Intracranial MRI Findings in a Patient with FBXO11-Related Disorder

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Abstract

FBXO11-related intellectual developmental disorder with dysmorphic facies and behavioral abnormalities is a rare genetic disorder. Brain magnetic resonance imaging (MRI) findings associated with this disorder have been sparsely described in literature. This case report describes and depicts brain MRI of a patient with FBXO11-related disorder. The radiologic findings within this report aim to improve the knowledge of the radiologists and clinicians in the detection of this rare condition.

Keywords

► FBXO11
► brain
► MRI
► radiology

Introduction

FBXO11-related intellectual developmental disorder with dysmorphic facies and behavioral abnormalities (IDDFBA) (Online Mendelian Inheritance in Man 618089) is a rare genetic condition.1 Associated brain magnetic resonance imaging (MRI) findings have only been described in a few select papers. In the largest cohort study described by Jansen et al in 2019, brain imaging was performed in 17/24 individuals identified with de novo disease-causing variants within the FBXO11 gene. In this article, six patients had ventriculomegaly, and in three patients, brain abnormalities such as hypoplasia of the anterior pituitary, bilateral hippocampal malformations, borderline large cerebellum, Chiari 2 malformation, and syringomyelia were reported.1 In the second largest cohort study describing 20 patients, 12 had brain MRI, and reduced white matter volume was reported in three patients.2 In another case report, microcephaly and periventricular hyperintensities with dilatation of the frontal and temporal sulci were reported.3 However, no radiologic imaging was included in these papers, and to our knowledge, no other radiologic resource exists in the literature that visually represents the central nervous system findings of patients with IDDFBA.

In this case report, we describe brain MRI findings in a 4-year-old with a pathogenic variant in FBXO11 with typical clinical findings and distinct abnormalities involving the subcortical white matter of the entorhinal and perirhinal cortex of the parahippocampal gyri and optic radiations. To our knowledge, this is the first detailed description of brain MRI findings and can aid clinicians and radiologists in the diagnosis of this rare, highly variable genetic disorder.

Case Description

We describe a 4-year-old male who was born via spontaneous vaginal delivery at 39 weeks’ gestation. Birth length was 53 cm, birth weight was 2.8 kg, birth head circumference (occipital frontal circumference [OFC]) was 34 cm, and Apgar scores were 7, 8. Pregnancy history was unremarkable, and the family history was noncontributory. He had failure to
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thrive since birth. Growth parameters were: weight 5.9 kg (0.01th percentile), length 66.7 cm (6.6th percentile), and OFC 41.9 cm (1st percentile). He had global hypotonia, global developmental delay with early atypical autism spectrum disorder, self-injurious behavior, strabismus, recurrent otitis media, and mild conductive hearing loss. Physical exam features included arched/thick eyebrows, long eyelashes, depressed and wide nasal bridge, anteverted nares, smooth/long philtrum, short neck, and hypoplastic scrotum. Trio exome sequencing revealed a de novo pathogenic variant c.2060 G > A in FBXO11 (NM_001190274.1). Genetics testing revealed a maternally inherited 754 kb copy number gain of uncertain clinical significance in 3p26.1.

The patient had abnormal eye movements, lack of depth perception, and strabismus. He underwent two strabismus surgeries. He did not have a visual field deficit as determined by confrontational visual fields performed at age 3. At the age of 4, the patient presented to the emergency room with seizures consisting of altered awareness, eye deviation, rigidity, and low amplitude shaking. Treatment was initiated with levetiracetam; however, the seizures continued to recur. Seizure semiology included him tensing up when standing, falling over, and then having full body tonic-clonic movements with arms flexed at the chest and eyes rolling back. Electroencephalogram (EEG) was notable for multifocal epileptiform activity in the left centroparietal region and right posterior quadrant. Seizures were captured on EEG and were indicative of generalized activity at onset. Due to concern for possible generalized epilepsy, he was started on valproic acid and weaned off levetiracetam with subsequent improvement in seizure frequency.

A brain MRI with seizure protocol was performed as part of his epilepsy evaluation, and the scan showed global microcephaly. Although the myelination was appropriately completed for 4 years of age, there was generalized paucity of the supratentorial white matter. There was associated proportionate mild dilatation of sulci and lateral ventricles. Imaging of the hippocampus revealed disproportionately dilated temporal horns with complete loss of subcortical white matter underneath the entorhinal and perirhinal cortex of the parahippocampal gyri with a unique appearance of the temporal horns, occupying entirely the vicinity of ventral parahippocampal subcortical U-fibers (►Fig. 1). There was no atrophy, abnormal signal, or malrotation of the hippocampal gray matter. On the oblique coronal T2 and fluid-attenuated inversion recovery, there was bilateral symmetric focal abnormal T2 hyperintense signal and discontinuation of the white matter tracts in the posterior medial aspect of the temporal stem, corresponding to the vicinity of posterior Meyer’s loop of the optic radiations. The sella turcica was slightly shallow with borderline small pituitary gland. Pituitary stalk and posterior pituitary bright spots were preserved. There was no midline or cortical congenital anomaly. The brainstem was relatively normal sized, and no Chiari malformation was noted. Diffusion-weighted images and susceptibility-weighted images were unremarkable. Retrospective review of prior radiologic exams was performed. Previous brain MRI obtained at the age of 9 months due to global developmental delay showed similar findings (►Fig. 2). A spine MRI obtained at the age of 2 years was normal.

Discussion

F-box protein 11 is part of the F-box protein group, which comprises one of four subunits of SCFs or SKP1-cullin-F-box, which is a ubiquitin protein ligase complex. This complex plays an important role in promoting the degradation of many cellular proteins. F-box protein 11 is important for the substrate-recognition component of this larger complex.1

IDDFBA is caused by heterozygous pathogenic/likely pathogenic variants in the FBXO11 gene. Gregor et al and Fritzen et al reported 20 and 2 patients, respectively, with IDDFBA. In the Gregor et al. paper, only 12 cases had a brain MRI and overall, there had small cerebral volume.2 In one case, periventricular hyperintensities were reported by Fritzen et al.3 Most recently, 24 additional individuals were reported by Jansen et al. Brain imaging was performed in 17 patients, and ventriculomegaly was seen in 6 of them. These were all clinical papers without any imaging content and brain MRI findings were limited per their description. It is also important to note that there were a small number of reports of IDDFBA linked to a novel FBXO11 variant that described an absence of brain MRI abnormalities.4

The radiologic imaging in our case displays the following abnormalities: microcephaly, low supratentorial white matter volume, dilated lateral ventricles with abnormal looking medial temporal lobes and particular involvement of the subcortical U-fibers underneath the entorhinal and peri-rhinal cortices, abnormal optic radiations, and borderline small pituitary gland (►Fig. 1). Jansen et al. also described anterior pituitary hypoplasia and bilateral hippocampal malformations in three of their patients.5 Additional radiologic findings such as borderline large cerebellum, Chiari 2 malformation, and syringomyelia were also reported with the FBXO11-related disorder.6 However, we did not observe these findings in our case. Although there was no dysmyelination pattern, there was a supratentorial dominant low white matter volume which explains the ventriculomegaly without hydrocephalus.

In the eight cases by Gregor et al, and two cases by Fritzen et al, there was a clinical history of strabismus at an early age, similar to our patient. Fritzen et al reported abnormal T2 hyperintense signal in the periventricular region on MRI in one of their patients with strabismus. Unfortunately, those MRI images were not provided for review. Temporal lobe lesions/insults such as anterior temporal lobe resection to treat epilepsy can cause visual field deficit, more specifically contralateral superior quadrantanopia (a “pie in the sky” defect) by damaging the Meyer’s loop.5,6 Although there was no definite diagnosis of visual field deficit in our case, determination of visual field deficits is difficult in small children, and in our case, MRI shows bilateral symmetric circumscribed T2 hyperintense lesions within the vicinity of the Meyer’s loop of optic radiations. Another possibility is partial affection of these white matter
tracts without a severe vision defect. There is also evidence that in some cases of perinatal central nervous system insults there may not be the expected corresponding visual defect, perhaps secondary to plasticity of the forming visual system.

Epilepsy can be associated with structural etiologies such as congenital cortical malformations, tumors, intracranial hemorrhage, vascular anomalies, or hippocampal anomalies. In our patient, there was no congenital cortical anomaly. While the cortical gray matter of the hippocampi showed normal signal on multiple sequences, there was a unique disproportionate dilation of the temporal horns extending to the subcortical U-fibers immediately underneath the entorhinal and perirhinal cortex of the ventral parahippocampal gyri (solid white arrows), different than rest of the brain. Oblique coronal FLAIR (G) and T2 (H) slices show bilateral circumscribed T2 hyperintense white matter lesions in the vicinity of bilateral Meyer’s loop of the optic radiation (dashed white arrows).

Epilepsy can be associated with structural etiologies such as congenital cortical malformations, tumors, intracranial hemorrhage, vascular anomalies, or hippocampal anomalies. In our patient, there was no congenital cortical anomaly. While the cortical gray matter of the hippocampi showed normal signal on multiple sequences, there was a unique disproportionate dilation of the temporal horns extending to the subcortical U-fibers of the ventral hippocampal gyri, and poor white matter volume along the parahippocampal gyri, which was not seen elsewhere in the brain. Therefore, this imaging finding may be a unique feature of this specific gene mutation and may place the patient at risk for focal seizures arising from the temporal lobe; however, the patient’s EEG evaluation is not diagnostic of temporal lobe epilepsy. Another possibility is that the myelination of the white matter tracts at this region could be further delayed as the temporal lobe is the last region to become myelinated; however, this possibility is considered much less likely given the myelination was completed at the age of 4 in the remainder of the temporal lobe as seen in Fig. 1. Thus, the underlying pathophysiology of epilepsy in FBXO11-related IDDFA disord remains unclear.
Gregor et al describe 20 patients with de novo variants in FBXO11. Of those patients, three had epilepsy consisting of
generalized tonic-clonic seizures (15%). Of those patients
with epilepsy, all but one had a missense mutation.² Our
patient has a missense mutation, a c.2060 G > A; however,
this exact mutation did not occur in the previously reported
cohort. The clinical observations for the seizures of the
patient in this study seem to align with typical epileptic
events experienced by patients with a missense mutation in
FBX011 according to the Gregor et al study.

Levetiracetam is a broad-spectrum antiseizure medica-
tion; however, it was not effective at controlling the patient’s
epilepsy as monotherapy. Valproic acid is generally known as
an extremely effective medication for primarily generalized
seizures, including generalized tonic-clonic seizures, such as
those seen with temporal lobe epilepsy. The findings of
generalized discharges at seizure onset on EEG as well as
the report of primarily generalized seizures at onset in this
cohort in the literature may suggest that epilepsy in
this disorder could not be secondary to the observed tempo-
ral lobe finding described in this patient, but it could be
related to an unknown mechanism.

As we discussed above, there is a variability in the
radiologic findings described in FBX011-related IDDFBA
condition and these findings are not well demonstrated
or documented in the literature. Therefore, some of the
subtle findings we have described here in this article may
have been missed or underestimated during diagnostic
workup of some subjects with this rare entity. Perhaps,
advanced imaging methods such as tractography or higher
resolution MRI exams may provide further evidence in the
structural alterations in the brain. Based on the limited
information, there may be an imaging variability in these
individuals. Still, the imaging findings described here may
 correspond to some of the neurologic disorders we see in
these subjects, particularly involvement of the medial tem-
poral lobe may partly explain seizure activity, and poor
white matter volume particularly involving the entorhinal
and perirhinal gyri may explain behavioral abnormalities and
intellectual disabilities seen in these subjects. It is
unknown how exactly the mutation causes these structural
changes in the brain. However, as these genetic mutations
cause permanent constitutional alterations in the brain
morphology, treatment is targeted to symptoms, such as
management of seizures, behavioral therapies, or ophthal-
mological interventions.

This report demonstrates brain MRI findings in a patient
with a FBX011-related IDDFBA. To our knowledge, this is the
first detailed radiologic description demonstrating possible
associated abnormalities in the ventral parahippocampal
gyri and inferior medial optic radiations, known as Meyer’s
loop. While these imaging abnormalities may not be specific
to this condition, the imaging abnormalities described in this
case report may correspond with certain clinical features and
may guide other radiologists and clinicians in the future to
better identify or examine this uncommon disorder and help
supportive treatment.

Conflict of Interest
None declared.

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