Clinical Imaging 51 (2018) 160–163

Contents lists available at ScienceDirect

Clinical Imaging

journal homepage: www.elsevier.com/locate/clinimag

Case Report

Neuroimaging findings of extensive sphenoethmoidal dysplasia in NF1

Allison Tam[a,1], Joseph M. Sliepka[a,1], Sunil Bellur[a], Collin Douglas Bray[b], Christie M. Lincoln[b], Sandesh C.S. Nagamani[a,c,d,*]

[a] Department of Molecular and Human Genetics, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030, USA
[b] Department of Radiology, Baylor College of Medicine, Houston, One Baylor Plaza, Houston, TX 77030, USA
[c] Department of Medicine, Baylor College of Medicine, Houston, One Baylor Plaza, Houston, TX 77030, USA
[d] Texas Children's Hospital, 6621 Fannin Street, Houston, TX 77030, USA

ARTICLE INFO

Keywords:
Neurofibromatosis type 1
Sphenoid wing dysplasia
Sphenoethmoidal defect

ABSTRACT

Whereas isolated sphenoid wing dysplasia (SWD) is a well-known clinical feature in neurofibromatosis 1 (NF1), extensive cranial defects involving multiple bones have been rarely reported in this disorder. In this report, we describe the clinical course of a 20-year-old male with NF1 and an extensive cranial bone dysplasia. The large sphenoethmoidal defect was associated with transethmoidal and orbital cephalocele as well as inferolateral herniation of the frontal lobe. In spite of the large defect, the individual did not have any symptoms or complications resulting from the osteopathy. We review the current knowledge of the pathogenesis and management of cranial bone dysplasia in NF1.

1. Introduction

Neurofibromatosis 1 (NF1), the most common Mendelian neurocutaneous disorder has an estimated prevalence of 1 in 3000 births [1]. It is a multisystem disorder caused by heterozygous pathogenic variants in *NF1*, which encodes for neurofibromin, a protein that can affect multiple cellular processes by modulation of RAS-cyclic AMP and ERK-MAP kinase pathways [2]. The cardinal manifestations of NF1 include café-au-lait macules, axillary and inguinal freckling, Lisch nodules of the iris, optic pathway tumors, cutaneous neurofibromas, and bone dysplasias. Involvement of bone may be in the form of a generalized metabolic bone disease with low bone mineral density, or focal developmental anomalies such as tibial dysplasia, scoliosis, and sphenoid wing dysplasia [3,4].

Sphenoid wing dysplasia (SWD), the classic cranial bone abnormality in NF1, is characterized by the partial or complete absence of the greater wing of the sphenoid. SWD is found only in a minority of individuals with NF1; however, more than half of all reported cases of SWD in the literature have been in individuals with NF1 [5]. Whereas SWD can be associated with other cranial bone abnormalities, extensive cranial bone defects have only rarely been reported in NF1 [6,7]. In this report, we present a 20-year-old male with NF1 and an extensive sphenoethmoidal defect that was associated with transethmoidal and orbital cephalocele. We review the literature about the pathogenesis of SWD in NF1, indications for treatment, and published surgical techniques for treatment of this rare bone dysplasia.

2. Clinical report

The study participant underwent clinical evaluation at Baylor College of Medicine, Houston, TX. Informed consent was obtained to publish the medical history and radiographic data. The proband was a male child born to non-consanguineous Caucasian parents. A detailed family history did not reveal any known Mendelian disorders in the family. The history during early childhood was unremarkable, except for mild speech delay and attention deficit hyperactivity disorder. At 12 years of age, the subject developed a lesion over his right eyelid and was referred to the genetics clinic for further evaluation. Physical examination performed at the time revealed multiple café-au-lait spots, bilateral axillary and inguinal freckling, bilateral Lisch nodules, and cutaneous neurofibromas including a plexiform lesion over the right eyelid. He was thus diagnosed with NF1 based on the clinical findings. Fluorescent in-situ hybridization, which was used to detect deletions using region-specific probes for chromosome 17q11.2, revealed two copies of the interrogated region.

At 17 years of age, he underwent imaging of the orbit and facial bones. A non-contrast computed tomography (CT) of the facial bones confirmed the partial absence of the right greater wing of the sphenoid (Fig. 1A) and the absence of the right orbital roof and lamina papyracea (Fig. 1B). Through this widely patent bony defect, the dura mater, right

* Corresponding author at: One Baylor Plaza, MS 227, Houston, TX 77030, USA.
E-mail address: nagamani@bcm.edu (S.C.S. Nagamani).
[1] These authors contributed equally to the work.

https://doi.org/10.1016/j.clinimag.2018.04.017
Received 30 January 2018; Received in revised form 12 April 2018; Accepted 24 April 2018

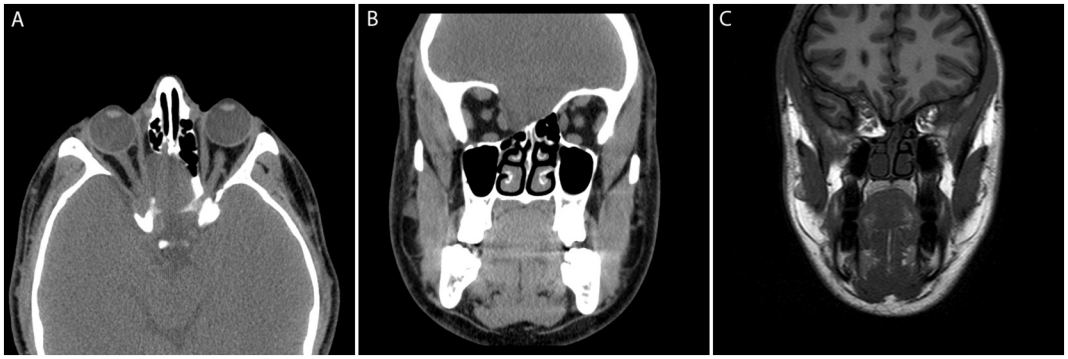

Fig. 1. Two cranial CT scans and 1 coronal MRI reveal extensive bone dysplasias. Panel A: An axial brain CT reveals absence of the right greater wing of the sphenoid bone marking the lateral wall of the orbit and the posterior and middle ethmoid air cells. Panel B: A coronal face CT shows the absence of the superior and medial right orbital walls. The anterior cranial fossa contents are herniating through the defect and are in communication with orbital contents. Panel C: Non-contrast, coronal T1 MR image demonstrating prolapse of anterior cranial fossa contents. There is also development of a small arachnoid cyst from expansion of the subarachnoid space.

orbitofrontal gyrus and bilateral gyri recti were inferiorly herniating. The herniated contents of the right anterior cranial fossa were inseparable from the right superior oblique and medial rectus muscles. A non-contrast T1-weighted magnetic resonance imaging confirmed the findings as seen on the CT scan, but with better resolution (Fig. 1C). Interestingly, despite this large defect, the subject denied any headaches, visual disturbances, diplopia, or any other symptoms suggestive compressive cranial neuropathy. The ocular movements were unrestricted and visual acuity was normal. Serial imaging over a 3-year period did not show any signs of progression of the cephalocele. In addition to the large cranial defect, the subject had other bone abnormalities including a nondystrophic scoliosis of the thoracic spine and low areal bone mineral density at the lumbar spine (0.854 g/cm^2; Z-score −2.2). Expert neurosurgery opinion was that the subject could be monitored conservatively without the need for any surgical intervention in the absence of symptoms. In the nine years following the diagnosis of the extensive cranial defects, the subject continued to have no compressive symptoms due to the bone dysplasia.

3. Discussion

Skeletal abnormalities are frequently found in individuals with NF1 [8]. Involvement of bone may be generalized and manifest with short stature and low areal bone mineral density; or may be limited to focal lesions that typically involve the sphenoid bone, vertebrae, and tibia. Similar to patient presented in this report, it is not unusual for individuals with NF1 to manifest specific focal bone defects along with other skeletal abnormalities. For example, previous studies have shown significant associations between SWD and long bone defects as well as vertebral anomalies [9].

3.1. Pathogenesis of SWD

SWD is one of the distinct craniofacial osteopathies in NF1. The incidence of SWD in NF1 has been estimated to be between 3 and 11% [10]. Since individuals with SWD can be asymptomatic, and as SWD can only be confirmed by imaging, it is possible that the actual prevalence of SWD in NF1 is higher than the current estimates. Though dysplasia of the greater wing of the sphenoid is the classical cranial osteopathy in NF1, rarely, other cranial bone defects involving lesser wing of sphenoid, lambdoid suture, temporal and parietal bones, and orbital plate of frontal bone have also been reported [11,12]. The simultaneous occurrence of SWD along with other cranial bone defects is rare. Although the role of neurofibromin in development of skeleton is well established, the mechanistic basis of cranial bone defects remains to be determined. The two proposed hypotheses for the pathogenesis of SWD in NF1 include: 1) developmental malformation of the bone, and 2) acquired destructive process.

In 1969, Binet and colleagues had proposed that SWD in NF1 was caused by defective ossification centers in the sphenoid bone [13]. *NF1* mRNA and neurofibromin are expressed in wide array of cells of the neuroectodermal and mesenchymal lineage including mesenchymal stem cells, chondrocytes, osteoblasts, and osteoclasts [14–16]. The key roles for NF1 in skeletogenesis from the murine models of the disease, and the evidence that focal lesions like tibial pseudoarthrosis in humans are due to biallelic loss of *NF1*, support the notion that the bone abnormalities could be due to a cell-autonomous deficiency of NF1 in skeletal tissues [15]. Clinically, there is further support for the developmental defect hypothesis as SWD in NF1 is associated with non-contiguous bone deformities and cephalometric measurements in individuals with NF1 demonstrate shorter sphenoid bones [17,18]. However, the lack of cranial defects in the murine mouse models of NF1 and the unilaterality of the lesions argue against the developmental hypothesis. The alternative hypothesis is that SWD in NF1 occurs due to destruction of the bone. As the head circumference size in children with NF1 is above average, Holt and colleagues suggested that higher intracranial pressure could result in osseous changes in the sphenoid [19]. Arrington and colleagues conducted a retrospective chart study of 21 individuals with NF1 and cranial bone abnormalities and reported that nearly all individuals with SWD had an associated plexiform neurofibroma or dural ectasia and that all calvarial defects were associated with plexiform lesions in nearly three-fourths of individuals' studies in their cohort [11]. Moreover, in 9 individuals who had serial imaging, more than half had radiographic evidence of progressive expansion of the middle cranial fossa with bony erosion alluding that SWD associated with NF1 is a dynamic abnormality. Similarly, few other reports have also suggested that SWD is associated with adjacent local lesions in NF1 patients [20,21]. However, if local factors were to be the main driver of cranial defects, the incidence of cranial abnormalities not involving sphenoid wing would be seen more frequently. Alwan and colleagues proposed that local factors such as adjacent neurofibromas or vascular lesions induce a vicious cycle of abnormal remodeling and repair in bone that is haploinsufficient in NF1, and therefore, responds abnormally to these mechanical stimuli [18].

3.2. Treatment options for SWD

Irrespectively of the pathogenetic mechanisms, SWD in NF1 can result in significant morbidity. Encroachment of the orbital space by prolapsing cephaloceles can result in exophthalmos, restriction of extraocular movement, conjunctival inflammation, and pressure on the optic nerve [18]. Thus, any of these findings should prompt imaging to