Research Article

Neuro-Ophthalmology Manifestations in Brain Tumor Patients and Its Related Factors at dr. Cipto Mangunkusumo Hospital

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Abstract

The visual system has complex connections with all brain areas and can be affected by a brain tumor. Neuro-ophthalmological examinations are important because early diagnosis and managing small tumors will improve outcomes. This study aimed to investigate brain tumors' neuro-ophthalmic (NO) manifestation and the affecting factors. A cross-sectional study using total sampling was conducted in patients undergoing pre-operative examinations from January 2014 to December 2019 in dr. Cipto Mangunkusumo National Referral Hospital. Variables studied in this paper are brain tumor characteristics, NO manifestations, and the relationship between them. Analysis was conducted using chi-square or Fisher's exact test and post hoc analysis. All subjects presented with NO manifestations, with fundoscopic abnormalities (72.9%) as the most common manifestation. The relationships between the tumor type with visual field disturbances (p=0.002) and multiple tumor lesions with funduscopic abnormalities (p=0.043) were significant. Lesion location also had a significant relationship with all NO variables (p<0.05). The NO manifestations were found in all subjects, predominantly the fundoscopic abnormalities. The tumor type, number of lesions, and location of lesions had a significant relationship with NO manifestations.

Keywords: *funduscopic abnormalities, neuro-ophthalmic abnormalities, neuro-ophthalmic manifestations, brain tumors.*

Manifestasi Neuro-Oftalmologi Pasien Tumor Otak dan Faktor-faktor yang Berhubungan di RSUPN dr. Cipto Mangunkusumo

Abstrak

Sistem visual memiliki hubungan kompleks dengan seluruh area otak dan dapat dipengaruhi oleh keberadaan tumor otak. Pemeriksaan neuro-oftalmologi penting karena diagnosis dini dan manajemen tumor kecil akan memberikan hasil yang lebih baik. Penelitian ini bertujuan untuk mengetahui manifestasi neuro-oftalmik (NO) dari tumor otak dan faktor-faktor yang memengaruhinya di Rumah Sakit Rujukan Nasional dr. Cipto Mangunkusumo. Studi potong lintang dengan total sampling dilakukan untuk menentukan pola manifestasi NO dan hubungannya dengan karakteristik tumor otak pada pasien yang menjalani pemeriksaan pre-operatif dari Januari 2014 hingga Desember 2019. Variabel yang dikaji adalah karakteristik tumor otak, manifestasi NO, dan hubungan antara keduanya. Data dianalisis dengan uji chi-square atau uji Fisher's exact, dan analisis post hoc. Semua subjek mengalami manifestasi NO dengan kelainan funduskopi (72,9%) sebagai manifestasi paling umum. Terdapat hubungan antara jenis tumor dengan gangguan lapang pandang visual (p=0,002) dan lesi tumor ganda dengan kelainan funduskopi (p=0,043). Lokasi lesi juga berhubungan dengan semua variabel NO (p<0,05). Manifestasi NO ditemukan pada semua subjek, terutama kelainan funduskopi. Jenis tumor, jumlah lesi, dan lokasi lesi berhubungan dengan manifestasi NO.

Kata kunci*: kelainan funduskopi, kelainan neuro-oftalmik, manifestasi neuro-oftalmik, tumor otak.*

Introduction

Brain tumor refers to a collection of tumor cells that arise from different cells, originating within the brain (primary tumors) or systemic tumors that have metastasized to the brain (secondary tumors). Brain tumors have high morbidity and mortality due to the progression of symptoms.[1-3] The visual system has contact with all areas of the brain, which the presence of a brain tumor can destroy. Thus, examination of the visual afferent and efferent systems, which includes an examination of visual acuity, visual field, fundoscopy, and examination of eye movements, becomes important for neurologists.[4-6]

Some brain tumors have specific neuro-ophthalmic (NO) manifestations that indicate their locations.[3,6,7] More than 50% of patients with primary and secondary brain tumors present with NO symptoms or signs as initial manifestations. This NO manifestation can even have a higher percentage if it is a continuation manifestation of a brain tumor.[8,9] The main principle of tumor management, especially primary tumors, in general, is as much resection as possible. However, in brain tumors, this can not always be done, especially if the tumor is in a functional area, the size is too large, or the location is difficult to reach. This underlies the importance of diagnosing brain tumors with routine neuro-ophthalmological examinations because treatment of small tumor masses will give a better prognosis.[9,10]

Acomplete NO examination in suspected cases of a brain tumor can provide information, among others, regarding the location of the prediction of the type of brain tumor lesion so that efficiency can be achieved in requesting investigations and treatment. Lesions that have not provided morphological changes on imaging may also be detectable because the neuro- ophthalmological examination is an examination that assesses the function of visual afferent and efferent pathways.[11] At the Department of Neurology, dr. Cipto Mangunkusumo National Referal Hospital, data regarding neuro-ophthalmic disorders due to brain tumors has not been processed, so conclusions cannot be drawn regarding the distribution of neuro-ophthalmic disorders in brain tumor patients and the associations between clinical manifestations of neuro-ophthalmology and brain tumor characteristics. Thus, this study aimed to determine the pattern of NO manifestations of brain tumors and their associations with brain tumor characteristics.

Methods

This study used cross-sectional observational analytical design to determine the pattern of neuro-ophthalmic manifestations of brain tumors and their associations with brain tumor characteristics. Data were collected from medical records between January 2014 and December 2019 in the Neuro-ophthalmology division at Neurology Clinic, dr. Cipto Mangunkusumo National Referral Hospital, Jakarta, Indonesia.

The inclusion criteria for this study were primary and secondary brain tumor patients aged >18 years diagnosed by imaging and histopathology data. The patients had to undergo pre-operative NO examination at the Neurology clinic. Exclusion criteria in this study were brain tumors which were infiltration of orbital tumors, and ear, nose, and throat tumors.

Categorical data is presented in frequency and percentage. Numerical data with normal distribution was presented as the mean, while data with abnormal distribution was presented as the median and maximum-minimum values. Numerical data were tested for normality with the Kolmogorov-Smirnov test. The relationship between two categorical variables was analyzed using the chi-square or Fisher's exact test. The relationship between more than two categorical variables was analyzed using a chi-square test with post hoc analysis to see if it was feasible to test. The relationship between variables was declared significant if $p < 0.05$. The data was processed and arranged as frequency distribution tables and cross tables using SPSS version 20. This study was approved by the Ethics Committee of the Faculty of Medicine, University of Indonesia, under approval number KET-625/UN2.F1/ETIK/PPM.00.02/2021.

Results

There were 70 patients with confirmed intracranial tumors diagnosed by brain imaging and histopathology findings who underwent a pre-operative NO examination in the Neuro-ophthalmology division, Neurology clinic, between January 2014 and December 2019. The assessed variables were recorded at one time.

Among 70 subjects, female dominated (62.9%). The mean age of the subjects was 41.9±12.8 years. Based on the origin, the most common types of tumors were primary tumors (68.6%), with the domination of meningioma (31.3%) and pituitary adenomas (29.2%). Among 22 secondary brain tumor patients, breast (36.4%), malignant lymphoma (27.3%), and lung (22.7%) were the primary source of metastases. The number of lesions at one location is similar to multiple locations (48.6%% and 51.4%) but mainly unilateral (55.7%). The most common tumor locations were in the frontal lobe (41.4%),

followed by the sella region and the occipital lobe (37.1%, each). The description of the brain tumor characteristics can be seen in Table 1.

Table 1. Brain Tumor Characteristics

Characteristics	n (%)
Types of Brain Tumors (n=70)	
Primary brain tumors	48 (68.6)
Secondary brain tumors	22 (31.4)
Primary Brain Tumors (n=48)	
Meningioma	15 (31.3)
Adenoma Hipofisis	14 (29.2)
Schwannoma	5 (10.4)
Kraniofaringioma	5 (10.4)
Astrositoma	5 (10.4)
Solitary Fibrous Tumor	2 (4.2)
Oligodendroglioma	1 (2.1)
Epidermoid Cyst	1 (2.1)
Metastases source of secondary brain tumors (n=22)	
Breast	8 (36.4)
Limfoma Malignum	6 (27.3)
Lung	5 (22.7)
Sarcomas	2 (9.1)
Colon	1 (4.5)
Tumor Locations (n=70)	
Frontal Lobe	29 (41.4)
Parietal Lobe	23 (32.9)
Temporal Lobe	14 (20)
Occipital Lobe	26 (37.1)
Sella Region	26 (37.1)
Subcortical dan Ventricle region	8 (11.4)
Skull base	9 (12.9)
Leptomeningeal	1 (1.4)
Cerebellum	9 (12.9)
Brain Stem	7 (10)
Cerebellopontin angle	7 (10)
Tumor Locations based on Tentorial Marker (n=70)	
Supratentorial	49 (70)
Infratentorial	9 (12.9)
Supratentorial dan Infratentorial	12 (17.1)
Number of Tumor Locations (n=70)	
One Location	34 (48.6)
Multiple Locations	36 (51.4)
Distribution of Tumor Lesion (n=70)	
Unilateral	31 (55.7)
Bilateral	19 (27.1)
Midline	28 (40)

In this study, NO abnormalities were present in 100% of the subjects (Table 2). The abnormalities were funduscopic (72.9%), followed by visual disturbances, eye movement disorders, and visual field disturbances. The number of eyes that can be examined by fundoscopy is 138 from the supposed 140 eyes due to the opacity of the refractive media.

Table 2. Neuro-ophthalmic Manifestation of Brain Tumors

Manifestations	n (%)
Subjects with Neuroophthalmic disorders (n=70)	70 (100)
Visual Impairment (n=70)	46 (65.7)
Eyes which Visual Acuity Can Be Examined (n=140)*	140 (100)
Number of eyes with visual impairment (n=140)*	82 (58,6)
Visual Field Disturbance (n=54)	23 (42.6)
Type of Visual Field Disturbances (n= 23)	
Bitemporal Hemianopsia	17 (73.9)
Homonimous Hemianopsia	3 (13.0)
Tunnel Vision	2 (8.7)
Central Scotoma	1 (4,3)
Eye Movement Disorders (n= 70)	36 (51.4)
Type of Eye Movement Disorders (n= 36)	
Central Eye Movement Disorders	7 (19.4)
Peripheral Eye Movement Disorder	24 (66.7)
Mixed Eye Movement Disorder	5 (13,9)
Funduscopic Abnormalities (n= 70)	51 (72.9)
Number of Eyes Examined by Funduscopy (n=140)*	138 (98.6)
Number of Eyes with Fundus Abnormalities (n=138)*	92 (66.7)
Type of Funduscopic Abnormalities (n= 92)	
Primary Disc Atrophy	37 (40.2)
Secondary Disc Atrophy	13 (14.1)
Papil Edema	42 (45.7)

*data was taken from the number of eyes examined

Based on fundoscopic findings per eye, papil edema (45.7%) was the most common finding. There were 65.7% of subjects with visual impairment. Eye movement disorders were found in 51.4% of subjects as peripheral eye movement disorders (66.7%). Visual field disturbances can only be examined in 54 subjects because there was a disturbance of higher cortical function.

Among 54 subjects examined, 42.6% had visual field disturbances. Among patients with visual field disturbances, bitemporal hemianopsia was the most common form of visual disturbance (73.9%).

Table 3 describes the association of brain tumor characteristics with NO manifestations. It appears that the type of tumor has a significant relationship with visual field disturbances; that is, in primary tumors, visual field disturbances are significantly more common (p=0.002). The table also shows that the location of the lesion has a significant relationship with all NO manifestation variables (p<0.05). In supratentorial tumor locations, visual disturbances (p<0.001), visual field disturbances (p=0.003), and fundoscopic abnormalities were significantly more common (p<0.001), while infratentorial locations caused more eye movement disorders than supratentorial locations (p<0.001). The number of lesion locations is related to fundoscopic abnormalities, which is the number of lesions >1 location that causes more fundoscopic abnormalities significantly (p=0.043). In the variable distribution of tumor lesions, the distribution of lesions does not have a significant relationship with all the variables of NO manifestations present.

Discussion

Characteristics of Brain Tumors

In this study, most subjects were female (62.9%). Previous studies obtained similar results, such as Ardhini et al[12] at Kariadi Hospital, Semarang (61.7%), Aninditha et al[13] (65.9%) at dr. Cipto Mangunkusumo General Hospital and Dharmais National Cancer Hospital, and Masaya-anon et al[3] (71.4%) in Thailand. The female predominant finding in this study subjects was in line with the majority of primary tumors in the form of meningiomas, which epidemiologically have a twice higher incidence in women.[1] Similarly, breast malignancy is the most common malignancy causing secondary brain tumors in this study. The age limit in this study was >18 years of age. Only a few studies with the same theme examined the manifestation of NO having an age limit of >18 years, including studies by Masaya-anon et al[3] and Desmukh et al[9] The mean age in this study was 41.9±12.8 years. The mean age was similar in the study by Masaya-anon et al[3] (43.5 years)[3] and the study by Desmukh et al[9] (43.2±11.04 years).

In this study, 68.6% of the subjects suffered from primary brain tumors, with meningioma being the most common type (31.3%), followed by a pituitary adenoma (29.2%). A similar range of results was shown by the Masaya-anon et al[3] study, which showed primary tumors (8.6%) with a predominance of ioma (45.0%) and pituitary adenoma (32.9%).[3] Research by Ekpene et al[14] also showed a primary tumor rate of 94.1%, with meningiomas being the second most common primary tumor (36.2%) after gliomas (38.2%).

The study data, which showed the predominance of meningioma and pituitary adenoma in primary tumors type, were in accordance with the results of the highest location data in the frontal lobe (41.4%), occipital lobe, and sella region (each 37.1%). These locations are places where meningiomas and pituitary adenomas often grow.[15,16] Secondary tumor data in this study also supports the existing theory, which states that metastatic brain tumors are mostly found in the cerebral hemispheres area as much as 85%. This is in line with the data of this study, which showed that tumors located in the supratentorial area were 61 subjects (87.1%).

The number of lesion locations in this study was balanced between one area and multiple locations. Although the most common types of tumors were primary tumors, which were generally single, the number of multiple lesion locations dominated this variable (51.4%). This is probably because when the tumor was found, the primary tumor was large enough to cover more than one lesion site even though it was distributed in the same hemisphere, as unilateral locations dominated (55.7%) in this study. The lesion distribution into unilateral, bilateral, and midline was made to see its relationship with NO disorders, which are discussed in the following section.

Neuro-ophthalmic Manifestations of Brain Tumors

NO abnormalities occurred in 100% of subjects in this study. This is probably because all subjects with suspected brain tumors were only consulted by the Neuro-ophthalmology clinic when there were complaints or abnormalities during a physical examination. Neuro-ophthalmic manifestations in this study include visual disturbances, visual field disturbances, eye movement disorders, and funduscopic abnormalities. Each neuro-ophthalmological manifestation has a high percentage, with 3 of them reaching more than 50% proportion: fundoscopic abnormalities (72.9%), visual disturbances (65.7%), and eye movement disorders (51.7%). The high percentage of incidence and variation of neuro-ophthalmological manifestations in brain tumors indicates that brain tumors have localizing and non-localizing effects on afferent and visual afferent pathways.[17]

Table 3. Relationship between Brain Tumor Characteristics and Neuro-ophthalmic Manifestations

Brain Tumor Characteristics	Neuro-ophtalmic Manifestations											
	Visual Impairment			Visual Field Disturbance			Eye Movement Disorder			Funduscopic Abnormalities		
	Yes n (%)	No n (%)	p	Yes n (%)	No n (%)	p	Yes n (%)	No n (%)	p	Yes n (%)	No n (%)	p
Type of tumors	n=70			n=54			n=70			n=70		
Primary	33(68.8)	15(31.2)	0.429*	22(55.0)	18(45.0)	**0.002***	21(43.8)	27(56.2)	**0.058***	36(79.6)	12(25.0)	0.552*
Secondary	13(59.1)	9(40.9)	1(7.1)	13(92.9)	15(68.2)	7(31.8)		15(68.2)	7(31.8)			
Location of tumor	n=58			n=49			n=58			n=58		
Supratentorial	37(75.5)	12(24.5)	**<0.001****	22(55.0)	18(45.0)	**0.003****	18(36.7)	31(63.3)	**<0.001****	39(79.6)	10(20.4)	**<0.001****
Infratentorial	0	9 (100)	0	9 (100)	9 (100)	0		1 (11.1)	8 (88.9)			
Number of locations	n=70			n=54			n=70			n=70		
One location	19(55.9)	15(44.1)	0.092*	15(45.5)	18(54.5)	0.594*	15(44.1)	19(55.9)	0.234*	21(61.8)	13(38.2)	0.043*
Multiple locations	27(75.0)	9(25.0)	8(38.1)	13(61.9)	21(58.3)	15(41.7)		30(83.3)	6(16.7)			
Distribution of lesions	n=62			n=48			n=62			n=62		
Unilateral-midline	30(62.5)	18(37.5)	0.539*	19(47.5)	21(52.5)	0.116**	22(45.8)	26(54.2)	0.224*	34(70.8)	14(29.2)	0.263*
Bilateral	10(71.4)	4(28.6)	1(12.5)	7(87.5)	9(64.3)	5(35.7)		12(80.0)	3(20.0)			

***Chi-square test; **Fischer's exact test**

Fundoscopic abnormalities in this study were categorized into two categories: fundoscopic abnormalities in one subject and fundoscopic abnormalities based on the number of eyes examined. Based on the number of subjects examined, 72.9% of the subjects had fundoscopic abnormalities, while the number of eyes with fundus abnormalities was 92 of the 138 fundus that could be examined (66.7%). Fundoscopic abnormalities in this study were dominated by secondary atrophic papillae and papilledema (59.8%), which described the non-localizing effect of increasing intracranial pressure (ICP). This aligns with the large number of research subjects with multiple locations, representing the effect of crowding out mass, thereby increasing ICP. Meanwhile, the results of primary atrophic papillary funduscopy in this study (40.2%) described a localizing effect on the optic nerve, which usually occurs in tumors that have an anatomical location close to the optic nerve, such as tumors in the intercostal region.[3,18,19]

The second highest NO manifestation in brain tumors is visual disturbances. This is in line with the number of fundoscopic abnormalities that describe lesions on the optic nerve, so if the function of the optic nerve lesion decreases, visual disturbances will also occur. The percentage of similar visual impairment was also reported by Masaya-anon et al[3], i.e. 74.4%.

Eye movement disorders are divided into central and peripheral eye movement disorders. Peripheral eye movement disorders were more dominant (66.7%) in this study, with the highest number being paresis of the 6th nerve only (51.7%). The sixth nerve is a long nerve that runs in the subarachnoid space of the skull base, which will be disturbed when there is an increase in ICP. This finding is referred to as a non-localizing neuro-ophthalmological effect.[8,10,20] In localizing disorders, paresis of the 6th nerve is generally combined with other focal neurological deficits of similar location, for example, in the case of cerebellopontine angle tumors.[17] Central eye movement disorders were found in 33% of subjects. This small percentage is thought to be because the examination of central eye movements has limitations; that is, the examination requires cooperation, so it will be challenging to do in impaired higher cortical functions or impaired consciousness. Among the central eye movements, nystagmus dominates (58.3%).

Visual field disturbances in this study had a slightly different range from other NO manifestations, in which the incident was less than 50%. This is probably because 22.9% of subjects cannot be assessed due to higher cortical function disorder. In addition, visual field disturbances are commonly caused by localizing effects, while other disorders can be caused by both localizing and non-localizing due to increased ICP.[17,21] Among subjects with visual field disturbances, hemianopsia was the most common finding (86.9%), with bitemporal hemianopsia predominant. The hemianopsia that occurred in this study was a binocular visual field disorder indicating a chiasm-retrochiasmic lesion that was relevant to the subject.

The Associations Between Brain Tumor Characteristics and NO Manifestations

Based on the tumor type, the primary tumor type had a significantly higher incidence of visual field disturbance (p=0.002). This is because the field of vision is a specific pathway with localizing manifestations. One of the most common primary tumors in this study is a tumor in sella region which has a characteristic visual field disorder, as well as a tumor with a unilateral location that can cause homonymous hemianopsia manifestations.

The tumor location has a significant relationship with all variables of neuro-ophthalmic manifestations. The sites included in this analysis were single sites. It means that tumors with supratentorial and infratentorial locations were excluded from the analysis because they may lead to confusion about which location causes abnormal NO manifestations. Fundoscopic abnormalities, visual impairment, and visual field disturbances are more common in supratentorial tumors, mainly because the supratentorial area is an area of visual afferent pathways reflected in those three clinical manifestations. On the other hand, in infratentorial tumors, eye movement disturbances are more common. This happens because the center of eye movement is located in the infratentorial area in the brain stem and the cerebellum. Thus, it seems that all NO manifestations are thought to have a role in determining the location of the lesion.

However, the relationship between tumor location and visual impairment, fundoscopy, and eye movement disorders should be interpreted with caution. First, this is because eye movement disorders can occur in the supratentorial location, especially non-nystagmus central eye movement disorders, due to the eyeball movement coordination center also in the supratentorial area. Secondly, the infratentorial location may also cause

fundoscopic abnormalities and visual disturbances due to the non-localizing effect of increased ICP in infratentorial tumors with obstructive hydrocephalus. However, most of the subjects who came to this hospital with infratentorial tumors accompanied by obstructive hydrocephalus had undergone a ventriculoperitoneal shunt (VP shunt) surgery in the ER or external health facility before being consulted by the NO clinic. So, these subjects were not included in the inclusion criteria for this study. In the study by Tagoe et al,[18] there was also no significant relationship between tumor location and fundus abnormalities (p=0.505) and visual disturbances (p=0.257). Therefore, the NO manifestation, which is thought to have good localizing value, is visual field disturbance.

Based on the number of lesion locations, it was found that there was a significant relationship between locations and multiple tumor locations, causing more fundoscopic abnormalities (p=0.043). This is thought to be because the presence of brain tumors and peritumoral edema in many locations can cause changes in the morphology of the optic disc, either due to direct compression of the tumor or due to indirect compression due to increased ICP. The distribution of lesions in this study did not have a significant relationship with all NO manifestations. This is because both unilateral, bilateral, and midline lesions can cause various abnormalities, depending on the location of the lesion.

NO manifestations in this study are global and do not show specific characteristics of each NO manifestation (visual disturbances, visual fields, eye movements, fundoscopic abnormalities), so they must be interpreted cautiously. In conclusion, several NO manifestations have a relationship with brain tumor characteristics, as fundoscopic abnormalities happen more commonly in supratentorial tumors and tumors with multiple locations. Visual disturbances are more common in supratentorial tumors. Visual field disturbances are more common in primary tumors and supratentorial tumors. Eye movement disorders are more common in secondary tumors and infratentorial tumors.

Conclusions

From the results of this study, it can be seen that the NO manifestations in brain tumors have a high percentage; three of them had a percentage >50%, i.e., funduscopic abnormalities (72.9%), visual disturbances (65.7%), and impaired eye movement (51.4%). Visual field disturbances had the smallest percentage of 42.6%. The NO manifestation could reflect brain tumors' localizing and non-localizing effects. NO manifestations are thought to have a role in determining the tumor's location (supratentorial/infratentorial). Third, visual field disturbances are believed to have the best localizing value, while funduscopic disorders have the best non-localizing value.

Conflict of Interest

The authors declare no conflicts of interest and are responsible for the article's content and writing.

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