TOPICAL APRACLONIDINE TO DIAGNOSE BERNARD-HORNER SYNDROME

KOCABORA M.S, GOCMEZ E*.,*
TASKAPILI M.*

SUMMARY

This study aimed at developing through three clinical cases, the usefulness of topical apraclonidine 0.5% to confirm a diagnosis of Bernard-Horner syndrome. Pupil diameter measurements were performed in indoor, bright and dim light successively. Apraclonidine 0.5% was then applied topically to both eyes, and pupils were observed at 30 and 60 minutes. Apraclonidine demonstrated denervation hypersensitivity in all three cases. Anisocoria was reversed in two cases and corrected in the third case. Although the cocaine test should still be considered as the gold standard for BHS diagnosis, apraclonidine seems to be a useful drug to confirm clinically diagnosed Bernard-Horner syndrome

APPORT DE L'APRACLONIDINE TOPIQUE AU DIAGNOSTIC DU SYNDROME DE BERNARD-HORNER

RESUME

Cet article a pour objectif de développer à partir de trois observations cliniques, l'utilité de l'apraclonidine en collyre à 0.5% dans le diagnostic du syndrome de Bernard Horner. La mesure des diamètres pupillaires a été réalisée au départ successivement en éclairage d'intérieur normal, en illumination forte et en faible illumination, puis a été répétée 30 et 60 minutes après instillation d'apraclonidine. Le test à l'apraclonidine a permis dans les trois cas de démontrer l'hypersensibilité de dénervation pupillaire en réversibilisant l'anisocorie dans deux cas et en le corrigeant dans le troisième. L'apraclonidine apparait être une drogue utile pour confirmer un syndrome de Bernard-Horner mais l'épreuve à la cocaïne doit être encore considérée comme le test diagnostique de référence

KEY WORDS

Bernard-Horner Syndrome, Apraclonidine, Oculosympathetic palsy

MOTS-CLES

Syndrome de Bernard-Horner, apraclonidine, paralysie oculo-sympathique.

.....

* *Vakif Gureba Education and Research Hospital, Istanbul, Turkey*

Submitted: 10-04-08
Accepted: 08-06-09

INTRODUCTION

Bernard-Horner syndrome (BHS) is caused by sympathetic denervation of the eye. Signs include pupillary miosis, lid ptosis, facial anhidrosis and iris heterochromia (1- 3). Although the topical cocaine test is the gold standard confirmatory test, topical apraclonidine has been reported as an alternative method (4-10). We describe three cases of BHS confirmed by the topical apraclonidine test, and discuss the utility of apraclonidine in the confirmation of a clinically diagnosed BHS.

CASE REPORTS

None of the patients was found to have an ocular abnormality or a reduction of central visual acuity after an extensive ophthalmologic examination. Pupil diameter was measured to the nearest 0.5 mm by a pocket-sized gauge in normal indoor lighting, then in bright and dim lighting successively. Then apraclonidine 0.5% was applied topically in both eyes, and the pupils were inspected at 30 and 60 minutes.

Case 1

A 30 year-old woman with a recent history of thyroid surgery presented with a chief complaint of right upper eyelid drooping. The examination revealed anisocoria with indoor lighting and right-sided ptosis. A systemic workup did not reveal any other plausible aetiology than a previous thyroid surgery that could be compatible with a BHS.

Dilation lag of the right pupil was observed upon changing from bright to dim lighting. Topical apraclonidine 0.5% both reversed the anisocoria causing right pupillary dilation and left pupillary constriction and corrected right-sided ptosis within the 30 minutes following instillation (Figure1).

Case 2

A 38 year-old man presented with a complaint of minor corneal epithelial laceration and was observed to have a mild ptosis of the upper eyelid, anisocoria, iris heterochromia, and ipsilateral facial anhidrosis on the left side. An extensive systemic workup including computed to-

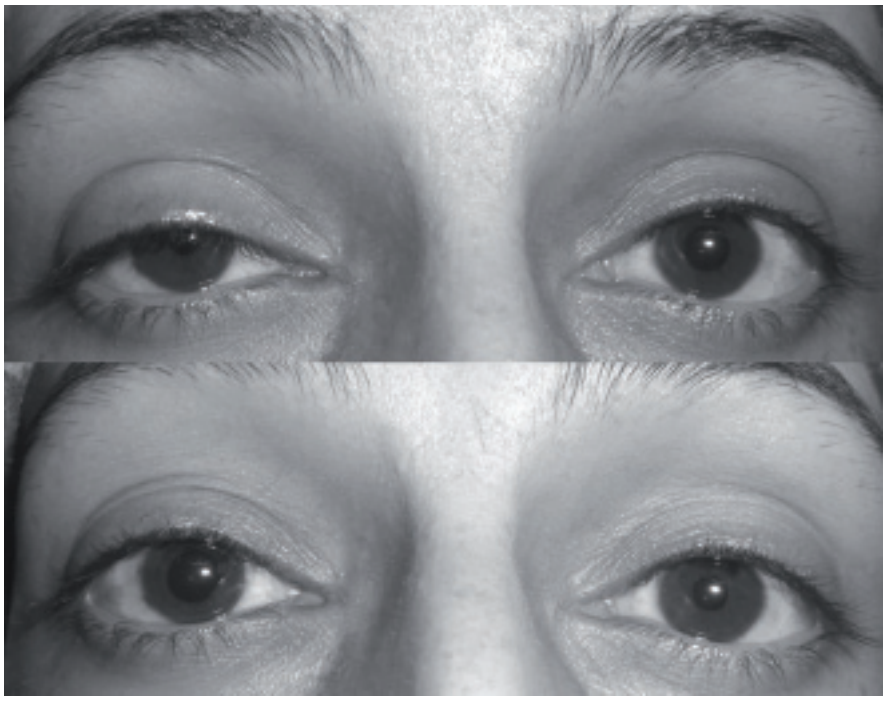

Figure 1:
Upper: Right ptosis of 2.5 - 3 mm and under ordinary indoor illumination pupil diameters of 2 mm and 3.5 mm on the right and the left eye, respectively.
Lower: 30 minutes after apraclonidine application, reversal of anisocoria with a dilation of the right pupil to 5.5 mm and minimal constriction to 3 mm of the left pupil and the correction of the left ptosis.

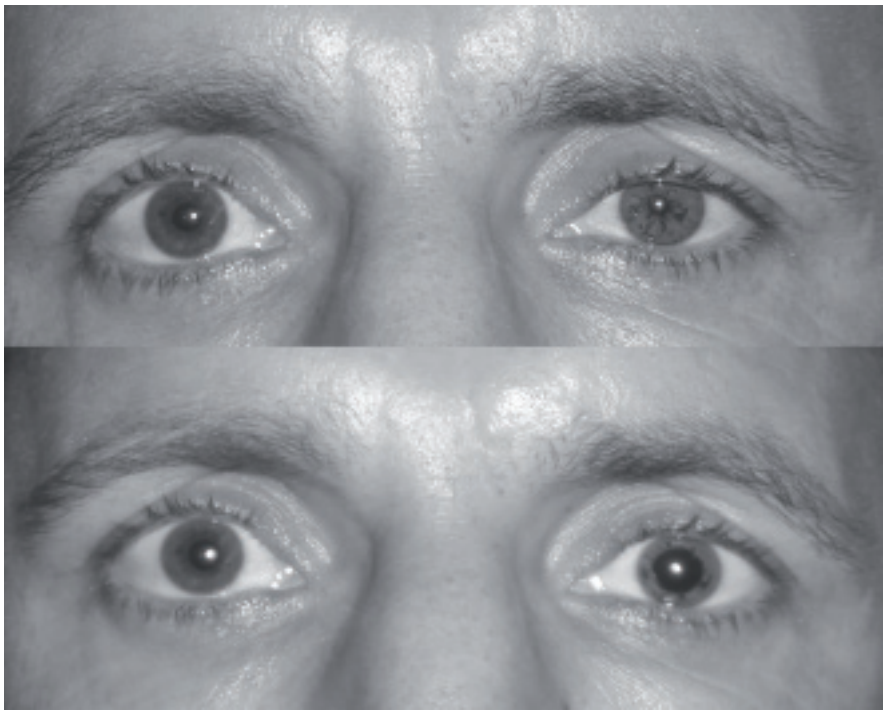

Figure 2:
Upper: left ptosis of 1.5 mm and under normal indoor illumination right pupil of 3 mm and left pupil of 1.5 mm diameters.
Lower: 30 minutes after apraclonidine instillation, reversal of anisocoria with dilation of the left pupil to 5.5 mm and correction of the left ptosis.

mography of the head, cervical spine, neck, and chest could rule out any other pathology. In addition to the patient's awareness of iris hypochromia and ptosis since childhood, the presence of anhidrosis was suggestive of a second order neuron involvement that could be congenital or acquired in early childhood.
The left pupil showed dilation lag with change from bright to dim lighting. Topical apraclonidine caused reversal of anisocoria, triggering left pupillary dilation, and also correction of left-sided ptosis within 30 minutes following instillation (Figure 2).

Case 3

A 10 year-old girl presented with a complaint of a left eyelid drooping and anisocoria. She had an imprecise history of ipsilateral anhidrosis. The systemic workup and the computed tomography of the head and neck, cervical spine, chest, and abdomen were completely normal. The patient's family denied a history of known congenital BHS or birth trauma, but provided photographs showing eyelid drooping when their little daughter was 3 year-old.
The left pupil demonstrated dilation lag with change from bright to dim lighting. Apraclonidine 0.5% instillation corrected the left-sided ptosis but did not obviously affect the pupil size or correct the anisocoria in dim light as it did in the previous two cases. Anisocoria was only corrected in bright light (Figures 3A and 3B).

DISCUSSION

Bernard-Horner syndrome is an uncommon but important entity that is primarily diagnosed on patient history and clinical presentation. However, pharmacologic testing is needed to confirm the clinical diagnosis and to differentiate BHS from simple anisocoria, especially in elderly patients with senile ptosis (1,2,3,5).
Anisocoria in BHS is more obvious in dim lighting because iris dilation on the affected side occurs only passively through a reduction of iris constrictor muscle tone in reduced light. This causes also "dilation lag", which is a very characteristic feature of BHS although it may not always be evident. Repeated inspection may be necessary to document this finding (1,2, 3,5).

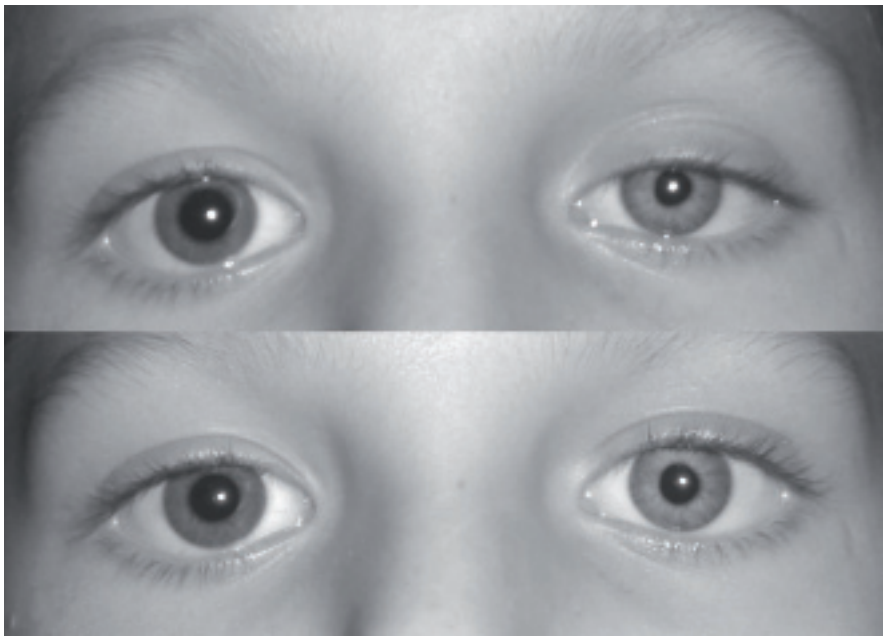

Figure 3A:
Upper: Under indoor illumination, right and left pupil diameters of 5.5 mm and 2.5 mm, respectively.
Lower: 30 minutes after apraclonidine instillation, the anisocoria was not corrected but subsided under indoor illumination.

Pharmacological diagnosis of BHS with topical 2% - 10% cocaine and hydroxyamphetamine has been proven to be the gold standard diagnosis method since many years. Cocaine is a noradrenaline (NE) re-uptake inhibitor that results in increased NE levels at the neuromuscular junction of the normal pupil. Hence mydriasis occurs in the normal pupil but not in the noradrenaline-deficient Horner's pupil. Confirmation of BHS is typically made by instilling cocaine in both eyes. While cocaine blocks the reuptake of NE from the synaptic junctions, the normal pupillary response to topical cocaine is dilatation (1-3). Dilation failure may occur in some normal irises because of the weak dilatory effect of cocaine**.** Successful use of the cocaine test also requires a normal control pupil to assess the effect of the drug (2, 5). Other disadvantages of topical cocaine testing include difficulty in obtaining the drug, low acceptability by patients, and a short shelf-life**.** After confirmation of BHS with cocaine, hydroxyamphetamine can be helpful to distinguish central and preganglionic sympathetic lesions from postganglionic lesions. Hydroxyamphetamine causes the release of NE from the nerve endings, producing pupillary mydriasis in preganglionic lesions (1, 3, 5). Unfortunately cocaine and hydroxyamphetamine are controlled substances which are practically impossible to obtain in most countries, including ours.

Low concentrations of alpha-1 agonists on their, like phenylephrine 1% and tetrahydrozoline 0.05%, may also be used to confirm BHS by demonstrating denervation hypersensitivity. However, their concurrent topical use was reported to mask BHS in some patients (11). Furthermore, their effectiveness may vary because low concentrations of these drugs may fail to penetrate sufficiently the anterior chamber in some patients (1).

Apraclonidine, which is a selective alpha-2 adrenergic drug with a weak alpha-1 activity, has been approved by the FDA for use in reducing the intraocular pressure rise that may occur after anterior segment laser procedures. Its good penetration into the anterior chamber allows it to reach the iris dilator muscle at 0.5% concentration (10). Poor alpha-1 adrenergic effect of apraclonidine is capable to induce obvious pupil dilation only if the iris alpha-1 receptors are up-regulated such as in miotic pupil in BHS whereas it is able to enlarge minimally the unaffected normal pupil. This weak alpha -1 activity induces significant dilation in affected pupil indicating that denervation hypersensitivity

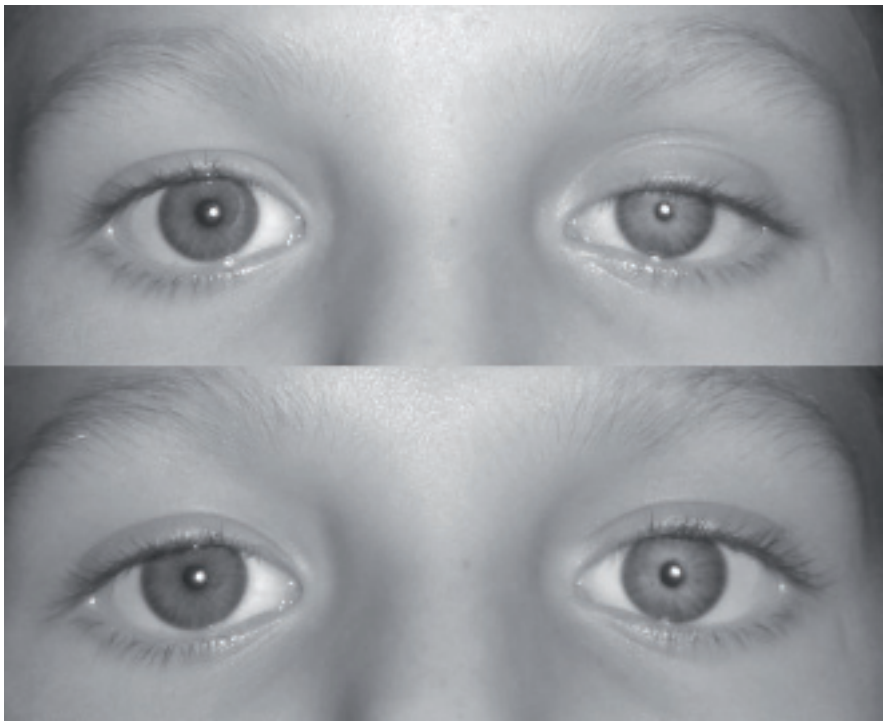

Figure 3B:
Upper: Left ptosis of 2 mm. Under bright illumination, right and left pupil diameters of 2.5 mm and 1 mm, respectively.
Lower: 30 minutes after apraclonidine instillation, correction of anisocoria under bright illumination with a weak dilation to 2 mm of the left pupil and minimal constriction to 2 mm of the right pupil. Simultaneous correction of the left ptosis.

has been developed in the setting of BHS (4, 10,12).
The alpha-2 activity of apraclonidine causes Müller muscle constriction with transient reversal of eyelid ptosis (10,13). The lid elevation observed after topical apraclonidine has not been considered as a specific sign for BHS, because it has also been found to occur in about 45% of normal eyes (10). However Garibaldi et al. have suggested that the resolution of ptosis might be an additional marker for the diagnosis of the BHS because the alpha-2 receptors might have been up-regulated in tarsal muscles due to oculosympathetic paresis (13).
Unlike cocaine, apraclonidine is an easily available drug and does not require a normal control pupil. So it is potentially also effective to confirm a bilateral BHS (2, 5,10) . A drawback to apraclonidine is that it is not useful until two weeks following BHS onset because alpha-1 receptors in the iris dilator muscle have not yet up-regulated (4 ,10, 12). Moreover it should be used with caution in infants under the age of 6 months due to a possible well known systemic toxicity of topical apraclonidine at this age that can promote depression in central nervous, respiratory and cardiovascular systems (14).
An overview of the pharmacologic agents used in the diagnosis of BHS is shown in Table1.
Previous studies have shown varying proportions of sensitivity to topical apraclonidine in detecting oculosympathetic paresis of the pupil and are summarised in Table 2.
All of our three cases exhibited anisocoria and mild lid ptosis. Our case 1 was considered as an iatrogenic case since there was a history of acute BHS after a thyroid surgery. Our case 2 was regarded as an idiopathic BHS since no etiological factor was found, although the presence of iris heterochromia and mild ptosis could be suggestive of a congenital or long standing acquired BHS. Case 3 concerned a child and could also be considered as an idiopathic BHS since the family denied any birth trauma and the possible life threatening aetiologies such as neuroblastoma and brainstem vascular malformation could have been ruled out.
In the present study, upper eyelid ptosis resolved in all of our three cases 30 minutes after apraclonidine instillation. Cases 1 and 2 experienced anisocoria reversal 30 minutes fol-

Table 1: *Summary of the pharmacologic agents that may be used in BHS diagnosis.*

TOPICAL DRUG	*Purpose of test*	*Mechanism*	*Effect*
COCAINE 4-10%	To confirm or deny the presence of BHS	Sympathomimetic that blocks the reuptake of NE	Normal pupils dilate; BHS pupils do not dilate as the 3rd neuron pathway has been interrupted
HYDROXYAMPHETAMINE 1%	To confirm 3rd neuron damage in BHS	Stimulates the release of NE from neurons	Central or preganglionic lesions dilate as the 3rd neuron is intact; Post-ganglionic lesions do not dilate
APRACLONIDINE 0.5%	To confirm or deny the presence of BHS	Denervation hypersensitivity of α_1 receptors in the pupil dilator muscle	Reversal of anisocoria (the miotic pupil of BHS becomes larger than the normal pupil)
ALPHA-1 AGONISTS IN LOW CONCENTRATIONS (PHENYLEPHRINE 1% OR TETRAHYDROZOLINE 0,05%)	To confirm or deny the presence of BHS	Denervation hypersensitivity of α_1 receptors in the pupil dilator muscle	Reversal of anisocoria (the miotic pupil of BHS becomes larger than the normal pupil)

Table 2: *Evaluation of apraclonidine for the diagnosis of BHS according to previous studies.*

	Bacal and Levy(9)	*Koc et al.(4)*	*Morales et al.(6)*	*Brown et al.(8)*	*Chen et al.(7)*	
Sensitivity (%)	100	100	100	88	100 bright light)	70 (dim light)
Specificity (%)	100	100	–	–	–	

lowing apraclonidine application. In both patients, pupils dilated more than 2 mm in the affected eye. In cases 1 and 3, the unaffected pupils were minimally constricted due to alpha-2 activity. In case 3, the affected pupil dilated approximately 0.5 -1 mm following apraclonidine instillation, whereas anisocoria was not reversed in dim light (Table 3).

In our three cases, apraclonidine has achieved the correction of anisocoria in one case and the reversal of anisocoria in two cases. Additionally it corrected the lid ptosis in all cases. These results suggest that, in addition to its easy availability, apraclonidine is apparently a useful drug in confirming the BHS diagnosis.

In case 3, anisocoria was fully corrected in bright light but only decreased in dim light. This finding is in agreement with Chen et al who found in a small series of 10 paediatric patients that the correction of anisocoria was better observed in bright light than in dim light in 7 out of 10 children and that reversibility was only observed in bright light in 3 children (7).

It is still unclear if a denervation hypersensitivity develops in all sympathetic interruptions, and if this denervation is clinically apparent on examination. For this reason and as been stated by Kadron, it is not appropriate to justify substitution of cocaine by apraclonidine in all cases (12). Since the mechanism of apraclonidine depends on receptor hypersensitivity, an incomplete hypersensitivity may give false negative results with topical apraclonidine with no reversal of anisocoria (7, 15). Similarly in our case 3, anisocoria was corrected but not reversed by topical apraclonidine. In clinically suspect cases with negative apraclonidine test, cocaine testing is mandatory for further assessment of the case to ascertain the diagnosis (8, 15).

Table 3: *Comparison of case-reports characteristics*

	BASELINE PD (MM)		*PD (MM) APRACLONIDINE*		*BASELINE PTOSIS (MM)*	*PTOSIS CORRECTION*
	RIGHT	*LEFT*	*RIGHT*	*LEFT*		
CASE 1 INDOOR ILLUM.	2	3.5	5.5	3	3	+
CASE 2 INDOOR ILLUM.	3	1.5	3	5.5	1.5	+
CASE 3 INDOOR ILLUM.	5.5	2.5	4.5	3	2	+
CASE 3 BRIGHT ILLUM.	2.5	1	2	2	2	+

CONCLUSION

These three case-reports demonstrate the utility of topical apraclonidine to confirm clinically suspected sympathetic denervation of the eye and establish a diagnosis of Bernard Horner syndrome. Easy availability of apraclonidine makes its use attractive to the physician, although the cocaine test should still be considered as the gold standard in the pharmacologic testing of BHS.

REFERENCES

(1) KAWASAKI A. – Disorders of Pupillary Function, Accommodation and Lacrimation. In Volume I Walsh & Hoyt's Clinical Neuro-Ophthalmology, 6th Edition Ed: Miller N.R; Newman N.J.. Lippincott Williams & Wilkins, 2005, 739- 805.

(2) WALTON K.A., BUONO L.M. – Horner syndrome. *Curr Opin Ophthalmol 2003, 14: 357-63.*

(3) WILHELM H. – The pupil. *Curr Opin Neurol 2008; 21: 36-42*.

(4) KOC F, KAVUNCU S., KANSU T, ACAROGLU G, FIRAT E. – The sensitivity and specificity of 0.5% apraclonidine in the diagnosis of oculosympathetic paresis. *Br J Ophthalmol 2005; 89: 1442-44.*

(5) MARTIN T. – Horner's syndrome, Pseudo-Horner's syndrome, and simple anisocoria. *Curr Neurol Neurosci Rep 2007; 7: 397-406.*

(6) MORALES J., BROWN S.M., ABDUL-RAHIM A.S., CROSSON C.E. – Ocular effects of apraclonidine in Horner Syndrome. *Arch Ophthalmol 2000; 118: 951-54*.

(7) CHEN P.L, HSIAO C.H., CHEN J.T., LU D.W., CHEN Y.W. – Efficacy of apraclonidine 0.5% in the diagnosis of Horner Syndrome in pediatric patients under low or high illumination. *Am J Ophthalmol 2006; 142: 469-74*.

(8) BROWN S.M., AOUCHICHE R, FREEDMAN K.A. – The utility of 0.5% apraclonidine in the diagnosis of Horner syndrome. *Arch Ophthalmol 2003; 121: 1201-3.*

(9) BACAL D.A, LEVY S.R. – The use of apraclonidine in the diagnosis of Horner syndrome in pediatric patients. *Arch Ophthalmol 2004; 122: 276-9.*

(10) FREEDMAN K.A., BROWN S.M. – Topical Apraclonidine in the diagnosis of suspected Horner Syndrome. *J Neuro-Ophthalmol 2005; 25: 83-5.*

(11) LEE M.S., HARRISSON A.R., KARDON R.H. – Patient use of Visine (tetrahydrozoline) masks Horner syndrome. *Br J Ophthalmol 2008; 92:149-150.*

(12) KARDON R. – Are we ready to replace cocaine with apraclonidine in the pharmacologic diagnosis of Horner Syndrome? (Editorial). *J Neuro-Ophthalmol 2005; 25: 69-70.*

(13) GARIBALDI D.C., HINDMAN H.B., GRANT M.P., ILIFF N.T., MERBS S.L. – Effect of 0.5% apraclonidine on ptosis in Horner syndrome. *Ophthal Plast Reconstr Surg 2006; 22: 53-5.*

(14) WATTS P., SATTERFIELD D, LIM M.K. – Adverse effects of apraclonidine used in the diagnosis of Horner syndrome in infants. *J AAPOS 2007; 11: 282-3.*

(15) KAWASAKI A, BORRUAT FX. – False negative apraclonidine test in two patients with Horner syndrome. *Klin Monatsbl Augenheilkd 2008; 225: 520-2.*

.....

Correspondance and reprints:
Prof M. SELIM KOCABORA, MB*
Sanatcilar Sitesi, 27 E Blok Daire: 12
TARABYA-SARIYER
34457 ISTANBUL-TURKEY
E-mail: kocabora@gmail.com

** Ophthalmologist, Assistant-Director and Associate Professor in Ophthalmology Clinic, Vakif Gureba Education and Research Hospital, Istanbul, Turkey*