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Temporal Lobe Malformations in Achondroplasia: Expanding the Brain Imaging Phenotype Associated with *FGFR3*-Related Skeletal Dysplasias

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ABSTRACT

SUMMARY: Thanatophoric dysplasia, achondroplasia, and hypochondroplasia belong to the *fibroblast growth factor receptor 3* (*FGFR3*) group of genetic skeletal disorders. Temporal lobe abnormalities have been documented in thanatophoric dysplasia and hypochondroplasia, and in 1 case of achondroplasia. We retrospectively identified 13 children with achondroplasia who underwent MR imaging of the brain between 2002 and 2015. All children demonstrated a deep transverse temporal sulcus on MR imaging. Further common neuroimaging findings were incomplete hippocampal rotation (12 children), oversulcation of the mesial temporal lobe (11 children), loss of gray-white matter differentiation of the mesial temporal lobe (5 children), and a triangular shape of the temporal horn (6 children). These appearances are very similar to those described in hypochondroplasia, strengthening the association of temporal lobe malformations in *FGFR3*-associated skeletal dysplasias.

ABBREVIATION: *FGFR3* = *fibroblast growth factor receptor 3*

Achondroplasia is the most frequent form of short-limb dwarfism, affecting more than 250,000 people worldwide,¹ with an incidence of 0.36–0.60 per 10,000 live births.² Achondroplasia is inherited as an autosomal dominant condition, in which most cases result from a glycine-to-arginine substitution at codon 380 in the transmembrane domain of the *fibroblast growth factor receptor 3* (*FGFR3*) gene.³ Thanatophoric dysplasia (a perinatal lethal skeletal dysplasia), achondroplasia, and hypochondroplasia belong to the *FGFR3* group of genetic skeletal disorders; different allelic mutations result in the variable severity of expression.^{4,5}

Temporal lobe abnormalities have been documented in thanatophoric dysplasia and hypochondroplasia.^{6–8} These changes were first reported in 1 case of an achondroplastic fetus in 2014⁹ but are not commonly described findings in the postnatal brain imaging of affected individuals, despite relatively frequent neuro-

imaging of the brain and craniocervical junction in infants and children with achondroplasia.^{10,11} Well-documented features of MR imaging of the brain in children with achondroplasia are narrowing of the subarachnoid space at the level of the foramen magnum, ventriculomegaly, and bifrontal widening of the subarachnoid space.¹²

Abnormal gyration of the temporal lobes has been described in thanatophoric dysplasia on prenatal sonography^{13–15} and prenatal MR imaging, which showed abnormal gyration of the temporal and occipital lobes and deep sulci on the medial aspects of both temporal and occipital lobes.¹⁴ One case of prenatal MR imaging in an achondroplastic fetus was published in 2014 by Pugash et al,⁹ describing temporal and occipital lobe abnormalities characteristic of hypochondroplasia in addition to the finding of short bones. Achondroplasia was subsequently confirmed on postnatal clinical and genetic testing.

In a review of postmortem neuropathologic changes in cases of confirmed thanatophoric dysplasia, megalencephaly and hippocampal dysplasia were found in all patients. Other very common findings were the following: polymicrogyria, enlarged temporal lobes, deep transverse temporal sulci, and neuroglial heterotopia. The combination of megalencephaly, an enlarged temporal lobe, and aberrant deep sulci was suggested to be specific for thanatophoric dysplasia.⁶

We hypothesized that the association of temporo-occipital developmental brain malformations with *FGFR3* osteochondrodysplasias extends to include individuals with achondroplasia, the most common nonlethal skeletal dysplasia.

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 Indicates article with supplemental on-line table.

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Case Series

Approval for the study was obtained from the Royal Children's Hospital Melbourne Human Research Ethics Committee. A retrospective search was conducted of the Radiology Information System to identify children (from birth to 18 years of age) with a diagnosis of achondroplasia (determined by clinical, radiologic, or genetic evaluation) who had MR imaging of the brain performed between January 1, 2002, and December 31, 2015, for any clinical indication. Seventeen children with achondroplasia were

retrospectively identified from the Radiology Information System; ranging in age from 3 months to 12 years, with a median age of 2.5 years at the time of MR imaging. Four patients were excluded due to inadequate sequences for evaluation of the specific imaging criteria. Thirteen subjects were, therefore, included in the study (On-line Table). In the 9 children who underwent genetic testing, a common G-to-A transition at nucleotide 1138 (c.1138G>A G380R mutation) in the *FGFR3* gene was confirmed. In the remaining 4 children who did not undergo genetic testing, the diagnosis of achondroplasia was confirmed clinically and radiographically by a clinical geneticist.

The MR imaging studies were performed with 1 of three 1.5T imaging systems. The slice thickness of the T2WI sequences ranged from 1.5 to 4 mm. The T1WI was either reconstructed from 3D-T1WI or acquired with a slice thickness of 1.5–3 mm. Two pediatric neuroradiologists (S.A. Mandelstam, A.M.F.) and a pediatric neurologist (K.B.H.) reviewed the imaging for the presence of malformations of cortical development.

The MR images were assessed for the presence of the following: temporal lobe enlargement (defined as bulging of the surface of the temporal lobe beyond the contour of the adjacent frontal and parietal lobes), loss of gray-white matter differentiation of the mesial temporal lobe, incomplete hippocampal inversion, oversulcation of the mesial temporal lobe (assessed on coronal T2WI and 3D-T1WI), extension of oversulcation to the calcar avis, a

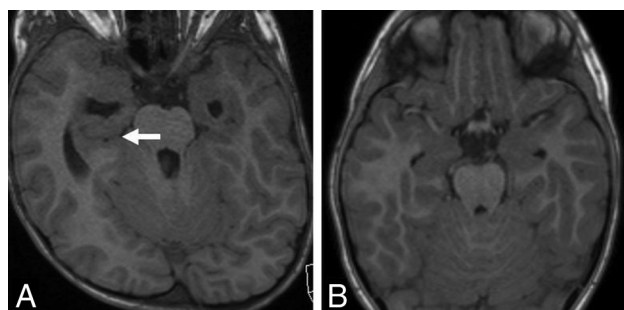


FIG 1. A, Axial T1-weighted MR image in a 5-year-old boy with achondroplasia shows a deep transverse sulcus within the temporal lobe (arrow) and abnormal configuration of the temporal horns of the lateral ventricles. B, Axial T1-weighted MR image in a 5-year-old male control shows the normal configuration of the mesial temporal lobes and temporal horns.

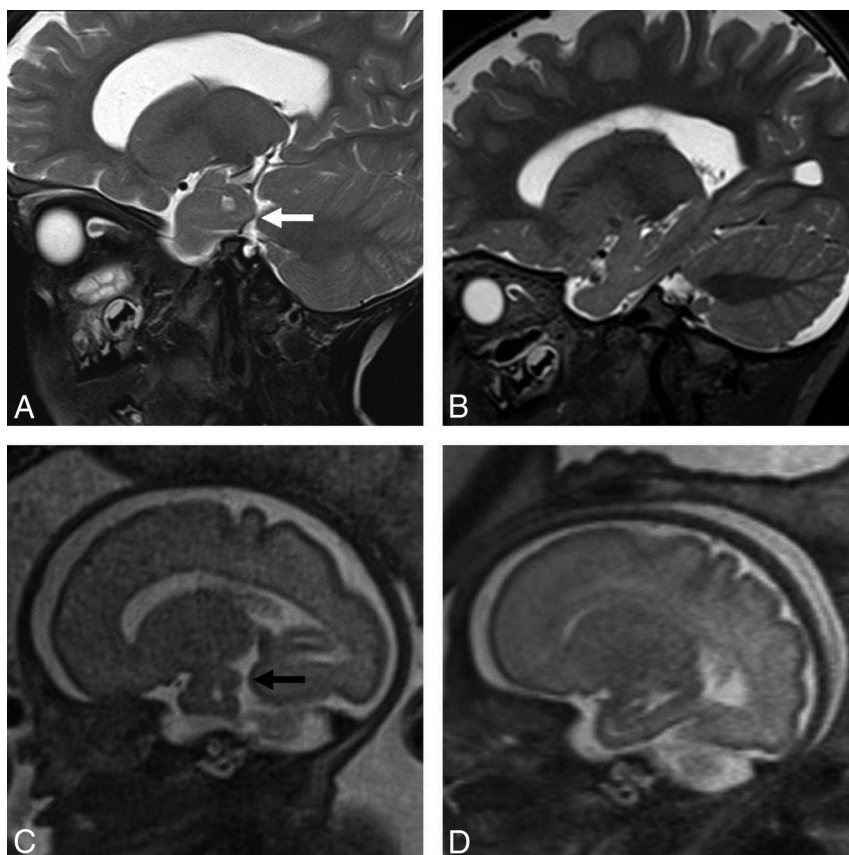


FIG 2. A, Sagittal T2-weighted MR image in a 2-year-old boy with achondroplasia shows a sagittal cleft within the temporal lobe (white arrow). B, Sagittal T2-weighted MR image of the child with achondroplasia in A demonstrates the prenatal appearance of the sagittal clefting within the temporal lobe at 30 weeks (black arrow). D, Antenatal sagittal T2-weighted MR image of a control fetus shows the normal appearance of the temporal lobe at the same gestation.

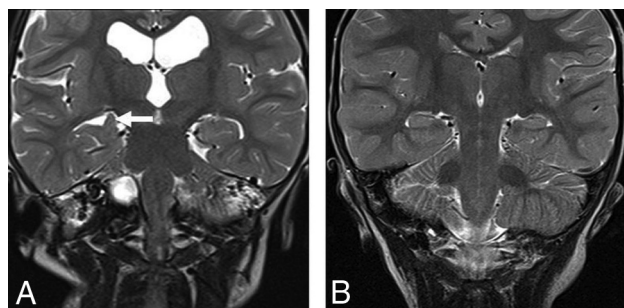


FIG 3. A, Coronal T2-weighted MR image in a 30-month-old boy with achondroplasia shows incomplete hippocampal inversion (arrow) and ventriculomegaly. B, Coronal T2-weighted MR image in a 30-month-old male control shows the normal appearance of the hippocampi.

Prevalence of MRI findings in children with achondroplasia

MRI Finding	Prevalence
Deep transverse temporal sulcus (axial T1WI)	13/13 (100%)
Sagittal clefting in the medial temporal lobe (sagittal T2WI)	13/13 (100%)
Incomplete hippocampal inversion	12/13 (92%)
Ventriculomegaly	12/13 (92%)
Oversulcation of the mesial temporal lobe	11/13 (85%)
Extension of oversulcation to the calcar avis	9/13 (69%)
Loss of gray-white matter differentiation of the mesial temporal lobe	5/7 ^a (71%)
Abnormal triangular shape of the temporal horn	6/13 (46%)
Megalencephaly	5/13 (38%)
Temporal lobe enlargement	1/13 (8%)

^a In the 6 children younger than 36 months of age, loss of gray-white matter differentiation of the mesial temporal lobe could not be accurately assessed on available sequences due to the incomplete myelination.

deep transverse temporal sulcus (assessed separately on axial T1WI and sagittal T2WI), triangular shape of the temporal horn, ventriculomegaly (defined as frontal horns of the lateral ventricles measuring >10 mm), megalencephaly, polymicrogyria, and subependymal heterotopia. The results were consensus-based.

MR imaging studies in all children showed the presence of a deep transverse temporal sulcus, visible on axial T1WI (Fig 1) and sagittal T2WI (Fig 2). Incomplete hippocampal inversion (Fig 3) and ventriculomegaly were found in 12 children (92%) (Table). The next most prevalent finding was oversulcation of the mesial temporal lobe in 11 (85%) (Fig 4), with extension of oversulcation to involve the calcar avis in 9 (69%) (Fig 5). Further common findings were loss of gray-white matter differentiation of the mesial temporal lobe in 5 children (71% of the children older than 36 months of age in whom this could be accurately assessed), a triangular shape of the temporal horn in 6 (46%) (Fig 1), and megalencephaly in 5 (38%). In our cohort, all children with megalencephaly also exhibited ventriculomegaly. Subependymal heterotopia and polymicrogyria were not demonstrated in any children. In one of the children, the temporal lobe changes were also recognized antenatally at 30 weeks' gestation, after the detection of short limbs and mild ventriculomegaly in the fetus on sonography. Comparison of the postnatal with the fetal imaging (Figs 2C and 4C) illustrates the evolution of the findings with brain maturation.

Seizures were reported in only 1 child who had focal seizures between 3 and 12 months of age. Seizures occurred in clusters and were characterized by behavioral arrest, apnea, facial suffusion,

and tachycardia. Electroencephalography recorded seizures arising independently in the left and right temporal regions.

DISCUSSION

Temporal lobe malformations have been previously described in other conditions composing the *FGFR3* family of skeletal dysplasias and were first reported in 2014 by Pugash et al⁹ in 1 case of an achondroplastic fetus with prenatal and subsequent postnatal imaging. In 2012, Linnankivi et al⁷ described 8 patients with hypochondroplasia and an *FGFR3* N540K mutation in whom brain MR imaging demonstrated bilateral temporal lobe dysgenesis, with abnormally shaped temporal horns and an aberrant hippocampal configuration. In a further cohort of children with hypochondroplasia, Philpott et al,⁸ in 2013, additionally described temporal lobe enlargement, deep transverse temporal sulci, overly sulcated mesial temporal lobes, megalencephaly, and mild ventriculomegaly. Correlating our findings with those of previous studies evaluating brain appearances in thanatophoric dysplasia and hypochondroplasia revealed common findings of temporal lobe sulcation abnormalities, incomplete hippocampal inversion, and ventriculomegaly.^{6,8} Polymicrogyria and subependymal heterotopia have been described in postmortem cases of thanatophoric dysplasia on neuropathology⁶ and in imaging of a case with hypochondroplasia,⁸ but these were not seen in our study. It may be that these are less common features that our sample size was not large enough to detect, or it may reflect differential effects of the different *FGFR3* mutations on the brain. It is also possible that subtle cases of polymicrogyria or subependymal heterotopia may be present pathologically, however, not visible on the MR images assessed.

There is a growing body of literature elucidating the role of *FGFR3* mutations in neural and skeletal development. FGFR is a membrane tyrosine kinase encoded by 4 genes (*FGFR 1–4*). In embryonic tissues in mice, *FGFR3* expression is limited principally to neural tube derivatives (developing brain and spinal cord), cartilage rudiments of developing bone, the cochlea, and the lens.¹⁶ All 4 fibroblast growth factor receptors are expressed in the developing brain and contribute to its development.⁶ The *FGFR3* gene in mice is expressed in a gradient in the developing cortex, with the highest levels adjacent to the hippocampal primordia and cortical hem.⁶ Mice with constitutive activation of *FGFR3* in the forebrain demonstrated selective promotion of growth of the caudolateral (occipitotemporal) cortex, which is highly correlated with the gradient of *FGFR3* expression in the ventricular zone at early stages of neurogenesis.¹⁷

Seizures are reported in *FGFR3* disorders, but rarely in achondroplasia. Our patient had temporal lobe seizures in infancy, similar to that reported in hypochondroplasia⁷ and Muenke syndrome,¹⁸ raising the possibility that *FGFR3*-associated temporal lobe dysgenesis predisposes to seizures. It is of clinical importance, however, to note that in our series, most children did not have seizures despite having temporal lobe malformations. It is not clear whether this is the case in the other *FGFR3* disorders.

Similar temporal lobe malformations are described in Apert syndrome, which is the result of localized gain-of-function mutations of *fibroblast growth factor receptor 2* (*FGFR2*) and characterized by craniosynostosis and syndactyly of the hands and feet.¹⁹

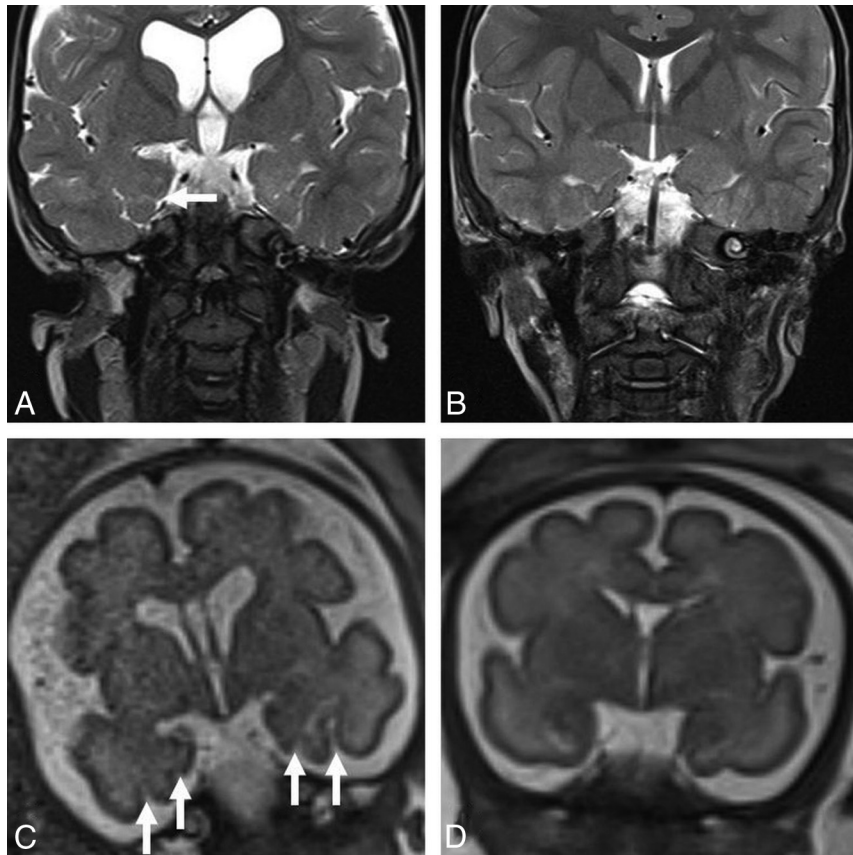


FIG 4. A, Coronal T2-weighted MR image in a 30-month-old boy with achondroplasia shows oversulcation and loss of gray-white matter differentiation of the mesial temporal lobes (*arrow*) and ventriculomegaly. B, Coronal T2-weighted MR image in a 30-month-old male control shows the normal sulcation and gray-white matter differentiation of the temporal lobes. C, Antenatal coronal T2-weighted fetal MR image of the child with achondroplasia in A obtained at 30 weeks shows oversulcation of the mesial temporal lobes (*white arrows*) and mild ventriculomegaly. D, Antenatal coronal T2-weighted MR image of a control fetus shows the normal appearance of the temporal lobes at the same gestation.

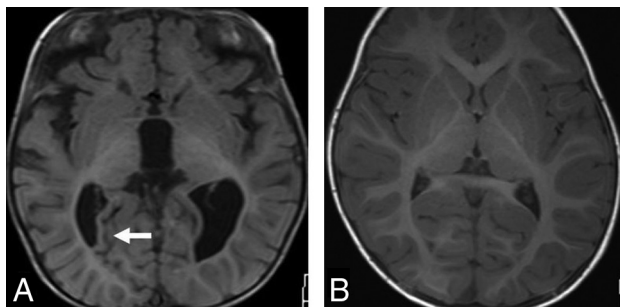


FIG 5. A, Axial T1-weighted MR image in a 1-year-old girl with achondroplasia shows oversulcation of the calcar avis (*arrow*) and moderate ventriculomegaly. B, Axial T1-weighted MR image in a 1-year-old female control shows the normal sulcation pattern of the calcar avis.

The findings described in prenatal and postnatal imaging include expansion and overconvolution of the temporal lobes and temporal lobe clefts.^{20–22}

The major limitations of our study are that it is retrospective, with a small sample size. It is not possible to determine what proportion of patients with achondroplasia have temporal lobe changes on the basis of such small numbers or to clarify the clinical and radiologic correlations. A further limitation is the qualitative rather than quantitative assessment of these cortical malformations on conventional MR imaging sequences.

In conclusion, this case series demonstrates the frequent presence of temporal lobe malformations in children with achondroplasia, the most common nonlethal skeletal dysplasia. The findings herein strengthen the association of temporal lobe malformations and skeletal dysplasias due to different mutations in the *FGFR3* gene.

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