Determination of Systemic and Local Causes of Orbital Proptosis Diagnosed by Neuroradiological Modalities

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ABSTRACT

Purpose: To determine the demographic and etiological characteristics in patients with orbital proptosis diagnosed by neuroimaging studies.

Materials and Methods: We retrospectively analyzed neuroradiological images taken in the obtained during 11-years period (between January, 2009 and July, 2020) by extracting from in the hospital information system. Record system were analyzed retrospectively. An exophthalmometer was performed on the orbital images. The patients diagnosed as orbital proptosis with available clinical and histological data were included in the study.

Results: The study included 167 patients (including 30 pediatric patients). It was found that the most common cause of orbital proptosis was inflammatory diseases of orbit, namely orbital cellulitis in children and thyroid orbitopathy in adults; followed by the primary benign tumors of orbit. Among the malignant tumors, primary orbital tumors were more common in children whereas secondary orbital tumors extending from the systemic or local regions were more common in adults. Bilateral proptosis was found in 43.1% of all cases. It was observed that the numbers of systemic (69 cases, 50.3%) and local diseases causing proptosis (68 cases, 49.6%) were comparable in adults while the local diseases causing proptosis (28 cases, 93.3%) were more common than systemic diseases causing proptosis (2 cases, 6.6%) in children.

Conclusion: It was found that there was both local and systemic causes of orbital proptosis including those can threaten vision and life. The knowledge of etiological reasons in this series will assist the clinician in assessment of orbital proptosis detected at presentation in patients living in the same geography, ensuring early diagnosis and treatment.

Key words: Orbit; proptosis, neuroradiology, exophthalmometer

INTRODUCTION

Orbit is an important intersection point for central nervous system due to its vicinity to surrounding bones, paranasal sinuses (paraorbital region), intracranial space, face and soft tissue supporting eyes.[1] Any lesion in this region can lead anterior displacement of eye on axial axis, in other words, proptosis, when extended to orbit. The proptosis of the eye, also known as exophthalmia, is one of the most common symptoms caused by orbital pathologies.[2]

The factors leading proptosis may differ based on the localization and structure of the lesion.[3] These lesions may be neoplastic, vascular, traumatic, metabolic or inflammatory; they may originate from adjacent areas such as paraorbital region where paranasal sinuses are located or intracranial space; however, they may also result from distant metastasis of a tumor or systemic disease such as endocrine diseases which affect orbit. The early recognition of proptosis is important to prevent permanent orbital injury and to protect ocular health and movements. In particular, proptosis may be the first sign of malignant neoplasms; thus, early diagnosis is of important.[4] Thus, neuroimaging studies are important in the diagnosis of proptosis, identifying underlying pathologies and assessing treatment response.[5, 6]

In this study, it was aimed to determine demographic and etiological characteristics in patients diagnosed with proptosis based on neuroimaging studies in our clinic.

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MATERIALS AND METHODS

This retrospective study was approved by Ethics Committee on Non-Interventional Clinical Research of Hatay Mustafa Kemal University (approval#03.09.2020-16). The study was conducted in accordance with tenets of Helsinki Declaration. In the study, we reviewed axial, coronal and sagittal reformatted images obtained from patients aged 0-95 years using 64-row multi-slices computed tomography (Toshiba Aquilon 64) and magnetic resonance imaging modalities (1.5 Tesla Philips Achieva, Ingenia 1.5T MRI imaging system) between January, 2009 and July, 2020. All sections were 1 mm in thickness in computed tomography (CT) scan while coronal sections were 3 mm in thickness in magnetic resonance (MR) imaging. In MR, field of view was 0.7 mm and 180 mm between sections and axial sections were 3 mm in thickness with field of view of 0,5 mm and 140 mm between sections.

The orbital and cranial CT images and contrast-enhanced images from T1- and T2-weighted MR sequences were extracted from hospital information system. The images were reviewed at a workstation in radiology department by a single radiologist (GB) and an ophthalmologist (AİÇ). The exophthalmometric measurements were performed on most clear images obtained from orbital axial CT scans and axial T1-weighted MRI sequences. The exophthalmometer was performed by measuring distance from interzygomatic line drawn anterior to zygomatic arcs to cornea located at anterior margin of glob. The proptosis was defined as the distance ≥21 mm or inter-globe distance >2 mm (Figure 1).[7]

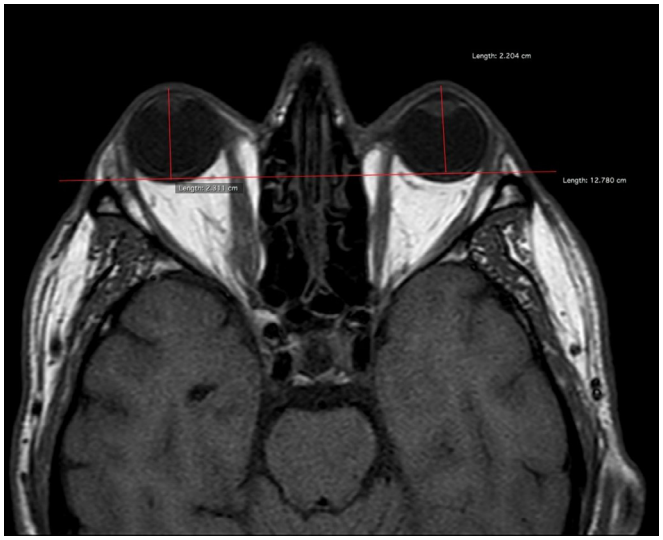

Figure 1: *Orbital magnetic resonance imaging: The distance from interzygomatic line drawn anterior to zygomatic arcs to cornea located at anterior margin of glob is measured on axial T1-weighted images.*

In cases diagnosed as proptosis based on exophthalmometer on radiological images, histopathological and clinical data from hospital information system was reviewed by researchers (GB and AİÇ). The cases without diagnosis of proptosis in exophthalmometric measurements and those not fulfilling inclusion criteria were excluded. The inclusion criteria were:

1. Detection of proptosis based on exophthalmometer performed on radiological images,
2. No diagnosis of congenital disease which may lead to proptosis caused by orbital and craniofacial anomalies (Crouzon-Apart syndrome, anophthalmia, microphthalmia, craniosynostosis etc.),
3. Available clinical or histological data supporting diagnosis in hospital information system,
4. No motion artifact or artifact caused by metallic material in radiological images,
5. No asymmetrical eye size such as high myopia or buphthalmia or morphological corneal abnormality such as keratoconus,
6. No acute disease due to trauma which interrupts integrity of brain, orbit and eye globe (subdural hematoma, retrobulber hemorrhage, perforation etc.),
7. No previous surgery which might have impacted integrity of brain, orbit or eye (cranial surgery, perforation repair, keratoplasty etc.),

The cases identified were assigned into two distinct study group as pediatric (<18 years) and adult cases (≥18 years). In all cases included, demographic characteristics (age, gender), site of proptosis, and diseases causing proptosis were recorded. The diseases detected were recorded as tables including count and percent for each age group.

FINDINGS

We reviewed 695 orbital MR imaging studies and 1752 CT scans obtained during 11 years period between January, 2009 and July, 2020. Overall, 167 patients (84 women, 83 men), who were diagnosed with proptosis based on exophthalmometric measurements and had medical records compatible with underlying medical diagnosis, were included in the study. Of the cases included, 30 (14 girls, 16 boys) were children with mean age of 8.33±5.15 years (range: 1-17 years). Remaining 137 cases (70 women, 67 men) were adults with mean age of 44.70±15.72 years (range: 18-92 years). The age range was 18-59 years in cases with orbital proptosis and the highest number of proptosis cases were observed in the age group of 40-49 years in the patient group (Table 1).

Table 1: *Age and gender distributions of cases with proptosis.*

AGE AND GENDER DISTRIBUTION OF CASES WITH PROPTOSIS			
Age	**Female (n)**	**Male (n)**	**Total (n)**
0-9	7	10	17
10-17	7	6	13
18-29	14	12	26
30-39	14	15	29
40-49	17	16	33
50-59	14	12	26
60-69	7	8	15
70 -79	2	4	6
80-89	1	-	1
90-99	1	-	1
Total n (%)	84 (50.3%)	83 (49.7%)	167

Table 2 presents eyes affected. It was found that there was bilateral proptosis in 43.1% of all cases (n=72), 49.6% of adult cases (n=68) and 13.3% of pediatric cases (n=4). Of the cases with bilateral proptosis, there was thyroid orbitopathy in 53 (77.9%), metastatic orbital tumors (non-Hodgkin lymphoma [NHL],multiple myeloma [MM], acute myeloid leukemia [AML], osteosarcoma of sphenoid bone, squamous cell carcinoma of maxillary sinus, bilateral neurofibroma) in 6, idiopathic orbital inflammatory syndrome (pseudotumor) in 7, a carotid cavernous fistula in 2 and mucocel in 1 case. Of 4 pediatric cases with bilateral proptosis, there was fibrous dysplasia in 2, bilateral optic glioma associated with neurofibromatosis in 1 and osteitis fibrosa cystica (Brown tumor) in 1 case.

In each group, etiological causes of proptosis were classified in two groups as systemic and local disease; the local diseases were assessed in 3 subgroups as orbital, paraorbital intracranial disorders (Table 3). It was found that proptosis was due to local causes in 28 cases (93.3%) and systemic causes in 2 cases in pediatric group while it was due to local causes in 68 cases (49.6%) and systemic causes in 69 cases. In adult patients, it was found that the most common cause was thyroid orbitopathy (62 cases; 45.2%) (Table 3). It was calculated that orbitopathy accounted for 89.8% of all cases with proptosis due to systemic causes whereas 45.2% of all adult cases and 37.1% of all cases in the study.

In addition, there was 4 cases with neurofibromatosis (2 adults, 2 children) among systemic diseases found to lead proptosis. These included neurofibroma extending to orbit in 2 adult patients and optic glioma in 2 pediatric patients.

It was found that orbital inflammatory disorders were most common local cause of proptosis (42 cases, 25.1%) (Table 3). In pediatric patients, the most common orbital inflammatory disease causing proptosis was orbital cellulitis secondary to paranasal sinus infection (9 cases, 30%). In one pediatric case, idiopathic orbital inflammatory syndrome was detected at retro-orbital region. In adult patients, orbital cellulitis was detected in 15 cases (10.9%) and idiopathic inflammatory syndrome in 14 cases (10.2%). It was found that the initial diagnosis was orbital myositis in 6 adult cases and Wegener's disease in 3 adult cases among adult patients with idiopathic orbital inflammatory syndrome.

Among lesion originating from intracranial space, it was found that intracranial arachnoid cyst caused proptosis in only one pediatric cases while proptosis was caused by intracranial diseases in 11 cases including carotid-cavernous fistula in 6 male patients, central nervous system meningioma extending to orbit in 3 cases and CNS-originated non-Hodgkin lymphoma in 2 cases (Table 3).

The diseases causing proptosis were classified in 4 major

Table 2: *Distribution of proptosis site in pediatric and adult groups.*

PROPTOSIS	RIGHT	LEFT	BILATERAL	TOTAL
PEDIATRIC	15	11	4	30
ADULT	35	34	68	137
ALL CASES	50	45	72	167

Table 3: *Distribution of systemic and local disease causing proptosis in pediatric and adult groups.*

DISEASE (n)		PEDIATRIC	(n)	ADULT	(n)
SYSTEMIC (71)		Neurofibromatosis: Optic glioma **Total**	2 **2**	Thyroid orbitopathy Tumors with orbital metastasis: - Lung - Prostate - Acute myeloid leukemia - Multiple Myeloma Neurofibromatosis: Neurofibroma **Total**	62 4 2 1 1 1 2 **69**
LOCAL (90)	**Orbital (71)**	Orbital cellulitis Dermoid cyst Cavernous hemangioma Rhabdomyosarcoma Retinoblastoma IOIS **Total**	9 3 5 3 1 1 **22**	Orbital cellulitis Dermoid cyst Cavernous hemangioma Optic glioma Optic nerve meningioma Fibrous solitary tumor Lacrimal gland adenocarcinoma IOIS **Total**	14 4 13 1 1 1 1 14 **49**
	Paraorbital (14)	Fibrous dysplasia Brown tumor Mesenchymal tumor of maxillary sinus **Total**	3 1 1 **5**	Mucocel Fibrous dysplasia Chondrosarcoma of maxillary bone Squamous cell cancer of maxillary bone Osteosarcoma of sphenoid bone **Total**	3 1 1 1 1 **7**
	Intracranial (12)	Arachnoid cyst **Total**	1 **1**	Meningioma Non-Hodgkin Lymphoma Carotid-cavernous fistula **Total**	3 2 6 **11**

IOIS: idiopathic orbital inflammatory syndrome;

groups including inflammatory, neoplastic, vascular and cystic disorders (Table 4). Based on this table, it was found that inflammatory diseases were most common cause of proptosis among both systemic and local disorders (104 cases, 62.3%); followed by neoplastic disorders (55 cases, 32.9%).

The neoplastic diseases were assessed in 4 groups including orbital, paraorbital, intracranial tumors and tumors with systemic metastasis (Table 4). In addition, primary and secondary tumors were assessed in two groups as malignant and benign tumors (Table 5). It was found that there was orbital neoplastic disorders in 56.6% (n=17) of pediatric cases and in 27.7% (n=38) of adult cases. In both pediatric and adult cases, it was observed that primary orbital tumors were most common neoplastic disorders leading proptosis, majority of which were benign orbital tumors. In general, benign tumors were most common cause of proptosis, including mainly cavernous hemangioma and dermoid cyst (Table 3 and Table 4). It was found that fibrous dysplasia was the most common paraorbital tumor leading proptosis as a local cause in pediatric patients whereas maxillary sinus tumors in adult patients (Table 3).

In adult cases, those with systemic or local metastasis to orbit were leading cause of proptosis among malignant tumors while malignant primary orbital tumor (lacrimal gland adenocarcinoma) was detected in only one adult patient. Tumors with local invasion to orbit included a malignant bone tumor extending from maxillary sinus to orbit, a CNS-originated meningioma extending through sphenoid bone and NHL. Tumors with distant metastasis to orbit included malignant primary solid tumor of lung, prostate cancer, myeloid leukemia and multiple myeloma (Table 5).

In pediatric cases, the malignant tumors leading proptosis were mainly primary orbital tumors. Among these, rhabdomyosarcoma was most common tumor while malignant mesenchymal tumor originating from maxilla sinus was detected in one case. It was also found that retinoblastoma was the only intraocular tumor which

Table 4: *Distribution of inflammatory, neoplastic, vascular and cystic diseases causing proptosis.*

DISEASES (%)*	n
INFLAMMATORY (62.3%)	
Thyroid orbitopathy	62
Orbital cellulitis	24
Idiopathic orbital inflammatory syndrome	15
Mucocel	3
NEOPLASTIC (32.9%)	
Orbital	
Cavernous hemangioma	18
Dermoid teratoma	7
Rhabdomyosarcoma	3
Retinoblastoma	1
Optic glioma	3
Optic nerve meningioma	1
Fibrous solitary tumor	1
Lacrimal gland adenocarcinoma	1
Paraorbital	
Fibrous dysplasia	4
Mesenchymal tumor of maxillary sinus	1
Chondrosarcoma of maxillary bone	1
Squamous cell cancer of maxillary bone	1
Osteosarcoma of sphenoid bone	1
Intracranial	
Neurofibroma	2
Meningioma	3
Non-Hodgkin lymphoma	2
Systemic Metastasis	
Lung cancer	2
Prostate cancer	1
Acute myeloid leukemia	1
Multiple myeloma	1
VASCULAR (3.6%)	
Carotid-cavernous fistula	6
CYSTIC (1.2%)	
Arachnoid cyst	1
Osteitis cystica	1

*: percent values are rounded.

extended to retroorbital region and caused proptosis. No orbital metastasis from a distant tumor was detected in pediatric cases.

DISCUSSION

In this retrospective study, it was found that thyroid orbitopathy was the most common underlying cause of proptosis in 167 cases diagnosed as orbital proptosis based on exophthalmometric measurements on MR images and CT scans obtained during 11-years period in agreement with literature.[8, 9] In addition, it was also found that thyroid orbitopathy was the most common disease which led bilateral orbital proptosis in the study population. It was observed that orbital inflammatory diseases were most common local disorders which caused proptosis. Among local causes, it was found that orbital cellulitis was the most common cause of orbital proptosis in both adult and pediatric patients; followed by idiopathic orbital inflammatory syndrome in adult patients.

In a study from India, 25 cases with unilateral proptosis were assessed in tertiary ophthalmology clinic, reporting that inflammatory diseases were most common etiology, mainly orbital cellulitis.[10] Unlike our study, the proptosis was diagnosed using classical methods in the ophthalmology clinic and most cases were male patients aged >60 years; in addition, no thyroid orbitopathy was detected in the study.

In our study, primary orbital tumors were most common cause of orbital proptosis among neoplastic diseases; cavernous hemangioma and dermoid cyst were most commonly seen primary orbital tumors which cause orbital proptosis; and rhabdomyosarcoma was also observed in pediatric cases. In general, it was found that primary and benign orbital tumors were more common than malignant and secondary orbital tumors. Among secondary orbital tumors leading proptosis, it was observed that these mainly included fibrous dysplasia originating from paraorbital

Table 5: *Distribution of primary and secondary orbital tumors (benign and malignant).*

NEOPLASTIC DISORDERS CAUSING PROPTOSIS					
GROUP	**ORBITAL TUMORS**	**BENIGN (n)**	**MALİGNANT (n)**	**INTRAGROUP TOTAL (n)**	**(%*)**
PEDIATRIC (n=30)	**Primary**	9	4	13	43.3
	Secondary	3	1	4	13.3
	Total	**12**	**5**	**17**	**56.6**
ADULT (n=137)	**Primary**	20	1	21	15.3
	Secondary	6	11	17	12.4
	Total	**26**	**12**	**38**	**27.7**
ALL CASES (n=167)	**Total**	**38**	**17**	**55**	**32.9**

*: percent values were rounded.

region in pediatric patients whereas tumors originating from maxillary bone in adult patients. In addition, it was seen that malignant tumors causing proptosis were often intracranial or paraorbital tumors invading orbit or distant tumors with orbital metastasis. In a study on patients with unilateral proptosis, Calcaterra et al. reported that majority of primary orbital tumors originated from distance between orbital wall and cone of extra-ocular muscles and that 90% of these tumors manifested with orbital proptosis.[11] In a series from India, it was detected that 50 of cases with orbital proptosis was associated with malignant tumors in paraorbital region.[12] Similarly, in a study on 75 Nigerian patients with unilateral proptosis, Majekodunm et al. reported that there was primary orbital diseases in 13% and secondary orbital diseases in 87% of the cases. Authors found that there was orbital cellulitis in 52% and malignant disease in 29% of the cases. Unlike our study, authors included only patients with unilateral proptosis and detected no proptosis case caused by thyroid disorders.[13]

In fact, Johnson et al. showed that 75% of malignant tumors arising from nasal and paranasal region tends to extend and that 45% of cases extended to orbit.[14] Authors reported that 61% of cases were associated with tumors originating from maxillary sinus in agreement with our study. In a study on 25 patients with nasal and paranasal tumors, Soysal et al. showed that 25% of patients initially presented to ophthalmology clinic with proptosis; in addition, authors reported that squamous cell cancers were those most commonly associated with orbital metastasis and that these tumors most commonly originated from maxillary sinus.[15]

In a study on 38 patients scheduled to surgery for proptosis, Said et al. detected primary orbital tumors in 13 patients and paraorbital tumors in remaining 25 patients.[16] In the study including 11 pediatric cases, it was found that orbitonasal encephalic lymphoma, dermoid cyst and rhabdomyosarcoma originating from rectus muscles were main diseases which caused proptosis in children. In addition, unlike our study, orbital cyst hydatid was detected in 2 children. Moreover, in this observational study, it was found that intracranial diseases such as fungal infection skull base carcinomas and local bone cysts with aneurysms which extend to orbit were common in adolescents and adults. Saha et al. reported that there was primary orbital tumor in 45% and paraorbital tumor in 55% of 31 cases.[17] In agreement with our study, authors found that hemangioma, dermoid cyst and rhabdomyosarcoma were most common primary orbital tumors while nasopharyngeal, maxillary and nasoethmodial tumors were most common paraorbital tumors. They found that there was primary orbital tumor (hemangioma, primary orbital lymphoma and rhabdomyosarcoma in 3 and paraorbital nasopharyngeal tumors in 4 of 7 children included to their study. In our study, no primary orbital lymphoma was detected among diseases causing proptosis.

In our study, it was found that there are similarities as well as differences when causes of proptosis based on neuroimaging studies in 30 children were compared to literature. This may be due to fact that our proptosis cases included cases detected based on radiological exophthalmometer rather than those diagnosed with orbital proptosis in our study. For example, in a retrospective study reviewing records of 50 children who presented to ophthalmology clinic with proptosis during 15-years period, it was found that orbital cellulitis was the most common cause of proptosis, followed by optic glioma, orbital rhabdomyosarcoma, orbital hemangioma and orbital dermoid cyst in agreement with literature; however, unlike our study, it was also observed that the causes of orbital proptosis in children also included thyroid orbitopathy, metastatic neuroblastoma, orbital neurofibroma and metastatic Ewing's sarcoma.[18] In our study, idiopathic orbital inflammatory disease and retinoblastoma were detected in one pediatric case but no lymphoma was detected. Authors also reported that they observed no idiopathic orbital inflammatory syndrome; in addition, no lymphoma case in agreement with our study. Moreover, they also reported that there was no retinoblastoma, one of the most common intraocular tumors in childhood, in their study. By citing a study in 1960s which showing that there was retinoblastoma extending to orbit in 20 of 65 children with proptosis, authors attributed this difference to current screening programs allowing early diagnosis and treatment of retinoblastoma.[19]

Intracranial diseases may manifest in orbital cavity by passing orbital wall.[20-22] Some skull base tumors, intracranial tumors and diseases such as angiofibroma, meningioma, capillary hemangioma, fungal infection, metastatic tumors, post-traumatic hematoma and arteriovenous fistula may present with proptosis. In our study, it was found that intracranial tumors which originated from CNS and caused proptosis by extending orbit were meningioma in 3 and non-Hodgkin lymphoma in 2 of adult cases. In pediatric cases, no intracranial tumor originating from CNS were detected; however, it was found that there was arachnoid cyst which extended from intracranial space to orbit, leading proptosis. In addition, it was found that there were 6 adult cases with proptosis secondary to carotid-cavernous fistula. In a study including 34 cases with unilateral proptosis, Choudhurt et al. reported that there was carotid-cavernous fistula in 4 of 12 cases with intracranial lesions extending to orbit.[23] In this study including cases presenting to neurosurgery clinic, it was found that number of cranial lesions were higher than orbital lesions. Unlike this study,

post-traumatic retrobulbar and intracranial hemorrhage and hematoma were excluded from our study. In another study, Kang et al. reported that proptosis was detected in 30 of 37 children who underwent surgery due to orbital mass lesion in neurosurgery clinic.[24] Authors reported that there was optic glioma in 7, neurofibroma in 5 and neurofibromatosis in 2 of these cases. In a study, Margalit et al. reviewed orbital mass lesions in 41 cases underwent surgery via transcranial approach and they reported that proptosis was the most common symptom in these cases. Authors reported that there was primary orbital tumor in 5 and secondary orbital diseases in 34 cases.[25] It was reported that the most common lesion was meningioma; followed by osteoma.

In our study, we reviewed cases with orbital proptosis due to local and systemic diseases which were referred to radiology department from many different clinics during 11 years. Thus, unlike other studies in the literature a large number of patients were assessed, which were ordered orbital MR imaging and CT scan by many different clinic rather than single clinic in our study. Due to this fact, our results differ from previous studies on etiology and incidence of orbital proptosis in the literature. In addition, retrospective design is the major limitation in our study. There are some cases excluded from the study due to insufficient clinicopathological data although radiological studies indicated orbital proptosis. In addition, the cases with suspected orbital tumor might have been referred to another facility due to absence of ocular oncology department in our hospital. Moreover, there may be cases known to have idiopathic orbital inflammatory syndrome; thereafter, underlying vasculitis or rheumatoid diseases were detected in another facility. Thus, true incidence of these disorders may be unclear.[26] To best of our knowledge, there is no study using radiological exophthalmometer to detect cases with orbital proptosis; in addition, the previous studies investigated orbital proptosis in different patients groups using different methodologies. These are major factors which limit ability to compare our results with literature.

In summary, it was concluded that both local and systemic causes play role in the etiology of orbital proptosis that these causes include diseases threatening vision and life; thus, careful assessment and multidisciplinary approach are required in such cases where proptosis is detected either clinically or radiologically. In addition, it was observed that radiological exophthalmometer can be an important ancillary method to detect proptosis overlooked or underlying etiological cause. This is the first study investigated lesions causing orbital proptosis by reviewing CT scans and MR imaging studies obtained in a tertiary clinic during 11 years; thus, it may help to identify etiological causes in this series; in the assessment and differential diagnosis of patients presented with orbital proptosis in our region; and allowing early diagnosis and treatment.

Financial Disclosure

During the study process, no financial and/or moral support was provided by any corporation or commercial organization having direct relationship with study subject or producing medicinal products, medical device or material which may have negative influence on decision-making process about product.

Conflict of Interest

In the context of the present study, authors and/or family members have no membership and/or relationship with members in scientific or medical advisory committees and are not consultant, expertise, employment or shareholder in any corporation; which may lead conflict of interest. In this manuscript, there is organization which has direct-indirect commercial relationship or there is no organization granting financial support; authors have no commercial relationship with any product or corporation.

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