with dentato-rubro-thalamo-cortical (DRTC) tract disruption, diffusion tractography is an excellent modality with which to study the condition. Several reports detail the feasibility of reconstructing the DRTC using tractography in healthy adults[58–60] and in pre-term neonates[61].

The first use of DTI in pCMS was by Morris *et al.*[18] who used a single-shell (b=1000 s/mm^2) acquisition with 6 diffusion encoding directions. The diffusion tensor was modelled to derive FA maps, and tract-based spatial statistics[62] were used to identify group differences between data from children with pCMS and those without. This study showed reduced FA in bilateral SCPs in pCMS, corroborating the theory of DRTC involvement. In addition, reduced FA was seen in various supratentorial loci (columns of the fornix, right angular gyrus and left superior frontal gyrus), which were suggested to be linked to the neurobehavioural abnormalities seen in pCMS.

Ojemann *et al.*[63] used DTI to generate direction-encoded colour FA maps which were visually inspected to describe the presence or absence of SCPs post-operatively in 16 children with posterior fossa neoplasms. In the 5 patients who developed pCMS, SCPs “could not be discerned” bilaterally. SCPs were, however, identifiable in patients whom did not develop pCMS, whether their tumours were midline or hemispheric. No tractography reconstructions were performed – rather, putative cerebellothalamic connections were traced visually on colour FA maps – and no tensor-derived metrics are provided in the report, making this essentially a qualitative study.

In a large cohort of children with posterior fossa tumours treated in Canada, Law *et al.*[32] used DTI and probabilistic tractography with standardised seed and waypoint regions of interest, to define cerebello-thalamo-cortical connections in a large cohort of children with posterior fossa tumours. They demonstrated disruption of the pathway connecting the right cerebellar hemisphere with the left frontal cortex to be closely associated with pCMS, inferring that unilateral cerebellar damage led to an interference in cerebello-cerebral connectivity with a strongly lateralised preponderance.

As mentioned above, the diffusion tensor is a limited model of the diffusion signal as it suffers from a number of drawbacks; most importantly, it is unable to resolve crossing fibres within a given voxel. The decussation of the SCP in the pontomesencephalic tegmentum is one such region where there is a great degree of white matter fibre crossing. Van Baarsen *et al.*[64] used higher-order diffusion MRI modelling with constrained spherical deconvolution, a technique which has been shown to be superior to DTI in accurately demonstrating fibre tracts in a neurosurgical setting[65]. Their study was limited to a single adult patient with cerebellar mutism syndrome following a post-neurosurgical left pontine ischaemic event. Reduced FA and increased MD were seen in the region corresponding to the left SCP – in keeping with disruption of the presumed underlying fibre tract – and visual comparison of the fibre orientation distribution functions showed less coherent directionality in the left SCP. Another case report of a 20 year old female with cerebellar mutism following arteriovenous malformation-related cerebellar haemorrhage utilised an automated tool to reconstruct white matter pathways from dMRI data[66]. Qualitative analysis of the results showed an equivocal reduction in “fibres” between the right cerebellum and left frontal cortex, and apparent loss of callosal “fibres” in the patient compared to a healthy control.

A key assumption in these two reports is that the mutism syndrome described is analogous to pCMS; whilst it may be so phenotypically, the pathophysiological mechanism in these instances are known to be vascular, whereas in pCMS mechanistic explanations of the syndrome are yet to be established. However, both cases demonstrate that *unilateral* SCP damage can be associated with a mutism phenotype, where previously it had been thought that bilateral damage was required. Moreover, one of the main pitfalls pitfall of diffusion tractography is the misconception that the algorithm-generated streamlines are anatomically analogous to real-world white-matter tracts, or “fibres”; such interpretations must be regarded with some caution given the inherent limitations in the relationship between diffusion signal and underlying brain microarchitecture.

Soelva *et al.*[67] used DTI-based deterministic tractography with generous seed and target regions of interest in the prefrontal cortex and the entire cerebellum to

generate streamlines which were ascribed to fronto-cerebellar fibre tracts. The authors describe three linked metrics of signal disruption in these tracts in patients with pCMS. Firstly, reduced overall tract volume; secondly, reduced signal intensity in SCPs of patients with pCMS compared to healthy peers, as judged by a semi-quantitative method. Thirdly, patients undergoing surgery showed reduced FA compared to healthy peers, but the results were not more marked in patients whom developed pCMS. The authors recognise that this inclusive and deterministic methodology is not specific in delineating diffusion signal associated with neuroanatomically discrete ascending (i.e. DRTC tract) or descending cerebro-cerebellar connections. A corollary of this is that the results do not support a functional explanation for the development of pCMS, as there was no specificity of prefrontal cortical involvement. Nevertheless, this study is another example of the feasibility of studying pCMS *in vivo* from an anatomical perspective using dMRI.

Tractography is uniquely placed as a technique to allow the study of long-range neural connections inferred from local orientation distributions modelled upon diffusion-weighted MR data. The studies described above have contributed to the notion that the cerebellar outflow pathway, and its distal neural connections to subcortical and cortical structures, may be involved in the development of pCMS. However, several questions remain unanswered. The studies presented above focus on the ECP as the primary effector of pCMS, yet there is a growing literature base on the feasibility of mapping afferent cerebellar pathways[68], and their contribution to motor and non-motor processing in humans. Thus, the possible contributions of the middle cerebellar peduncle to pCMS should not be overlooked. The question of whether uni- or bilateral neuronal damage is required to cause pCMS is also unresolved at present, with conflicting evidence from studies to date.

dMRI results have yet to be temporally related to an episode of pCMS, and no reports yet exist of pre-operative DTI metrics in patients at risk of pCMS to serve as a comparator for more easily obtained post-operative imaging. This is often due to the logistical difficulty of acquiring the necessary sequences as children with posterior fossa tumours often present on an emergency basis. Additionally, the presence of tumour causes oedema in and distortion of relevant structures, such as the SCP, making these regions of interest difficult to define. Nevertheless, there is

some evidence that abnormalities exist on conventional diffusion-weighted (DWI) sequences[69,70] and DTI[18,64] prior to clinical manifestation of the syndrome.

This has two important implications for future research. Firstly, if dMRI sequences can be obtained on patients with posterior fossa tumours in the immediate peri-operative period, and later correlated with clinical semiology, we may be able to use this modality not only to predict development of pCMS, but also to employ state-of-the-art tractography methods in surgical guidance to avoid causing it in the first place. Secondly, it is well known that DWI sequences can be a sensitive temporal marker for stroke[71], yet studies serially recording conventional MRI signal change or dMRI-derived parameters such as ADC or FA in single patients with pCMS are lacking. Answering questions such as these will depend on temporally precise acquisition of quantitative MRI scans, which can be challenging in the paediatric clinical environment.

Perfusion imaging

Perfusion, the process of delivering oxygen and nutrients to tissue, is intimately linked to brain function, and there are many imaging modalities which exploit this relationship in the clinical setting. Several single photon emission computed tomography (SPECT) studies have shown perfusion deficits in patients with pCMS both in the cerebellum[72,73] and in several supratentorial regions[73–76]. When scans were repeated after resolution of clinical symptoms, areas of hypoperfusion returned to normal. Miller *et al.* used dynamic susceptibility-weighted contrast-enhanced perfusion MRI (DSC-MRI) to demonstrate widespread (but especially frontal) cortical hypoperfusion in patients with pCMS[77]. Structural MRI in the same cohort also showed an association between bilateral ECP damage and pCMS. The authors thus provided the first evidence of a link between structural and functional domains in this condition, mediated by a hypothesised mechanism of crossed cerebellocerebral diaschisis[78].

One drawback of many modalities of perfusion imaging is their limited spatial resolution (typically around 2-5mm in-plane), and thus their inability to identify smaller-scale functional cortical units. In this regard, the cortical regions seen to have reduced perfusion in pCMS patients are rather extensive – in some cases the

whole hemisphere is involved – and these non-specific findings are based largely on small patient cohorts and case reports. Furthermore, there are conflicting findings from the evidence base so far. In a prospectively-designed case-control study[33], SPECT findings were similar in patients with pCMS and in those without, indicating that results from a single imaging modality are unlikely to yield enough specificity to fully explain the onset of pCMS. More fundamentally, many perfusion studies are based around the phenomenon of neurovascular coupling (the spatiotemporal relationship between neuronal activity and cerebral blood flow), and the nature in which this is altered in supratentorial regions in paediatric patients following posterior fossa craniotomy is currently not known.

Whilst SPECT and DSC-MRI studies require the injection of exogenous agents to generate contrast, arterial spin labelling (ASL) MRI has recently emerged as an alternative, and wholly non-invasive, means of imaging perfusion in the brain (Figure 4). Briefly, inflowing arterial blood in the neck is ‘tagged’ or labelled with a radiofrequency pulse, and then imaged at a suitable interval once it has distributed in brain tissue. Subtraction of these labelled images from unlabelled ones yields a map of cerebral perfusion. ASL is thus able to quantify relevant measures of perfusion, such as cerebral blood flow, and has been used to study cerebral physiology, stroke and in neurosurgical applications[79]. A single case report exists of its use in pCMS[80]. Similar to the SPECT studies listed above, hypoperfusion was found in widespread brain areas, from cerebellum to thalamus and frontal lobe; ASL repeated upon recovery from pCMS again showed the restoration of normal perfusion in affected brain areas, although the authors provide no quantitative metrics of their results. Future uses of this technique in pCMS might include ‘territorial’ or ‘vessel selective’ ASL[81], to investigate the postulated role of vasospasm in the pathophysiology, or to tease out the temporal and spatial details of changes in perfusion during recovery from pCMS.

Functional MRI

The prevailing model of pCMS – surgical damage to the ECP leading to diaschisis – inherently eludes investigation using the imaging modalities mentioned above, because diaschisis provides no structural clues to its presence, being a deficit observed in the functional sphere. Functional MRI (fMRI), sequences which measure

the fluctuations of blood oxygenation signal to provide dynamic estimates of neuronal activity, may provide insights into the changes in brain function in pCMS. Task-based fMRI has been successfully employed in adults with post-neurosurgical speech pathology[82], and in children to determine language lateralisation[83], yet in the cohort in question – children recovering from major brain surgery – the feasibility of fMRI remains to be determined. Studies of this kind may be able to drive forward our understanding of pCMS by identifying the supratentorial regions underlying the florid motoric, linguistic and cognitive symptoms of pCMS.

Conclusions and future directions

pCMS is a well-recognised complication of posterior fossa tumour resection in children. It has been increasingly well characterised clinically in recent years, but validated severity scales to enable comparable clinical research outcomes across centres are still lacking. Advanced MRI sequences have begun to supersede conventional imaging to provide a window into the underlying neural circuitry of pCMS. Several dMRI studies have shown that the DRTC is disrupted in patients with pCMS, placing the cerebellar outflow pathway at centre stage. Serial quantification of perfusion metrics of forebrain structures thought to be affected in pCMS has enabled a deeper understanding of pCMS' pathophysiology; and application of functional and non-invasive perfusion MRI sequences will drive forward our underlying of the neural basis of this intriguing and debilitating syndrome. Only by precisely identifying the neural nodes involved in its pathophysiology will clinicians be able to predict, avoid and treat pCMS.

Figures

Risk factor	Strength	References
Tumour histology medulloblastoma	+++	Doxey 1999, Kupeli 2011 Catsman-Berrevoets 1999, 2010 Kotil 2008, Law 2012
Brainstem infiltration / compression	+++	Doxey 1999, Robertson 2006 McMillan 2009, Korah 2010 Wells 2010, Ersahin 2002, Pols 2017
Vermian location of tumour	++	Catsman-Berrevoets 1999 Kupeli 2011, Korah 2010
	-	Ersahin 2002 Robertson 2010
Tumour size	+	Pols 2017, Law 2012 Catsman-Berrevoets 1999
	-	McMillan 2009
Younger age	+ -	Korah 2010 Law 2012
Rostral location of tumour within Fourth ventricle	+	Morris 2009
Higher core bore body temperature post-op	+	Pols 2017
Low socioeconomic level	+	Kupeli 2011
Left handedness	+	Law 2012
Pre-operative language impairment	+	Di Rocco 2011
Surgical approach	+ -	Ersahin 2002, Kotil 2008, Grill 2004 Zaheer & Wood, 2010
Gender	-	Robertson 2006 Catsman-Berrevoets 1999
Extent of resection	-	Robertson 2006 Law 2012
CSF leak / meningitis (infective or aseptic)	-	Wells 2010 Catsman-Berrevoets 1999 Robertson 2006
Pre-operative hydrocephalus	-	Catsman-Berrevoets 1999 Wells 2010
Surgeon type	-	Robertson 2006

Table 1. Risk factors for development of pCMS reported in the literature. +, positive association; -, no association.

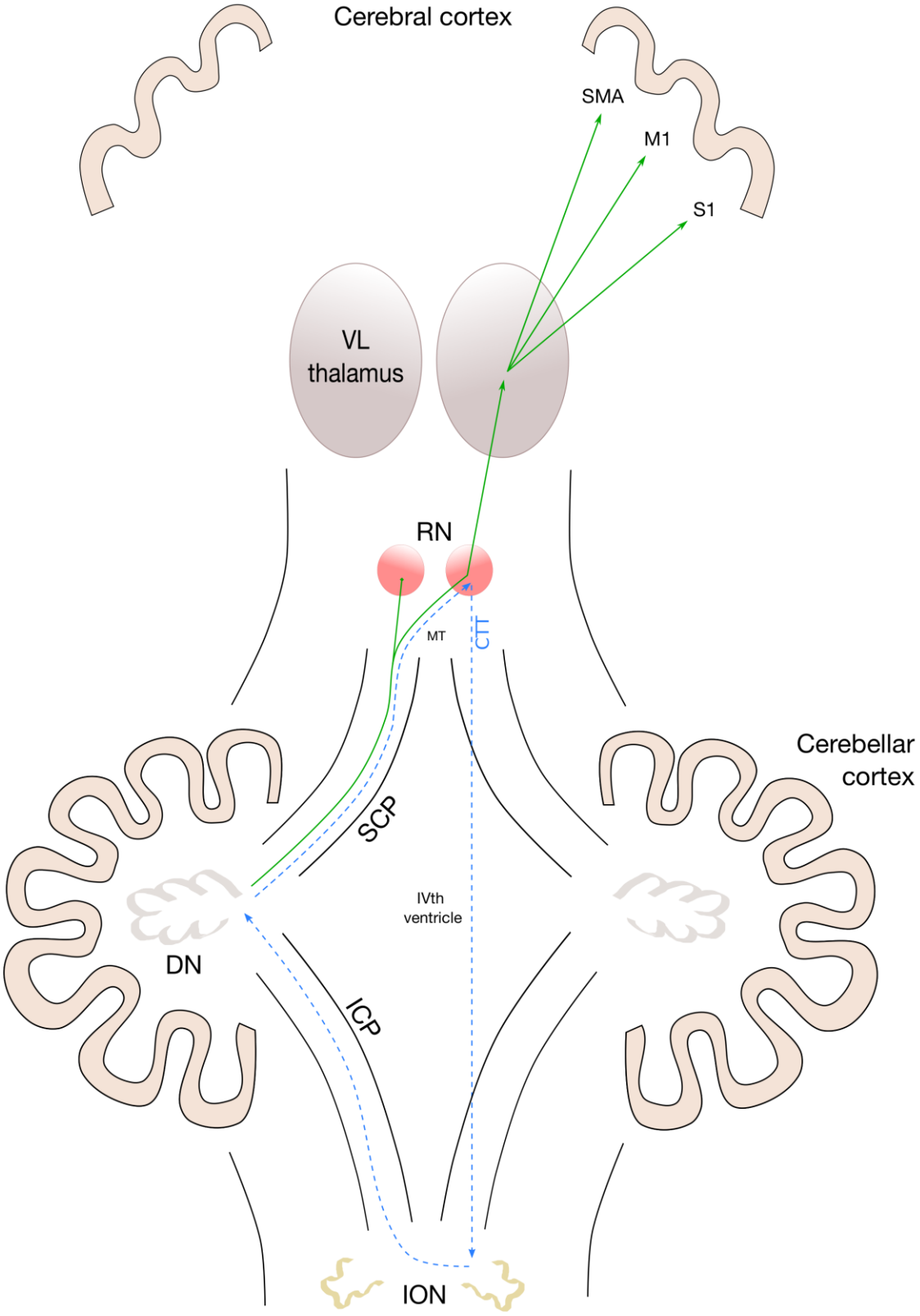

Figure 1. Schematic anatomical figure showing the dentato-rubro-thalamo-cortical tract (green) and triangle of Guillain-Mollaret (blue) in relation to cerebellar afferent and efferent pathways. CTT, central tegmental tract; DN, dentate nucleus; ICP,

inferior cerebellar peduncle; ION, inferior olivary nucleus; M1, primary motor cortex; MT, mesencephalic tegmentum; RN, red nucleus; S1, primary sensory cortex; SMA, supplementary motor area; VL thalamus, ventrolateral nucleus of thalamus. Figure reproduced in unedited form from Toescu *et al.*[50], originally distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0).

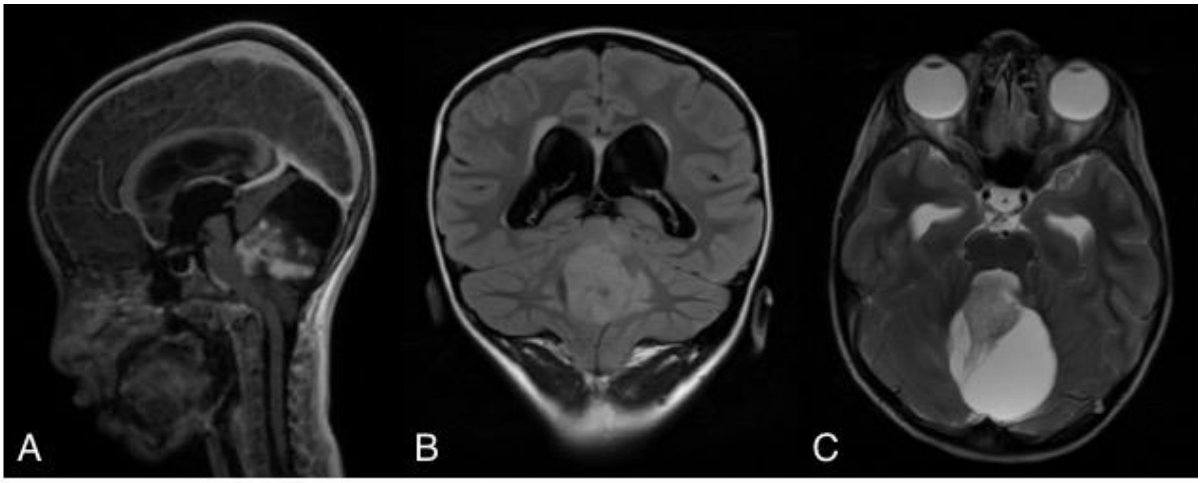

Figure 2. Conventional structural MRI scans of a patient with pilocytic astrocytoma, treated surgically at our institution, who did not develop pCMS. A, sagittal T1-weighted post-Gadolinium; B, coronal FLAIR; C, axial T2-weighted sequences. Note the rostral location of the tumour in the posterior fossa, elevation of the cerebellar vermis and splaying of the superior cerebellar peduncles in these pre-operative sequences.

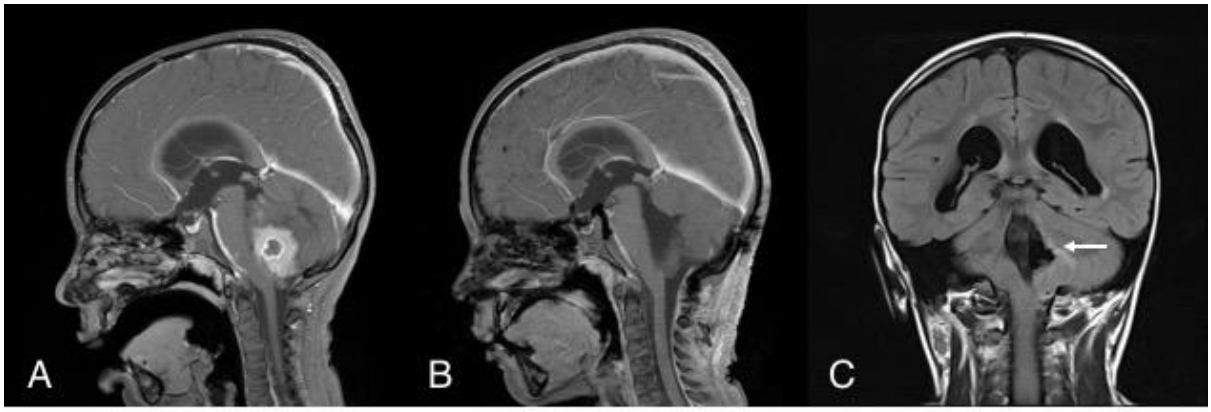

Figure 3. Conventional structural MRI scans of a patient with medulloblastoma, who developed pCMS after surgical resection at our institution. A, pre-operative sagittal T1-weighted post-Gadolinium; B, post-operative sagittal T1-weighted post-Gadolinium; C, post-operative coronal FLAIR sequences. Note the gross total resection of tumour and signal change in the region of the left dentate nucleus (white arrow), extending rostrally towards the ipsilateral superior cerebellar peduncle.

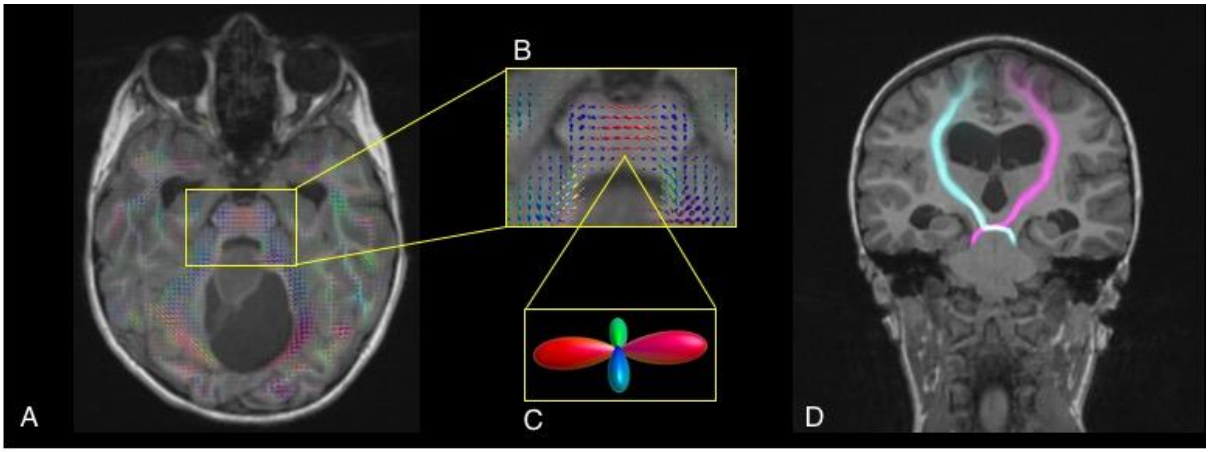

Figure 4. A, voxel-wise white matter fibre orientation distributions functions (fODF) derived from constrained spherical deconvolution modelling of dMRI data, projected on an axial T1-weighted slice. Note the excellent angular resolution of principal diffusion directions in the mesecephalic tegmentum (enlarged in B) where the DRTC tracts decussate. C, high resolution view of single voxel fODF. Red lobes indicate diffusion in left-right, green in anterior-posterior, blue in superior-inferior directions respectively. D, tractography streamlines generated using probabilistic algorithms. The left DRTC tract (cyan, tractography seeded from left superior cerebellar peduncle) and the right DRTC tract (magenta, tractography seeded from right superior cerebellar peduncle) are shown projected on a single coronal T1-weighted slice. Note the anatomically plausible decussation of both DRTC tracts as they travel towards the thalamus and frontal cortex. Images processed from the same patient as in Figure 2, at our institution, using MRtrix 3.0[84].

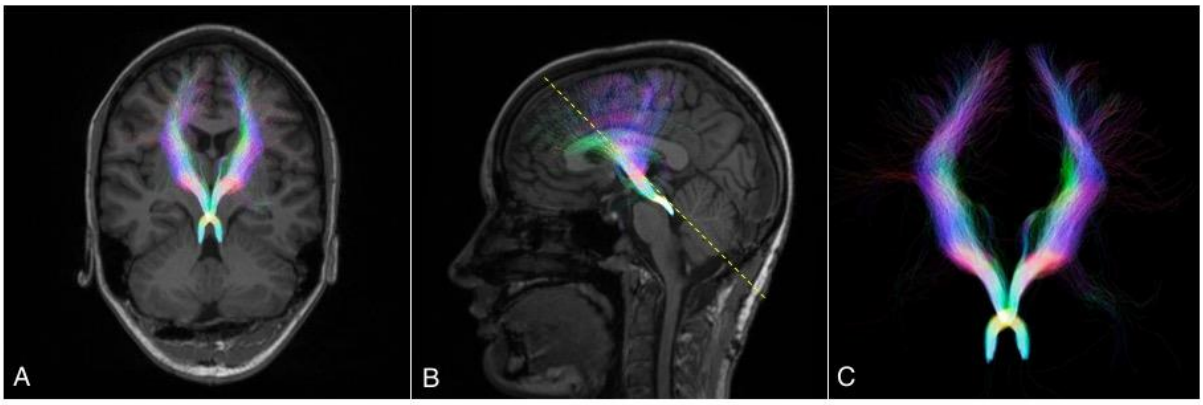

Figure 5. Probabilistic tractography streamline reconstructions of both DRTC tracts in a patient who recovered well after exophytic brainstem tumour debulking. A, bilateral 3-dimensional DRTC tract streamlines overlaid on a single T1-weighted slice in axis as per dotted yellow line in B. Note the decussation of both DRTC streamlines and their passage through the thalami towards widespread areas of cerebral cortex. B, bilateral 3-dimensional DRTC tract streamlines overlaid on a single T1-weighted sagittal slice. The majority of streamlines terminate in areas of frontal cortex. C, bilateral 3-dimensional DRTC streamlines viewed in isolation in coronal projection, depicted in standard radiological convention and with directional colour encoding as described in Figure 4C. Images acquired and processed at our institution using MRtrix 3.0[84].

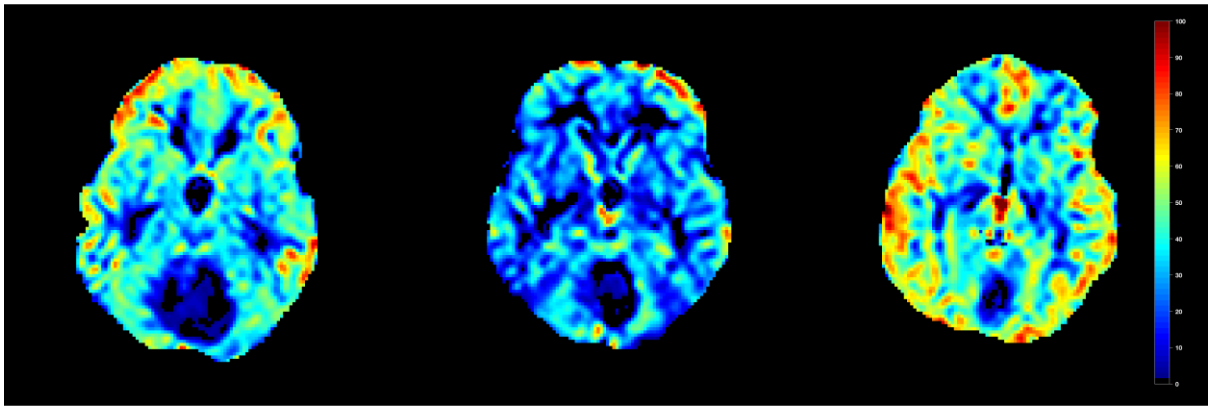

Figure 6. Cerebral blood flow (CBF) maps calculated from single inflow-time pCASL (pseudo-continuous labelling ASL) data. Scale bar shown on right (units ml/100g/min), images from same slice in *z*-axis. A, pre-operative CBF map; B, CBF map taken 4 days after posterior fossa craniotomy for tumour resection; C, CBF map at 3 months post surgery. The images show a global reduction in cerebral blood flow in the post-operative phase, although the patient did not have pCMS at the time of the scan, with subsequent global improvement in perfusion at follow up. Images processed from the same patient as in Figure 2, at our institution.

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