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Review Article

Benign Eyelids, Conjunctival, Intraocular and Orbital Tumors in Children: Epidemiology and Review of Literature

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Abstract: Benign eyelid, conjunctival, intraocular and orbital tumors are the most common neoplasm in daily ophthalmology practice. Benign tumors largely predominated over malignant ones, representing about 84% of cases in many series, and the 5 most frequent subtypes of eyelids tumor were squamous cell papilloma (26%), seborrheic keratosis (21%), melanocytic nevus (20%), hidrocystoma (8%), and xanthoma/xanthelasma (6%). Basal cell carcinoma was the most frequent malignant tumor (86%), followed by squamous cell carcinoma (7%) and sebaceous carcinoma (3%). For several tumor subtypes, there was a poor correlation between clinical and histological diagnosis, stressing the numerous pitfalls in the diagnosis of these tumors. Further discussionis needed with reference to previously published data.
Keywords: Benign, Tumor, Eyelid, Conjunctiva.

INTRODUCTION

The benign tumors of the eyelid, conjunctival, intraocular and orbital tumors of eye in children occurred more frequent (64.3%) than malignant tumors (35.7%) and the most often observed benign tumor was nevus pigmentosus (23.7%) of all ocular tumors in childhood [1]. Eyelid, conjunctival, intraocular and orbital tumors are the most common neoplasm in daily ophthalmology practice. Among them, skin cancers are a particular concern in sun-exposed older patients with an estimated 60,000 malignant eyelid tumors diagnosed yearly in the United States. Because the eyelid contains many tissue types, a wide variety of benign and malignant tumors can develop, sometimes mimicking common inflammatory conditions such as chalazion or botryomycoma. General data on the relative frequency of benign eyelid, conjunctival, intraocular and orbital tumors are available from only a limited number of biopsy series. In such studies, the relative frequency of the various tumor subtypes not only depends on thegeographic location and genetic background of the population surveyed but also on its socioeconomical status and access to medical care. In addition, histological classification of tumors is continuously refined, limiting the comparison with older reports.

Benign eyelid tumors

The four most common eyelid tumors of patients younger than 17 years old, in order of frequency, were epidermal cysts (23.1%), dermoid cysts (17.9%), squamous cell papillomas (11.5%) and compound nevi (9,0%) which were histopathologically diagnosed during 1991 to 2000 [2].Benign eyelid tumors seen in children occurred in 17.8 percent (142 cases) of all benign and malignant eye tumors (800 cases) [3]. However, Abdi et al. [4] found that of 122 eyelid tumors and tumor like lesions the most common were vascular tumors (23.3%), then neural tumors (18.0%),dermoid cysts (16.4%), squamous cell papilloma (13.1%), and nevi (12.3%), diagnosed histopathologically in 1951 to 1991[4]. Castillo and Kaufrnanzg found chalazion being the most common pediatric eyelids tumor [5]. Benign eyelids tumors were usually seen in the last two decades of live [4].

Benign tumors of the conjunctiva and cornea

It is studied in the same chapter because epithelium of cornea topographically is continued to epithelium of the conjunctiva. In children, benign

conjunctival tumors occur in more than (99.0%) cases[6].

Of 41 benign tumors of conjunctiva in children aged from 1 to 17 years the most common were pigmented nevi accounting for 83.0 percent (35 cases) of the histopathologically diagnosed lesions, then in decreasing order of frequency were angioma (4.9%), dermolipoma (4.9%), dermoid (2.4%), and papilloma (2.4%) [7]. The first place for nevi was also found by Cunha et al [8] but then other benign tumors were choristomas, epithelial inclusion cysts, and papillomas. However, Elsas and Green [9] in over a 49 years period found that in 302 children from birth through 15 years of age, the most common epibulbar tumors were choristomas (33.0%). Nevi were the second most frequent lesion, present in 29.0 percent, epithelial inclusion cysts in 11.0 percent, papillomas in 7.0 percent, pyogenic granulomas in 6.0 percent, granulomas in 5.0 percent, vascular hamartomas in 2.0 percent, and lipomas in 2.0 percent. In majority cases tumors were localized at the corneoscleral limbus [7, 9]. The mean age of children at the time of surgical excision was 10 years, 45 percent were males [7].

Benign intraocular tumors

These are uncommon in children and there is very little information on their incidence, most information about them has come from single case reports or from the rare study of children, which wasundertaken in children together with adults.

Adenoma of the iris pigment epithelium or benign epithelioma

It is a rare benign malignancy in children that may remain relatively stable for years [10].Age of patients ranged from 11 t0 85 years, male/female ratio was 1:1. All lesions were solitary and unilateral [11].

Iris cysts

These are uncommon in children. Primary cysts of the iris pigment epithelium as well as anterior chamber epithelial cysts may develop as a complication of penetrating trauma of intraocular surgery or they may be congenital in origin [12]. Of 57 iris cysts of children under age 20 years 53 (93.0%) were primary and only 4 cases 7.0 percent were secondary. Peripheral or iridociliary type of iris cysts accounted for 59.0 percent of all childhood iris cysts. It was most commonly diagnosed in the teenage years. Girls were more frequently affected in 68.0 percent, than boys and was not recognized in infancy [12].

Iris melanocytoma

It is also rare benign type of iris nevus tumor in children. The term "melanocytoma" was suggested by Zimmerman [13] in 1965 to describe this tumor and reported two adult patients with iris melanocytoma after enucleation. Iris melanocytoma is generally diagnosed in adults and has been uncommon tumor in children. So, of 13 well-documented cases of iris melanocytoma in the literature only 2 patients (15.4%) were under the age of 10 years. In the authors' own series of 47 patients with iris melanocytoma there were 4 patients (8.5%) under the age of 10 years [14].In rare instances melanocytoma can arise in iris, ciliary body, choroids or conjunctiva [15]. Melanocytoma of optic disk or magnocellular nevus is extremely rare in children, which can be dark brown to black because of very pigmented melanocytes [9, 16]. Bilateral melanocytoma of optic disk is also extremely rare tumor in children. For example, of 115 patients with such a tumor there was only one (0.9%) 10-month-old boy with bilateral involvement [16].

Medulloepithelioma is another benign intraocular tumor, which is so rare that " a few clinicians have had experience with more than one case'' [17]. For the first time medulloepithelioma was described by Badal and Lagrange in 1892 as carcinoma primitive. In 1904, Verhoeff pathohistologically in detail described this tumor as teratoneuroma and Fuchs in 1908 termed it as dictioma because of the net-like arrangement or ribbons of poorly differentiated cells. In 1931, Grinkel provided that tumor developed from medullary epithelium and termed it as medulloepithelioma. This historical aspect of the name of medulloepithelioma was published elsewhere [18, 19, 21, 22].Medulloepithelioma arises from the primitive medullary epithelium and most often occurs in the ciliary bodym being very rare tumor in the ophthalmic part of the retina and is identic with medulloepithelioma of ciliary body [17]. It may be benign or malignant depending on whether poorly differentiated cells are present [5, 8] Malignant medulloepithelioma is such a rare tumor that only 2 cases occurred during 10 years [20].This malignancy accounts for almost all the tumors in the congenital group, but they are much rare than retinoblastoma. For benign medulloepithelioma the longest interval between onset of signs or symptoms and diagnosis was 5 years [19], or age from 2 months to 10 years [17]. It is generally a tumor of childhood [19]. Medulloepithelioma of iris occurs in children from 6 l months to 6 years [21]. In all cases whether benign or malignant this tumor was unilateral and there was an equal distribution between the right and left eyes.

No racial predilection was observed and males and females were equally affected [19]. However, Canning et al [22] in small series of 15 children over 25 years observed period found a predilection of girls 6 of 9 children, 66.7 percent, with benign medulloepithelioma aged from 11 months to 14 years when benign tumor occurred in 60.0 percent (9 of 15 children). These tumors rarely involve the optic nerve

and are classified as nonteratoid and teratoid types; the later contains heterologous tissue. Benign nonteratoid medulloepithelioma of the retinais also possible tumor [23]. Although medulloepitheliomas unilateral tumor and bilateral cases are uncommon presumed bilateral medulloepithelioma of ciliary body in a 7-year-old boy was described in the literature [24].

Leiomyoma

It is a rare benign smooth muscle intraocular tumor, which can occur in younger patients but more common in adults with distinct predilection for females [25, 26]. However, 3 females and 2 males aged 5, 8, 11, 12 and 16 years respectively were found by Richter et al [27]who analyzed 32 cases of a ciliary body leiomyomas described in the literature from 1950 to 2000. If include author's case of a 13-year-old boy than it became equal number of boys and girls with a ciliary body leiomyoma.

Intraocular leiomyoma may be more common than previously believed. It is possible that some cases of leiomyoma have been misdiagnosed histopathologically as a low-grade amelanotic melanomas. It is also possible that some tumors, which are treated with irradiation as suspected melanomas actually may be leiomyomas [26]. It tends to affect the ciliary body and rarely occurs purely in the choroids [25].

Choroidal osteoma

It is a rare benign, ossifying tumor, described by Goss and villains in 1978, typically found in health young females [26, 28] which can be unilateral[29] or bilateral. [30] The youngest patient with osteoma reported in the literature was an 8-month-old infant [31]. This tumor may occur in siblings. Three siblings (a sister and two identical-twin brothers) had bilateral choroidal osteoma. The sister was seen at 11 years of age and the tumor showed significant growth two years later. The twin brother's tumor was diagnosed at 9 years of age. The siblings' mother had a yellow mottling situated nasal to the disk in each eye that was similar in appearance to that in one eye of one of the twins [32]. A long-term follow-up of choroidal osteoma for a mean of 10 years (range, 2-22 years) found growth observed for (41.0%). The probability of loss of visual acuity was (58.0%) by 10 years and (62.0%) by 20 years [29]. There is a case of familial choroidal osteoma in two brothers of 12 and 15 years old with bilateral choroidal osteomas. To the author's opinion. familial choroidal osteoma might have separate etiologic or motioned factors [33].

Choroidal hemangioma

It is an uncommon benign vascular tumor especially in children. It can be circumscribed or diffuse. The circumscribed choroidal hemangiomas occur sporadically without any associated local or systemic anomalies and usually diagnosed between the second to fourth decade of life [34], or from 9 to 86 years [35],or from 10 to 60 years [21]. More frequently, this kind of vascular tumors occur in adults [36, 37] and in children they rare occurred. The circumscribed type has an equal incidence in the right and left eyes [37]. In contrast, diffuse choroidal hemangiomas are usually evident at birth and generally occur as a part of neuro-oculocutaneous hemangiomas (Sturge- Weber syndrome) [9, 26, 37]. Diffuse type of choroidal hemangiomas appears to be slightly more common in Whites, than in Blacks, the left eye involved moreoften than the right one, ipsilateral to an associated facial angioma occurred at a median age of 8 years [37].

Retinal benign tumors

It occur in children very rare and, as a rule, they represented by tumors of vascular capillary, cavernous or racemouse lesions [21] Singh et al. [38] found that retinal vascular tumors can be classified into four distinct clinical entities: retinal capillary hemangioma, retinal arteriovenous communication (Wyburn-Mason syndrome, about it below), and retinal vasoproliferative tumors. According to the **"**Histological typing of the eye tumors'' [10]there are angiomatosis of the retina (hemangioblastoma) and capillary telangiectasia (milliary aneurism of Leber) except capillary and cavernous retinal hemangioma. Capillary retinal hemangioma at first was described by Eugen von Hippel, coined the term angiomatosis retina in 1902 and Arvid Lindau described an association between cerebral and retinal hemangioblastomas and the term von Hippel-Lindau disease (VHL) was established in 1964 [21, 38]. Capillary retinal hemangioma can occur inassociation with VHL an autosomal dominant disease, or sporadically. The risk of association VHL disease is higher in younger patients and is the most common and earliest manifestation of VHL disease. The maximal probability of VHL disease in patients with a retinal capillary hemangioma was estimated to be 30.0 percent to 46.0 percent [38]. In children with intraocular tumors and simulating conditions retinal capillary hemangioma in 7.0 percent was clinically diagnosed [39] and only 5.0 percent of patients with VHL presentretinal capillary hemangioma before the age of 10 years; it was already found in children [40].The median age at diagnosis of retinal capillary hemangioma in patients with VHL disease (range 2.8-46.7 years) was almost 18 years less than those without VHL disease (range 7.0-74 years) [41].Of all capillary hemangiomas retinal capillary hemangiomas occur in 6.0 percent with incidence 1:85000; about 25.0 percent of patients have familial history, 50.0 percent of patients have bilaterally lesions [21]. Capillary telangiectasia or military aneurysms of Leber can associate with exudative retinopathy and is famous as syndrome or disease of Coats [9]. Retinal

cavernous hemangiomas are believed to be congenital hamartomas that may not be detected in childhood [42].However, Messmer et al. [43] in small series of 9 patients found the age of presentation ranged from 1 to 55 years. This tumor can be sporadic and syndromic associating with cerebral cavernous malformation syndrome and this tumor should be included with neuro-oculocutaneous (phakomatoses) syndrome [38]. On the other side, 5.0 percent of patients with familial cerebral cavernomas have retinal cavernomas [44]. Familial malformations have been linked to three loci on chromosomes 3q, 7p and 7q [44, 45, 46, 47].

Wyburn-Mason syndrome

It is a rare sporadic order characterized by congenital arteriovenous malformation principally of the retina and brain [48].In a small series of 14 patients with Woburn-Mason syndrome 10 patients 71.4 percent were children aged from 4 to 16 years, 5 girls and 5 boys. The age of patients when they presented with symptoms was younger than the age of patients with sporadic brain arteriovenous malformations [49]. Cerebral hemangiomas usually become symptomatic by the second or third decade of live [38]. Of 26 literature and 1 author's cases of Woburn-Mason syndrome 11 cases 40.7 percent were children aged from "birth" to 14 years, males were 3, females were 8, of the lesion described 3 were right-sided, 6 were left-sided and 1 patient was bilateral. With regard to ethnicity 1 patient was Middle Eastern, 3 were Caucasian and 7 were of uncommon ethnicity [50].

Retinal vasoprolipherative tumors

It is an uncommon lesions that have only recently been recognized as a distinct clinical entity. Although retinal vasoproliferative tumors usually present in the third or fourth decade of life they may present in childhood [38] and bilaterally in twins [51]. The presence of either retinal cavernous or choroidal hemangioma should alert the physician to search for features suggestive of systemic and familial involvement[47] and strongly support the recommendation to undertake screening of the children of VHL parents [52].

Retinal astrocytoma in typically cases develops from the atrocities of the retina or of the optic nerve disk, more often they are growing towards corpus vitreous not frequently on the cases of sclerosis tuberoses. In1921 at first this type of tumor described by Van der Hoeva. However, later Schwab found that retinal astrocytoma can occur in patients with sclerosis tuberoses only in 20.0 percent of cases. It can be asymptomatic in children and young adults.[21] In the literature, there is report about solitary astrocytoma in an infant of 5-month- old [53]. The median age of 4 children with retinal astrocytoma was 3 years [54]. It is possible to develop cysts in the retinal astrocytoma [9, 21].

In total, intraocular benign tumors occurred in children only in 10.6 percent (38 children) of all benign and malignant intraocular tumors (358 children) and in 4.8 percent of all ocular tumors (800 children) [3].

Benign orbital tumors

These occur with the frequency according to the type of study (clinical, histopathological, or radiological) and whether the series comes from a primary or tertiary facility. Orbital cellulites, inflammatory pseudotumor, capillary hemangioma, optic nerve glionia, and fibrous dysplasia often do not require biopsy and can be diagnosed and treated based on clinical information alone. Therefore, in these cases, the incidence of orbital tumors may be erroneous [55]. Perhaps therefore, the registration rate in Britain may be about 10.0 percent less than the true incidence [56]. The most common benignorbital tumors in children from neonatals up to 16 years of age were represented by epidermal cyst (18 patients), followed by orbital capillary hemangioma (4 patients) of all 41 consecutive patients with orbital clisease [57], or in 53.7 percent of all orbital tumors in children [58]. Dermatomas and angiomas werethe most frequently encountered primary orbital tumors in children between 1981 and 1990 years [59]. In children less than 10 years old, the most common tumors were dermoid cyst (26.0%), capillary hemangioma 11.0 percent, and hemorrhagic lymphangioma 11.0 percent [60].Benign cystic lesions (excluding lacrimal gland cysts) accounted for 6.8 percent of all biopsed orbital lesions of patients 18 years and younger [61] or in 6.0 percent of all intraorbital tumors [62].Another percentage of cysts and vascular lesions were found in the reviewed cases of histopathologically verified orbital tumors from 340 patients aged 18 years and younger for the period 1932 to 1991. Cysts 23.2 percent and vascularlesions 17.6 percent were the most common tumors and they are in as muchas 3.3 percent of all ophthalmic surgical procedures in cliildren [63]. Iohansen et al [63]. found cystic tumors (dermoid, teratoma and epithelial) in (13.8%) in children aged 0.0 to 18.8 years of all orbital space-occuping biopsied/Surgically removed lesions in the period 1974 to 1997. Of all dermoids in the body orbital and periorbital dermoid account for 37.0 percent [65]. Other authors also found that cystic lesions mostly 64.1 percent occur in patients aged 18 years or less, or in the 0 to 20 age group and the number of cysts progressively decreased from age group 0-20 to >30.

Hemangiomas of the orbit

It occur in 3.3 percent of all orbital tumors in children 0 to 18.8 years (cavernous was in 2.0 percent, capillary in 0.7 percentand arteriovenous in 0.7 percent) [64]. Capillary hemangiomas mostly occurred in

children in the first year of life [61, 68]. However, in children less than 10 years old with orbital tumors capillary hemangioma was in 11.0 percent.

Lacrimal gland's epithelial tumors

Lacrimal gland's epithelial tumors such as pleomorphic adenoma (benign mixed tumor) very seldom develop in prepubescent children and they are never bilateral [9].For example, of 250 consecutive biopsies for orbital space-occupying lesions in children aged 18 and younger there were no cases of pleomorphic adenoma in the period 1962 to 1983 [61] or during 24 years (1974- 1997) there was only 1 patient (0.7%) of all orbital lesions [64]. However, in the literature a rare case of 5-month-old child with primary pleomorphic adenomaof lacrimal fossa lesion described [69].The cystic lesions of lacrimal gland had the largest number for 10-year-old or younger. Lacrimal fossa lesions was in age group in 4.8 percent and in10 years age group in 3.9 percent. Yearly incidencesof lacrimal fossa lesions is 0.04 and 0.026 per 100000 people by decade in these age groups respectively. Yearly incidences of primary pleomorphic adenoma of lacrimal fossa lesion in these age groups were 0.008 and 0.009 per 100000 people by decade respectively [69].A malignant transformation of a formerly benign pleomorphic adenoma of the lacrimal gland is possible and occurred in a 11 years old patient nine years after the first operation [70].

Optic nerve gliomas

These are slowly growing astrocytic neoplasms of the anterior visual pathways, the majority of which occur within the first decade of life in 65.0 percent and only 5.0 percent of orbital gliomas occur before two years of life [21]or within the first two decades of life with equal sex incidence in about 1 to 200000 patients with eye complaints. The incidence is greater in neurofibromatosis. There is possible bilateral optic nerve involvement [71].Glioma of the optic nerve is the most frequent lesion seen in children and it occurs in 26.3 percent of all orbital biopsed or surgically removed lesions or in 57.4 percent [72],or in 81.6 percent[64]of all optic nerve neoplasms. In children less than 10 years old with orbital tumors optic nerve glioma occurred in 11.0 percent [60].More frequently this tumor occurs in females in 32.7 percent (33 females of 101 children with tumors of optic nerve [72].

Optic nerve meningiomas

These arise from the nerve sheath and are to be distinguished from orbital meningiomas arising from ectopic arachnoidal cells or those secondarily involving the orbit by extension from adjacent sites. Up to (80.0%) of orbital meningiomas occur in females, in two peaks, (25.0%) in the first decade, and the rest in the 5th decade [71]. As a rule meningiomas are unilateral, but it is possible bilateral cases [73]. There were six cases ofoptic nerve or Meningeal tumors, accounted for (2.4%) [61], or (1.9%)[64] of all childhood orbital tumors. Five of six cases of optic nerve tumors were juvenile pilocyticastrocytomas (optic nerve gliomas), and one was a primary optic nerve meningioma [61]. However, Lindegaard et al [72]found meningioma of optic nerve in (23.3%) of all optic nerve tumors with significantly prevalence of boys in (80.6%) (25 boys and 6 girls). Totally, benign orbital tumors seen in childrenoccurred in 50.9 percent [3] or in 66.2 percent [3] or in 77.6 percent [64] or approximately in 90.0 percent [74]. Miscellanous benign lesions were in children in 24.0 percent of 290 ophthalmic specimens of children and adults [75].

Other benign orbital tumors such as oxyphillic adenoma of the lacrimal gland, orbital lymphangioma, osseous, fibro-osseous and histiocytic lesionsare extremely rare in children. For example, of 250 consecutive biopsies there were only two juvenile ossifying fibromas and only one case of eosinophilic granuloma [61]. Leiomyoma of the orbit, a benign tumor of smooth muscle occurs in sporadic cases and is very rare orbital pediatric benign tumor[76].

CONCLUSION

Lumps and bumps around the eye are very common. As a general rule, they are more commonly benign in the younger age groups, and could well be malignant in the older age group. Several big series confirms that, in the eyelid, conjunctival, intraocular and orbital tumors, benign tumors largely predominate over malignant ones. Despite a wide variety of histological subtypes, more than 80% of cases can be assigned to less than a dozen of predominant subtypes. However, clinicians and pathologists should be aware of the pitfalls that can affect both clinical and histological diagnosis. This is particularly important for sebaceous carcinoma presenting like inflammatory lesions and for hair follicle tumors mimicking basal cell carcinoma. In children, benign orbital tumors can masquerade malignant orbital tumors, inflammatory orbital diseases and even non-tumor disease such as Echinococcus.

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