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Case Report

De novo development of gliomas in a child with neurofibromatosis type 1, fragile X and previously normal brain magnetic resonance imaging

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ABSTRACT

Fifteen to 20% of children with neurofibromatosis type 1 develop low-grade glial neoplasms. However, since neuroimaging is not routinely obtained until a child is clinically symptomatic, little is known about presymptomatic radiographic characteristics of gliomas in this at-risk population. Herein, we describe a child with neurofibromatosis type 1 who initially had normal brain imaging before the development of multifocal gliomas. Comparison of these serial images demonstrated that brain tumors can arise de novo in children with this cancer predisposition syndrome, further underscoring the limited prognostic value of normal baseline magnetic resonance imaging.

Introduction

Children with the neurofibromatosis type 1 (NF1) inherited tumor predisposition syndrome are prone to the development of low-grade gliomas, which occur in 15%-20% of these children [1]. Although tumors can arise anywhere within the central nervous system, nearly 75% of these occur in the optic pathway, 15% in the brainstem, and fewer than 5% elsewhere in the brain [2]. Although histologically similar to their sporadic counterparts, the clinical course of NF1-associated gliomas is generally more indolent [3]. Characteristically, these tumors are hyperintense on T2-weighted sequences, isointense to slightly hypointense on T1-weighted sequences and demonstrate mass effect or expansion over time as well as variable enhancement with gadolinium administration [2–4]. When they arise in the brainstem, they are frequently asymptomatic or cause only subtle symptoms (e.g., lethargy or localized itching [5]), often discovered incidentally on magnetic

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resonance imaging (MRI). Uncommonly, these tumors may produce cranial neuropathies, gait instability, or hydrocephalus [4]. Most tumors do not require treatment, although some may require shunting if hydrocephalus develops, or may warrant surgical resection or chemotherapy in the setting of clinical progression [6]. MRI screening in an asymptomatic child is not routinely performed, as early detection does not usually improve outcome, and radiographic findings have not been shown to predict clinical behavior [7–9]. Since neuroimaging is not obtained, little is known about presymptomatic radiographic characteristics of gliomas in children with NF1.

Case report

A 20-month-old boy presented for initial evaluation of NF1. He was born at ~38 weeks of gestation but was lethargic with significant hypotonia and had poor feeding after birth, requiring neonatal intensive care unit care. These findings eventually led to the diagnosis of Fragile X syndrome at 9 weeks of age. He then developed profound developmental delay across all domains, and only began to roll over at one year of age. He was noted to have multiple café-au-lait macules and right axillary freckling. Both Fragile X and NF1 (c.2041C>T; p.Arg681*) were subsequently confirmed by molecular genetic testing.

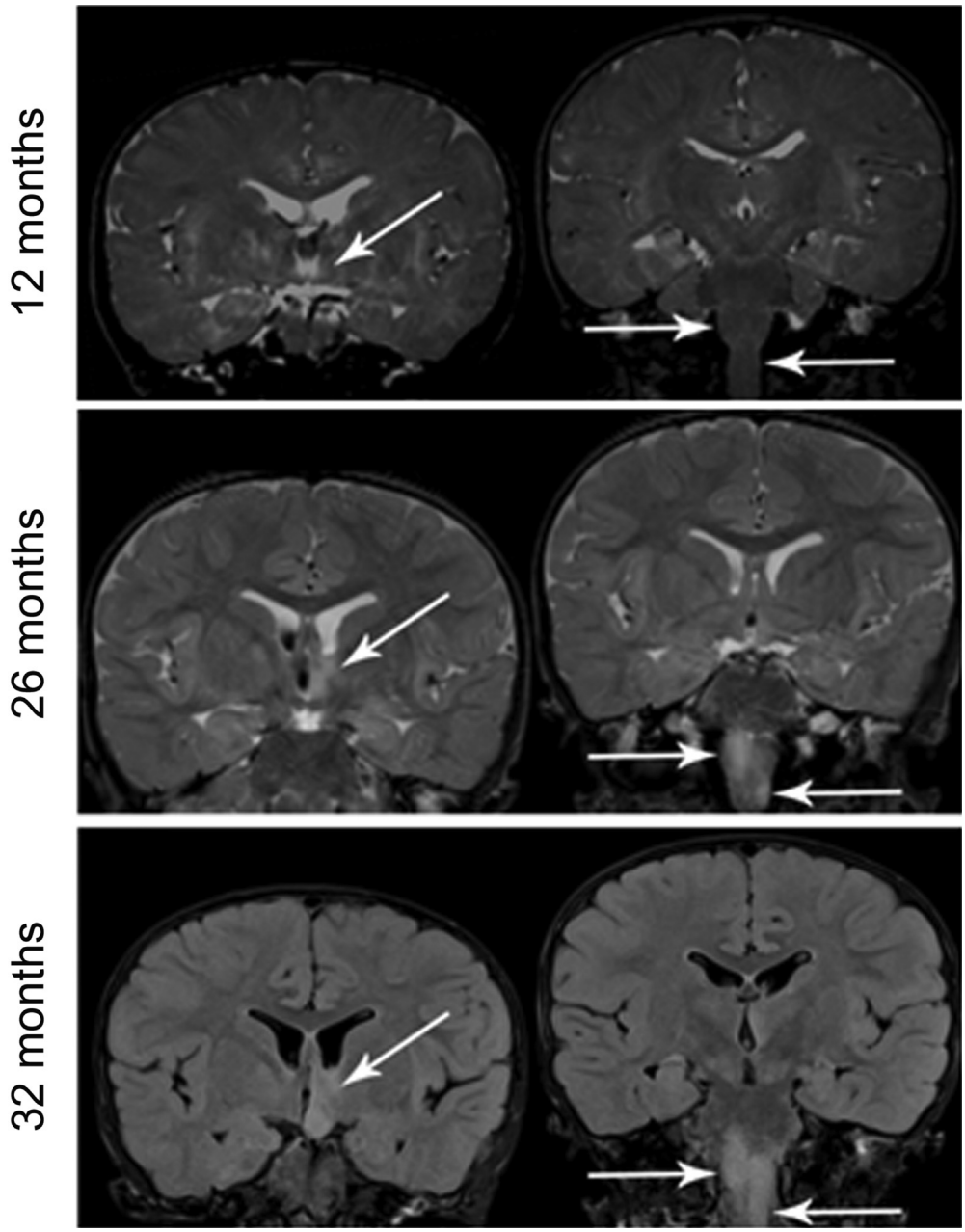

Fig. 1 – Neuroimaging reveals the de novo development of a hypothalamic glioma. Coronal reconstructions of serial brain MRI scans at 12 (T2-weighted), 26 (T2-weighted), and 32 (fluid-attenuated inversion recovery; FLAIR) months of age, demonstrating the development of multifocal gliomas beginning at 26 months in regions previously appearing normal at 12 months (arrows).

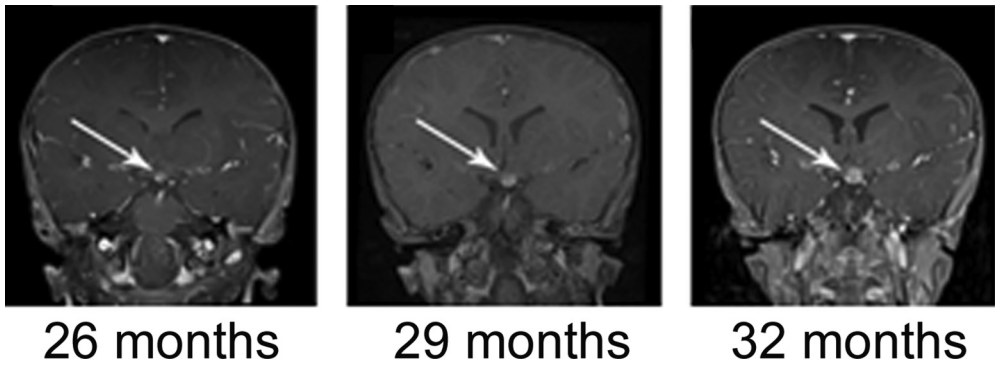

Fig. 2 – Neuroimaging reveals radiographic progression of the hypothalamic glioma. Coronal reconstructions of serial contrast-enhanced T1-weighted brain MRI scans, demonstrating progression of contrast enhancement in the left hypothalamic glioma (arrows) at 26, 29, and 32 months of age.

As part of a Fragile X-related study (K.N.B.), a brain MRI was obtained at 12 months of age (Fig. 1). This was reviewed by his clinical team as well as by neuroradiology (R.C.M.), and there was no evidence of neoplasm. However, at 24 months, repeat neuroimaging demonstrated a right optic nerve glioma (not shown), a left hypothalamic glioma extending along the lateral wall of the third ventricle, and a brainstem glioma extending from the medulla to the upper cervical cord. Comparison of these 2 scans confirmed that there was no evidence of these tumors on the initial scan.

Clinically-indicated MRI evaluations were subsequently obtained at 26 and 29 months of age, with no evidence of radiographic progression. However, at 32 months of age, a repeat MRI revealed a significant increase in both the size and enhancement of his hypothalamic lesion (Fig. 2). Based on this radiographic progression, treatment was initiated with carboplatin and vincristine. Three months later, the brainstem glioma increased in size, and his chemotherapy was changed to Avastin and irinotecan, with no further radiographic or clinical progression, now 18 months later.

Discussion

The serial images shown in Figure 1 demonstrate that brain tumors can arise de novo in children with NF1. This observation, coupled with a prior report highlighting the limited prognostic utility of a baseline MRI in asymptomatic individuals [8], support the primary use of neuroimaging to investigate clinically-symptomatic children with NF1 as revealed by serial neurologic and ophthalmologic examinations and to follow the progression of previously identified brain tumors [9–11].

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