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Clinical Observations

Does the Co-occurrence of *FGFR3* Gene Mutation in Hypochondroplasia, Medial Temporal Lobe Dysgenesis, and Focal Epilepsy Suggest a Syndrome?

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ABSTRACT

BACKGROUND: Hypochondroplasia is a rare skeletal dysplasia characterized by disproportionately short stature, lumbar lordosis, and limited extension of the elbow caused by mutations in the fibroblast growth factor receptor 3 *(FGFR3)* gene that plays a role in controlling nervous system development. Hypochondroplasia with *FGFR3* mutation associated with bilateral medial temporal lobe anomalies and focal epilepsy was previously reported in several patients. **PATIENT:** We report clinical, electroclinical, and neuroradiological findings of one patient affected by hypochondroplasia. **RESULTS:** Clinical diagnosis was confirmed by molecular analysis of the *FGFR3* gene, which showed a N540 K mutation. The patient had normal psychomotor development and showed early-onset focal seizures with left temporal localization on interictal and ictal electroencephalograph. The seizures were well controlled, and the patient has been seizure-free since infancy. Magnetic resonance imaging showed abnormal anteriorly posteriorly infolding in the hippocampus and abnormally oriented parahippocampus sulci, and additional cortical rim dysplasia with gray-white matter junction blurring in the hippocampus. **CONCLUSIONS:** The present case of hypochondroplasia and *FGFR3* mutation in Asn540Lys associated with characteristic abnormalities involving bilaterally medial temporal lobe structures, probable hippocampal cortex focal dysplasia, and early onset of focal epilepsy underscores the possibility of a rare syndrome.

Keywords: Hypochondroplasia, *FGFR3* gene, focal temporal epilepsy, medial temporal lobe dysgenesis, hippocampus abnormalities, focal dysplasia

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Introduction

Hypochondroplasia (HCH, OMIM 146000) is an autosomal dominant inherited skeletal dysplasia with clinical, radiological, and histopathological features similar to but milder than achondroplasia. The clinical and radiological diagnostic criteria remain controversial because of the absence of a typical feature specific to hypochondroplasia and the variable phenotype. Hypochondroplasia is caused by mutations in the *FGFR3* gene, which maps to chromosome 4p16.3, but genetic heterogeneity is suspected.[1-3]

Hypochondroplasia with mutations in the fibroblast growth factor receptor 3 *(FGFR3)* gene associated with bilateral medial temporal lobe dysgenesis and focal epilepsy has previously been reported in several patients.[4-8] The authors propose that *FGFR3* mutations can specifically cause brain dysgenesis and epilepsy.

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We report a further case of hypochondroplasia with medial temporal lobe dysgenesis and early-onset seizures with normal psychomotor development.

Case report

A female was born to nonconsanguineous, healthy parents. Family history was positive for a *de novo* chromosomal abnormality (8p23.1 duplication syndrome) in the father's first cousin. No family history of epilepsy was reported.

Pregnancy was unremarkable except for shortness of the long bones detected on the third-trimester ultrasound examination. The child was born at 40 weeks; birth weight was 2510 g, length 47 cm, head circumference 34 cm, and Apgar score 8/9. The neonatal period was uneventful. The patient experienced the first episode of right focal tonic seizure when she was 23 days old. At 50 days of age, she had focal repetitive seizures during sleep and while awake, characterized by eye and head right deviation with cyanosis, which were interrupted by that were more prominent. Interictal electroencephalography (EEG) showed bilateral slow waves predominantly in the left temporal regions.

Subsequently, brief seizures with the same clinical features occurred monthly in clusters of 3-10 seizures within 12-24 hours during sleep and while awake.

At the age of 3 months, she was referred to our clinic. Her weight was 4.5 kg (third percentile), height 52 cm (< third percentile), and head circumference 39 cm (25th percentile). She had a round face, frontal bossing, and small occipital hemangiomas.

Psychomotor development was within the normal range. Routine blood tests and serum and urinary amino acid levels were normal.

Interictal EEG showed an occasional sharp wave over both temporal regions with left predominance, and ictal video-EEG showed polymorphic theta wave discharges in the left-central temporal areas, followed by rhythmic theta waves and slow spike wave complexes without diffusion. This EEG pattern corresponded to staring, cyanosis with tonic extension of the right arm, eye and head right deviation with oral automatisms, and pédalage-like movements (Fig 1).

Magnetic resonance imaging was performed at 1.5 Tesla using high spatial resolution, 2-mm-thick sections, and dedicated neonatal head coil (Fig 2). The image showed clear dysmorphism of the anterior–medial temporal lobe region and of the anterior hippocampus symmetrically in both hemispheres, with abnormally backward infolded hippocampus and abnormally radially oriented parahippocampal sulci. Anterior hippocampus focal cortical rim dysplasia with gray–white matter junction blurring and cortical rim thickening was noted. Enlarged temporal horns of the lateral ventricles and probable cortical rim focal abnormality were also detected.

A clinical diagnosis of hypochondroplasia was hypothesized because of the mildly short stature associated with particular hippocampal structures. This hypothesis was subsequently confirmed by molecular analysis of the *FGFR3* gene, which detected a c.1620C- > A mutation, resulting in p.Asn540Lys.

Carbamazepine was started, and phenobarbital was gradually tapered, resulting in improved seizure control. The patient is now 7 years old, her neurological development is normal, and she has been seizure-free since age 23 months.

Discussion

Hypochondroplasia is an autosomal dominant condition with a wide spectrum of intrafamilial and interfamilial severity; in the literature, only in 60% to 72% of cases *FGFR3* gene mutations are found.[1,3,9] Song et al.[3] recently documented that only 32.8% of hypochondroplasia patients showed *FGFR3* mutations. These findings also suggest there may be other undiscovered gene mutations associated with this phenotypic entity.

The mutation N540 K in *FGFR3* gene has been reported previously in hypochondroplasia.[1,3-10] Other skeletal dysplasias with variable clinical expression are related to different *FGFR3* mutations (e.g., lethal thanatophoric dysplasia, severe achondroplasia with developmental delay, acanthosis nigricans dysplasia, two craniosynostosis

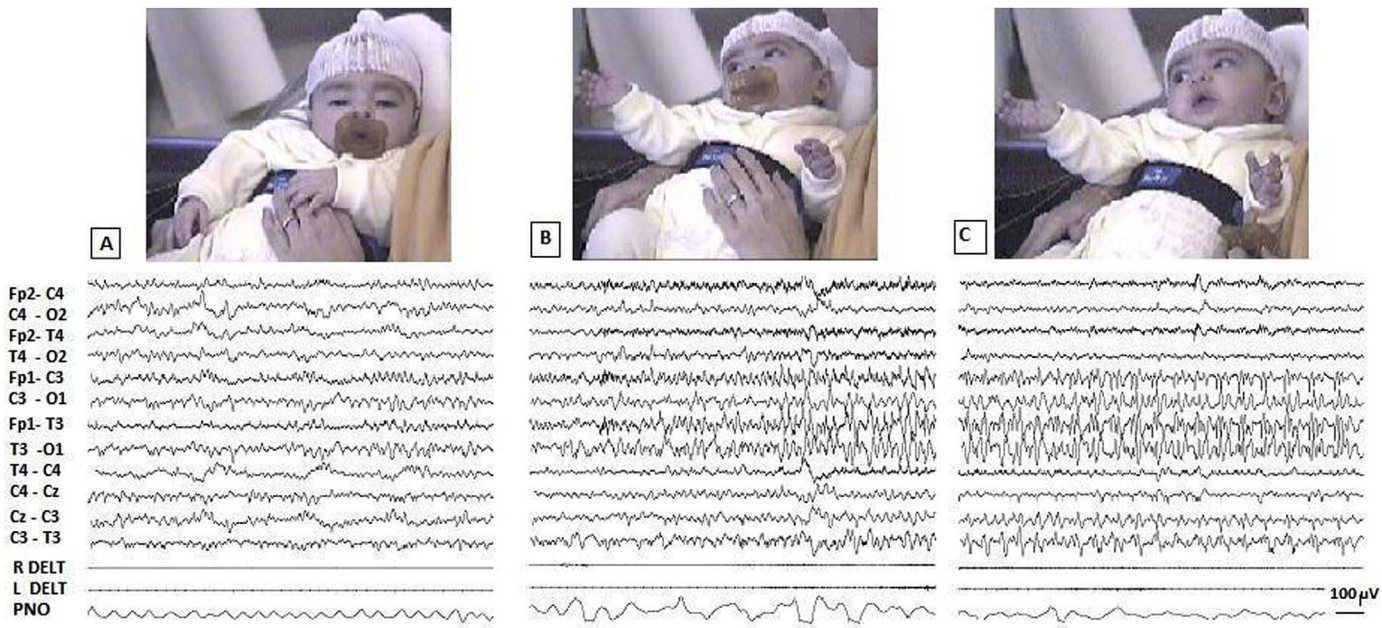

FIGURE 1.
Ictal video-electroencephalograph recording showed (A) polymorphic theta wave discharges, appearing in the left central-temporal areas, corresponding to staring and cyanosis. This was followed by (B) tonic extension of right arm, eye, and head right deviation corresponding to rhythmic theta waves and slow spike wave complexes and (C) rhythmic slow spike wave complexes related to oral automatisms and pédalage-like movements. (The color version of this figure is available in the online edition.)

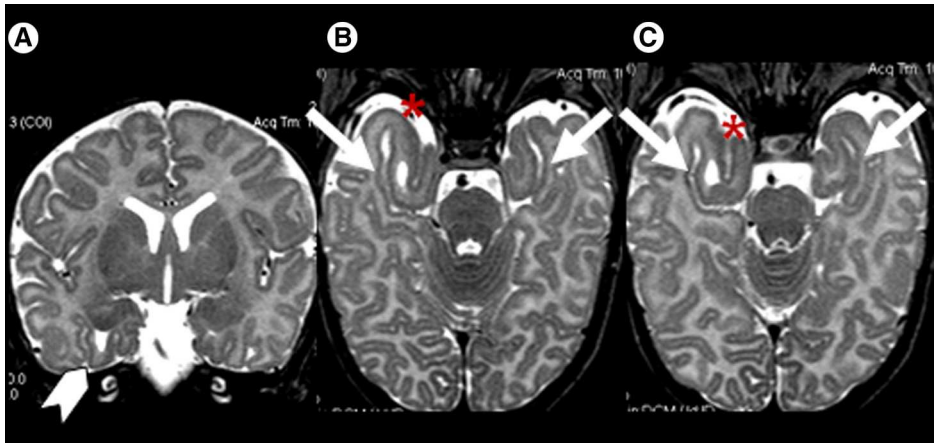

FIGURE 2.
(a) Coronal (b) and (c) axial fast spin-echo 2-mm-thick magnetic resonance imaging T2-weighted sections, showing abnormally anteriorly posteriorly infolded hippocampus (arrows) and parahippocampal sulci (arrowhead). The finding is more conspicuous on the right side. Asterisks show very probable anterior hippocampus focal cortical rim abnormality, with gray–white matter junction blurring and cortical rim thickening (more appreciable on the right side). (The color version of this figure is available in the online edition.)

disorders [Muenke syndrome and Crouzon syndrome]).[2,4,11] *FGFR3* mutations have been described in a wide spectrum of skin disorders[2,11] and may cause a syndrome characterized by systematized epidermal nevous and cerebral defects.[11] Therefore, *FGFR3* is postulated to play a role in brain development, mainly in hippocampal development.[7,12-14] Additionally, *FGFR3* mutations are known to interfere with brain development in mouse embryos.[12-14] In mice, the expression is high during development in the rhinal and piriform cortices (which correspond to the anterior parahippocampal gyrus in humans), hippocampus, amygdala, and striatum as well in the caudolateral cortical size[13]; furthermore, reportedly, *FGFR3* knockout (*FGFR3*$^{-/-}$) mice have a reduction in the volume of the cerebral cortex and the hippocampus.[14]

Our patient shares the same clinical, neuroimaging, and genetic features with patients described in the literature, with hypochondroplasia associated with general gross abnormal morphology including cortical infolding in the medial temporal lobe region, as previously reported.[4-8] Moreover, besides the known temporal lobe abnormal infoldings, our patient also shows a focal cortical rim dysplasia in the anterior hippocampus, because gray-white matter junction blurring was present. It is conceivable that the latter focal cortical anomaly may play a role in the epileptogenic activity present in our patient.

In previous cases, the pattern of cerebral abnormalities due to the *FGFR3* mutation (N540 K) appeared to be specific. Different from previous reports, we used high spatial resolution magnetic resonance sections (2-mm thick); this could account for the hippocampal focal cortical anomaly that we detected as gray–white matter junction blurring. However, other studies using similar high spatial resolution protocol in hypochondroplasia patients are needed to confirm this observation.

Focal seizures have been described previously in literature; in most cases, they started in the first year of life.[4-8] The seizures are characterized by short-term manifestations of staring, fixed gaze, apnea, cyanosis, and eye deviation, with occasional secondary generalization. Most patients showed a remission of seizures. The interictal EEG patterns described were normal or demonstrated the presence of epileptiform abnormalities in the bilateral temporal regions.[4] Our patient showed early-onset seizures, characterized by staring, cyanosis with tonic extension of the right arm, eye and head right deviation with oral automatisms, and pédalage-like movements during sleep and while awake. Interictal and ictal EEG clearly demonstrated temporal localization. She has been seizure-free since the age of 23 months and shows a normal psychomotor development as other patients described in the literature.[4,5,7]

In conclusion, our patient with hypochondroplasia and *FGFR3* mutation in N540 K, associated with characteristic abnormalities of bilateral medial temporal lobe structures with probable hippocampal cortex focal dysplasia and early onset of focal epilepsy, suggests the possibility of a rare syndrome.

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