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Research Article

Astrocytomas of Retina: Why Do Many Authors Still Refer to These Lesions as Astrocytic Hamartomas?

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Abstract

Objective: To determine the prevalence of retinal astrocytic tumors in newborns.

Methods: Analysis of published articles describing large-scale screening studies of newborns (pre-term and term) performed using wide-field digital fundus imaging in which authors reported fundus lesions and abnormalities other than retinopathy of prematurity and retinal hemorrhages; counting of the cases in which an ocular fundus lesion diagnosed as retinal astrocytoma or retinal astrocytic hamartoma was reported.

Results: Fourteen published articles on ocular fundus screening examinations of > 1,000 newborns using digital wide-field fundus imaging (13 articles) or smart phone fundus imaging (1 article) reported fundus lesions and abnormalities other than retinopathy of prematurity in an aggregate total of over 300,000 cases. Only 1 newborn was reported to have a discrete retinal tumor diagnosed as a retinal astrocytic tumor by the authors.

Conclusion: Although a few congenital lesions diagnosed as retinal astrocytic tumors have been documented, most lesions of this type do not appear to be congenital. In view of this, the term "retinal astrocytic hamartoma" (implying a congenital malformation) for all lesions of this type appears to be inappropriate.

Keywords: Astrocytic Hamartomas; Retina; Fundus Lesions; Retinal Tumor

Introduction

The generic term "retinal glial tumors" encompasses a spectrum of ocular fundus lesions that has been described as including focal circumscribed malformations, acquired neoplasms and reactive post-inflammatory and post-traumatic non-neoplastic proliferations (focal nodular and massive gliosis of the retina) [1]. This article concerns only those lesions in the first two of these categories. Some authors have suggested that retinal astrocytic tumors in these 2 categories are distinct clinical and pathological entities that can be differentiated in most affected persons [1,2]. Other authors refer to all lesions in both categories as "retinal astrocytomas" (a distinct type of benign neoplasm) and still others refer to all such tumors as "retinal astrocytic hamartomas" [3-8]. In preparation for the study described below, the author of this article performed a quick search of PubMed for articles published between 2020 and 2025 that had the term "retinal astrocytic hamartoma" in their title. That search identified 50 articles. The author then performed a similar search of PubMed for articles that had the term "retinal astrocytoma" in their title. That search identified only 9 articles. These results indicate that the majority of authors currently use the term "retinal astrocytic hamartoma" to described these lesions. According to the American Academy of Ophthalmology's instructional Basic and Clinical Science Course, a "hamartoma" is a "congenital anomaly" (i.e., malformation, focal overgrowth) of normal or near normal cells that exist normally in the involved anatomic site [9]. The resultant lesion can exhibit tissue features that are near normal to highly disorganized. The text of this booklet does not mention any exceptions to the congenital nature of such lesions.

The prevalence of retinal lesions of these types in the general adult population has never been estimated in a large-scale screening study. However, the prevalence of retinal astrocytic tumors in persons with the 3 most commonly associated disorders Tuberous Sclerosis (TS), Neurofibromatosis type 1 (NF1) and Retinitis Pigmentosa (RP) and the relative frequencies of such lesions in the most commonly associated disorders and isolated cases have been estimated (Table 1) [10-20]. This published information suggests that the expected number of adult patients with a retinal astrocytic tumor in the "astrocytoma" vs "astrocytic hamartoma" category is probably somewhere in the range of slightly less than 5 to slightly more than 6.5 per 100,000 persons in the general population (Table 1).

During recent years, a number of articles describing large-scale screening studies of both premature and full-term infants in which wide field digital imaging was used to evaluate the ocular fundi have been published. A number of these articles contain information about ocular fundus lesions and abnormalities other than retinopathy of prematurity and retinal hemorrhages detected by that screening. If retinal astrocytic tumors of the type mentioned above are really congenital and as common as estimated from published prevalence data, then a substantial number of them should have been detected by those screening studies.

The author searched the peer-reviewed literature for reports of fundus screening examinations of both selected (e.g., premature births) and unselected full-term newborns evaluated within the first 3 months of life in which the authors reported ocular fundus findings other than retinopathy of prematurity and retinal hemorrhages in an attempt to determine how frequently "retinal astrocytoma" or "retinal astrocytic hamartoma" was detected and reported in those studies.

Column 1: Associated disorder	**Column 2: Prevalence of disorder in general population**	**Column 3: Proportion of persons in group with retinal astrocytic tumor**	**Column 4: Expected number of affected persons per 100,000 in general population***	**Column 5: Percentage of retinal astrocytic tumors in category**	**Column 6: Expected number of affected persons per 100,000 in general population†**
TS	7-12 per 100,000 [13] *7 per 100,000*	29%-81% [16] *50%*	3.5	57% [21]	3.5
NF1	1 per 2500-3000 [14] *1 per 3000* *33 per 100,000*	"Rare" [17] <1 per 1600-2000 [18] *<1 per 2000* *<0.05%*	<0.165	14% [21]	0.85
RP	1 per 4000 [15]	2% [19]	0.005	NEA	<0.01
	25 per 100,000	*0.02%*		*<1%*	
None	NA	"Extremely rare" [20] <1/50,000 [18] *<0.002%*	<1.75	29% [21]	2
Total	—	—	<5.4	100%	6.4+
TS = Tuberous Sclerosis; NF1 = Neurofibromatosis type 1; RP = Retinitis Pigmentosa; NA = Not Applicable; NEA = No Estimate Available					

Table 1: Frequency data on different subcategories of retinal astrocytic tumors (neoplasms vs hamartomas). Values in italics are those used for computation of expected numbers of affected persons in columns 4 and 6. Numbers in brackets refer to cited references.

Methodology

The author used PubMed to search for English language articles describing the results of ocular fundus screening evaluations of newborns performed within the first 3 months following birth published in peer-reviewed journals during years 2013 through 2023. The author reviewed the identified articles and determined both the method of fundus examination employed and the

number of newborns evaluated in the reported study. The author excluded reports that described a study group of < 1000 cases, ones that used direct ophthalmoscopy only to examine the fundus and ones that included a substantial number of newborns screened after the neonatal period (i.e., after the age of 3 months). The author counted the number of cases in which one or more discrete ocular fundus lesions consistent with retinal astrocytoma or retinal astrocytic was identified, diagnosed and reported in each of them.

Results

The author's PubMed search identified 13 English language articles that reported results of neonatal ocular fundus screening evaluations performed using a wide-field digital imaging system on study groups consisting of >1000 newborns (Table 2) [21-33]. Table 2 identifies these articles, indicates their respective years of publication, describes the nature of the evaluated study group and lists the number of newborns reported to have undergone ocular fundus screening in each study. The largest study group in these articles numbered 199,851 and the smallest numbered 1,152. Two of these articles report cases included in a subsequent publication and these duplicate cases are therefore not counted in the total of screened newborns shown in Table 2 [21,24,26]. The authors of these articles in aggregate reported identifying 248 cases of choroidal or chorioretinal coloboma, 21 cases of retinoblastoma, 12 cases of choroidal nevus, 4 cases of capillary hemangioma of the optic disc and at least 1 case of Coats' disease. However, the authors in aggregate reported zero newborns having an ocular fundus lesion they diagnosed as either a retinal astrocytoma or retinal astrocytic hamartoma. One preliminary study whose cases were included in two subsequent publications did describe a single case the authors categorized initially as a retinal "hamartoma versus retinoblastoma" [21,24,26]. The authors indicated that this patient was treated as retinoblastoma. The subsequent publications do not mention any case of astrocytic retinal tumor, suggesting that the authors ultimately decided that this lesion was indeed a retinoblastoma.

Although it was not identified by the PubMed search criteria mentioned in the Methods section above, one article the author identified during a general search for articles on retinal astrocytic tumors reported ocular fundus findings in 5527 infants evaluated within the first 3 months of life by smartphone-based fundus imaging [34]. The authors of that article indicated that they detected one fundus lesion diagnosed as a retinal astrocytic hamartoma in their series. The authors did not provide any supplemental information about the size, morphologic growth pattern or fundus location of this lesion or mention whether this patient had any associated systemic or ocular disorder. The authors of this article also indicated that they detected 11 choroidal nevi and one case each of retinoblastoma and combined hamartoma of the retina in their screened cases.

Ref. #	Study Authors / Center(S)	Publication Year	Subjects Screened	Number Screened
[21]	Tang, et al., / 8 Chinese centers	2018	Pre-term and term newborns	1,99,851
[22]	Fei, et al., / 9 Chinese centers	2021	Pre-term and term newborns	64,632
[23]	Liu, et al., / 1 Chinese center	2021	Pre-term and term newborns	23,861
[24]	Li, et al., / 1 Chinese center*	2017	Healthy term newborns	15,284
[25]	Ranjan, et al., / 1 Indian center	2022	Pre-term and term newborns	9,105
[26]	Li, et al., / 1 Chinese center*	2013	Healthy term newborns	3,573
[27]	Gursoy, et al., / 1 Turkish center	2018	Pre-term and term newborns	3,440
[28]	Ozturk, et al., / 1 Turkish center	2022	Pre-term newborns	1,569
[29]	Jayadev, et al., / 1 Indian center	2015	Pre-term newborns	1,450
[30]	Dabir, et al., / 2 Indian centers	2023	Pre-term newborns	1,437
[31]	Ali, et al., / 1 Arabian center	2021	Term newborns	1,220
[32]	Sitorus, et al., / 2 Indonesian centers	2021	Term newborns	1,208
[33]	Goyal, et al., / 1 Indian center	2018	Term newborns	1,152
—	Total	—	—	3,08,924
*The cases reported in these articles were almost certainly included in the subsequent report by Tang, et al., so these cases are not included in the total of reported screened newborns [21].				

Table 2: Identified reports of large-scale ocular fundus screening studies of newborns published in peer-reviewed journals between 2013 and 2023, listed in decreasing order of number of newborns in the screened study group.

Discussion

The number of screened newborns identified in Table 2 plus those evaluated in the smart phone fundus imaging study totaled 314,451. According to the published prevalence data and relative frequency data contained in Table 1, one should have expected at least 5 retinal astrocytic tumors to have been detected for every 100,000 screened newborns if such lesions are truly congenital. If this expectation is valid, one should have expected to find approximately 15 to 20 such retinal tumors in those newborns if such lesions are truly congenital. The fact that only 1 discrete retinal lesion was identified as a retinal astrocytic tumor in the aggregate number of screened newborns suggests strongly that most lesions of this type are not congenital (or at least not detected ophthalmoscopically or by fundus imaging performed in the neonatal period) and therefore not hamartomas but rather benign acquired neoplasms. Retinal astrocytic tumors diagnosed as "retinal astrocytoma" or "retinal astrocytic hamartoma" are commonly divided into (1) isolated and (2) associated categories. The ocular fundus lesions in the former category occur in persons without any associated heritable (i.e., genetic) multisystem disorder or bilateral ocular disease. They are usually unifocal and unilateral. In contrast, the fundus lesions in the latter category occur in persons with a specific heritable multisystem disorder, most commonly tuberous sclerosis and less commonly neurofibromatosis type 1 and occasionally in persons with specific types of retinitis pigmentosa. Lesions of this type are much more likely to be multifocal, bilateral or both. Most retinal astrocytic tumors tend to remain stable or enlarge to a limited extent post-detection during long-term follow-up, but a few have been documented to grow rapidly and exhibit aggressive growth and malignant histopathologic features [10,35-37].

A few neonatal and early infantile lesions of both isolated and associated types have been reported, but the median age at diagnosis of associated lesions in reported series tends to be in the second decade of life while the median age at diagnosis of isolated lesions in reported series is typically about 25 to 35 years [10,20,34,35,38-41]. Despite the fact that most lesions of these types are not detected and diagnosed shortly after birth or during the first year of life, lesions of both types are commonly assumed by authors who regard them as "astrocytic hamartomas" to be congenital (i.e., present and detectable at or shortly after birth) [1,2,42]. Contradicting this impression about the congenital nature of all such lesions, new retinal astrocytic tumors of both isolated and associated types have been documented to develop from retinal sites that appeared normal on prior fundus examinations [10,43-45].

Because the author of this article did not have access to any of the wide-field digital fundus photos obtained in the cited studies except for those the authors published as illustrations, the author cannot vouch independently for the accuracy of the diagnosis of the lesions identified in the non-illustrated cases. There are several reasons to be skeptical about the accuracy of some of the reported diagnoses in the cited newborn screening studies. The first reason is the substantial difference in frequency of certain diagnoses that were identified in the various cited studies. For example, Liu, et al., reported finding a choroidal or chorioretinal coloboma in 42 of 23,861 screened newborns and Fei, et al., reported finding a lesion of this type in 99 of 64,632 screened newborns while five of the cited sets of authors did not report detecting such a lesion in a single case [22,23]. A second reason is the unusually high frequency of diagnosis of certain lesions (e.g., choroidal nevus) which are generally acknowledged to be extremely rare in newborns [46]. As mentioned in the Results section above, the authors of one article based on wide-field digital fundus imaging reported finding 12 congenital choroidal nevi in 1568 screened newborns and the authors of the study based on smartphone fundus imaging reported finding 14 such cases in 5527 screened infants [28,34]. I suspect strongly that many if not most or all of these lesions were either small patches of isolated choroidal melanocytosis or prominent Focal Aggregates of Normal or Near Normal Uveal Melanocytes (FANNUMs) in the choroid and not true choroidal nevi. If these diagnoses were erroneous, then some of the others in the various studies were probably also erroneous [47,48].

Is it possible that a classic solitary retinal astrocytic tumor was actually present in many of the screened eyes but not detected? Some authors have described retinal astrocytic lesions in infants with TS that were so subtle that they were only detected by multimodal imaging [49]. Given the characteristic translucency of some type 1 lesions when they are small, this is certainly a possible explanation for failure to find some lesions. However, given the fact that small retinoblastoma tumors (which can look very similar to small retinal astrocytic tumors) were detected in a substantial number of the screened eyes, this seems unlikely to be a satisfactory explanation for failure to detect congenital lesions in most of these screened newborns. Is it possible that lesions of this type were present and detected in many of the evaluated eyes in the cited series but not mentioned by the authors because they did not believe them to be noteworthy? Recognizing that the authors in aggregate reported at least 22 retinoblastomas and other discrete ocular fundus tumors, this also seems highly unlikely.

Is it possible that lesions of this type were present and detected in many of the evaluated eyes in the cited series but misdiagnosed as something other than a retinal astrocytic tumor? I suppose this is possible, but many other lesions that would be as likely to be misdiagnosed were detected and reported in the screened eyes.

It's generally recognized that ocular lesions of many different types can be congenital. For example, as the screening studies summarized in this article indicated, several evaluated newborns were observed to have a congenital retinoblastoma. The fact that some retinoblastomas are congenital certainly does not warrant categorizing all retinoblastomas as congenital. The same can be said about retinal astrocytic tumors. Although a few such cases in newborns have been reported, it appears inappropriate to categorize all lesions of this type as congenital. In view of this, this author strongly advocates for rejecting the term "astrocytic hamartoma" for all such lesions and recommends use of the more appropriate term "retinal astrocytoma".

Conclusion

There seems to be considerable overlap in clinical and histopathological features of retinal astrocytic tumors in isolated and associated categories and in congenital and the much more common acquired cases. Because of this, neither clinical features nor histopathological features of individual retinal lesions can be relied upon for distinguishing isolated from associated lesions or congenital from acquired lesions. It seems likely that all of these tumors will have some underlying genetic mutation or mutations in the component cells that are responsible for the observed focal proliferation of the aberrant astrocytes. However, there has never been (and, given the benign nature of most lesions of this type, probably never will be) a large-scale genetic study of the retinal lesions in the different types of cases.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Data Availability Statement

Not applicable.

Ethical Statement

The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore, was exempt.

Informed Consent Statement

Informed consent was taken for this study.

Authors' Contributions

The author solely contributed to the conception, design, analysis, drafting and final approval of the manuscript.

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