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CASE REPORT

Hypochondroplasia and epilepsy: temporal lobe dysgenesis in *FGFR3* mutations

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ABSTRACT

Hypochondroplasia is a rare disorder most often caused by Fibroblast Growth Factor Receptor type 3 (*FGFR3*) mutations. It is characterized by short limbs and stature and can be associated with temporal lobe malformations. This pattern of skeletal dysplasia and temporal lobe dysgenesis is common to other *FGFR3*-related disorders, including thanatophoric dysplasia, achondroplasia, and Muenke syndrome.

We present a 6-month old boy with hypochondroplasia and epilepsy. His brain magnetic resonance imaging (MRI) revealed bilateral temporal lobe dysplasia, with redundant sulci and a rotated hippocampus. While our case is not novel, the neuroimaging findings of our case illustrate the molecular mechanisms of the cerebral pathogenesis in *FGFR3*-related disorders. In addition, through this case, we provide an overview of epilepsy and structural brain abnormalities in other *FGFR3* –related disorders.

Keywords: Hypochondroplasia; Receptor, Fibroblast Growth Factor, Type 3; epilepsy; temporal lobe dysplasia

BACKGROUND

Hypochondroplasia is a rare disorder with an estimated incidence of 3,3 per 100,000 live birth [1]. Genotypically, in 70% of cases, it occurs due to a mutation in the Fibroblast Growth Factor Receptor 3 (*FGFR3*) gene, most often c.1620C>A or c.1620C>G lead to a p.Asn540Lys [2].

Phenotypically, patients present with a skeletal dysplasia resulting in short limbs and stature. Neurological involvement, however, is increasingly reported, including the presence of epilepsy and temporal lobe dysgenesis, expanding the phenotypical spectrum of *FGFR3* mutations [3-8]. Other *FGFR3*-related disorders include thanatophoric dysplasia, achondroplasia and Muenke syndrome, which can also present with both skeletal dysplasia and temporal lobe dysgenesis.

The case presented here is not novel but illustrates the neurological involvement in *FGFR3*-related disorders. First, through a review of neuroimaging findings, we review the molecular pathogenesis of cerebral dysgenesis in these disorders. Next, we provide an overview the neurological spectrum in *FGFR3* mutations, with an emphasis on epilepsy and brain structural abnormalities.

CASE PRESENTATION

A 6-month old boy presented with short stature. Pregnancy and delivery at 38 weeks were uncomplicated, birth weight was 3.2 kg (-0.75 SD), length 50 cm (-0.31 SD) and head circumference 36 cm (-0.12 SD). At 6 months, weight was 7.730 kg (-0.19 SD); length 64 cm (-1.31 SD), head circumference 45 cm (0.90 SD). With a paternal height of 173 cm and a maternal height 163 cm, the child's calculated target height for age was 66.5 cm (-0.33 SD). A diagnosis of hypochondroplasia was made clinically, and confirmed radiologically, based on the rhizomelic shortening of upper and lower extremities, and short metacarpals, metatarsals, and phalanges.Genetic testing with conventional sequencing revealed a heterozygous c.1620 C>G variant leading to a p.(Asn540Lys) amino acid substitution in the *FGFR3* gene. Parents were not tested.

At seven months of age, he developed focal dyscognitive seizures of approx. 30 seconds, consisting of behavioral arrest, decreased responsiveness, staring, oromotor automatisms and perioral cyanosis. Seizure frequency was erratic, with clusters of several in a day followed by none for weeks, with a near-complete response to oxcarbazepine.

Early developmental milestones were reassuring: At seven months he was able to sit independently, reached and transferred objects, was babbling and recognized parents and strangers. Family history was notable for a maternal history of febrile seizures.

On examination, he had mild frontal bossing but no other cranial dysmorphism. The general pediatric exam was normal, apart from limb shortening as described. Neurological examination revealed a mild head lag on horizontal suspension but was unremarkable otherwise.

Two routine electroencephalography (EEG) studies in between clusters were normal. 3 Tesla Magnetic Resonance Imaging (3T MRI) showed a dysplastic configuration of the medial temporal lobe, a malrotated hippocampus, and redundant sulci bilaterally. Figure 1 shows details of the temporal lobe dysplasia in the patient and compares them to a structurally normal brain MRI.

DISCUSSION

Our case illustrates neuroimaging findings typically seen in *FGFR3*. While the case itself is not novel, this case illustrates the molecular mechanisms that lead to cerebral dysgenesis. Other *FGFR3*-related disorders can present with similar temporal lobe abnormalities but vary in severity and neurological phenotype as a result of the genotypic variety. – in an apparent dose-dependent effect.

FGFR3 is a member of a family of four FGF tyrosine kinase receptors [9]. Each receptor has a distinctive role in embryogenesis, childhood and adult life. During embryogenesis, the *FGFR3* has a high level of expression in the cochlear duct and in the neural tube, while during childhood its expression is predominant in rudimentary cartilage in long bones during growth [10].

Two mutations account for the majority of cases of hypochondroplasia [2]: c.1620C>A and c.1620C>G, leading to a p.(Asn540Lys) change in the *FGFR3* gene. This p.(Asn540Lys) mutation is also typically identified in patients presenting with seizures [5,8].

On MRI (Figure 1), our case shows bilateral temporal lobe dysgenesis typical for hypochondroplasia: abnormally triangular shaped temporal horns, a vertically orientated collateral sulcus, and an abnormally formed hippocampus. Mild ventriculomegaly in the setting of reduced occipital white matter, present in half of the patients in another study, however, was not present in our patient8. Previously described abnormal grey-white matter differentiation and immature myelination was also not appreciated in our patient [3-8].

The MRI in this case is illustrative of the neuropathogenic process during embryologic development. Progenitor cells in the ventricular zone contain a protomap with predetermined plans for neocortical thickness and anatomy. This protomap is formed under the influence gradients of transcription factors, including FGF3, for which *FGFR3* is one of the receptors [11,12]. In hypochondroplasia, an activating *FGFR3* gene mutation stimulates proliferation of these progenitor cells and suppresses apoptosis, resulting in a thickened cortex with redundant folds [11] (Figure 1A' and 1D'). Higher caudomedial levels of *FGFR3* expression explain why brain malformations are mainly seen in the mesial occipital and temporal lobes [12]. *FGFR3* is also expressed in the hippocampal primordium, which indirectly results in a dysplastic but not enlarged hippocampus (Figure 1E'). Transcription factors from the cortical hem, another patterning center, normally contribute to the hippocampal formation but are suppressed by FGF [12].

Clinically, other *FGFR3*-related disorders are thanatophoric dysplasia, achondroplasia and Muenke syndrome (Table 1). The phenotype reflects the genotype as well: in-

Table 1: Spectrum of *FGFR3* mutation disorders with neurological involvement

Disease	Hypochondroplasia	Achondroplasia	Thanatophoric Dysplasia	Muenke syndrome
OMIM #	146000	100800	187600	602849
Incidence	3.3 per 100,000 live births	1:10,000-1:30,000 live births	1:20,000–1:50,000 births	1:30,000 births
Mutation	p.(Asn540Lys)	p.(Gly380Arg)	p.(Lys650Glu)/ (Lys650Met)	p.(Pro250Arg)
Skull	Mild frontal bossing and macrocephaly	Frontal bossing and macro-megacephaly	Macrocephaly, Large anterior fontanel, Frontal bossing, Cloverleaf skull	Bi/Unilateral coronal synostosis, pan- synostosis, turribrachycephaly or cloverleaf-shaped skull, macrocephaly or normal skull
Epilepsy	Several cases reported	Not reported	2/6 long-term survivors described	20.2% of patients
Development	Language and attentional problems, learning disabilities	Dependent of comorbidities	Non-verbal, non ambulatory	Mild intellectual disability,behavioral problems, delay in walking
Cortex	Temporal lobe dysplasia, white matter reduction, abnormally shaped lateral ventricles	Hydrocephalus	Temporal lobe dysplasia, hydrocephalus, polymicrogyria neuronal migration abnormalities	Abnormal temporal horns and abnormal differentiation grey/ white matter in one case
Hippocampus	Dysplastic [3-8]	Normal	Dysplastic12	Abnormal gyri in one case [16]

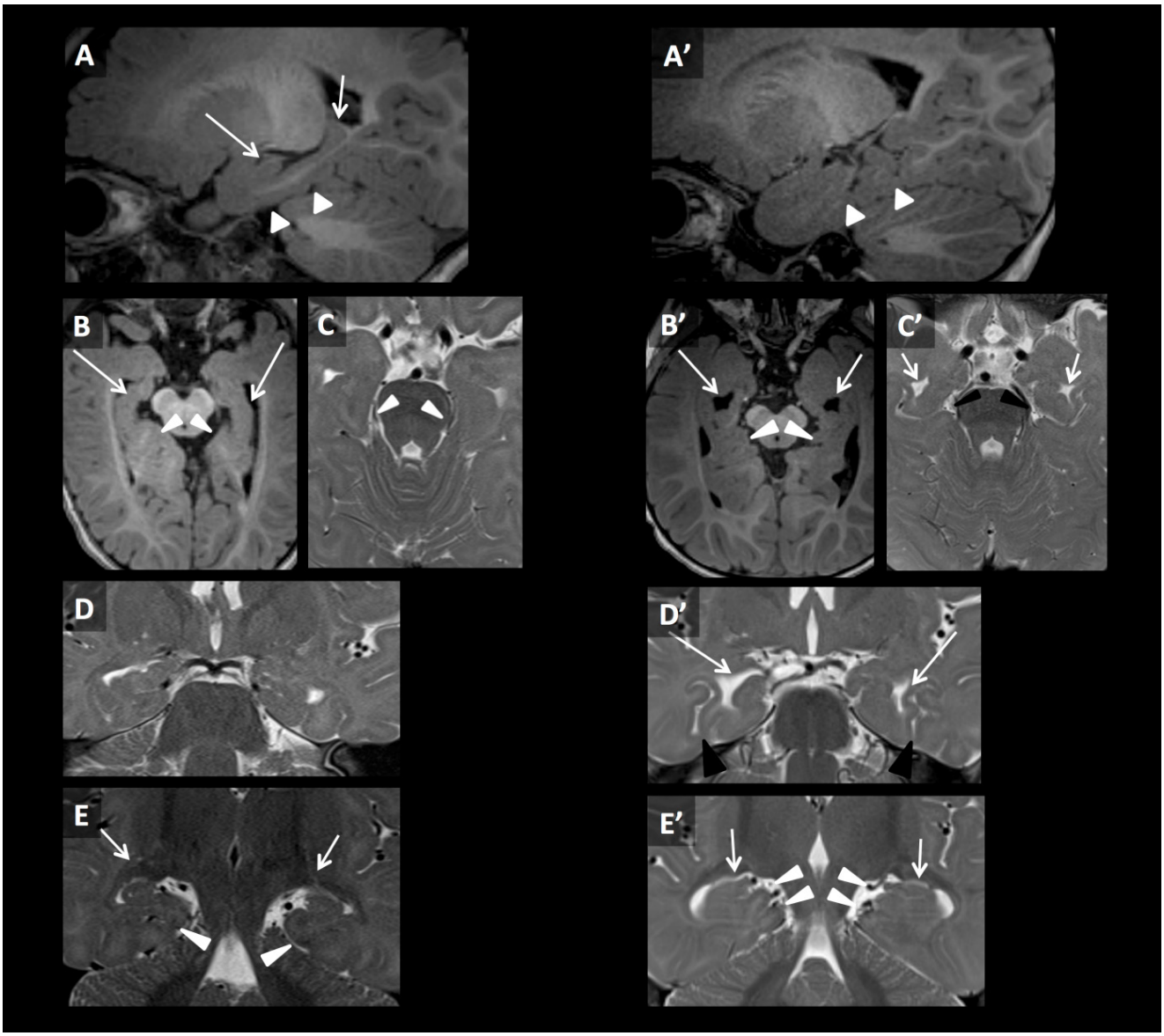

Figure 1: Normal MRI (left) and bilateral temporal lobe dysplasia (right)

A-E: Structurally normal brain MRI from an 8mo evaluated for focal seizures
(A) Left parasagittal T1 image through the mesial temporal structures demonstrates a continuous, well-formed hippocampus (arrow) and smooth contour of the parahippocampal gyrus (arrowheads)
(B) Axial T1 and (C) Axial T2 weighted images of the brain demonstrate normal sized temporal horns, normal hippocampi (arrow), and a smooth surface of the parahippocampal gyri (arrowhead)
(D) Coronal T2 image shows a normal ventricular size of the temporal horn on the right (arrow). The left side is out of the image plane.
(E) Coronal T2 image highlights the normal size and internal architecture of the hippocampi (arrows), horizontally oriented collateral sulci (arrowheads), and a single parahippocampal gyrus on each side.
A'-E': MRI with bilateral temporal lobe dysplasia of 8 month old patient with hypochondroplasia
(A') Left parasagittal T1 weighted image through the mesial temporal structures demonstrates abnormal coronally oriented sulci that disrupt the parahippocampal gyrus (arrowheads). A normal hippocampus is not identified.
(B') Axial T1 and C') Axial T2 demonstrate abnormally dilated and dysmorphic temporal horns (arrows) and the abnormal coronal sulci along the parahippocampal gyrus (arrowheads).
(D') Coronal T2 weighted image. Dilated dysmorphic temporal horns (arrows) are noted. The image also shows abnormally deep, vertically oriented collateral sulci (arrowheads). (E') Coronal T2 weighted image reveals redundant folds of the parahippocampal gyrus (arrowheads) and lack of a normally defined hippocampus (arrows).

creased *FGFR3* activity from gain of function mutations is directly proportional to the severity of endochondral long bones abnormality in hypochondroplasia and thanatophoric dysplasia [13]. Thanatophoric dysplasia is associated with lethal rib and brain malformations and achondroplasia with severe skeletal dysplasia [14,15]. Muenke syndrome, however, has broad phenotypical variability with craniosynostosis, temporal bossing, developmental delay and hearing loss [16].

Epilepsy in hypochondroplasia typically presents with focal dyscognitive seizures, which may secondarily generalize [3-6,8]. Seizure onset is in the first year of life, and about half become seizure free on medication, but case series are too small to assess the efficacy of specific antiepileptic drugs [3-8]. A temporal clustering of seizures in hypochondroplasia has been described before, similar to the pattern that our patient displayed [5,8]. In Muenke syndrome, seizure types are similar but may be preceded by febrile seizures [17]. While temporal lobe dysplasia has been reported, seizures in Muenke syndrome have also been attributed to intracranial hypertension and perinatal hypoxic-ischemic injury [6,17]. In one case series, 4 of 7 patients with Muenke syndrome suffered from anoxia in the neonatal period [17].

Development is variable in the spectrum of *FGFR3* mutations. In achondroplasia, intelligence is normal unless there is hydrocephalus or inadequately treated hearing loss [15]. In hypochondroplasia, language and attentional problems are common [8]. With Muenke syndrome, however, 40% of patients have intellectual disability likely due to *FGFR3* mutation-related brain malformations [16]. Cranioplasty does not alter the cognitive outcome and patients not needing surgery have a comparable intellectual function, too [16]. The long-time survivors of thanatophoric dysplasia have severe intellectual disability, are non-verbal, non-ambulatory and are not able to perform activities of daily living such as toileting, bathing, dressing and feeding [18].

CONCLUSIONS

Our patient featured a classic orthopedic and neurologic phenotype, albeit neurologically mild, with age-appropriate development and good control of seizures to date. Through a detailed review of the neuroimaging findings and we illustrate the neuropathogenic process of temporal lobe dysplasia in *FGFR3*-related disorders.

With this case, we want to raise awareness and provide insight into the mechanisms of childhood epilepsy in hypochondroplasia and other *FGFR3*-related disorders

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Competing interest / Disclosure of conflict of interests

The authors report no competing interests or conflict of interest relevant to the manuscript. The authors report no funding relevant to this report.

Ethical approval

The Boston Children's Hospital & Harvard Medical School IRB does not require a formal IRB for a case-report. Nonetheless, we have parental permission on file.

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