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Case Report

Filippi Syndrome: A Lesser Reported Craniodigital Syndrome with Unique Features

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Abstract

Filippi syndrome is a sporadic craniodigital syndrome with autosomal recessive inheritance characterized by microcephaly, dysmorphic face, prenatal and postnatal growth failure, syndactyly of fingers and toes, and varying degrees of mental retardation. Approximately 30 cases have been reported in the literature so far. This study aims to report and document a case of a 13-year-old girl with classical features of Filippi syndrome who had, in addition, a shovel-shaped maxillary permanent central incisor. We believe this dental finding could represent an uncommon feature observed in only a subset of patients with Filippi syndrome.

Keywords: Dysmorphic face, filippi syndrome, genetics, shovel-shaped incisor, syndactyly

Introduction

Filippi syndrome (MIM 272440) is a genetic disease characterized by microcephaly, dysmorphic face, prenatal and postnatal growth failure, syndactyly of fingers and toes, and varying degrees of mental retardation. [1-6] This syndrome belongs to a group of craniodigital syndrome. The other names of this condition are Scott craniodigital syndrome with mental retardation and type one syndactyly with microcephaly and mental retardation. Gene analysis revealing a loss of function variant in the cytoskeleton-associated protein 2 like (CKAP2L) gene is responsible for Filippi syndrome.[3,7]

In 1985, Filippi described three siblings of male and female genders with unusual facial features (bulging forehead, broad and prominent nasal bridge, and diminished alar flare), retarded physical and mental development, bilateral syndactyly of third and fourth fingers and second and third toes.[1]

The condition is sporadic, and nearly 30 cases have been reported to date.[3,7,8] Here, we report a case of a 13-year-old girl with classical features of Filippi syndrome.

Case Presentation

A 13-year-old female was accompanied by her mother to our department with the chief complaint of a toothache. She was the youngest child of a non-consanguineous couple. Her family history was not significant. She had two healthy siblings with no craniofacial or skeletal abnormalities. The patient was born at home following a normal vaginal delivery after an uneventful pregnancy. Unfortunately, her prenatal history and anthropometric measurements were not available. History revealed that the patient did not cry after birth and had no speech development until 4 years. Furthermore, she had delayed psychomotor development and showed poor social interaction. Her medical

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history revealed that the child suffered from seizures and was under medication.

The patient's developmental milestones were delayed. She had short stature (124.46 cm vs 155 cm±1.4 SD) as well as mental retardation (Fig. 1). General examination showed coarse hair, high hairline, triangular face, pseudoproptosis, hypertelorism, curved eyebrows, long palpebral fissures, depressed nasal bridge, broad nose with everted nares, low set ears, and bow-shaped upper lip (Fig. 2). There was bilateral syndactyly of the second, third, and fourth fingers (Fig. 3). Feet examination revealed a broad first toe and syndactyly of the second, third, and fourth toes on both sides (Fig. 4).

Intra-orally, the patient presented with a high arched palate. She also had a fissured tongue and an irregular arrangement of upper and lower teeth (Fig. 5). The two maxillary central incisors were large and shovel-shaped. The mandibular right and left permanent first molars were grossly carious (Fig. 6). Her oral hygiene was poor.

Her ophthalmology and audiometry examinations were normal. Other investigations such as magnetic resonance imaging (MRI) and chromosomal analysis were not performed due to ongoing restrictions because of COVID-19 pandemic. Based on clinical evaluation, a diagnosis of Filippi syndrome was considered. In a subsequent appointment, the carious tooth was restored. Oral prophylaxis was performed, followed by explaining oral hygiene instructions to the parents.

Figure 1. Short stature of child for her age

Discussion

Diagnosis of Filippi syndrome is usually made at birth or early childhood by thorough clinical evaluation and observing characteristic physical features. We report a case of a 13-year-old female with the typical facial features of this syndrome, including short stature, coarse hair, high hairline, pseudoproptosis, hypertelorism, curved eyebrows, long eyelashes, depressed nasal bridge, broad nose with everted nares, low set ears, and thin lips.

Syndactyly of fingers and toes is one of the cardinal features of Filippi syndrome, and in the majority of cases, this is bilateral in distribution. Syndactyly usually affects third and fourth fingers and/or second, third, and fourth toes. In our patient, bilateral syndactyly of second, third, and fourth fingers and toes is observed. In addition, she presented brachydactyly or unusually short fingers and toes, a feature occasionally present in Filippi syndrome.

Intelligence is variable in patients with this syndrome ranging from mild to severe mental retardation. Mental retardation, delayed expression of language, and epilepsy observed in our patient are commonly reported features of Filippi syndrome. However, some of the less commonly reported features of this condition, such as dislocation of the elbows with hypoplasia of the radial heads, atrial septal defect, and cleft palate, were not present in our case.

Some common dental abnormalities are reported in a few patients with Filippi syndrome, such as congenital

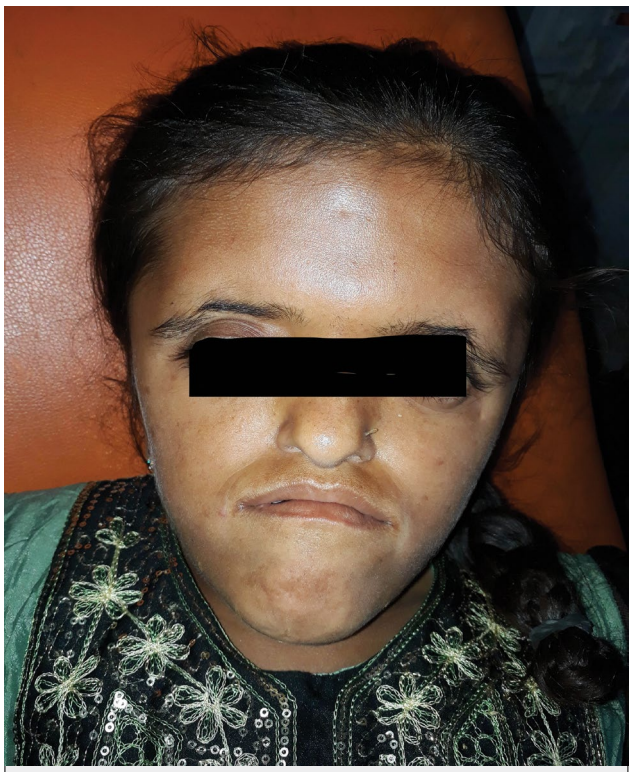

Figure 2. Extraoral photograph showing triangular face

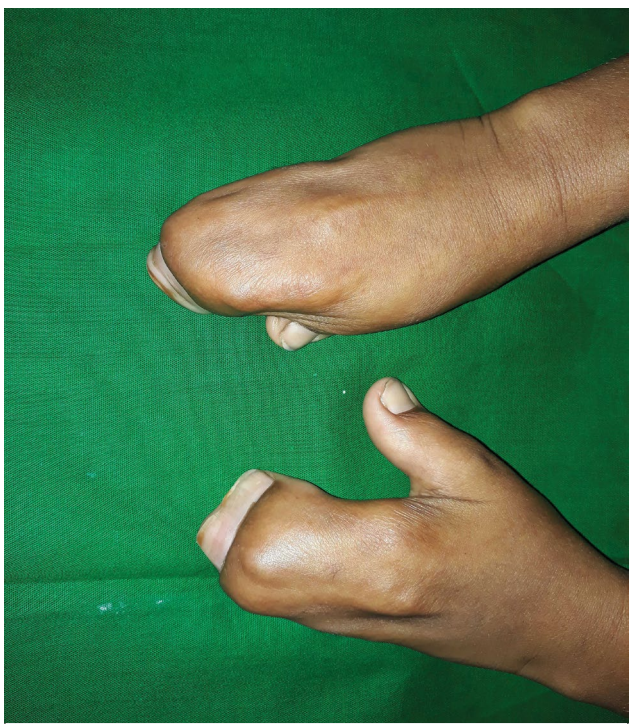

Figure 3. Syndactyly of the second, third and fourth fingers

absence of lateral incisors and third molars, microdontia, interdental spacing, enlarged pulp chambers, and shortened crown root length.[4,8,9] However, these dental abnormalities were not present in this patient;

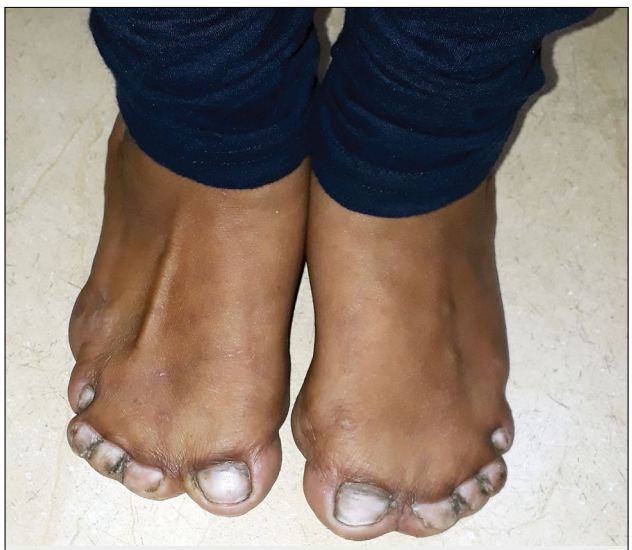

Figure 4. Syndactyly of the second third and fourth toes

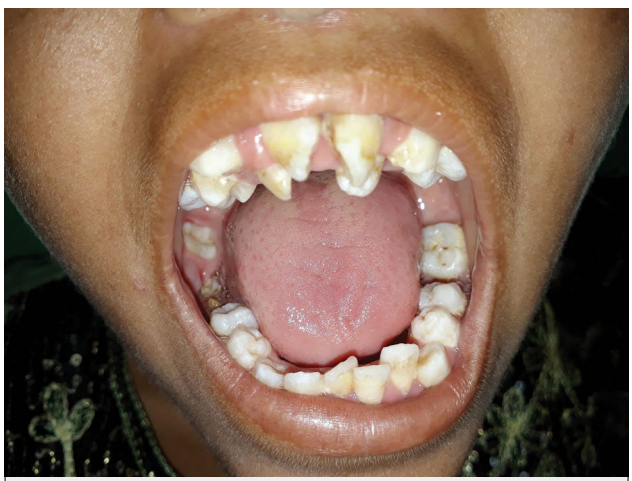

Figure 5. Fissured tongue and an irregular arrangement of teeth

instead, this patient presented with shovel-shaped maxillary central incisors and malocclusion, which were incidental findings rather than characteristic findings. Sharif and Donnai also reported teeth and hair abnormalities in patients with Filippi syndrome and concluded that ectodermal involvement is probably an underreported feature of this syndrome.[4]

The disease shows no specific gender predilection and is observed in both consanguineous and non-consanguineous families. Therefore, an autosomal recessive mode of inheritance has been suggested.[2,5] Although many familial cases of Filippi syndrome have been reported, we believe this patient is a sporadic case in her family. Recently, Hussain et al[3] showed that mutation of CKAP2L gene causes Filippi syndrome. CKAP2L is a protein-coding gene. Mitotic spindle protein encoded by this gene is critical for the development of neural stem or progenitor cells.

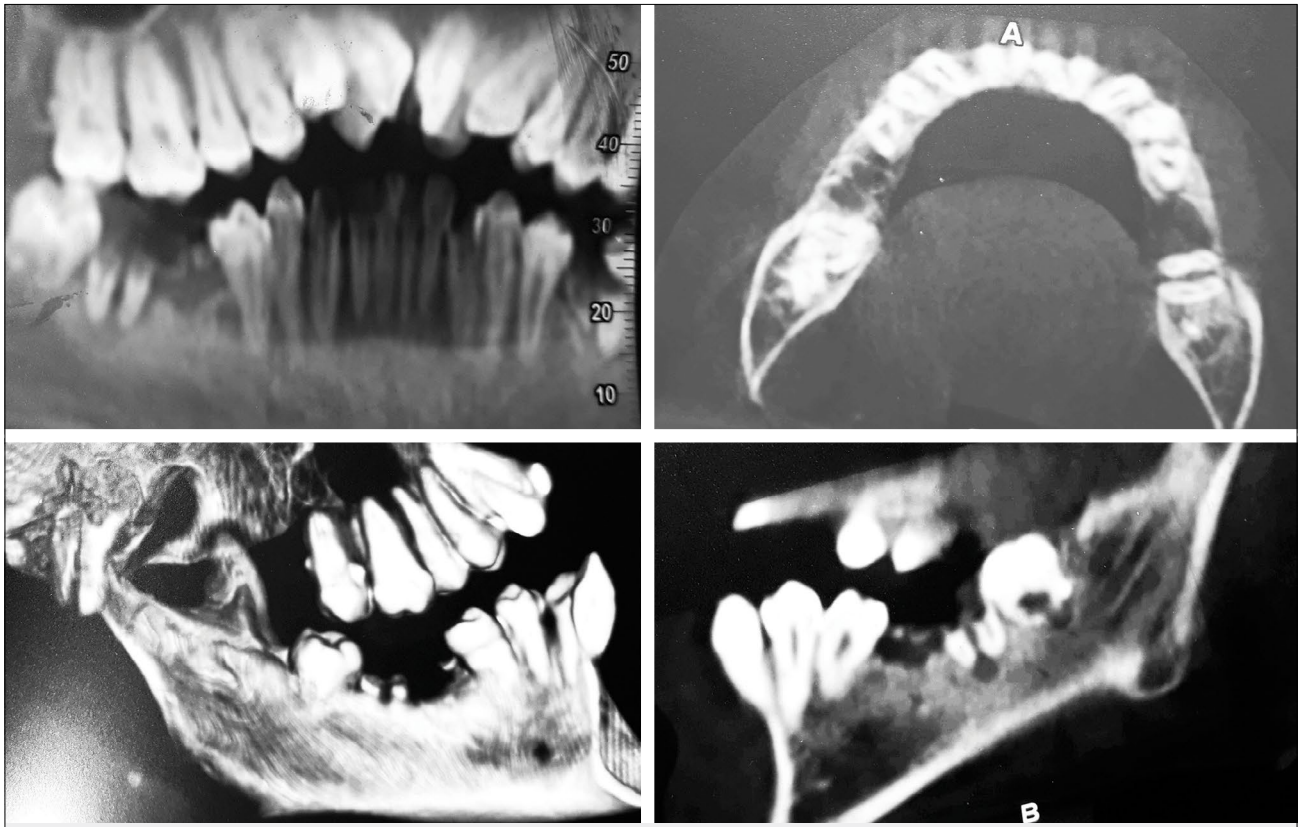

Figure 6. Radiographs and CBCT

CBCT: Cone-beam computed tomography

Dysmorphic facial features, short stature, mental retardation, and syndactyly are present in some congenital disorders, including KBG syndrome, Scott craniodigital syndrome, and Blepharonasofacial syndrome. KBG syndrome (OMIM 148050) is an autosomal dominant condition caused by a missense mutation in ANKRD 11 gene or microdeletion on chromosome 16q24.3 involving ANKRD 11 gene. Patients with this syndrome show vertebral and limb abnormalities and large central incisors.[10] Scott craniodigital syndrome is an x-linked recessive genetic trait based on the presence of conditions in males only. Carrier females generally have mild manifestations only. In Scott craniodigital syndrome, the patient usually shows a small and pointed nose, mild syndactyly, and only postnatal growth retardation. Blepharonasofacial syndrome (OMIM 110050) is an autosomal dominant syndrome that presents with distinctive facial abnormalities, such as expressionless facies, thickened facial skin, telecanthus with blepharophimosis, lacrimal duct anomalies, unusual nasal shape, and mental retardation, along with mild excess interdigital webbing.[11] To date, there have been only two cases reported from India. The present case is the third case of Filippi syndrome reported from India. Table 1 summarizes all the cases of Filippi syndrome reported to date worldwide.[1,2,4,8,9,12-24]

Management of Filippi syndrome is often individualized, and a multidisciplinary approach is required, which may include surgical correction of syndactyly of fingers and toes, speech therapy, and treatment of seizure disorders.[9] Diagnostic modalities such as MRI of the brain, electroencephalography, hand wrist radiography, and various metabolic tests like arginine challenge test facilitate the diagnosis. In addition to these modalities, genetic analyses are helpful in arriving at a confirmatory diagnosis. We suggest a thorough evaluation of this condition for better patient management.

Conclusion

Filippi syndrome is an exceedingly rare disease characterized by dysmorphic facial features and varying degrees of mental retardation. We report a patient with the typical features of Filippi syndrome. But the presence of shovel-shaped incisors in our patient is remarkable and a rare finding. It is possible that they represent uncommon features present in only a subset of patients with Filippi syndrome.

Table 1. Clinical Features of all the cases of Fillipi Syndrome reported till date world wide

Author	Year	Country	Age	Sex	Findings
Filippi [1]	1985	Italy	4,5,7 Yrs	2M & 1F	Syndactly of hands and feet, mental retardation, normal karyotype, intrauterine growth retardation, unusual facies
Zerres [12]	1992	Germany	2 Yrs	M	Syndactyly of hands and feet, severe mental retardation, seizures, ventricular enlargement on CT scan, normal standard karyotype
Woods [13]	1992	UK	10,8,2 Yrs	2F ,1M	Syndactly of hands and feet, severe mental retardation, normal karyotype, intrauterine growth retardation, broad bridge, thin alae nasi, growth retardation, seizures.
Meinecke [14]	1993	Germany	18,15 Yrs	M, F	Syndactyly of hands and feet, severe mental retardation, prominent root, hypoplastic alae, seizures, intrauterine growth retardation, normal standard karyotype.
Toriello and Higgins [15]	1995	USA	18 Mo	M	Syndactyly of hands and feet, severe mental retardation, thin alae, broad nasal bridge, high frontal hairline, long eyelashes, long philtrum, thin upper lip, overfolded left ear, cleft soft palate, mild micrognathia, bilateral single palmar crease intrauterine growth retardation, normal standard karyotype
Herons [16]	1995	France	9 Yrs	F	Syndactyly of feet, major microcephaly, severe mental retardation with speech involvement, dislocation of the elbows with hypoplasia of the radial heads and carpal synostosis. prominent root, intrauterine growth retardation, normal standard karyotype, normal CT scan.
Fryer [17]	1996	UK		2M	Syndactyly of hands in one case and feet in both the cases, depressed nasal bridge, flaring alae, intrauterine growth retardation, mental retardation.
Orrico and Hayek [18]	1997	Italy	8 Yrs	M	Syndactyly of hands and feet, broad nasal bridge, intrauterine growth retardation, severe mental retardation, normal CT scan, normal standard karyotype.
Williams [19]	1999	USA	27 Mo,7 Yrs, 2 Yrs	M, F, F	Syndactyly of hands in 2 cases and feet in all the cases, mental retardation, normal MRI, normal standard karyotype. Accommodative esotropia with possible type 1 Duane syndrome, brachycephaly and mild ptosis in one case, small pinched nasal bridge, deviated nasal septum and high arch palate, indistinct palmar creases, epicanthic folds, small palpebral fissures (1.9 and 2.1 cm right and left) that slant up, prominent glabella, broad, flat nasal base, moderate micrognathia, inability to open the mouth, and mild skin redundancy of the neck in third case
Walpole [20]	1999	Australia		3M	Syndactyly of hands in 2 cases and feet in all the cases, normal IQ in two cases and mental retardation in one case, normal standard karyotype.
Franceschini [21]	2002	Italy		F	Syndactyly of hands and feet, broad protruding nasal bridge, thin alae nasi, normal karyotype and telomere analysis, CT scan and MRI normal, severe mental retardation.
Schroderet [22]	2002	Switzerland		2M	Syndactyly of hands in one case and feet in both the cases, seizures, cerebellar atrophy and arachnoidal cyst on MRI, severe mental retardation, Normal HRB, 7-DHC, and telomere analysis.
Sharif and Donai [4]	2004	UK		2M	Syndactyly of hands and feet, broad prominent nasal bridge, hypoplastic alae nasi, seizures, intrauterine growth retardation, Normal HRB, FISH 22q11 and 16p13.3, and telomere analysis.
Battalagia A et al. [2]	2008	ITALY		M	Syndactyly of hands and feet, prominent nasal root and hypoplastic alae nasi, intrauterine growth retardation, diffuse enlargement of subarachnoid spaces, and lateral ventricles; megacisterna magna on MRI, partial symptomatic epilepsy, mental retardation, Normal karyotype, FISH 4p-, 7-DHC, telomere analysis, aCGH, and GJA1 (Cx43) gene analysis.
Sandhu M et al. [8]	2013	India	18	F	Syndactyly of hands, mental retardation, short stature, Loss of vision in left eye, Dental findings includes Congenital absence of all third molars, Horizontal bone loss, Shortened crown root length in multiple teeth, Enlarged pulp chambers in molars
Goyal L et al. [9]	2015	India	4 Yrs	M	Head circumference 42 cm (<3 SD), height 79 cm, weight 9 kg, broad/depressed nasal bridge, developmental delay, syndactyly, micrognathia, mental retardation, obliterates philtrum, impaired hearing/speech, high hairline, short stature, delayed eruption of teeth, upper deciduous central incisor carious, bilateral maxillary and mandibular lateral incisors

Table 1. Cont.

Author	Year	Country	Age	Sex	Findings
Sabır A et al. [23]	2019	UK	9 Yrs	F	Dysmorphic facial features included facial asymmetry (left lip was higher than the right), frontotemporal sparse hair, a high hairline, high arched thick eyebrows, a long narrow face, bilateral mild ptosis, a broad nasal bridge and base, hypoplastic nasal alae, hypertrichosis in the philtral area (and across her upper limbs), thin vermillon borders of the upper lip, wide spaced teeth, micrognathia, and microcephaly at 9 years. Type-1 syndactyly [cutaneous 3–4 syndactyly of her fingers with y-shaped osseous 2-4 syndactyly of toes . Hypertrophy of the labia minora.
Karakaya T [24]	2021	USA	2 ½ Mo	F	Classic features of Filippi syndrome with additional unilateral congenital talipes equinovarus (CTEV), a feature not previously recorded, is described. Genetic testing revealed a novel homozygous frameshift pathogenic variant (c.552_555delCAAA, p.Asn184Lysfs*8) in CKAP2L .

Informed Consent: The authors declare that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients were assured that their names and initials would not be published and due efforts would be made to conceal their identity, but anonymity cannot be guaranteed.

Financial Disclosure: Nil.

Conflict of Interest: None declared.

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