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REVIEW ARTICLE

Optic nerve melanocytoma: pathophysiology, clinical considerations, and diagnostic novelties

Melanocitoma del nervio óptico: fisiopatología, consideraciones clínicas y novedades diagnósticas

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Abstract

Optic nerve melanocytoma is a rare, benign, pigmented tumor of the optic disc that may cause visual complications in few cases and can be easily confused with malignant melanoma. This review aims to highlight its clinical characteristics and pathophysiology, as well as to update the diagnostic methods available, like optical coherence tomography angiography.

Key words: *Optic nerve. Melanocytoma. Benign neoplasm. Pathophysiology. Clinic. Diagnostic.*

Resumen

El melanocitoma del nervio óptico es un tumor raro, benigno, pigmentado, de la papila, que en algunos casos puede causar alteraciones visuales e incluso puede confundirse con una patología maligna del polo posterior como el melanoma. En esta revisión se destacan sus características clínicas y fisiopatológicas, y se realiza una actualización en el tema del diagnóstico con las nuevas tecnologías disponibles, como por ejemplo, la tomografía-angiografía de coherencia óptica.

Palabras clave: *Nervio óptico. Melanocitoma. Neoplasia benigna. Fisiopatología. Clínica. Diagnóstico.*

Introduction

Optic nerve melanocytoma is a benign neoplasm that, due to its characteristics, confuses its observers, since it appears to be a malignant neoplasm with possible vital compromise for the patient. Previously, patients with this neoplasm were enucleated due to suspected malignancy and systemic compromise.

Thanks to Zimmerman, in 1962[1-8] a series of enucleated cases were documented in which, when performing the corresponding histopathological study, the benign characteristics of melanocytoma were discovered. This, associated with new technologies such as photography, angiography and optical coherence tomography (OCT), has made it possible to approach these patients better and avoid unnecessary enucleations, preserving vision and anatomy. Likewise, this condition has been associated with rare complications, such as visual field alterations (40-90%)[9,10], neoplasm growth (15%) and malignant transformation (1-2%)[10]. Among others, it is

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worth mentioning papilledema (25%), vascular compression (3%) and retinal exudates (12%)[2,4,5].

The purpose of this review is to identify basic and updated information on the subject to highlight the importance of diagnosis and management for its application in the ophthalmic context.

Methods

A review of the literature was performed using the PubMed and Web of Science databases. A search strategy with terms (MeSH) was used in the PubMed database (MEDLINE), with the Boolean operators AND and OR as follows: («Optic Nerve Neoplasms»[Mesh] OR «Optic Nerve Diseases»[Mesh]) AND «Melanocytes»[Mesh]. As a result, 13 articles were obtained. The search in Web of Science was carried out with the search strategy: Optic Nerve AND Melanocytoma. As a result, 50 articles were obtained. The word "Melanocytoma" does not exist as a Mesh term, so other terms were used to try to encompass the latter and to complete the search. A total of 63 articles were obtained as a result. The gray literature was not reviewed and no limitation filters were used (for example, publication date). Only articles in English and Spanish were selected, so nine articles were removed due to language. When reading the abstracts, the other ten articles were removed, since they did not correspond to the topic of this review. A chapter from a book and an article from the references of one of the selected articles were included, and repeated articles were eliminated. That left a total of 45 documents to review.

Epidemiology

The average age at diagnosis is 50 years, with a range between 1 and 91 years, according to a review by Shields[9-14]. However, in other articles there is a reported range between 17 and 74 years[14]. A similar finding was observed in a study in Korean population with a mean age at diagnosis of 46 years.[15]

Melanocytoma is part of the 0.55% of pigmented intraocular tumors, and its most frequent intraocular location is the optic nerve[16]. There are reports with an increased incidence in female (62%) than in male (38%)[14,17], data that correspond to the Korean (63%)[15] and European (62%) populations[7]. The same incidence has been observed between races[9]; however, other reports indicate a higher frequency in people with densely pigmented skin and Caucasians[4,14]. Shields, et al., in a study of 115 patients, observed an incidence of 65% in white people, 29% in black people and 7% among Indians (1%), Arabs (1%), Asians (3%) and Hispanics (2%)[2,10,18]. Most cases are unilateral[9] (99% of patients[10]), and it affects more the right (56%) than the left eye (43%)[2].

Due to the absence or low incidence of symptoms, it is usually diagnosed in a routine ophthalmologic evaluation.

A study in a European population published by Dr. Zografos found visual symptoms in 26% of patients[7]. Similarly, in a Korean population, 22% of patients had visual symptoms[15], as well as 26% of the American patients evaluated by Shields[9,10,19].

Despite being a benign lesion, its counterpart, melanoma, is a fatal condition. Malignant melanocytoma is rare; however, it has been documented in 1 to 2% of cases[2,10,12,14,15,17,19-25].

Clinical presentation

Optic nerve melanocytoma is asymptomatic in most cases, which is why its diagnosis is mainly made in a routine ophthalmologic evaluation[3,23,24]; however, there are reports of symptoms in patients with this condition. Decreased visual acuity has been observed in up to 26% of patients[9,10,19] with an ischemic compromise of the central retinal artery or tumor necrosis[7,9,10,22,26-28]; however, visual loss may also be secondary to axonal swelling due to nerve compression[3,7,21,22,27,29]. A case of blindness secondary to compression due to melanocytoma was described in a 12-year-old male; however, a profound visual loss is rare[30].

Apart from decreased vision, other symptoms have been described. For example, Shields, in his study of 115 cases, found as reported symptoms blurred vision (16%), light flashes (4%), myodesopsia (4%) and no symptoms (76%)[2].

The presence of a relative afferent pupillary defect (RAPD) has been documented in 30% of eyes with melanocytoma, even without visual acuity impairment[19,31]. Shields reports RAPD in 9% of the patients in one of their studies[2].

These symptoms, apparently, are secondary to small compressions of the nerve fibers or due to the size of the tumor, which also led to questioning visual field affectation, and it was observed that up to 90%[9] of the patients with RPAD had some type of visual field defect.

The best way to observe the tumor and its characteristics is by fundoscopy. Regarding the color of the tumor, it is known that it varies between dark brown and black[26,31]. Particularly, in Shields's study they observed 97% black tumors and only 3% brown tumors[2,10].

Its location in the optic disc is usually inferotemporal[11,15,24,32,33]. The location is exclusive in the optic nerve in 15% of cases; however, in 54% it can compromise the adjacent choroid and in 30%, the neurosensory retina[9,10,19]. Regarding the compromised area, Shields found that in 75% of cases, 50% or less of the disc area is compromised, while in 12% it affects more than 90%[4].

Regarding the shape, the disc margins tend to be fibrillated or feathery[4,16,19,24].

These lesions have been associated with ocular melanocytosis in 8% of patients[2,9]. Other ocular disorders have been observed in patients with melanocytoma; however, there is no evidence of their correlation, such as optic nerve hypoplasia (2%), retinitis pigmentosa (1%) and congenital hypertrophy of the retinal pigment epithelium (RPE)[2]. The presence of a choroidal nevus concurrent with melanocytoma has also been described in 47% to 50% of patients[3,4,13,33].

Two reported cases indicated the correlation of melanocytoma with a peripapillary choroidal neovascular membrane, which caused decreased vision and questioned the benign nature of the lesion. The criteria that allowed surgeons to critically approach the case were the stability of the tumor size by angiography and ultrasound, as well as the absence of other characteristics that led to suspicion of malignancy[27]. In the first case, they decided to remove the membrane by surgery, achieving an improvement of visual acuity[27]. In the second case, there was a choroidal neovascular membrane with macular edema, which was treated with bevacizumab with good visual results[12]. The incidence of this pathology has been described in 1% of patients with melanocytoma[12,34].

Among other correlations, typical findings of polypoidal choroidal vasculopathy has been reported in a patient with optic nerve melanocytoma[18], that presented as small red-orange rounded subretinal lesions, close to the optic nerve[35]; however, this is not the only case reported in the literature. Specifically, Dr. Rouvas described this correlation and its possible treatment with photodynamic therapy + intravitreal aflibercept with good results[18].

On the other hand, some investigations have found optic nerve melanocytoma concurrent with tumors derived from the neural crest cells (meningioma-like). However, as they are case reports, the implications are unknown; therefore, it can only be stated that meningioma and melanocytoma may concur in the same patient[36].

Kaliaperumal, et al. found a link between hypertension (HT) and melanocytoma based on the origin of pigment cells, adrenal medullary cells, and pheochromocytes, since they are all derived from the neural crest[11]. These authors found HT associated with optic disc melanocytoma and hormonal metabolites in urine[11].

Regarding the above, in Korea, 19% of the patients showed an association with HT and 8% with coexisting tumors derived from the neural crest[15].

Concerning other systemic diseases, melanocytoma has been associated with neurofibromatosis type 2[2,9], basal cell carcinoma[9], vitiligo[9], phakomatosis pigmentovascularis[10] and intracranial meningioma[9,10], although there are only some case reports and therefore, a correlation has not been confirmed.

There is a strange case report about the presence of phosphenes induced by loud sounds, predominantly under dark conditions, in a patient with unilateral melanocytoma. This relationship is believed to have a central component, as the persistence of phosphenes occurred after enucleation[29].

Some complications associated with the presence of melanocytoma that have been reported are papilledema (25%)[19], disc pallor (2%)[2.10], intraretinal edema (16%)[19.26], subretinal fluid (14%)[19,26], intraretinal exudates (12%)[19,26], retinal/choroidal neovascularization (1%)[2,10] and focal hemorrhages (5%)[19]. The latter are usually mild, and are believed to be secondary to juxtapapillary vascularization.

Vitreous seeds have been reported in 4%[2,9,19], sometimes extending to the anterior chamber and causing a black pseudohypopyon. In addition, these patients may have ischemic necrosis of the tumor with severe visual impairment.

Vascular occlusions are reported in 3% of the cases[19,26], divided as follows: central retinal artery (2%) and branch occlusions (1%)[2], causing a considerable decrease in visual acuity. The malignant growth and transformation of a melanocytoma was described in one Australian patient, who showed vascular occlusion and secondary neovascular glaucoma. Due to the associated pain and the mass effect, the patient had a symptomatic bradycardia due to oculocardiac reflex[17].

The presence of neuroretinitis secondary to necrosis and inflammation has also been reported in the literature[8].

Some studies have shown that these lesions are stable, with an average baseline size of 2 mm (1-10 mm) and a thickness of 1 mm (0.5-3 mm) in an American population[2.10], and 3.1 mm (1.6-4.4 mm) and 1.9 mm (0.8-2.4 mm), respectively, in a Korean population[15].

The growth of benign lesions confirmed by post-enucleation histopathology study, has been documented in

10-15% of cases[9-13,16,17,21-24,30,31,33,37,38], after several years of follow-up (approximately 5 to 20 years)[4].

Therefore, minimal growth should not be confused with malignant transformation. Likewise, a decrease in size has been evidenced in 3% of cases[4].

Malignancy, although rare, is also possible, and has been evidenced in 1 to 2% of the cases[12,14,15,17,19-23,25,34]. Some of the characteristics that may lead to suspicion of malignant transformation are, for example, a small lesion that initially only compromises the optic disc and then grows and extends causing visual loss secondary to vascular occlusion[9,10]. Another suspicious characteristic is a thickness greater than 1.5 mm at the time of diagnosis, which is a risk factor for tumor growth[10,15,19]. Among the case reports where malignancy has been documented, they reported initial flat lesions (2 mm), with a growth in height of 4 and 6.7 mm in a period of 5 and 6 years of follow-up, respectively[3]. Therefore, in the report of Dr. Sharma, in India, they suspected a malignant lesion that had all the characteristics of a melanocytoma except for an height by ultrasound of 5.2 mm[3].

Regarding genetic studies, a genetic association with the GNAQ/11 mutation has recently been demonstrated in various pigmented lesions, such as blue nevus, ocular melanosis, ciliochoroidal melanocytoma, melanoma and skin lesions. Another study confirmed its association with optic nerve and iris melanocytoma[6]. On the other hand, BAP1 mutations are found in up to 84% of metastatic uveal melanomas, and in this study they suggest exploring in larger samples their finding of BAP1 in a patient with melanocytoma, since its presence could imply the need for aggressive treatments in patients with apparently benign lesions[6].

Histopathology

Two types of cells have been described in histopathological evaluations:

– Type 1 cells: They are oval or rounded cells, with abundant intense cytoplasmic pigment located in large melanosomes, with a low nucleus-to-cytoplasm ratio, a uniform size of cells and nucleus. Scarce prominent organelles and nucleoli. The characteristics of these cells are similar to those found in patients with melanocytosis[14,16,27,29,39].
– Type 2 cells: They are spindle-shaped, less pigmented, with small rod-shaped melanosomes, a high nucleus-to-cytoplasm ratio, with more prominent nucleoli and a greater number of cytoplasmic organelles[9,14,16,27,39].

Likewise, pigment-filled macrophages can be observed floating in the vitreous, that may cause secondary glaucoma[14].

A study performed a histopathological correlation of the tumor, showing edema of the prelaminar neural tissue, retinal displacement and folds. The compressed layers were also observed as folds by histopathologic evaluation[5].

Pathophysiology

It is thought to be a congenital hamartoma-like lesion that develops from aberrant melanocytes of the choroidal lamina[3,11,23,32,39,40]; however, it is rarely observed in children. Shields reported one case, in which the appearance of a pigmented optic nerve lesion was documented in a patient with previously normal photographic reports, suggesting *de novo* appearance in adulthood or pigmentation of a congenital amelanotic lesion[9,10,40].

Diagnosis

The diagnosis of these lesions is typically made by fundoscopy; however, certain tests such as photographs, fluorescein angiography, OCT and ultrasound are usually necessary as part of the diagnostic support of possible complications and symptoms associated with the lesion, as well as to document its stability and growth. Shields suggests photographic monitoring of the lesions every 1 to 2 years[2,4], and Sharma considers monitoring the size of the lesion by ultrasound[3].

Retinal fluorescein angiography

By retinal fluorescein angiography, there is hypofluorescence and autohypofluorescence[4,19,21,34,38], probably secondary to pigmented and densely compacted cells[19.38], with relatively little vascularization and lipofuscin absence[38]. By autofluorescence, the adjacent retina is isoautofluorescent[41]. The adjacent region of the tumor may be hyperfluorescent when it is associated papilledema[4,19] or subretinal fluid[2] (Fig. 1). This is consistent with the findings by indocyanine green angiography, a technique that shows hypofluorescence of this lesion[10,21].

In terms of fluorescence, a study with infrared autofluorescence was carried out in China. This test shows hyperfluorescence in places with a high concentration of melanin such as the choroid, especially in the fovea,

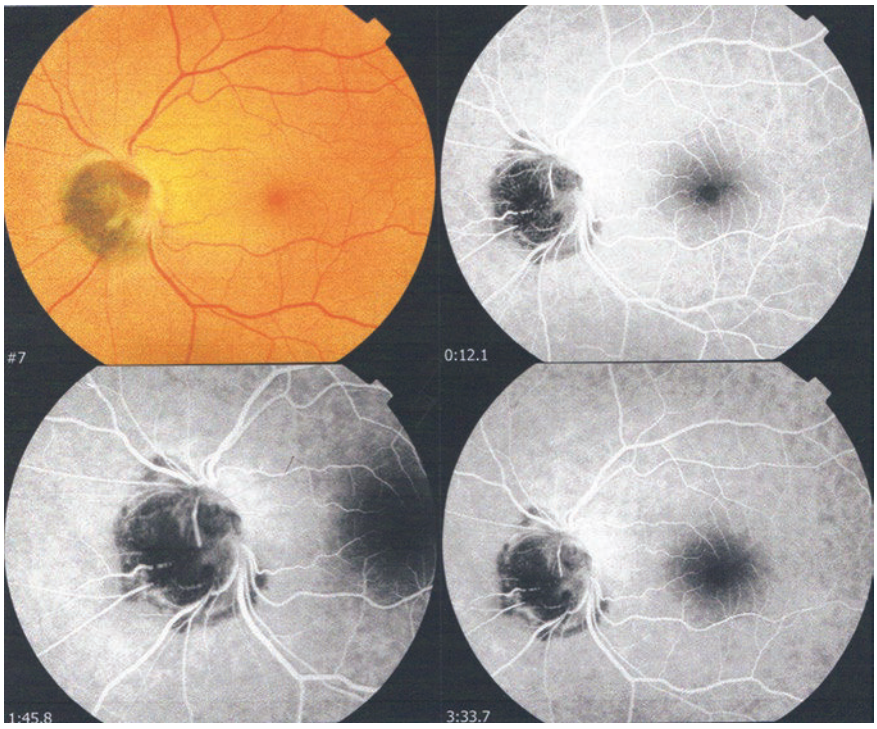

Figure 1. Upper left: Color photography of an optic nerve melanocytoma. Upper right: Fluorescein angiography. Lower left: Early phase. Bottom right: Late phase. This photograph shows compromise of the optic disc due to the pigmented lesion, and blocked fluorescence secondary to dense pigmentation (*courtesy of Dr. Zeiad Eldaly, from Eldaly, et al.*[23]).

thus showing hyperfluorescence of the melanocytoma that allows to highlight and adequately delineate the lesion[38].

Ocular ultrasound

A lesion with an elevation of more than 0.5 mm can be detected by an ocular ultrasound or a computerized axial tomography; however, this test cannot differentiate a melanocytoma from other types of elevated lesions, and it cannot show microscopic extension of the tumor[9,10,19, 38]. Typical findings by B-mode ultrasound in cases of melanocytoma are acoustic solidity and medium to high internal reflectivity (Fig. 2)[3.19].

Optical coherence tomography

It is also possible to perform an OCT, however, it will be useful to evaluate only associated conditions, such as subretinal fluid and cystoid retinal edema[9,20,38,41], as well as retinal thickness on the tumor[20], since the density of the tumor blocks the passage of light and avoids observing other internal details.

Between spectral domain (SD) or time domain (TD) OCT, SD shows advantages over TD, since it is faster and has a higher resolution[32]. It is possible to observe a smooth, highly reflective, dome-shaped prepapillary mass that is continuous with the adjacent nerve fiber layer[5,19,26,32,38,39], that generates a dense acoustic shadow[5,10,19, 26,32,38,39] representing the optically empty mass without other details (Fig. 3)[5.26]. Histopathological correlation shows that the hyperreflective surface corresponds to an area of glial degeneration and hyperpigmentation[5]. In some cases, it is also possible to document vitreous seeding[10], especially when OCT is combined with scanning laser ophthalmoscopy[5].

A study carried out in Japan used SD-OCT to identify the characteristics of retinal vessels in patients with optic disc melanocytoma. They observed tubular structures on the apical and retinal surface of the tumor corresponding to the first branches of the central retinal artery and vein, that are presumed to generate the irregular component of the surfaces. The deepest vessels are obscured by acoustic shadow, and these typically showed perivascular hyperreflective points of

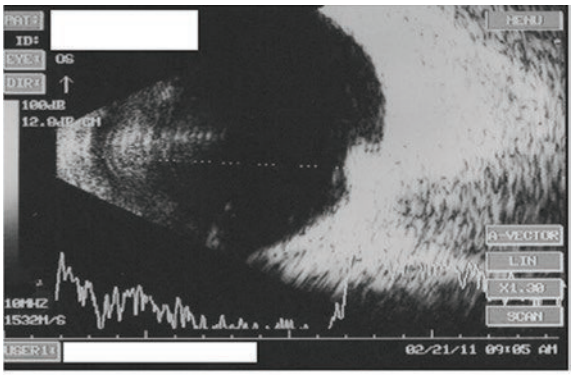

Figure 2. Mode-B ultrasound serial photographs of the left eye of a patient with optic nerve melanocytoma in 2011 (upper), 2012 (central) and 2013 (lower). This images evidence that there was no change in mass size, echogenicity, or choroidal excavation (*courtesy of Dr. Zeiad Eldaly, from Eldaly, et al.*[23]).

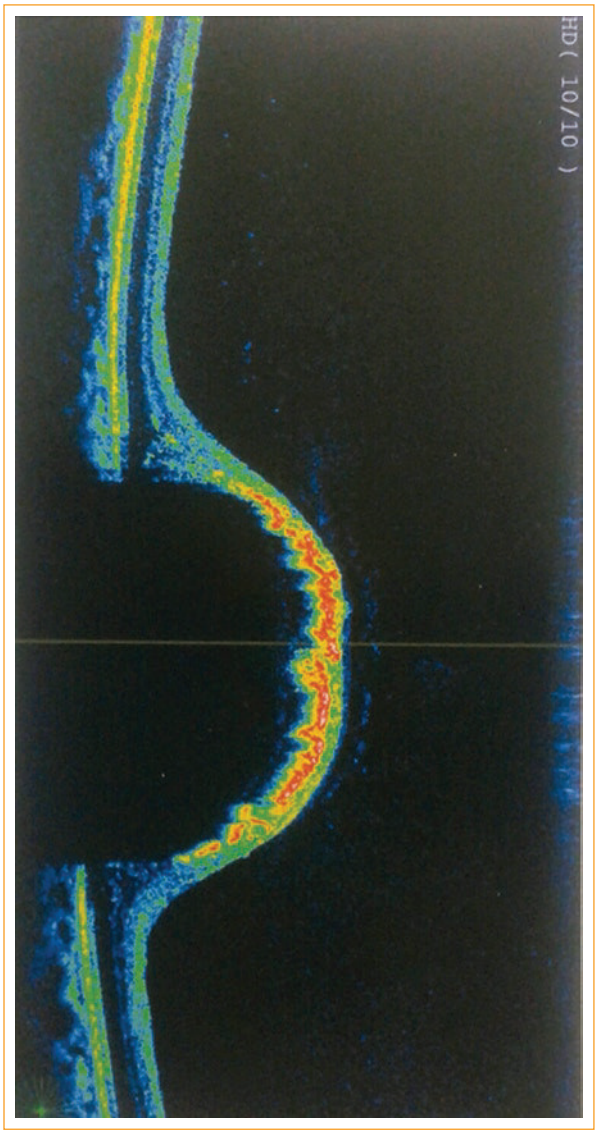

Figure 3. Optical coherence tomography of the optic nerve head. Evidence of a highly reflective surface with back-shadowing over the underlying structures (*courtesy of Dr. Zeiad Eldaly, from Eldaly, et al.*[23]).

different sizes, unlike the main branches and vessels in the areas where there was no tumor[20].

These vessels also showed tortuosity from the tumor surface to the retina, which may be associated with the vascular complications of the tumor[20]. The perivascular hyperreflective points may correspond to lipid and protein extravasation from the tumor, melanophages or tumor cells[20]. A study evaluated the presence by OCT of optic disc drusen associated with melanocytoma, which due to absence of calcification, are not visible by any other technique[42].

Optical coherence tomography angiography

With angio-OCT (OCT-A), the peripapillary radial capillary network is observed over the mass in cases where there is no retinal compromise. With this technique it may not be possible to observe deep vessels[10]. However, it allows to observe deeper vascular layers

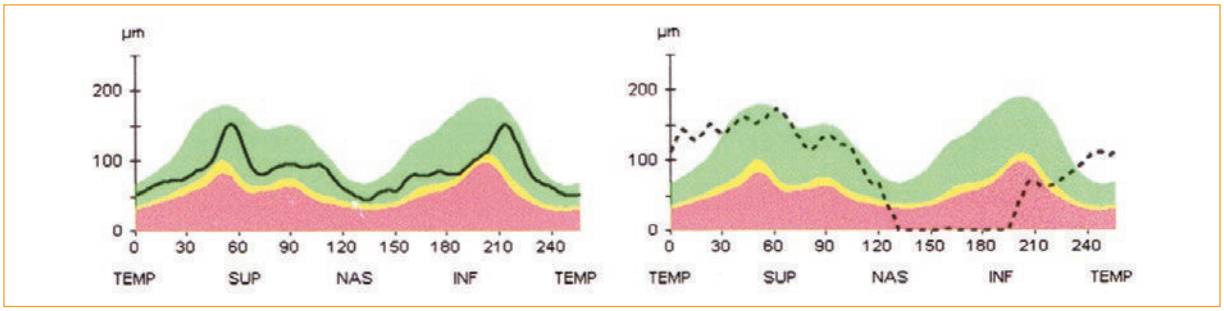

Figure 4. Nerve fiber layer thickness map (right and left eye, respectively). Normal bi-hump configuration is observed in the right eye, as well as loss of nerve fiber layer corresponding to the location of the lesion in the left eye (*courtesy of Dr. Zeiad Eldaly, from Eldaly, et al.*[23]).
TEMP: temporal quadrant; SUP: upper quadrant; NAS: nasal quadrant; INF: lower quadrant.

that cannot be evaluated by angiography due to dense pigmentation[21].

It is important to mention that OCT-A is not influenced by pigmentation, since it is based on the movement of red blood cells. In a case report of a patient with stable melanocytoma, changes in the visual field suggestive of glaucoma were detected. OCT-A identified a decrease in vascular flow in the affected areas of the disc corresponding to the visual field defects, suggesting a glaucomatous and non-compressive etiology[21]. OCT-A is a promising diagnostic method since, unlike angiography, it is non-invasive. It can also evaluate deep vascular layers, tumor vascularization and the nerve fiber layer separately[19,21,43]. However, more studies are needed since until now there are only case reports in the literature that support this hypothesis.

Visual fields

Visual field alterations have been observed in 40%[10] to 90%[9,23,34] of the patients. They include defects such as minimal and major enlargements of the blind spot[4] in 15% and 75% of patients, respectively[4,9,16], nasal step in 10%[9], and relative and absolute arcuate defects of the nerve fiber bundle in 20% each[4,9]. Shields found that 24% of his patients had visual field alterations, 32% with enlarged blind spot, and 24% with a defect in one of the quadrants[2] (Fig. 4).

Magnetic resonance

Magnetic resonance imaging can detect macroscopic progressions in the retrolaminar portion of the nerve when used concomitantly with gadolinium; however, it does not detect microscopic progressions[5,26]. MRI is also crucial to rule out retro-orbital lesions and malignant tumors such as melanoma[22]. It does not distinguish between a melanoma and a melanocytoma, since both are hyperintense on T1 and hypointense on T2[19].

Visual evoked potentials

In India, they reported a clinical case of a patient whose evoked visual potentials showed altered results due to visual acuity, with delayed conduction of the optic nerve[3].

Differential diagnosis

Among the lesions that must be considered when evaluating a patient with suspected melanocytoma, are juxtapapillary choroidal melanocytoma, choroidal nevus, RPE hyperplasia, combined retinal hamartoma and RPE, RPE adenoma, melanoma of the optic nerve, peripapillary vitreous hemorrhage, choroidal melanoma and optic nerve pit, among others[24-26,34,37,40].

Treatment

Given its benign condition, no treatment is necessary. Annual photographic documentation and fundoscopic evaluation of the lesion, as well as monitoring of potential symptoms that suggest progression, are sufficient in these cases[9,10]. There are cases in which it may be necessary to perform a fine needle biopsy and subsequent enucleation if malignancy is demonstrated due to the characteristics of the biopsy or genetic expression[10,14,24,28]. Treatment of conditions associated with melanocytoma such as epiretinal membranes, macular edema, or glaucoma may be necessary to preserve or improve visual acuity, as well as the management of possible complications.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Conflicts of interest

The authors declare no conflicts of interest.

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