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Report of Concomitant Intracranial Cysts in Unrelated Patients With Heterozygous Germline *NF1* Pathogenic Variants

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Abstract

Neurofibromatosis 1 (NF1) is one of the most common genetic diseases of the central nervous system. The nature of intracranial lesions that are associated with NF1 are yet to be fully defined. Arachnoid, velum interpositum, and odontogenic cysts are among the more common intracranial cystic lesions that can be congenital. Although odontogenic cysts are well known to be associated with Gorlin–Goltz syndrome, the possibilities of other genetic disorders in patients with odontogenic and other intracranial cystic lesions have continued to stir research interests. Here, we report 2 cases of unrelated patients, each patient having concurrent intracranial cystic lesions in the setting of a diagnosis of NF1. Individual I had concomitant arachnoid and odontogenic cysts in parallel with a novel heterozygous germline *NF1* pathogenic frameshift variant, *NF1* [NM_000267.3] c.40del (p.Val14Serfs*10). Individual II had concomitant arachnoid and vellum interpositum cysts in the context of a heterozygous likely pathogenic *NF1* germline variant [*NF1* (NM_000267.3) c.4265C>T, p.(Ser1422Leu)]. Our observations suggest that clinicians should consider NF1 among the differential diagnosis for intracranial cystic lesions such as arachnoid, vellum interpositum, and odontogenic cysts.

Keywords

Cysts; Lesions; Differential diagnosis; Pathogenesis; Diagnostic medicine; Genetic testing; Genetic diseases; Genomics; Genetics; ADHD; NF1; Arachnoid; Odontogenic; Cyst; Intracranial

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Disclosures

Disclosure forms are available with the article online.

Background

Neurofibromatosis 1 (NF1) is a multisystemic, autosomal-dominant disorder that tends to present with neurocutaneous manifestations (including café-au-lait macules, freckling, multiple cutaneous neurofibromas, etc.), tumors, intracranial lesions, and learning as well as behavioral challenges (1). Neurofibromatosis 1 arises from mutations in the *NF1* gene at chromosome 17q11.2 that encodes neurofibromin, which has been implicated in neuronal abnormalities that occur in NF1 (2). Neurofibromatosis 1 can be diagnosed on clinical grounds based on preset criteria that include any 2 of the following: a first-degree relative, at least 6 qualifying (with well-defined borders and a diameter >1.5 cm) café-au-lait macules, intertriginous freckling, at least 2 iris Lisch nodules, optic pathway glioma, at least 2 cutaneous or subcutaneous neurofibromas or 1 plexiform neurofibroma, and a characteristic bony dysplasia (1). The multisystemic manifestations of NF1 encompass several congenital anomalies, including cystic lesions. Hence, imaging modalities in NF1 can reveal a wide range of lesions (3). An improved understanding of imaging findings, including intracranial cystic lesions, in patients with NF1 can help improve diagnostic and management approaches for NF1 patients.

Arachnoid cysts arise from abnormalities in the arachnoid membrane and are found in many brain areas, including the suprasellar region and middle and posterior cranial fossa, as well as the spinal cord (4, 5). Cysts of the velum interpositum originate from a fold of pia mater protrusion above the third ventricle. Odontogenic cysts arise from remnants of the odontogenic epithelium, including the reduced enamel epithelium, the rests of Serres, and the rests of Malassez (6). Arachnoid, velum interpositum, and odontogenic cysts can be congenital or acquired. Arachnoid abnormalities and cysts have been reported in patients with NF1 and may be associated with NF1 (4). Even though odontogenic cysts are known to be associated with Gorlin–Goltz syndrome, the possibilities of other genetic disorders in patients with odontogenic cysts have continued to arouse research interest (7–10). Although odontogenic cysts were reported previously (10 years ago) in a patient with a clinical diagnosis of Neurofibromatosis–Noonan syndrome (8), suggesting possible relevance of the Ras/mitogen-activated protein kinase pathway (11), the patient did not undergo genetic testing to confirm the clinical diagnosis. Herein, we report 2 cases of unrelated patients, each patient having concurrent intracranial cystic lesions in the setting of a genetically confirmed diagnosis of NF1.

Case Report

We observed the simultaneous presence of arachnoid and odontogenic cysts in Individual I, an 18-year-old man who was followed in a genetics clinic for NF1. The patient was diagnosed with NF1 in childhood in the context of having multiple café-au-lait macules and intertriginous freckling. The patient was born at full-term after an uncomplicated pregnancy. Except for concerns of macrocephaly and history of neonatal jaundice, his perinatal and postnatal adaptations were essentially normal. His medical history includes Lisch nodules, odontogenic and arachnoid cysts, and concerns for attention deficit hyperactivity disorder. He had no known family history of NF1 or arachnoid or odontogenic cysts.

Upon physical examination, diffuse café-au-lait macules were identified across his torso, with 6 qualifying café-au-lait macules (having well-defined borders, oval shape, and a diameter of >1.5 cm). Axillary freckles were also present bilaterally. He was found to have macrocephaly, with head circumference measuring around 60.1 cm at age 18 years. There were no apparent craniofacial dysmorphisms, palmar or plantar pits, or other findings that may be suggestive of Gorlin–Goltz syndrome. The patient had magnetic resonance imaging of the brain for surveillance of NF1 in the context of the clinical diagnosis (12), which showed concomitant arachnoid and odontogenic cysts (Figure 1). The patient also pursued custom gene panel testing via the Invitae laboratory RASopathies (San Francisco, CA) and the Noonan Spectrum Disorder Panel (https://www.invitae.com/us/providers/test-catalog/test-04151) with the addition of genes that are known to be associated with Gorlin–Goltz syndrome [*PTCH1*, *SUFU*, and *PTCH2*].

In the context of the clinical diagnosis of NF1, the germline gene panel test came back positive, establishing a genetic diagnosis of NF1, with a heterozygous pathogenic variant that is denoted as *NF1* [NM_000267.3] c.40del (p.Val14Serfs*10). Importantly, there were no reportable variants in *PTCH1*, *SUFU*, and *PTCH2*. The *NF1* c.40del (p.Val14Serfs*10) variant was absent from the control database, gnomAD v4.1.0 (https://gnomad.broadinstitute.org). The *NF1* c.40del (p.Val14Serfs*10) fulfilled the very strong evidence of pathogenicity level 1 (PVS1) and moderate evidence of the pathogenicity (PM2) criteria of the American College of Medical Genetics and the Association for Molecular Pathology variant classification system (13). The *NF1* c.40del (p.Val14Serfs*10) variant is classified as pathogenic on ClinVar [ID: 3 722 417] by Invitae. Individual I's parents and family members were not interested in undergoing testing for the *NF1* c.40del (p.Val14Serfs*10) variant.

We subsequently observed the vellum interpositum (Figure 2, A) and arachnoid cyst (Figure 2, B) in Individual II (unrelated to Individual I), a 33-year-old woman with multiple qualifying café-au-lait macules and neurofibromas as well as a heterozygous likely pathogenic *NF1* germline variant [*NF1* (NM_000267.3) c.4265C>T, p.(Ser1422Leu)] that has been previously reported in other NF1 patients in the clinical scientific literature (14). Individual II had targeted testing for the *NF1* c.4265C>T variant owing to her family and personal history. Individual II's medical history includes congenital pulmonary valve stenosis, dural ectasia, herniated disc (at the L4–5 and L5–S1 levels), attention deficit hyperactivity disorder, migraine, and angioedema. Although Individual II has a family history of NF1, information regarding the details of the health history of her relatives (including imaging findings) with NF1 are unavailable. The intracranial cystic lesions in Individuals I and II have remained stable in the past 3 to 5 years on surveillance neuroimaging.

Discussion

The mechanisms underpinning the development of intracranial cystic lesions (including arachnoid, velum interpositum, and odontogenic cysts) are yet to be fully delineated but are subjects of active investigations (10, 15, 16). Although intracranial cystic lesions have been increasingly reported in NF1 patients (17, 18), it is still unclear whether these lesions are

associated *per se* with NF1. The prevalence of intracranial cystic lesions in NF1 patients is also unclear. To underscore the growing need for an improved understanding of intracranial cystic lesions in NF1 patients, the present study describes concomitant intracranial cystic lesions in 2 unrelated NF1 patients.

Although odontogenic cysts are very common forms of cysts that occur in the jaw (6) and have been reported in some genetic disorders, including Gorlin–Goltz syndrome (15, 19) and Simpson–Golabi–Behmel syndrome (9), there has been only 1 previous case report potentially relating odontogenic cysts to neurofibromatosis (8). Even though odontogenic cysts were reported previously by Yamashita and colleagues in a setting of a clinical diagnosis of Neurofibromatosis–Noonan syndrome, suggesting possible relevance of the Ras/mitogen-activated protein kinase pathway (11), the patient described by Yamashita and colleagues did not undergo genetic testing to confirm the clinical diagnosis (8). Arachnoid cysts have been previously reported in NF1 patients (5, 20). However, to our knowledge, this is the first report of concurrent arachnoid and odontogenic cyst in a patient with a genetically confirmed NF1 diagnosis. Of the Mendelian disorders, Gorlin–Goltz syndrome (involving the Sonic Hedgehog pathway) has the most recognized association with odontogenic cysts (19). Although the precise mechanisms underpinning the development of intracranial cysts (including arachnoid, velum interpositum, and odontogenic cysts) are yet to be fully defined, findings from previous studies have suggested potential roles for genes that are known to be involved in the Sonic Hedgehog pathway (including *SMO*, *PTCH1*, *SUFU*, and *GLI1*) as well as other genes involved in the regulation of cell growth and development (such as *CDKN2A*, *TP53*, *MCC*, *CADMI*, and *FHIT*) (16). Our findings in the context of the potential crosstalk between MAPK and Sonic Hedgehog signaling pathways (11) further highlight the growing need for an improved understanding of the mechanisms underpinning the development of intracranial cystic lesions. Our observations underscore the need for clinicians to consider NF1 among the differential diagnosis for arachnoid and odontogenic cysts.

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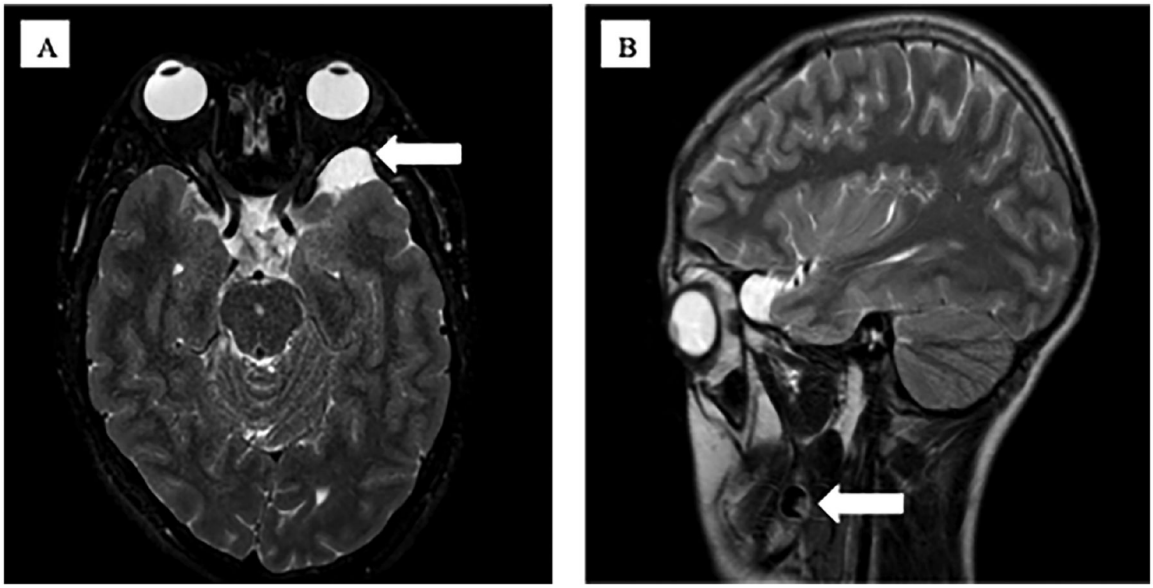

Figure 1.

Individual I. A. Axial T2 sequence showing evidence of left middle cranial fossa arachnoid cyst overlying the left anterior temporal pole (*arrow*). B. Sagittal T2 sequence showing cystic structure in the left mandibular ramus (*arrow*).

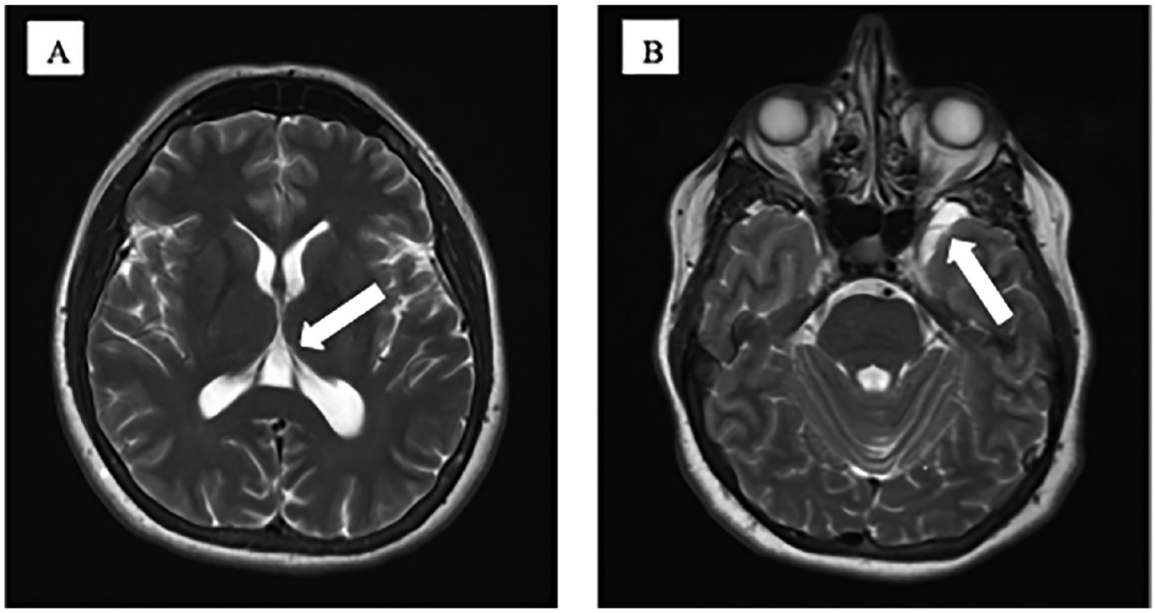

Figure 2.

Individual II. A. Axial T2 sequence showing the cyst of the velum interpositum, within the roof of the third ventricle, a triangular cystic-appearing lesion (*arrow*). B. Axial T2 sequence showing evidence of left arachnoid cyst overlying the left anterior temporal pole (*arrow*).