European Journal of Radiology 108 (2018) 43–51

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Review

Quantitative MRI in post-operative paediatric cerebellar mutism syndrome

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ARTICLE INFO

Keywords:
Cerebellar mutism
Posterior fossa syndrome
Medulloblastoma
Tractography
Arterial spin labelling

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.

1. 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.

2. Nomenclature and semiology

The syndrome of pCMS as it relates to surgery of theposterior 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 6the patient will initially recover well from

Abbreviations: DTI, diffusion tensor imaging; pCMS, post-operative paediatric cerebellar mutism syndrome; ASL, arterial spin labeling; dMRI, diffusion MRI; PFS, posterior fossa syndrome; ECP, efferent cerebellar pathway; DRTC, dentato-rubro-thalamo-cortical; SMA, supplementary motor area; HOD, hypertrophic olivary degeneration; ION, inferior olivary nucleus; FA, fractional anisotropy; MD, mean diffusivity; SCP, superior cerebellar peduncle; ADC, apparent diffusion coefficient; SPECT, single photon emission computed tomography; DSC-MRI, dynamic susceptibility-weighted contrast-enhanced perfusion MRI; fMRI, functional MRI

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https://doi.org/10.1016/j.ejrad.2018.09.007
Received 3 July 2018; Received in revised form 17 August 2018; Accepted 6 September 2018

surgery of the posterior fossa, with normal speech immediately post-operatively. 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 multicentre 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.

3. 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].

4. 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; Fig. 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

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

Risk factor	Strength	References
Tumour histology medulloblastoma	+ + +	Doxey et al. [28], Kupeli et al. [31], Catsman-Berrevoets et al. [29], Catsman-Berrevoets and Aarsen [20], Kotil et al. [30], Law et al. [32]
Brainstem infiltration / compression	+ + +	Doxey et al. [28], Robertson et al. [25], McMillan et al. [35], Korah et al. [34], Wells et al. [27], Ersahin et al. [33], Pols et al. [36]
Vermian location of tumour	+ +	Catsman-Berrevoets et al. [29], Kupeli et al. [31], Korah et al. [34]
	–	Ersahin et al. [33], Robertson et al. [25]
Tumour size	+	Pols et al. [36], Law et al. [32], Catsman-Berrevoets et al. [29]
	–	McMillan et al. [35]
Younger age	+	Korah et al. [34], Law et al. [32]
	–	
Rostral location of tumour within Fourth ventricle	+	Morris et al. [18]
Higher core bore body temperature post-op	+	Pols et al. [36]
Low socioeconomic level	+	Kupeli et al. [31]
Left handedness	+	Law et al. [32]
Pre-operative language impairment	+	Di Rocco et al. [39]
Surgical approach	+	Ersahin et al. [33], Kotil et al. [30], Grill et al. [37], Zaheer and Wood [38]
	–	
Gender	–	Robertson et al. [25], Catsman-Berrevoets et al. [29]
Extent of resection	–	Robertson et al. [25], Law et al. [32]
CSF leak / meningitis (infective or aseptic)	–	Wells et al. [27], Catsman-Berrevoets et al. [29], Robertson et al. [25]
Pre-operative hydrocephalus	–	Catsman-Berrevoets et al. [29], Wells et al. [27]
Surgeon type	–	Robertson et al. [25]