Hypothalamic hamartomas are rare nonneoplastic developmental lesions arising from the tuber cinereum and inferior hypothalamus. They can be identified incidentally in association with precocious puberty alone or with a syndrome of intractable epilepsy, disruptive behavior, and intellectual deterioration. The epilepsy syndrome associated with HH usually begins in early childhood with gelastic seizures and continues, later on, with a generalized epileptic encephalopathy characterized by other types of seizures (complex partial seizures with or without secondary generalization, tonic-clonic seizures, tonic seizures, and drop seizures). Predominantly gelastic seizures, but also other types, are extremely refractory to antiepileptic drugs. Studies report more than 95% of these seizures are refractory to medical treatment. Because of this epilepsy syndrome’s high degree of pharmacological resistance, different surgical and radiosurgical treatment options have been advocated to resect or disconnect HHs with varied success. The rationale for the resection was based on electrophysiological and functional imaging data that demonstrate that the hamartoma itself is intrinsically

Object. Hypothalamic hamartomas (HHs) often cause pharmacoresistant epilepsy, incapacitating behavioral abnormalities, and cognitive decline. Surgical intervention offers the patient the best opportunity of seizure resolution, which occurs in approximately 50%–60% of patients, and improvement in both cognitive and behavioral difficulties. For those in whom the initial operation has failed, further medical treatment options remain quite limited, whereas, in some cases, a second surgery may improve seizure outcome. The authors retrospectively reviewed their surgical cases to document the success rate and complications of reoperations in patients with HHs.

Methods. Data were obtained from the HH epilepsy surgery database at the Barrow Neurological Institute between 2003 and 2010. Surgical treatment consisted of open and endoscopic procedures, as well as radiosurgery. Demographic details, seizure history, presurgical evaluation, and postoperative follow-up data were evaluated.

Results. In the last 7 years, 21 (13%) of 157 patients underwent reoperation after an initial epilepsy operation. The initial surgical approach in the 21 patients included: endoscopic (8 patients [38%]), transcallosal (8 patients [38%]), orbitozygomatic (3 patients [14%]), and radiosurgery (2 patients [10%]). Of the 8 patients who initially underwent endoscopic resection, repeat procedures included: radiosurgery in 4 (50%), an orbitozygomatic approach in 2 (25%), repeat endoscopy in 1 (12.5%), and a transcallosal approach in 1 (12.5%). Repeat procedures after an initial transcallosal resection included: endoscopic resection in 2 (25%); radiosurgery in 1 (12%); an orbitozygomatic approach in 2 (25%); and repeat transcallosal surgery in 3 (38%). Predominant seizure types that recurred after the first surgery were gelastic seizures, complex partial seizures, and tonic–clonic seizures. Magnetic resonance imaging in all patients prior to reoperation demonstrated either residual HH and/or connection with the mammillary bodies. Review of patients with more than 6 months of follow-up since the last surgery showed greater than 90% reduction in seizures in 4 patients (19%) and by 50%–90% in 10 patients (48%). Two patients were seizure free, and in 5 patients (24%) there was no change in seizure frequency. Following reoperation, none of the patients had any worsened behavioral issues such as increased rage attacks or disruptive violent behavior. New postoperative complications after reoperation included hemiparesis, thalamic stroke (asymptomatic and symptomatic), hyperphagia, and panhypopituitarism.

Conclusions. Reoperation should be considered in selected patients with HH in whom initial epilepsy surgery fails because more than half the patients have significant reductions in seizures. (DOI: 10.3171/2010.11.FOCUS10248)
epileptogenic and propagates generalized seizures through mammillothalamic pathways.\textsuperscript{3} In accordance with this, different resective treatments have demonstrated that seizures can be arrested and that improved behavior and cognitive function are possible.\textsuperscript{11} Debate still continues whether HH disconnection offers any benefit over, or is even comparable to, complete resection. The choice of surgical technique for resection is often dictated by the specific surgical anatomy of each HH lesion. Most importantly, this choice depends on the size and location of the base of attachment and whether the majority of the tumor lies below the third ventricle or within it.

The surgical management of HHs associated with gelastic seizures has been shown to be an effective strategy that results in seizure resolution in approximately 50\%–60\% of patients; the remainder of patients have experienced significant improvement in seizure burden, associated symptoms, and quality of life.\textsuperscript{2} For those in whom the first surgery fails, further medical treatment options remain limited; at times, a second surgery may improve seizure outcome. We retrospectively reviewed our surgical cases to document the success and complications of reoperation after a failed first surgery. Our intention was to identify possible factors associated with poor seizure control and to improve selection criteria for reoperation. Information reviewed includes preoperative clinical history, electrophysiological data, MR images, operative procedures, follow-up clinical data, and complications.

Methods

Review of Clinical Database

All patients included in this study had refractory epilepsy and symptomatic HH, and were referred to our institution. This series includes all patients who underwent different types of resection and radiosurgery between October 2003 and January 2010. A minimum of 6 months of follow-up review was an inclusion criterion. During the study period, 157 patients underwent different resective procedures. Twenty-one (13\%) of the 157 patients underwent 25 surgical procedures after the first epilepsy surgery. Indications for repeat surgeries included persistent or recurrent seizures, postoperative MR imaging suggestive of incomplete resection, and/or an initial operation that was aborted because of intraoperative complications. Prior treatment for epilepsy associated with HH before referral to our institute included temporal lobe resection, partial frontal lobe resection, and corpus callosotomy in one patient each; two patients had undergone implantation of vagus nerve stimulators. This study was approved by the hospital institutional review board.

Classification of Hypothalamic Hamartoma

The Delalande and Fohlen Classification was used to describe HH.\textsuperscript{4} This instrument consists of 4 descriptors: Type I has a horizontal implantation plane and may be lateralized on one side (parahypothalamic), Type II has a vertical insertion plane and resides in an intraventricular location (intrahypothalamic), Type III is a combination of Types I and II, and Type IV includes all giant hamartomas.

Preoperative Evaluation

Presurgical evaluation comprised detailed history, examination, and assessment of electroencephalograms, brain MR images, and neuropsychological test results when feasible. Endocrinological assessment was done only when there were clinical features suggestive of endocrine abnormalities. All patients were imaged in a 1.5- or 3.0-T MR imaging unit (General Electric). At least 3 antiepileptic drugs had failed in all cases before the patient was considered for repeat surgery. All patients were examined preoperatively by an epileptologist. Results of all studies were reviewed, and the choice of the specific treatment modality was made at a multidisciplinary HH conference composed of a dedicated pediatric neuroradiologist, pediatric neurosurgeons, pediatric epileptologists, pediatric endocrinologist, and neuropsychologist.

Preoperative and Postoperative Imaging

Preoperative and postoperative MR images were used to determine the size of the HH, surface area of the base of attachment, HH type according to Delalande Classification, site of attachment, extent of resection, amount of disconnection, and possible surgical complications. Preoperative and postoperative imaging sequences used for tumor-volume measurement included volumetric T2-weighted coronal and sagittal images and a T1-weighted axial spoiled gradient echo image. Preoperative and postoperative HH lesion volumes were calculated by summation of manually measured regions of interest (area of region of interest × slice thickness) on sequential, contiguous coronal T2-weighted images by using Voxel 3D imaging software (DR Systems). Likewise, pre- and postoperative surface areas of the base of HH attachment (for the purpose of determining the percentage of surgical disconnection of HHs in patients with residual postoperative HH tissue) were determined by summation of surface area (linear measurement of base of attachment × slice thickness) on contiguous coronal T2-weighted image slices. All patients underwent routine diffusion-weighted imaging and apparent diffusion coefficient imaging.

Neuropathology

Resected specimens were reviewed by a neuropathologist. Histopathological examination showed subependymal tissue composed of disorganized glial and neuronal elements consistent with hypothalamic hamartoma.

Follow-Up

In addition to the follow-up interview conducted by our neurologist and endocrinologist, long-term follow-up was maintained via telephone and email contacts. A self-reported questionnaire querying change in seizure frequency was used by patients and family members.

Results

Characteristics of the Patient Population

At the last clinic visit, the median age of the 13 male and 8 female patients was 19 years (range 11 months–41
Repeat surgery for hypothalamic hamartoma in epilepsy

All patients had refractory epilepsy associated with HH and at least 3 antiepileptic drugs had failed to resolve seizures. The median age of patients at epilepsy onset was 1.5 years (range birth–29 years); the mean lifetime duration of epilepsy prior to the first HH resection was 12.2 years (range 1–30 years). The initial seizure type in 19 patients (90.5%) was gelastic. Prior to HH resection, all patients had gelastic seizures. The other 2 common types of seizure were complex partial (in 17 cases [80.9%]) and generalized tonic-clonic (in 12 cases [57.1%]). In patients with a given seizure type, the mean seizure frequency of gelastic seizures was 30 per day, that of complex partial seizures was 26 per day, and that of generalized tonic-clonic seizures 2 per day. Three patients’ seizures were described as “rage attacks,” which constituted an emotional and anger outburst lasting for a few minutes. Two patients in this series had episodes of status gelasticus and had emergency resection; the details have been published elsewhere. Status gelasticus is defined as a prolonged cluster of gelastic seizures (that is, those lasting > 20–30 minutes, a duration similar to that for status epilepticus) but does not necessarily involve loss of awareness between seizures. Patients were taking a mean of 4 antiepileptic drugs prior to repeat surgery. Three patients had previously undergone implantation of a vagus nerve stimulator. One patient had previously undergone a temporal lobectomy and another had undergone biopsy of the HH.

Distribution of cases among different types of HHs per Delalande and Fohlen Classification is as follows: 2 with Type I Delalande lesions, 14 (66.6%) with Type II, 4 with Type III, and 1 with Type IV Delalande lesion. The median volume of the 21 HHs at the time of the initial operation was 1.27 cm$^3$ (range 0.77–15.6 cm$^3$).

Seventeen patients (81%) had mental retardation (based on full-scale IQ or estimated development quotient < 70). Age-appropriate Wechsler Scales (including the Wechsler Adult Intelligence Scale, 3rd edition, and the Wechsler Intelligence Scale for Children, 3rd or 4th edition) were used in neuropsychological testing. Behavioral problems, including rage attacks, were noted in 14 patients (66.7%). Three patients (14.3%) had a history of central precocious puberty. Alterations in electroencephalography ranged from focal to multifocal sharp waves, and bilateral spikes and spike-wave discharges with a variable degree of synchronicity.

Types of Surgical Intervention

In the last 7 years, 21 (13%) of 157 patients underwent reoperation after the first epilepsy surgery. The initial surgical approach in the 21 patients included the following: endoscopic (8 patients [38%]), transcallosal (8 patients [38%]), orbitozygomatic (3 patients [14%]), and radiosurgery (2 patients [10%]) (Fig. 1). Of the 8 patients with initial endoscopic resection repeat procedures, 4 (50%) underwent radiosurgery, 2 (25%) underwent orbitozygomatic surgery, 1 (12.5%) underwent repeat endoscopy, and 1 (12.5%) underwent a transcallosal approach. Reoperation in patients who had already undergone the transcallosal approach included the following procedures: endoscopy (2 patients [25%]); radiosurgery (1 patient [12%]); orbitozygomatic (2 patients [25%]), and repeat transcallosal resection (3 patients [38%]). All 3 patients in whom the initial approach was orbitozygomatic underwent further endoscopic resection. Two patients who had received radiosurgery also underwent endoscopic resection.

Seizure Outcome

At last follow-up after the last surgery (median 9 months, range 6–21 months), 2 patients were seizure free. Seizures were reduced more than 90% in 4 patients (19%) and by 50%–90% in 10 patients (48%). In the 5 patients (24%) who reported no change in seizure frequency, 2 had behavioral improvement with resolution of rage attacks. None of the patients reported worsening of seizures; no patients suffered worsening behavioral issues (for instance, increased rage attacks or disruptive violent behavior). Parental perception of their child’s overall postoperative behavioral functioning compared with the preoperative baseline functioning suggested improvement in 18 (85%) of the patients. The results are further detailed in Tables 1 and 2.

Complications

The mortality rate in this multiple-surgery series was 0%. The most common adverse event was transient diminished short-term memory, which was noted in 13 patients (62%) after the first surgery. Typically this deficit would last less than 2 weeks, with ongoing improvement to baseline functioning. In 3 patients, although gradual improvement from the immediate postoperative short-term memory deficit was noted, we observed residual difficulties in short-term recall compared with baseline. New postoperative complications after reoperation included: transient hemiparesis (1 case) without MR imaging infarcts, thalamic
stroke (asymptomatic in 3 cases and symptomatic 1 case),
hyperphagia (5 cases), and panhypopituitarism (2 cases).
Four patients had hypernatremia following the second sur-
gery, 1 of whom required short-term desmopressin acetate
therapy. In one patient, a headache developed due to com-
municating hydrocephalus, which resolved after placement
of a lumboperitoneal shunt.

Discussion
The results from this cohort indicated that repeat sur-
gery in patients with HH-associated refractory epilepsy
resulted in improvement in seizure burden. In individual
patients, this was accompanied by neuropsychological
and behavioral improvement. The results also demon-
strate the relative safety of repeat surgery in HH patients
with refractory epilepsy. Prior to this study there was a
paucity of evidence in the literature on outcome of re-
peat surgeries in HH for refractory epilepsy. This study
demonstrates the importance of reevaluating patients
with persistent seizures after first surgery and encourag-
ing further resection when residual tumor is present and
patients are neurologically deteriorating or are debilitated
by the seizures and associated symptoms. The surgical
approach to the lesion should be tailored to each case. No
single approach is best for every patient.

Historically, epilepsy surgery in general has been di-
rected toward the total removal of the seizure focus. Be-
cause electrophysiological studies have demonstrated the
intrinsic epileptogenicity of HHs, based on our previous
experiences and the experiences at other centers, surgical
(transcallosal/endoscopic/orbitozygomatic)1,10,11 or radio-
surgical14 intervention offers the best chance for seizure
resolution. Resection or Gamma Knife irradiation of the
HH tissue often reduces the seizure frequency and inten-
sity. However a minimum of several months must elapse

TABLE 1: Summary of the patients and their surgical outcomes*

<table>
<thead>
<tr>
<th>Patient Data</th>
<th>Seizure Type &amp; No. Affected (%)</th>
<th>Outcome After Repeat Op (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age at Seizure Onset (yrs)</td>
<td>Median Age at 1st Op (yrs)</td>
<td>Gelastic</td>
</tr>
<tr>
<td>Total</td>
<td>Males</td>
<td>1.5</td>
</tr>
</tbody>
</table>

* Unless otherwise specified, values reflect the number of patients. Abbreviation: GTC = generalized tonic-clonic seizure.

TABLE 2: Patient information and seizure outcome following surgeries*

<table>
<thead>
<tr>
<th>Case No.,</th>
<th>Age at Seizure Onset (yrs)</th>
<th>Age at 1st Op (yrs)</th>
<th>Delalande &amp; Fohlen Class</th>
<th>1st Op</th>
<th>% Resection After 1st Op</th>
<th>% Disconnection After 1st Op</th>
<th>Subsequent Ops</th>
<th>Subsequent Ops</th>
<th>Seizure Outcome at Last FU</th>
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</thead>
<tbody>
<tr>
<td>1, F</td>
<td>2</td>
<td>27</td>
<td>III</td>
<td>endoscopy</td>
<td>100</td>
<td>100</td>
<td>OZ</td>
<td>seizure free</td>
<td></td>
</tr>
<tr>
<td>2, M</td>
<td>0.6</td>
<td>1.2</td>
<td>III</td>
<td>TAIF</td>
<td>100</td>
<td>0</td>
<td>TAIF</td>
<td>seizure free</td>
<td></td>
</tr>
<tr>
<td>3, F</td>
<td>1.5</td>
<td>12</td>
<td>II</td>
<td>endoscopy</td>
<td>22</td>
<td>100</td>
<td>OZ</td>
<td>&gt;90% seizure reduction</td>
<td></td>
</tr>
<tr>
<td>4, F</td>
<td>6</td>
<td>30</td>
<td>II</td>
<td>radiosurgery</td>
<td>NA</td>
<td>NA</td>
<td>endoscopy</td>
<td>&gt;90% seizure reduction</td>
<td></td>
</tr>
<tr>
<td>5, M</td>
<td>2</td>
<td>5</td>
<td>II</td>
<td>OZ</td>
<td>100</td>
<td>100</td>
<td>endoscopy, OZ</td>
<td>&gt;90% seizure reduction</td>
<td></td>
</tr>
<tr>
<td>6, M</td>
<td>12</td>
<td>17</td>
<td>IV</td>
<td>TAIF</td>
<td>88</td>
<td>76</td>
<td>radiosurgery, OZ</td>
<td>&gt;90% seizure reduction</td>
<td></td>
</tr>
<tr>
<td>7, M</td>
<td>0.5</td>
<td>2</td>
<td>II</td>
<td>endoscopy</td>
<td>88</td>
<td>84</td>
<td>endoscopy</td>
<td>50–90% seizure reduction</td>
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</tr>
<tr>
<td>8, F</td>
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<td>I</td>
<td>TAIF</td>
<td>22</td>
<td>100</td>
<td>TAIF</td>
<td>50–90% seizure reduction</td>
<td></td>
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<td>9, M</td>
<td>3</td>
<td>15</td>
<td>II</td>
<td>radiosurgery</td>
<td>NA</td>
<td>NA</td>
<td>endoscopy</td>
<td>50–90% seizure reduction</td>
<td></td>
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<td>10, F</td>
<td>17</td>
<td>17</td>
<td>II</td>
<td>endoscopy</td>
<td>95</td>
<td>69</td>
<td>radiosurgery</td>
<td>50–90% seizure reduction</td>
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<td>11, M</td>
<td>2</td>
<td>11</td>
<td>II</td>
<td>TAIF</td>
<td>75</td>
<td>40</td>
<td>TAIF</td>
<td>50–90% seizure reduction</td>
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</tr>
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<td>13</td>
<td>II</td>
<td>endoscopy</td>
<td>90</td>
<td>83</td>
<td>radiosurgery</td>
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</tr>
<tr>
<td>13, M</td>
<td>0.4</td>
<td>1.8</td>
<td>II</td>
<td>TAIF</td>
<td>100</td>
<td>100</td>
<td>OZ</td>
<td>50–90% seizure reduction</td>
<td></td>
</tr>
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<td>14, M</td>
<td>1.5</td>
<td>7</td>
<td>III</td>
<td>endoscopy</td>
<td>51</td>
<td>0</td>
<td>TAIF</td>
<td>50–90% seizure reduction</td>
<td></td>
</tr>
<tr>
<td>15, M</td>
<td>0.4</td>
<td>4</td>
<td>II</td>
<td>TAIF</td>
<td>75</td>
<td>90</td>
<td>OZ</td>
<td>50–90% seizure reduction</td>
<td></td>
</tr>
<tr>
<td>16, M</td>
<td>29</td>
<td>30</td>
<td>II</td>
<td>endoscopy</td>
<td>80</td>
<td>0</td>
<td>radiosurgery</td>
<td>50–90% seizure reduction</td>
<td></td>
</tr>
<tr>
<td>17, M</td>
<td>1</td>
<td>14</td>
<td>II</td>
<td>TAIF</td>
<td>69</td>
<td>64</td>
<td>endoscopy</td>
<td>no change in seizure frequency</td>
<td></td>
</tr>
<tr>
<td>18, M</td>
<td>0.4</td>
<td>2</td>
<td>I</td>
<td>OZ</td>
<td>100</td>
<td>100</td>
<td>endoscopy</td>
<td>no change in seizure frequency</td>
<td></td>
</tr>
<tr>
<td>19, F</td>
<td>3</td>
<td>27</td>
<td>II</td>
<td>TAIF</td>
<td>58</td>
<td>67</td>
<td>endoscopy</td>
<td>no change in seizure frequency</td>
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<td>18</td>
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<td>radiosurgery</td>
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<td></td>
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<td>21, F</td>
<td>0.5</td>
<td>2</td>
<td>III</td>
<td>OZ</td>
<td>74</td>
<td>91</td>
<td>endoscopy</td>
<td>no change in seizure frequency</td>
<td></td>
</tr>
</tbody>
</table>

* FU = follow-up; NA = not applicable; OZ = orbitozygomatic approach.
before significant improvements can be seen with radiosurgery, a feature considered disadvantageous compared with surgery. Multiple surgical approaches and techniques have been used to resect HHs, and of these 2 have emerged as the most popular: the TAIF approach and the endoscopic resection. The seizure-free outcomes following both of these surgeries are comparable. The choice of surgical approach is based on the specific anatomical features of each HH lesion. The surgical approach to the lesion should be determined individually for each case to minimize morbidity. No single approach is best for every patient. As described previously, our center has adopted and published outcomes following endoscopic and transcallosal approaches as well as following orbitozygomatic and radiosurgical approaches. Numerous patients in this study underwent both open surgery and endoscopic procedures. Debate exists as to whether complete resection or anatomical disconnection is necessary to cure patients, and the results from the literature have not settled this debate. Complete disconnection and resection were achieved in 5 patients. In 2 of these patients greater than 90% decrease in seizure burden was achieved, in another 2 seizure frequency decreased by 50%–90%, and in 1 no change in seizure frequency occurred. However, all of these patients had a subjective improvement in behavior.

The most common adverse effect was transient diminished short-term memory, which was noted in 13 patients (62%). This is comparable to prior published studies suggesting short-term memory loss in 50%–60% of patients. Endocrine abnormalities were reported in other studies including asymptomatic hypernatremia with polyuria, overt diabetes insipidus requiring vasopressin therapy, hypothalamic obesity, or panhypopituitarism. Four of our patient had postoperative hypernatremia following the second surgery; one of them required desmopressin acetate therapy for a short time.

We are encouraged by the parental perception of overall cognitive and behavioral changes after surgery. The potential for improvement in neurobehavioral functioning after repeat surgery for HH resection requires additional study before drawing firm conclusions. In light of recent developments in surgical technique, our bias is for earlier surgery in patients with hypothalamic hamartomas associated with epilepsy. Earlier surgical intervention in those symptomatic cases that present during infancy may avoid the deterioration of seizures and possibly the decline in cognitive and psychiatric functioning that is seen in many of these patients. With experience, we are resecting larger volumes using an endoscopic technique, but in general it is difficult to achieve total resection or disconnection when a mass is greater than 1.5 mm in largest diameter. In general each individual patient should be evaluated in a multidisciplinary meeting involving neurosurgeon, neuroradiologist, and neurologist to decide on the safest approach for resection of the HH.

Conclusions

Repeat surgery of HHs associated with epilepsy has been demonstrated to be an effective strategy resulting in decrease in seizure burden in more than half of the patients. In addition, many patients have experienced subjective improvements in behavior and cognitive functioning following surgery. The results also demonstrate the relative safety of repeat surgery in HHs with refractory epilepsy. Prior to this study there has been a paucity of reports in the literature on the outcome of repeat surgeries in HH patients with refractory epilepsy. This study demonstrates the importance of reevaluating patients with persistent seizures after a first surgery and encourages further resection when residual hamartoma is present and patients are debilitated by the seizures and associated symptoms.

Acknowledgments

The authors thank neurology residents Drs. Kristen, Donlon, and Rastogi for their help in data collection. They also thank Ms. Varland, our Hypothalamic Hamartoma Program Coordinator. They acknowledge the perseverance of their HH patients and their families.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Pati, Ng. Acquisition of data: Pati. Analysis and interpretation of data: Pati. Drafting the article: Pati, Abla, Ng. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it for submission: Abla, Ng. Study supervision: Rekate, Ng.

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