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# Cranial nerve disorders in nasopharyngeal carcinoma cases at Dr. Kariadi General Hospital Semarang-Indonesia, 2014-2016

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## ABSTRACT

**Background:** Cranial nerve disorders among nasopharyngeal carcinoma (NPC) patients were around 15-30%. Complaints that encourage patients to come for treatment are due to symptoms of the spread of tumor cells to the lymph nodes in the neck and symptoms of cranial nerve disorders. There was no previous data regarding cranial nerve involvement on NPC cases at Dr. Kariadi General Hospital Semarang. This study aimed to determine the proportion of neurologic abnormalities in NPC patients.

**Methods:** This was a descriptive retrospective study conducted in Dr. Kariadi General Hospital Semarang. Data were collected retrospectively from medical records from January 2014 to December 2016. The diagnosis of NPC was based on several examinations such as medical history, physical examination, nasopharyngoscopy, histopathology, chest radiography, ultrasound and nasopharyngeal MSCT Scan.

**Results:** Within 3 years (2014-2016), 141 new NPC cases were obtained, which were found commonly in third, fourth and fifth decades of life with 3:1 male to female ratio. Neurological disorders were found in 27.7% of NPC, in the form of impaired eyeball movement (most affected to cranial nerve VI followed by cranial nerves III and IV), swallowing disorders (cranial nerves IX, X) and facial sensibility disorder (cranial nerve V).

**Conclusion:** The proportion of cranial nerve involvement in NPC was 27.7%. The most affected cranial nerves were a group cranial nerves innervating eye movement muscles followed by the nerves controlling swallowing activities and facial sensibility.

**Keywords:** nasopharyngeal carcinoma, cranial nerve disorders

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## INTRODUCTION

Nasopharyngeal carcinoma (NPC) is the most common malignancy among malignant tumors of ear, nose, throat (ENT), head and neck in Indonesia.[1] Cranial nerve involvement in NPC patients in Indonesia have been reported with estimation ranging from 15-30%, with higher was reported in overseas which accounted for 40-50%.[1,2]

Complaints that encourage patients to come for treatment were owing to the symptoms of the spread of tumor cells to the lymph nodes in the neck and symptoms of cranial nerve disorders. Neurologic abnormalities might appear due to direct suppression of tumor into the surrounding tissue and indirect suppression by lymph nodes enlargements (due to lymphogenic spreading).[3]

Symptoms of neurologic disorder may arise preceding the clinical manifestations or diagnosis of carcinoma. Otherwise, it might occur long after carcinoma diagnosis has been established. If cranial nerve disorders discovered in NPC patients, it indicates an intracranial extension, whose prognosis was generally poor.[1,4,5]

In Dr. Kariadi General Hospital Semarang, new cases of NPC tend to increase annually. However, there was no previous data regarding the proportion of neurologic disorders in NPC patients. Hence, we conduct a study to determine the proportion of neurologic abnormalities in NPC patients.

## MATERIALS AND METHODS

This study was a descriptive study conducted in Dr. Kariadi General Hospital Semarang. Data were taken retrospectively from medical records from 1 January 2014 to December 2016. The diagnosis of NPC was based on several examinations such as medical history, physical examination, nasopharyngoscopy, histopathology, chest radiography, ultrasound and Nasopharyngeal MSCT Scan. The determination of NPC stage was based on those examinations, and WHO classification of NPC was based on histopathological examination.

## RESULTS

Based on table 1, the prevalence of NPC increased year by year both in male and female. The ratio of male to female subjects with NPC was 3: 1. Most NPC cases were found in third, fourth, fifth decades

**Table 1** The distribution of 141 patients with NPC based on sex at ENT – Head and Neck Division of Dr. Kariadi General Hospital Semarang in January 2014 to December 2016

| | Male | | Female | | Total | |
|---|---|---|---|---|---|---|
| Year | n | % | N | % | N | % |
| 2014 | 31 | 77.5 | 9 | 22.5 | 40 | 28.4 |
| 2015 | 34 | 72.3 | 13 | 27.7 | 47 | 33.3 |
| 2016 | 38 | 70.4 | 16 | 29.6 | 54 | 38.3 |
| Total | 103 | 73.1 | 38 | 26.9 | 141 | 100 |

**Table 2** The distribution of 141 patients with NPC based on age at ENT – Head and Neck Division of Dr. Kariadi General Hospital Semarang in January 2014 to December 2016

| | 2014 | | 2015 | | 2016 | | Total | |
|---|---|---|---|---|---|---|---|---|
| Age group | n | % | n | % | n | % | N | % |
| 0-9 | 0 | 0 | 1 | 2.1 | 0 | 0 | 1 | 0.7 |
| 10-19 | 6 | 15.0 | 3 | 6.4 | 1 | 1.8 | 10 | 7.1 |
| 20-29 | 6 | 15.0 | 3 | 6.4 | 3 | 5.6 | 12 | 8.5 |
| 30-39 | 9 | 22.5 | 12 | 25.5 | 9 | 16.7 | 30 | 21.3 |
| 40-49 | 7 | 17.5 | 12 | 25.5 | 16 | 29.6 | 35 | 24.8 |
| 50-59 | 10 | 25.0 | 10 | 21.3 | 15 | 27.8 | 35 | 24.8 |
| 60-69 | 2 | 5.0 | 5 | 10.7 | 8 | 14.8 | 15 | 10.7 |
| 70-79 | 0 | 0 | 1 | 2.1 | 2 | 3.7 | 3 | 2.1 |
| Total | 40 | | 47 | | 54 | | 141 | 100 |

**Table 3** The distribution of 141 patients with NPC based on chief complaints and presence of cranial nerve disorders at ENT – Head and Neck Division of Dr. Kariadi General Hospital Semarang in January 2014 to December 2016

| | Presence of Cranial Nerve Disorders | | | | | |
|---|---|---|---|---|---|---|
| | Yes | | No | | Total | |
| Chief Complaints | N | % | N | % | n | % |
| Enlarged neck lymph nodes | 16 | 41.0 | 80 | 78.4 | 96 | 68.1 |
| Nose disorders | 5 | 12.8 | 17 | 16.6 | 22 | 15.6 |
| Eyes disorders | 10 | 25.7 | 2 | 2.0 | 12 | 8.5 |
| Ear disorders | 0 | 0 | 2 | 2.0 | 2 | 1.4 |
| Dysphagia/Odynophagia | 3 | 7.7 | 0 | 0 | 3 | 2.2 |
| Headache | 5 | 12.8 | 1 | 1.0 | 6 | 4.2 |
| Total | 39 | 27.7 | 102 | 72.3 | 141 | 100 |

of life. The youngest patient was found in 0-9 year old group (table 2). Cranial nerve disorders were found in 39 cases (27.7%) from total 141 cases of NPC. Enlarged neck lymph node was the most frequent chief frequent complaint among NPC patients (68.1%). The proportion of NPC patients with enlarged neck lymph node and cranial nerve disorders is about 41.0%, followed by the proportion of NPC patients with eyes disorder (25.7%) (table 3).

One patient might suffer more than one cranial nerve disorders. The most commonly affected cranial nerve was cranial nerve VI (92.3%), followed by cranial nerve III (64.1%), cranial nerve IV (53.8%), cranial nerve V (35.9%), cranial nerve IX (35.9%), and cranial nerve X (33.3%). NPC patients with cranial nerve VII and XI disorders were uncommon. There was no disorder found of cranial nerve I and VIII in NPC patients (table 4). Based on the histopathological finding, cranial nerve disorders of NPC patients were most characterized by histopathological findings of WHO type 2 (46.2%) and WHO type 3 (53.8%) (table 5). Cranial nerve disorders of NPC patients were commonly found at stage III (76.9%) and stage IV (23.1%) (table 6). There was found 20.5% of the destructive lesion from MSCT Scan of Cranium in NPC patients (table 7).

**Table 4** The distribution of 141 patients with NPC based on cranial nerve disorders at ENT – Head and Neck Division of Dr. Kariadi General Hospital Semarang in January 2014 to December 2016

| Cranial nerve disorders | Total | | Cranial nerve disorders | Total | |
|---|---|---|---|---|---|
| | n | % | | n | % |
| Nerve I | 0 | 0 | Nerve VII | 2 | 5.1 |
| Nerve II | 2 | 5.1 | Nerve VIII | 0 | 0 |
| Nerve III | 25 | 64.1 | Nerve IX | 14 | 35.9 |
| Nerve IV | 21 | 53.8 | Nerve X | 13 | 33.3 |
| Nerve V | 14 | 35.9 | Nerve XI | 1 | 2.6 |
| Nerve VI | 36 | 92.3 | Nerve XII | 6 | 15.4 |

**Table 5** The proportion of cranial nerve disorders in NPC patients based on histopathological findings at ENT – Head and Neck Division of Dr. Kariadi General Hospital Semarang in January 2014 to December 2016

| Histopathological finding | Cranial nerve disorders | |
|---|---|---|
| | N | % |
| WHO type 1 | 0 | 0 |
| WHO type 2 | 18 | 46.2 |
| WHO type 3 | 21 | 53.8 |
| Total | 39 | 100 |

**Table 6** The proportion of cranial nerve disorders in NPC patients based on staging at ENT – Head and Neck Division of Dr. Kariadi General Hospital Semarang in January 2014 to December 2016

| Stage | Cranial nerve disorders | |
|---|---|---|
| | N | % |
| I | 0 | 0 |
| II | 0 | 0 |
| III | 30 | 76.9 |
| IV | 9 | 23.1 |
| Total | 39 | 100 |

**Table 7** The proportion of cranial nerve disorders in NPC patients based on MSCT Scan of Cranium at ENT – Head and Neck Division of Dr. Kariadi General Hospital Semarang in January 2014 to December 2016

| MSCT Scan | Cranial nerve disorders | |
|---|---|---|
| | N | % |
| Destruction (-) | 31 | 79.5 |
| Destruction of the petrous bone | 2 | 5.1 |
| Destruction of the sella turcica | 6 | 15.4 |
| Total | 39 | 100 |

## DISCUSSIONS

There were 141 cases of NPC consisted of 103 men (73.1%), and 38 women (26.9%). The prevalence of NPC in both sexes increased year by year with the ratio of male to female cases was 3:1. These results were consistent with previous study by Maubere and Nuaba in Denpasar in 2014 which also stated that men with NPC were more likely than women with a men to women ratio was 2.78:1.[6] NPC could affect people of all ages, mostly in fourth to fifth decades of life.[7] Similarly, this study found younger affected people those aged around third to fifth decades of life, with the youngest patient aged 9 years old. The supporting findings suggested that the incidence of NPC occurred most often in the middle age due to prolonged and continuous exposure of carcinogenic substances, accumulation of gene mutations, decreased efficiency of DNA repair and weakening of the immune system.[8,9]

In this study, common symptoms which encourage patients to come for treatment was swollen lymph nodes in the neck as much as 96 cases (68.1%) accompanied by nose disorders, both congestion and epistaxis, accounted for 22 cases (15.6%). The proportion of the neck lumps as common symptom was similar according to the previous study which reported 75-90% of new cases of metastatic NPC with 50% presenting with bilateral neck masses.[10] Another supporting study also found that cervical lymphadenopathy was a common presentation of NPC which was classically located at the level II or VIII or VI lymph nodes or at any other levels of the lymph nodes in the neck.[11]

Symptoms of cranial nerve disorder included eye disorders were usually preceded by disturbing subjective symptoms such as headaches or dizziness, cheek and nose hypesthesia, occasionally dysphagia.[1] 39 patients (27.7%) of total 141 NPC patients experienced cranial nerve disorders. The amount of cranial nerve involvement in NPC patients correspond to reported data in the Education Hospital with estimates ranging from 15-30% whereas the higher prevalence abroad which accounted for 40-50%.[1]

The spread of NPC occurred via surrounding tissue invasion, lymphatic system or bloodstream.[5,6,12] The spread of NPC through the olfactory foramen in the cribriform plate led to cranial nerve I deformity.[13] In addition, NPC cases with endophytic growth was more common than exophytic growth form.[1,2] Olfactory nervous disorder because of NPC expansion was very rare.


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The compression of olfactory nerve was caused by exophytic growth form of NPC. In this study, no cranial nerve I abnormalities were found. A rare case of cranial nerve I involvement was found as Garcin's syndrome presenting as an early sign of NPC. Garcin's syndrome is an ipsilateral step-by-step deterioration of cranial nerves I to XII caused by a malignant osteoclastic lesion at the skull base or other malignancies.[14]

The spread of NPC can directly through the damaged cranial base or through the foramen lacerum and the foramen ovale and then enter the middle cranial fossa (endocranium) lead to extradural spread. This spread is common because the location of foramen lacerum is about 1.5-2 cm from the fossa of Rosenmuller which is the most common site of predilection for NPC, hence the abnormalities of the nerves located close to the foramen will be more frequent. At the top of the foramen lacerum, there is a cavernous sinus through which nerve VI passes and more superiorly there are nerves V, III, and IV respectively.[5,12,15] Group of cranial nerves III, IV, VI is a group of nerves innervating the eyeball muscles. If there was dysfunction in this nervous group, would result in limited ocular movement leading to diplopia.[16]

In this study, there were 92.3% nerve VI disorders, 64.1% nerve III disorders, 53.8% nerve IV disorders. Nerve VI is generally most affected because of its location is the lowest among the cervical groups through the cavernous sinus. Thus, eye movement disorders are most commonly encountered in NPC in Dr. Kariadi General Hospital Semarang for three years. Nerve V abnormality leads to facial sensibility disorder. Anatomically the nerve V is located superior to the nerve VI, but inferior to the nerves III and IV. Nerve V disorder is usually not so perceived by the patients compared to eye movement disorder. In this study, nerve V abnormalities found were 35.9% which less than nerves III and IV abnormalities. With the spread of NPC in the same direction, it can also cause nerve II defect via superior orbital fissure into the orbital cavity and then spread forward. This nerve II disorder is also due to the spread of the NPC directly through the optic foramen or by increased intracranial pressure because of NPC invasion in the endocranium.[13] The nerve II abnormalities were only found in 2 cases (5.1%).

Nerve VII and VIII disorders are rare, probably due to the location of nerves VII and VIII in the internal acoustic canal (petrous bone) which far away from the predilection site of NPC.[5,13,15] Nerve VII abnormalities may occur without destruction of the petrous bone, when NPC invade to tuba or spread to the lymph nodes surrounding the eustachian tube induce blockage and disturbance of the middle ear further lead to purulent otitis media which generate nerves V and VII abnormalities.[13,15]

The jugular foramen is the exit for the nerves IX, X, XI from the cranial cavity during the hypoglossal canal for the nerve XII. NPC invasion to this site generates nerves IX, X, XI, XII abnormalities.[13] It also occurs due to enlarged lymph nodes compression in the parapharyngeal space (NPC spread via lymph vessels). The parapharyngeal lymph nodes (Rouviere) receive lymph flow from the lymphoid tissue of the nasopharyngeal region. The lymph nodes are located at the very top of the parapharyngeal space close to cranial base anterosuperolaterally, adjacent to the cranial nerves IX, X, XI, XII. These lymph nodes are the most frequently affected by the lymphatic spread of NPC. Thus that nervous group disorder often occurs.[13]

Cranial nerve IX and X abnormalities usually occur together because both nerves are always passing together from its own nucleus until exit through the jugular foramen. Nerves IX and X abnormalities induce swallowing disorders.[13] In this study, the proportion of nerve IX abnormalities was 35.9%, and nerve X abnormalities were 33.3% which similar to the previous study by Prado et al. Which suggested that nasopharyngeal carcinoma can cause disturbances in the glossopharyngeal and vagal nerves by mass suppression on the perineural sheath.[17] Hence, swallowing disorders were the second most common symptom of impaired eyeball movement in NPC patients in Dr. Kariadi General Hospital Semarang for 3 years. The cranial nerves XI and XII disorders are less common. In this study, cranial nerve XII involvement was 15.4% similar to one study from China where cranial nerve XII was involved in 11.0% cases.[18]

NPC staging is based on the size and extension of tumor growth (T), lymphatic invasion (N), and distant metastatic spread (M). These stages determine the severity and prognosis of NPC.[1,4] NPC patients with cranial nerve disorders indicate intracranial invasion with poor prognosis, since the tumor cells spread out from the nasopharynx with or without bone destruction accompanied by or without the tumor cells spread to the lymph nodes (Stage III and stage IV).[1,4,5] 39 cases of NPC with neurologic disorders were commonly found in stage III in this study.

Histologically, malignant epithelial cells of NPC are large polygonal cells. The nuclei are round or oval with scanty chromatin and distinct nucleoli. In 2005, World Health Organization (WHO) classified NPC into 3 histological types: keratinizing squamous cell carcinoma (type I), non-keratinizing squamous carcinoma which is further subdivided

into differentiated and undifferentiated types (type II) and basaloid squamous cell carcinoma (type III).[19] However, the histological classification of NPC used in Dr. Kariadi General Hospital Semarang is old histological classification from WHO 1978 consisted of keratinizing squamous cell carcinoma (type I), non- keratinizing epidermoid carcinoma (Type II) and undifferentiated squamous carcinoma (type III). This study found 39 cases of NPC with neurological abnormalities which were mostly classified into WHO type 3 (53.8%) followed by WHO type 2 (46.2%).

## CONCLUSION

NPC cases in Dr. Kariadi General Hospital Semarang for 3 years (2014-2016) were 141 cases with a male to female ratio was 3:1. The highest incidences were found between the ages 30 and 50 years. The most common chief complaint was swollen neck lymph nodes. The proportion of cranial nerve abnormalities was 27.7%. The most affected cranial nerves were a group cranial nerves innervating eye movement muscles (nerves III, IV, VI) followed by the nerves controlling swallowing activities (nerves IX, X) and facial sensibility (nerve V). Cranial nerve disorders were commonly found at NPC stage III and mostly classified into WHO histological type 2 and type 3.

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