The Use of Magnetic Resonance Imaging Screening for Optic Pathway Gliomas in Children with Neurofibromatosis Type 1

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Objective To evaluate the utility of screening brain/orbital magnetic resonance imaging (MRI) in a large population of children with neurofibromatosis type 1 (NF1) over a 20-year period.

Study design A retrospective analysis of clinical and imaging data from children with NF1 seen at a single center between 1990 and 2010 was performed.

Results During the 20-year study period, 826 individuals with NF1 (402 females, 424 males) ages 1-9 years were screened for optic pathway gliomas (OPGs) using brain/orbital MRI; 18% were identified with OPGs with a median age at detection of 3 years. Fifteen percent of patients with OPGs had radiologic or clinical progression requiring therapy. Children with chiasmatic and postchiasmatic tumors were more likely to require therapy compared with patients with prechiasmatic OPGs ($P < .0001$). Patients with visual deficits at the time of diagnosis were more likely to experience visual decline despite therapy when compared with patients treated based on radiologic progression ($P < .012$).

Conclusions Our findings confirm that chiasmatic and postchiasmatic OPG in children with NF1 have the highest risk for progression and vision loss. Early identification of OPG by screening MRI prior to the development of vision loss may lead to improved visual outcomes. Children with negative brain and orbital MRI screening at age 15 months or later did not develop symptomatic OPGs. *(J Pediatr 2015;167:851-6)*.

Neurofibromatosis type 1 (NF1) is a common autosomal dominant disorder with an incidence of 1 in 3000 individuals and which affects multiple systems of the body.[1,2] Central nervous system (CNS) complications associated with NF1 include CNS tumors, learning disabilities, and attention deficit hyperactivity disorder. Optic pathway gliomas (OPGs) are the most common CNS tumors seen in NF1 and represent 3%-6% of all childhood brain tumors.[3,4] They are found in 15%-21% of individuals with NF1 and are typically benign, low grade gliomas that predominantly occur in early childhood.[1,5-8]

OPGs in children with NF1 frequently remain indolent. This differs from OPGs in the general population, which are more aggressive tumors. However, when symptomatic, OPGs can lead to vision loss, hypothalamic abnormalities including precocious puberty, and account for significant morbidity in a subset of children with NF1.[3] There is a lack of data regarding optimal imaging surveillance of OPGs. Most centers recommend annual ophthalmology examinations for young children with NF1, but there is no consensus on the utility of magnetic resonance imaging (MRI) in this population.[4] Several authors have advocated that asymptomatic young children with NF1 should be screened with ophthalmologic examinations only and that brain MRI screening is unwarranted.[9] However, many other physicians still routinely perform screening brain MRIs, and this has remained a controversial area within the NF1 field.

At present, treatment options for OPGs include surgery, radiotherapy, and chemotherapy. Surgical treatment of NF1 OPGs is generally to be avoided for these tumors.[4,10] Radiotherapy causes unnecessary neurovascular, endocrinologic, and neuropsychological sequelae, particularly in young patients, and for the most part is not indicated for patients with NF1 and OPG.[4,10] Chemotherapy has become the preferred treatment for OPGs, particularly in children under the age of 5 years,[10] and avoids the long-term toxicities associated with surgery and radiotherapy.[4]

The objective of this study was to evaluate the utility of screening brain and orbital MRIs in a large population of children with NF1 over a 20-year period in a single neurofibromatosis (NF) center.

CCHMC	Cincinnati Children's Hospital Medical Center
CNS	Central nervous system
MRI	Magnetic resonance imaging
NF	Neurofibromatosis
NF1	Neurofibromatosis type 1
OPG	Optic pathway glioma

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Methods

Children who met the National Institutes of Health NF1 consensus diagnostic criteria[11] were identified from the NF Center of the Cincinnati Children's Hospital Medical Center (CCHMC) by chart review from 1990-2010. During that time period, all children with NF1 at CCHMC underwent baseline MRI of brain and orbits with and without contrast at approximately 15 months of age or at the time an NF1 diagnosis was made, whichever was later. Those children identified with OPG were followed with detailed ophthalmologic examinations and repeat brain/orbital MRI every 3-6 months until stability of the OPG was documented. All other patients had annual ophthalmology examinations, with attention to visual acuity, afferent pupillary defect, color vision, and visual fields (in those old enough to cooperate). Patients were seen by members of the multidisciplinary NF team; they were initially seen by a geneticist and subsequently referred to a pediatric neuro-oncologist after diagnosis of OPG was made.

A retrospective analysis of data from clinical information, imaging data, and treatment history of this patient population was performed. The chart for each patient was reviewed with regards to age at NF1 diagnosis, age at OPG diagnosis, evidence of tumor progression, sex, ethnicity, ophthalmologic examination findings, and family history. MRI scans for each patient had been read by one of a group of neuroradiologists familiar with NF1; the images were not reinterpreted by a radiologist for the purposes of this study. When an OPG was identified, the location was recorded as prechiasmatic, chiasmatic, and/or postchiasmatic; and as unilateral or bilateral. OPG location was classified according to the most posteriorly involved structure of the visual pathway. Information regarding type of chemotherapy, response, relapse, surgeries, endocrine abnormalities, and visual outcomes was obtained from the 22 patients who underwent treatment for symptomatic OPGs. This population was followed until December 2010. The study was approved by the CCHMC Institutional Review Board. Clinical data were abstracted from medical charts and entered into a password-protected database for analysis.

Statistical Analyses

Baseline clinical characteristics and treatment outcomes were analyzed in children with NF1 and OPGs. To characterize this population, basic descriptive statistics were used (frequencies for dichotomous measures and medians for continuous measures). To determine whether the frequencies of outcomes differed between groups, χ^2 goodness of fit tests, and the 2-sample median test were performed as appropriate. Kaplan-Meier curves were calculated and log-rank tests were used to compare differences between recurrence-free survival curves based on tumor location.

Results

A total of 826 children with NF1 (402 females, 424 males) ages 1-9 years (median 2 years) were screened for OPGs using MRI of brain and orbits, with and without contrast (**Figure**, A). The majority of patients with NF1 were Caucasian (81.2%), followed by African American (12%), multiracial (3.4%), Hispanic (2.2%), and Asian (1.2%). OPGs were identified on brain/orbital MRI in a total of 149 children (18% of patients), and 22 patients were treated with chemotherapy for OPG (15% of those with OPG; 2.7% of total population). Decision for treatment was made based on a combination of ophthalmologic and MRI findings. OPGs were less likely to be identified in African American patients with NF1 compared with Caucasians (10.2% vs 17.5%) ($P < .01$) (**Table I**). Females more frequently had OPGs than did males (20.6% vs 15.6%), ($P < .01$). The majority (134/149, 90%) of OPGs were identified in patients less than 6 years of age. Median age at detection of OPGs was 3 years (range 1-12 years). An additional 955 surveillance brain/orbital MRI scans were performed in the subset of 149 patients with OPGs at established intervals to monitor tumor growth. Patients with chiasmatic (15/42) and postchiasmatic (4/11) tumors were more likely to need therapy compared with patients with isolated prechiasmatic OPGs (3/96) ($P < .0001$; **Figure**, B). The 3 patients with isolated prechiasmatic OPG who required therapy had bilateral lesions. Bilateral involvement was identified in 52 of the 149 patients (34.8%) with OPG; of the 22 treated patients, 11 (50%) had bilateral OPG involvement ($P < .02$). Hypothalamic involvement was seen in 5 of the 22 treated patients. None of the patients requiring treatment had an orbital plexiform neurofibroma, and proptosis was seen in only 2 patients. Only 1 of the 677 patients with a normal screening brain/orbital MRI performed after 15 months of age later developed an OPG. This was a girl who developed an enhancing unilateral prechiasmatic optic nerve glioma on imaging at age 11 years, which had not been present on earlier imaging at ages 17 months and 7 years. However, she remained asymptomatic and never required treatment.

Therapeutic Interventions and Outcomes

Time to therapy after initial tumor identification by MRI ranged between 0.2 and 5 years (**Figure**, C). Vision loss and tumor growth were the most frequent reasons to initiate therapy. Twenty-two children (15%) with OPGs required therapeutic interventions, none of who were African American and 14 (63%) of whom were females ($P < .01$). Prior to therapy, 12 children had vision abnormalities and 10 children had normal ophthalmologic evaluations. Patients with postchiasmatic tumors (3/4) and chiasmatic tumors (8/15) were more likely to develop vision abnormalities compared with patients with isolated prechiasmatic OPGs (1/3) ($P < .01$). The most common ophthalmologic findings were decreased visual acuity (11/22), abnormal/atrophic optic disc (8/22), visual field