Screening children with NF1 for optic pathway glioma – Yes

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A great deal has been written about the optimal approach to children with neurofibromatosis type 1 (NF1). NF1 predisposes children to a number of different neoplasia, one of which is optic pathway glioma (OPG). These tumours are grade 1 pilocytic astrocytomas that do not have malignant potential themselves and, as such, it has been argued recently that genotoxic chemotherapy and neurotoxic radiotherapy are therefore not indicated.¹ These tumours do grow and, as we will discuss below, can be treated resulting in stabilisation of the disease.

There is no universally agreed approach to screening of asymptomatic NF1 patients for OPG. In a major review article, which has yet to be seriously challenged, Listerink *et al*² have recommended regular ophthalmological surveillance as a key non-interventional screening tool. They have also suggested that children be reviewed 3 monthly for a year after the diagnosis of OPG has been made. This paper is published in the neurological literature. The US committee on genetics published a clinical report concerning health supervision for children with NF1 in 2008.³ They recommended visual screening at 2, 4, 6, 9, 12, 15, 18, 24, 36, and 48 months, which would represent a significant workload for ophthalmic departments for a relatively common condition (~1 in 4000).

In the United Kingdom, children with OPGs are managed across 22 regional paediatric neuro-oncology centres. There are dedicated NF1 clinics in units that have a clinical genetics department. Paediatric ophthalmology departments are asked to review children with NF1 on a regular basis, but the frequency and complexity of examination varies considerably depending on ophthalmological interest, experience, and the degree of orthoptic support. There is, at present, no nationally agreed policy with regard to ophthalmic screening of NF1 children with and without OPG.

The natural history of NF1 in general and associated OPG in particular, is incompletely understood. The US National Cancer Institute opened an NF1 natural history study in 2008, which is aiming to evaluate 200 patients over a 10-year period.⁴ The multi-national European SIOP-Low Grade Glioma trial opened in 2004 and has recruited over 350 patients. Those data are now available for analysis.⁵ Hegedus *et al*⁶ have looked at optic nerve dysfunction in genetically engineered mice, which have demonstrated pre-glioma changes in the visual-evoked potential. They have also used this model to test temozolamide (a drug used in children for gliomas) and have been able to show decreased proliferation and increased apoptosis of tumour cells.⁷ Through clinical trials and animal models, we will learn more about the natural history of the disease and new treatments that might help.

Regular visual testing is the least invasive and cheapest screening tool to assess whether an NF1 child has an OPG. There is evidence that children identified early through a screening programme have reduced complications from their OPG.⁸ Children can develop visual problems as a result of secondary raised intracranial pressure and can benefit hugely from a third ventriculostomy. Children managed by a multi-disciplinary team (MDT) involving paediatric neurosurgeons are likely to be dealt with more efficiently.

There is a misconception that children with NF1 are difficult to examine and ophthalmologically tested. As an NF1 centre managing a large number of children on a regional basis, this has not been our experience. Involving a lead orthoptist in the MDT approach to these children does, however, increase the reliability and repeatability of visual testing. In the United Kingdom, the visual impairment support teacher service can offer considerable support to affected families and should be engaged at an early stage in children with 6/18 vision or worse.

Although visual-evoked potential testing can be used to detect OPGs at an earlier stage^{9,10} the expense of the system and difficulties standardising assessment probably confine this modality to research interest alone.

Although not recommended as a screening tool, many practitioners perform a baseline MRI scan at diagnosis.¹¹ This is not a routine practice in our unit and generally in the NHS. To inform the parents of a child with NF1 that a 'brain tumour' has been found but no treatment is going to be given can be challenging news to cope with. Neuro-oncologists will not treat OPGs on the basis of radiological change alone. If that is the case, without routine ophthalmological screening, how is the oncologist to know that there has been clinical deterioration?

Regular screening of a significant NF1 population with OPG will allow an understanding of the true incidence of spontaneous regression, which has been cited as a reason not to treat.¹² There have been a number of papers that have shown visual and radiological stabilisation, and sometimes improvement, in children with progressing OPG treated with chemotherapy.^{13,14} This prompted the Listerick group to recommend this treatment.² There are currently a number of phase I and II trials in the United States looking at new treatments for OPG, including Everolimus (RAD001),¹⁵ Erlotinib (Tarceva),¹⁶ and Sirolimus (Rapamycin).¹⁷ Rapamycin has been shown to cause regression of astrocytomas in tuberous sclerosis.¹⁸

Although traditional radiotherapy is contraindicated as it leads to a poorer neuropsychological outcome,¹⁹ second tumours, and vascular complications,²⁰ the Mayo Clinic is currently running a phase II study of the use of conformal radiotherapy.²¹ Only by understanding the natural history of the disease in more depth will we know how best to use these new emerging treatments.

Conclusion

We think there are sufficient reasons to continue to ophthalmologically screen NF1 children with and without OPG. A national (and/or international) protocol should be developed that determines where, how, and how often children should have visual assessment. All data from children enrolled in national cancer trials (which includes all OPGs in the United Kingdom and participating countries in Europe) should be entered in nationally held databases (Children's Cancer and Leukaemia Group in the United Kingdom). If a national NF1 database were created, ophthalmic examination results from asymptomatic children, and those without OPGs, could also be collected. This information could subsequently help in our understanding of the natural history of this condition.

Conflict of interest

The authors declare no conflict of interest.

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