The Evaluation of Patient Demographics, Etiologies and Apraclonidine Test Results in Adult Horner's Syndrome

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Abstract

Purpose: We aimed to demonstrate the patient demographics, etiologies and apraclonidine test results in adult Horner's syndrome

Methods: This retrospective study was performed by the analysis of medical data of patients who were given 0.5% apraclonidine test. Patients' past medical history, demographic data, etiologies, accompanying neurological findings, and pharmacological test results were assessed.

Results: Forty patients (21 females and 19 males) with a mean age of 50.3 ± 11.6 years were evaluated. Apraclonidine 0.5% test was positive in 37 patients (92.5%). An etiology could be identified in 20 patients (central (9 patients, 45%), preganglionic (9 patients, 45%), and postganglionic (2 patients, 10%)). Neurological findings accompanying Horner’s syndrome were present in 9 patients.

Conclusion: Despite detailed investigations, in a significant number of patients with Horner's syndrome an underlying cause may not be detected. Among the identifiable lesions, central and preganglionic involvements are still the first leading causes of Horner's syndrome. In addition, apraclonidine test may not be positive in all patients and a negative response does not exclude Horner's syndrome.

Introduction

Horner’s syndrome (HS) also termed as "oculosympathetic paresis" results from interruption of the sympathetic pathway anywhere from the hypothalamus to the orbit [1-4]. This pathway is made up of three-neuron arc and the conditions causing the syndrome are clinically classified as central (first-order neuron), preganglionic (second-order neuron), and postganglionic (third-order neuron) according to the lesion localization. Its classical triad consists of ipsilateral ptosis, myosis, and anhydrosis though anhydrosis is unlikely to be present in postganglionic lesions [1]. It is easy to diagnose HS. However, determining the lesion localization is often challenging sometimes requiring great effort. Besides clinical findings, pharmacologic testing is helpful for both the diagnosis and lesion localization [1-4]. Cocaine and apraclonidine are the most commonly used agents for the diagnosis [3]. However, drug choice for the diagnosis is still controversial. Furthermore, many researchers have reported that apraclonidine or cocaine tests could be negative in some patients with HS.

This clinical study aimed to demonstrate the baseline demographics, underlying etiologies, and concomitant neurological findings in patients with adult HS. In addition, we reported the rate of apraclonidine positivity in adult HS.

Materials And Methods

Study Design and Patient’s selection

This retrospective study was adhered to the Declaration of Helsinki. The data have been carefully collected by examining the medical records of the patients with adult HS who applied to the Neuro-ophthalmology clinic at Ege University and Bozyaka Training and Research Hospital between 2014-2019. We examined 45 patients' files. After the initial assessment of the records, five patients were excluded due to incomplete data. We identified 40 patients who had undergone apraclonidine test. Past medical history, demographic data, underlying etiology, accompanying neurological findings, and pharmacological tests used for the diagnosis were recorded. The results of comprehensive radiological imaging (chest X-ray, thorax computed tomography (CT), head CT, Magnetic Resonance Imaging (MRI) and Magnetic Resonance Angiography (MRA) of the head and neck ultrasound) and laboratory tests were noted. Detailed neuro-ophthalmologic examination including eye movements, pupil size and its light and near responses were also examined.

The Diagnosis of HS

In this study, patients who had anisocoria with normal pupillary constriction to the light and near in both pupils were pre-diagnosed with HS, and then the diagnosis was confirmed by clinically and pharmacologically. Clinically, it was defined as miosis with or without ptosis with one or more of the following: a) the presence of pupillary dilation lag of the smaller pupil, b) anhidrosis, c) hypochromic heterochromia iridis. On the other hand, apraclonidine 0.5 % eye drop (Iopidine, Alcon, Fort Worth, TX, USA) was used for pharmacological test. Baseline photos in dim light in a darkened room was obtained at first, and then apraclonidine 0.5% drop was placed in each eye. Approximately 30-45 minutes after the administration, the repeated photographs were taken under the same light conditions. When the reversal anisocoria were determined, the diagnosis of HS was supported.

All statistical analysis was performed using SPSS (Statistical Package for the Social Sciences) for Windows (version 21.0; Chicago, SPSS, Inc). All data are expressed as the mean ± standard deviation.

Results

Forty patients' medical data were assessed in this study (21 females and 19 males). The mean age was 50.3 ± 11.6 years. Patient demographics, accompanying neurological findings and the results of 0.5% apraclonidine test were summarized in **Table 1**. When the patients were assessed according to the underlying etiologies, 16 patients (40 %) were idiopathic and 4 patients (10%) were congenital. In 20 patients (50%) an underlying etiology was present; central lesions in 9 patients (45%), preganglionic in 9 patients (45%) and postganglionic lesions in 2 patients (10%). Among the central lesions, stroke was the most common cause (7 patients). Other causes were brain stem metastasis (1 patient) and syringomyelia (1 patient). Preganglionic causes were previous neck (2 patients) and thorax (1 patient) surgery, trauma (1 patient), spinal root cyst (1 patient), pancoast tumor (1 patient), laryngeal cancer (1 patient), and orbital invasion by neuroblastoma (1 patient). Postganglionic lesions were detected in 2 patients and were due to cluster headache. Neurological findings accompanying HS was detected in 9

patients due to central lesion. Apraclonidine 0.5 % test was positive in 37 patients (92.5 %), in remaining 3 the test was negative (idiopathic; 2 patients, central lesion: 1 patient).

Table 1
Patient demographics, accompanying neurologic findings and the results of 0.5% apraclonidine test.

Etiology		Age	Gender	Additonal neurologic findings	Apraclonidine 0.5 % test
1	Idiopathic	43	M	-	Negative
2	Idiopathic	37	M	-	Negative
3	Idiopathic	55	F	-	Positive
4	Idiopathic	36	F	-	Positive
5	Idiopathic	55	F	-	Positive
6	Idiopathic	26	M	-	Positive
7	Idiopathic	49	M	-	Positive
8	Idiopathic	54	M	-	Positive
9	Idiopathic	44	M	-	Positive
10	Idiopathic	29	F	-	Positive
11	Idiopathic	40	M	-	Positive
12	Idiopathic	59	F	-	Positive
13	Idiopathic	65	F	-	Positive
14	Idiopathic	58	F	-	Positive
15	Idiopathic	40	F	-	Positive
16	Idiopathic	60	F	-	Positive
17	Congenital	65	F	-	Positive
18	Congenital	43	F	-	Positive
19	Congenital	55	F	-	Positive
20	Congenital	62	F	-	Positive
First-Order Neuron					
21	Syringomyelia (C5-T12)	45	F	-	Positive
22	Stroke	52	M	Hemiparesis	Positive
23	Stroke	64	M	Hemiparesis	Positive
24	Brainstem metastases (Breast)	52	F	Ipsilateral 6.CN palsy and hemiparesis	Negative

25	Stroke	35	M	-	Positive
26	Stroke	67	M	Ataxia, skew deviation and nystagmus	Positive
27	Stroke	53	M	Upgaze palsy	Positive
28	Stroke	77	M	Skew deviation	Positive
29	Stroke	52	M	Vertical gaze palsy	Positive
Second-Order Neuron					
30	Spinal root cyst (C7-T1)	61	F	-	Positive
31	Nasopharynx Ca	55	M	Ipsilateal 6.CN palsy and facial hypoesthesia	Positive
32	Pancoast tumor	36	F	-	Positive
33	Previous neck surgery	61	F	-	Positive
34	Orbital invasion by neuroblastoma	40	F	-	Positive
35	Previous neck surgery	47	M	-	Positive
36	Trauma (Falling from height)	29	M	-	Positive
37	Larynx cancer	60	M	-	Positive
38	Previous thoracic surgery	54	F	-	Positive
Third-Order Neuron					
39	Cluster headache	54	M	-	Positive
40	Cluster headache	43	M		Positive

Discussion

HS was first reported by Claude Bernard in 1854. However, Johann Friedrich Horner described this syndrome in detail for the first time in 1869 and suggested that it originated from oculosympathetic paresis [2].

Despite advances in neuroimaging and other diagnostic tests, in some patients with HS an underlying etiology cannot be identified. In a study by Wilhelm et al [5]., this rate was reported as 28% in preganglionic HS. Sabbagh et al [6]. demonstrated that a cause was identified in 61% of patients with apraclonidine-confirmed HS. Similarly, Maloney et al [7]. found a detectable cause in only 65% of patients. The authors reported that preganglionic (44%) and postganglionic (43%) causes were found in similar rates, whereas central lesions (13%) were very infrequent [7]. In a large series reported by

Thompson et al [8]., malignancy was responsible from approximately 25% of the preganglionic HS cases. The most common tumor associated with preganglionic lesions have been reported as breast and lung cancers. This syndrome may rarely be the first presentation of the malignancy, but it usually occurs long after the diagnosis of cancer [2]. In our study, we did not find any etiology that could be related HS in 40% of the cases. This rate was similar to previous reports in the literature. We, however, reported that the rate of central lesions between the identifiable causes was higher than postganglionic lesions in contrast to the literature.

In posterior cavernous sinus or brainstem involvement, HS may be accompanied by abducens paralysis. This condition, also called Parkinson's syndrome [9], was observed in two cases. One was cavernous sinus invasion due to nasopharyngeal tumor and the other one was brain stem metastasis.

Apraclonidine, an alpha-2 adrenergic agonist with weak alpha-1 adrenergic activity, is used for decreasing intraocular pressure in glaucoma patients. Although it has no obvious effect on pupil's size, iris dilation is observed due to supersensitivity of the postsynaptic alpha-1 adrenergic receptors located on the dilator muscle affected by oculosympathetic paresis. [1,10]. It is still so controversial which test used in the diagnosis of HS is more reliable. In a research conducted by Bremner [11], apraclonidine was found to have higher sensitivity (93%) when compared with cocaine (40%). Similarly, apraclonidine sensitivity was determined as 87% by Koc et al [12]. The other disadvantages of cocaine are it’s being more expensive and less available. Therefore, it is recommended that apraclonidin should be the “gold standard” pharmacological test for diagnosing HS [11]. However, the test must be performed cautiously within hours after symptom onset, and infants under 1 year of age [11]. There are two main issues restricting the clinical use of apraclonidine. The first issue is the potential side effects, especially in children. In a study conducted by Watts et al [13]., drowsiness and unresponsiveness has been reported in infants under the age of 6 months after topical administration of 1% apraclonidine. Furthermore, hypotension, bradycardia, somnolence, and lethargy have been reported as other side effect related to alpha-adrenergic receptor agonism [2,13-15]. Although there are limited reports on the safety of apraclonidine in children younger than 10 years old [16,17], it is still the preferred drug diagnosing HS in infants and young children [1,18]. Another concern associated with topical apraclonidine usage is that the test results are negative in the early period after interruption of the sympathetic innervation. Because upregulation of the postsynaptic adrenergic receptors may require a certain period after sympathetic denervation, pupil dilation may not be achieved in an acute case [19]. The apraclonidine test can be positive between 1 month and 10 years after sympathetic interruption [7,20-27]. In our study, we found a high rate of apraclonidine positivity (92.5%) similar to Bremner's study. When we evaluated apraclonidine negative cases, we noticed that 2 patients were idiopathic and 1 patient was related to a central metastasis. However, the test was positive in all patients with second and third order neuron involvement. As the clinical picture was very typical we did not perform further evaluation such as cocaine test in 3 patients who had negative response to 0.5% apraclonidine.

This study has some limitations. First, it has limited statistical power due to relatively small sample size. Second, cocaine test was not used as a diagnostic test. We therefore could not compare the two agents.

Third, we could not detect whether the apraclonidine test became positive after the acute period in patients who had a negative response initially. Fourth, our findings do not reflect the entire population as we only evaluated adult HS patients.

Conclusions

HS, an important clinical entity, has a large number of causes. Though often idiopathic or benign, the causes can sometimes be complex and life threatening. Central and preganglionic disorders are still the first leading causes in the identifiable group. Although apraclonidine test is positive with high sensitivity in the majority of patients the clinicians should keep in mind that negative apraclonidine test does not exclude the syndrome.

Declarations

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Competing Interests:

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Author contribution:

All co-authors have contributed to the study, and all have read and approved the final version of the manuscript. Concept: O.K., D.T.K., Design: O.K., D.T.K., N.C.,F.G. Data Collection or Processing: F.G., N.C., O.K., D.T.K., G.S.D. Analysis or Interpretation: D.T.K., O.K., F.G., N.C., G.S.D. Literature Search: D.T.K., O.K., N.C., G.S.D., FG. Writing: O.K., D.T.K., N.C., G.S.D., F.G.

Data Availability:

All data obtained during the study process were used in the study.

Animal Research (Ethics):

There was no research on animals in this manuscript.

Consent to Participate (Ethics):

Verbal consent for participation was obtained from from all study patients.

Consent to Publish (Ethics):

Verbal consent for publication was obtained from all study patients.

Ethics approval:

This study was conducted in accordance with the tenets of the Helsinki Declaration after obtaining the approval of local ethics committee.

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