The term medulloblastoma was first coined in 1925 by Bailey and Cushing. Medulloblastoma is a highly malignant embryonal tumor/primitive neuroectodermal tumor of the cerebellum. It is the most common CNS tumor in children, with an estimated incidence of 0.6 per 100,000 in children ages 0 to 16 years old. Medulloblastoma accounts for approximately 20% of all pediatric CNS tumors and 40% of all posterior fossa tumors. The peak incidence of these tumors occurs between the ages of 5 and 7 years old with a predilection for boys compared with girls. These tumors are rarely observed in adults, comprising only 1% of all adult brain tumors. On MRI, medulloblastomas are commonly hypointense on T1- and T2-weighted images, and most are heterogeneously contrast enhancing after Gd administration. It is estimated, however, that as many as 35% of medulloblastomas are minimally enhancing or even nonenhancing, and some authors suggest that this subtype may have prognostic significance.

Determining clinical and molecular prognostic factors is helpful in risk stratification, optimal treatment determination, and targeted therapy assignment. In

Object. Vascular endothelial growth factor (VEGF) is the major proangiogenic factor in many solid tumors. Vascular endothelial growth factor receptor (VEGFR) is expressed in abundance in pediatric patients with medulloblastoma and is associated with tumor metastasis, poor prognosis, and proliferation. Gadolinium enhancement on MRI has been suggested to have prognostic significance for some tumors. The association of VEGF/VEGFR and Gd enhancement in medulloblastoma has never been closely examined. The authors therefore sought to evaluate whether Gd-enhancing medulloblastomas have higher levels of VEGFR and CD31. Outcomes and survival in patients with enhancing and nonenhancing tumors were also compared.

Methods. A retrospective analysis of patients with enhancing, nonenhancing, and partially enhancing medulloblastomas was performed. Primary end points included risk stratification, extent of resection, and perioperative complications. A cohort of 3 enhancing and 3 nonenhancing tumors was selected for VEGFR and CD31 analysis as well as microvessel density measurements.

Results. Fifty-eight patients were analyzed, and 20.7% of the medulloblastomas in these patients were nonenhancing. Enhancing medulloblastomas exhibited strong VEGFR1/2 and CD31 expression relative to nonenhancing tumors. There was no significant difference in perioperative complications or patient survival between the 2 groups.

Conclusions. These results suggest that in patients with medulloblastoma the presence of enhancement on MRI may correlate with increased vascularity and angiogenesis, but does not correlate with worse patient prognosis in the short or long term.

Key words: medulloblastoma • tumor enhancement • VEGF • CD31 • oncology

Abbreviations used in this paper: hpf = high-powered field; HPRT = hypoxanthine phosphoribosyltransferase; RT-PCR = reverse transcription-polymerase chain reaction; VEGF = vascular endothelial growth factor; VEGFR = VEGF receptor.

This article contains some figures that are displayed in color online but in black-and-white in the print edition.
addition, understanding the molecular mechanisms associated with prognosis may enhance the current treatments for medulloblastoma.5

In many cases, angiogenesis and neovascularization play fundamental roles in tumor growth.9,28 Angiogenesis is a dynamic process involving a range of both pro- and antiangiogenic molecules.3,12 The major proangiogenic factors involved in medulloblastoma include vascular endothelial growth factor (VEGF), basic fibroblast growth factor, angiopoietin, integrins, matrix metalloproteinases, and CD31.7,12,24,29 The primary proangiogenic factor produced by medulloblastomas is VEGF.6,26 Both soluble and receptor isotypes of VEGF are found in most medulloblastomas.12,14 Some have suggested that VEGF expression and microvessel density correlate with medulloblastoma prognosis.16 Targeted inhibitors of VEGF, primarily VEGF receptor (VEGFR1/2), have been developed for several trials involving children with other tumor types.15,17,25,36

Recently, Gd enhancement has been found to have prognostic significance for some tumors.33,35 Tumor intra-vascular enhancement is complex and reflects intratumoral vasodilation, hyperemia, and neovascularity.28 It has been suggested that tissue enhancement due to vascularity depends on arterial input function, kinetic distribution of blood into the capillary bed, leakage across the capillary walls, and volume of the interstitial space.6

The association of VEGF/VEGFR and Gd enhancement in medulloblastoma has never been directly examined. Vascular endothelial growth factor receptor inhibitors are currently under investigation as antitumor agents in the treatment of medulloblastoma. Identifying whether Gd enhancement on MRI is associated with higher levels of proangiogenic factors such as VEGFR and CD31 may be useful in predicting which patients may benefit from treatment with VEGFR inhibitors. In this study, we evaluated whether Gd-enhancing medulloblastoma tumors have higher levels of VEGFR and CD31 than nonenhancing medulloblastoma tumors. In addition, we compare perioperative outcomes and survival in pediatric patients with enhancing versus nonenhancing medulloblastomas.

Methods

Study Population

Following approval by the University of Michigan Institutional Review Board, we reviewed the records of children treated for medulloblastoma at our institution between 1991 and 2010. A total of 58 patients had complete medical records and were included in the analysis. Tumors were graded as enhancing, partially enhancing, or nonenhancing, on the basis of the consensus opinion of 3 pediatric neurosurgeons (C.O.M., H.J.L.G., and K.M.M.) and 1 neuroradiologist (D.J.Q.) who were blinded to each other’s opinions (Fig. 1). There was 100% consensus among reviewers based on greater than 50% enhancement (enhancing tumor), less than 50% enhancement (partially enhancing), and complete absence of contrast enhancement (nonenhancing). For patient outcome analysis, enhancing and partially enhancing cohorts were combined as the enhancing cohort and compared with patients exhibiting a complete absence of enhancement (the nonenhancing cohort). Children were considered high risk if residual tumor size was larger than 1.5 cm3, age was less than 3 years, or they had distant metastasis at the time of diagnosis. Using the equation (A)(B)(C)/2, we estimated tumor volume on MRI, in which (A) represented the greatest tumor diameter, (B) represented greatest tumor volume 90° perpendicular to diameter (A), and (C) was the number of slices containing tumor on MRI multiplied by slice thickness. A cohort of 6 patient medulloblastoma samples representing 3 enhancing and 3 nonenhancing tumors were selected for VEGFR, CD31, and microvessel density analysis (no partially enhancing tumors were used). All 3 enhancing specimens had the classic histological signs, while the nonenhancing specimens included 2 with classic histology and 1 with desmoplastic histology. All specimens were handled in accordance with the policies established by the Institutional Review Board at the University of Michigan.

Tissue Analysis

Rabbit monoclonal antibody against VEGFR that recognizes the R1 and R2 isoforms was used at a 1:200 dilution. Mouse CD31 IgG2b endothelial cell marker antibody was used at a 1:500 dilution. Anti-mouse and anti-rabbit Cy2 and Alexa Fluor secondary antibodies were used at a 1:100 dilution (Jackson ImmunoResearch Laboratories, Inc.). Nuclear counterstaining was performed with DAPI (Invitrogen). In each tumor specimen, 10 representative sections were analyzed. Images were visualized using a fluorescence microscope (Carl Zeiss). Expression of VEGFR1/2 and CD31 was assessed using a semiquantitative scoring system for the number of positive vessels or cells. Ten random ×40 objective fields within tumor tissue were photographed and counted. Two independent observers (including D.A.) performed scoring of all samples.

To measure intratumoral microvessel density, medulloblastoma tissue from 6 patients was sectioned and mounted (3 enhancing and 3 nonenhancing specimens).38 Intratumoral vessel density was determined from areas of each tumor containing the highest vessel density. These areas were identified using ×40 magnification by 2 independent observers. Endothelial cells were stained by CD31 immunofluorescence according to established protocols.3,14 Microvessel density (number of microvessels per high-powered field [hpf]) was counted at ×40 magnification. The presence of vessel lumens and the absence of red blood cells were used to confirm the presence of a microvessel. Vessels were considered large and therefore excluded on the basis of the presence of a thick lamina muscularis and more than 8 red blood cells within the lumen.

Real-Time RT-PCR Assays

Human-specific VEGF reverse transcription-polymerase chain reaction (RT-PCR) primers were designed using the following sequence: 5′-GGCAGAAGGAGG AGGGACAGAATC (sense), and 5′-CATTTAACGCT TCAGGATCTTGT (antisense). RNA was isolated from medulloblastoma specimens in pediatric patients using an RNA extraction kit, following the manufacturer’s instructions (Qiagen Inc.). TaqMan 1-step quantitative RT-PCR
VEGF receptor expression in medulloblastoma

for VEGFR was performed according to the manufacturer’s specifications (Applied Biosystems) with all reactions normalized to hypoxanthine phosphoribosyltransferase (HPRT). Fifty nanograms of medulloblastoma RNA template was used in combination with 10.0 μl RT-PCR 2× TaqMan mix, 1.0 μl TaqMan gene expression assay, 0.5 μl TaqMan RT enzyme 40× mix, and RNase-free water, for a total volume of 20.0 μl. The mix was incubated on a Mastercycler ep realplex (Eppendorf; 1 cycle of 48°C for 15 minutes, 95°C for 10 minutes; 40 cycles of 95°C for 15 seconds, 60°C for 60 seconds; followed by a melting-curve assay) with a 1-μl mixture of gene-specific forward and reverse primers (each 5 mM), 10 μl of 2× SYBR Green SuperMix (Bio-Rad Laboratories), and 1 μl of diethylpyrocarbonate-H2O. Realplex software was used to calculate cycle threshold (CT) values for all target genes and for the reference gene HPRT. The expression values for VEGFR1/2 are presented as a fold expression in relation to HPRT; the actual values were calculated using the 2-ΔΔCT equation, in which ΔΔCT = [CT_target – CT_HPRT(VEGFR) – [CT_target – CT_HPRT(VEGFR)]).

Statistical Analysis

Statistical analyses were performed using PASW Statistics software (version 20, SPSS, Inc.). Data graphed with error bars represent mean and standard error from experiments performed in triplicate unless otherwise noted. Statistical analyses were performed using the Pearson chi-square test for categorical analyses and the ordinal chi-square test, and the 2-sided Student t-test was performed for mean comparisons of continuous variables. The Fisher exact test was used if more than 80% of values were less than 5. Averages are presented as means ± standard deviation. A 2-sided p value of < 0.05 was considered statistically significant.

Results

Expression of Proangiogenic Factors VEGFR and CD31

Gadolinium-enhancing medulloblastoma specimens exhibited a strong expression of VEGFR1/2 by immunofluorescence, while nonenhancing tumors showed minimal fluorescence. Tissue was sectioned, mounted, and exposed to the VEGFR antibody specific to the R1 and R2 isoforms (Fig. 2 upper). Green fluorescence represents antibody stained with VEGFR1/2. As observed in Fig. 2 lower, enhancing medulloblastomas had a mean of 12.75 cells per hpf, while nonenhancing tumors had 3.5 VEGFR1/2-positive cells (p = 0.004). In addition, RT-PCR demonstrated 1.8-fold higher levels of mRNA VEGFR levels in enhancing tumors (p = 0.15; Fig. 3). We also examined CD31 expression on established endothelial cells in medulloblastoma specimens. All enhancing medulloblastoma specimens showed high levels of CD31 (Fig. 4 upper). Enhancing tumors expressed on average 42.7 CD31-positive cells per hpf, while nonenhancing tumors expressed fewer CD31-positive cells (7.67 cells per hpf; p = 0.048; Fig. 4 lower).

Microvessel Density

Microvessel density was evaluated in enhancing and nonenhancing medulloblastomas in pediatric patients and determined by the number of microvessels per hpf.13,14 Enhancing medulloblastomas exhibited more microvessels per hpf than nonenhancing tumors (p = 0.0005) (Fig. 5 upper). In enhancing tumors, the mean number of microvessels per hpf was 5.75 compared with a mean of 2.0 for nonenhancing medulloblastomas.

Clinical Characteristics

A total of 58 patients were included in the clinical analysis (Table 1). In this cohort, 58.6% of the patients were male and the mean age at diagnosis was 6.9 years of age. Most patients (79.3%) had enhancing tumors, whereas 20.7% had nonenhancing tumors. Between the two groups, there was no significant difference in sex (p = 0.74), race (p = 0.51), age at diagnosis (p = 0.56), risk stratification (p = 0.69), or histological subtype (p = 0.94). Mean tumor size was 33 cm3, and 22.4% of patients had metastasis at presentation. Although the contrast-enhancing group had larger tumor size on presentation (39 cm3 vs. 27 cm3), this difference was not significant (p = 0.45). Also, although patients with enhancing medulloblastomas had a lower incidence of metastasis on presentation (17.4% vs. 41.7%), this difference was also not statistically
significant (p = 0.12). Patients with enhancing tumors had modestly higher rates of hydrocephalus (89.1%) compared with patients with nonenhancing tumors (66.7%), but this difference did not reach statistical significance (p = 0.06).

Table 1 shows the comparative results of perioperative outcomes between patients with enhancing and nonenhancing medulloblastomas. Forty-four percent (n = 20) of patients with enhancing tumors and 50% of patients with nonenhancing tumors were high risk (p = 0.69). Fifty patients (86.2%) required external ventricular drain placement. There was no significant difference in external ventricular drain placement between patients with enhancing tumors and nonenhancing tumors (p = 0.67). There was no significant difference in the rate of complications between patients with enhancing and nonenhancing medulloblastomas (p = 0.10; Table 1).

Mean overall survival for children with medulloblastoma in this series was 10.7 years. There was no significant difference in mean progression-free or overall patient survival between the enhancing and nonenhancing groups (p = 0.60). Patients who had enhancing tumors lived a mean of 9.2 years and patients with nonenhancing tumors lived a mean of 12.3 years (p = 0.60). Fifty percent of the patients with enhancing tumors and 45% of patients with nonenhancing tumors were alive 5 years after surgery (p = 0.79).

**Discussion**

We found that 20% of medulloblastomas in this
VEGF receptor expression in medulloblastoma

A cohort were nonenhancing. These results are consistent with data from other published reports. Tumor enhancement may be associated with other tumor characteristics. Tynninen et al. retrospectively studied microvessel density, tumor proliferation rate, and degree of enhancement in 62 gliomas. Tumor enhancement was determined on the basis of the opinions of 2 neuroradiologists. They identified a correlation between degree of contrast enhancement, Ki-67 tumor proliferation, and microvessel density. Similarly, Vaquero et al. analyzed the prognostic significance of oligodendroglioma enhancement. They used CD34 immunostaining in low-grade oligodendroglioma samples to determine an enhancement score (tumor angiogenesis index). Using this index, they noted a relationship between tumor enhancement, endothelial surface area, and patient survival. Novel chemo-therapeutic agents and targeted therapies are essential, particularly for children with high-risk disease. Vascular endothelial growth factor has been recognized as one of the most potent proangiogenic factors in primary CNS tumors. Several different isoforms of soluble VEGF exist, which bind to 1 of the 2 dominant tyrosine kinase VEGFRs (VEGFR1 or VEGFR2), resulting in receptor phosphorylation and intracellular signaling. High VEGF levels have been associated with tumor metastasis, proliferation, and poor prognosis in various cancer types, particularly medulloblastoma. Vascular endothelial growth factor receptors are expressed in abundance in pediatric patients with medulloblastoma. Vascular endothelial growth factor receptors are endothelial cell specific and are therefore rarely expressed in normal human brain vasculature. Slongo et al. and Grau et al. both demonstrated robust expression of VEGFR1/2 in medulloblastoma patient samples and medulloblastoma cell lines, and VEGFR1/2 (along with VEGF receptor A) has been the focus of several preclinical studies to block angiogenesis in primary CNS malignancies. In this study, we set out to determine differences in VEGFR1/2 expression in contrast-enhancing and nonenhancing medulloblastomas. Our results revealed a marked increase in VEGFR-expressing cells in enhancing tumors.

The potent proangiogenesis agent VEGF, as expressed by endothelial cells as well as medulloblastoma tumor cells, suggests neovascularization. The immunofluorescence in this study shows morphological evidence of both tumor and endothelial cell positivity within medulloblastoma specimens (Fig. 2), supporting prior published reports. To further investigate this process in enhancing and nonenhancing tumors, we aimed to determine if this proangiogenesis agent truly results in the formation of new microvessels in pediatric patients with medulloblastoma. To accomplish this, we examined microvessel density (number of microvessels per hpf) as well as CD31 positivity within our sample populations. The use of anti-CD31 antibodies in vivo has been shown to inhibit the formation of new blood vessels within the CNS. In our study, enhancing medulloblastomas demonstrated 2.8 times more microvessels than nonenhancing tumors (5.75 microvessels per hpf in enhancing tumors).
vs 2.0 microvessels per hpf in nonenhancing tumors). We also found a markedly more robust expression pattern of CD31-positive cells in enhancing medulloblastomas, suggesting that there are a greater number of microvessels within the tumors of enhancing medulloblastomas as well as a more robust expression of factors promoting angiogenesis. This suggests that tumors with Gd enhancement have not only more proangiogenic factors within the tumor, but also the formation of newly formed blood vessels.

Angiogenesis is one of the hallmarks of medulloblastoma progression. In the past decade, investigators have sought to test targeted antiangiogenic therapies in clinical as well as preclinical medulloblastoma models. At the time this paper was prepared, there were 5 active clinical trials utilizing antiangiogenic agents for pediatric patients with medulloblastoma (clinicaltrials.gov). Although the efficacy and toxicity of anti-VEGF therapies in pediatric patients with medulloblastoma are still being determined, the addition of contrast enhancement on MRI as a marker for robust VEGFR expression may allow for better patient selection in the use of these therapies.

Although contrast enhancement appears to correlate with robust VEGFR1/2 and CD31 expression, it does not appear to correlate with perioperative outcome and survival. Several studies have suggested that a more malignant tumor phenotype is associated with higher expression levels of VEGF. We were unable to validate this observation with our small clinical series. Although VEGF appears to have a strong effect on promoting angiogenesis, patient outcome is multifactorial.

Contrast enhancement in the CNS is a complex process, relying on both intravascular and interstitial mechanisms. Our study investigating the proangiogenic factors VEGF and CD31 in medulloblastoma addresses only the intravascular contribution to medulloblastoma enhancement. Other potential limitations to the study include the retrospective nature of our analysis and the relatively small sample size. Our sample of 58 children with medulloblastoma (including 6 with available tissue for molecular analysis) was not large enough for powerful survival analysis. Given these limitations, medulloblastoma subtype analysis by either histopathology or transcriptional subtype was not included.

**Conclusions**

Our results suggest that contrast-enhancing medulloblastomas in pediatric patients have increased VEGFR1/2 expression and that these tumors are able to attract new microvessels, as noted by increased microvessel density and robust CD31 expression. Enhancement pattern does not appear to correlate with 5-year patient survival. Future studies with larger sample sizes will be required to validate our findings. It is possible that the presence of Gd contrast enhancement in pediatric patients with me-
TABLE 1: Patient demographics for contrast-enhancing and nonenhancing study groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Enhancing Group* (n = 46)</th>
<th>Nonenhancing Group (n = 12)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>26 (56.5)</td>
<td>8 (66.7)</td>
<td>0.74</td>
</tr>
<tr>
<td>female</td>
<td>20 (43.5)</td>
<td>4 (33.3)</td>
<td></td>
</tr>
<tr>
<td>race</td>
<td></td>
<td></td>
<td>0.51</td>
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<tr>
<td>Caucasian</td>
<td>29 (63.0)</td>
<td>8 (66.7)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>4 (8.7)</td>
<td>2 (16.7)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>1 (2.2)</td>
<td>1 (8.3)</td>
<td></td>
</tr>
<tr>
<td>biracial</td>
<td>2 (4.3)</td>
<td>1 (8.3)</td>
<td></td>
</tr>
<tr>
<td>other</td>
<td>10 (21.7)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>mean age at diagnosis (mos)</td>
<td>77</td>
<td>88</td>
<td>0.56</td>
</tr>
<tr>
<td>risk†</td>
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<td></td>
<td>0.69</td>
</tr>
<tr>
<td>high</td>
<td>20 (43.5)</td>
<td>6 (50.0)</td>
<td></td>
</tr>
<tr>
<td>standard</td>
<td>26 (56.5)</td>
<td>6 (50.0)</td>
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</tr>
<tr>
<td>tumor histology</td>
<td></td>
<td></td>
<td>0.94</td>
</tr>
<tr>
<td>classic</td>
<td>38 (82.6)</td>
<td>11 (91.7)</td>
<td></td>
</tr>
<tr>
<td>desmoplastic</td>
<td>5 (10.9)</td>
<td>1 (8.3)</td>
<td></td>
</tr>
<tr>
<td>large cell</td>
<td>2 (4.3)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>nodular</td>
<td>1 (2.2)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>mean tumor volume (cm³‡)</td>
<td>39</td>
<td>27</td>
<td>0.45</td>
</tr>
<tr>
<td>metastasis at diagnosis</td>
<td>8 (17.4)</td>
<td>5 (41.7)</td>
<td>0.12</td>
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<td>hydrocephalus at diagnosis</td>
<td>41 (89.1)</td>
<td>8 (66.7)</td>
<td>0.06</td>
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<td>postop placement of external ventricular drain</td>
<td>40 (87.0)</td>
<td>10 (83.3)</td>
<td>0.67</td>
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<td>postop complications§</td>
<td>32 (69.6)</td>
<td>5 (41.7)</td>
<td>0.10</td>
</tr>
<tr>
<td>cerebellar mutism</td>
<td>12 (26.1)</td>
<td>1 (8.3)</td>
<td>0.27</td>
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<td>postop shunt or 3rd ventriculostomy</td>
<td>19 (41.3)</td>
<td>6 (50.0)</td>
<td>0.62</td>
</tr>
<tr>
<td>early reoperation (&lt;30 days)</td>
<td>17 (37.0)</td>
<td>4 (33.3)</td>
<td>0.99</td>
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<tr>
<td>late reoperation (30 days to 3 mos)</td>
<td>9 (19.6)</td>
<td>3 (25.0)</td>
<td>0.69</td>
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<tr>
<td>postop chemotherapy</td>
<td>44 (95.7)</td>
<td>11 (91.7)</td>
<td>0.38</td>
</tr>
<tr>
<td>postop brain radiation</td>
<td>35 (76.1)</td>
<td>10 (83.3)</td>
<td>0.99</td>
</tr>
<tr>
<td>tumor recurrence</td>
<td>11 (23.9)</td>
<td>2 (16.7)</td>
<td>0.99</td>
</tr>
<tr>
<td>mean overall survival (mos)</td>
<td>110</td>
<td>147</td>
<td>0.60</td>
</tr>
</tbody>
</table>

* Enhancing group includes partial or complete tumor enhancement. Nonenhancing tumors included if tumor exhibited complete absence of enhancement as determined by consensus opinion of 3 blinded pediatric neurosurgeons and 1 neuroradiologist. Values expressed as number of patients (%) unless otherwise indicated.

† High risk = > 1.5 cm² remaining tumor, age < 3 years, or distant metastasis at the time of diagnosis. Standard risk = total or subtotal resection with no distant metastasis.

‡ Tumor volume calculated by (A)(B)(C)/2 (see text).

§ Deep venous thrombosis, hyponatremia, pseudomeningocele, hydrocephalus, cerebellar mutism.


dulloblastoma should be considered when contemplating targeted antiangiogenic therapies for patients.

Discussion

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Author contributions to the study and manuscript preparation include the following. Conception and design: Hervey-Jumper, Maher, Garton, Muraszko, Quint, Robertson. Drafting of the article: Hervey-Jumper, Maher, Garton, Muraszko, Quint, Robertson. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Maher. Statistical analysis: Hervey-Jumper. Study supervision: Maher, Garton, Quint, Robertson, Muraszko.

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