The Tadpole Pupil: Case Series With Review of the Literature and New Considerations.

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The Tadpole Pupil: Case Series with Review of the Literature and New Considerations

THOSE

préparée sous la direction de la Professeure Aki Kawasaki

et présentée à la Faculté de biologie et de médecine de l'Université de Lausanne pour l'obtention du grade de DOCTEUR EN MEDECINE

par

Morgane Udry

Médecin diplômée de la Confédération Suisse
Originaire de Vétroz et Conthey (Valais)

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Vu le rapport présenté par le jury d'examen, composé de

Directeur de thèse  Madame la Professeure Aki Kawasaki
Co-Directeur de thèse  Expert
Vice-Directeur de l’École doctorale  Monsieur le Professeur John Prior

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Madame Morgane Udry

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The Tadpole Pupil: Case Series with Review of the Literature and New Considerations

Lausanne, le 6 février 2020

pour Le Doyen
de la Faculté de Biologie et de Médecine

Monsieur le Professeur John Prior
Vice-Directeur de l’École doctorale
Résumé :

La pupille têtard (PT), tadpole pupil en anglais, est un phénomène rare créé par un spasme segmentaire du muscle dilatateur de la pupille. Ceci résulte en une déformation de la pupille, en une forme ressemblante à celle d’un têtard. Ce phénomène touche principalement des femmes jeunes en bonne santé, par épisodes d’une durée de 5 minutes ou moins d’apparition spontanée. La fréquence des épisodes varie d’un épisode tous les quelques mois à 10-50 épisodes par jour. Les épisodes semblent groupés en clusters de quelques jours à quelques semaines avec un intervalle variable et souvent long entre les clusters. Les épisodes sont généralement unilatéraux et n’importe quel segment de l’iris peut être affecté, changeant même parfois d’un épisode à l’autre chez la même personne. Entre les épisodes, les pupilles sont rondes et réagissent normalement à la lumière. Dans 46% des cas, on retrouve un syndrome de Horner comme condition associée.

Ce phénomène a été décrit pour la première fois en 1912, avant d’être caractérisé dans un papier seminal de Thompson en 1983. Dans ce travail, nous avons passé en revue la littérature et trouvé 43 cas publiés jusqu’à aujourd’hui. Nous avons également rapporté 4 nouveaux cas. La pathophysiologie de la PT n’est pas encore éclaircie de nos jours. Quelques hypothèses ont été émises mais aucune ne parvient à en expliquer toutes les caractéristiques. Dans ce travail, nous avons compilé tous les cas publiés avec l’objectif de réexaminer le profil clinique de la PT et de considérer les différents mécanismes possibles pour en déterminer l’étiologie et proposer un éventuel traitement. Nous avons discuté les mécanismes proposés par différents auteurs et proposé une nouvelle hypothèse.

Etant donné l’association fréquente avec le syndrome de Horner, une hypersensibilité de dénervation a été considérée comme étant un possible mécanisme de PT. Quelques cas dans la littérature soutiennent cette hypothèse mais ce mécanisme n’explique pas les cas de PT apparaissant chez des patients sans déficit sympathique sous-jacent ou le fait que le segment affecté ne soit pas toujours stéréotypé.

Le muscle dilatateur de la pupille est un muscle lisse de type multi-unit, permettant l’activation directe et indépendante de chaque cellule musculaire, au contraire par exemple des muscles lisses intestinaux qui agissent en syncytiun. En plus de réagir aux stimuli neurologiques, les muscles lisses peuvent répondre directement à la stimulation hormonale. Il a été montré que les estrogènes influencent la contractilité des muscles lisses et la présence de récepteurs aux hormones sexuelles a été démontrée dans l’iris de lapins et d’humains. Ainsi, notre hypothèse est qu’un vaisseau transitoirement perméable de manière focale pourrait diffuser les hormones circulantes localement au dilatateur de l’iris, provoquant une PT. Cette hypothèse pourrait expliquer en partie la propension d’apparition de la PT chez des femmes non-ménopausées et le changement de segment affecté d’épisode en épisode. Cependant, elle explique moins bien l’apparition du phénomène chez des hommes ou des enfants, de même que le timing très bref des épisodes.

En conclusion, la PT semble avoir plusieurs mécanismes physiopathologiques différents et pourrait regrouper plusieurs phénomènes sous un seul nom. La PT semble être une condition bégnine, ne cachant pas de pathologie grave sous-jacente. Elle peut cependant être gênante à expérimenter, et nous proposons dans le travail d’éventuels moyens de traitement.
The Tadpole Pupil: Case Series With Review of the Literature and New Considerations

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Tadpole pupil is a rare phenomenon in which segmental spasm of the iris dilator muscle results in a tadpole-shaped pupil. The pupillary distortion is usually unilateral, lasts several minutes, and can recur in clusters. Any segment of the iris can be affected; thus, for some patients, a different-shaped tadpole pupil is noticed from episode to episode. Tadpole pupil most commonly appears spontaneously in young women. Tadpole pupil is not associated with any systemic disorders, but an ipsilateral Horner syndrome is noted in 46% of patients. In this article, we have reviewed the existing literature of tadpole pupil, compiling all the published cases in a table and reporting four additional cases to re-examine the clinical profile of this disorder and to consider the different purported mechanisms as means to understand its possible etiology and treatment. The common denominator in the pathophysiology of tadpole pupil is a focal excessive contraction (segmental spasm) of the iris dilator muscle. Based on various proposed pathophysiologic mechanism of tadpole pupil, we can consider potential forms of treatment.

Keywords: pupil, tadpole pupil, pupillary distortion, iris dilator muscle, mydriasis, Horner syndrome

INTRODUCTION

The term tadpole pupil refers to episodic, focal distortion of the pupillary shape. In 1983, Thompson et al. (1) presented the largest series of 26 patients and described the characteristic profile of tadpole pupil. It most commonly concerns young otherwise healthy women, arises spontaneously in one eye and disappears in 5 min or less. The tadpole pupil can be accompanied by a blurring of vision or an unusual sensation in the affected eye or on the ipsilateral side of the face. This segmental spasm of the iris dilator can involve any segment of the iris and is usually unilateral. In their series, two patients had bilateral simultaneous tadpole pupils during one episode and eight patients reported episodes of tadpole pupil that alternated sides. The episodes may recur several times a day for several days or weeks before subsiding spontaneously without leaving any sequelae. Between episodes, the pupil is round and reacts normally to light.

Since the seminal paper of Thompson et al. (1), individual reports of tadpole pupil have appeared in the literature. Various associations and mechanisms have been proposed. In this review, we have compiled all the published cases of tadpole pupil and added an additional four cases to re-examine its clinical profile and consider the different purported mechanisms as means to understand possible etiology and treatment. Written informed consent was obtained for each patient presented in the following paragraphs.
CASES

Case 1
A 47-year-old healthy woman noted painless episodic distortion of her right pupil. The pupil became tear-shaped or oval-shaped then returned to a round shape within 1 min (Figures 1A, B). The peak of the tear shape was slightly different with each episode. These episodes occurred spontaneously several times daily in clusters of 2 to 3 days followed by pauses of weeks to months. The episodes have persisted for over 1 year. Recently, the patient noted right upper eyelid ptosis and a smaller right pupil (Figure 1C).

Ophthalmologic and neurologic examinations were normal except for anisocoria and right upper and lower lid ptosis. Instillation of one drop of 1% apraclonidine resulted in reversal of anisocoria and subtle retraction of the right upper lid, confirming a right oculosympathetic defect.

The patient’s episodes of pupillary distortion were diagnosed as tadpole pupil. The anisocoria and lid ptosis were pharmacologically confirmed as a right Horner syndrome, which, though recently noticed by the patient, was apparent on old photographs about 1 year before the onset of tadpole pupil. Imaging studies of the head, neck, and chest were negative.

Case 2
A 41-year-old healthy woman noted painless episodic distortion of her right pupil (Figure 2A). The pupillary distortion occurred three to four times in 1 week and each episode lasted < 1 min without other accompanying symptoms. No other episodes have occurred in the year since onset.

Past medical history revealed high myopia and myopic maculopathy of the right eye. She had undergone refractive surgery 11 years ago.

The patient had previously noticed a smaller pupil in her left eye. A review of old photographs dated this anisocoria to 15 years prior (Figure 2C). Ophthalmologic examination was normal except for an anisocoria with left pupillary miosis (Figure 2B). The palpebral fissures were symmetric. Instillation of topical 1% apraclonidine resulted in reversal of the anisocoria. A diagnosis of left tadpole pupil was made. While a concomitant left Horner syndrome was suspected on clinical grounds, sympathetic denervation hypersensitivity was not demonstrated.

Case 3
A 42-year-old healthy woman noted painless episodic distortion of her left pupil accompanied by blurry vision in her right eye. She had undergone refractive surgery 11 years ago.

The patient had previously noticed a smaller pupil in her left eye. A review of old photographs dated this anisocoria to 15 years prior (Figure 2C). Ophthalmologic examination was normal except for an anisocoria with left pupillary miosis (Figure 2B). The palpebral fissures were symmetric. Instillation of topical 1% apraclonidine resulted in reversal of the anisocoria. A diagnosis of left tadpole pupil and a chronic left Horner syndrome was made.

Case 4
A 32-year-old healthy man was presented with three to four episodes of spontaneous painless left pupillary distortion associated with mild visual blurring in the previous 2 months. Each episode lasted about 1 min. During one episode, he took a self-photograph and showed it to his neuroophthalmologist (FS), who confirmed a tadpole-shaped pupil. The episodes remitted several months and recurred.

His past medical history revealed only retinal laser treatment to both eyes for a retinal break 3 years previously.

Examination showed an anisocoria with left pupillary miosis and left upper lid ptosis (1 mm). The onset of anisocoria could not be confirmed from old photographs. Testing with topical apraclonidine did not show any dilation of the smaller left pupil, and the anisocoria remained unchanged. A diagnosis of left tadpole pupil was made. While a concomitant left Horner syndrome was suspected on clinical grounds, sympathetic denervation hypersensitivity was not demonstrated.

DISCUSSION

To search the literature about tadpole pupil, we used the Medline (PubMed) using the term “tadpole pupil,” “pupillary distortion,” and “iris dilator spasm” without restriction of publication date. We also reviewed the reference lists from retrieved articles to find articles not revealed by database search. Abstracts from meeting proceedings were not included.

Tadpole pupil is an episodic pupillary distortion resulting in a tadpole-shaped pupil. It is a rare condition, first described in 1912 by Erlenmeyer (2) and termed by Thompson et al. in 1983 (1). At present, only 43 cases have been described in the literature (39 reported previously and 4 additional cases presented in this article) (1, 3–14) (Table 1). Similar to the Thompson et al. series, we have found that the majority of patients with tadpole pupil are women (34/43, 79%). Likewise, they are relatively young with a median age at onset of 35.5 years old; the range is between 22 and 48 years old. More recently, however, pediatric cases (two patients age 2 years and one patient age 12 years) have been reported (7, 11, 13).

Tadpole pupil is usually unilateral (40/43, 93%), and rarely bilateral (10, 13). Most of the time, the same eye is affected with each episode, though Thompson et al. found that the side of the tadpole pupil switched in 6 of 26 patients (23%). The tail of the tadpole shape (the peaked or pulled segment) can involve any segment of the iris and the affected segment can vary with each episode, leading to a changing tadpole shape in 16 of 43 patients (37%). Nine patients (20%), however, demonstrated the same distortion of shape with every episode. In 18 patients (41%), the history and observation could not definitively determine if the tadpole shape changed or not.
The duration of each episode is short, 5 min or less in 34 of 43 (79%) and 15 min or less in 37 of 43 (86%). Longer episodes are distinctly unusual. The pupillary distortion appeared spontaneously in 39 of 43 patients (91%) and was accompanied by a blurring of vision or an unusual sensation in the affected eye or on the ipsilateral side of the face in 31 of 43 (72%).
### TABLE 1 | Summary of tadpole pupil cases reported in the literature.

| Author | Sex/Age | Side | Duration of episodes | Frequency of episodes | Known trigger | Associated symptoms | Associated condition | Timing of HS |
|--------|---------|------|----------------------|-----------------------|---------------|---------------------|----------------------|--------------|
| Thompson | F/48 | L (1x bilat) | 20 s | 2 clusters of 3–5 days with 8–10 attacks/days | Blurred vision /abnormal periocular sensation | No |
| Thompson | F/32 | R | 5–10 s | From 2 to a lot of episodes/day | Blurred vision | No |
| Thompson | F/47 | L or R | 10–15 s | From 1 to several episodes/day | Blurred vision /headache prior to episodes | Areas of intermittent sweating on the left flank and right neck |
| Thompson | F/32 | R | <1 min | 2–3 episodes/year | Blurred vision | Congenital right HS Before tadpole dx |
| Thompson | M/30 | R | 1 min | Several clusters of 3 h with several episodes | Light-headedness | Before tadpole dx |
| Thompson | F/young | L | 15 min | Once Every 6 months | Blurred vision /left orbital pain | Possible migraine |
| Thompson | F/37 | R | A few seconds | Clusters of 2 weeks with several episodes/days | No | Right HS At time of tadpole dx |
| Thompson | F/35 | R (1xL) | 3–5 min | Clusters of 90 min with several episodes | Blurred vision /funny sensation in the right eye | No |
| Thompson | F/27 | R | A few seconds | Clusters of 2 weeks with several episodes/days | No | Right postganglionic HS At time of tadpole dx |
| Thompson | F/48 | R | 20 s to 2 min | Clusters of 3–4 days with 15–30 episodes/day | Blurred vision | Right postganglionic HS / intermittent sweating over the medial part of the right brow |
| Thompson | F/36 | R | 1 min | Clusters of 3 h with 10–12 episodes | Blurred vision | No |
| Thompson | F/39 | R | 2 h | | Blurred vision | Migraine |
| Thompson | F/43 | L | A few seconds | Either clusters or single episodes separated with long intervals | Funny sensation in the left eye | No |
| Thompson | F/33 | L | | | Blurred vision | Probable left preganglionic HS /left tonic pupil At time of tadpole dx |
| Thompson | F/30 | L or R | A few min | 1–3 episodes/month | Blurred vision /funny sensation in the eye | No |
| Thompson | F/38 | R | | Very frequent episodes during 2 months | Funny sensation in the right eye | Tonic pupil in both eyes |
| Thompson | F/24 | L | 1–2 min | Clusters of 1 to several days with episodes every 5–10 min | Light-headedness | Left postganglionic HS / probable migraine / left tonic pupil At time of tadpole dx |
| Thompson | M/37 | L | 1–2 min | Clusters of 2–3 days with several episodes | Blurred vision /abnormal sensation in the ipsilateral face | Left postganglionic HS / migraine At time of tadpole dx |
| Thompson | F/33 | L or R | 1 min | | Blurred vision | Migraine |

(Continued)
| Author       | Sex/Age | Side | Duration of episodes | Frequency of episodes | Known trigger | Associated symptoms                          | Associated condition                      | Timing of HS                      |
|-------------|---------|------|----------------------|-----------------------|---------------|---------------------------------------------|-------------------------------------------|------------------------------------|
| Thompson    | F/32    | R    | A few minutes        | Frequent episodes     | Blurred vision/funny sensation in the right eye | Right postganglionic HS/migraine         | At time of tadpole dx                    |
| Thompson    | F/44    | L or R | Frequent episodes    | Clusters of several hours with up to 50 episodes | Left postganglionic HS/migraine | At time of tadpole dx                    |
| Thompson    | M/34    | R    | < 1 min              | Daily episodes since 3 years | Blurred vision | Right HS/migraine                           | At time of tadpole dx                    |
| Thompson    | M/29    | L or R or bilat sec–min | Daily episodes since 3 years | Blurred vision/funny sensation in the eye | No                 | Before tadpole dx                          |
| Thompson    | F/46    | R    | 1 h                  | Clusters of 2 days with several episodes/days | Right postganglionic HS/migraine | At time of tadpole dx                    |
| Thompson    | M/36    | L    | 3–5 min              | Blurred vision         | Probable left HS/migraine | At time of tadpole dx                    |
| Thompson    | F/27    | L or R | < 3 min              | Clusters of 2 days with 1–5 episodes/day | Funny sensation in the eye | At time of tadpole dx                    |
| Tang        | M/29    | R    | < 1 min              | Since 2–3 months, only with exercise | Blurred vision | Right postganglionic HS/hypoplastic right internal carotid artery | Before tadpole dx                       |
| Balaggan    | F/32    | L    | 3–15 min             | 2 clusters of 3 days with several attacks per day in 6 months | Blurred vision/abnormal periorcular sensation | Left preganglionic HS                          | 2 months after tadpole dx            |
| Koay        | F/33    | R    | A few minutes        | From several episodes/days to 1 episode every several weeks | Periorcular sensation | Right postganglionic HS | At time of tadpole dx                    |
| Lüke        | F/42    | L    | 10 min               | Blurred vision         | Right postganglionic HS | At time of tadpole dx                    |
| Lüke        | F/22    | L    | A few minutes        | Funny sensation in the left eye | Morbus Charcot-Marie-tooth/papillary druse | No | At time of tadpole dx                    |
| Weir        | M/2     | L    | 45 min               | During strabismus surgery | No                  | No | At time of tadpole dx                    |
| Kawasaki    | F/young | L    | A few minutes        | Clusters of 4–15 episodes/day for several days with a break of 1 year between the 1st and 2nd cluster | No                  | No | At time of tadpole dx                    |
| Höh         | F/44    | R    | 10–15 s              | Clusters of 4–15 episodes/day for several days with a break of 1 year between the 1st and 2nd cluster | No                  | No | At time of tadpole dx                    |
| Vijayagavan | M/19    | Bilateral | Long               | 1 episode during recurrent seizures and hyponatremia | Recurrent seizures | No | Congenital erythropoietic protoporphyria/seizure/hyponatremia |
| Hansen      | F/12    | Bilat (or unilat) | 20 min              | Initially spontaneously, then only with exercise | Physical exercise | No | Juvenile idiopathic arthritis |

(Continued)
The frequency of episodes varies from one episode every few months to 10–50 episodes per day. Episodes of tadpole pupil seem to occur in clusters lasting days to weeks with a variable and often long interval between clusters. In some patients, a cluster recurs after months to years of remission and in others it subsides spontaneously without leaving any sequelae after several months to years of recurrence. Very rarely, the patient undergoes only one cluster (3/44, 7%) or experiences a single episode of tadpole pupil (3/44, 7%) without recurrence.

An ipsilateral oculosympathetic deficit, or Horner syndrome, is the most frequently associated condition and found in 20 of 43 patients with tadpole pupil (46%; 15 demonstrated and 5 probable), consistent with the finding by Thompson et al. in their series (11/26 patients, 42%) (1). For 5 out of 20 patients (25%), the Horner syndrome was present before the appearance of tadpole pupil and for 3 patients (15%), the Horner syndrome developed after the tadpole pupil. Generally, the Horner syndrome was diagnosed concomitantly with the tadpole pupil, probably because the patient never noticed a pre-existing anisocoria. Thus, it is uncertain as to whether the Horner syndrome typically precedes the tadpole pupil or vice versa. Thompson et al. described also a potential association with Adie’s pupil (4/26 patients, 15%) and migraines (8/26 patients, 31%) (1). However, those associations have not been reported in subsequent studies, except for our Case 3, who presented an Adie’s pupil in the contralateral eye. None of our patients had migraine.

The pathophysiologic basis of the tadpole pupil remains undefined. Several mechanisms have been proposed but none can explain all the features of the tadpole pupil.

Given the frequent association with Horner syndrome, sympathetic denervation hypersensitivity has been considered to be one mechanism of tadpole pupil. Tang et al. reported a patient who seems to support such a hypothesis. The patient had a right Horner syndrome presumably related to a hypoplastic internal carotid artery. Topical hydroxyamphetamine failed to dilate the Horner pupil in the superotemporal quadrant, indicating...
a segmental postganglionic sympathetic deficit (partial Horner syndrome). Following physical exercise, this segment became excessively contracted and pulled the pupil into a distorted shape. Thus, the focal area of denervation corresponded to the focal segment of iris dilator spasm, presumably due to denervation hypersensitivity to circulating catecholamines during exercise (3). Hansen et al. described a patient in whom bilateral tadpole pupil appeared following physical exercise and they suggested a focal hypersensitivity to circulating catecholamines. However, pharmacologic evidence of sympathetic denervation was not provided (13). A 2-year-old girl with a congenital right Horner syndrome who developed right tadpole pupil upon awakening was reported by Aggarwal et al. The authors suggested that morning cortisol that peaks 20 to 45 min after awakening is a possible explanation in their patient (11). The hypothesis of segmental denervation with hypersensitivity may explain tadpole pupil following exercise or waking up, and in these rare cases, the distortion of pupillary shape would be expected to be stereotyped because only the denervated segment demonstrates excessive muscular contraction. Also in these patients, one might expect topical apraclonidine to reproduce the tadpole shape as evidence of a focal hypersensitivity reaction.

Though an attractive hypothesis for these specific aforementioned cases, focal denervation hypersensitivity to circulating adrenergic substances would not explain the tadpole pupil phenomenon in those patients without an underlying sympathetic defect. In the physiologic state, we must consider that a focal contraction of the iris dilator muscle occurs either from focal neurogenic stimulation or direct non-neurogenic activation.

Thompson et al. demonstrated that the effector muscle causing the tadpole pupil is the iris dilator and not the iris sphincter. They first confirmed normal pupil light reflex during tadpole distortion as indication of normal iris sphincter function. Thereafter, they applied 10% viscous phenylephrine, a direct-acting adrenergic agonist, to a focal area of the corneoscleral limbus and reproduced the tadpole-shaped distortion (1).

The neuronal stimulus to the iris dilator is the sympathetic system. Can sympathetic neurons destined to the eye fire spontaneously and intermittently? Apparently they can. The Pourfour du Petit syndrome refers to spontaneous discharge of oculosympathetic neurons causing episodic unilateral mydriasis, often in association with lid retraction and conjunctival blanching (15). It is the clinical opposite of a Horner syndrome. Except for occasional cases of patients with headache (16–18), the Pourfour du Petit syndrome largely occurs in the setting of cranio-cervical pathology (19, 20). In the event of spontaneous oculosympathetic neuronal discharge, one possible mechanism of tadpole pupil is firing of only a few sympathetic fibers. There are, however, no experimental data to indicate that spontaneous sympathetic discharge to the eye can be focal or segmental.

Another possible mechanism for muscle spasm is non-neurogenic activation of the iris dilator muscle. The iris dilator is a smooth muscle. Unlike gastrointestinal or urinary tract smooth muscle in which contractility has autonomic pacemaker properties and gap junction excitation (21), the iris dilator is classified as a multunit smooth muscle in which each cell is activated directly and independently, like striated muscles (22, 23). This organization allows the contraction of a focal portion of the iris dilator. Like striated muscles, the iris dilator receives neural stimulation at the neuromuscular junction (23, 24). However, unlike striated muscles, smooth muscles may respond directly to hormonal stimuli. For example, estrogen and progesterone receptors located on smooth muscles surfaces can influence muscle contractility (25–28). Sex hormone receptors have been demonstrated in the iris of rabbits (29) and humans (30). Thus, we wonder if circulating hormones, while not the principal stimulus, have the capacity to activate the iris dilator muscle. The iris is well vascularized and radially oriented vessels lie alongside the iris dilator muscle fibers. Intermittent dilator muscle stimulation by hormones may explain, in part, the propensity for tadpole pupil to occur in non-menopausal women and to vary in shape and peak from episode to episode. Thompson et al. had noted that 4 of 21 women (19%) reported tadpole episodes during or around menstrual periods (1). We recognize that the hormonal hypothesis fails to explain the appearance of tadpole pupil in men, children, and post-menopausal women as well as the brief timing of tadpole pupil. It is interesting to note that when tadpole pupil occurs in men, there is a greater association with an external trigger or underlying pathology (3/9, 33%). These have included hypoplastic internal carotid artery (3), strabismus surgery (7), and hyponatremia (10). Further investigations are needed to clarify any potential role of hormones in the development of a tadpole pupil.

The iris dilator, being a multunit smooth muscle, does not possess autonomic pacemaker contractility. However, Lee et al. have shown that in vitro muscle fibers of the vas deferens, also a multunit smooth muscle, develop spontaneous contractions after denervation (31). Thus, spontaneous contractility of a denervated iris dilator muscle can be a predisposing factor for why patients with Horner syndrome have a greater risk for developing tadpole pupil compared to the general population. It remains unclear why tadpole pupil, as a manifestation of denervation, is so rare among all cases of Horner syndrome.

How might the proposed causes of tadpole pupil have clinical implications for treatment?

If hormonal influences are clearly associated with the development of clusters of tadpole pupil, for example, occurrence during menses, it may be possible that systemic regulation of estrogen, e.g., oral contraceptive agents or estrogen patch, offers a potential solution to modulating or halting the clusters. In any event, any type of hormonal manipulation must be discussed as empiric therapy with the patient’s general internist or gynecologist.

As focal iris dilator spasm is the common final effector to produce a tadpole pupil, application of a topical alpha-1 adrenergic antagonist, like brimonidine, during the attack or during a cluster period can be expected to reverse the tadpole pupil and stop further episodes. Alpha-1 adrenergic antagonists induce a pharmacologic Horner syndrome. In anecdotal trials, we have found that treating a patient with topical brimonidine did abort further episodes of tadpole pupil, as well as another episodic pupillary phenomenon.
called a benign episodic mydriasis (RK, personal experience and communication). It is not clear if brimonidine will have a similarly favorable effect on tadpole pupil in patients who already have an oculosympathetic deficit. Without or with Horner syndrome, the tadpole pupil appears to be a benign condition, which itself does not lead to any chronic sequelae nor portends more serious underlying pathology.

**AUTHOR CONTRIBUTIONS**

MU, RK, FS, and AK contributed to conception of the manuscript. AK and MU performed literature review and drafted the manuscript. MU created the table and formatted the figures. AK, RK, and FS provided the original data. AK, MU, RK, and FS revised the draft and reviewed the figures. All authors reviewed and approved the final manuscript.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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