RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART A

Neuroimaging and Neurological Findings in Patients With Hypochondroplasia and *FGFR3* N540K Mutation

Tarja Linnankivi,[1]* Outi Mäkitie,[2] Leena Valanne,[3] and Sanna Toiviainen-Salo[3]

[1]Department of Pediatric Neurology, Children's Hospital, Helsinki University Central Hospital, University of Helsinki, Helsinki, Finland

[2]Department of Pediatrics, Children's Hospital, Helsinki University Central Hospital, University of Helsinki, Helsinki, Finland

[3]Department of Radiology, University of Helsinki, HUS Radiology (Medical Imaging Center), Helsinki, Finland

Manuscript Received: 2 June 2012; Manuscript Accepted: 2 August 2012

Hypochondroplasia (HCH), an autosomal dominant skeletal dysplasia caused by mutations in the *FGFR3* gene, has not been commonly associated with neurological problems. Temporal lobe dysgenesis associated with epilepsy was recently described in single patients. In this retrospective study, we assessed neurological and neuroimaging aspects of 13 *FGFR3* (N540K) mutation verified HCH patients in Finland. Eight patients had neurocognitive difficulties, ranging from specific learning disorder (2/13) to mild intellectual disability (5/13) or global developmental delay (1/13). Six of 13 patients had a history of seizures or epilepsy. Eight patients had undergone MRI. They all had structural abnormalities consistent with temporal lobe dysgenesis. Six patients had peritrigonal white matter reduction, and 4 had abnormally shaped lateral ventricles. We recommend a close follow-up of development in patients with HCH and a low threshold for neuroimaging.

Key words: hypochondroplasia; skeletal dysplasia; temporal lobe dysgenesis; epilepsy; intellectual disability

How to Cite this Article:
Linnankivi T, Mäkitie O, Valanne L, Toiviainen-Salo S. 2012. Neuroimaging and neurological findings in patients with hypochondroplasia and *FGFR3* N540K mutation
Am J Med Genet Part A 158A:3119–3125.

INTRODUCTION

Hypochondroplasia (HCH, OMIM 146000) is an autosomal dominant skeletal dysplasia caused by mutations in the fibroblast growth factor receptor 3 gene (*FGFR3*). HCH belongs to the achondroplasia family of skeletal dysplasias, which also includes the more severe achondroplasia and neonatally lethal thanatophoric dysplasia [Spranger et al., 2002]. These three disorders are allelic, caused by different activating mutations in the *FGFR3* gene. Two recurrent mutations, C1620A and C1620G, which both result in N540K substitution in the protein, are found in 50–70% of patients with HCH [Bellus et al., 1995; Prinos et al., 1995; Bellus et al., 2000; Spranger et al., 2002]. Other less frequent mutations in *FGFR3* have also been described [Bellus et al., 2000]. However, not all patients with presumed HCH have demonstrable *FGFR3* mutations, suggesting heterogeneity.

The major clinical and radiographic findings in HCH include short stature with a relatively long trunk and short limbs, increased lumbar lordosis, occasional macrocephaly and frontal bossing, moderate narrowing of lumbar interpediculate distances, and shortness and "squaring" of the tubular bones. The skeletal changes resemble but are milder than those seen in achondroplasia [Spranger et al., 2002].

HCH has not been commonly associated with neurological problems. Some authors have reported increased prevalence of mental deficiency (up to 9% of patients) [Hall and Spranger, 1979] but this observation has been controversial [Wynne-Davies and Patton, 1991]. Recently, four patients with HCH and *FGFR3* (N540K) mutations were reported separately to have medial temporal lobe dysgenesis, accompanied by epilepsy [Grosso et al., 2003; Kannu et al., 2005; Kannu and Aftimos, 2007]. Brain structure has not been studied systematically in HCH patients and thus the frequency of brain dysgenesis, and its possible association with epilepsy or intellectual disability, remains unknown.

The aim of this study was to assess neurological, developmental, and neuroradiological characteristics in *FGFR3* mutation-positive HCH patients.

The authors have no conflicts of interest to declare.

*Correspondence to:
Tarja Linnankivi, MD, PhD, Department of Pediatric Neurology, Children's Hospital, Helsinki University Central Hospital, Stenbäckinkatu 11, FIN-00290 Helsinki, Finland.
E-mail: tarja.linnankivi@hus.fi

Article first published online in Wiley Online Library (wileyonlinelibrary.com): 19 November 2012
DOI 10.1002/ajmg.a.35642

MATERIALS AND METHODS

Patients

As part of an ongoing research program on skeletal dysplasias in Finland, approved by the institutional Research Ethics Board, altogether 14 patients with HCH and verified mutations in *FGFR3* were identified and their findings were analyzed retrospectively. Clinical information was available on 13 patients. Data on patients' previous medical history including birth records, growth, skeletal phenotype, psychomotor development, neurological symptoms, and brain imaging were collected from hospital records. Information regarding the skeletal phenotype, deformities, growth failure, and orthopedic procedures were used to estimate the overall severity of the phenotype. All patients had been screened for *FGFR3* mutations as part of the initial diagnostic work-up. Findings of the genetic testing were collected from hospital records.

Analysis of Brain Imaging

Neuroimaging data (brain MRI) were collected from hospital archives. All brain MRI images available were re-analyzed by two experienced radiologists (a neuroradiologist and a pediatric radiologist with special interest in pediatric neuroradiology) who were blinded for the patients' clinical data apart from the diagnosis of HCH. Structural brain aberrations, signal intensity changes, gray- and white matter differentiation, and the state of myelination were recorded. The size and shape of corpus callosum and lateral ventricles as well as the sizes of posterior fossa and foramen magnum were recorded.

RESULTS

Clinical Findings

Clinical data were available on 13 sporadic patients and are summarized in Table I. Patients (five males, eight females) ranged in age from 0.9 to 18 years at the time of the latest follow-up. One patient was born preterm (33 + 5 gestational weeks), one was born from a twin pregnancy and three patients were born by cesarean (Table I). The birth lengths and weights were appropriate for gestational age but the head circumference was usually increased (+1.3 SDS, range −0.8–4.0 SDS). One child had history of fetal alcohol exposure and neonatal herpes simplex virus encephalitis. All patients were clinically diagnosed with HCH in early childhood and the diagnosis was subsequently confirmed by *FGFR3* mutation analysis; all were heterozygous for N540K mutation (Table I).

The height Z-scores at the latest follow-up ranged from −1.9 to −6.2. Due to the progressive nature of the growth failure older patients tended to have lower height Z-scores than the younger patients, otherwise the severity of the skeletal phenotype was fairly uniform and similar in degree of severity. One patient had required surgery for foramen magnum stenosis; none of the patients had required orthopedic surgeries.

Psychomotor Development and School Performance

Eight of the 13 patients had been evaluated by a pediatric neurologist in our tertiary care hospital and, when necessary, by other members of a multidisciplinary team (speech therapist, occupational therapist, physiotherapist, and/or neuropsychologist).

Three patients were under 3 years of age at the latest follow-up and mild cognitive impairment cannot be reliably excluded at such age. However, two of them had normal early development and one had mildly delayed speech development.

Ten patients were over 3 years of age at the latest follow-up: three of them had normal development and attended mainstream school. However, only one of them had unequivocally normal school performance. Two of these patients went to a mainstream school, but needed special education, mainly in mathematics. One 5-year-old was reported to have poor attention, but formal neuropsychological assessment was lacking.

In six patients, early development was globally delayed. An assessment of neuropsychologist /psychologist showed mild intellectual disability in five of them and one reached borderline cognitive performance at the age of 3 years. The most prominent difficulties concerned speech and language development. All these patients also had marked attention deficits. School-aged children attended full-time special education groups (Table I).

Children learned to walk at the age of 12–19 months (mean 14.5 months). Mild gross motor delay was noted in four patients and was associated with mild hypotonia.

Epilepsy

Six of 13 patients had a history of seizures. Two neonates had partial seizures that responded to phenobarbital treatment, but one of them was also diagnosed with herpes encephalitis, based on HSV1 PCR findings in the cerebrospinal fluid.

Three of 13 children had focal epilepsy that manifested in infancy with staring, apnea, perioral cyanosis, and eye deviation with or without secondary generalization. Seizures were usually brief, lasting 10 sec to 2 min and occurred typically in clusters up to 10 times per day. One of these three patients also had an episode of febrile status epilepticus. Ictal EEG was caught in two patients and showed frontotemporal or lateralized spike discharges. Interictal EEGs were normal. Their seizures only partially responded to antiepileptic drugs (AED), including phenobarbital, valproic acid, carbamazepine, oxcarbazepine, topiramate, and clobazam. Despite this drug-refractoriness at onset, seizures spontaneously ceased in two patients at ages of 13 months and 3 years. One of the patients still has refractory epilepsy at the age of 5 years.

One patient had a single psychomotor seizure at the age of 1.8 years. Her EEG showed a few frontocentral spikes and slow waves during sleep, independently from both hemispheres and normal background activity.

Other Neurological Symptoms and Findings

One of the patients had hydrocephalus, which was shunted at the age of 2.5 years. At age 12, bilateral sensorineural hearing impairment was diagnosed. Her posterior fossa was small and she developed symptomatic Chiari I malformation and syringomyelia; syringotomia and foramen magnum decompression were performed at the age of 15 years (Table I).

TABLE I. Characteristics of the 13 Patients With Hypochondroplasia

Patient # Gender Age[a] (y)	*FGFR3* mutation[b]	Height Z-score	Birth history, BW, height (Z score), OFC (Z score)	Cognitive development, school performance	Seizures	Other remarks
#1 M 0.9	N540K	−2.3	Cesarean H 38, 3,640 g, 50 cm (0.0), 37.5 cm (+2.5)	Normal milestones	No	
#2 F 1.9	N540K	−2.4	At term, 3,200 g, 47 cm (−1.8), 34 cm (−0.8)	Delayed speech	No	MRI at 1.9 years
#3 F 2.5	N540K	−2.1	At term, 4,165 g, 50 cm (−0.1), 39.5 cm (+4.0)	Normal milestones	A single partial seizure at 1.8 years	
#4 M 4.6	N540K	−4.2	At term, 3,434 g, 46 cm (−2.5), 36 cm (+0.3)	Global delay, prominent difficulties in expressive language and attention	Partial epilepsy, onset 2.5 months. Seizure-free from age 13 months	3 MRIs at 0.4–3.4 years
#5 M 4.8	N540K	−2.9	Cesarean H 41, 4,740 g, 53 cm (+1.2), 40 cm (+3.5)	Mild intellectual disability, prominent difficulties in language and attention	No	VSD (muscular), 2 MRIs at 0.7–3.0 years
#6 M 5	N540K	−2.6	At term, 4,080 g, 51 cm (+0.2), 38.5 cm (+2.2)	Mild intellectual disability, prominent difficulties in expressive language and attention	Refractory partial epilepsy, onset 3 months	2 MRIs at 2 months to 2.9 years
#7 F 5.5	N540K	−1.9	Fetal alcohol exposure. At term 3,590 g, 46.5 cm (−2.1), 36.5 cm (+1.5)	Mild intellectual disability, prominent difficulties in expressive language and attention	Neonatal HSV encephalitis and apneic seizures. PB for 5 months. Seizure-free	ASD secundum operated, MRI at 5.7 years
#8 F 5.7	N540K	−3.0	IVF, cesarean H 38, 4,080 g, 49 cm (0.0), 38.5 cm (+2.5)	Poor attention. No neuropsychological evaluation.	Neonatal partial seizures, PB for 3 months. Seizure-free	MRI at age 2 weeks
#9 F 11.6	N540K	−2.1	At term, 3,520 g, 50 cm (−0.1), 35 cm (+0.2)	Mild intellectual disability, prominent difficulties in language and attention. Full-time special education	No	
#10 F13.5	N540K	−3.9	At term, 3,510 g, 48 cm (−1.2), 34.5 cm (−0.2)	Normal milestones. Difficulties in visual perception. Mainstream school, special education in maths	No	Migraine-type headaches
#11 M 15	N540K	−3.2	At term, 3,770 g, 49 cm (−0.9), 35 cm (−0.5)	Mild intellectual disability, prominent difficulties in visuospatial and visuomotor skills and attention. Full-time special education	Partial epilepsy, onset 8 months, offset 3 years. AED tapering at 5 years. Seizure-free	Strabismus. MRI at 2.6 years
#12 F 15.8	N540K	−6.2	Partial ablation, H 33+5, Apgar 4/6/7, 2,394 g, 42 cm (−2.2), 34 cm (+2.0)	Normal milestones, difficulties in visuospatial and visuoconstructive skills. Mainstream school, adjusted education in maths	No	Hydrocephalus, Chiari I malformation, syringomyelia, sensorineural hearing impairment. MRI at 15.8 years
#13 F 18	N540K	−5.6	Twin pregnancy. At term, 3,060 g, 47 cm (−1.8), 35 cm (+0.2)	Normal milestones. Mainstream school (senior high school)	No	

[a]Age at the end of the follow-up.
[b]All patients had either 1620C>A or 1620C>G, which both result in N540K substitution; BW, birth weight; OFC occipitofrontal circumference; mo, months; y, years; PB phenobarbital; AED, anti-epileptic drug.

Brain MRI Findings

Brain MRI was performed on eight patients, three had also follow-up examinations; thus altogether 12 brain MRI studies were available for analysis. The clinical indications for brain MRI examinations were seizures in five patients and disproportionate increase in head size in two patients; only one patient without neurological findings except delayed speech development at age 1.9 years had undergone screening MRI. At the time of the first MRI study the patients ranged in age from 2 weeks to 15.8 years (median 1.3 years/mean 3.4 years).

All eight patients with neuroimaging had similar symmetric structural medial temporal lobe abnormality consistent with bilateral temporal lobe dysgenesis with abnormally shaped temporal horns, aberrant hippocampal configuration, poorly formed and abnormally oriented anterior parahippocampal gyri and vertical orientation of the collateral sulci (Fig. 1; Table II). Abnormal anterior temporal lobe white matter hyperintensities on T2-weighted (Fig. 1D) or on FLAIR images and poor gray–white matter differentiation were noted in all eight patients. Reduction of peritrigonal white matter (Fig. 1G and H) was evident in six out of eight patients, and delayed myelination in anterior temporal lobes was observed in three patients. Lateral ventricles were abnormally "squared" in four, with ventricular enlargement (Fig. 1G and H) evident in two patients. Apart from one patient with a thin corpus callosum and another with a small callosal splenium and thin corpus callosum (Fig. 1F), no other supratentorial midline structure abnormalities were noted. Posterior fossa was small in two patients of whom one developed symptomatic Chiari I malformation and concomitant syringomyelia; the other had a narrow foramen magnum and on follow-up imaging increasing OFC and enlargement of the ventricular size with frontal bossing. One patient had a large posterior fossa with arachnoid cyst (Fig. 1F). Another patient with a history of both fetal alcohol exposure and neonatal herpes simplex encephalitis had microcephaly and flattening of nasal bridge consistent with fetal alcohol effects but no evidence of post-herpetic parenchymal changes on MRI (Table II). In six out of eight patients, brain MRI was initially reported as normal.

DISCUSSION

This study showed that in patients with HCH with the common N540K mutation in the *FGFR3* gene, epilepsy and neurocognitive problems are significantly more common than previously reported.

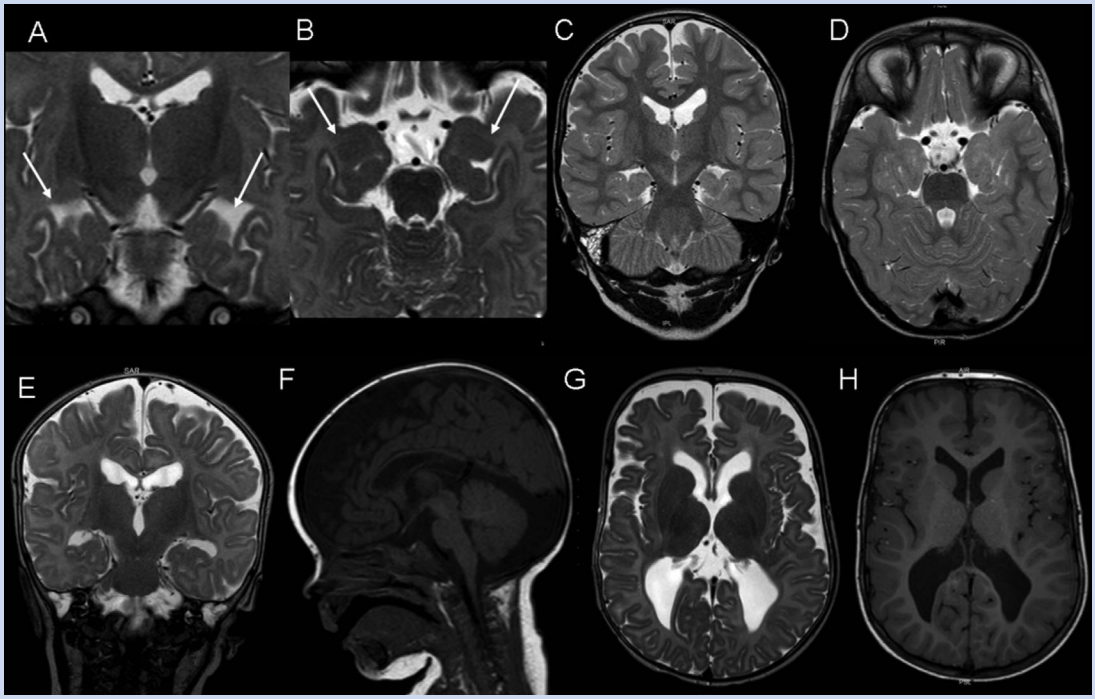

FIG. 1. Brain MRI in a patient with *FGFR3* mutation-verified hypochondroplasia. T2-weighted coronal and axial slices (A,B at age 4 months and C,D at 3 years 4 months) show symmetric bilateral temporal lobe dysgenesis (arrows) with abnormally shaped temporal horns, and aberrant hippocampal configuration with poorly formed and abnormally oriented anterior parahippocampal gyri and vertical orientation of the collateral sulci. The patient had also squared anterior horns of the lateral ventricles (C) and abnormal white matter T2 hyperintensity and poor gray–white matter differentiation in anterior and mesial temporal lobes (D). Another *FGFR3* mutation verified patient had a similar temporal lobe dysgenesis (E; T2-weighted coronal image at age 7 months) and abnormal anterior and mesial temporal lobe white matter signal intensity (not shown) but also mild callosal dysgenesis with a small splenium and thinning of corpus callosum, and an arachnoid cyst in the posterior fossa (F; T1-weighted sagittal image at age 7 months). The lateral ventricles were squared and enlarged and peritrigonal white matter was reduced (G; T2-weighted axial image at age 7 months and H; T1-weighted axial image at age 3 years).

TABLE II. Brain MRI Findings of Eight Patients With Hypochondroplasia

Patient #	Age at MRI (years)	Temporal lobe structures	Abnormal temporal lobe WM signal	Peritrigonal WM reduction	Lateral ventricles; size, shape	Corpus callosum	Posterior fossa size, foramen magnum	Other findings
#2	1.9	TD	+	–	N	N	N	
#4	0.4	TD	+	+	Squared	N	N	
	1.3	TD	+	+	Squared	N	N	Frontal bossing
	3.4	TD	+, Myelination delay	+	Squared	N	N	Frontal bossing
#5	0.7	TD[a]	+	++	Squared, enlarged	Small splenium, thin	Large+ arachnoid cyst	
	3.0	TD	+	++(+)	Squared, enlarged		Large+ arachnoid cyst	Frontal bossing
#6	0.15	TD[a]	+	+	N	Thin	N, narrow FM	
	2.9	TD	+, Myelination delay	++	Squared, enlarged	Thin	Small, narrow FM	Frontal bossing
#7	5.7	TD[a]	+/–	+	N	N	N	Microcephaly + flattening of nasal bridge
#8	0.02	TD[a]	+/–	no	N	N	N	
#11	2.6	TD[a]	+, Myelination delay	++	N	N	N	
#12	15.8	TD[a]	(+)	+	Squared	N	Small, Chiari I operata	Syringomyelia

MRI, magnetic resonance imaging; WM, white matter; TD, temporal lobe dysgenesis including abnormal hippocampal formation and irregular shape of temporal horns;
[a]Unreported at initial interpretation by radiologist in other institution; FM, foramen magnum; N, normal.

In addition, all patients with brain MRI available had similar structural aberrations in temporal lobes consistent with temporal lobe dysgenesis suggesting that this brain malformation is intrinsic to the N540K mutation.

Cognitive Problems in HCH

Hall and Spranger [1979] reviewed medical history of HCH patients and reported mental deficiency in 9% (3/32) of them. In a later study, no cases of intellectual disability among 27 patients with familial or sporadic HCH were observed [Wynne-Davies and Patton, 1991]. Of the four previously reported *FGFR3* mutation-verified HCH patients with temporal lobe dysgenesis, one had delayed speech at 2 years and one was globally delayed and autistic [Grosso et al., 2003; Kannu et al., 2005; Kannu and Aftimos, 2007].

Six of our 13 patients had either global developmental delay or intellectual disability. Even if one child with contributory fetal alcohol exposure and neonatal herpes simplex encephalitis is excluded, severe neurodevelopmental problems were evident in 42% of patients. Typically, these patients had prominent problems in expressive language and in attention. In addition, two patients with normal general intelligence had a specific learning disorder and needed special educational support at mainstream school. These findings highlight the need for neurodevelopmental follow-up in children with hypochondroplasia.

Epilepsy in HCH

HCH has generally not been considered to associate with epileptic seizures, although previous case reports have described this association in a few children with temporal lobe dysgenesis [Grosso et al., 2003; Kannu et al., 2005; Kannu and Aftimos, 2007]. In our study cohort, however, 6 of 13 children had a history of seizures and in one half of them a diagnosis of partial epilepsy was established. The semiology of seizures—hypomotor seizures with apnea in early infancy and psychomotor seizures later in childhood—was similar in all patients and is consistent with mesial temporal lobe origin. Although seizures responded poorly to AEDs during the first years of life, most patients had remission of epilepsy by school-age.

Temporal Lobe Dysgenesis in HCH

In the present study, all HCH patients with neuroimaging available, showed anterior and mesial temporal lobe dysgenesis similar to the previously described four patients with *FGFR3* N540K mutations. The MRI pattern seems to be quite uniform; it comprises bilateral aberrant hippocampal and parahippocampal configuration and gyration, abnormal shape of temporal horns, and abnormal gray–white matter differentiation and white matter changes in mesial and anterior poles of temporal lobes. In addition, half of the patients had abnormally squared lateral ventricles and the majority (6/8), had evidence of more general peritrigonal white matter reduction which has not been described previously. The patients in our cohort and in previous case reports were imaged with clinical indications and thus, the prevalence of temporal lobe dysgenesis in neurologically

intact patients remains unknown. Furthermore, as all described patients with temporal lobe dysgenesis had similar recurrent mutations leading to N540K substitution, it is currently unknown whether other less frequent mutations associated with HCH present with similar structural brain abnormalities.

FGFR3 Mutant Mice

Fibroblast growth factors (FGFs) are a family of polypeptides known to have diverse functions in the control of cell proliferation, differentiation, and migration. FGF signals are mediated by high-affinity receptor tyrosine kinases, FGF receptors (FGFRs). [Iwata and Hevner, 2009]. *FGFR3* is expressed in the brain during embryogenesis [Peters et al., 1993; Walshe and Mason, 2000; Reimers et al., 2001; Sleptsova-Friedrich et al., 2001]. The exact role of *FGFR3* in brain development has been uncertain. In mice, its expression is high during development in the rhinal and piriform cortices (which correspond to anterior parahippocampal gyrus in humans), hippocampus, amygdala, and striatum. Therefore, it is postulated to play a role in the formation of these structures. Indeed, *Fgfr3* knockout (*Fgfr3*$^{-/-}$) mice have reduction in volume of the cerebral cortex and the hippocampus [Moldrich et al., 2011]. The exact effects of activating N540K mutations on FGFR3 function have not yet been established.

Other FGFR3 Disorders and Brain

Hypochondroplasia, achondroplasia (Gly380Arg), and thanatophoric dysplasia (Lys650Glu) are allelic disorders, caused by different activating mutations in the *FGFR3* gene. *FGFR3* mutations can also result in severe achondroplasia with developmental delay and acanthosis nigrans (SADDAN, Lys650Met) and in two craniosynostosis syndromes: Muencke coronal craniosynostosis and Crouzon syndrome with acanthosis nigrans [Vajo et al., 2000]. These disorders present with skeletal abnormalities of variable location and severity. Involvement of central nervous system is also variable. In ACH, children have generally average cognitive abilities, but may have mild deficits in visuo-spatial skills, probably caused by effects of hydrocephalus. In thanatophoric dysplasia, fetuses have severe brain malformation which predominantly involves temporal lobes; malformation consists of megalencephaly, abnormal sulcation of the temporal lobes, and dysplastic hippocampi. Histopathologic examination shows evidence of disorganization of the hippocampus, polymicrogyria-like pattern of the lateral temporal neocortex, and subependymal heterotopia. [Hevner, 2005; Miller et al., 2009]. Hippocampal dysgenesis of similar appearance to that seen in HCH has been reported in one patient with Muenke coronal synostosis syndrome, [Grosso et al., 2003] but not in achondroplasia or in SADDAN.

Study Limitations

This study has some limitations. First, it was performed in a retrospective nature and had a relatively small sample size despite the fact that nearly all (13/14) mutation-verified pediatric patients followed at our national center were included. Secondly, there was certain ascertainment bias, because MRI was performed only on clinical indication, and therefore it is uncertain whether neurologically intact patients or patients with only mild neurodevelopmental disorders also have the same structural abnormality. Thirdly, our cohort consisted only of patients with common HCH-associated *FGFR3* mutations resulting in N540K substitution. Whether the HCH patients with less common mutations have the similar temporal lobe dysgenesis remains to be elucidated in future studies.

CONCLUSIONS

We conclude that cognitive problems are common in patients with HCH and N540K *FGFR3* mutations and the development of these patients needs to be followed carefully to provide necessary support as early as possible. In this study, a uniform pattern of temporal lobe dysgenesis was seen in all patients who had undergone brain MRI. This temporal lobe dysgenesis may predispose to epileptic seizures. We recommend a low threshold for neuroimaging in patients with HCH.

ACKNOWLEDGMENTS

We thank Dr. Tuula Lönnqvist for critical reading of the manuscript.

REFERENCES

Bellus GA, McIntosh I, Smith EA, Aylsworth AS, Kaitila I, Horton WA, Greenhaw GA, Hecht JT, Francomano CA. 1995. A recurrent mutation in the tyrosine kinase domain of fibroblast growth factor receptor 3 causes hypochondroplasia. Nat Genet 10:357–359.

Bellus GA, Spector EB, Speiser PW, Weaver CA, Garber AT, Bryke CR, Israel J, Rosengren SS, Webster MK, Donoghue DJ, Francomano CA. 2000. Distinct missense mutations of the FGFR3 lys650 codon modulate receptor kinase activation and the severity of the skeletal dysplasia phenotype. Am J Hum Genet 67:1411–1421.

Grosso S, Farnetani MA, Berardi R, Bartalini G, Carpentieri M, Galluzzi P, Mostardini R, Morgese G, Balestri P. 2003. Medial temporal lobe dysgenesis in Muenke syndrome and hypochondroplasia. Am J Med Genet A 120:88–91.

Hall BD, Spranger J. 1979. Hypochondroplasia: Clinical and radiological aspects in 39 cases. Radiology 133:95–100.

Hevner RF. 2005. The cerebral cortex malformation in thanatophoric dysplasia: Neuropathology and pathogenesis. Acta Neuropathol (Berl) 110:208–221.

Iwata T, Hevner RF. 2009. Fibroblast growth factor signaling in development of the cerebral cortex. Dev Growth Differ 51:299–323.

Kannu P, Aftimos S. 2007. FGFR3 mutations and medial temporal lobe dysgenesis. J Child Neurol 22:211–213.

Kannu P, Hayes IM, Mandelstam S, Donnan L, Savarirayan R. 2005. Medial temporal lobe dysgenesis in hypochondroplasia. Am J Med Genet A 138:389–391.

Miller E, Blaser S, Shannon P, Widjaja E. 2009. Brain and bone abnormalities of thanatophoric dwarfism. AJR Am J Roentgenol 192:48–51.

Moldrich RX, Mezzera C, Holmes WM, Goda S, Brookfield SJ, Rankin AJ, Barr E, Kurniawan N, Dewar D, Richards LJ, Lopez-Bendito G, Iwata T. 2011. Fgfr3 regulates development of the caudal telencephalon. Dev Dyn 240:1586–1599.

Peters K, Ornitz D, Werner S, Williams L. 1993. Unique expression pattern of the FGF receptor 3 gene during mouse organogenesis. Dev Biol 155: 423–430.

Prinos P, Costa T, Sommer A, Kilpatrick MW, Tsipouras P. 1995. A common FGFR3 gene mutation in hypochondroplasia. Hum Mol Genet 4:2097–2101.

Reimers D, Lopez-Toledano MA, Mason I, Cuevas P, Redondo C, Herranz AS, Lobo MV, Bazan E. 2001. Developmental expression of fibroblast growth factor (FGF) receptors in neural stem cell progeny. Modulation of neuronal and glial lineages by basic FGF treatment. Neurol Res 23: 612–621.

Sleptsova-Friedrich I, Li Y, Emelyanov A, Ekker M, Korzh V, Ge R. 2001. Fgfr3 and regionalization of anterior neural tube in zebrafish. Mech Dev 102:213–217.

Spranger J, Brill P, Poznanski A. 2002. Hypochondroplasia. In: Spranger J, Brill P, Poznanski A, editors. Bone dysplasia. An atlas of genetic disorders of skeletal development. New York: Oxford University Press Inc. pp 90–94.

Vajo Z, Francomano CA, Wilkin DJ. 2000. The molecular and genetic basis of fibroblast growth factor receptor 3 disorders: The achondroplasia family of skeletal dysplasias, Muenke craniosynostosis, and Crouzon syndrome with acanthosis nigricans. Endocr Rev 21: 23–39.

Walshe J, Mason I. 2000. Expression of FGFR1, FGFR2 and FGFR3 during early neural development in the chick embryo. Mech Dev 90:103–110.

Wynne-Davies R, Patton MA. 1991. The frequency of mental retardation in hypochondroplasia. J Med Genet 28:644.