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Unilateral Symptomatic Hypertrophic Olivary Degeneration Secondary to Midline Brainstem Cavernous Angioma: A Case Report and Review of the Literature

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Title: Unilateral Symptomatic Hypertrophic Olivary Degeneration Secondary to Midline Brainstem Cavernous Angioma: A Case Report and Review of the Literature

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Key words: cavernous angioma, cavernoma, midbrain, pons, hypertrophic olivary degeneration, Guillain and Mollaret triangle, dento-rubro-olivary pathway, Holmes tremor.

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Abbreviations: hypertrophic olivary degeneration (HOD), inferior cerebellar peduncle (ICP), middle cerebellar peduncle (MCP), superior cerebellar peduncle (SCP), inferior olivary nucleus (ION), central tegmental tract (CTT), Guillain and Mollaret triangle (GMT), computed tomography (CT), magnetic resonance imaging (MRI), Gradient Echo (GRE), Stereotactic Radiosurgery (SRS), Cerebral cavernous malformation (CCM)

Abstract

Background: Hypertrophic olivary degeneration (HOD) is a rare phenomenon in the dento-rubro-olivary pathway due to lesion or disruption of the fibers of the Guillain-Mollaret Triangle. Hemorrhage of pontine and midbrain cavernous angiomas rarely can lead to hypertrophic olivary degeneration (HOD) portending neurological deterioration and possible concomitant life-threatening complications; for this reason, it may define a poignant consideration in planning intervention.

Case Description: 57-year-old female with known midbrain-pontine cavernous angioma. For several years, the lesion was stable, as demonstrated by imaging follow-up until 10 months prior to presentation with falls, dysarthria and headache. Imaging demonstrated some decrease in size as well as blood product around the cavernous angioma suggesting interim period hemorrhage and interval development of unilateral hypertrophic olivary degeneration.

Conclusions: Herein, the literature regarding imaging recommendations for stable cavernous angioma in the midbrain-pontine junction is reviewed. The implication of hypertrophic olivary degeneration for patient outcome is discussed and a comment is made on how the development of HOD may impact management of the cavernous angioma.
Introduction:

Hypertrophic olivary degeneration is a rare entity caused by a lesion in the dento-rubro-olivary tracts or Guillain-Mollaret triangle. It has been noted as a result of resection of midbrain-pontine cavernous angiomas and suggested in case reports as a consequence of interval bleed in midbrain-pontine cavernous angiomas. Herein we present a case of an adult with multiple known stable cavernous angiomas, one located in the midbrain with extension into the pons. The patient presented in the interval between imaging follow up with new onset falls, dysarthria, and headache and was found to have interval hemorrhage of the midbrain-pontine cavernous angioma with development of hypertrophic olivary degeneration. Our purpose is to describe the case, describe the pathophysiology of hypertrophic olivary degeneration, review the literature on the development of hypertrophic olivary degeneration in the setting of midbrain-pontine cavernous angiomas, and comment on the recommendations for follow up on these lesions using development of hypertrophic olivary degeneration as a measure of progression of these entities.

Case Report

Clinical History

A 57-year-old female with past medical history significant for multiple known cavernous angiomas in the frontal and parietal lobes and midbrain as well as hypertension, chronic kidney disease, and ruptured and clipped intracranial aneurysm, presented to emergency department with worsening gait, imbalance, multiple falls, headache, blurred vision and dysarthria. The patient also previously had an occipital approach ventriculoperitoneal shunt placed for obstructive hydrocephalus.
**Imaging Findings**

Initial MRI study 10 months prior to presentation demonstrated a large “popcorn” lesion with central T1/T2 hyperintensity, peripheral rim of T2 hypointensity, and diffuse susceptibility signal in the midbrain and upper pons. Vasogenic edema extending into the left cerebral peduncle was noted. The medulla appeared preserved on the original study. This was consistent with midbrain-pontine cavernous angioma as seen in Figure 1 A-D. Initial CT scan of the head at presentation showed the previously identified cavernous angiomas with no significant change as compared to prior studies. MRI of the brain following admission shown in figure 2 A-C showed a well-defined lobulated lesion in the left parasagittal midbrain and superior pons with characteristic “popcorn” or “mulberry” appearance. The lesion demonstrated heterogeneous appearance with T1- and T2- hyperintensity centrally and a thin margin of T2 hypointensity peripherally and diffuse susceptibility signal on Gradient Echo (GRE) sequence, similar to the prior study as shown in figure 2 A-D. The lesion appeared to have decreased in size from 17 x 15 x 22 mm 10 months prior, to 11 x 10 x 13 mm at present with a focus of GRE susceptibility extending caudally from the midbrain-pontine junction, consistent with blood product from interval hemorrhage. There was interval development of a 7mm round T2 hyperintense focus within a slightly enlarged left lateral superior medulla, consistent with hypertrophic olivary degeneration. The two additional cavernous angiomas—in the frontal and parietal lobes—were noted to be stable since prior studies (Figure 2B).
Discussion

Pathogenesis

Hypertrophic olivary degeneration (HOD) is a rare phenomenon in the dento-rubro-olivary pathway first described by Oppenheim in 1887. It occurs as a consequence of a lesion or disruption in the dento-rubro-olivary pathway which was defined by Guillain and Mollaret. Thus, it is referred to as the Guillain-Mollaret triangle as depicted in figure 3. The triangle is formed by the parvocellular red nucleus, inferior olivary nucleus (ION), and contralateral dentate nucleus. The parvocellular red nucleus receives input from the contralateral dentate nucleus via efferent dentatorubral fibers which project through the superior cerebellar peduncle (SCP), decussating via the brachium conjunctivum within the midbrain, and the ipsilateral cortex via corticorubral fibers. The parvocellular red nucleus then communicates with efferent fibers in the ipsilateral ION via descending rubroolivary fibers within the central tegmental tract (CTT). The ION then completes the dento-rubro-olivary pathway by projecting via efferent olivodentate fibers through the inferior cerebellar peduncle to the contralateral dentate nucleus within the cerebellum. HOD is unique in that trans-neuronal degeneration leads to hypertrophy. Presumably disinhibition to ION leads to de-afferentiation of ION and resultant hypertrophy as neurons within ION become overexcited. Only lesions including and between the dentate nucleus and descending rubro-olivary fibers within the CTT can cause HOD. Lesion at the level of ION or to the olivodentate fibers leads to contralateral cerebellar atrophy. Pathologically, vacuolation in the ION and enlargement of the cell bodies represent the hypertrophic appearance of HOD. Lesions in the CTT or red nucleus lead to ipsilateral HOD, whereas lesion involving the dentate nucleus or the SCP lead to a contralateral HOD and lesions in the brachium conjunctivum or involving structures on both side (SCP and CTT) result in
bilateral HOD which is more common in midline lesions\textsuperscript{11, 12}. The midbrain/pontine lesion in this case was in the left superior cerebral peduncle extending to the midline of the pons and displacing midline midbrain structures. Thus, unilateral HOD was found on the left. Twenty-three percent of unilateral HOD cases are symptomatic while 39% of bilateral HOD cases are symptomatic\textsuperscript{13}. The rest are incidental radiological findings\textsuperscript{14}. However, this is not specific to their presentation in cavernous angiomas in the midbrain and pons.

**Presentation**

The classic presentation of HOD includes palatal tremor, cerebellar symptoms—including ataxia, slurred speech, and dysmetria—ocular symptoms such as nystagmus, ophthalmoplegia and ocular myoclonus with resultant ocular oscillopsia, or involuntary movements such as dentatorubral tremor, referred to as “Holmes tremor,” and myoclonus\textsuperscript{15-18}. There is a loss of inhibitory control by damage to the dentate nucleus and to the rubroolivary pathway with consequent hyperactivity of the olivary neurons leading to palatal myoclonus—presenting before the peak of ION hypertrophy and persisting after the hypertrophic stage due to disruptions in natural rhythmicity—and involuntary movements\textsuperscript{19}. The symptoms could persist even after the resolution of hypertrophy due to the lack of feedback mechanisms and disturbance of natural rhythmicity\textsuperscript{6}. Patients with HOD may develop a dentatorubral tremor which is also referred as a Holmes tremor of the upper limbs\textsuperscript{20}. In a cohort study recently published, ataxia was the most frequent symptom and was associated with both types of HOD\textsuperscript{14}.

The hallmark finding of HOD is palatal myoclonus, with 1-3 Hz frequency of rhythmic involuntary movements of the oropharynx most often involving the levator veli palatini muscle, which can produce a self-audible clicking sensation, rarely involving the larynx, tongue and
muscles of the face\textsuperscript{21} It takes on average one year from the time of the lesion to develop palatal myoclonus\textsuperscript{22}. The patient herein described presented with a combination of worsening gait, imbalance, headache, vision deterioration, dysarthria and interval change in size of the cavernous angioma and appearance of HOD within 10 month follow up. This patient's constellation of maladies is consistent with Nothnagel syndrome\textsuperscript{23} a unilateral or bilateral oculomotor nerve paralysis in the setting of an ipsilateral cerebellar ataxia. Most often associated with lesions occupying the midbrain affecting the tectum (specifically the quadrigeminal plate).

\textit{Causes}

HOD has been reported in the literature due to the following: prior surgery in the posterior fossa, inflammation with or without pursuant demyelination, abscesses, Wilson's disease, gluten sensitivity, metronidazole intoxication, and progressive multifocal leukencephalitis\textsuperscript{14}. The most common causes of injury in the GMT were found to be intraparenchymal hemorrhage, arteriovenous malformation, and infarction\textsuperscript{20}. Resection of cavernous angioma was the most common cause of HOD\textsuperscript{1, 20}.

Despite the presence of the midbrain-pontine junction cavernous angioma in our patient on previous imaging, HOD was not present and the patient was asymptomatic. Progressive neurological deterioration followed apparent interval bleed of the cavernous angioma evidenced by reduced size of the cavernous angioma, surrounding GRE sensitive blood product, and 7mm round T2 hyperintense focus within a slightly enlarged left lateral superior medulla consistent with HOD.

Review of the literature found HOD following surgical resection of low-grade astrocytoma attached to floor of fourth ventricle, surgical resection of posterior fossa epidermoid cyst, and
posterior inferior cerebellar infarct as a complication of microvascular decompression for trigeminal neuralgia. HOD has been reported in the literature following resection of midbrain and pontine cavernous angiomas, a more common presentation. Previous cases have previously described hemorrhage of pontine cavernous angioma with pursuant HOD—a far less commonly reported presentation. Such cases developed MRI apparent HOD within three- and four- months following the causative bleed.

Pathologic Description and Correlation with Clinical Course
Pathologic changes have been divided into six distinct stages which roughly correlate to certain radiologic findings in HOD which proceed chronologically from the time of central tegmental tract (CTT) interruption. These respective timelines are summarized in table 1. Interruption of neuronal structures involving the dentate nucleus to the rubroolivary pathway can lead to ION hypertrophy (ipsilateral and contralateral depending on site of the lesion). Hypertrophy is the initial result exclusively of neuronal soma and axon enlargement characterized by developing abnormal soma-somatic gap junctions which is then eclipsed by astrogliosis that persists even after neuronal degeneration. Studies have demonstrated greater glucose metabolism of the ION in HOD patients with palatal myoclonus (via PET studies). This corresponds pathologically to mitochondrial proliferation within glia; the result of greater metabolic demands from overexcited neurons. Several genes have been linked to HOD such as POLG which encodes a mitochondrial DNA polymerase, SURF1, TTC19, and AIFM1, supporting the hypothesis above.
Among other considerations, loss of medullary reticular formation, itself causing respiratory ataxia and profound hypotension, and nucleus ambiguous, governing motor control to branchial arch musculature including intrinsic muscles of the larynx, is sufficient for generating loss of automatic respiration and possible collapse of laryngeal musculature\textsuperscript{35}. Additionally, palatal tremor itself has been associated with respiratory difficulty\textsuperscript{36}. Both the nucleus ambiguous and medullary reticular formation are in close apposition to the inferior olive within the caudal medulla, with the nucleus ambiguous potentially receiving innervation from the CTT, and may be effected by ION hypertrophy\textsuperscript{37}.

\textit{Management Considerations}

With the aforementioned complications considered and that HOD 1) is a possible complication of resection, 2) portends neurologic deterioration, and that 3) 77\% of unilateral HOD are asymptomatic at presentation\textsuperscript{14}, HOD in the setting of midbrain-pontine cavernous angioma hemorrhage may represent an informative finding to guide closer imaging follow up and possible intervention for midbrain-pontine cavernous angiomas. This affords an opportunity for intervention prior to irreversible neurologic deterioration outlined by the proposed algorithm based on review of literature supported by this case presentation show in Figure 4. Of course, larger review of cases is required to make a definitive statement.

The approach to management of brainstem cavernous angiomas is historically complex and considers familiarity and training in surgical approach and the associated risks, benefits, options, and possible outcomes\textsuperscript{38, 39}. The options for treatment include observation and follow up, stereotactic radiosurgery to decrease rate of recurrent hemorrhage following a 2-year latency
period in which risk increases, and microsurgical resection, which has a high rate of neurologic complications. Literature review reveals some variation in these rates, but the risk can be summarized as follows. Microsurgical resection carries a 0.4-8.8% risk of recurrent hemorrhage and a 10.8-36% risk of permanent neurologic deficit depending on the study\textsuperscript{38, 39}. The risk of recurrent hemorrhage with stereotactic radiosurgery in the 2-year latency period is reported as 7.06-14%, which declines to 0.6-2.03% thereafter, again depending on the study\textsuperscript{38, 27}.

Stereotactic radiosurgery (SRS) carries with it a 7.3% risk of permanent neurologic deficits in one study and a 22.2% risk in a larger study\textsuperscript{38, 39}. In addition, SRS carries the risk of radiation induced adverse effects ranging from 4.1-18.4% depending on the study\textsuperscript{38, 39}.

\textit{Suggested Algorithm}

The above considerations when viewed with the given severity of symptomatology and one year average time to development of symptomatic HOD and progressive neurologic deterioration led us to the algorithm proposed herein as shown in figure 4. Classically, cavernous angiomas having hemorrhaged once in non-eloquent cortex have been considered for resection while those in eloquent cortex have been observed for recurrent hemorrhage\textsuperscript{40}. This is due to the weight of the risk of neurologic compromise with microsurgical resection or SRS. Cavernous angiomas presenting with classical severe symptoms including intractable seizures, or other neurologic deterioration have and continue to warrant intervention.

The management of the severely symptomatic brainstem cavernous angioma with impending or current respiratory compromise, and other neurologic deficits portending life-threatening deterioration especially coma, cardiac instability, loss of automatic respiratory control remains
microsurgical resection\textsuperscript{35, 41}. Patients with previous hemorrhage are more likely to re-hemorrhage at a rate of \textsuperscript{30\% person/year} and \textsuperscript{21\% lesion/year} and patients with repeated hemorrhages incur more severe neurological deficits\textsuperscript{44}.

Stereotactic radiosurgery has represented a critical and continually evolving component in the management of cavernous angiomas. The body of evidence supports the use of SRS in management of cavernous angiomas with interval hemorrhage to prevent re-bleeding\textsuperscript{45}. Lunsford et al 2010 and Nagy et al 2010 have demonstrated a decrease in re-bleeding from 32.5\% and 30.5\% to 1\% and 2.4\% respectively after 2-year follow-up, defining the latency period\textsuperscript{46, 47}. They also note that no imaging modality demonstrates radiographic evidence of treatment. The authors acknowledge that interval hemorrhage can be substantial; furthermore, infratentorial cavernous angiomas that grow or bleed to cause mass effect typically present with neurological deficits and thus with a more severe symptomatology\textsuperscript{48}. The authors suggest that SRS be considered in cavernous angiomas with interval bleeding.

Based on the above evidence, the proposed algorithm herein suggests interval MRI follow-up of asymptomatic and mildly symptomatic cavernous angioma should occur every 6 months. This is in-an-effort to find asymptomatic HOD as a sign of continued degeneration of the Guillain-Mollerait triangle by presence and hemorrhage of cavernous angiomas. HOD is progressively neurologically deteriorating and does not recover function upon removal of the insulting lesion. Therefore, it would stand to reason that intervention should be considered when HOD is radiographically present and asymptomatic in 77\% of unilateral case\textsuperscript{14}; such as the one presented herein. The development of HOD is a possible complication of resection of cavernous angiomas
and causes respiratory compromise and neurologic deterioration, which may be a component of this seen in patients presenting with midbrain cavernous angiomas.

Recent consensus by The Angioma Alliance\textsuperscript{49} in reviewing 1,270 publications (between January 1, 1983 and September 31, 2014) arrived at 23 management recommendations. A variety of topics were discussed including, among others: bleeding risk per cerebral cavernous malformation (CCM), impact of interventions, frequency of routine MRI follow-up, and indications for surgical intervention and how to manage particular co-morbid symptoms or concomitant CCMs, and summary of knowledge gaps and controversies in management.

Consensus recommendations relevant to surgical resection of brainstem CCMs, was class III level B with the provision that surgical resection is reasonable for second symptomatic bleeds (class IIb, level B) and indicated for disabling bleeds (class IIb, level C).

Given the paucity of cases of HOD relevant to midbrain and brainstem CCMs considerations in management of this entity could not be addressed; leaving opportunity to examine previous literature, acknowledging the spectrum of symptomatology from asymptomatic to complications portending life-threatening prognosis in cases relevant to HOD, and contemplating a management algorithm as set forth (see figure 4).

**Conclusions**

This case demonstrates neurologic deterioration following interval bleed of the known midbrain-pontine junction cavernous angioma with interval development of HOD. Appearance of HOD has been reported in the literature following resection of midbrain-pontine cavernous angiomas.
HOD has also been seen in several reports of midbrain-pontine cavernous angiomas prior to resection at the time of hemorrhage. Thus, this may represent a compelling benchmark for intervention given that it 1) is a possible complication of resection, 2) contributes to neurologic deterioration, and that 3) 77% of unilateral HOD are asymptomatic at presentation\textsuperscript{14}. This may warrant retrospective study to determine if this indeed affords an opportunity for intervention prior to irreversible neurologic deterioration outlined by our proposed algorithm based on review of the literature and this case presentation.
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Conflicts of interest: none
References:


Figure Legends

**Figure 1 A-D:** Initial brain MRI 10 months prior to presentation. A and C— Axial T2WI, B—Sagittal T1WI. D--- Axial GRE. A large “popcorn” lesion with central T1/T2 hyperintensity, peripheral rim of T2 hypointensity and diffuse susceptibility signal in the midbrain and upper pons. Vasogenic edema extending into the left cerebral peduncle is noted. The medulla appears preserved. Findings compatible with cavernous angioma.

**Figure 2 A-C:** Follow up brain MRI at presentation. A and C— Axial T2WI, B—Sagittal T1WI. Involution with decreased blood products and vasogenic edema within the midbrain-pontine cavernous angioma. Interval development of mild enlargement and T2 hyperintensity in the left aspect of the medulla (the pyramid and olive), compatible with hypertrophic olivary degeneration.

**Figure 3.** The Guillain-Mollaret Triangle formed by the parvo cellular red nucleus, inferior olivary nucleus (ION), and contralateral dentate nucleus. Fibers are represented by blue arrows originating at circles in the nuclei which are shown as orange circles. DR is dentatorubral fibers; CTT is central tegmental tract; OD is olivodental fibers; RO is rubro-olivary fibers; BC is brachium conjunctivum; ICP is inferior cerebellar peduncle; SCP is superior cerebellar peduncle.

**Figure 4.** Proposed algorithm for management and follow-up of midbrain-pontine cavernous angiomas. Finding of cavernous angioma on MRI of the brain is first considered with symptomatology. Severe symptomatology warrants microsurgical resection on diagnosis as in prior algorithms. Otherwise, the imaging recommendation of 6 month follow up here is guided
by the time to develop asymptomatic HOD in the literature. In the absence of HOD on follow up imaging, development of respiratory compromise and severe symptoms guides management. We suggest that with asymptomatic or symptomatic HOD microsurgical resection should be considered because of the higher rate of re-bleed in the latency period with stereotactic radiosurgery which would lead to progression of HOD, a potential consequence of resection.

Table 1: Pathologic and Radiologic Progression of HOD. This table summarizes the radiologic timelines observed in the literature with pathologic findings and pathogenesis. There are six pathologic stages that progress radiologically from T2 hyperintensity of the olivary amiculum to hypertrophy of the olive and finally atrophy of the olive. Note, the olivary amiculum is the capsule of white matter composing the periphery of the inferior olive.
### Table 1: Pathologic and Radiologic Progression of HOD

<table>
<thead>
<tr>
<th>Pathologic Timeline and Pathogenesis Post CTT- Interruption</th>
<th>Radiologic Timeline</th>
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<tbody>
<tr>
<td><strong>Stage I (24-hours): No changes</strong></td>
<td>After 1-month: T2-hyperintensity is notable (may persist indefinitely)</td>
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<td><strong>Stage II (2-7-days): Olivary amiculum degeneration</strong></td>
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<tr>
<td><strong>Stage III (at 3-weeks): Olivary Hypertrophy</strong></td>
<td>After 6-months: Significant focal enlargement of ION within medulla</td>
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<td>Neuronal hypertrophy without astrogliosis</td>
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<tr>
<td><strong>Stage IV (at 8.5 months): Culminating olivary enlargement</strong></td>
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<tr>
<td>Neuronal hypertrophy and astrogliosis</td>
<td></td>
</tr>
<tr>
<td><strong>Stage V (at 9.5 months or later) Olivary pseudohypertrophy</strong></td>
<td>6-months – 3-4-years: Continued volume expansion</td>
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<tr>
<td>Neuronal dissolution with astrogliosis</td>
<td></td>
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<tr>
<td><strong>Stage VI (after 3-4-years) Olivary atrophy:</strong></td>
<td>After 3-4-years: Atrophy of ION</td>
</tr>
<tr>
<td>Total neuronal disappearance and prominent degeneration of olivary amiculum with olivary atrophy.</td>
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Management and Follow up of Midbrain/Pontine Cavernous Angioma

**Diagnosis by MRI of the brain**

- **(-) Symptomatology**
  - Incidental Discovery on MRI
- **(+\*) Severe Symptomatology**
  - Optimal 6 Month Follow Up by MRI
  - **(+\*) Mild Symptomatology**
    - Microsurgical Resection

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(-) Symptomatology

- **(-) Interval Hemorrhage**
  - (-) HOD
  - (-) Symptomatology
  - Continue MRI follow up 6 months intervals indefinitely Evaluate HOD

(+\*) Interval Hemorrhage

- (-) HOD
- (-) Respiratory Compromise
- (-) Severe Symptoms
  - Consider Stereotactic Radiosurgery to Decrease Re-bleed Rate
  - 6 Month MRI Follow up Through Latency Period

(+\*) Interval Hemorrhage

- (+) HOD
- (-) Respiratory Compromise
- (-) Severe Symptoms
  - Consider Microsurgical Resection to Prevent Progression of HOD and Development of Respiratory Compromise

(+\*) Interval Hemorrhage

- (+) HOD
- (+) Respiratory Compromise
- (+) Severe Symptoms
  - Microsurgical Resection
Highlights

- We describe a patient with a midbrain-pontine cavernous angioma presenting following 10 month interval hemorrhage with development of hypertrophic olivary degeneration (HOD)
- HOD is a rare entity that occurs as a consequence of lesions in the Guillain-Mollaret triangle and has been reported following both midbrain-pontine cavernous angioma resection and hemorrhage
- 77% of HOD are asymptomatic at presentation and thus this may afford an opportunity to consider intervention prior to further progression into respiratory compromise and neurologic deterioration as proposed in our algorithm