

Management of Children with Optic Gliomas and Neurofibromatosis Type 1

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Optic pathway gliomas (OPG) are a common cancer in children with neurofibromatosis type 1. OPGs can cause clinical symptoms such as reduction of visual acuity, alterations of the visual field, pallor of the optical papilla, strabismus, endocrinological alterations up to diencephalic syndrome. The current guidelines provide for wait and see as the main approach if the tumor is not causing visual deterioration and adapting treatment only in the event of significant impairment of the visual function. Therefore, it is essential to early detect the visual deterioration changes as well as the identification of children eligible for treatment.

Keywords: children, optic pathway glioma, neurofibromatosis type 1.

Neurofibromatosis type 1 (NF1) is a rare autosomal dominant disease with full penetration and variable expressivity, with an incidence of 1 in 3000. It is caused by mutations or very rarely by microdeletion in the tumor suppressor gene NF1 located on chromosome 17q11.2 which encodes for a protein (neurofibromine 1) regulating cell growth and differentiation; it is an oncosuppressive gene with an important biological role in a pathway of signal transduction that regulates cell proliferation.^{1,2}

It is a very heterogeneous disease from the clinical point of view, so the diagnosis is placed in the presence of two or more of the following criteria: more than 5 coffee-milk spots; 2 or more neurofibromas or a plexiform neurofibroma; glioma of the optical pathways; freckles; 2 or more Lish

nodules; specific skeletal dysplasia; a family history.

One of the most relevant features of NF1 is the predisposition of affected patients to the development of neoplasms mainly of the central and peripheral nervous system or exceptionally of tumors outside the nervous system: in most cases they are benign tumors, very rarely malignant tumors.¹⁻³

Optic Pathway Glioma in NF1

Optic pathway gliomas are the most common cancers in children with NF1: 15-20% of children with NF1 develop before the age of 7 years (with a peak between 4 and 6 years) a low grade glioma (LGG) along the optical pathways (Optic Pathway Glioma, OPG).⁴

Such tumors can be found along all optical pathways, with a higher incidence on optical nerves and optical chiasm, while more rarely they affect the post-chiasmatic optical pathway (optical tracts and radiations).⁵ Gliomas that arise at the level of the optic nerve are usually monolateral, while in sporadic forms (non-NF1-related) the optic chiasm is more frequently involved.

The brain stem is the second most affected site (15% of NF1-related LGG), while neoplasms of the cerebellum, cerebral cortex and base nuclei rarely affect pediatric patients with NF1, involving mainly adolescents and adults.⁶⁻⁸

These are infiltrating tumors with a low proliferative index: data in the literature highlight that the LGGs that arise in children with NF1 exhibit different biological behaviour, although with great clinical variability, compared to sporadic tumors, with a particularly slow clinical course, up to the description of some cases of spontaneous regression.^{5,9-13}

Despite this about half of children with NF1 and LGG develop clinical symptoms in relation to localization: reduction of visual acuity, alterations of the visual field, pallor of the optical papilla, strabismus, endocrinological alterations up to diencephalic syndrome.^{9,14-18}

Monitoring and diagnosis

A major problem in NF1 clinical management lies in the absence of validated methods that can predict the development of a LGG in these patients and, similarly, in patients where the tumor has developed and diagnosed, it is not possible to predict reliably which forms will be symptomatic (that is, cause visual deterioration) and therefore deserving of treatment. So, a careful clinical and radiological follow-up programme is essential to identify early onset of symptoms.

The eye evaluation must include the evaluation of visual acuity, fundus oculi and visual field: in order to obtain a more complete and exhaustive evaluation, the execution of visual Evoked Potentials (PEV) should be performed in order to acquire more accurate data, that guide to the execution and timing of surveillance examinations or the decision to start a treatment.¹⁹⁻²²

The gold standard investigation to assess the presence and extent of the tumor is cerebral MRI (possibly requiring high resolution sequences of optic nerves and chiasm), also used

to monitor radiological progression and response to therapy. Typically, sequences weighed in T1 with and without contrast and sequences weighed in T2 are used. Since contrast enhancement is often heterogeneous and variable, T2-weighted sequences are the most useful to define the tumor involvement in the optical pathway.²³

However, even with this type of sequence, the definition of the neoplasm margins is sometimes problematic due to presence in NF1, up to 70% of NF1 patients, of the so-called Focal Areas of Signal Intensity (FASI) or Unknown Bright Objects (Ubos), isointense focal lesions in T1 and hyperintense lesions in T2/FLAIR representing areas of myelin vacuolization. The FASI mainly involve optical pathways, brain stem, basal ganglia and cerebellum and their appearance in regions where NF1 related gliomas can arise, may pose differential diagnostic problems.^{10,14} However, the FASI do not have mass effect nor contrast-enhancement and often disappear with advancing age; their increase in size or number after 10 years of age should give rise to suspicion of cancer.^{24,25}

Children with NF1 (suspected or diagnosed) but without an associated OPG must undergo an annual examination by an experienced medical equipe and, up to 8 years of age, a complete eye examination. After the age of 8, since visual decline is less likely to occur, eye examinations can be carried out every other year.

For children diagnosed with NF1-OPG, the eye check should be performed every 3 months for the first year, every 6 months for the second year and then move on to an annual visit up to the age of 18 in the event of a stable illness. In these patients, the eye examination must be integrated with neuroimaging (i.e. with the execution of an MRI of the brain with or without contrast) every 3 months for the first year, every 6 months for the second year, every year up to the fifth year and then, less frequently (according to the clinicians judgement up to 18 years of age). It is not recommended to perform MRI as screening for OPG (baseline MRI) in patients with NF1, as it has been demonstrated that the forms diagnosed at the onset of symptoms do not differ substantially from those diagnosed incidentally by MRI in terms of clinical outcomes.^{10,11}

Treatment

The current guidelines provide for wait

and see as the main approach, using treatment only in the event of significant deterioration of the visual function and/or radiological progression of the disease. It is possible to distinguish, with reference to this aspect, between absolute indications of therapy, indications related to therapy and signs and symptoms of alarm.¹⁰

Absolute indications for therapy

Those that define a clinically significant worsening of the visual function are considered absolute indications for therapy, namely: a) worsening of visual acuity >0.2 log MAR; b) reduction of the field of view of new appearance.

Indications relating to therapy

The indications related to therapy are the same as those that indicate therapy, also considering other prognostic factors, such as the site of the neoplasia, the tumor progression, the reliability of the measurement of visual acuity. This includes the following: a) visual acuity <1 logMAR in an eye at <0.2 log MAR in the other eye; b) Visual acuity between 0.6 and 1 logMAR in one eye; c) Significant progression of disease documented by MRI, associated with suspected visual decline but with no reliable ability to test visual acuity.

Warning signs and symptoms

A number of clinical signs and symptoms are able to raise suspicion of disease progression in patients with OPG. The combined evaluation of these factors in an appropriate clinical setting may support the decision to subject the patient to chemotherapy, but in themselves they are intended as indications for closer surveillance and not necessarily treatment. Such warning signs and symptoms include:

- Radiological progression of the OPG without alterations of visual acuity or visual field is not an indication for starting chemotherapy;
- Other ophthalmological findings, such as worsening of the chromatic vision, pallor of the optical disc, swelling of the optic nerve, afferent pupil defect, strabismus, nystagmus required an increased close vigilance in order to evaluate their progression for starting chemotherapy.
- New visual field loss or change in visual acuity worse than 0.2 logMAR require prompt treatment.

When treatment is indicated for NF1-OPG, there is no indication to surgery as in most

cases it is not possible to obtain a radical removal while preserving visual functionality. Therefore the choice necessarily falls on non-surgical therapeutic options.¹⁴

Radiation therapy plays a very limited role in the management of patients with NF1, as it has been shown that it involves a particularly high risk of developing secondary malignant tumors, neurocognitive disorders, neuroendocrine disorders and radiation-induced vasculitis, such as moyamoya syndrome.²⁶⁻³⁰

Therefore, when it is necessary to treat a patient with NF1-OPG, chemotherapy is the main therapeutic option. The most widely used chemotherapy scheme involves the combination of Carboplatin and Vincristine: this schedule is usually well tolerated, although about 40% of patients may have hypersensitivity reactions to Carboplatin.³¹⁻³⁴ As an alternative therapy, the treatment with Vinblastine has been proven to be effective. Other proposed schemes include the PCV (Procarbazine, CCNU, Vincristine), the association between Cisplatin and Etoposide and Temozolomide. Etoposide or alkylating agents are generally avoided as their use carry a risk of secondary tumors as NF1 patients have predisposition of patients to the development of malignant neoplasms.³⁵⁻³⁸

Despite being the best therapeutic option currently available and despite its effectiveness in stopping the growth of the tumor,^{39,40} traditional chemotherapy is notoriously burdened with short and long-term adverse effects and, above all, is not always effective in improving or preserving visual function.^{5,41-51}

Although for a long time LGGs were considered tumours with few molecular alterations, numerous authors have reported the spectrum of the biological characteristics of these tumors, paving the way for the discovery of personalized therapies. These include MEK inhibitors, Bevacizumab and especially Vemurafenib if the BRAF mutation is present.⁵²⁻⁵⁷

In order to improve the visual function in such patients, promising studies are underway on the use of Nerve growth factor (NGF) administered locally as eyedrops: in some patients an improvement in the field of vision and PEVs were observed following this treatment.⁵⁸⁻⁶³

CONCLUSIONS

In children with NF1 the appearance of OPGs is relatively frequent: in such patients accurate clinical-radiological monitoring is essential in order to allow the early diagnosis of visual deterioration changes and therefore the identification of children for treatment.

The available treatments do not always allow improved visual outcome, hence it is important to identify new treatments for these patients.

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Conflict of interest

The authors declare that they have no conflict of interest.

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