Case Report

Two novel features in Lin-Gettig Syndrome: Double nuchal fold and nail hypoplasia

Sultan Kaba*, Murat Dogan, Keziban Bulan, Selami Kocaman, Serap Kılıç Karaman

Department of Pediatrics, Division of Pediatric Endocrinology, School of Medicine, Yuzuncu Yil University, Van, Turkey

Abstract. We presented two brothers with craniosynostosis, severe mental retardation, atypical facial appearance, camptodactyly and hypogonadism. In the literature, Lin-Gettig syndrome has been identified in 3 patients so far. To date, only one novel case was reported in 2002 since 1990 when Lin-Gettig syndrome was first identified. These cases have diverse characteristics. The patient who presented with growth failure and his brother with similar clinical characteristics who recently died were considered as compatible with Lin-Gettig syndrome. In addition, our cases have differential clinical characteristics compared to all previous 3 cases in some degree and double nuchal fold and nail hypoplasia were novel features. We will discuss these cases as it is an extremely rare entity.

Key words: Lin-Gettig syndrome, craniosynostosis, hypogonadism, growth failure

1. Introduction

The clinical characteristics of the cases reported by Lin and Gettig included midline craniosynostosis, corpus callosum agenesis, severe mental retardation, atypical facial appearance, contractures, camptodactyly, hypospadias, hypogonadism and gastrointestinal malformation such as small omphalocele and multiple small bowel atresia. The atypical facial features of 2 brothers reported by authors included small downslanting palpebral fissures, ptosis, strabismus, long hypoplastic philtrum, short columetitilla and thin lips (1). While no other case had been reported compatible with these cases until 2002, Hedera and Innis (2) reported a boy having clinical characteristics reported by Lin and Gettig. There were variations in clinical characteristics of these previously reported cases. Additionally, there was cleft palate in the most recent case but there was no gastrointestinal malformation and weight and height were within normal range of percentiles.

*Correspondence: Dr. Sultan Kaba
Department of Pediatrics, Division of Pediatric Endocrinology, School of Medicine, Yuzuncu Yil University, Van 65100, Turkey
Tel: 0533 495 02 94
E-mail: sultan33kaba@hotmail.com
Received: 20.07.2013
Accepted: 22.07.2013

2. Case report

The patient (a boy) was 1 year and 23 days old when he was referred to endocrinology outpatient clinic with growth and neurodevelopmental retardation since birth, hypotonia in whole body and failure in growth of head. The body weight was found as 8kg (-2.5 SDS), while height as 59 cm (-7.2 SDS) and head circumference as 34.7 (-10.3 SDS). He was born at term via vaginal route with a birth weight of 2400g as the sixth child of his parents (father 34 and mother 30 years old) who had consanguinity (first-degree cousins). He had 3 healthy siblings; however, he also had a history of two brothers who died at 2 years of age (with similar clinical features with index case) and 4 days of age (sudden infant death syndrome). There was no available information about weight and head circumference at birth. The body weight of the patient with short stature and obese appearance was estimated as 163% of ideal body weight relative to height. There was an atypical facial appearance including microcephaly, trigonocephaly, double nuchal fold, bilateral auricular malformation, short neck, flat nasal bridge, prominent philtrum and downslanting palpebral fissures, ptosis, blepharophimosis (Figure 1,2). There was also cleft palate and micrognathia. Chest was normal. In the examination of extremities, there was camptodactyly and hypoplasia at toenails. There was no limitation of movement in other joints. On

bone survey radiographs, no osseous anomaly was observed other than craniosynostosis. There was no hemangioma or café-au-lait spots at skin. External genitalia had an appearance of a male, but testicles are non-palpable and there was micro-penis and scrotal hypoplasia (Figure 3). On pelvic MR imaging, testicles were observed at the localization of inguinal canal. Caryotype was 46 XY. Anal examination was normal. There was decreased muscular tone and no head control.

Complete blood count, liver and kidney functions, thyroid functions were within normal range according to age. Follicle stimulating hormone (FSH), luteinizing hormone (LH) and growth hormone were found to be low according to age.

On the brain CT scan, it was seen that lambdoid sutures, posterior part of sagittal suture, lateral parts of coronal suture and metopic suture were closed. On the brain MR imaging, there was corpus callosum dysgenesis and cleft palate as well as polymicogri and delayed myelinization. No anomaly was observed on abdominal sonography. On echocardiography, no defect was observed other than patent foramen ovale. On pelvic MR imaging, testicles were found to be at inguinal canal.

3. Discussion

In our case, facial appearance included trigonocephaly, double nuchal fold, auricular malformation, microphthalmia, downslanting palpebral fissures, blepharophimosis, ptosis, flat nasal bridge and prominent philtrum. Moreover, there was hypoplastic scrotum, cryptorchidism, micro-penis, camptodactyly, short stature and obesity. The patient also had cleft palate. The mother could feed the patient with small amounts of food by frequent intervals. On imaging studies, there was no gastrointestinal malformation or urinary anomaly. It was found that the brother of the patient who died at 2 years of age had similar clinical features based on the parents' expressions and photographs. Differently, the brother had hypertelorism and convulsion at 4 months of age with spike wave paroxysm at bilateral fronto-centro-temporal regions. Thus, the brother of the patient had received phenobarbital therapy. While our case had corpus callosum dysgenesis, the brother had had normal MR imaging. In addition, our case had craniosynostosis at lambdoid suture, posterior part of sagittal sutures, lateral parts of coronal suture and metopic sutures while only metopic and lambdoid sutures had been involved in his brother on brain CT scan.

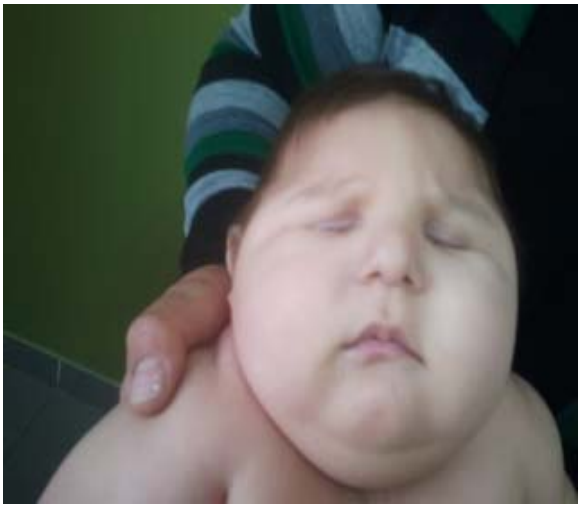

Fig. 1. Microcephaly, trigonocephaly, flat nasal bridge, prominent philtrum and downslanting palpebral fissures, ptosis, blepharophimosis.

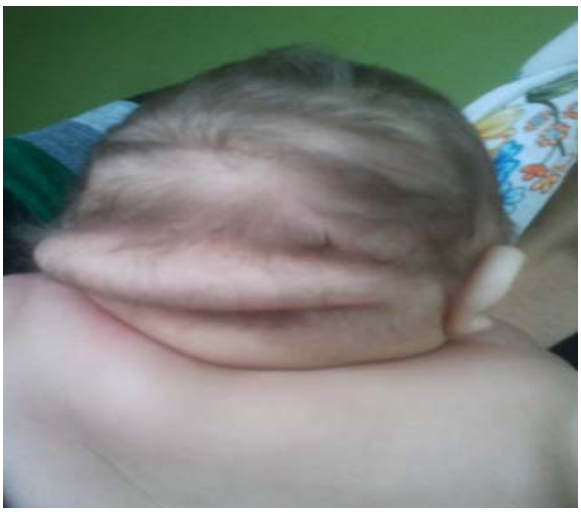

Fig. 2. Double nuchal fold, auricular malformation, short neck, microcephaly, trigonocephaly

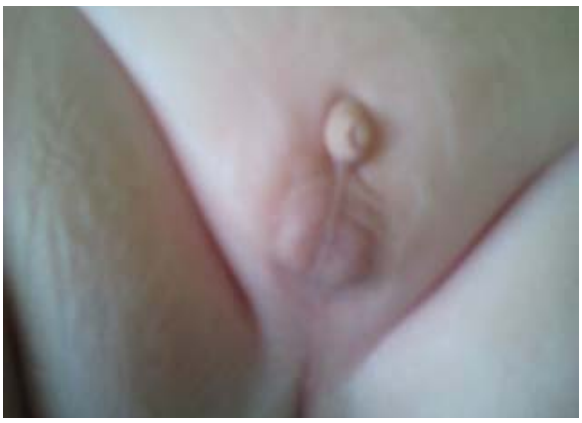

Fig. 3. Micro-penis and scrotal hypoplasia.

In the differential diagnosis, Greig cephalopolysyndactyly syndrome, Shprintzen-Goldberg syndrome, Jacobsen syndrome and Opitz-Kaveggia syndrome were take into account as all these syndromes has association of craniosynostosis and atypical facial appearance.

Trigonocephaly and corpus callosum agenesis have been also reported in Greig cephalopolysyndactyly syndrome (GCS) (3). GCS phenotype shows variable expressivity and can also include craniosynostosis but affected individuals usually have normal psychomotor development. However, characteristic features of GCS such as frontal bossing, scaphocephaly, hypertelorism associated with pre- and postaxial polydactyly and variable syndactyly were not present in our case, but there was retardation in psychomotor development (4).

Shprintzen-Goldberg syndrome (SGS) is one of the syndromes which are associated with microcephaly, craniosynostosis, camptodactyly and typical facial appearance. It is a disorder comprising craniosynostosis, a marfanoid habitus, and skeletal, neurologic, cardiovascular, and connective tissue anomalies. It is obvious that our case isn't compatible with SGS as he had short stature (5).

The cases with Jacobsen syndrome (JS) also have growth failure and typical facial appearance; however, these cases also have abnormal platelet function, thrombocytopenia or pancytopenia which are usually present at birth. In our case, complete blood count was normal and skeletal malformations were absent (6). Hypogonadism isn't a common feature in JS and iris, choroid, and retina colobomata frequently seen in JS were not present in our case (7); thus, it should be suggested that our case was rather different than JS.

Opitz Kaveggia syndrome (OKS) has characteristic features including relative macrocephaly, hypertelorism, downslanting palpebral fissures, prominent forehead with frontal hair upsweep, and broad thumbs and halluces. Most cases of OKS have hypotonia, constipation, and partial agenesis of the corpus callosum (8). The craniosynostosis, cryptorchidism and micro-penis have been rarely reported in OKS (9,10). In this syndrome, macrocephaly is one of the most commonly seen features (8) and constipation, with or without anal anomalies, is a distinctive major finding of FG syndrome (11).

Our case could be conveniently distinguished from OKS due to the lack of prominent forehead with frontal hair upsweep, presence of microcephaly rather than macrocephaly, lack of constipation, hypogonadism and craniosynostosis.

Based on above-mentioned features, Greig cephalopolysyndactyly syndrome (GCS), Shprintzen-Goldberg syndrome (SGS), Jacobsen syndrome (JS), and Opitz-Kaveggia Syndrome (OKS) were excluded in our case.

Both siblings had atypical facial appearance including microcephaly, craniosynostosis, hypogonadism, hypotonia, growth failure, trigonocephaly, double nuchal fold, bilateral auricular malformation, flat nasal bridge, prominent philtrum and ocular dysmorphism. These findings were compared with Lin-Gettig syndrome. The shared features with the first cases reported by Lin-Gettig (1) and the following case reported by Hedera-Innis (2) were craniosynostosis, mental retardation, small downslanting palpebral fissures, camptodactyly, cryptorchidism, micro-penis, abnormal muscular tone and micrognathia. While there was no growth failure in the case reported by Hedera-Innis (2), it was present in both two brothers reported by Lin-Gettig (1) and two brothers in our case report. In addition, there was cleft palate in the case reported by Hedera-Innis but not in first cases reported by Lin-Gettig. In our cases, the cleft palate was present in our index case but not in his death brother. The corpus callosum was present in all 3 previous cases; whereas it was dysgenetic in our index case and brain MR imaging was normal in his death brother. The contractures were acquired in one of the cases reported by Lin-Gettig, whereas congenital in the other. Of our cases, camptodactyly became apparent at 6 months of age in our index case whereas it was congenital in death brother. The ears were low set in previously reported cases, while they were at normal localization and size with malformed appearance in our cases. There was ptosis as well as hypertelorism in one of the brothers reported by Lin-Gettig (1) and following case reported by Hedera-Innis (2), as in our case. The other case reported by Lin-Gettig had hypotelorism. The hypospadias and gastrointestinal malformation was present in first reported cases, while they were absent in the following case and our cases. There was cleft palate in the case reported by Hedera-Innis and our cases, while it was absent in cases reported by Lin-Getting. Hemangioma and ventricular septal defect were present in the case reported by Hedera-Innis. It might be present in cases reported by Lin-Gettig. Of our cases, there was patent foramen ovale in our index case, while echocardiography was normal in death brother.

The craniosynostosis were present in different sutures in all 3 cases. It was present in sagittal sutures in one of the cases reported by Lin-Gettig, while metopic suture was involved in the other. In the case reported by Hedera-Innis, sagittal and lambdoid sutures were involved. In our case, there was early closure at lambdoid, sagittal, coronal and metopic sutures in index case, while metopic and lambdoid sutures were involved in his death brother.

There was double nuchal fold and hypoplasia at toenails in our cases in addition to previously reported features. There was abnormal EEG in death brother.

The normal cytogenetic studies in all 3 previous cases and presence of identical clinical presentation in both children of healthy parents suggest that Lin-Gettig syndrome may have autosomal recessive inheritance.

We aimed to emphasize that Lin-Gettig syndrome should be kept in mind among the rare reasons of short stature as there was growth failure in first cases and in our cases. We presented two brothers compatible with Lin-Gettig syndrome as it is an extremely rare syndrome with 3 previously reported cases in literature.

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