ORIGINAL ARTICLE

A Descriptive, Cross-sectional Study on the Ophthalmic Symptoms and Signs in Patients with Nasopharyngeal Carcinoma

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ABSTRACT

Objective. This study described the ophthalmic symptoms and signs in patients with nasopharyngeal carcinoma (NPCA).

Methods. This was a retrospective, cross-sectional, descriptive study involving patients with histologically-confirmed NPCA seen in two subspecialty eye clinics in a single referral hospital from January 2014 to December 2018. Chart review obtained data on symptoms and ophthalmic findings of patients with NPCA on the first visit. Descriptive statistics was used to analyze the data.

Results. There were 36 patients in the study. There were 27 males (75%) and mean age was 47 years (Range: 13 - 83). Delay to consult was marked, with 28 patients (78%) presenting later than three months; 19 (53%) had invasion to distant sites on presentation. Almost all of the patients (35/36 or 97%) had either diplopia or blurring of vision, with nasal symptoms as the most common extra-ophthalmic accompanying symptom. Multiple cranial nerve palsies, particularly optic nerve plus at least one ocular motor nerve, was a prominent feature. The combination of nasal symptoms with ophthalmoparesis was noted in 24 patients (67%) and was identified as a red flag for NPCA.

Conclusion. Blurred vision and diplopia were the most common ocular complaints of patients with NPCA who were evaluated at the ophthalmology department of a tertiary hospital. Blurred vision is frequently from optic nerve involvement while diplopia is due to ophthalmoparesis secondary to multiple ocular motor cranial nerves involvement. Male patients in their 40s who present with combination of optic neuropathy or ocular motor palsies should be probed for presence of otologic or nasal symptoms as well as neck masses as these are the common presentation of NPCA in the ophthalmology clinics.

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INTRODUCTION

Nasopharyngeal carcinoma (NPCA) is a relatively rare condition for most populations, presenting with an incidence of <1/100,000. However, based on the 2016 Asia-wide study, it has a higher incidence of 3.2% in the Philippines.[1] In a 1998-2002 survey, it ranked as the 7th most common cancer among Filipino men, accounting for 4.6% of malignancies in males.[2] Initial consult for patients with NPCA tends to be late in the disease.[3,4] In a study by Sarmiento and Mejia, 78% of patients presented with locally advanced stages (Stage II-IVB)[5] thus,

emphasizing the value of establishing a clinical picture that would increase the index of suspicion for the disease. What complicates the management of this endemic disease is that it presents with non-specific signs and symptoms in the head and neck region that render it difficult to catch at the outset. In 1986, Roxas et al. reported the neurologic abnormalities in Filipino patients with NPCA. The earliest neurologic signs were diplopia, facial numbness/pain, dysarthria, dysphagia, blurred vision, ptosis, and hoarseness.[6] Other localizing symptoms include nasal congestion or discharge, epistaxis, otologic symptoms, and neck masses.[7] Given these range of symptoms, as many as a quarter of patients can be given an incorrect initial diagnosis.[7] They may also seek initial consult with an ophthalmologist, underscoring the need for ophthalmologists to recognize NPCA in the clinic. To date, there is no local published studies on the ophthalmologic signs and symptoms of patients with NPCA.

This study described the ophthalmic symptoms and signs of patients with NPCA in in the ophthalmology clinics at a tertiary hospital in the Philippines. Findings from this study may aid ophthalmologists in recognizing the disease and minimize delays in management.

MATERIALS AND METHODS

This study was retrospective, cross-sectional, descriptive study that employed a review of the medical charts of patients with NPCA evaluated at the Orbit and Neuro-ophthalmology Clinics of the UP-Philippine General Hospital Department of Ophthalmology and Visual Sciences (PGH DOVS) from January 2014 to December 2018. The Orbit and Neuro-Ophthalmology clinics are subspeciality clinics that evaluate patients with ophthalmic complaints from disorders of orbit and central nervous system, respectively.

Patients with consideration of NPCA were identified, and those with histologically- confirmed diagnosis presenting prior to treatment were included in the study. In order to identify and isolate the ophthalmic signs and symptoms from the carcinoma alone, patients who presented at the clinics with prior treatment for NPCA, whether radiation or chemotherapy, were excluded since neuro-ophthalmologic complications may occur as a result of these treatments and may confound the results of the study. Patients who had NPCA but were not referred to the Orbit or Neuro-ophthalmology subspecialty clinics were not included in the study. Those who did not have histopathologic diagnosis were also excluded from the study.

A convenience sampling was employed. Medical records of all patients with NPCA that met the screening criteria were included in the study.

The clinic charts, histopathological reports, and imaging findings were reviewed and the following information were recorded: (1) demographic data including age, sex, family history of NPCA, smoking history; (2) histologic diagnosis; (3) presenting ophthalmic symptom; (4) onset and duration of symptoms; (5) other general symptoms including headache, nasal and otologic symptoms, neck mass; (6) presenting ophthalmic signs; (7) referring service or point of initial consultation; (8) type of neuroimaging procedure performed whether computed tomography (CT) or magnetic resonance imaging (MRI); and (9) neuroimaging findings.

Visual acuity (VA) using the Snellen chart was converted to LogMAR. Measurements of hand movement, light perception, and no light perception were converted to their LogMAR equivalent based on the Freiburg Visual Acuity testing done by Lange et al.[8] and the imputations done by Bach et al.[9] The various presenting ophthalmologic symptoms recorded included but was not limited to blurred vision, diplopia, eye protrusion, eyelid drooping, and pain. While the various neuro-ophthalmologic signs that were considered consistent with NPCA invasion were optic neuropathy, palsies affecting cranial nerves II to VIII, Horner syndrome, and proptosis. Eyes with compressive optic neuropathy were identified and the VAs were then analyzed separately.

To allow for systematic analysis of the diagnostic imaging done for the NPCA patients in the study, results were classified using the study of Liang et al.[10] In their study, radiographic landmarks were identified as high, medium, or low risk for being involved in NPCA. Structures proximal to the nasopharynx such as the parapharyngeal space, petrous apex, clivus, foramen lacerum, pterygoid process, and nasal cavity were considered high risk; while more distal structures such as the inferior or superior orbital fissure, cervical vertebrae, orbital apex, frontal or maxillary sinus, hypopharynx, and meninges were classified as low risk. Invasion of the foramen ovale or rotundum, greater wing of the sphenoid, cavernous or sphenoid sinus, jugular foramen or pterygopalatine fossa were identified as medium risk. Their study was applied to our patients by using the most distal anatomical site involved on imaging for the classification.

This study was approved and assigned with the code number 2019-28601 by the University of the Philippines Manila Research Ethics Board. Data collection and analyses were completed in September 2021.

Statistical Analysis

Data were anonymized and encoded in Microsoft Excel version 16 (Microsoft Corporation, Washington, USA). Missing data was not imputed. Descriptive statistics was used to analyze the data. Percentages was used for categorical data such as gender, smoking history, initial point of care, histopathology type, presenting symptoms and signs, type of imaging, and imaging findings. While measures of central tendency were used for continuous variables such age and duration of symptoms.

RESULTS

Sixty-two (62) patients with consideration of NPCA were identified. Of these, 26 patients were excluded: 11

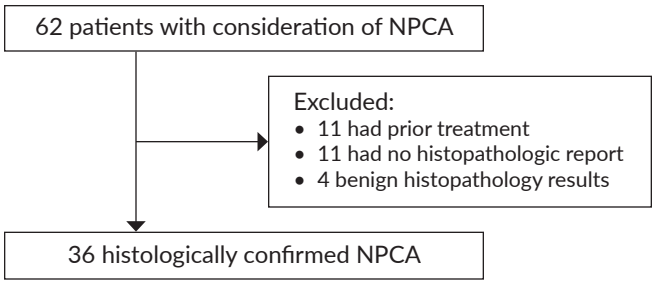

Figure 1. Flow diagram showing the final number of charts that met the screening criteria.

presented post-treatment, 11 did not have histopathologic confirmation, and 4 had benign histopathology. Thirty-six (36) patients with histologically confirmed NPCA were included in the study (Figure 1).

Table 1 shows the clinical profile of patients with NPCA. Majority were male (75%), nonsmokers (58%) and presented in their 5th decade (39%). Mean age at presentation was 47 years old with range of 13 to 73 years. Most (94%) had no family history of NPCA. The most common histopathologic diagnosis was undifferentiated carcinoma (50%).

Majority of the patients had initial point of care outside ophthalmology and were referred to the Ophthalmology department for evaluation (64%). Thirteen (13) patients (36%), however, had opted to consult with the ophthalmology department first.

The mean duration of symptoms was 18.3 months (range: 0.5- 228 months). Majority (78%) had symptoms for more than three months (Table 2).

Table 2 shows the frequency of ocular and extraocular symptoms at initial visit. Thirty-five (35) patients had ophthalmic complaints (97%). Blurred vision (72%) and diplopia (64%) were the most common.

Among the extra-ophthalmic symptoms, most common were nasal symptoms (24 patients or 67%). Otologic symptoms were present in 10 patients (28%). Neck mass was present in 12 patients (33%).

Compressive optic neuropathy was diagnosed in 26 eyes of 20 patients. Mean LogMAR VA of affected eyes was 2.33. On examination, 20 eyes had normal appearing optic discs, four had optic disc edema, and two had optic pallor.

All patients had cranial nerve involvement. Three patients (8%) had isolated cranial nerve VI palsy while 33 patients (92%) had multiple cranial nerve palsy. The combination of cranial nerve involvement was variable and may involve CN II to VIII. Proptosis was seen in 15 patients (42%).

Looking into the combination of symptoms and signs, we note that 24 patients (67%) had ophthalmoparesis with nasal symptoms (Table 3). Ophthalmoparesis with neck mass occurred less frequently.

Computed tomography (CT) scan was the more common imaging modality requested for patients (27 patients, 75%). The rest had magnetic resonance imaging (MRI) done (Table 4).

Table 1. Clinical Profile of 36 Patients with NPCA

Clinical Characteristics	Value
Mean Age at presentation, in years	47 years
Age at presentation, n (%)	
10-19 years old	2 (6%)
20-29 years old	1 (3%)
30-39 years old	5 (14%)
40-49 years old	14 (39%)
50-59 years old	7 (19%)
60-69 years old	5 (14%)
70-79 years old	2 (6%)
Gender, n (%)	
Male	27 (75%)
Female	9 (25%)
Cigarette smoking history, n (%)	
Nonsmoker	21 (58%)
Smoker	15 (42%)
Positive family history of NPCA, n (%)	2 (6%)
Primary Service, n (%)	
Ophthalmology	13 (36%)
Otorhinolaryngology	20 (56%)
Oncology	2 (6%)
Dentistry	1 (3%)
Histopathology	
Undifferentiated	18 (50%)
Squamous Cell	7 (19%)
Adenoid Cystic	7 (19%)
Round Cell	4 (11%)

Table 2. Symptoms at Initial Consult

Symptomatology at Presentation	N (%)
Symptom Duration, n (%)	
<3 months	8 (22%)
≥3months	28 (78%)
Ophthalmic Symptoms, n (%)	
Blurring of Vision	26 (72%)
Unilateral	18 (50%)
Bilateral	8 (22%)
Doubling of Vision	23 (64%)
Eye Protrusion	13 (36%)
Eyelid Drooping	11 (31%)
Tearing	8 (22%)
Eye Pain	7 (19%)
Eye Redness	4 (11%)
Extra-Ophthalmic Symptoms, n (%)	
Nasal Symptoms	24 (67%)
Epistaxis	13 (36%)
Nasal Congestion	11 (31%)
Rhinorrhea	5 (22%)
Nasal Mass	2 (6%)
Otologic Symptoms	10 (28%)
Decreased Hearing	6 (17%)
Ear Fullness	3 (8%)
Tinnitus	3 (8%)
Constitutional Symptoms	14 (39%)
Headache	9 (25%)
Weight loss, anorexia, malaise	6 (18%)
Neck Mass	12 (33%)
Dysphagia	7 (19%)

Table 3. Presenting Symptoms and Signs in Patients with NPCA

Symptoms and Signs	N (%)
Ophthalmoparesis + nasal symptoms	24 (67%)
Ophthalmoparesis + nasal symptoms + blurring of vision	16 (45%)
Ophthalmoparesis + neck mass	12 (33%)
Ophthalmoparesis + neck mass + blurring of vision	6 (17%)

Table 4. Imaging in NPCA Patients

Imaging Results	N (%)
Type of Imaging	
Computed Tomography (CT) Scan	27 (75%)
Magnetic Resonance Imaging (MRI)	9 (25%)
Imaging Findings*	
High risk sites for invasion	5 (14%)
Medium risk sites for invasion	5 (14%)
Low risk sites for invasion	19 (53%)
Orbital invasion	15 (42%)
Incomplete data for stratification	7 (19%)

**Based on the risk of involvement by Liang[10]*

Following the classification of Liang in his 2009 study looking into risk of involvement of anatomic structures on imaging, 19 patients (53%) already had tumor spread in areas deemed low risk for invasion.[10] Five patients had invasion in sites deemed medium risk, and another 5 in those with high risk (13.9%). Orbital invasion was seen in 15 patients (41.7%).

DISCUSSION

This descriptive study characterized the clinical profile and presentation of patients with NPCA seen at the Ophthalmology department of a single referral hospital. Our study shows that NPCA is most common among males in their 40s which is consistent with previous studies.[6,11-14]

Genetics and smoking are known risk factors for NPCA.[15-18] However, our study data showed majority of patients were non-smokers and had no family history of NPCA. This is comparable to a local study by Yatco and Uy where only 30% of the patients were smokers, indicating that there were other factors that contribute to the development of NPCA.[11,19-21]

In this study, the mean duration of symptoms at the time of first consult was 18.3 months. Majority also had symptoms for more than three months which signifies chronicity of symptoms before consultation with a health professional was done. This delay in seeking consultation could have contributed to a high proportion of patients with invasion of distant structures on imaging or advanced disease. Two other local studies also reported high rates of advanced disease at initial presentation.[5,6] There are several reasons why a patient may delay seeking medical consult for this condition, including behavioral tendencies, socio-economic and demographic factors. In patients with head and neck cancer, the tumor site and its associated symptoms largely influence the time to first consult. Presence of a neck mass causes shorter delays while nasal obstruction, which can be easily dismissed, leads to increased delay for seeking medical consult.[22] Delays in diagnosis also contribute to late presentation of the disease.[23] Roxas et al. enumerated the reasons for the late detection of NPCA among Filipino patients and this included insidious growth of the tumor, the varied and non-specific presentation as well as the relatively inaccessible tumor location which renders it difficult to routinely examine.[6]

This study finding show that almost all of the patients with NPCA seen in the Ophthalmology department had ocular symptoms (97%). This is in contrast to a Nigerian study where medical records of patients with NPCA were retrieved from the Otorhinolaryngology department and showed a much lower rate of neuro-ophthalmologic symptoms (25%).[14] This huge discrepancy in the results is due to differences in the sampled population. Nevertheless, a significant proportion of patients with NPCA present with ophthalmologic symptoms and signs.

In addition, a notable finding of this study is that initial point of care of a third of patients with NPCA was with an ophthalmologist. This emphasizes the role played by ophthalmologists in the prompt recognition, diagnosis, and management of NPCA.

Similar to previous studies, this study demonstrated that blurred vision and binocular diplopia were the most common ocular complaints of patients with NPCA.[6,7] Blurred vision and diplopia are nonspecific symptoms. An astute ophthalmologist should then carry out a meticulous ophthalmic history-taking and examination to uncover the etiology. In this study, extra-ophthalmic symptoms were present in 34 out of 36 patients, with nasal symptoms being more common than otologic symptoms. Symptomatology varied, were largely non-specific, and included epistaxis, nasal congestion, rhinorrhea, nasal mass, decreased hearing, ear fullness, tinnitus, headache, etc. Epistaxis, the most common extra-ophthalmic symptom, was only reported in a third of patients. The four cardinal symptom manifestations of NPCA include nasal, otologic, neuro-ophthalmic, and metastatic symptoms.[14] Experts recommend that presence of 2 of 4 cardinal symptom manifestation should alert the clinician of NPCA.[14]

Cranial nerves III, IV, V, VI as well as the oculosympathetic fibers are known to be commonly affected in NPCA. A striking finding in the study is that majority of the patients had multiple cranial nerve involvement on examination. A high rate of multiple cranial nerve involvement in patients with NPCA was also reported by Roxas.[6] In addition, previous studies identified the abducens nerve

as the most commonly affected in NPCA.[6,12,13] Several permutations of cranial neuropathies was seen in this study, and not one arose as a clear-cut telltale sign for NPCA. This lays out the difficulty of attempting to paint a syndromic picture for NPCA since there is no distinct clinical feature.[23]

It should also be noted that NPCA may present as neurologically-isolated CN VI palsy, seen in three patients in the study. Two of the patients were older than 50 years of age and can be mistaken as cases of ischemic CN VI palsy. Traditionally, close observation with deferral of neuroimaging is the standard management of acute-onset, isolated palsy of the abducens nerve in older individuals.[24] However, both patients in this study presented with progressive diplopia and a nasal mass. One patient had a two-month history of diplopia, and was found to already have bilateral CN VI palsy. These features are atypical of an ischemic process and thus warrant neuroimaging.

Ophthalmoparesis, defined as weakness in one or more extraocular muscle, plus nasal symptoms were found in 2/3 of patients with NPCA in this study. Additionally, ophthalmoparesis with neck mass was found in another 1/3 of patients. Combination of these signs and symptoms may be better clues to NPCA.

Better understanding of the cranial nerve involvement brings us to the histopathologic subtype. The results of this study are in agreement with Carpiso and Vicente that undifferentiated carcinoma is the most common NPCA amongst the Filipino population.[12] Compared with squamous non-keratinizing type, undifferentiated tumors are less aggressive but their origin at the Rosenmuller's fossa favors spread along the skull base and into the cavernous sinus where cranial nerves pass through. Three mechanisms have been hypothesized for the spread to the cavernous sinus: 1) via the foramen lacerum which lies superior to the Rosenmuller fossa, 2) via perineural spread, 3) via skull base erosion. The small size and location of the CN VI in the cavernous both contribute to why it is the most commonly affected nerve.[12] The rest of the nerve palsies follow with further growth of the tumor in the cavernous sinus.

Compressive optic neuropathy is a common finding of NPCA as the mass expands and invades the orbital apex and orbit. Almost half of patients in this study were found to have compressive optic neuropathy from NPCA. This is in contrast to the study by Nwogbo and Peterside wherein visual impairment secondary to compressive optic neuropathy from NPCA was seen in 16%.[14] In the present study, eyes with compressive optic neuropathy from NPCA had Snellen VA ranging from 6/15 to hand movement. While optic disc edema is a rare and remains to be the subject of several case reports, optic disc pallor is a late finding noted in some studies.[25,26] In this study, majority of eyes had normal appearing discs. Astute clinicians must therefore look to other clues like the presence of a relative afferent pupillary defect, proptosis, dyschromatopsia, or involvement of other cranial nerves.

Roxas recommended that NPCA be a consideration for any cranial nerve involvement, whether it be single or multiple, combined with a neck mass, unilateral headache, and nasal and otologic complaints.[6] In this study, CN VI palsy with nasal symptoms particularly stood out, manifesting in two-thirds of the patients. It is therefore recommended, that in the presence of an abduction deficit, ophthalmologists must routinely evaluate for concomitant nasal problems in the history.

After the first crucial step of having NPCA as a consideration, appropriate clinic examination must be done to maximize yield from the visit. In addition to a thorough neuro-ophthalmic examination, a simple neck exam checking for masses or enlarged lymph nodes will be of value.[11]

This high index of suspicion must be followed through with prompt neuroimaging. More than half of patients showed presence of a tumor in distant areas that were deemed at low risk for invasion implying locally advanced disease. Although CT scan was requested for most of the patients in this study, Chang recommends MRI be the primary imaging modality for the following reasons: 1) skull base involvement seen in more patients, 2) identifies deep soft tissue or brain invasion, 3) defines radiotherapy area better, 4) 15-30% improvement in local tumor control and survival seen vs. CT scan.[27] We therefore recommend good quality brain MRI for evaluation of such cases.

The findings of this study have to be interpreted in light of its limitations. Only patients with NPCA who were evaluated in 2 subspecialty clinics in the Ophthalmology department were included in the study. The high rate of ocular abnormalities observed in this study is due to sampled population. Established NPCA cases managed by other services but were not referred to the Ophthalmology department were not included. Ophthalmic signs and symptoms may be overreported. This also resulted in a smaller number of patients for inclusion in this study. Sampling bias is also noted, with more advanced cases analyzed due to the tertiary referral hospital setting of this study. The retrospective, cross-sectional design of this study is a major limitation. The completeness of history and examination varied across charts. Radiologic data were collected from the paper print-out of the radiologist's interpretation. A prospective study with a standard questionnaire screening patients with NPCA regardless of ophthalmic symptoms may address these limitations.

CONCLUSION

In summary, majority of patients with NPCA seen in the Ophthalmology department have neuro-ophthalmic manifestations and more locally advanced disease. Blurred vision and diplopia are the most common ocular complaints. Blurred vision is frequently from optic nerve involvement while diplopia is due to ophthalmoparesis secondary to multiple ocular motor cranial nerves involvement. Male

patients in their 40s who present with neuro-ophthalmic signs should be probed for presence of otologic or nasal symptoms as well as neck masses as these are the common presentation of NPCA in the ophthalmology clinics.

Statement of Authorship

Both authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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