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Longitudinal cerebellar diffusion tensor imaging changes in posterior fossa syndrome

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ABSTRACT

Posterior fossa syndrome is a severe transient loss of language that frequently complicates resection of tumors of the cerebellum. The associated pathophysiology and relevant anatomy to this language deficit remains controversial. We performed a retrospective analysis of all cerebellar tumor resections at Seattle Children's Hospital from 2010 to 2015. Diffusion tensor imaging was performed on each of the patients as part of their clinical scan. Patients included in the study were divided into groups based on language functioning following resection: intact ($N = 19$), mild deficit ($N = 19$), and posterior fossa syndrome ($N = 9$). Patients with posterior fossa syndrome showed white matter changes evidenced by reductions in fractional anisotropy in the left and right superior cerebellar peduncle following resection, and these changes were still evident 1-year after surgery. These changes were greater in the superior cerebellar peduncle than elsewhere in the cerebellum. Prior to surgery, posterior fossa patients did not show changes in fractional anisotropy however differences were observed in mean and radial diffusivity measures in comparison to other groups which may provide a radiographic marker of those at greatest risk of developing post-operative language loss.

1. Introduction

Aggressive treatment of pediatric midline posterior fossa tumors is a critical part of neuro-oncologic care but can be complicated by characteristic deficits, including severe loss of language ability and other neuropsychological dysfunction. Having first been described 20–30 years prior in sizable cases series (Pollack et al., 1995; Rekate et al., 1985), this is one of several cerebellar disease processes known to create language deficits (Baillieux et al., 2007; Ersahin et al., 1997; Fujisawa et al., 2005). In the largest series to date, 25% of patients undergoing cerebellar tumor resection showed symptoms of this language loss (Robertson et al., 2006b) and incidence has been reported as high at 40% (Gudrunardottir et al., 2010; Küper and Timmann, 2013). As tumors located in the posterior fossa represent 50–70% of solid tumors in children (Gajjar et al., 2004), major loss of language ability represents a major burden in cancer treatment side effects to patients and their families.

Beyond an understanding of its clinical significance, little consensus exists around this condition. Authors refer to this loss of language by multiple names. These include: cerebellar mutism, ataxic mutism, akinetic mutism, cerebellar mutism syndrome, syndrome of mutism and subsequent dysarthria, transient cerebellar mutism, and posterior fossa syndrome. Though efforts have been made to systematize more precise definition of each term, a significant overlap of the usage exists in the literature. Much of this codification effort focuses on the symptoms of language change and on frequently occurring comorbid findings. There is no formally agreed upon criteria regarding the degree of language loss with some investigators emphasizing a strict definition of mutism as complete language loss and others allowing for a broader definition of language deficit. Particular focus has been given to the timing of language changes, requiring that language loss occur 1–2 days following surgery (Dailey et al., 1995), while others allow for development immediately post-operatively (Robertson et al., 2006b).

Abbreviations: AD, axial diffusivity; AP, anterior-posterior; CBW, cerebellar white matter; CTC, cerebellar-thalamic-cortical; FA, fractional anisotropy; KW, kruskal-wallis; MCP, middle cerebellar peduncle; MD, mean diffusivity; MPRAGE, Magnetization Prepared Rapid Acquisition Gradient Echo; PFS, posterior fossa syndrome; RD, radial diffusivity; RESTORE, Robust Estimation of Tensors by Outlier Rejection; SCP, superior cerebellar peduncle; SWI, Susceptibility weighted imaging; TORTOISE, Tolerably Obsessive Registration and Tensor Optimization Indolent Software Ensemble; TE, echo time; TR, relaxation time.

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Additionally, the duration of language deficit is reported as limited to days to several months (Ildan et al., 2002). Still further disagreement exists regarding the presence of other neurological symptoms, with various authors including or excluding patients with dysarthria, dysphagia, incontinence, emotional lability, dysmetria, long tract signs and cranial nerve deficits (Gudrunardottir et al., 2011; Tamburrini et al., 2015). For the purposes of this paper we use the terminology posterior fossa syndrome (PFS), in which we refer to severe language loss following cerebellar tumor resection with the possible presence of the above mentioned comorbidities if not otherwise explainable by a lesion outside of the cerebellum.

The pathophysiological cause of PFS remains unclear. A number of non-mutually exclusive mechanisms have been proposed. Some of these mechanism attempt to account for the transient nature the mutism. SPECT and PET case studies have shown hypoperfusion of the cerebellum as well as cortical language and motor areas that resolved with mutism symptoms leading some to speculate a role for vasospasm in the transient language loss (Gedik et al., 2014). Other have reported increased areas of the edema which resolved with language improvement (Pollack et al., 1995). Still others have speculated that transient neurotransmitter or transient changes in autoregulation due to thermal injury may explain the syndrome (Siffert et al., 2000). Furthermore, it has been hypothesized that there may in fact be more permanent white mater changes resulting from direct damage from surgical resection, axonal injury, and/or damage to the white matter from an inflammatory response (Avula et al., 2015b; Gudrunardottir et al., 2010).

Additionally, a number of different anatomical regions have been implicated in the pathogenesis of this disorder. An early hypothesis of pathogenesis focused on the mechanisms of surgical disruption to the tracts in the vermis (Dailey et al., 1995; Zaheer and Wood, 2010). This led some surgeons to adopt a telovelar approach rather than sectioning the vermis when excising cerebellar tumors (Mussi and Rhoton, 2000). However, prospective studies in which the vermis was spared failed to show reproducible evidence of reduction in PFS incidence (Zaheer and Wood, 2010). Recently, increased focus has been placed upon the disruption of the ascending projections from the cerebellar nuclei as a cause of the clinical condition. The middle cerebellar peduncle was implicated in an early description of PFS (Pollack et al., 1995). More recent studies implicate ascending signal through the superior cerebellar peduncle (SCP) in the cerebellar (dental)-thalamic-cortical pathway (Avula et al., 2015a; Morris et al., 2009; Ojemann et al., 2013). An animal model has similarly implicated dentate outflow (Buzunov et al., 2010) in the pathogenesis of PFS. Projections from the cerebellum, especially the dentate nucleus, ascend through the superior cerebellar peduncle and decussate in the rostral pons and midbrain. These projections then travel to the ventral lateral nucleus of the thalamus and project broadly to cortical regions including the areas associated with language production in the frontal and temporal lobes.

Given the lack of clarity regarding diagnostic criteria, pathophysiology and associated anatomy, it is logical that disagreement in the literature exists regarding risk factors for posterior fossa syndrome. A number of pre-operative radiographic findings have been associated with development of PFS, but not in a consistent fashion. Location of tumor in the midline has been associated with increased risk of mutism; however, it has also been occasionally reported in resections of tumors of the lateral cerebellum (Gelabert-Gonzalez and Fernandez-Villa, 2001). Some studies have reported tumor size is associated with PFS (Catsman-Berrevoets et al., 1999), while other investigators did not find an association with size (Robertson et al., 2006a; Wells et al., 2010). A more superior tumor location and compression of the brainstem have also been shown to be associated with increased risk of PFS (McMillan et al., 2008; Morris et al., 2009).

Diffusion imaging techniques have played a role in investigating potential pathophysiological basis of PFS. These efforts have included diffusion-weighted studies (Avula et al., 2015a) and diffusion-tensor/tractography techniques (Law et al., 2012; Morris et al., 2009; Ojemann et al., 2013; Soelva et al., 2012; van Baarsen et al., 2013). They have predominately compared post-operative scans to clinical variables of the condition, and have generally supported the hypothesis that PFS results from perturbations in the ascending cerebellar-thalamic-cortical (CTC) projections. However, each study presents only a specific time period in relation to symptoms and resection with some focusing on the immediate post-operative scan (Law et al., 2012; Ojemann et al., 2013) or a scan performed over a year after PFS onset (Soelva et al., 2012). One study presents pre- and post-op conventional imaging findings but only post-op DTI finings (Morris et al., 2009), while another presents both pre- and post-op DTI findings (Ojemann et al., 2013) but with no long term follow-up.

We employed a retrospective longitudinal, serial imaging study of patients with PFS to further investigate underlying pathophysiological changes involved with this syndrome. We compared these patients with both functionally intact tumor controls and those with only mild language deficit following resection. This study employs diffusion tensor imaging (DTI) at three time points across all three groups. Imaging was performed prior to surgical resection, immediately following resection, and at the 1-year interval to examine white matter changes in the (CTC) projections. This is a novel study in that we assessed patients throughout their clinical course from tumor diagnosis, through development of PFS, and to language resolution. By analyzing pre-operative DTI scans, we also investigated whether radiographic and clinical markers exist that can aide in the early identification of patients most at risk of developing PFS. Immediate post-surgical resection scans allow us to assess white matter changes contemporaneously with mutism development to determine potentially disrupted fiber tracts.

Finally, we evaluated DTI parameters at 1 year post-resection to characterize the evolution of white matter changes. The aim of this longitudinal study is to analyze the previously proposed theories on the pathophysiology of cerebellar mutism by following the progression of the condition.

2. Materials and methods

2.1. Patient characteristics

All patients undergoing resection of intraparenchymal cerebellar tumors at Seattle Children's Hospital (SCH) from June 2010 through June 2015 were retrospectively reviewed (Fig. 1). The study protocol was approved by the SCH institutional review board prior to accessing patient records. Inclusion criteria were presence of an intrinsic tumor of the cerebellum that involved the midline and was radically resected at our institution. Exclusion criteria included redo resection, surgery involving only biopsy, or age <2 years. Patients with pre-existing co-morbid neurological disease or severe development delays were also excluded. Clinical information was gleaned retrospectively from review of the patient's electronic medical record. Patients were divided into three groups based on post-operative verbal performance. The *verbally intact* group ($n = 19$) demonstrated intact verbally fluency after surgery and unchanged cognitive ability. The *mild language impairment* group ($n = 19$) included patients who continued to speak in multi-word sentences but showed some decrement in cognitive performance (e.g., shorter sentence length, trouble with orientation questions). The *posterior fossa syndrome* (PFS) group ($n = 9$) included the patients with complete loss of language production or production of only single words. Concern for PFS must have been raised contemporaneously by qualified medical personnel including their neurosurgeon, rehab medicine physician, oncologist, or speech pathologist documented in the patient's record.

2.2. Imaging methods

Imaging was acquired as part of routine diagnostic evaluation on either a 1.5 T or 3 T Siemens MRI scanner (Erlangen, Germany) at the Seattle Children's Hospital. Given the narrow selection of scanner