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The Association Between Hypotonia and Brain Tumors in Children With Neurofibromatosis Type 1

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Abstract

Children with the neurofibromatosis type 1 (NF1) inherited tumor predisposition syndrome are at risk for the development of brain tumors. In addition, children with neurofibromatosis type 1 often exhibit low tone (hypotonia). In this study, the authors explored the hypothesis that hypotonia could be a clinical indicator of glioma in children with neurofibromatosis type 1. A total of 56 children between 1 and 7 years of age with a confirmed diagnosis of neurofibromatosis type 1 were evaluated. Brain magnetic resonance imaging (MRI) was available for 19 of these children. Chi-square analysis demonstrated a statistically significant correlation between hypotonia and glioma in children with neurofibromatosis type 1 (90% sensitivity and 78% specificity). These results suggest that hypotonia might be a clinically useful indicator of brain tumor in this at-risk population.

Keywords

neurofibromatosis type 1, brain tumor, optic glioma, hypotonia

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Individuals with neurofibromatosis type 1 are prone to the development of both benign and malignant tumors. In the pediatric population, children with neurofibromatosis type 1 are at risk for the development of low-grade astrocytic neoplasms (gliomas) involving the optic pathway and brainstem.[1-4] Current screening for the development of an optic pathway glioma involves annual neurological and ophthalmological examinations, looking for evidence of brain or visual dysfunction.[5] However, these tumors arise in young preverbal children who often demonstrate significant attention deficits and sensory integration problems,[6-11] which compromise our ability to reliably assess this at-risk group of children for glioma.

In addition, children with neurofibromatosis type 1 have been reported with reduced muscle tone (hypotonia),[12] which currently lacks a structural or anatomic basis.[13] Since the hypotonia in this patient population is not associated with primary muscle weakness or peripheral nervous system dysfunction, it is possible that the reduction in muscle tone is central in origin, raising the intriguing possibility that hypotonia may be a clinical indicator of central nervous system pathology. The purpose of the current study was to determine whether the presence of hypotonia correlated with brain tumors in children with neurofibromatosis type 1.

Materials and Methods

A total of 56 subjects with diagnoses of neurofibromatosis type 1 between the ages of 1 and 7 years old enrolled in the study between June 1, 2011, and June 1, 2012. The diagnosis of neurofibromatosis type 1 was established using National Institutes of Health Consensus Development Conference criteria.[14] The same physician (DHG), pediatric nurse practitioner (ACA), and physical therapist (CMD) performed all hypotonia evaluations. Magnetic resonance imaging (MRI) results were reviewed and confirmed with an experienced neuroradiologist. Subjects were consented to participate in the study in accordance with an approved Human Studies Protocol at the Washington University School of Medicine.

Assessment by the physician and pediatric nurse practitioner were denoted "nontherapist assessments." The physician or pediatric nurse practitioner assessed each patient for subjective muscle tone, "slip-through" (a test in which the child is suspended by an examiner's hands in the child's axilla and the child slips through the examiner's hands if lateral pressure is not applied), and elbow/knee free range of motion (to evaluate resistance to passive motion). The physical therapist repeated the subjective measures performed by the practitioners. In addition, the therapist performed a pull to sit test and recorded the presence or absence of head lag. In all cases, the physical therapist was blinded to the MRI results.

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Table 1. Neurofibromatosis Type 1 Pediatric Population

	Hypotonia (n = 20)	Normal Tone (n = 29)	*P* Value
Gender			1.000
Male	6/20 (30%)	9/29 (31%)	
Female	14/20 (70%)	20/29 (69%)	
Race			.2160
Caucasian	19/20 (95%)	23/29 (79%)	
African American		4/29 (14%)	
Mixed	1/20 (5%)	1/29 (3%)	
Other		1/29 (3%)	
Age	4.15 ± 1.91	4.86 ± 1.37	.1595
Family history of neurofibromatosis type 1			1.000
Yes	11/20 (55%)	15/29 (52%)	
No	8/20 (40%)	13/29 (45%)	
Unknown	1/20 (5%)	1/29 (3%)	
Dermal neurofibromas	5/20 (25%)	9/29 (31%)	.7536
Plexiform neurofibromas	3/20 (15%)	3/29 (10%)	.6773
Scoliosis	0/20 (0%)	1/29 (3%)	1.000
Tall stature	1/20 (5%)	0/29 (0%)	.4082

Table 2. Correlation Between Hypotonia and Brain Tumor

	Brain Tumor	No Brain Tumor
Hypotonia	9	2
Normal tone	1	7

$P = .005$.

Of the 56 enrolled subjects, 7 did not receive assessments from a physician/pediatric nurse practitioner or a physical therapist and were excluded from analysis. The remaining 49 subjects were segregated into a "hypotonia" cohort and a "normal tone" cohort, according to the physical therapist assessment. Interrater agreement between the nontherapist assessment and the physical therapist assessment was determined based on concordance between the findings of the 2 parties.

Of the 49 subjects, 19 had previous MRI studies performed as part of routine care. Chi-square analysis, sensitivity, specificity, and relative risk calculations were performed to assess the relationship between hypotonic presentation and glioma.

Descriptive statistics among cohorts were calculated for demographics including gender, race, age, family history of neurofibromatosis type 1, presence of dermal neurofibromas, plexiform neurofibromas, scoliosis, and tall stature (≥ 94th percentile). The same presenting features related to neurofibromatosis type 1 were analyzed for their relationship to glioma to determine whether there were any other independently significant indicators for brain tumor in neurofibromatosis type 1 patients.

Results

Hypotonia in Individuals With Neurofibromatosis Type 1

Of 56 enrolled subjects, both a physician or pediatric nurse practitioner and a physical therapist assessed 49 children for muscle tone. The clinical characteristics for each group were similar (Table 1). Of the study participants, 27% (20/49 individuals) were scored as hypotonic. Overall, interrater agreement between the physical therapist and nontherapist assessments was 76% (37/49) ($\kappa = 0.485$). It should be noted that a significant improvement in interrater agreement was observed between first 6 months and the last 6 months of the study. For the first 6 months, interrater agreement was 63% (15/24; $\kappa = 0.485$), which improved to 88% (22/25) during the last 6 months of the study ($\kappa = 0.746$).

Relationship Between Hypotonia and Glioma

For the 19 subjects with MRI available, there was a statistically significant correlation between hypotonia and glioma (Fischer exact *P* value, 2-tailed = .005), resulting in a 6.5-fold increase (95% CI = 1.3-131.7) in relative brain tumor risk in this subgroup of children. The sensitivity and specificity of these findings were 90.0% (95% CI: 64.1%-99.5%) and 77.8% (95% CI: 49.0%-88.3%), respectively (Table 2). All measures of hypotonia were independently associated with the presence of an intracranial tumor, including abnormal slip-through ($P = .0001$), head lag ($P = .0001$), and reduced resistance to passive movement at the elbow ($P = .0001$) or knee ($P = .0076$).

In the group of children with brain tumors, there were 9 individuals with an optic pathway tumor, while gliomas involving the tectum, cerebellar peduncle, and medulla were each identified in a single patient. Of these children, 4 exhibited decreased vision or proptosis, while another presented with worsening headaches. Only 1 child was treated for a symptomatic optic glioma, but this therapy occurred after the evaluation for hypotonia. Two subjects who presented with hypotonia had tortuous optic nerves, but lacked conclusive evidence of an optic pathway glioma.

In contrast, there was no association between glioma and the presence of dermal neurofibromas ($P = .6499$), plexiform neurofibromas ($P = 1.000$), scoliosis ($P = .4737$), or tall stature ($P = .4082$). Similarly, the average number of T2 hyperintensities was not found to be associated with glioma (neurofibromatosis type 1 with brain tumor, average = 4.67, 95% CI: 3.41-5.92; neurofibromatosis type 1 without brain tumor, average = 2.71, 95% CI: 1.25-4.18).

Discussion

Currently, the discovery of a brain tumor in a child with neurofibromatosis type 1 is prompted by the identification of abnormalities on neurologic or ophthalmologic assessment. Given that these assessments are often limited by patient cooperation in young preverbal children with significant behavioral problems (attention deficits, learning problems, sensory integration issues),[7-9,15-16] the availability of prognostic biomarkers of glioma in this at-risk population would facilitate a more directed approach to anticipatory management. In the current study, we demonstrate that hypotonia carries a 6.5-fold increased relative risk for intracranial neoplasm in children with neurofibromatosis type 1. In addition, we found no other clinical feature to be correlated with the presence of glioma. We also show that the screening test for hypotonia is simple and rapid to perform (< 2 minutes), and can be easily adapted to a busy outpatient clinic setting to yield reliable results.

While the sensitivity and specificity of hypotonia for glioma was excellent in our small series, there were 2 children with hypotonia and no brain tumor as well as 1 individual with normal tone and a known intracranial neoplasm. The 2 children with hypotonia exhibited tortuous optic nerves with meningeal enhancement, but no obvious glioma. Tortuous optic nerves have been previously reported in children with neurofibromatosis type 1;[17] however, their clinical significance relative to future tumor development is unknown. The 1 child with an intracranial neoplasm and normal tone harbored an intraconal optic glioma, and exhibited signs of precocious puberty, but was otherwise similar to the other children with neurofibromatosis type 1–associated optic glioma.

Expert clinicians have long recognized hypotonia as a feature of neurofibromatosis type 1 in children.[13] We found that 37% of children (20/49) were scored as hypotonic on routine assessment. Specifically, hypotonia has been reported in children harboring type 1 *NF1* gene microdeletions.[18] These individuals often exhibit dysmorphic facial features, tall stature, significant cognitive delays, scoliosis, joint hyperflexibility, and the presence of subcutaneous neurofibromas. In our series, the typical type 1 *NF1* microdeletion phenotype was not observed in this population of hypotonic children, as hypotonic subjects did not exhibit significantly increased frequencies of dermal neurofibromas, scoliosis, tall stature, or plexiform neurofibromas.

The association between hypotonia and type 1 *NF1* microdeletions is also intriguing in light of previous findings demonstrating an increased lifetime risk for cancer (malignant peripheral nerve sheath tumor) in this population.[19-20] However, there was no report of increased incidence of brain tumors reported in cases with type 1 *NF1* gene microdeletion.[21] Future studies will require genetic testing to determine whether children with hypotonia are more likely to harbor type 1 *NF1* gene microdeletions.

Several limitations are inherent to our study. The group of 19 subjects with available imaging studies was small, which limited our ability to perform meaningful subcohort analysis regarding tumor characteristics and location. However, because of the expense related to neuroimaging and the risks associated with sedation anesthesia to image clinically asymptomatic young children with neurofibromatosis type 1,[18] MR imaging was not available for all individuals in this study. Given the small number of patients with neuroimaging results in this study, these intriguing results should be regarded as preliminary. Future prospective studies incorporating hypotonia as a criterion for obtaining neuroimaging in the management of children with neurofibromatosis type 1 will be required to formally evaluate the utility of this clinical finding for identifying brain tumors in this at-risk population.

Conclusion

The presence of hypotonia in children with neurofibromatosis type 1 carries a 6.5-fold elevated relative risk for glioma. As muscle tone assessment of a child is a simple and rapid evaluation, the finding of hypotonia in a child with neurofibromatosis type 1 may warrant subsequent neuroimaging studies to identify an intracranial neoplasm.

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Author Contributions

LEW performed the data analysis and wrote the initial drafts of the manuscript. ACA, DHG, and CMD performed the clinical assessments. DHG performed the final editing of 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

Subjects consented to participate in the study in accordance with an approved Human Studies Protocol at the Washington University School of Medicine.

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