Chapter 7

Neuropsychiatry: Aspects of Childhood Cranial Tumours

Alexander Hegarty and Yulia Furlong

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.75679

Abstract

More than 90 years have passed since Baily and Cushing first introduced a histogenetic classification for tumours of the cranial nervous system (CNS). More recently, our knowledge of the genetic and molecular basis of tumorigenesis has caused a major paradigm shift towards defining tumours genetically, thus allowing greater diagnostic accuracy and prognostication to better guide tumour management. Correspondingly, successes in integrated management and improved survival rates have shifted attention towards overall quality of life studies, where psychosocial sequelae and adjustment implications are of particular interest to mental health professionals. To date, research relevant to this field has focused on the identification of neuropsychiatric symptoms at manifestation of illness. Such studies indicate that mood, cognition and psychosocial functioning are important factors in early diagnosis, mediating health outcomes, especially following radical and risk-adapted antineoplastic treatment. In addition to psychological burden, the neuropsychiatric aspects of childhood CNS tumours, including posterior fossa syndrome and cerebellar cognitive affective syndrome, are increasingly recognised as crucial causes of poor outcomes. The chapter ahead will initially address the shifting landscape of neuro-oncology, and then provide an overview of the neuropsychiatric aspects of CNS tumours in childhood, highlighting the underlying neurobiological and pathogenic mechanisms, whenever possible.

Keywords: childhood CNS tumours, cerebellar cognitive affective syndrome, posterior fossa syndrome, cerebellar mutism, neuropsychiatric presentation, neuropsychiatric outcomes

1. Introduction

Central nervous system (CNS) tumours are one of the most common cancers among children and adolescents, with an incidence rate of 5.57 per 100,000 population [1]. Among children

(aged 1–14 years) they account for 26% of all childhood cancers, and are thus second only to leukaemia (29%); in adolescents (aged 15–19 years) they remain the second most common cancer (17%), following lymphoma (21%). Overall, CNS tumours represent the leading cause of cancer mortality in all individuals aged <20 [2]. However, a multitude of advancements in early diagnosis and risk-adapted treatment has resulted in increased survival; the importance of psychological and neurocognitive outcomes is thus more apparent than ever. Of course, childhood neuropsychiatry remains a nascent discipline and therefore it is prudent to begin with an overview of the current landscape of neuro-oncology.

The most utilised classification system for brain tumours—the 4th edition of the 'World Health Organisation (WHO) Classification of Tumours of the CNS' (2007)—was recently updated in 2016 [3]. It marks a conceptual milestone, finally enhancing the century-old principle of histogenesis-based nosology; this is largely due to the addition of molecular markers into CNS tumour classification. Evidently, we are entering a new era of neuro-oncology, with promise of superior clinical, experimental and epidemiological methods that may bring 'personalised' or 'precision medicine', within reach [3, 4].

Previously, tumours of the CNS were exclusively recognised by their morphological resemblance to constituent cells, including astrocytes, oligodendrocytes and ependymal cells. However, this system had three major deficiencies: first, differentiation can co-exist within the tissue of a single tumour; second, the accuracy of the prognosis was suboptimal; and most crucially, inter-observer differences were very apparent among neuropathologists [5].

With regards to diagnostic concordance, the discovery of a codeletion of chromosome 1p and 19q in oligodendroglioma signalled marked progress; it likely contributed to the inspiration behind the molecular underpinning of 'WHO 2016' [6]. Indeed, oligodendroglia-like cells in various neuroepithelial tumours have always been a diagnostic challenge due to diverse differentiation and biological behaviour; alternatively, the 1p/19q codeletion correlated with the classic oligodendroglioma morphology as well as the clinical, radiological and biological characteristics, i.e., gliomas harbouring 1p/19q are a coherent single entity, and thus provide superior inter-observer reliability [5].

Moreover, these molecular stratifiers provide prognostic and predictive information: for example, Isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2, respectively) mutations are found almost exclusively in infiltrating astrocytomas and oligodendrogliomas [7, 8]; conversely, a medulloblastoma with genetic alterations in the wingless (WNT) pathways suggests excellent long-term survival rates [9]. As these tumour sub-classifications are informed by transcriptomes with similar biological behaviour, they will likely respond to corresponding targeted treatments, an approach that will drive many other successful anti-neoplastic therapies in the future [10, 11].

1.1. CNS tumour classification

The new nomenclature in CNS tumour classification empowers a clinician to pragmatically and scientifically construct a diagnosis by combining the histopathological name with the genetic determinant (if unavailable, 'NOS' suffix is used, i.e., not otherwise specified): conventional

http://dx.doi.org/10.5772/intechopen.75679

histology determines the initial stratification (e.g., 'diffuse glioma'); and secondly, a molecular defined genotype is added to denominate the subset, e.g., IDH-mutant (note: the genotype follows a comma and includes an adjective). Therefore, examples read as follows: 'Diffuse astrocytoma, IDH-mutant'; 'Medulloblastoma, WNT-activated' and so forth. Of note, the WHO grading system remains informed by histology only; thus each tumour is graded between I and IV (note: Roman numerals), in accordance with the degree of anaplasia, mitotic activity with microvascular proliferation and/or necrosis [8].

1.2. Medulloblastoma

Medulloblastoma (MB), a small blue cell malignancy of the cerebellum, is an embryonal tumour and represents the most common malignant brain tumour of childhood. Asides from its importance in paediatric neuro-oncology, MB will be discussed frequently in this chapter due to its relevance in childhood and adolescent neuropsychiatry. The 'medulloblastoma'—originally named in 1925 for its anatomical and histopathological traits [12]—is nowadays defined by a genetic biomarker: namely, either 'WNT-activated', 'SHH-activated', 'group 3' or 'group 4'. Nevertheless, diagnosis is gleaned from genome-wide transcriptomic and DNA methylation patterns, in addition to these distinct clinicopathological and molecular features. The wingless (WNT) and Sonic Hedgehog (SHH) subgroups are named for the signalling pathways thought to play prominent roles in their individual – and eponymously titled - pathogenesis, i.e., these MB subgroups are underpinned by WNT or SHH-activating mutations [5]. In contrast, MB group 3 and MB group 4 have few mutations but exhibit multiple DNA copy number alterations [13]. MB typically develops in children aged between 4 and 9 years, with a higher rate in boys. This predilection for onset in childhood is illustrated by the US incidence rate of 6 per million in children (1–9 years), a rate 10 times higher than that seen in the adult population [14], a statistic underpinned by histological and genetic differences, with more mutations observed in medulloblastoma of childhood when compared to that of adult-onset [15].

The subgrouping of MB has been useful in facilitating direct treatment strategies and reducing long-term intellectual and neuro-endocrine impairments associated with existing multimodal therapies [16]. The subgroups also add prognostic and predictive value; for example, in contrast to adult WNT-activated MB, children in this subgroup have an excellent overall prognosis (>90%) [17, 18]. Therefore, individualised and reduced intensity risk-adapted therapies are in development [19]. Moreover, SHH pathway inhibitors have had success in treating SHH-activated disease in early-phase trials [20]. Of note, the prognosis of SHH-activated MB is dictated by the presence of TP53 mutations, half of which are underlined by germline mutations and thus associated with secondary tumours [21, 22]. Evidently, genetic counselling is paramount for all families of children with MB with SHH-activation [23].

There are other high risk clinical factors in MB, and include: metastatic disease; large-cell, anaplastic (LCA) pathology; incomplete surgical resection; and MYC amplification [16]. Of note, the histological subtypes of MB have not been dramatically changed in 'WHO 2016'. However, large cell and anaplastic variants have been married to reflect their typical co-occurrence; this single entity (LCA) has a very poor prognosis. Furthermore, molecular and histological subtypes coexist in many cases, e.g., 'WNT-activated' MB almost always has classic histology (**Figure 1**).

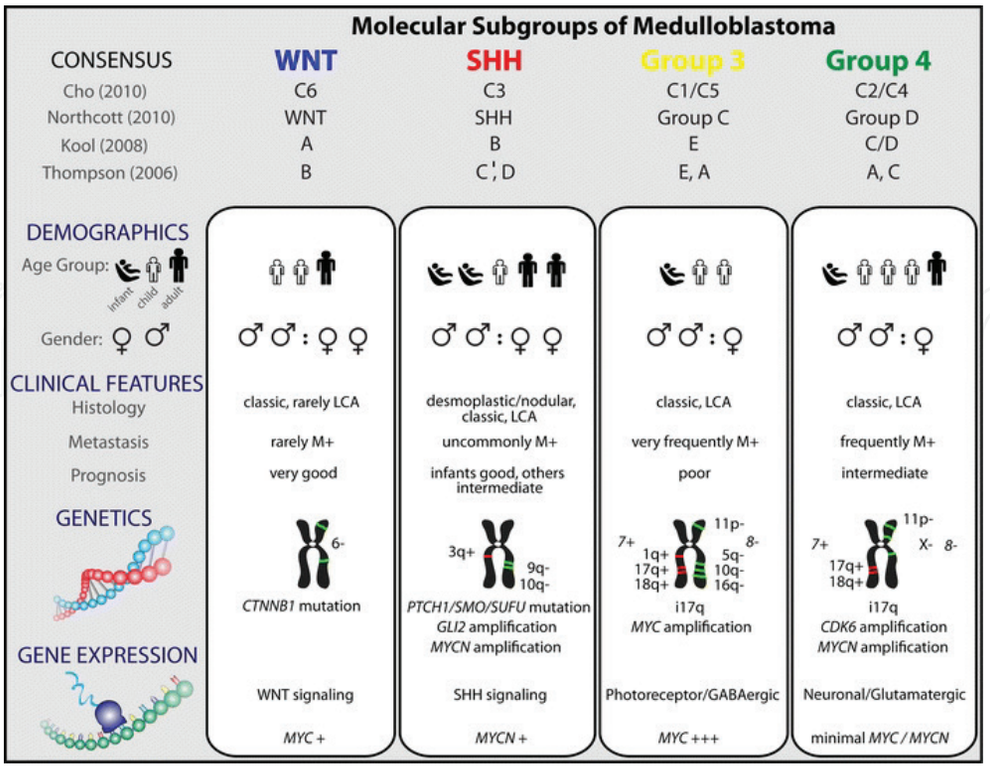

Figure 1. Molecular subgroups of medulloblastoma: A comparison of the various subgroups of medulloblastoma, adapted from Taylor et al. [10] with permission.

Evidently, the molecular era has sparked a rapidly propagating area of research which will further optimise CNS tumour diagnosis, treatment and outcomes. The latter is inextricably linked to psychological well-being; thus, it is crucial that psychiatric illness and neurocognitive deficits are investigated, recognised and addressed in order that a truly optimal and holistic clinical outcome is achieved. Therefore, the many guises of neuropsychiatry and its management will be the main focus of the remaining chapter.

1.3. Neuroanatomical correlates

The differential of a suspected CNS tumour can be narrowed by designating its location as 'supratentorial' or 'infratentorial', depending on whether it originates above or below the tentorium cerebella/cerebellar tentorium (Latin for 'tent of the cerebellum'); the tentorium is an extension of the dura matter that separates the cerebellum from the inferior portion of the occipital lobes [24]. A cancer's 'tentorial topography' varies across the lifespan: toddlers (aged 2–3 years) and adults are most likely to have supratentorial tumours; conversely, an infratentorial origin is more common in young children (aged 4–10); however, in older children and teenagers (i.e., aged 10–18 years) supratentorial and infratentorial tumours may occur with equal frequency [25] (**Figure 2**).

The supratentorial region—specifically the supra or (para)sellar area—hosts three main paediatric cancer types: craniopharyngioma, optic pathway/hypothalamic glioma and germ cell tumours. Several studies have shown that supratentorial tumours generally result in greater morbidity than infratentorial tumours in surviving children and adults [4].

http://dx.doi.org/10.5772/intechopen.75679

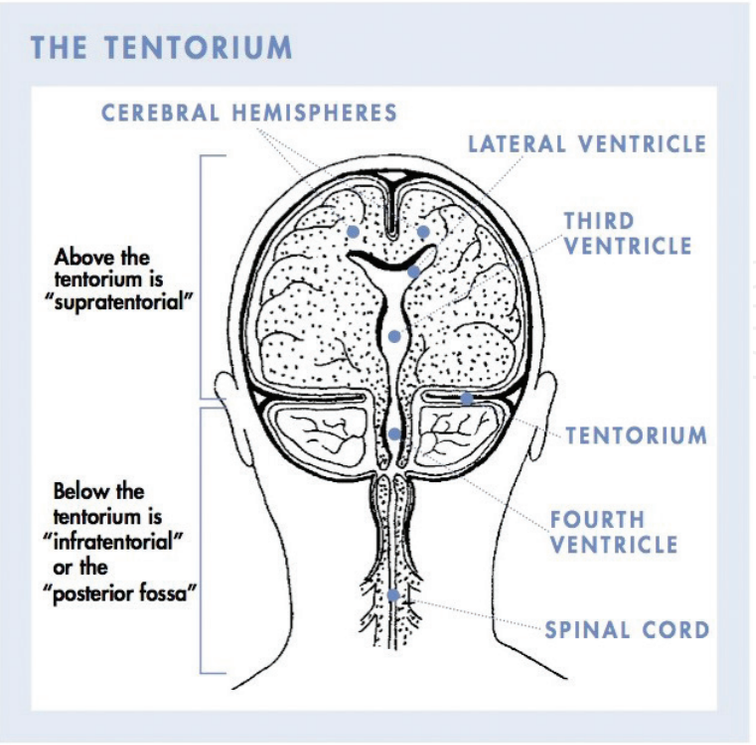

Figure 2. Illustration of the tentorium; including supratentorial and infratentorial view. Adapted from The American Brain Tumor Association with permission.

Supratentorial tumours are most commonly associated with the non-specific symptoms of raised intracranial pressure, seizures and papilledema. Any centrally localised neoplasm will also present vaguely (bar visual symptoms); headache, nausea and vomiting are commonly reported [26].

In the infratentorial region, the common tumours are MB, low-grade cerebellar astrocytoma, brain stem glioma and ependymoma; the commonest posterior fossa tumours of childhood are brainstem glioma, MB, ependymoma and cerebellar astrocytoma. When presenting as posterior fossa tumours, MB (and other cancers) cause vague symptoms such as nausea, vomiting, headache and papilledema. Additionally, they may present with gait disturbance and/or incoordination, i.e., signs that are also seen in brain stem and spinal cord tumours. Of note, back pain is a common manifestation of spinal cord tumours, whereas cranial nerve palsies and pyramidal signs would suggest brain stem tumours [26].

At times, clinical suspicion may be strengthened by comparatively specific signs and symptoms of infratentorial lesions: for example, brainstem involvement can cause extra-ocular muscle impairment, facial paresis, swallowing difficulties, hemiparesis, quadriparesis, ataxia or dysmetria; similarly, ataxia, dysmetria, headache, nausea, vomiting, neck pain or extra-ocular muscle impairment can correspond with posterior fossa involvement [27].

MB typically develops in the midline, within the vermis; however, paediatric MB is also characterised by growth into the fourth ventricle [28]. Radiologically, MB is hyperdense on CT but

hypointense on T1-W MRI and T2-W MR [29] usually demonstrating homogeneous enhancement with gadolinium administration [30].

2. Neuropsychiatric presentation of brain tumour

Unsurprisingly, a child with a brain tumour rarely presents to a psychiatrist at the manifestation of illness. Nevertheless, neuropsychiatric presentations in children with brain tumours can, and do, come to the attention of psychiatrists, albeit infrequently. The psychiatric and behavioural presenting symptoms of CNS tumours and/or subsequent iatrogenic sequelae include internalising presentations (mood and anxiety disorders), mutism, pseudobulbar symptoms, somatic problems, externalising presentations (such as aggression), eating disorders, psychosis, and hyperkinetic disorders. The clinical course is multi-faceted: the symptoms may appear early as the presenting complaint; later, following a confirmed (tumour) diagnosis; as a complication of anti-neoplastic therapy; or as an 'adjustment disorder'. Nevertheless, there is a relative paucity of studies that describe the neuropsychiatric symptoms associated with this cohort of patients [26].A literature review was conducted by Zyrianova et al. [26] to address childhood CNS tumour presentations of a 'neuropsychiatric' nature; the many possible combinations of symptoms—from psychiatric to physical/neurological—largely depended on the location and extent of the tumour [26]. Interestingly, the location of the lesion strongly correlated to neuropsychiatric prognosis. Supratentorial, right-sided cerebellar and vermal lesions all demonstrated the poorest outcomes [31–34]. Specifically, lesions of the vermis were associated with dysregulation of affect [33].

In certain cases, neurobehavioural disorders are known to increase the risk of developing a childhood brain tumour. For example, children with Autism Spectrum Disorder are more likely than the general paediatric population to develop a CNS malignancy [34]. Furthermore, mere behavioural (and 'mental') symptoms existed pre-morbidly in a quarter of children with a subsequent diagnosis of thalamic tumours in a case series [35]. A retrospective case note review of 200 children with brain tumours demonstrated that neurological symptoms (present in 88% of patients) were only twice as common as 'educational or behavioural problems'; moreover, the latter represented the initial presentation in 10% of cases [36].

2.1. Case series

There are no large-scale studies that specifically assess the presenting symptoms of childhood brain tumours in a psychiatric context. Nevertheless, several case reports/small case series have highlighted specific psychiatric symptoms that heralded a brain cancer, as follows:

- An intracranial germinoma presented in an adolescent male as a first episode psychosis. This followed a 3-month history of negative symptoms, daytime somnolence, 'distorted thought processes' and memory loss; the only positive symptoms were 'sporadic visual sensations' at the edge of the visual field [37].

- A left temporal lobe tumour presented as psychosis in an 18-year-old girl. It was characterised by withdrawal, paranoia, ideas of reference and derealisation. Of note, her neurological examination had been normal [38].
- A case series of three paediatric patients illustrated cerebral malignancies which had imitated neuropsychiatric diagnoses, namely one case of Giles de la Tourette Syndrome(GTS) and two cases of obsessive-compulsive disorder (OCD) [39]. The first patient, initially diagnosed at 18 months with a malignant hypothalamic tumour (with local spread), developed vocal and facial tics in childhood. Surgery successfully resolved the tics; nevertheless, compulsions, such as 'rocking', 'skin picking' and hyperphagia emerged post-operatively. The second case, parietal malignancy in a male child, was heralded by a worsening of a pre-morbid obsessive-compulsive syndrome, although eye signs and seizures ultimately developed. The third case, a 4-year-old boy with pre-morbid diagnoses of OCD, GTS and attention deficit hyperactivity disorder (ADHD), developed a severe depressive illness and worsening ('incapacitating') motor and verbal tics prior to a diagnosis of midbrain glioma.
- Anorexia, including cognitive distortions—'feeling fat and ugly'—preceded the diagnosis of a 'lobular mass within the pituitary fossa' in a 14-year-old girl. Although she had demonstrated possible seizure activity (i.e., 'eyes would roll back into her head' and 'staring' were reported), the patient had initially presented to an eating disorder specialist unit [40]. Of note, a review article in 2005 described 54 previously published case reports about 'eating disorders in brain damage' (the majority of these cases were brain tumours) [41]. Many of these cases, among all age groups, described the typical presentation of an eating disorder, i.e., the classic behaviours and expected cognitions. However, almost all the subjects had co-existing positive neurological signs and/or complications, including headache, seizures, visual impairment, diabetes insipidus and hypopituitarism.

2.2. Posterior fossa syndromes

Of particular relevance to neuropsychiatrists are lesions within the posterior fossa (PF), a portion of the intracranial cavity that contains the cerebellum and brainstem. Over half of childhood tumours are located in the PF [42]. These lesions account for the largest number of cancer deaths in children and may initially present with neuropsychiatric signs and symptoms [43]. Within the PF, in addition to the co-ordination of balance and motor functions, the cerebellum has a role in functions such as cognition, emotion and language [44]. Indeed, the independent role of the cerebellum in higher order brain function is expansive: internal architecture and wide connectivity co-ordinate and integrate this crucial regulation of neuropsychiatric functions. Such orchestration is only possible due to the cerebellum's connections to prefrontal cortex, subcortical limbic structures, and catecholamine-containing brainstem nuclei [45]. Similarly, the brainstem—once almost exclusively known for its involvement in vital functions (breathing, heart rate, sleeping)—is increasingly recognised for affective and cognitive functioning. A recent critical review of the literature published (between 1950 and 2012) on the affective and cognitive symptoms that follow brainstem lesion has revealed neuropsychiatric symptoms in almost half the cases: apathy, emotional lability, irritability, mania, executive dysfunction, memory impairment, and inattention were among the symptoms

listed; moreover, the authors hypothesised that the brainstem constitutes an inherent part of the cerebello-cerebral network that subserves cognition and affect. Therefore, isolated brainstem damage can cause symptoms that resemble the cerebellar cognitive affective syndrome (CCAS) [46]. Furthermore, children with midline tumours with brainstem invasion are at increased risk of posterior fossa syndrome (PFS) [47].

Of note, CCAS consists of neuropsychological and lingusitic deficits but does not include verbal mutism or neurological/motor symptoms. Conversely, posterior fossa syndrome (PFS) is a sprawling spectrum of neuropsychological, neurological and lingusitic symptoms [47]. Thus, lesions in the brainstem, but mostly those involving the fourth ventricle and cerebellum – or their surgical removal – can engender a variety of clinical outcomes. Confusingly, the literature has a formidable tapestry of definitions. Excluding both CCAS and 'Cerebellar Syndrome' (i.e. isolated cereballar signs), it is 'Cerellar Mutism' (a verbal mutism also known as 'Transient Cerebellar Mutism' or TCM) that is the defining hallmark of the relevant post-operative syndromes: (the aforementioned) Posterior Fossa Syndrome (PFS); the less expanisive 'Cerebellar Mutism Syndrome' (CMS) – which is limited to mutism, ataxia, hypophonia and irritability; and finally, the self-explanatory 'Mutism and Subsequent Dysarthri'a (MSD). Importantly all of the aforementioned syndromes (i.e. CM or TCM, CMS, CCAS, MSD and Cerebellar syndrome) are subsumed by the term Posterior Fossa Syndrome, i.e. they can be a presentation of PFS (**Figure 3**) [48].

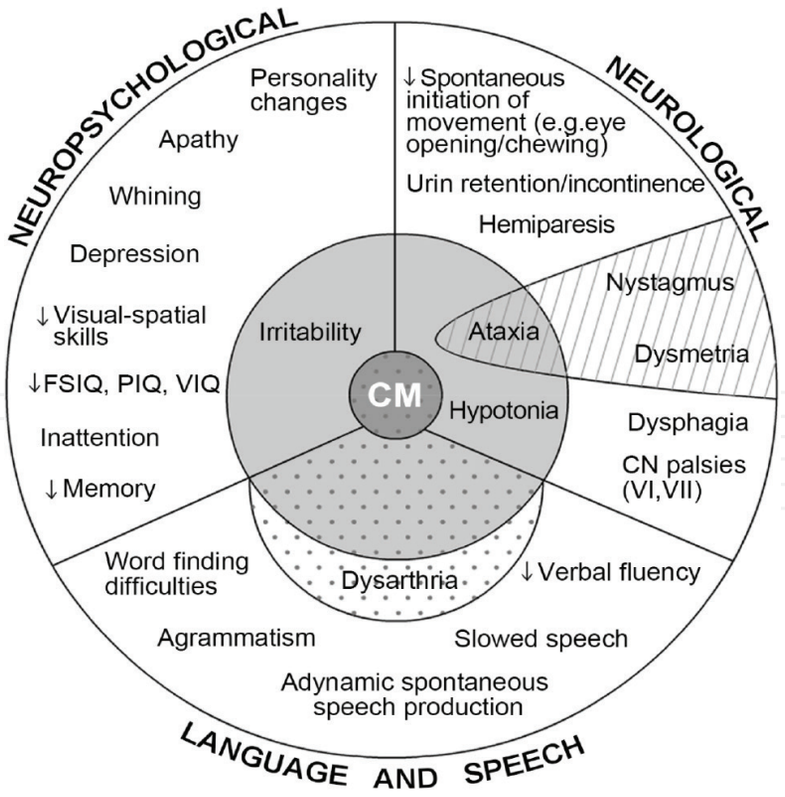

Figure 3. Symptomatic spectrum and relationship between the PFS, CCAS and related conditions. Adapted with permission from the Posterior Fossa Society [48]. Entire Figure = PFS, Left Half (Excluding CM) = CCAS, Inner Circle (Light Grey) = CMS, Dotted Area = MSD, Core (Dark Grey) = CM or TCM, Stripped Area = Cerebellar Signs or Cerebellar Syndrome.

The reader is also informed that in 2016 a new definition, 'Post-operative pediatric CMS' (POP-CMS), was devised by experts ('Iceland Delphi group') in the feld: "Post-operative pediatric cerebellar mutism syndrome is characterized by delayed onset mutism/*reduced speech* and emotional lability after cerebellar or 4th ventricle tumour surgery in children. Additional common features include hypotonia and oropharyngeal dysfunction/dysphagia. It may frequently be accompanied by the *cerebellar motor syndrome, cerebellar cognitive affective syndrome* and brain stem dysfunction including long tract signs and cranial neuropathies. The mutism is always transient, but recovery from CMS may be prolonged. Speech and language may not return to normal, and other deficits of cognitive, affective and motor function often persist"[49].

The Posterior Fossa Society has provided further guidance for clinicians when following this definition:

1. *Reduced speech*: "speech production that is severely reduced and limited to single words or short sentences that can only be elicited after vigorous stimulation".

2. *Cerebellar motor syndrome*: "impairment of gait (ataxia), extremity coordination (dysmetria), disordered eye movements, poor articulation (dysarthria), impaired swallowing (dysphagia) and tremor".

3. *Cerebellar cognitive affective syndrome*: "a pattern of behavioural abnormalities that includes impairments of executive function (planning, set-shifting, abstract reasoning, verbal fluency, working memory), often with perseveration, distractibility or inattention; visual-spatial disorganization and impaired visual-spatial memory; personality change with blunting of affect or disinhibited and inappropriate behaviour; and difficulties with language production including dysprosodia, agrammatism and mild anomia".

4. *Long tract signs*: "symptoms such as urinary retention/incontinence and hemiparesis, which are frequently observed in this patient population" [48].

Of note, like many of its predecessors, the hallmark of POP-CMS is CM (see discussion on CM below).

POP-CMS as a definition represents the foundation for more consistent research. However, its validity requires more testing and it may be subject to further revision. Therefore, for the remainder of the chapter, we will use the terms which are more established in the literature.

2.3. Cerebellar mutism

The term 'cerebellar mutism' refers to a muteness which results from lesions of the cerebellum as opposed to the cerebrum or lower cranial nerves. A severe dysregulation of volitional motor functions of speech creates a recognizable clinical signature: an absence of speech (verbal mutism) is seen, rather than an absence of non-verbal sounds (i.e. whining, laughter, crying) [49]. Although most commonly seen after resection of posterior fossa tumours, there are reports of non-surgical cases of paediatric CM, including trauma, vascular incidents, infections and inflammatory syndromes [48, 50, 51]. CM has been reported to resolve after as little as 6 days or as long as 52 months [52]. Indeed, a hallmark of CM is its

idiosyncratic temporality: the onset is typically delayed, often emerging 24–48 hours post-operatively. The duration is variable, albeit self-limiting and usually resolving in weeks; the resolution often occurs rapidly, i.e. over days. However, many patients experience dysarthria throughout the recovery period and then suffer long-term speech and language dysfunction; this includes ataxic dysarthria, dysfluency and slowed speech rate [26]. Crucially, the duration of CM (i.e., whether 4 weeks or 4 months) will correlate with the functional prognosis. An absence of speech after PF tumour surgery was first described as "akinetic mutism" (AM) by Daly and Love in 1958 following the removal of a cerebellar tumour in a child [53]. However, a 1985 case series reporting on six children with cerebellar lesions is credited for the first reports of CM [54]. A complete absence of speech and up to 3 months of dysarthria was described following each posterior fossa craniectomy ('or a complication thereof'). The authors concluded that 'transient muteness may result from acute bilateral cerebellar injury' [55].

Since then, over 400 cases of CM have been reported in the literature. Law et al. [52] compared three groups of children—PF tumours with CM, PF tumours without CM, and healthy controls—to examine the clinical and neuroanatomical predictors of CM. The results of this study concluded that there was a statistically significant positive correlation between tumour size and the likelihood of developing CM. It also found that a greater proportion of children with CM were left-handed, compared to those without CM. However, medulloblastoma and/or brainstem invasion appear to pose the greatest risk of CM, while cerebellar hemisphere involvement is associated with highest risk of permanent motor and non-motor-speech related deficits [54]

In 2011, Di Rocco et al. [56] carried out a study on 34 children with PF tumours with the aim of determining whether there was a correlation between pre-operative language impairment (PLI) and post-operative development of CM. In their study, 11 out of 34 children had PLI; all 11 of these patients were among the subjects that ultimately developed CM (20.6%). Other pre-operative findings in this study included behavioural disorders (sleep, hyperkinetic and somatic complaints). As well as a number of neuropsychological deficits [56]. The children with pre-operative behavioural problems continued to experience these difficulties post-operatively. The primary status of CM as a neuro-surgical sequela is thought to be due to bilateral perturbation of the dentate nuclei and their efferent pathway. As we will discuss, the pathophysiological mechanisms of delayed onset and resolution of CM are hypothesised to be due to axonal damage, oedema, perfusional defects and metabolic disturbances [54].

In 1994, Crutchfield et al. [57] were the first to appreciate the role of the dentato-thalamo-cortical (DTC) pathway as an anatomical substrate in CM. They illustrated a phenomenon called bilateral crossed cerebello-cerebral diaschisis (BCCCD): a cerebellar lesion causes a lack of excitatory impulses from the cerebellum and hypoperfusion, decreased oxygen consumption, hypometabolism and functional inhibition subsequently occur in anatomically connected supratentorial structures [58].

Essentially, symmetrical dentate nuclei that are located in the paravermal regions of lobules VI and VII of the cerebellum give rise to a cerebello-cerebral connection (see **Figure 4**), a complex

http://dx.doi.org/10.5772/intechopen.75679

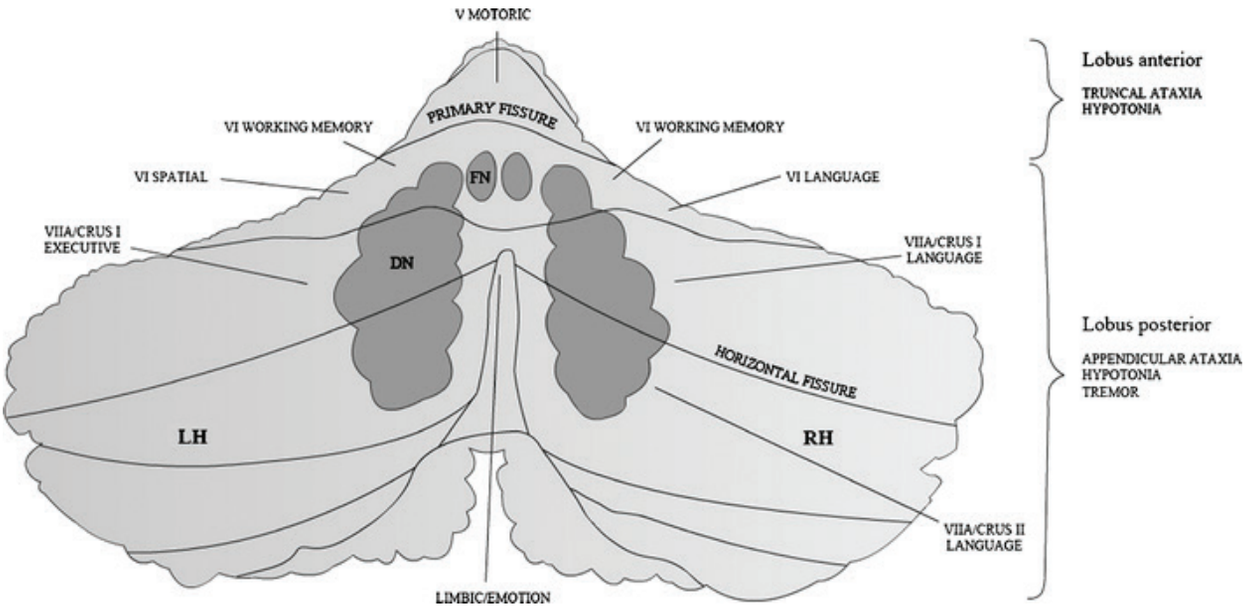

Figure 4. The topographic arrangement of functions in and around the vermis, dentate and fastigial nuclei. Language is lateralised to the right cerebellar hemisphere, executive functions and spatial processing to the left hemisphere and limbic/emotional functions to the vermis. Lesions of the anterior lobe result in truncal ataxia and hypotonia, while lesion of the posterior lobe result in appendicular ataxia, hypotonia and tremor. DN = dentate nucleus, FN = fastigial nucleus, LH = left hemisphere, RH = right hemisphere. Reprinted with permission from Gudrunardottir et al. [54].

system required for initiating voluntary movement and higher cognitive functions, including speech [54]. A literature review by Gudrunardottir et al. [54] highlights evidence that bilateral lesions of the dentate nuclei and their connections (i.e., a bilateral interruption of the DTC pathway) are the principal causes of CM [59–62].

Under normal circumstances, the cerebral cortex and cerebellum are in circuit via afferent and efferent signalling. Impulses originating within the cerebral cortex travel along axons via the cortico-ponto-cerebellar pathway to deliver input to the cerebellum, i.e., ultimately synapsing on the Purkinje cell layer of the cerebellum. Axons from these neurons form inhibitory synapses on the deep cerebellar nuclei, from which excitatory projections carry efferent signals travel throughout the CNS—to the spinal cord, brainstem and cerebral cortex—i.e., areas known for co-ordination of movement. The efferent pathway which finally communicates with the cerebral cortex is the DTC pathway. The tract is comprised of axons originating within the dentate nuclei (DN). The DN act as relay stations and send efferent signals back to the cerebral cortex via the DTC pathway; this tract travels through the ipsilateral superior cerebellar peduncle, and after decussation in the midbrain tegmentum, synapses within the contralateral ventrolateral nucleus of the thalamus. From the thalamus, second order axons terminate in the primary motor cortex as well as secondary and tertiary association areas within the frontal and parietal lobes. Thus, via the DTC pathway/tract, cognition and behaviour are likely modulated, a theory supported by the cognitive, linguistic and behavioural-affective impairments seen with an injury of the cerebellum and/or proximal DTC tract [63, 64].

Indeed, it is this vulnerable (i.e., peri-operatively) efferent white matter DTC tract that, if damaged, may be responsible for CM: therefore, any direct (i.e., trauma) or indirect (i.e., oedema)

circulatory disturbance may cause hypoperfusion and metabolic related hypofunction in both cerebellar hemispheres, and a loss of function (diaschisis) in the areas mediated by the DTP [65]. CM thus results from a lesion anywhere along this path: bilateral thalamotomies; SMA lesions; bilateral oedema in the brachium pontis; and finally, superior cerebellar peduncles are also potential lesions. Nevertheless, bilateral injury to the dentate nuclei is the most frequently implicated cause [54].

Clinically, anatomical correlates of cerebellar lesions are relatively distinct: anterior lesions cause ataxia and hypotonia; while those in the posterior induce appendicular ataxia, hypotonia and tremor [66] (see **Figure 4**). The origin of the hemiparesis and lower cranial nerve dysfunction seen in the PFS is not known, although brainstem injury and/or damage to the dentate nuclei/DTC pathway are hypothesised [54]. In addition to its role in balance and co-ordination, the cerebellum is integral to higher cognitive processses (the cerebellar hemispheres) and regulation of affect (the vermis) [66]. The left cerebellar hemisphere is designated spatial and executive responsibility, and the right is tasked with language [64, 67]. The disruption between the right cerebellum and left frontal cortex likely contributes to the linguistic difficulties observed in CM. Interestingly, a study also found that all left-handed patients with MB had a 100% risk of developing CM post-operatively. It is possible that such correlates will pave the way for pre-op clinical profiles to inform post-operative rehabilitation, across the allied health spectrum [68]. As discussed, the dentate nuclei, the vermis, and the right cerebellar hemisphere are all important in cognitive performance; accordingly, damage to these structures, informed by MRI, can be used to predict the degree of post-operative neurological and neuropsychological impairment in children following PF tumour resection [69].

Of note, mutism that occurs immediately after surgery is indicative of bulbar dysfuction from damage to cranial nerve nuclei in the nuclie, rather than CM [70]. However, in typical CM, 'secondary processes' initiated by the tumour resection, are the likely underlying pathophysiological mechanism, and four have been described in literature: (1) dynamic perfusional disturbances, (2) oedema, (3) transient disturbances in neurotransmitter release, and (4) axonal injury.

First, dynamic perfusional disturbances in the cerebellum and the cerebrum are suspected causes of CM due to the delayed onset (i.e., possible vasospasms), type of disturbance (i.e., transient ischemia) and resolution (i.e., normalisation of blood flow). Surgical manipulation of the cerebellum [71], intra-operative coagulation of perforating vessels [72] and arterial embolic occlusion [73] are the suspected catalysts of such disturbances; cerebello-cerebral diaschisis is implicated when the proximal DTC pathway is damaged [54]. In fact, two small single proton emission computed tomography (SPECT) studies demonstrated a cerebellar hypoperfusion in mute patients which resolved as speech returned [72, 73]. Two other possible mechanisms of recovery are neuronal plasticity and reassignment of speech function within the cortical processing network.

Secondly, the latency of CM reflects post-operative swelling, with imaging studies (CT, MRI and DTI) demonstrating mutism occurring with bilateral oedema in the superior cerebellar peduncles and/or the pons or mesencephalon after PF tumour resection. Indeed, corticosteroids may prove useful in the context of this mechanism. Thirdly, dysregulation of

neurotransmitter release has been postulated by Siffert et al. [74] in their concept that the cerebellum and its connections are tantamount to a 'modulatory system', controlling motor and non-motor functions. Finally, imaging studies imply that pathogenesis of CM could be from surgical manipulation, traction and release of tumour compression, resulting in axonal distortion and/or injury [63, 75].

CM risk is increased by several tumour-related factors: brainstem involvement [76]; (iatrogenic) brainstem compression; and midline (vermal and fourth ventricle) location [77]—i.e., MB is by far the most common cause of CM in the paediatric population. To illustrate this, two large studies found that the incidence of CM in children with medulloblastoma was 24% [78], and 44% if brainstem was involved [76]. Radical tumour removal [77] and young age at diagnosis [76] have inconsistent evidence [78], although some reports these as risk factors for CM [79]. Conversely, theories such as hydrocephalus, post-operative CNS infection (like meningitis), gender, length of vermal incision, type of neurosurgeon (paediatric vs. adult) and oedema/swelling have been refuted over recent years [80].

The prognosis and course of recovery in CM is variable, albeit largely unfavourable, even in spite of the resolution of mutism: two-thirds of patients will still suffer motor-speech deficits even after 12 months [81]; one-third will have persistent dysarthria; the remainder show a residual phonological impairment (including adynamic spontaneous speech production, impaired verbal fluency, word-finding difficulties and grammatical disturbances) [58]. Dysarthric features are more protracted and less amenable to recovery in children with associated combined procedural memory and defective neurocognitive functions present at diagnosis.

With regards preventing CM, surgical mitigation is a possibility: piecemeal removal (to protect the vermis) [82]; sparing of (cognitively significant) right cerebellar hemisphere [69], and finally, using a specific (telovelar) approach to access the fourth ventricle and avoid splitting the vermis [83]. In support of this approach, a series of telovelar cases showed no incidence of mutism; splitting the vermis reduced rates in one hospital and at another site similar surgical practices (e.g., less aggressive retraction) resulted in fewer cases of CM [84, 85].

2.4. Posterior fossa syndrome

Once regarded as an isolated deficit, CM is now well recognised as the predominant feature of the more expansive 'posterior fossa syndrome' (PFS; see below). Although CM and PFS appear to have separate anatomical substrates, topographical proximity ensures posterior fossa surgery can result in any combination of the shared phenomena.

In the relevant literature, across almost four decades, CM has been confused with other terms, including TCM, CMS [86] and MSD [87]. Furthermore, some authors use two or more of these terms interchangeably, including CM and PFS [48].

The essence of PFS is the constellation of four core symptoms: mutism, ataxia, behavioural disturbance and emotional lability; they occur in about 25% of children after the surgical resection of a posterior fossa tumour (**Figure 5**).

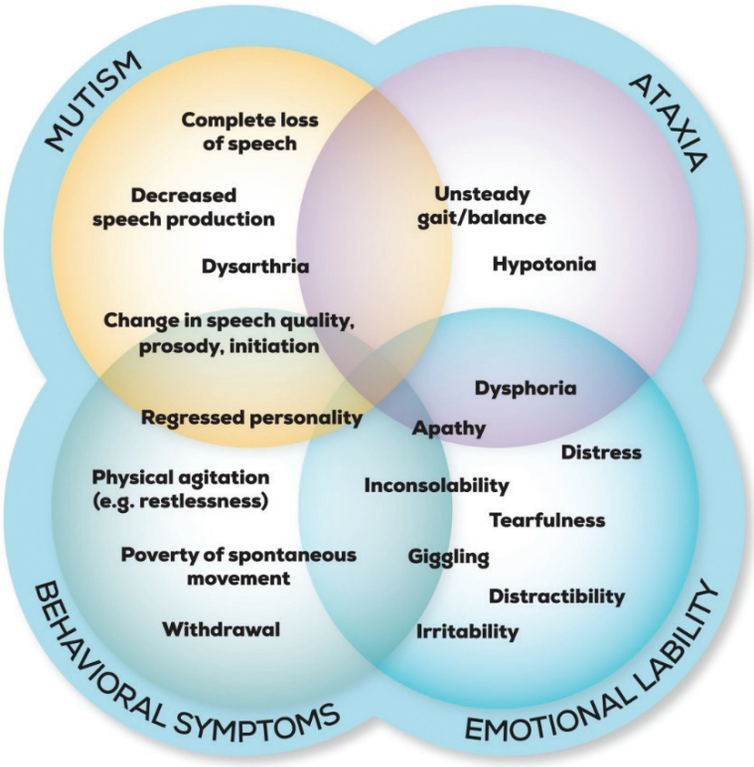

Figure 5. Posterior fossa syndrome. Reprinted with permission from Lanier et al. [84].

2.5. Posterior fossa syndrome cases

In a review of PFS, Lanier and Abrahams [88] summarised proposed theories/risk facors for PFS: 1. involvement of the vermis, 2. brainstem involvement, 3. bilateral edema within the cerebellar peduncles post surgery, 4.aggressive surgery of the cerebellum, 5. transient impairment of the DTC pathways, 6. midline location of the tumor, 7. focal vasospasms, 8. neurotransmitter dysfunction and 9. hydrocephalus. As expected, most overlap with those already discussed with regards to CM. These authors also presented a case series of PFS from their own institution, the Massachussetts General Hospital for Children. Three cases of resected medulloblastoma are described with regards boys aged 7–13 years. Post-operatively, two of the four cases suffered from mutism and another two cases had paucity of speech (e.g. monosyllabic) and dysarthria, respectively. All four cases had evidence of ataxia, emotional lability and behavioural symptoms. Of the mutism cases, both fully resolved with complete return of speech and good emotional stability; however, both had ongoing ataxia and one later died of a tumour recurrence. The third case (post-op paucity of speech) had screaming episodes with "screeching" and subsequently developed depression. At follow-up 5 years later, although in school he continued to have social and emotional difficulties. The final case (post-op dysarthria) initially had serious emotional dyscontrol with self-harming behaviour; this resolved with low dose risperidone. At her 5 year follow-up, she had no speech or behavioural issues, although balance remained problematic. Of note, three of these cases required psychotropic medication (low dose risperidone or lorazepam) to manage the emotional lability and behavioural issues.

In 1995, Pollack et al. [89] described a case series of children with open resection of infratentorial tumours. Following review of case records, 12 of these patients manifested with post-operative mutism. There was considerable variation between the clinical presentation, (i.e., pseudobulbar, neurobehavioural symptoms); however, a "stereotypical response" was observed in 11 cases; these patients were "curled up in bed and whining inconsolably, without actually uttering intelligible speech". All the children achieved full recovery within 4 months of surgery, bar one exception with persistent mild dysarthria. This finding is supported by a case series of children with cerebellar astrocytoma and vermal lesions who were surgically treated for their respective PF tumours [90]. Positive findings were seen in a number of the children with vermal lesions: post-operative mutism in six; behavioural disturbances in five, e.g., irritability, avoidance of others; and severe autistic behaviours in one. Similar to the study by Pollack et al. [89], almost all subjects achieved full or almost full recovery within a month.

2.6. Cerebellar cognitive affective syndrome

Another syndrome, cerebellar cognitive affective syndrome (CCAS), has been reported following acquired cerebellar lesions, such as infarction and inflammation [91, 92]. Some authors consider PFS to represent the acute manifestation of CCAS [92]. CCAS is primarily characterised by a deficit in emotional regulation that causes personality change; thus, a flattening or blunting of affect, and disinhibited/inappropriate behaviour are commonly seen. The syndrome also manifests as impairment of executive function (planning, set-shifting, verbal fluency, abstract reasoning and working memory difficulties) and visuospatial cognition. Finally, language deficits, including agrammatism and dysprosody are recognised features. This syndrome, described originally by Schmahmann et al. [93], is neurobiologically underpinned by the cerebellar organisation of higher order function, and more specifically, the associated modulatory role in mental and social function, operative early in childhood [26]. Hopyan et al. [91] compared cognitive control of emotions in cerebellar tumours against healthy matched controls. In their study, they tested the ability to identify happy and sad emotions in music. Contrary to their hypothesis, this study demonstrated largely normal emotional identification in both groups, but the control group performed better at emotional regulation tasks. The fact that in the study, childhood acquired cerebellar tumours disrupted cognitive control of emotion, rather than identification of emotion, provides support for a hypothesis of CCAS as a disorder not so much of emotion, but more so the regulation of emotion by cognition. A case series of 19 patients with cerebellar lesions also succeeded in illustrating cases of emotional dyscontrol in cerebellar tumours: an acute syndrome of inattention, dysphoria and emotional distress followed surgery of midline PF [92].

A case series by Hargrave et al. [94] described a slightly different manifestation of emotional dyscontrol in paediatric patients (aged 3–11) with pontine glioma. In 36% of the cases, outbursts of inappropriate laughter (i.e., "pathological laughter") were observed in wakefulness and sleep. Of note, symptoms improved in all cases following treatment but often returned in cases of tumour recurrence. Beckwitt-Turkel et al. [95] compared PFS symptoms before and after paediatric PF surgery in a naturalistic study. PFS was associated

with midline and vermis involvement (and not lateral involvement) and was characterised by mutism, apathy and dysphoria. These symptoms presented early post-operatively, although affective and behavioural disturbances appeared at a later stage, with all symptoms, bar depression, resolving over time. In 2010, Larysz et al. [96] looked at a group of 34 children (mean age 12.3 years) with PF tumours (14 cerebellar, 20 extracerebellar) to establish whether neuropsychological deficits related to tumour location: neoplasms in the brainstem and vermis had a better outcome than those in the cerebellum. This finding was consistent with Riva et al. [97] whose sample showed an association between non-vermal tumours with language dysfunction; in the same sample, vermal tumours were more likely to present with neurobehavioural changes (emotional lability, irritability, weepiness, impulsiveness and shyness).

2.7. Psychological and adjustment disorder

In 2013, an article published by Pastore et al. [98] compared the neuropsychological profiles and behavioural symptoms in pre-school children with brain lesions: 18 of the 55 patients were brain tumour survivors and the remainder had traumatic, vascular or infectious lesions. The brain tumour group had high levels of internalising problems (77.8%); specifically, a combination of anxiety and/or depression and/or somatic symptoms and withdrawal were present in about half of the sample. However, the group with traumatic brain injury and non-cancerous brain lesions presented with externalising behaviours and aggression. These findings are consistent with those from a study of paediatric brain tumour survivors, in which the child behaviour checklist indicated that internalising behaviours (depression/anxiety) were the most common (48.4%) psychological disorder, while externalising behaviours were present in just 11.8%. Furthermore, those aged 7–13 were most predisposed to psychological problems, whereas social maladjustment was more frequent in those older than 13. These findings were relevant as they indicated the long-term psychosocial outcome of these individuals [99].

Campen et al. [100] found a high rate of depression and adjustment disorders (30.4%) in 56 children treated for MB, particularly if they were older and male. Importantly, the multimodal therapy in MB—which is generally a protracted process—influences the neurodevelopmental maturation that is implicated in the pathogenesis of depression. Therefore, their low mood is not just explainable as an expected psychological burden; rather, it is also engendered by neurobiological mechanisms such as a disruption of hippocampal cell formation and the saturation of the limbic system. Therefore, Campen et al. found a significant difference in age at diagnosis between those who developed depression, anxiety and adjustment disorder (median 9.5 years) and those who did not (median 5.9 years), with a median time to first psychiatric symptom of 7 months. Similarly, a study of children treated for craniopharyngioma highlighted a high rate of psychiatric morbidity in the study population; 100% of subjects experienced depression; 75% suffered poor frustration tolerance and 40% had anger dyscontrol [22]. Likewise, a case series of 20 subjects described poor neurobehavioural outcomes in post-operative paediatric craniopharyngioma: 85% of subjects had some degree of internalising (apathy, poor motivation) and externalising (irritability, hyperactivity, aggression)

behaviour, as well as neuropsychological deficits, social maladjustment and poor school performance [23]. Finally, a study of paediatric and adult survivors of childhood brain tumours in 2013 revealed that more than 1 in 10 had reported suicidal ideation on at least one occasion, as documented in their medical records. The older patients, with greater co-morbidities (i.e., seizure disorder) were at highest risk [24].

2.8. Clinical guidelines

Around 9000 new primary brain and CNS tumours (CNST) are diagnosed every year in the UK, suggesting that a GP will diagnose a case every 3–5 years. Presenting complaints range from well recognised symptoms (i.e., headaches, new-onset seizures) to the more insidious, such as personality change. A combined retrospective and prospective study of 104 consecutive paediatric patients with brain tumours found that the median time from symptom onset to diagnosis was 3 months. However, diagnosis of CNST (whether primary or secondary) can be performed with the GP retaining clinical responsibility, i.e., ordering necessary diagnostic neuro-imaging tests [101].

'NICE alert symptoms' (e.g., neurological, headache, fatigue, back pain, bruising, lymphadenopathy, lump/mass/swelling, urinary symptoms, hepatosplenomegaly) and any new pattern of recurrent attendances to the GP are ominous warning signs for childhood CNST [102]. Ansell et al. [103] advised that 'the key to identifying the one child among many who merits prompt investigation is recognition of unusual symptoms, or specific symptom patterns'; these included head tilt, odd head movements, odd posture, back or neck stiffness and unsteadiness without obvious cause [103]. In concert with clinical acumen and intuition, the GP must respect the value of a parent's instinct that their child 'is not right', regardless of a specific problem *per se* [104].

The 2015 NICE guidelines, entitled 'Suspected Cancer: Recognition and Referral', features a section on 'Brain and CNS cancer' that informs clinicians about which specific symptoms in children and adolescents require investigation and/or neuro-oncological referral. Based on these symptoms, the positive predictive values (PPV) of having CNST varied in range: from <0.013% (for vomiting or headache, with loss of appetite) to 0.15 (for vomiting, in combination with unsteadiness) for patients aged 0–14 years old; and, from 0% (for primary headache) to 0.03% (for undifferentiated headache) for patients aged 5–17 years; and from 0.0029% (for pain) to 0.0238% (for seizure) for patients aged 15–24 years [101].

Adult referral was recommended for those symptoms with a PPV of 3% or above, i.e., the advantages of a suspected CNST pathway referral outweighed any disadvantages. However, in childhood cancer, such a threshold was deemed too stringent for the following reasons: (1) the high levels of treatability of these cancers, (2) early diagnosis can reduce mortality and morbidity, and (3) the number of life-years gained.

Referral at lower levels of risk than 3% is therefore permitted in children and adolescents. Accordingly, GPs/physicians/psychiatrists 'should consider a very urgent referral (for an appointment within 48 h) for a suspected brain or central nervous system cancer in children

and young people with newly abnormal cerebellar or other central neurological function'. Furthermore, referral should be for urgent specialist assessment (and not a cancer pathway) in order to circumnavigate any issues with weekend cover, differences in local service configuration, etc.

The guidelines point out that trade-off between net health benefits and resource utilisation are not supported by published economic analysis. It is likely that the above recommendations will result in an increase in MRI scanning with a subsequent reduction in GP attendance, because of fast-tracking medical clearance or diagnosis. In fact, the guidelines predict that such action will actually constitute a small decrease in overall costs [101].

An evidence-based clinical guideline, 'Diagnosis of Brain Tumours in Children', was developed in 2010 by Wilne et al. [105]; it was informed by a systematic literature review, meta-analysis and cohort study [36]. As a result, six main categories of symptoms were identified: headache, nausea and vomiting, visual abnormalities, motor abnormalities, growth, development and behavioural abnormalities. Within the category of behavioural symptoms, lethargy and withdrawal were important neuropsychiatric signs of childhood CNS tumours. The importance of lethargy in diagnosing paediatric CNST has been highlighted by other studies [106, 107]. In fact, the prominence of lethargy in a series of 'sudden death from obstructive hydrocephalus due to intracranial lesions' prompted the authors to conclude that persistent lethargy should be considered a neurological symptom instead of a non-specific clinical sign [108].

The relevance of such symptoms in childhood CNST was also highlighted by an earlier study by Wilne et al. [36], in which 'behavioural and educational' symptoms were the presenting feature of brain tumours in children in 10% of cases, and were apparent in 44% of the patients. The behavioural symptoms included: lethargy (majority), irritability, personality change, aggression and emotional lability; and the educational symptoms included deterioration in reading and writing (majority), memory difficulty, poor concentration, global deterioration and decrease in school attendance.

Nevertheless, lethargy remains an unspecific symptom with many faces: it is prominent among physical syndromes relating to malignancy, infection, and inflammation; it is also a core psychiatric symptom in both affective (i.e., depression) and psychotic disorders (i.e., negative syndrome of schizophrenia). Despite such diagnostic opaqueness, the guidelines produced by Wilne et al. [105]—which recommend CNS imaging if lethargy or withdrawal persists for 4 weeks or more—have demonstrated promising results in initial UK studies. These successes include a reduction in median symptom interval, time between symptom onset, and ultimately, the diagnosis of brain tumours in children [105].

In addition to knowledge about when to suspect a brain tumour, it is important for those practicing in primary and secondary care to be familiar with the most comprehensive and current guidelines for childhood neuropsychiatric presentation of brain tumours, as outlined below [26].

http://dx.doi.org/10.5772/intechopen.75679

3. Summary

3.1. Red flags

Recommendations for detecting malignancy in a childhood neuropsychiatric case:

- Childhood cancer is rare and may present initially with symptoms and signs associated with common conditions, e.g., headache, nausea and vomiting. Repeated presentation with the same problem and with no clear diagnosis should raise the suspicion and facilitate further assessment and referral.
- Psychiatric symptoms are best to be considered dynamically and in combination with other signs and symptoms that are listed here. It is very rare for a childhood cranial malignancy to present with only psychiatric symptoms.
- Common psychiatric symptoms:
  - internalising behaviour,
  - withdrawal,
  - social problems,
  - somatic complaints,
  - externalising problems,
  - depression and/or anxiety
  - hyperactivity.
- Rare psychiatric symptoms:
  - eating disorder and
  - first episode of psychosis.
- Also watch for:
  - atypical psychiatric symptoms,
  - unexplained behavioural and/or mood changes,
  - unexplained deteriorating school performance or developmental milestones,
  - personality change,
  - disinhibited or inappropriate behaviour,
  - pathological laughter,
  - emotional lability,

- especially emotional reactions disproportionate to significance or severity of trigger,
- flattening or blunting of affect,
- impairment of working memory,
- agrammatism and dysprosody of speech,
- impaired executive function and
- poor attention.

- Psychiatric symptoms (including behavioural) with a headache (i.e., advised to directly enquire about presence of a headache) constitute a red flag. Persistent headache that can occur at any time of the day or night requires a neurological examination. Younger children and those with communication difficulties may not be able to report headache, thus watch for behavioural representation, e.g., pointing at, holding or squeezing head.
- Headache and vomiting that cause early morning waking or occur on awakening are classical signs of raised intracranial pressure and an immediate referral should be made. In cases of persistent vomiting, exclude pregnancy where appropriate. Psychiatric symptoms (including behavioural) with neurological signs warrants a neurological examination. However, a normal neurological examination does not exclude a brain tumour.
- Neurological and motor symptoms:
  - new-onset seizures—including focal (with/without loss of awareness) and generalised onset
  - altered consciousness,
  - cranial nerve abnormalities,
  - regression in motor skills,
  - gait abnormalities and/or abnormal motor co-ordination,
  - focal motor weakness and
  - swallowing difficulties.
- Visual symptoms and signs including:
  - papilledema,
  - reduced visual acuity,
  - reduced visual fields,
  - new-onset nystagmus,
  - new-onset paralytic squint,
  - optic atrophy,

http://dx.doi.org/10.5772/intechopen.75679

- abnormal fundoscopy
- proptosis.

- Visual assessment including fundoscopy:
  - acuity,
  - eye movements,
  - pupil responses,
  - visual fields in school age children and older and
  - optic disc appearance.
- Growth and developmental abnormalities:
  - growth failure and
  - delayed, arrested or precocious puberty.
- Diabetes insipidus presenting with polyuria and polydipsia.
- Persistent back pain can be a symptom of cancer.

In children aged younger than 2 years, any of the following symptoms may suggest a CNS tumour and require following:

- Immediate referral:
  - new-onset seizures,
  - bulging fontanelle,
  - extensor attacks and
  - persistent vomiting.
- Urgent referral:
  - abnormal increase in head size,
  - arrest or regression of motor development,
  - altered behaviour,
  - abnormal eye movements,
  - lack of visual following and
  - poor feeding/failure to thrive.
  - Urgency contingent on other factors: squint.

Following the diagnosis

- Screening for internalising problems in children and adolescents with brain tumours.
- Baseline and follow-up screening/assessment for ADHD symptoms prior to treatment
    - Externalising problems are less common than internalising problems but, if missed, will have significant implications for educational abilities.
- In those for whom the symptoms represent an adjustment reaction, there is an improved outcome if a truthful, complete and consistent approach to communication is taken.

When considering posterior fossa tumour resection

- The complication of cerebellar mutism is rarely mentioned to parents during the consent for surgery of a posterior fossa tumour. It is a common syndrome and, reassuringly, to the authors' knowledge there have been no reported cases of a child with cerebellar mutism not returning to some functional speech.

4. Conclusion

The era of molecular informed neuro-oncology has set a foundation for precise diagnosis and tailored anti-neoplastic therapy. Such changes may lead to great improvements in overall survival of paediatric patients and so inadvertently marks an auspicious time for neuropsychiatry, which has never been more relevant. In concert with an optimal medical model, neuropsychiatric informed care is required to ensure a truly holistic and integrated approach. In their ability to weave together so many disparate perspectives—psychiatric, neurological, cognitive, psychosocial and many more—these specialists will be invaluable in leading multidisciplinary rehabilitation programs. Contemporary studies indicate that mood, cognition and psychosocial functioning are important factors in early diagnosis, as well as mediating health outcomes following radical and risk-adapted anti-neoplastic treatment. In addition to psychological burden, the neuropsychiatric aspects of childhood CNS tumours, including posterior fossa syndrome and cerebellar cognitive affective syndrome, are increasingly recognised as crucial causes of poor outcomes. Current research highlights the necessity for routine psychological and psychiatric screenings of children with suspected brain tumours and at follow-up of childhood brain tumour survivors. Thus, we provided a review of the available neuropsychiatric guidelines for identification of brain tumours in primary, secondary and tertiary health services. However, further progress is still required in these areas and in the sphere of public awareness. In the future, neuropsychiatric intervention should aim to complement the anticipated challenges of neuro-oncological management, e.g., a left-handed child treated for medulloblastoma would have intensive neuropsychiatric screening and linguistic rehabilitation.

As our understanding of the neuroscience relevant to childhood neuro-oncology expands, neuropsychiatric input will be invaluable at crucial stages of care, including at time of diagnosis, pre- and post-operatively. Earlier intervention will consolidate a child's resilience through a multi-axial combination of psychometrics, psychoeducation, psychosocial support, psychotherapy and psychopharmacological intervention. Specifically, neuropsychological

profiling will enrich the clinical pre-operative prognostication and determine treatment goals post-operatively.

Author details

Alexander Hegarty[1,2] and Yulia Furlong[1,2]*

*Address all correspondence to: alexander.hegarty@health.wa.gov.au

1 Perth Children's Hospital, Perth, WA, Australia

2 University of Western Australia, Crawley, WA, Australia

References

[1] Ostrom QT, Gittleman H, Fulop J, Liu M, Blanda R, Kromer C, et al. CBTRUS statistical report: Primary brain and central nervous system tumors diagnosed in the United States in 2008-2012. Neuro-Oncology. Oxford University Press. 2015;**17**(Suppl 4):iv1-iv62. DOI: 10.1093/neuonc/nov189

[2] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA: a Cancer Journal for Clinicians. 2017;**67**(1):7-30. DOI: 10.3322/caac.21387

[3] Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization classification of Tumors of the central nervous system: A summary. Acta Neuropathologica. Springer Berlin Heidelberg. 2016;**131**(6):803-820. DOI: 10.1007/s00401-016-1545-1

[4] Ramkissoon SH, Bandopadhayay P, Hwang J, Ramkissoon LA, Greenwald NF, Schumacher SE, et al. Clinical targeted exome-based sequencing in combination with genome-wide copy number profiling: Precision medicine analysis of 203 pediatric brain tumors. Neuro-Oncology. Oxford University Press. 2017;**19**(7):now294. DOI: 10.1093/neuonc/now294

[5] Komori T. The 2016 WHO classification of tumours of the central nervous system: The major points of revision. Neurologia Medico-Chirurgica (Tokyo). 2017;**57**(7):301-311. DOI: 10.2176/nmc.ra.2017-0010

[6] Reifenberger J, Reifenberger G, Liu L, James CD, Wechsler W, Collins VP. Molecular genetic analysis of oligodendroglial tumors shows preferential allelic deletions on 19q and 1p. The American Journal of Pathology. American Society for Investigative Pathology. 1994; **145**(5):1175-1190

[7] Hartmann C, Meyer J, Balss J, Capper D, Mueller W, Christians A, et al. Type and frequency of IDH1 and IDH2 mutations are related to astrocytic and oligodendroglial differentiation and age: A study of 1,010 diffuse gliomas. Acta Neuropathologica. 2009; **118**(4):469-474. DOI: 10.1007/s00401-009-0561-9

[8] Ichimura K. Molecular pathogenesis of IDH mutations in gliomas. Brain Tumor Pathology. 2012;**29**(3):131-139. DOI: 10.1007/s10014-012-0090-4

[9] Ellison DW, Kocak M, Dalton J, Megahed H, Lusher ME, Ryan SL, et al. Definition of disease-risk stratification groups in childhood medulloblastoma using combined clinical, pathologic, and molecular variables. Journal of Clinical Oncology. 2011;**29**(11):1400-1407. DOI: 10.1200/JCO.2010.30.2810

[10] Taylor MD, Northcott PA, Korshunov A, Remke M, Cho Y-J, Clifford SC, et al. Molecular subgroups of medulloblastoma: The current consensus. Acta Neuropathologica. 2012;**123**(4): 465-472. DOI: 10.1007/s00401-011-0922-z

[11] Wen PY, Kesari S. Malignant gliomas in adults. The New England Journal of Medicine. 2008;**359**(5):492-507. DOI: 10.1056/NEJMra0708126

[12] Bailey P. Medulloblastoma cerebelli. Archives of Neurology and Psychiatry. 1925;**14**(2): 192. DOI: 10.1001/archneurpsyc.1925.02200140055002

[13] Jones DTW, Jäger N, Kool M, Zichner T, Hutter B, Sultan M, et al. Dissecting the genomic complexity underlying medulloblastoma. Nature. 2012;**488**(7409):100-105. DOI: 10.1038/nature11284

[14] Smoll NR, Drummond KJ. The incidence of medulloblastomas and primitive neurectodermal tumours in adults and children. Journal of Clinical Neuroscience. 2012;**19**(11):1541-1544. DOI: 10.1016/j.jocn.2012.04.009

[15] Parsons DW, Li M, Zhang X, Jones S, Leary RJ, Cheng J, et al. The genetic landscape of the childhood cancer medulloblastoma. Science. 2011;**331**(6016):435-439. DOI: 10.1126/science.1198056

[16] Schwalbe EC, Lindsey JC, Nakjang S, Crosier S, Smith AJ, Hicks D, et al. Novel molecular subgroups for clinical classification and outcome prediction in childhood medulloblastoma: A cohort study. The Lancet Oncology. 2017;**18**(17):958-971. DOI: 10.1016/S1470-2045(17)30243-7

[17] Zhao F, Ohgaki H, Xu L, Giangaspero F, Li C, Li P, et al. Molecular subgroups of adult medulloblastoma: A long-term single-institution study. Neuro-Oncology. 2016;**18**(7):982-990. DOI: 10.1093/neuonc/now050

[18] Gajjar A, Pfister SM, Taylor MD, Gilbertson RJ. Molecular insights into pediatric brain tumors have the potential to transform therapy. Clinical Cancer Research. 2014;**20**(22): 5630-5640. DOI: 10.1158/1078-0432

[19] Pizer BL, Clifford SC. The potential impact of tumour biology on improved clinical practice for medulloblastoma: Progress towards biologically driven clinical trials. British Journal of Neurosurgery. 2009;**23**(4):364-375. DOI: 10.1080/02688690903121807

[20] Robinson GW, Orr BA, Wu G, Gururangan S, Lin T, Qaddoumi I, et al. Vismodegib exerts targeted efficacy against recurrent sonic hedgehog–subgroup medulloblastoma: Results from phase II Pediatric brain tumor consortium studies PBTC-025B and PBTC-032. Journal of Clinical Oncology. 2015;**33**(24):2646-2654. DOI: 10.1200/JCO.2014.60.1591

[21] Zhukova N, Ramaswamy V, Remke M, Pfaff E, Shih DJH, Martin DC, et al. Subgroup-specific prognostic implications of *TP53* mutation in medulloblastoma. Journal of Clinical Oncology. 2013;**31**(23):2927-2935. DOI: 10.1200/JCO.2012.48.5052

[22] Kool M, Jones DTW, Jäger N, Northcott PA, Pugh TJ, Hovestadt V, et al. Genome sequencing of SHH medulloblastoma predicts genotype-related response to smoothened inhibition. Cancer Cell. 2014;**25**(3):393-405. DOI: 10.1016/j.ccr.2014.02.004

[23] Pickles JC, Hawkins C, Pietsch T, Jacques TS. CNS embryonal tumours: WHO 2016 and beyond. Neuropathology and Applied Neurobiology. 2017. DOI: 10.1111/nan.12443

[24] Bican O, Pruitt AA. The spinal cord: A review of functional neuroanatomy. Neurologic Clinics. Elsevier. 2013;**31**(1):1-18. DOI: 10.1016/j.ncl.2012.09.009

[25] Raybaud CBA. Intracranial, orbital and neck masses of childhood. In: Barkovich AJRC, editor. Pediatric Neuroimaging. Philadelphia: Lippincott Williams & Wilkins; 2012. pp. 637-807

[26] Zyrianova Y, Alexander L, Faruqui R. Neuropsychiatric presentations and outcomes in children and adolescents with primary brain tumours: Systematic review. Brain Injury. 2016;**30**(1):1-9. DOI: 10.3109/02699052.2015.1075590

[27] Pollack IF, Jakacki RI. Childhood brain tumors: Epidemiology, current management and future directions. Nature Reviews. Neurology. Nature Publishing Group. 2011;**7**(9):495-506. DOI: 10.1038/nrneurol.2011.110

[28] Koci TM, Chiang F, Mehringer CM, Yuh WT, Mayr NA, Itabashi H, et al. Adult cerebellar medulloblastoma: Imaging features with emphasis on MR findings. American Journal of Neuroradiology (AJNR). 1993;**14**(4):929-939

[29] Meyers SP, Kemp SS, Tarr RW. MR imaging features of medulloblastomas. American Journal of Roentgenology. American Public Health Association. 1992;**158**(4):859-865. DOI: 10.2214/ajr.158.4.1546606

[30] Poussaint TY, Panigrahy A, Huisman TAGM. Pediatric brain tumors. Pediatric Radiology. Springer Berlin Heidelberg. 2015;**45**(S3):443-453. DOI: 10.1007/s00247-015-3326-8

[31] Larner AJ. Referral guidelines for suspected central nervous system or brain tumours. Journal of Neurology, Neurosurgery, and Psychiatry. BMJ Publishing Group. 2006;**77**(12): 1305-1306. DOI: 10.1136/jnnp.2005.077453

[32] Fuemmeler BF, Elkin TD, Mullins LL. Survivors of childhood brain tumors: Behavioral, emotional, and social adjustment. Clinical Psychology Review. 2002;**22**(4):547-585. DOI: 10.1016/S0272-7358(01)00120-9

[33] Levisohn L, Cronin-Golomb A, Schmahmann JD. Neuropsychological consequences of cerebellar tumour resection in children: Cerebellar cognitive affective syndrome in a paediatric population. Brain. 2000;**123**(Pt 5):1041-1050

[34] Lumsden DE, Woodthorpe C, Hargrave D, Hedderly TJ. Pre-existing neurodevelopmental and neuropsychiatric difficulties in children with brain tumours: Implications for future outcome studies. Developmental Medicine and Child Neurology. Blackwell Publishing Ltd. 2011;**53**(1):93-93. DOI: 10.1111/j.1469-8749.2010.03822.x

[35] Martínez-Lage JF, Pérez-Espejo MA, Esteban JA, Poza M. Thalamic tumors: Clinical presentation. Child's Nervous System. 2002;**18**:405-411. DOI: 10.1007/s00381-002-0605-0

[36] Wilne SH, Ferris RC, Nathwani A, Kennedy CR. The presenting features of brain tumours: A review of 200 cases. Archives of Disease in Childhood. 2006;**91**(6):502-506. DOI: 10.1136/adc.2005.090266

[37] Undurraga J, Baeza I, Valentí M, Lázaro ML. Brain germinoma presenting as a first psychotic episode in an adolescent male. European Child & Adolescent Psychiatry. 2010; **19**(9):741-742. DOI: 10.1007/s00787-010-0107-7

[38] Zugman A, Pan PM, Gadelha A, Mansur RB, Asevedo E, Cunha GR, et al. Brain tumor in a patient with attenuated psychosis syndrome. Schizophrenia Research. 2013;**144**(1-3):151-152. DOI: 10.1016/j.schres.2012.11.036

[39] Peterson BS, Bronen RA, Duncan CC. Three cases of symptom change in Tourette's syndrome and obsessive-compulsive disorder associated with paediatric cerebral malignancies. Journal of Neurology, Neurosurgery, and Psychiatry. BMJ Publishing Group. 1996;**61**(5):497-505. DOI: 10.1136/jnnp.61.5.497

[40] Sokol MS, Fujimoto CK, Jackson TK, Silberberg PJ. Anorexia nervosa and brain tumor in a 14-year-old girl. CNS Spectrums. Cambridge University Press. 2006;**11**(9):669-673. DOI: 10.1017/S1092852900014759

[41] Uher R, Treasure J. Brain lesions and eating disorders. Journal of Neurology, Neurosurgery, and Psychiatry. BMJ Publishing Group. 2005;**76**(6):852-857. DOI: 10.1136/jnnp.2004.048819

[42] Zakrzewski K, Fiks T, Polis L, Liberski PP. Posterior fossa tumours in children and adolescents. A clinicopathological study of 216 cases. Folia Neuropathologica. 2003;**41**(4): 251-252

[43] Varela M, Liakopoulou M, Alexiou GA, Pitsouni D, Alevizopoulos GA. Presurgical neuropsychological and behavioral evaluation of children with posterior fossa tumors. Journal of Neurosurgery. Pediatrics. American Association of Neurological Surgeons. 2011;**8**(6):548-553. DOI: 10.3171/2011.8.PEDS11223

[44] Riva D, Giorgi C. The cerebellum contributes to higher functions during development: Evidence from a series of children surgically treated for posterior fossa tumours. Brain. 2000;**123**(Pt 5):1051-1061. DOI: 10.1093/brain/123.5.1051

[45] Konarski JZ, McIntyre RS, Grupp LA, Kennedy SH. Is the cerebellum relevant in the circuitry of neuropsychiatric disorders? Journal of Psychiatry & Neuroscience. 2005; **30**(3):178-186

[46] Daes T, Mariën P. Cognitive and affective disturbances following focal brainstem lesions: A review and report of three cases. Cerebellum. 2015. DOI: 10.1007/s12311-014-0626-8

[47] Korah MP, Esiashvili N, Mazewski CM, Hudgins RJ, Tighiouart M, Janss AJ, et al. Incidence, risks, and Sequelae of posterior fossa syndrome in pediatric medulloblastoma. International Journal of Radiation Oncology. 2010;**77**(1):106-112. DOI: 10.1016/j.ijrobp.2009.04.058

[48] Posterior Fossa Society [Internet]. [cited 2018 May 6]. Available from: http://www.posteriorfossa.org/posterior-fossa-syndrome-cerebellar-mutism-definitions/

[49] Gudrunardottir T, Morgan AT, Lux AL, Walker DA, Walsh KS, Wells EM, et al. Consensus paper on post-operative pediatric cerebellar mutism syndrome: The Iceland Delphi results. Child's Nerv Syst. 2016. Jul 3;**32**(7):1195-203. DOI: 10.1007/s00381-016-3093-3. [Epub 2016 May 3]

[50] Papavasiliou AS, Kotsalis C, Trakadas S. Transient cerebellar mutism in the course of acute cerebellitis. Pediatric Neurology. 2004;**30**(1):71-74. DOI: 10.1016/S0887-8994(03)00420-X

[51] Drost G, Verrips A, Thijssen MHO, Gabreëls MFJ. Cerebellar involvement as a rare complication of pneumococcal meningitis. Neuropediatrics. 2000;**31**(2):97-99. DOI: 10.1055/s-2000-7474

[52] Law N, Greenberg M, Bouffet E, Taylor MD, Laughlin S, Strother D, et al. Clinical and neuroanatomical predictors of cerebellar mutism syndrome. Neuro-Oncology. 2012;**14**(10):1294-1303. DOI: 10.1093/neuonc/nos160

[53] Daly DD, Love JG. Akinetic mutism. Neurology. 1958;**8**:238-242. DOI: 10.1212/WNL.8.3.238

[54] Gudrunardottir T, Sehested A, Juhler M, Schmiegelow K. Cerebellar mutism. Child's Nervous System. 2011;**27**(3):355-363. DOI: 10.1007/s00381-010-1328-2

[55] Rekate HL, Grubb RL, Aram DM, Hahn JF, Ratcheson RA. Muteness of cerebellar origin. Archives of Neurology. 1985;**42**(7):697-698. DOI: 10.1001/archneur.1985.04060070091023

[56] Di Rocco C, Chieffo D, Frassanito P, Caldarelli M, Massimi L, Tamburrini G. Heralding cerebellar Mutism: Evidence for pre-surgical language impairment as primary risk factor in posterior fossa surgery. The Cerebellum. 2011;**10**(3):551-562. DOI: 10.1007/s12311-011-0273-2

[57] Crutchfield JS, Sawaya R, Meyers CA, Moore BD. Postoperative mutism in neurosurgery. Report of two cases. Journal of Neurosurgery. 1994;**81**(1):115-121. DOI: 10.3171/jns.1994.81.1.0115

[58] De Smet HJ, Baillieux H, Wackenier P, De Praeter M, Engelborghs S, Paquier PF, et al. Long-term cognitive deficits following posterior fossa tumor resection: A neuropsychological and functional neuroimaging follow-up study. Neuropsychology. 2009;**23**(6):694-704. DOI: 10.1037/a0016106

[59] Erşahin Y, Mutluer S, Çağli S, Duman Y. Cerebellar Mutism: Report of seven cases and review of the literature. Neurosurgery. 1996;**38**(1):60-66. DOI: 10.1097/00006123-199601000-00015

[60] van Dongen HR, Catsman-Berrevoets CE, van Mourik M. The syndrome of "cerebellar" mutism and subsequent dysarthria. Neurology. 1994;**44**(11):2040-2046. DOI: 10.1212/WNL.44.11.2040

[61] Kotil K, Eras M, Akçetin M, Bilge T. Cerebellar mutism following posterior fossa tumor resection in children. Turkish Neurosurgery. 2008;**18**(1):89-94

[62] Wells EM, Walsh KS, Khademian ZP, Keating RF, Packer RJ. The cerebellar mutism syndrome and its relation to cerebellar cognitive function and the cerebellar cognitive affective disorder. Developmental Disabilities Research Reviews. 2008;**14**(3):221-228. DOI: 10.1002/ddrr.25

[63] Morris EB, Phillips NS, Laningham FH, Patay Z, Gajjar A, Wallace D, et al. Proximal dentatothalamocortical tract involvement in posterior fossa syndrome. Brain. 2009;**132**(Pt 11):3087-3095. DOI: 10.1093/brain/awp241

[64] Baillieux H, De SHJ, Paquier PF, De Deyn PP, Mariën P. Cerebellar neurocognition: Insights into the bottom of the brain. Clinical Neurology and Neurosurgery. 2008;**110**(8):763-773. DOI: 10.1016/j.clineuro.2008.05.013

[65] Sagiuchi T, Ishii K, Aoki Y, Kan S, Utsuki S, Tanaka R, et al. Bilateral crossed cerebellocerebral diaschisis and mutism after surgery for cerebellar medulloblastoma. Annals of Nuclear Medicine. 2001;**15**(2):157-160. DOI: 10.1007/BF02988609

[66] Stoodley CJ, Schmahmann JD. Evidence for topographic organization in the cerebellum of motor control versus cognitive and affective processing. Cortex. 2010;**46**(7):831-844. DOI: 10.1016/j.cortex.2009.11.008

[67] Stoodley CJ, Schmahmann JDJ. Functional topography in the human cerebellum: A meta-analysis of neuroimaging studies. NeuroImage. 2009;**44**(2):489-501. DOI: 10.1016/j.neuroimage.2008.08.039

[68] Law N, Greenberg M, Bouffet E, Taylor MD, Laughlin S, Strother D, et al. Clinical and neuroanatomical predictors of cerebellar mutism syndrome. Neuro-Oncology. 2012 Oct;**14**(10):1294-1303. DOI: 10.1093/neuonc/nos160

[69] Puget S, Boddaert N, Viguier D, Kieffer V, Bulteau C, Garnett M, et al. Injuries to inferior vermis and dentate nuclei predict poor neurological and neuropsychological outcome in children with malignant posterior fossa tumors. Cancer. 2009;**115**(6):1338-1347. DOI: 10.1002/cncr.24150

[70] Robertson PL, Muraszko KM, Holmes EJ, Sposto R, Packer RJ, Gajjar A, et al. Incidence and severity of postoperative cerebellar mutism syndrome in children with medulloblastoma: A prospective study by the Children's oncology group. Journal of Neurosurgery. Pediatrics. 2006;**105**(6):444-451. DOI: 10.3171/ped.2006.105.6.444

[71] Pollack IF. Posterior fossa syndrome. International Review of Neurobiology. 1997;**41**:411-432. DOI: 10.1016/S0074-7742(08)60362-1

[72] Asamoto M, Ito H, Suzuki N, Oiwa Y, Saito K, Haraoka J. Transient mutism after posterior fossa surgery. Child's Nervous System. 1994;**10**(4):275-278. DOI: 10.1007/BF00301168

[73] Nishikawa M, Komiyama M, Sakamoto H, Yasui T, Nakajima H. Cerebellar Mutism after basilar artery occlusion —Case report—. Neurologia Medico-Chirurgica. 1998;**38**(9):569-573. DOI: 10.2176/nmc.38.569

[74] Siffert J, Poussaint TY, Goumnerova LC, Scott RM, LaValley B, Tarbell NJ, et al. Neurological dysfunction associated with postoperative cerebellar mutism. Journal of Neuro-Oncology. 2000;**48**(1):75-81. DOI: 10.1023/A:1006483531811

[75] McMillan HJ, Keene DL, Matzinger MA, Vassilyadi M, Nzau M, Ventureyra ECG. Brainstem compression: A predictor of postoperative cerebellar mutism. Child's Nervous System. 2009;**25**(6):677-681. DOI: 10.1007/s00381-008-0777-3

[76] Doxey D, Bruce D, Sklar F, Swift D, Shapiro K. Posterior fossa syndrome: Identifiable risk factors and irreversible complications. Pediatric Neurosurgery. 1999;**31**(3):131-136. DOI: 10.1159/000028848

[77] Catsman-Berrevoets CE, Van Dongen HR, Mulder PG, Paz y Geuze D, Paquier PF, Lequin MH. Tumour type and size are high risk factors for the syndrome of cerebellar mutism and subsequent dysarthria. Journal of Neurology, Neurosurgery, and Psychiatry. 1999;**67**(6):755-757. DOI: 10.1136/jnnp.67.6.755

[78] Robertson PL, Muraszko KM, Holmes EJ, Sposto R, Packer RJ, Gajjar A, et al. Incidence and severity of postoperative cerebellar mutism syndrome in children with medulloblastoma: A prospective study by the Children's oncology group. Journal of Neurosurgery. Pediatrics. 2006;**105**(6):444-451. DOI: 10.3171/ped.2006.105.6.444

[79] Korah MP, Esiashvili N, Mazewski CM, Hudgins RJ, Tighiouart M, Janss AJ, et al. Incidence, risks, and Sequelae of posterior fossa syndrome in pediatric medulloblastoma. International Journal of Radiation Oncology. 2010;**77**(1):106-112. DOI: 10.1016/j.ijrobp.2009.04.058

[80] Gudrunardottir T, Sehested A, Juhler M, Schmiegelow K. Cerebellar mutism. Child's Nervous System. 2011;**27**(3):355-363. DOI: 10.1007/s00381-010-1328-2

[81] Gelabert-González M, Fernández-Villa J. Mutism after posterior fossa surgery. Review of the literature. Clinical Neurology and Neurosurgery. 2001;**103**(2):111-114. DOI: 10.1016/S0303-8467(01)00125-1

[82] Aguiar PH, Plese JP, Ciquini O, Marino R. Transient mutism following a posterior fossa approach to cerebellar tumors in children: A critical review of the literature. Child's Nervous System. 1995;**11**(5):306-310

[83] Mussi ACM, Rhoton AL. Telovelar approach to the fourth ventricle: Microsurgical anatomy. Journal of Neurosurgery. 2000;**92**(5):812-823. DOI: 10.3171/jns.2000.92.5.0812

[84] Grill J, Viguier D, Kieffer V, Bulteau C, Sainte-Rose C, Hartmann O, et al. Critical risk factors for intellectual impairment in children with posterior fossa tumors: The role of cerebellar damage. Journal of Neurosurgery. Pediatrics. 2004;**101**(2):152-158. DOI: 10.3171/ped.2004.101.2.0152

[85] El-Bahy K. Telovelar approach to the fourth ventricle: Operative findings and results in 16 cases. Acta Neurochirurgica. 2005;**147**(2):137-142. DOI: 10.1007/s00701-004-0407-0

[86] Van Calenbergh F, Van de Laar A, Plets C, Goffin J, Casaer P. Transient cerebellar mutism after posterior fossa surgery in children. Neurosurgery. 1995;**37**(5):894-898. DOI: 10.1227/00006123-199511000-00007

[87] Catsman-Berrevoets CE, Van Dongen HR, H Mulder PG, Paz Geuze D, Paquier PF, Lequin MH. Tumour type and size are high risk factors for the syndrome of "cerebellar" mutism and subsequent dysarthria. Journal of Neurology, Neurosurgery, and Psychiatry. 1999;**67**:755-757. DOI: 10.1136/jnnp.67.6.755

[88] Lanier JC, Abrams AN. Posterior fossa syndrome: Review of the behavioral and emotional aspects in pediatric cancer patients. Cancer. 2017;**123**(4):551-559. DOI: 10.1002/cncr.30238

[89] Pollack IF, Polinko P, Albright AL, Towbin R, Fitz C. Mutism and pseudobulbar symptoms after resection of posterior fossa tumors in children: Incidence and pathophysiology. Neurosurgery. 1995;**37**(5):885-893. DOI: 10.1227/00006123-199511000-00006

[90] Netson KL, Conklin HM, Ashford JM, Kahalley LS, Wu S, Xiong X. Parent and teacher ratings of attention during a year-long methylphenidate trial in children treated for cancer. Journal of Pediatric Psychology. 2011;**36**(4):438-450. DOI: 10.1093/jpepsy/jsq102

[91] Hopyan T, Laughlin S, Dennis M. Emotions and their cognitive control in children with cerebellar Tumors. Journal of the International Neuropsychological Society. 2010;**16**(6):1027-1038. DOI: 10.1017/S1355617710000974

[92] Turkel SB, Shu Chen L, Nelson MD, Hyder D, Gilles FH, Woodall L, et al. Case series: Acute mood symptoms associated with posterior fossa lesions in children. The Journal of Neuropsychiatry and Clinical Neurosciences. 2004;**16**(4):443-445. DOI: 10.1176/jnp.16.4.443

[93] Schmahmann JD, Sherman JC. The cerebellar cognitive affective syndrome. Brain. 1998;**121**(Pt 4):561-579. DOI: 10.1093/brain/121.4.561

[94] Hargrave DR, Mabbott DJ, Bouffet E. Pathological laughter and behavioural change in childhood pontine glioma. Journal of Neuro-Oncology. 2006;**77**(3):267-271. DOI: 10.1007/s11060-005-9034-8

[95] Beckwitt Turkel S, Krieger MD, O'Neil S, Jubran R, Tavaré CJ. Symptoms before and after posterior fossa surgery in pediatric patients. Pediatric Neurosurgery. 2012;**48**(1):21-25. DOI: 10.1159/000337730

[96] Larysz D, Blamek S, Larysz P, Pietras K, Mandera M. Posterior Fossa Brain Tissue Injury: Developmental, Neuropsychological, and Neurological Consequences of Brain Tumors in Children. Vienna: Springer; 2010. pp. 271-274

[97] Riva D, Giorgi C. The cerebellum contributes to higher functions during development: Evidence from a series of children surgically treated for posterior fossa tumours. Brain. 2000;**123**(5):1051-1061. DOI: 10.1093/brain/123.5.1051

[98] Pastore V, Colombo K, Villa F, Galbiati S, Adduci A, Poggi G, et al. Psychological and adjustment problems due to acquired brain lesions in pre-school-aged patients. Brain Injury. 2013;**27**(6):677-684. DOI: 10.3109/02699052.2013.775482

[99] Poggi G, Liscio M, Galbiati S, Adduci A, Massimino M, Gandola L, et al. Brain tumors in children and adolescents: Cognitive and psychological disorders at different ages. Psycho-Oncology. 2005;**14**(5):386-395. DOI: 10.1002/pon.855

[100] Campen C, Ashbey D, Fisher PG, MM. Psychiatric symptoms in children with medulloblastoma. Neuro-Oncology. 2012;**14**(Suppl 1):i25-i39

[101] National Institute for Health and Care Excellence. Suspected Cancer: Recognition and Referral. London: NICE; 2015 Available from: https://www.nice.org.uk/guidance/ng12

[102] Dommett RM, Redaniel MT, Stevens MC, Hamilton W, Martin RM. Features of childhood cancer in primary care: A population-based nested case-control study. British Journal of Cancer. 2012;**106**(5):982-987. DOI: 10.1038/bjc.2011.600

[103] Ansell P, Johnston T, Simpson J, Crouch S, Roman E, Picton S. Brain tumor signs and symptoms: Analysis of primary health care records from the UKCCS. Pediatrics. 2010; **125**(1):112-119. DOI: 10.1542/peds.2009-0254

[104] Dixon-Woods M, Findlay M, Young B, Cox H, Heney D. Parents' accounts of obtaining a diagnosis of childhood cancer. Lancet. 2001;**357**(9257):670-674. DOI: 10.1016/S0140-6736(00)04130-1

[105] Wilne S, Koller K, Collier J, Kennedy C, Grundy R, Walker D. The diagnosis of brain tumours in children: A guideline to assist healthcare professionals in the assessment of children who may have a brain tumour. Archives of Disease in Childhood. 2010;**95**(7): 534-539. DOI: 10.1136/adc.2009.162057

[106] Edgeworth J, Bullock P, Bailey A, Gallagher A, Crouchman M. Why are brain tumours still being missed? Archives of Disease in Childhood. 1996;**74**(74):148-151

[107] Mehta V, Chapman A, McNeely PD, Walling S, Howes WJ. Latency between symptom onset and diagnosis of pediatric brain tumors: An eastern Canadian geographic study. Neurosurgery. 2002;**51**(2):365-72-3. DOI: 10.1097/00006123-200208000-00012

[108] Shemie S, Jay V, Rutka J, Armstrong D. Acute obstructive hydrocephalus and sudden death in children. Annals of Emergency Medicine. 1997;**29**(4):524-528. DOI: 10.1016/S0196-0644(97)70227-0

IntechOpen