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Review

Posterior fossa tumors and their impact on sleep and ventilatory control: A clinical perspective☆

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ABSTRACT

The cerebellum, classically viewed as a motor structure of the brain, may play a role in respiration. Brainstem dysfunction has been implicated in sleep disordered breathing (SDB), but apnea after surgery of brain tumors in the posterior fossa, not involving the brainstem has been reported. We report four cases with posterior fossa tumors without brainstem invasion who suffered SDB after surgery diagnosed by polysomnography (PSG). Advanced MRI techniques with DTI were used to find correlations with SDB. Abnormal signals in the superior, middle and inferior cerebellar peduncles were seen in these patients with the most severe changes in the inferior peduncle. SDB may be under diagnosed in the setting of posterior fossa tumors without brainstem involvement. Damage to the cerebellar peduncles, especially the inferior cerebellar peduncle, without brainstem involvement, can cause significant disruption of respiration.

1. Introduction

The cerebellum is classically viewed as one of the primary structures involved in motor coordination and pattern generation (Stoodley et al., 2012). Since breathing is a repetitive cyclic motor act, injury to the cerebellum may lead to alterations in ventilatory muscle control (Lu et al., 2013). Affected muscles include the diaphragm and those in the thoracic cage, but also those involved in keeping the upper airway patent, particularly during sleep (Chen et al., 2005). In addition to the motor act of breathing and maintenance of dynamic airway patency, emerging data suggest that the cerebellum has a role in central respiratory control, modulating those functions primarily housed in brainstem structures (Feldman and Del Negro, 2006; Lu et al., 2013; Smith et al., 2009).

Naturally occurring models that can be utilized to investigate the role of the cerebellum in respiratory control are congenital posterior fossa malformations and neoplasms, many of which affect pediatric populations. Brain tumors are the second most common tumor of childhood, and tumors of the posterior fossa (cerebellum and brainstem) are responsible for over 25% of cancer deaths in children (Smith et al., 2010). Clinically observed complications of surgical resection of these tumors include motor, cognitive, and ocular morbidities (Cochrane et al., 1994). Respiratory disturbances, including apnea and sleep disordered breathing (SDB), have been canonically associated with brainstem dysfunction (from primary tumor burden or post-operative complications) (Ito et al., 1996; Manning and Leiter, 2000; Osanai et al., 1994; Valente et al., 1993), but SDB is not as systematically described in those with abnormalities limited to the cerebellum. Illustrative reports of those with SDB subsequent to posterior fossa surgery and associated with primary cerebellar abnormalities lend strength to the cerebellum's role in respiratory control (Adelman et al., 1984; Chokroverty et al., 1984; Cochrane et al., 1994; Losurdo et al., 2013; Wolfe et al., 2010). Outside of the clinical realm, animal models implicating deep cerebellar nuclei, specifically the fastigial nucleus and outflow tracts in respiratory reflexes, also suggest a role of disordered coordinated central respiratory control in those with cerebellar injury (Xu and Frazier, 1997, 2002). However, the gap connecting a cerebellar injury and subsequent clinically diagnosable SDB is apparent when current literature is reviewed.

Advanced magnetic resonance imaging (MRI) techniques may provide critical translational information linking neuroanatomic

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injury to clinical sequelae. These analytic techniques, which can be applied to routine MRI, help provide a translational bridge between "real-life" post-operative sequelae including SDB and neuroanatomic deficits. Thus, we present four pediatric cases with cerebellar tumors (without known brainstem involvement) who underwent surgical resection, and were later diagnosed with SDB after formal polysomnography (PSG). MRI correlates of clinical findings are reviewed. This clinical and translational approach to reviewing the impact of posterior fossa tumors on respiratory control will hopefully complement other approaches to the "Challenges of Ventilatory Control" discussed in this issue.

2. Materials and methods

2.1. Subject population

This study was conducted at Seattle Children's Hospital after obtaining standard IRB approval for retrospective study review. We reviewed medical records of all cases between the ages of 2–21 with the primary diagnosis of posterior fossa neoplasms from January 1, 2000, to November 30, 2012. Those subjects who underwent both surgical resection and PSG were identified. Information collected included age, gender, clinical presentation, operative findings, and results of PSG. Those cases with identifiable brainstem involvement of primary tumor, or lack of appropriate imaging were excluded. MRI data were compared to age/gender matched controls. Control subjects, who all had MRIs done on the same day and on the same scanner as matched cases, met the following criteria: (a) MRI obtained as evaluation for chronic headaches; (b) MRI was interpreted as normal; (c) lack of recurring MRI brain studies performed at our facility.

2.2. Polysomnography: techniques and analysis

Overnight PSG was performed at Seattle Children's Hospital's Sleep Disorders Center, which is an American Academy of Sleep Medicine accredited pediatric-specific center. The following physiologic parameters were monitored non-invasively: 8-lead electroencephalogram, bilateral electrooculogram, submental and bilateral anterior tibialis electromyograms, and 2-lead electrocardiogram. Using a nasal pressure cannula and thermistor, oronasal airflow and expired end-tidal carbon dioxide were measured. In the event that nasal cannula was not tolerated, transcutaneous carbon dioxide monitoring was used. Oxygen saturation was measured via pulse oximetry, and inductance plethysmography for thoraco-abdominal movement was used. Infrared video was recorded of the entire sleep study as part of standard protocol to corroborate any polygraphic findings and to rule out artifact. Direct observation of sleep was done by an attendant technologist. All data were recorded into a computer based acquisition and analysis program (Rembrandt® or XLTek®) and interpreted by a board-certified Sleep Medicine physician in accordance with pediatric practice parameters of the American Academy of Sleep Medicine (Iber et al., 2007). The Apnea Hypopnea Index (AHI) was defined as the total number of respiratory disturbances averaged per hour of total sleep time, and further divided into those caused by obstructive apneas/hypopneas and those caused by central events. The Oxygen Desaturation Index (ODI) was defined as the total number of desaturations of at least 3% averaged per hour of total sleep time.

Descriptive statistics on respiratory parameters from PSG on this cohort, as well as from a published referent group are provided, though no statistical comparisons were made.

2.3. MRI: techniques and analysis

All cases underwent clinical MR imaging of the brain with and without contrast. For case subjects, the imaging was performed as part of our institution's clinical standard pre- and post-operative protocols; for control subjects, images were obtained as part of a clinical evaluation of headaches. All images included Diffusion Tensor Imaging (DTI), which allowed for measure of white matter integrity through Fractional Anisotropy (FA) measures and demonstration of changes in large white matter tracts. Imaging was performed on Allegra 1.5 T and Trio 3 T scanners (Siemens, Erlangen, Germany) by using phased array coils. Standard clinical imaging included a high-resolution sagittal T1 magnetization-prepared rapid acquisition of gradient echo, axial T2, axial FLAIR. DTI used a single-shot echo-planar imaging sequence, with imaging parameters: TR/TE, 5800/96 ms; number of signal intensity-intensity averages: 2–4. The b-values for diffusion-weighting were 0, 1000 s/mm^2, with 10 gradient-encoding directions. Data were obtained with a matrix size of 128×128 and 1.8×1.8 mm in-plane resolution. Slice thickness was 3.5 mm, with 40 sections covering the entire brain. DTI data processing and analysis were performed using FSL software package (Version 4.1; FMRIB, Oxford, UK, http://www.fmrib.ox.ac.uk/fsl, (Smith et al., 2004)). Analysis of the FA data was carried out using Tract-Based Spatial Statistics (TBSS, http://www.fmrib.ox.ac.uk/fsl/tbss; Smith et al., 2006), part of FSL. TBSS projects all subjects' DTI parameters onto a mean FA tract skeleton using the nonlinear registration. We used JHU (Johns Hopkins University) DTI-based white-matter label atlas (Mori et al., 2005) to define the masks for Inferior, Middle and Superior Cerebellar Peduncles (ICP, MCP and SCP respectively). We then estimated FA average values within the white matter skeleton for ICP, MCP and SCP on left and right side per subject.

Mean FA measurements between case and control groups for each anatomic region were analyzed with standard descriptive statistics and compared using two-tailed *t*-tests, with statistical significance set at $p = 0.05$ for a null hypothesis that FA measurements were not different between groups. STATA 12® was used for this comparative analysis.

3. Results

Of 13 cases identified who had posterior fossa tumors and PSG, five cases were excluded for known brainstem involvement and one patient was excluded due to lack of operative resection (he was conservatively managed with surveillance imaging). Of the remaining seven cases, only four had adequate MRI images for analysis. One subject did not have follow-up imaging after his initial surgery due to cochlear implant placement, and two were excluded for poor quality DTI acquisition. Thus, we present 4 illustrative cases from our center.

3.1. Case illustrations

Table 1 shows a summary of baseline case subject characteristics. Figs. 1–4 contain MR images illustrating (a) original tumor location pre-resection, (b) post-operative T2 weighted MRI sequence, (c) DTI sequence color map from the same post-operative MRI, and d) DTI sequence color map from a matched control.

3.1.1. Case 1

A 7-year-old girl presented with a 1-month history of severe headaches and 5 days of intermittent vomiting. She underwent MRI evaluation, which revealed a heterogeneously enhancing mass, on T1 weighted images, expanding the fourth ventricle causing mass effect on the brainstem and pushing the cerebellar tonsils inferiorly with obstructive hydrocephalus. The mass