American Journal of Medical Genetics 110:380–383 (2002)

Clinical Report

Possible Third Case of Lin-Gettig Syndrome

Peter Hedera[1] and Jeffrey W. Innis[1,2]*

[1]*Department of Pediatrics, Division of Genetics, University of Michigan, Ann Arbor, Michigan*
[2]*Department of Human Genetics, University of Michigan, Ann Arbor, Michigan*

We report a patient with craniosynostosis, severe mental retardation, absence of the corpus callosum, camptodactyly, hypogonadism, and ventricular septal defect. We propose that he has Lin-Gettig syndrome and that he is the third reported patient with this entity. Our patient also had additional phenotypic features, including palatal cleft and absent rapid eye movement (REM) sleep that were not present in the two previously described patients with this syndrome. High-resolution karyotype and subtelomeric fluorescence in situ hybridization (FISH) for cryptic telomeric rearrangement were normal. The existence of an unrelated patient with Lin-Gettig syndrome supports that this is a separate and distinct clinical entity.

KEY WORDS: Lin-Gettig syndrome; mental retardation; craniosynostosis; REM sleep

INTRODUCTION

Two siblings with craniosynostosis, agenesis of the corpus callosum, severe mental retardation, distinctive facies, camptodactyly, and hypogonadism were reported in 1990 [Lin and Gettig, 1990]. This constellation of phenotypic features was unique and a new clinical entity, designated as Lin-Gettig syndrome (LGS; MIM 218649), was suggested. No additional cases have been reported since the first description of this novel syndrome. We report a male patient with a clinical picture similar to two previously reported cases with LGS. We propose that the phenotype of our patient is consistent with LGS. We also describe additional clinical features not present in the two previous patients.

CLINICAL REPORT

The patient was a full-term male born to a 26-year-old gravida 4, para 2 mother. The pregnancy was unremarkable with the exception of a maternal report of reduced fetal movements during the last month. His birth weight was 3,120 g (50th centile), length was 48 cm (75th centile), and head circumference was 35.5 cm (50th centile). He was hypotonic and multiple congenital anomalies were noticed, including a pointed occiput, prominent forehead, palatal cleft, stenosis of the external auditory canals, beaked nose, congenital contractures of hands, and undescended testes. Craniosynostosis of both lambdoid and sagittal sutures was diagnosed by computed tomography (CT), and subsequent brain magnetic resonance imaging (MRI) also demonstrated complete agenesis of the corpus callosum and Chiari I malformation. The patient developed signs of increased intracranial pressure and restrictive microcephaly at age one year, with head circumference falling to the fifth centile. He underwent decompression of the posterior fossa and reconstruction of the cranial vault in relation to the lambdoid and sagittal synostoses at age 13 months; additional surgeries included palatal cleft repair and gastric tube placement because of persisting feeding difficulties.

The patient had delayed acquisition of major milestones. He was able to sit independently at age two years and started to crawl two years later; at age six years he could not walk independently but was able to make a few steps with a walker. The patient remained non-verbal and did not show any evidence of comprehension at age six years. Repeated hearing tests showed stable, profound sensorineural hearing loss bilaterally. The patient was described as a happy child but had a very irregular sleep-wake cycle. A polysomnogram at age three years did not detect any rapid eye movement (REM) sleep during one night study; no epileptiform activity was observed.

Both parents were healthy and no consanguinity was reported. The patient had an older brother who was healthy and developed normally. The first pregnancy was electively terminated and the patient's mother had

*Correspondence to: Jeffrey W. Innis, Department of Human Genetics, 4811 Med Sciences II, Box 0618, 1500 E. Medical Center Drive, Ann Arbor, MI 48109-0618. E-mail: innis@umich.edu

Received 23 March 2001; Accepted 21 February 2002
DOI 10.1002/ajmg.10460

also had one miscarriage in the first trimester. The rest of the extended family history was unremarkable and noncontributory.

Physical examination at age five years revealed a height of 112 cm (75th centile), weight of 18.1 kg (50th centile), and head circumference of 49 cm (5th centile). The head was turricephalic with a prominent forehead and a flat occiput (Fig. 1 top). Ridging was observed along the sagittal suture. His palpebral fissures were small (2.5 cm; $<$ 5th centile) with bilateral ptosis; no slanting or epicanthal folds were present. The inner canthal distance was 3.8 cm ($>$ 95th centile), outer canthal distance was 8.8 cm (50th centile), and interpupilary distance was 6.2 cm ($>$ 95th centile). His nose was beak-shaped with mildly hypoplastic alae nasi. Both ears were low set and small (4.5 cm; $<$ 5th centile), and he had stenotic external auditory canals bilaterally. Other facial abnormalities included mild micrognathia and a small mouth and chin. The chest was narrow with low set nipples and a right accessory nipple; he had a mild pectus excavatum (Fig. 1 bottom). Auscultation revealed a IV/VI parasternal murmur without propagation. The right trapezoid muscle was hypertrophied. Examination of the abdomen demonstrated a small umbilical hernia. He had a hemangioma measuring 2.4×1.5 cm in the left upper abdominal quadrant. He had male genitalia, absent testes, a hypoplastic scrotum, and small penis; no hypospadias was present. The anus was placed normally. Examination of his extremities revealed limited supination of both elbows, more prominently on the left side. He had extension contractures of the interphalangeal joints of both thumbs, and camptodactyly of fingers two to five, with flexion contractures of the proximal interphalangeal joints. Bilateral hallux valgus was also present. Neurological examination was noticeable for gaze-evoked nystagmus bilaterally, diffusely increased muscle tone with more spasticity in the lower extremities, and significant axial ataxia with retropulsions. He could not stand or walk independently.

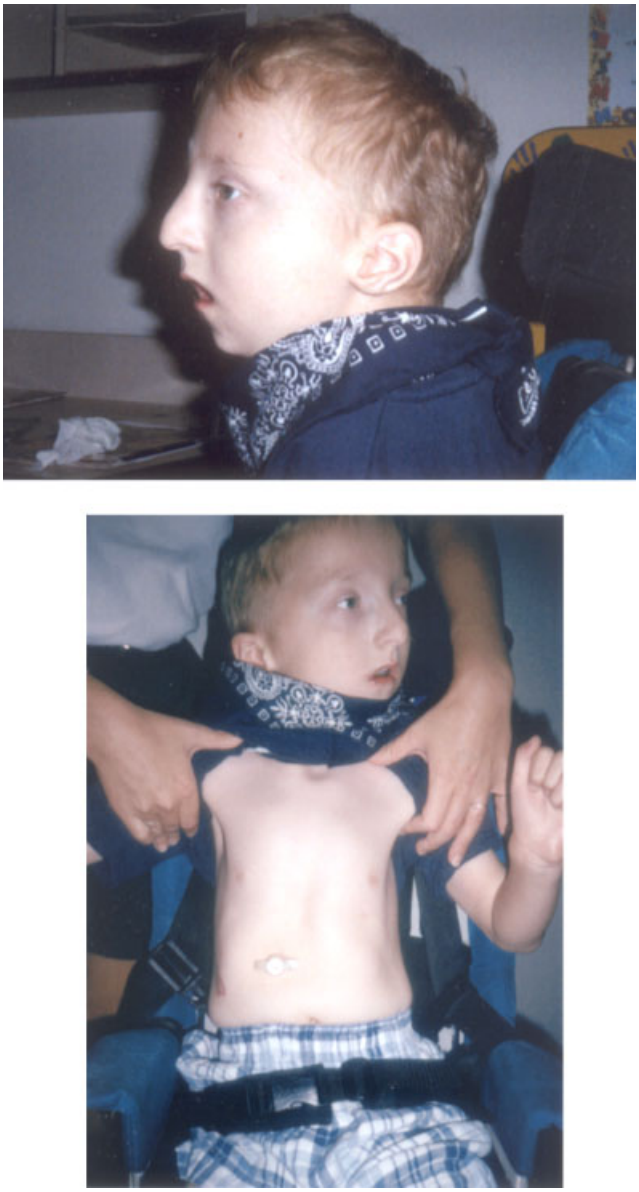

Fig. 1. Top: Photograph of the patient showing prominent forehead, small occiput, beaked nose, and a small chin. Bottom: Photograph of the patient showing a small thorax with wide-spaced nipples.

Cytogenetic evaluation using a routine 350–400 band resolution and a prometaphase study with 750–850 band resolution were normal with a male 46,XY chromosomal constitution. Fluorescence in situ hybridization (FISH) using a subtelomeric DNA probe panel (TelVision, Vysis, Downers Grove, IL) performed at Boston University did not detect cryptic telomeric rearrangement or deletion. Renal ultrasound was normal and testes were not detected in the scrotum, inguinal canal, or in the pelvis.

DISCUSSION

We report a male who shares striking similarities with the two known LGS patients (Table I). We propose that our patient's condition is consistent with LGS and that he is the third known patient with this syndrome. Craniosynostosis, severe mental retardation, absence of the corpus callosum, camptodactyly, stenosis of the external auditory canal with hearing loss, cryptorchidism with hypogonadism, and ventricular septal defect appear to be cardinal features of the syndrome, as they were present in all affected patients. However, we also identified some phenotypic differences. Our patient did not have hypospadias, which was present in both brothers in the original report. He also did not have significant gastrointestinal (GI) structural abnormalities, and our patient's dysphagia was due to neurological dysfunction; however, he had a small umbilical hernia similar to subject LB. Furthermore, the postnatal height and weight growth of our patient were normal, while the two previously reported patients had short stature and failure to thrive. The absence of these features in our patient suggests that they are not constant features of LGS. Significant phenotypic differences have also been noticed between the two siblings

TABLE I. Phenotypic Features of the Two Previously Reported Patients With Lin-Gettig Syndrome (LB and GB), Our Patient and Typical Characteristics of C (Opitz Trigonocephaly) and FG (Opitz-Kaveggia) Syndromes

Feature	LB	GB	Present case	C syndrome	FG syndrome
Gestation	42 weeks	42 weeks	42 weeks	N/A	N/A
Birth weight	45th centile	45th centile	50th centile	Normal	Normal
Birth length	90th centile	75th centile	75th centile	Normal	Normal
Birth HC	> 95th centile	50th centile	50th centile	Normal	Normal
Present/PN weight	10th centile	< 5th centile	50th centile	FTT	Normal
Present/PN height	10th centile	< 5th centile	75th centile	Short stature	Short stature
Present/PN HC	75th centile	15th centile	5th centile	Microcephaly	Macrocephaly
MR	+ (severe)	+ (severe)	+ (severe)	+ (severe)	+ (moderate)
Absent REM sleep	?	?	+	−	−
Craniosynostosis	+ sagittal	+ metopic	+ lambdoid, sagittal	+ metopic	± (very rare)
Agenesis CC	+	+	+	± (very rare)	± (partial)
Abnormal muscle tone	+ (hypertonia)	+ (hypertonia)	+ (hypotonia, later hypertonic)	+ (hypotonia)	+ (hypotonia)
Contractures	+ congenital	+ acquired	+ congenital (thumbs)	± (rare)	− (increased laxity)
Ears	Small, low set	Small, low set	Small, low set	Posteriorly rotated	Small, low set
Stenosis of EAC	+	+	+	−	± (rare)
Hearing loss	Possible	?	+ (SN)	± (rare SN)	± (rare SN)
Ptosis	+	−	+	−	−
Small palpebral fissures	+	+	+	− (upslanting)	− (downslanting)
Eye position	Hypertelorism	Hypotelorism	Hypertelorism	Hypotelorism	Hypertelorism
Epicanthal folds	+	+	−	+	+
Thin lips	+	+	+	−	− (prominent lips)
Nose	Small	Small	Small, beak-like	Hypoplastic root	Unremarkable
Short columella	+	+	+	−	−
Palatal abnormalities	−	−	+ (cleft)	+ (Midline furrow)	± (rare cleft)
Micrognathia	+	+	+	+	−
Congenital heart defect	+ (probably VSD)	+ (Murmur)	+ (VSD)	+	−
Chest	Wide-spaced nipples Pectus carinatum	−	Wide-spaced nipples Pectus excavatum	Normal	Normal
Hemangioma	+ (glabellar)	+ (glabellar)	+ (upper abdomen)	+	−
GI malformation	+ (small omphalocele)	+ (bowel atresia)	− (G tube due to reflux)	± (omphalocele)	+ (anal abnormalities)
GU malformation	+ (hydro-nephrosis)	+ (hydro-nephrosis)	+ (hydro-nephrosis)	± (renal agenesis)	± (hydro-nephrosis)
Hypospadias	+ (3rd degree)	+ (3rd degree)	−	+ (1st, 2nd degree)	± (rare)
Cryptorchidism	+	+	+	+	±
Micropenis	+	+	+	+	−
Fingers	Long, slender	Long, slender	Long, slender	Postaxial polydactyly	Broad thumbs
Camptodactyly	+	+	+	−	−

+, present; −, absent; ±, present in some patients, not a constant feature; ?, unknown; FTT, failure to thrive; PN, postnatal; HC, head circumference; MR, mental retardation; CC, corpus callosum; EAC, external auditory canal; SN, sensorineural hearing loss; VSD, ventricular septal defect.

from the first report of this condition. Moreover, palatal cleft, present in our patient, was a unique physical finding not reported in the two original cases.

Synostosis of different cranial sutures was detected in all three known cases of LGS. Thus, it appears that a premature suture closure is a constant feature of this syndrome. This may also account for facial differences in patients with LGS. The second case (GB) from the original report by Lin and Gettig [1990] had a metopic craniosynostosis with resulting trigonocephaly and hypotelorism, resembling Opitz-C syndrome [Antley et al., 1981] (Table I). Our patient resembled the subject LB, who had sagittal craniosynostosis, hypertelorism, and ptosis. Our patient was diagnosed with FG syndrome at an outside institution before his visit with us. We suspect that their diagnosis was based on a broad and tall forehead and neonatal hypotonia. However, he did not have anal abnormalities or constipation, and he had congenital camptodactyly, rather than increased joint laxity, with later development of joint contractures [Opitz et al., 1988]. Craniosynostosis and the degree of mental retardation with absent expressive and comprehensive language are not common features of FG syndrome [Graham et al., 1999]. Based on these phenotypic differences, we do not think that our patient's clinical picture is consistent with FG syndrome (Table I). Chiari malformation I with prominent cerebellar signs (gaze-evoked nystagmus, truncal ataxia) may have been caused by the underdevelopment of the hindbrain as a result of posterior fossa crowding due to lambdoid suture synostosis.

Our patient had a disrupted sleep-wake cycle, and a sleep study was performed at age three years. The polysomnogram did not detect any REM sleep, but his

sleep architecture was otherwise preserved. The absence of REM sleep does not correlate with the degree of mental retardation, and patients with otherwise severe mental retardation are capable of REM stage sleep [Elia et al., 2000]. Significant reduction or absence of REM sleep occurs in 75% of patients with Smith-Magenis syndrome (SMS) [Greenberg et al., 1996]. We did not perform a FISH study to exclude an interstitial deletion of 17p11.2 as observed in SMS; however, the clinical features of LGS and SMS are very different, making it unlikely that this chromosomal region is involved in LGS. The genetic factors affecting the REM stage of sleep are not characterized, although the short arm of chromosome 17 was suggested as a candidate region containing the gene controlling this phase of a sleep cycle [Tandan et al., 1990]. It would be interesting to know whether the other two LGS patients had disruption of REM sleep. Characterization of the molecular basis of LGS may provide additional insight into the genetic control of REM sleep.

In the presence of multiple congenital anomalies, it is prudent to consider a contiguous gene deletion syndrome. However, a high-resolution karyotype and subtelomeric FISH studies on our patient did not detect any chromosomal rearrangements. The two previously reported brothers with the same condition also had normal cytogenetic studies. Two affected offspring born to healthy parents suggested autosomal recessive mode of inheritance in the original report of LGS. Our patient was an isolated case born to unrelated parents and we cannot provide additional insight into the mode of inheritance. However, it is intriguing that all three cases with suggested LGS were males. Therefore, an X-linked mode of inheritance cannot be excluded.

ACKNOWLEDGMENT

We thank Dr. Angela E. Lin for review of the case and helpful comments.

REFERENCES

Antley RM, Hwang DS, Theopold W, Gorlin RJ. 1981. Further delineation of the C (trigonocephaly) syndrome. Am J Med Genet 9:147–163.

Elia M, Ferri R, Musumeci SA, DelGracco S, Bottitta M, Scuderi C, Miano G, Panerai S, Bertrand T, Grubar JC. 2000. Sleep in subjects with autistic disorder: a neuropsychological and sleep study. Brain Develop 22: 88–92.

Graham JM Jr, Superneau D, Rogers RC, Corning K, Schwartz CE, Dykens EM. 1999. Clinical and behavioral characteristics in FG syndrome. Am J Med Genet 85:470–475.

Greenberg F, Lewis RA, Potocki L, Glaze D, Parke J, Killian J, Murphy MA, Williamson D, Brown F, Dutton R, McCluggage C, Friedman E, Sulek M, Lupski JR. 1996. Multi-disciplinary clinical study of Smith-Magenis syndrome (deletion 17p11.2). Am J Med Genet 62:247–254.

Lin AE, Gettig E. 1990. Craniosynostosis, agenesis of the corpus callosum, severe mental retardation, distinctive facies, camptodactyly, and hypogonadism. Am J Med Genet 35:582–585.

Opitz JM, Richieri-da Costa A, Aase JM, Benke PJ. 1988. FG syndrome update 1988: note of 5 new patients and bibliography. Am J Med Genet 30:309–328.

Tandan R, Taylor R, Adesina A, Sharma K, Fries T, Pendlebury W. 1990. Benign autosomal dominant syndrome of neuronal Charcot-Marie-Tooth disease, ptosis, parkinsonism, and dementia. Neurology 40:773–779.