

Macrocephaly Is Not a Predictor of Optic Pathway Glioma Development or Treatment in Neurofibromatosis Type I

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Abstract

Neurofibromatosis type I is a common neurogenetic disorder characterized by significant clinical variability. As such, numerous studies have focused on identifying clinical, radiographic, or molecular biomarkers that predict the occurrence or progression of specific clinical features in individuals with neurofibromatosis type I. One of these clinical biomarkers, macrocephaly, has been proposed as a prognostic factor for optic pathway glioma development. In the current study, the authors demonstrate that macrocephaly is not associated with the development of these brain tumors or the need to institute treatment for clinical progression. These findings suggest that macrocephaly is not a robust biomarker of optic pathway glioma formation or progression in children with neurofibromatosis type I.

Keywords

heterogeneity, head circumference, brain tumor, neurofibromatosis type I, occipital-frontal circumference

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Neurofibromatosis type I is caused by a germline mutation in a single gene, the *NF1* gene, located on chromosome 17q11.2. While classified as a monogenic syndrome, the clinical expression of this disorder is highly variable from individual to individual, even within the same family with the same germline *NF1* gene mutation. In this respect, neurofibromatosis type I encompasses a broad spectrum of pathologies, ranging from benign and malignant tumors to motor delays,¹ cognitive impairment,^{2,3} and autism.⁴ This inherent variable expressivity presents a significant challenge to patients and physicians, since it is currently not possible to accurately predict which medical problems are likely to arise in a given individual and whether these problems will require treatment due to clinical progression.

In an effort to identify features that positively or negatively correlate with specific neurofibromatosis type I-associated symptomatology, prior investigations have attempted to identify prognostic relationships between specific features (e.g., hypotonia) and the development of more serious medical problems in this condition (e.g., optic pathway gliomas).⁵ As such, one study revealed a potential association between macrocephaly and the presence of optic pathway gliomas.⁶

Macrocephaly is one of the most commonly-observed clinical manifestations among individuals with neurofibromatosis type I.⁷⁻⁹ It is defined as an age- and sex-adjusted occipital-frontal circumference greater than the 97th percentile or greater

than 2.0 standard deviations above the mean. In the setting of neurofibromatosis type I, macrocephaly usually has no obvious etiology, and likely represents an increase in brain volume as revealed by magnetic resonance imaging (MRI).^{10,11}

To more formally investigate the potential relationship between macrocephaly in neurofibromatosis type I and optic pathway glioma, the authors examined a cohort of individuals with neurofibromatosis type I at least 10 years of age with MRI-confirmed absence of optic pathway glioma to those with MRI-documented optic pathway glioma.

Methods

Subjects

Sample size was calculated based on the primary null hypothesis that the proportion of patients with macrocephaly is equal between groups.

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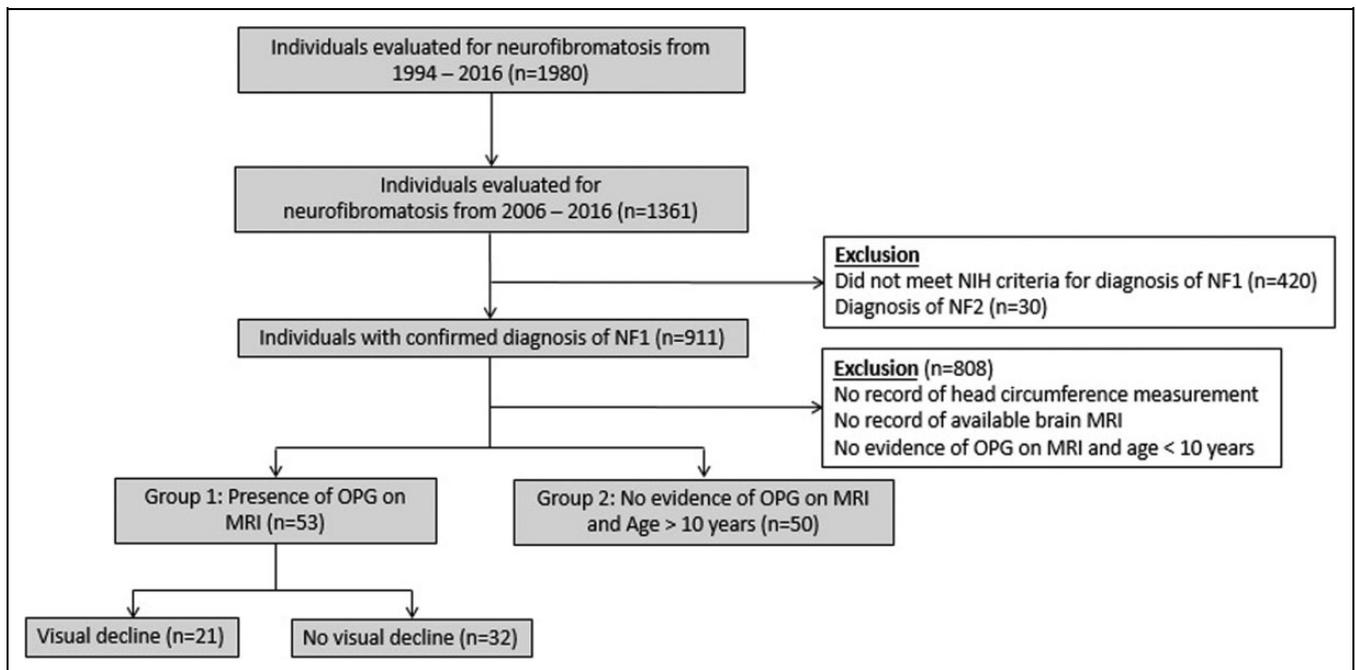


Figure 1. Flow chart of study sample. Flow-chart depicting the criteria used for identification of the study sample ($n = 103$), based on the presence (group 1) or absence (group 2) of radiographic evidence of optic pathway glioma in individuals with neurofibromatosis type 1, and further stratification of those with optic pathway glioma into 2 groups based on visual decline.

A power analysis using the G*power computer program¹² indicated that a total sample of 52 patients (26 individuals per group) would be needed to detect an effect size of 0.45⁶ with 90% power using a chi-squared test to detect difference in proportions with an alpha level at .05.

A total sample of 1980 individuals seen for evaluation of neurofibromatosis in the St. Louis Children's Hospital NF Clinical Program over the past 20 years was retrospectively identified. The sample was narrowed to include only those individuals seen in the last 10 years since the implementation of an electronic medical record system in which MRIs were routinely included for review. Subjects for whom a diagnosis could not be rendered ($n = 420$) and subjects with neurofibromatosis type 2 ($n = 30$) were excluded leaving a total of 911 subjects with a diagnosis of neurofibromatosis type 1 established using National Institutes of Health (NIH) diagnostic criteria.¹³ From this group, only those patients with head circumference measurements and available MRI scans either demonstrating an optic pathway glioma ($n = 53$; group 1) or lacking an optic pathway glioma on MRI in an individual older than 10 years of age ($n = 50$; group 2) were included for analysis (103 total subjects).¹⁴ Radiographic evidence of an optic pathway glioma was determined based on the presence of thickening of the optic nerve(s) or chiasm and/or the presence of associated gadolinium enhancement. Glioma of the optic tracts or radiations was determined based on the presence of hyperintensity on T2-weighted imaging with associated mass effect and/or associated gadolinium enhancement of these structures.

To investigate the association between macrocephaly and clinical progression of neurofibromatosis-related optic pathway glioma, subjects in group 1 were further stratified into 2 subgroups: individuals requiring treatment due to visual decline and those without visual decline (Figure 1). Recorded head circumferences were normalized by age and sex to establish percentiles and standard deviation relative to the general population mean. Macrocephaly was defined as a head

circumference greater than the 97th percentile or greater than 2.0 standard deviations above the mean based on age- and sex-matched norms. This study was performed under an approved Human Studies Protocol at Washington University.

Statistical Analysis

Categorical variables, reported as proportions, were compared using a chi-squared test of independence. Continuously-distributed traits adhering to both conventional normality assumptions and homogeneity of variances were reported as means with standard deviations, and compared using analysis of variance methods.

Results

Consistent with previous studies demonstrating increased head circumferences in the setting of neurofibromatosis type 1,^{8,15,16} analysis of the full sample ($n = 103$) revealed that the distribution of head circumference among individuals with neurofibromatosis type 1 was right shifted by 2.5 standard deviations relative to the general population mean for age- and sex-matched subjects (Figure 2).

The same pathological shift in occipital-frontal circumference was observed when investigating differences in head circumference between those with an optic pathway glioma (group 1) and those without an optic pathway glioma (group 2). No statistical differences between these groups were found (Table 1). Moreover, the proportion of individuals with macrocephaly was equal in each group (67.9% vs 68.0%, $P = .99$), and the distributions of head circumference were overlapping and indistinguishable between groups (Figure 3).

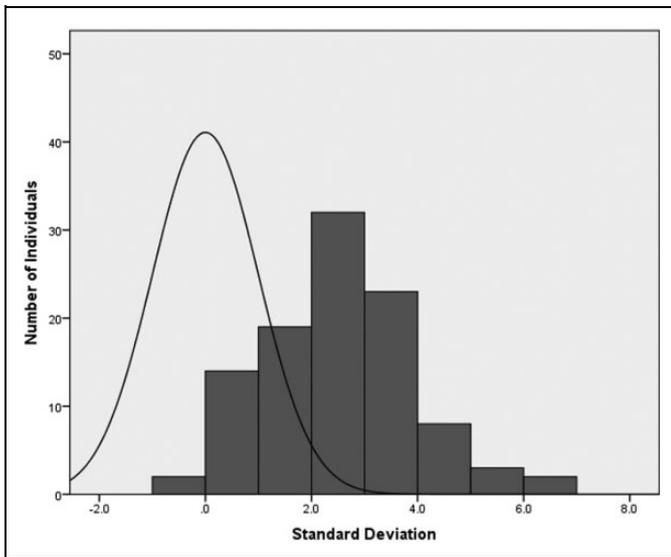


Figure 2. Distribution of head circumferences in neurofibromatosis type I (NF1) compared to the general population. Distributions of sex- and age-standardized head circumferences for the full sample of individuals with NF1 (n = 103) compared to the general population, as represented by the distribution curve.

Table 1. Summary of Mean Head Circumference.

	Group 1 (n = 53)	Group 2 (n = 50)	P value
Mean HC	55.23	56.02	.20
SD	2.51	2.49	.96

Abbreviations: HC, head circumference; SD, age- and sex-matched standard deviation. Children: age less than 18 years. Adult: age 18 years or older.

As expected, males had statistically larger mean head circumferences relative to females; however, using age- and sex-matched standardized measurements, no statistical differences were observed between sexes. The absence of a sexually-dimorphic phenotype persisted even when investigating differences in standardized head circumference measurements between males and females with neurofibromatosis type 1–optic pathway glioma (group 1). A similar trend was observed with respect to age (Table 2).

To investigate the association between macrocephaly and the clinical progression of neurofibromatosis type 1–related optic pathway glioma, individuals with neurofibromatosis type 1–optic pathway glioma (group 1) were stratified into 2 groups based on treatment (chemotherapy) for optic pathway glioma–related decline in visual acuity. Among those with neurofibromatosis type 1–optic pathway glioma, individuals with macrocephaly were equally as likely to develop optic pathway glioma–related vision loss requiring treatment as those without macrocephaly (OR 0.91; 95% CI: 0.28 – 2.95).

Taken together, these findings demonstrate that the presence of macrocephaly is not associated with either the development or clinical progression of optic pathway glioma in individuals with neurofibromatosis type 1.

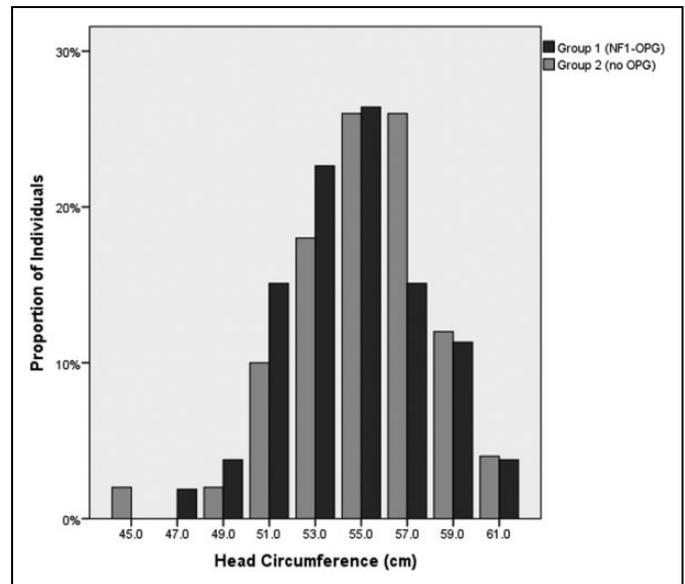


Figure 3. Distribution of head circumferences in individuals with neurofibromatosis type I (NF1), stratified by NF1–optic pathway glioma (OPG) detection. Distributions of head circumference measurements for the 2 groups (group 1 and group 2) stratified by the presence or absence of OPG. Group 2 (lighter bars) represents those without OPG, whereas group 1 (darker bars) denotes those with NF1-OPG.

Discussion

Macrocephaly is one of the most common features of neurofibromatosis type 1, observed in approximately 50-75% of affected individuals.^{9,16} In this setting, MRI studies have revealed that macrocephaly is associated with the enlargement of multiple brain structures, leading to increased cranial volumes and brain volumes.¹⁷ As such, some reports have described relative increases in white matter volumes, specifically involving midline structures, like the corpus callosum and brainstem,¹⁸ whereas others have described increased gray matter volumes.¹⁹ In some of these studies, relative white or gray matter changes were variably correlated with cognitive impairment,¹⁷ specific learning disabilities,^{18,19} and deficits in attention and social interaction.²⁰ It is currently not clear what the structural basis for macrocephaly is in the neurofibromatosis type 1 population.

Given the possibility that the relative degree of white matter versus gray matter affectedness might correlate with specific features of neurofibromatosis type 1, the use of macrocephaly as a clinical biomarker for other neurofibromatosis type 1–related complications, such as optic pathway glioma, merited further examination. In this regard, the ability to predict an optic pathway glioma in the absence of neuroimaging would represent an immediately actionable prognostic tool in this at-risk population, and would obviate the need for sedation to identify optic pathway gliomas in young children. It is for this reason that the authors sought to replicate the findings from an earlier report.⁶

Unfortunately, using strict criteria for determination of macrocephaly and optic pathway glioma, the authors were unable to demonstrate a statistically significant association between

Table 2. Sex- and Age-Standardized Head Circumference Stratified by Group, Sex, and Age.

Full sample (n = 103)						
	Males (n = 44)	Females (n = 59)	P value	Children (n = 81)	Adult (n = 22)	P value
Mean HC	56.38	55.06	.03	54.84	58.49	<.001
SD	2.56	2.46	.72	2.26	3.39	.001
Group 1 (n = 53)						
	Males (n = 21)	Females (n = 32)	P value	Children (n = 48)	Adult (n = 5)	P value
Mean HC	56.89	54.17	.001	56.89	54.17	.001
SD	2.71	2.37	.37	2.71	2.37	.37
Group 2 (n = 50)						
	Males (n = 23)	Females (n = 27)	P value	Children (n = 33)	Adult (n = 17)	P value
Mean HC	56.91	56.11	.81	54.87	58.25	<.001
SD	2.41	2.56	.75	2.06	3.33	.004

Abbreviations: HC, head circumference; SD, age- and sex-matched standard deviation. Children: age less than 18 years. Adult: age 18 years or older. Bold text is statistically-significant differences.

macrocephaly and optic pathway glioma development, and could not detect a positive association between the presence of macrocephaly and optic pathway glioma clinical progression necessitating treatment. The divergent conclusions between the current report and the previous observation may have reflected differences in methodology. While this study required that the population of subjects *without* an optic pathway glioma lack evidence of MRI-confirmed optic pathway glioma in children beyond the age of typical optic pathway glioma presentation (10 years of age), these inclusion criteria were not employed in the prior investigation. Moreover, whereas this study used strict age- and sex-adjustments for head circumference measurements, more subjective measures were employed in the earlier study.⁶

While the authors were unable to demonstrate a clear association between macrocephaly and optic pathway glioma, the authors validate that the presence of macrocephaly within this neurofibromatosis type 1 cohort represents a pathological shift of the general population distribution, recapitulating previous reports which systematically investigated the distribution of growth parameters in neurofibromatosis type 1.^{8,15} Importantly, similarly shifted distributions have been demonstrated in the neurofibromatosis type 1 population with respect to stature,^{8,15} intelligence,² and autistic symptomatology,⁴ representing cases in principle that mutations within the *NFI* gene are capable of producing the complete spectrum of phenotypic variability observed in nature. Furthermore, these data support the hypothesis that the *NFI* haploinsufficient state and the resulting abnormalities observed in CNS progenitor cells are likely the primary modulators of cerebral overgrowth and brain dysfunction in neurofibromatosis type 1.²¹

In contrast, the development of central nervous system tumors including optic pathway glioma in neurofibromatosis type 1 is thought to result from 'second hit' somatic mutations, leading to loss-of-heterozygosity within focal brain regions.²² The resulting bi-allelic *NFI* inactivation in specific CNS progenitor cells leads to cell expansion, and eventually

tumorigenesis.²³ While abnormal growth and differentiation of CNS progenitor cells may be responsible for the development of CNS tumors in neurofibromatosis type 1, the authors hypothesize that macrocephaly reflects the impact of the germline *NFI* gene mutation, rather than bi-allelic *NFI* loss. Interestingly, a few case reports have reported neurofibromatosis type 1–optic pathway glioma–induced endocrinologic dysfunction, leading to somatic overgrowth, suggesting a potentially causative relationship between optic pathway glioma and macrocephaly.^{24,25} However, the presence of macrocephaly has also been demonstrated to occur in the absence of optic pathway glioma in individuals with neurofibromatosis type 1 microdeletions,²⁶ further supporting the independence of these two different neurofibromatosis type 1 clinical manifestations.

There are a number of important limitations of this study. These include the use of cross-sectional retrospective data extracted from the electronic medical records of a relatively small sample of individuals with neurofibromatosis type 1. This precludes confirmation of the accuracy of occipital-frontal circumference measurements. Mitigating against these limitations, however, this study was sufficiently powered to detect statistical differences between groups based on a priori power calculations using best available data on effect size, and despite the relatively small sample, the distribution of head circumference measurements did not diverge from that observed in earlier reports.^{8,15} The authors cannot, unfortunately, exclude the possibility of a significantly smaller effect size between groups than previously reported which would require a much larger sample size to detect. However, the contribution of such minor differences in the proportion of macrocephaly or the absolute occipital-frontal circumference measurements between groups would be predicted to be small, especially given the potential for considerable interobserver variability in measurements.

Moreover, this study design also potentially prohibits us from excluding subjects who experienced the spontaneous

regression of an earlier optic pathway glioma, and therefore did not demonstrate radiographic evidence of an optic pathway glioma after 10 years of age (group 2). However, the phenomenon of spontaneous regression of optic pathway glioma, while a possible confounder in this cohort,^{27,28} typically represents a partial, rather than a complete, effect with persistent, although less conspicuous, radiographic findings of the previously identified optic pathway glioma remaining.^{28,29} It should be noted that spontaneous optic pathway glioma regression is an uncommonly-observed clinical event, and is a difficult clinical question to resolve, given the current clinical practice of foregoing neuroimaging in typical-developing and asymptomatic children with neurofibromatosis type 1. Such an investigation would require the implementation of a large prospective, longitudinal study with regular neuroimaging.

Last, the authors acknowledge that the proportion of individuals in this cohort with radiographic evidence of optic pathway glioma (53 of 911; 5.8%) is significantly smaller than the typically reported prevalence rate of optic pathway glioma within the neurofibromatosis type 1 population (10-15%).¹⁴ Further examination of this population reveals a more typical neurofibromatosis type 1–optic pathway glioma appearance rate, which is reduced as a result of the study-specific ascertainment requirements. It should also be recognized that the results of the current study are not immediately generalizable to other intracranial tumors seen in patients with neurofibromatosis type 1. The potential relationship between macrocephaly and other neurofibromatosis type 1–related intracranial tumors and phenotypes deserves further investigation.

In conclusion, the authors demonstrate that macrocephaly is neither a reliable clinical predictor of optic pathway glioma development in patients with neurofibromatosis type 1 nor is it an indicator of subsequent vision loss in those diagnosed with neurofibromatosis type 1–optic pathway glioma. As more becomes known about the nature of specific structural abnormalities and MRI characteristics found in children with neurofibromatosis type 1, more accurate clinical predictions may emerge.

Author Contributions

SMM performed statistical analysis. CLM and DHG collected clinical data. SMM, CLM, and DHG prepared the manuscript.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

The study protocol was approved by the Human Research Protection Office at the Washington University School of Medicine.

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