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OCULAR-AND-DERMATOLOGICAL-MANIFESTATIONS-OF-NEUROFIBROMATOSIS

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Abstract:

Introduction: *Optic nerve sheath meningiomas (ONSMs) are tumors of the meninges surrounding the optic nerve, they are usually benign neoplasms. It is usually presented with vision loss, optic atrophy, and optociliary shunt vessels on fundoscopy, in patients between 30-39 years old. Although the tumors of optic nerve are considered rare, ONSMs account for nearly 30% of optic nerve intrinsic tumors. ONSMs can be associated with type II neurofibromatosis. Usually, ONSMs are not associated with any mortalities and with very little nonvisual morbidities. On the other hand, they are often associated with visual loss in the affected eye. Treatment of ONSMs also have a high risk of loss of vision, so, the goal of the management of ONSMs patients is to balance the risk of progression leading to visual loss with the risk that accompany the treatment*

Aim of work: *In this review, we will discuss Ocular-and-dermatological-manifestations-of-neurofibromatosis.*

Methodology: *We did a systematic search for Ocular-and-dermatological-manifestations-of-neurofibromatosis using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.*

Conclusions: *ONSMs are considered difficult to diagnose and manage, due to the nature of this lesions, treatment-induced morbidity and the effect of the different lines of treatment on the vision in the affected eye. Given the variable natural history of these lesions, there will always be uncertainty around when and how to initiate treatment. Nevertheless, with earlier detection with improved imaging technology, more accurate radiotherapy delivery, and improved case selection for surgical management, it is hoped that outcomes will continue to improve for these patients.*

Key words: *Ocular, dermatological manifestations, neurofibromatosis.*

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INTRODUCTION:

Optic nerve sheath meningiomas (ONSMs) are tumors of the meninges surrounding the optic nerve, they are usually benign neoplasms. It is usually presented with vision loss, optic atrophy, and optociliary shunt vessels on fundoscopy, in patients between 30-39 years old [1]. Although the tumors of optic nerve are considered rare, ONSMs account for nearly 30% of optic nerve intrinsic tumors.2 ONSMs can be associated with type II neurofibromatosis. Usually, ONSMs are not associated with any mortalities and with very little nonvisual morbidities. On the other hand, they are often associated with visual loss in the affected eye. Treatment of ONSMs also have a high risk of loss of vision, so, the goal of the management of ONSMs patients is to balance the risk of progression leading to visual loss with the risk that accompany the treatment. In this review, we will discuss the most recent evidence regarding Ocular-and-dermatological-manifestations-of-neurofibromatosis.

METHODOLOGY:

We did a systematic search for Ocular-and-dermatological-manifestations-of-neurofibromatosis using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.

The terms used in the search were: Ocular, dermatological manifestations, neurofibromatosis

EPIDEMIOLOGY:

Generally, tumors of the orbit are considered to be rare, ONSMs account only for a portion of these tumors. According to a previous comprehensive review, ONSMs accounts for 2% of all orbital tumors. It is more predominance in female (61%–39% for males). The mean age at the time of diagnosis is around 40 years, with tendency to present earlier in male patients (36 years vs 42 years for females). ONSMs are usually unilateral tumors, it could be bilateral in 5% of the cases. Most of the orbital meningiomas have intracranial origin, only 10 percent of originate primary from the orbital area. Tumors that originate from other intracranial or intraorbital areas and secondarily affect the optic nerve sheath are called “secondary ONSMs”. ONSMs of the optic canal represent 8% of all ONSMs, they are considered important as they are more liable to compress the optic nerve in this tight anatomical space of the optic canal. Pediatric ONSMs are even more rare, with a prevalence between 1:95,000 and 1:525,000, they account for nearly 2–4% of all ONSMs3,14,15. About 30% of pediatric patients with are diagnosed with neurofibromatosis type 2 (NF2), and almost a third of children with NF2 are subsequently diagnosed with an ONSM. [2]

NF2:

NF2 is considered to be strongly associated with the development of neural tumors, including ONSMs.it has an incidence of approximately 1:25,000 to 1:40,000. It is an autosomal-dominant disease resulting from the mutation of the NF2 tumor suppressor gene located on chromosome 22q12.17,18 there is a high incidence of mosaicism in patients with sporadic mutations, making the genetic diagnosis difficult. [3] diagnosing NF2 is considered to be difficult. Thus, many patients are usually diagnosed at late stages.18 Patients are usually presented with a variety of neural tumors, like vestibular schwannomas and meningiomas, cutaneous lesions, ophthalmic manifestations like cataract, retinal abnormalities, amblyopia and strabismus. [4]

Usually, ONSMs are associated with NF2, ONSMs are more common in patients with NF2 than the general population.in a previous study the incidence of ONSMs was found to be 6.8% in NF2 patients.20 other study found the incidence of ONSM to be between 4.1% and 4.8% in NF2 patients.19 28% of Children diagnosed with meningiomas (not just ONSMs) are diagnosed with NF2. [5]

CLINICAL FEATURES:

ONSMs are usually presented with a triad of optic atrophy, visual loss, and optociliary shunt vessels; however, not all the cases are usually presented with the whole triad. Visual loss is the commonest manifestation (97%) in the affected eye. The degree of visual loss varies between patients, 45% of the cases have acuity of more than 20/40, and only 24% are presented with acuity of counting fingers or worse. 24 of patients present with “no light perception” (NLP). 83% of the patients are usually presented with variable degrees of visual field defect, such as peripheral constriction (35%), central, centrocecal, and paracentral scotomas (29%), enlarged blind spot (13%), and altitudinal defects (16%). Other common presentations are proptosis (59%), strabismus (47%).3 ONSM have been reported to be associated with orbital compartment syndrome. 98% of patients are usually presented with optic disc abnormalities such swelling and atrophy. optociliary shunt vessels occur in 30% of cases due to the compression of the retinal vein while passing the optic nerve. Changes in central retinal venous flow are seen using Doppler imaging. [6] furthermore,

shrinking of the optociliary shunt vessels after surgery suggests a reduction in central retinal venous pressure, this leads to vision improvement even if no macroscopic change in tumor is noticed. [7]

ONSMs can be presented with other orbital diseases. Cases of ONSM with optic nerve gliomas in the same nerve in NF1 patients, and thyroid orbitopathy with bilateral ONSM have been reported. [8]

DIAGNOSIS:

ONSMs can be difficult to diagnose as they are slow growing tumor mostly presented with sudden insidious loss of vision. Optic nerve can be either atrophied, normal or swollen in appearance. 30 Clinical presentation can also be variable. [9] The diagnosis of ONSMs is usually based on careful follow- up and the suspicion for retrobulbar pathology.

Imaging

Magnetic resonance imaging (MRI)

Orbital and cranial imaging technique are considered the best techniques for diagnosing ONSMs, MRI is considered to be the standard investigation. Usually ONSMs are best seen on T1-weighted, gadolinium-enhanced, fat-suppressed sequences. Optic canal ONSMs are harder to diagnose than other subtypes, the use of MRI is usually essential to establish a diagnosis. The better contrast of soft tissue in MRI images compared to computed tomography (CT), makes it easier to differentiation meningiomas from other enlargements optic nerve, inflammatory conditions, or other orbital lesions. Histological examination of biopsy is essential to confirm the imaging results.

ONSMs can appear on imaging modalities either as tubular expansion (62%), globular (23%), fusiform (11%), and focal enlargement of the optic nerve (4%). In 24% of cases the meningioma usually appears as hyperdense (or hyperintense) area on either side of the optic nerve. In 8-% of the cases, tumors have smooth margins. However, some tumors show alternative growth patterns.35 The presence of perioptic cysts can also be demonstrated using MRI. [10]

MRI is most useful in the assessing lesions near the apex of the orbit, it demonstrates the soft tissue effacement and the degree of compression in optic neuropathy. MRI is also useful in demonstrating the soft tissue involvement in the orbit and intracranial area.

CT:

Contrast-enhanced CT can be used in the demonstration of tram track sign, [11]. The calcification of ONSMs gives tram track appearance on CT in the without using intravenous contrast. CT is considered more useful than MRI in the assessment of calcification.

Ultrasound:

In anterior located tumors, Ultrasound can be used to demonstrate, [12] Doppler scanning can be used to assess the blood flow within the tumor. This imaging modality can be used in monitoring and follow up known lesions in children, as it non-invasive and does not require patient immobilization. On the other hand, it cannot be used as primary scanning tool, as posterior orbital tumors and intracranial ONSMs are not visible using ultrasound.

Multifocal visual-evoked potential

Multifocal visual-evoked potential (mfVEP) is a new technique used in assessing the function of optic nerve and monitoring the functional compromise and progression of visual decline. [13] this is most useful in pediatric tumors, as MRI scanning usually require general anesthesia, [14].

Biopsy

Optic nerve biopsy is required in cases with doubtful diagnosis, malignant or aggressive disease course, progressive vision loss or atypical lesion. Biopsy may also be useful in cases with medico-legal concerns. [15] Techniques of obtaining biopsy include medial transconjunctival approach and CT guided fine-needle aspiration biopsy. [16] Biopsies usually have a high risk of vision loss, and no longer commonly indicated to diagnose ONSMs .

Treatment options

Observation

Observation of ONSMs is associated with poor outcomes. According to Dutton 86% of demonstrated ONSM patients decline in vision, with no spontaneous improvement. Turbin reported that good vision was associated with having better long-term stability. ONSMs are mostly accompanied with progressive loss of vision. One patient with bilateral ONSMs (but not NF2) was observed for 27 years, without visual progression.47 Spontaneous improvement is rare 7%. [17] Although observation in ONSMs patient can be done if vision in the affected eye is normal, once visual decline is observed, vision loss becomes expected with observation.

Radiotherapy

The difficulty with management of ONSMs that confronted clinicians approximately 20 years ago has been elegantly summarized previously: [18] observation usually leads to visual deterioration, medical therapy is generally inadequate, and surgical therapy usually leads to vision loss, which, in a tumor that rarely causes local disfigurement, rarely causes bilateral vision loss, and never causes mortality, is precisely the outcome that treatment is aiming to prevent.

A previous study on the long-term outcomes of patients with ONSM in the year 2002 46 showed the visual outcomes for 64 patients compared between surgery, observation, radiotherapy, and combination surgery and radiotherapy. The best visual outcomes were in the group subjected to radiotherapy-only, with no significant decline in visual acuity in the period between the diagnoses until the last follow-up. Furthermore, radiation was associated with the best complication rate of 33.3% (including radiation retinopathy, vascular occlusion, persistent iritis, or temporal lobe atrophy), compared to the complication rate of surgery which is 66.7%. Similar results have been demonstrated in other studies.

Thus, radiotherapy, which has better visual outcomes and a less side effects, was identified as better treatment option for ONSMs. Many lines of radiotherapy treatment have been used treat ONSMs. Fractionated external beam radiotherapy delivers radiation to the target area over a number of sessions. On the other hand, radiosurgery delivers the radiation in a single session. Three-dimensional conformal radiotherapy (3D-CRT) uses beam-forming technology and specialized software to accurately model the target tissue, and then administer radiation conforming to the target tissue volume, minimizing the amount of radiation delivered to nontarget tissues.

Intensity- modulated radiotherapy (IMRT) is a specialized kind of 3D-CRT, it changes the dose distribution according to the volume of the target. In stereotactic methods, fixed markers are being used and invasively fixed to the patient, for registration of treatment machines with images, this technique deliver the right accurate amount of radiation a to the targeted affected tissues surrounded by important structures. Another line of treatment is Image-guided radiation therapy. This reacquires imaging at the time of therapy. This is usually useful when there may be interval change in the target tissue between image acquisition and treatment delivery. This is used in tumor with rapidly changing volumes, or in with mobile organs such as the eye.

Table 1 shows a summary of the results of previous studies for 3D-CRT, stereotactic 3D-CRT IMRT and stereotactic radiosurgery. no difference was noticed between deferent types of radiotherapy. More than 8-5 of cases showed improvement of visual function. A total radiation dose of less than 54 Gy over 30 fractions is typically used, as this is the ceiling for optic nerve tolerance. visual complications may be presented with radiosurgery, as larger dose fractions is being used. So radiosurgery only used in patients with poor vision.

Surgery

Previously, Surgery was the treatment of choice regarding ONSMs. surgery is usually associated with visual loss, as the tumor and the optic nerve have shared blood supply.3 other alternatives, such as incision decompression of the optic are associated with orbital invasion. In cases of blind eye, sacrificing the tumor and nerve has been reported,

Dermatologic Manifestations of Neurofibromatosis Type 1

OVERVIEW:

Neurofibromatosis type 1 is usually presented with many different dermatologic manifestations, varies from simple primarily cutaneous expression, up to life-threatening conditions or severely disfiguring complications.

Neurofibromatosis is an inherited autosomal dominant disorder. Usually, it affects the bone, nervous system, soft tissue, and skin. We have identify more than eight different clinical manifestations of neurofibromatosis, linked to at least two genetic disorders. Clinical manifestations become more severe with the time. Neurologic problems and malignancy development may occur later.

Although neurofibromatosis is considered a neurocutaneous, any organ or system can be affected. Thus, signs and symptoms may vary. Two major subtypes have been identified: type 1 neurofibromatosis, also known as von Recklinghausen neurofibromatosis.it is the most common subtype and is usually referred to as peripheral neurofibromatosis. type 2 neurofibromatosis is usually referred to as central neurofibromatosis. This is not an accurate description, as type 1 neurofibromatosis is often associated with central presentations.

Presentation

The commonest manifestation of type 1 neurofibromatosis are unusual pigmentary patterns. Patients may report cutaneous discoloration or disfigurement or more serious physical symptoms (like pain, pathologic fractures and headaches).

Café au lait spots

Neurofibromatosis patients usually have 6 or more café au lait spots larger than 1.5 cm in diameter. 5 macules larger than 5 cm in young children suggest neurofibromatosis and require further investigations. Healthy individuals could be presented with less than 3 café au lait macules.

Axillary freckling

Axillary and perineal freckling (crowe sign) can be seen in 8% of neurofibromatosis 1 cases. It usually follows the development of café au lait macules, and precede the development of Neurofibromas.

Neurofibromas

Neurofibromas are considered to be the most common benign tumor of type 1 neurofibromatosis. It consist of Schwann cells, fibroblasts, mast cells, and vascular components, and can develop anywhere along the nerve. It is have three subtypes cutaneous, subcutaneous, and plexiform. Cutaneous lesions and subcutaneous lesions are circumscribed lesions not specific for type 1 neurofibromatosis. Plexiform neurofibromas are described as irregular, non-circumscribed, lesions that can disfigure its supportive structures. It is specific for type 1 neurofibromatosis. Other tumors like schwannomas, granular cell tumors, and malignant peripheral nerve sheath tumors may be associated with neurofibromatosis.

Lisch nodules

Lisch nodules are associated with type 1 neurofibromatosis. They are considered hamartomas of the melanocyte in the iris. Although they are difficult to detect, they should be kept in mind, especially in children with café au lait macules.

CONCLUSIONS:

ONSMs are considered difficult to diagnose and manage, due to the nature of this lesions, treatment-induced morbidity and the effect of the different lines of treatment on the vision in the affected eye. Given the variable natural history of these lesions, there will always be uncertainty around when and how to initiate treatment. Nevertheless, with earlier detection with improved imaging technology, more accurate radiotherapy delivery, and improved case selection for surgical management, it is hoped that outcomes will continue to improve for these patients.

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