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Correlation of nasopharyngeal carcinoma symptoms based on Digby's score with biopsy results of nasopharyngeal masses of new patients in ENT-HNS clinic at prof. Dr. I.G.N.G Ngoerah State Hospital

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Abstract

Introduction: Nasopharyngeal carcinoma is a disease that may cause mortality and shows with many clinical symptoms in the nose, ear, eyes, and nervous system. This study aimed to help clinical workers decide which patient with these symptoms must be referred or not.

Methods: Primary data from the ENT Clinic of Prof. Dr. dr. I.G.N.G Ngoerah was used from January 2022 to March 2022. Descriptive analysis and logistic regression were employed to describe the relationship between patients' demographic, clinical symptoms with the diagnosis of NPC from histopathology examination.

Results: There are 40 patients in this study, with 22 patients have positive results of NPC, and 18 patients with negative results of NPC. Nasal mass, nasal symptoms and fulfillment of Digby's score are the most related to NPC's positive biopsy results (OR: 10, p=0.04; OR: 37. p=0,02; OR: 4.5, p=0,038 respectively).

Conclusion: NPC has wide variety of symptoms, and it must be kept in mind that these symptoms can be NPC and must consider to refer to ENT-HNS Specialist.

Keywords: Nasopharyngeal carcinoma; Digby's score; NPC symptoms; Biopsy

1. Introduction

Nasopharynx is a small tubular structure located at the back that connect the nose and the oropharynx. Cancer in this region is caused by squamous cell carcinoma with common region located in the Rosenmuller fossa. [1] Nasopharynx cancer (NPC) is a type of cancer with a variety of geographical distribution, where it is commonly caused by the Epstein-Barr virus (EBV) and Human Papilloma Virus (HPV). NPC is commonly found in the head and neck region. Worldwide incidence for NPC is less than 1/100.000 yearly. Around 81% new cases were found in Asia, 9% in Africa, and the rest is spread out worldwide [2,3].

Etiology of NPC is not exactly known, but its' carcinogenic nature is related to high EBV titer. Some risk factors that were included were eating preserved food or food that contained nitrosamine. In several epidemiological studies, family history with NPC were one of the main risk factors. Smoking and alcohol consumption were included in NPC risk factors. Several studies showed that high EBV circulation is strongly related to bad response to treatment, and lead to high mortality [1,2].

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Clinical manifestation of NPC is related to the location of the primary tumor, infiltration structure, or metastasis through neck lymph nodes. Based on these clinical manifestation, symptoms that occur on NPS patients could be classified into 4 parts: mass at neck region, nasal symptoms, ear symptoms, and weakness of cranial nerves [2,4].

Patients with nasopharynx mass could show nasal symptoms such as nasal blockage and overproduction of nasal mucus. In cases with smaller tumor, symptoms that occur are unilateral obstruction, and could develop into bilateral blockage due to tumor growth. NPC patients that experience nosebleed is commonly found due ulcers that is formed from the tumor. Tumor with ulcers could cause a small amount of bleeding and commonly accompanied with post nasal drip [1,2].

Tumor in nasopharynx is commonly related to symptoms found in eustachius tube, because the tumor have posterolateral extent inside the paranasopharyngeal cavity. Dysfunction in eustachius tube could cause unilateral conductive hearing problem. Otologic symptoms that could occur is otalgia and tinnitus. Primary tumor could also grow upwards and infiltrate cranial base and cause headaches. If tumor growth affects the carvenosus sinus and lateral walls, cranial nerves III, IV, and VI could be involved and cause diplopia. Tumor that growth towards the foramen ovale could affect the fifth cranial nerve, causing pain and loss of sensation in the facial region. NPC symptoms are commonly found in patients that present with painless mass in upper neck region [2,5].

NPC symptoms could be summarized in a diagnostic criteria called Digby score. Digby score contain points for each symptoms present, as shown at the table below. If the accumulated score is more than or equal to 50, then patient is very likely suffering from NPC. Score is deducted by 10 if patient is below 15 years old, and or in between 15-25 years old. This score is formerly known as “NPC Clinical Criteria for Statistics Purposes” and can be viewed in Table 1 [6]. This study aims to correlation of clinical symptoms of NPC, to the gold standard diagnosis of NPC and to help clinical workers decide which patient with these symptoms must be referred or not.

Table 1 Nasopharynx Clinical Criteria for Statitstics Purposes by Digby

| Symptom | Points |
|--|--------|
| Solid mass with a clear outline that can be seen from nasopharynx (nasal mass) | 25 |
| Enlarged cervical lymph nodes | 25 |
| Nasal symptoms | 15 |
| Ear symptoms | 5 |
| Nerve paralysis symptoms | 5 |
| Unilateral/Bilateral headache | 5 |
| Unilateral or bilateral exophthalmos and/or inflammation of cheeks and/or chin | 5 |
| Subtract 10 if the patient is under 15 years olf or between 15-25 years old with a frog face | |

2. Material and Method

This is a descriptive study that collects data from interviewing outpatients suffering NPC or suspected with NPC in Prof. Dr. dr. I.G.N.G. Ngoerah hospital, and data from Pathologic Anatomy division of Prof. Dr. dr. I.G.N.G Ngoerah. Sample is taken in Ear, Nose, Throat (ENT) division of the hospital from January 2022 until March 2022. The ethical clearance number for this research is No: 2602/UN14.2.2.VII.14/LT/2021.

The population for this study are patients that have been diagnosed with NPC or suspected with NPC based on the physical examination done at ENT polyclinic in Prof. Dr. dr. I.G.N.G. Ngoerah hospital. Sample taken is from the given population that passed the inclusion criteria. The inclusion criteria are patients that have been recently diagnosed with NPC or suspect NPC based on physical examination done within January 2022 – March 2022. Exclusion criteria are NPC patients that have been diagnosed before January 2022. Consecutive sampling is done when a patient fulfill the inclusion criteria as outpatient in ENT-HNS divison at Prof. Dr. dr. I.G.N.G Ngoerah hospital.

3. Results

The population of the patients that went to the ENT polyclinic at Prof. Dr. dr. I.G.N.G Ngoerah hospital since 1 January 2022 until 31 March 2022 were 40 patients. All patients have consented to this research. The demographic data can be seen at Table 2. Within 40 patients, 23 patients are male, and 17 are female. The youngest patient in this study is 15 years old, and the oldest patient is 75 years old. From 40 patients, 22 patients having positive result for NPC and 18 patients with negative result for NPC. The demographic of patients can be found in Table 2. Of the 22 patients with positive NPC, 18 patients have Digby score above 50 points, whereas 4 people is below 50 points. Within the 18 patients with negative results for NPC, 9 patients have Digby score above 50 points, and 9 patients with Digby score below 50 points.

Table 2 Demographic of outpatients in the ENT division for NPC treatment

| | Positive biopsy result for NPC (n=22) | Negative biopsy result for NPC (n=18) |
|--------------------|---------------------------------------|---------------------------------------|
| Age (years) | | |
| Mean ± SD | 45 | 42.5 |
| Range | 15-75 | 21-64 |
| Sex | | |
| Male | 14 (67%) | 9 (50%) |
| Female | 8 (33%) | 9 (50%) |
| Digby score | | |
| Positive (>50) | 18 (82%) | 9 (50%) |
| Negative (<50) | 4 (18%) | 9 (50%) |

Table 3 Logistic regression from each symptoms in Digby score towards histology results of NPC. The table underneath represents logistic regression from Digby score above 50 points and sex towards histopathologic result of NPC

| Symptoms | Odd Ratio | p |
|-----------------------|-----------|-------|
| Nasal mass | 10 | 0.04 |
| Nasal symptoms | 37 | 0.02 |
| Ear symptoms | 52.3 | 0.13 |
| Head symptoms | 2.6 | 0.36 |
| Neurological symptoms | 0.07 | 0.039 |
| Exophthalmos | 15 | 0.999 |
| Enlarged lymph nodes | 9.14 | 0.098 |
| Digby score | 4.5 | 0.038 |
| Sex | 1.75 | 0.387 |

In Table 3, it is shown the odd ratio for each symptoms in Digby score. Nasal mass can be found through palpation or inspection from the oral cavity, with distinct characteristic and solid texture. Other characteristics that is related to nasal mass is deviated uvula, descending soft palate, bloody mucus, and mass underneath the uvula. Mass has an odd ratio (OR) of 10 (p=0,04) which predicts the presence of NPC. Symptoms present on the nose could be unilateral nosebleed which can develop into bilateral nosebleed. Common symptoms from NPC is nasal obstruction. In this study, nasal symptoms have an OR 37 (p=0.02). Ear symptoms could be deafness with tinnitus. Symptoms of the ear have an OR 52.3 (p=0.13). Head symptoms that lead to NPC have an OR 2.6 (p=0.36). Neurological involvement could be from cranial nerves and could cause anosmia, and optic atrophy. Trochlear nerves, oculomotor, and abducens could also be

affected and thus abnormality in optic muscles. Symptoms from trigeminal nerves could produce loss of sensation in the facial region. Abnormality from pterygoid muscle could cause trismus. Abnormality in facial nerves could cause deviation of lips. Headache is commonly caused from erosion of the cranial base, nerves, and muscle that cause increase intracranial pressure later on. Neurologic symptoms shows OR 0.07 ($p=0.039$) towards NPC. Exophthalmos could happen with NPC patients, specifically carcinoma with cystic adenoid type. In addition, exophthalmos could decrease the range of motion of the affected eyeball. Exophthalmos have an OR of 15 ($p=0.999$) towards NPC. Enlarged lymph nodes in NPC could indicate the metastasis of NPC to the lymph nodes. This symptoms have an OR of 9.14 ($p=0.098$).

4. Discussion

Nasopharynx is small tubular structure that is part of the upper respiratory tract. Anatomically, nasopharynx connect the nasal cavity with larynx through oropharynx. Nasopharynx is the superior part of pharynx and act as a border for the skull base. Cancer arising from this area is commonly caused by squamous cell carcinoma, found mostly in Rosenmuller fossa [2,7,8]. NPC is a type of cancer with a variety of geographical distribution, where it is commonly caused by the Epstein-Barr virus (EBV) and Human Papilloma Virus (HPV). NPC is commonly found in the head and neck region. Worldwide incidence for NPC is less than 1/100.000 yearly. Around 81% new cases were found in Asia, 9% in Africa, and the rest is spread out worldwide [2,4].

The leading cause of NPC is not fully understood, but there are a few risk factors including eating habits of preserved food and food that contained nitrosamine. Smoking, alcohol consumption, and EBV infection could also be found. Several studies have shown that high EBV titer is related to poor response in therapy and level of metastasis have higher mortality rate. This is also the reason why male sex is more often to have NPC because of their stress of work and leads to consuming alcohol and smoking [2,9-11]. According to Chua et al., EBV infection could be found in different types of NPC, and not found on healthy epithelial cells of the nasopharynx. Thus, EBV infection is a crucial step in pathogenesis of NPC. Risk of EBV infection increases if there are intrinsic genetic deletion in 3p and 9p. These changes could affect the normal cell cycle with the process of irregularly inactivating p16 and overexpression from D1 cyclin causing EBV to transform low grade dysplasia epithelial cell into high grade dysplasia. Human Papilloma Virus (HPV) is also a risk factor for NPC, however, the pathogenesis and the process that are involved are not fully understood [2]. Study from Tsao et al., consumption of traditional drugs in Asia is also a risk factor for NPC due to the probability of increasing lytic expression of EBV antigen [12]. Study from Wu et al. stated that main risk factor in elderly patients is poor oral hygiene which causes periodontitis. Periodontitis could increase factors of inflammation and risk of having NPC, specifically in cases where teeth were not present anymore. This could cause a rapid growth of bacteria and produce nitrosamine which again, increase the risk of NPC [11]. Based on systematic reviews and meta-analyses from Okekpa *et al*, consumption of salted fish (OR:1.41; 95% CI 1.13-1.75; $p<0.01$), smoking (OR: 1.89; 95% CI 1.49-2.38), and alcohol consumption (OR: 1.42; 95% CI 1.23-1.65) are significant factors that leads to NPC. In addition, consumption of preserved meat and vegetables, and dust exposures could increase risk of NPC significantly ($p<0.05$) [13].

Symptoms arise from NPC are due to gradual increase of grading or the surface area on which the carcinoma is affected. In the early stages of NPC, symptoms that occur are mostly ear, nose, and eyes problem. Highlighting the problem on the nose, symptoms that arise are unilateral nasal obstruction, nosebleed, less sensitivity of smell, and altered perception of smell. Around 80% of NPC patients present with nasal problems. Nosebleed is commonly found due to trauma in the NPC. These symptoms occur due to the invasion of NPC to the nasal cavity, fossa pterygoid, and maxillary sinus [1,2,14-17]. Ear related symptoms that occur are recurrent ear infection with dysfunction of eustachius tube, deafen hearing, otorrhea, otorrhagia, effusion, and tinnitus. These may happen because of NPC's invasion to the middle ear. If the patient is treated with radiotherapy, sensorineural deafness could arise as a complication. These symptoms could arise if the NPC invade the pharyngobasilar fascia or the base of the skull [2,18,19]. Eye symptoms are related to neural symptoms since the carcinoma spread to the cranial nerves, and lesion of cranial nerves III, V, VI and XII happened often. Clinical manifestation that occur are bilateral loss of vision, difficulties in eyeball movements, blurry vision, proptosis, pain in the eye, and optic disc edema. Patients with eye symptoms could have worse prognosis [5,20-22]. Headache could be present due to NPC that spreads inside the cranial cavity thus leading to persistent headache [23]. In this study, symptoms that are found in NPC patients are nasal mass, nasal related symptoms, ear symptoms, exophthalmos and enlarged lymph nodes. These findings supports of the study found by Sinha which explained that the early symptoms are mostly ear, nose, and eye related symptoms. If health workers or doctors from the peripheral health facility and emergency department can find these symptoms, they can also use this study as one of many methods to decide which patient need to be referred to undergo biopsy.

NPC can be diagnosed from anamnesis, physical examination, and laboratory examination. Pathologic examination with biopsy or fine needle aspiration (FNA) is the gold standard for diagnosing NPC. Other examination could be done such as complete blood count or specific blood examination, CT scan or MRI [24]. The treatment for early stage of NPC (stage

I, stage II, or undifferentiated/ WHO type III) are with radiotherapy. Whereas the advanced stage of NPC (Stage III and IV) with severe metastasis, persistent and recurrent tumor is recommended to undergo chemotherapy. Latest recommendation is using chemotherapy *cisplatin*, *5-fluorouracil*, *taxane*, *gemcitabine*, *vinorelbine*. Patients with persistent or recurrent nasopharynx tumors could undergo a surgical procedure called nasopharyngectomy. Small NPC tumors yet thick in size could undergo a procedure called adequate resection using endoscope which is inserted through the oral or nasal cavity, whereas tumors with greater diameter will undergo open resection [10,24].

5. Conclusion

Based on this study, NPC can cause many symptoms at the nose, ear, eye, and neurological systems, and must be prevented early before NPC cause wider and worse damage. These symptoms must be kept in mind to decide which patient might have NPC and must be referred or which patient might not have NPC.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

This study was proposed in ethical clearance application in our institution and hospital, and was already approved to continue with this research. The approval allowed us to interview the patients involved in this study according to their symptoms.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study to interview according to their symptoms.

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