Abstract
Introduction: Focal dermal hypoplasia (Goltz syndrome), is an extremely rare genetic disorder characterized by distinct skin manifestations and a wide range of abnormalities involving the ocular, dental, skeletal, urinary, gastrointestinal, cardiovascular, and central nervous systems. The objective of the present series is to emphasize the different typical as well as unusual features of this rare syndrome.

Methodology: This cross-sectional observational study was performed over a period of 8 years in a tertiary care hospital of Eastern India. Consecutive patients with the clinical diagnosis of Goltz syndrome were studied.

Results: A total of 8 patients with Goltz syndrome were evaluated. Out of them, one patient was a boy and the rest were girls. The age ranged from 3 days to 9 years. There was no family history. A characteristic Blaschkoid hypo- and hyper-pigmented skin lesions, congenital nodular fat herniation, and skin atrophy were present in all patients. Congenital cutaneous aplasia was present in 50% of the patients. Facial asymmetry and ear deformity (megalopinna and low-set ears) were seen in 37.5% and 12.5% of patients, respectively. Congenital cutaneous aplasia was present in 50% of the patients. Facial asymmetry and ear deformity (megalopinna and low-set ears) were seen in 37.5% and 12.5% of patients, respectively. Cutaneous telangiectasia was noticed in 37.5% of patients. Freckle- and lentigines-like pigmentation within the hypopigmented macules was found in 25% of patients. Raspberry-like papillomas around mouth were documented in 6 (75%) patients. Dysplastic nail changes with ridging were seen in 7 (87.5%) patients. Genital abnormality in the form of bilateral undescended testes and microphthalmia with aniridia were found in one patient each. Limb defects were present in all patients. Left-sided renal agenesis was found in one patient. The patient also had multiple cortical cysts of the right kidney. Limitations: Genetic testing could not be performed in the present series.

Conclusions: Our case series showed a few unusual or extremely rare manifestations such as undescended testes, dermal sinus, kyphoscoliosis, aniridia, unilateral kidney agenesis, and renal cortical cysts among others.

Key Words: Focal dermal hypoplasia, Goltz syndrome, India

What was known?
• Focal dermal hypoplasia (Goltz syndrome) is a very rare genetic disorder characterized by characteristic skin manifestations and a wide range of abnormalities affecting the eyes, teeth, skeletal, urinary, gastrointestinal, cardiovascular, and central nervous systems.
• There is a dearth of data on this subject, particularly on Indian population.

Introduction
Goltz syndrome, synonymously known as focal dermal hypoplasia (FDH) (OMIM#305600), is an extremely rare genetic disorder characterized by distinctive skin manifestations and a wide range of abnormalities affecting the eyes, teeth, skeletal, urinary, gastrointestinal, cardiovascular, and central nervous systems. In 1962, Goltz et al. described three patients having a significant congenital decrease in the connective tissues of the skin under the title of FDH. However, cases with similar findings had been reported previously as atrophoderma linearis maculosa et papillomatosis congenitalis. The disease is inherited as an X-linked dominant condition. Recognition of the phenotypic presentation of Goltz syndrome is crucial since physicians rely to a great extent on appreciation of the key clinical characteristics to make a diagnosis. This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms. For reprints contact: reprints@medknow.com

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Although several cases of FDH have been reported in the literature, only a few cases have been described in Indian population. We present here a profile of eight Indian patients with Goltz syndrome. The objective of the present series is to highlight the different typical as well as unusual features of this rare syndrome. At the same time, we have reviewed the literature with special emphasis on Indian data.

**Methodology**

This cross-sectional observational study was performed over a period of 8 years (March 2008–February 2016) in a tertiary care hospital of Eastern India. This study was approved by the Institutional Ethics Committee. Consecutive patients with the clinical diagnosis of Goltz syndrome were studied. A detailed history and thorough clinical examination were done. Appropriate laboratory and radiological imaging were done as needed. Data were recorded in a pretested, predesigned, and semi-structured schedule. Statistical analysis was performed with the help of GraphPad Prism version 5 (GraphPad Software Inc., San Diego, CA, USA; 2007) software and Microsoft Excel.

**Results**

A total of 8 patients with Goltz syndrome were evaluated [Table 1]. Out of them, one patient was a boy and the rest were girl. The age ranged from 3 days to 9 years. None of the family members were affected with this condition. Parental consanguinity was not present in any of the patient. A characteristic Blaschkoid hypo- and hyper-pigmented skin lesions, congenital nodular fat herniation, and skin atrophy were present in all (100%) patients [Figures 1 and 2]. Clinical features suggestive of congenital cutaneous aplasia [Figure 3] were present in 4 (50%) patients. Facial asymmetry and ear deformity (megalopinna and low-set ears) were seen in 3 (37.5%) and 1 (12.5%) patients, respectively. Cutaneous telangiectasia was noticed in 3 (37.5%) patients. Freckle- and lentigines-like pigmentation within the hypopigmented macules was found in 2 (25%) patients. Raspberry-like papillomas [Figures 4 and 5] around mouth were documented in 6 (75%) patients. Dermal sinus over the sacral area was a notable feature in one of the patient. Dysplastic nail changes with ridging were seen in 7 (87.5%) patients.

Anonychia was noted in one patient. Gingivitis was seen in 2 (25%) patients, and caries teeth, perleche, and ridged gum were noted in one patient each. Enamel hypoplasia of the teeth was noted in 3 (37.5%) patients. Dental malocclusion was present in three patients. Diffuse alopecia was seen in 3 (37.5%) patients. Genital abnormality in the form of bilateral undescended testes [Figure 6] and microphthalmia with aniridia [Figure 7] were found in one patient each. Limb defects [Figures 8 and 9] were present in all patients. Ectrodactyly (lobster hand) was seen in 7 (87.5%) patients. Syndactyly (six patients; 75%), absent digits (four patients; 50%), transverse limb defects (three patients; 37.5%), and kyphoscoliosis (one patient) were the other bony abnormalities noted. Left-sided renal agenesis was found in one patient. The patient also had multiple cortical cysts of the right kidney as detected by abdominal ultrasonography and subsequent magnetic resonance imaging of the abdomen [Figure 10]. Psychological evaluation could be done in patients aged 4 years or more. A total of four such patients were evaluated. All of them had poor social interaction. Intellectual impairment was found in two patients. One of them had mild (Intelligence Quotient: 55) and the other had moderate (Intelligence Quotient: 41) mental retardation. No structural defect on computed tomography scan of the brain was found in this group of patients. Routine laboratory investigations were unremarkable except for the presence of iron deficiency anemia in one patient. Parents of four patients of our series gave consent.
to undergo skin biopsy. All of the patients showed almost similar histopathological picture [Figure 11] revealing that the dermis was almost replaced by adipocytes. The dermis was notably cell poor with an overlying thin epidermis.

**Discussion**

Goltz syndrome occurs due to mutations in *PORCN* gene. This gene encodes an endoplasmic reticulum transmembrane protein that is implicated in processing the embryonically critical Wnt signaling proteins. Wnt is a vital protein for skin and bone development.\(^1\) Approximately 10% of FDH cases are male.\(^6\) Only mosaic males are thought to survive as nonmosaic male are presumed to be lethal.\(^7\) There are several reports of familial cases of FDH with female-to-female transmission, and even three reports of transmission from father to

| Table 1: Profile of patients with Goltz syndrome |
|-----------------------------------------------|
| **Parameters**                                | 1   | 2   | 3   | 4   | 5   | 6   | 7   | 8   |
| **Age**                                       | 3 days | 4 years | 8 years | 9 years | 12 days | 4 months | 5 years | 14 days |
| **Gender**                                    | Female | Female | Female | Male | Female | Female | Female | Female |
| **Congenital nodular fat herniation**         | +    | +    | +     | +    | +    | +    | +     | +    |
| **Skin atrophy**                              | +    | +    | +     | +    | +    | +    | +     | +    |
| **Raspberry-like papilloma**                  | -    | +    | +     | +    | +    | -    | +     | +    |
| **Blaschkooid hypo- and hyper-pigmentation**  | +    | +    | +     | +    | +    | +    | +     | +    |
| **Congenital cutaneous aplasia**              | +    | +    | -     | -    | -    | -    | -     | -    |
| **Facial asymmetry**                          | -    | +    | +     | +    | -    | -    | -     | -    |
| **Ear deformity**                             | -    | -    | +     | +    | -    | -    | -     | -    |
| **Telangiectasia**                            | -    | +    | +     | +    | -    | -    | -     | -    |
| **Freckle-like pigmentation**                 | -    | -    | -     | +    | +    | -    | -     | -    |
| **Genital abnormalities**                     | -    | -    | -     | Undescended testis | -    | -    | -     | -    |
| **Ocular changes**                            | -    | -    | -     | Microphthalmia, aniridia | -    | -    | -     | -    |
| **Internal organ involvement**                | -    | -    | -     | -    | -    | -    | -     | Renal agenesis |
| **Psychological features**                    | Not evaluated | Poor social interaction, moderate MR | Poor social interaction, mild MR | Not evaluated | Not evaluated | Poor social interaction, intellectual impairment | Not evaluated |
| **Limb defect**                                |       |       |       |       |       |       |       |       |
| **Syndactyly**                                | -    | -    | +     | +    | +    | +    | +     | +    |
| **Ectrodactyly**                              | +    | +    | +     | +    | -    | +    | +     | +    |
| **Polydactyly**                               | -    | -    | -     | -    | -    | -    | -     | -    |
| **Absence digit**                             | +    | +    | -     | +    | -    | +    | +     | -    |
| **Transverse defect**                         | -    | +    | -     | +    | +    | -    | -     | -    |
| **Axial skeleton involvement**                | -    | -    | -     | Scoliosis | -    | -    | -     | -    |
| **Nail**                                      | Dysplasia, ridging | Dysplasia, ridging | Dysplasia, ridging | Dysplasia, ridging | Dysplasia, ridging | -    | Anonychia, dysplasia, ridging |
| **Alopecia**                                  | -    | Diffuse | Diffuse | Diffuse | -    | -    | -     | -    |
| **Oral changes**                              | -    | -    | Diffuse | Enamel hypoplasia, malocclusion | -    | -    | Gingivitis, enamel hypoplasia, dental malocclusion |
| **Miscellaneous**                             | -    | -    | -     | Dermal sinus on sacrum | -    | -    | -     | -    |

MR: Mental retardation, ‘+’ means present and ‘-’ means absent
Ghosh, et al.: Focal dermal hypoplasia (Goltz syndrome)

In patients with FDH, the affected areas of skin are typically erythematous and fragile at birth.

The distinctive cutaneous features of the disease may include asymmetric Blaschko-linear and reticulated atrophy, pigmentary changes, and telangiectasias. Lipomatous changes and papillomas were reported in the majority of patients. A newly described skin finding was progressive hyperpigmented freckling that occurred within the hypopigmented areas. However, none of the family members of the present series were involved with Goltz syndrome.

Two of our patients had similar skin lesion. Some of the patient may have patchy alopecia and many have diffuse thinning of hair. Three patients of our daughter.
series had diffuse hair loss without any other obvious reason.

Scanning electron microscopy of the hair shafts may reveal abnormalities, including atrophic hairs with reduced diameters, flattened hairs (as noted in cross-sectional views), trichorrhexis nodosa, pili torti, and pili trianguli et canaliculi. However, we did not find any structural hair shaft defect on light microscopy. Nail changes included V-nicking and longitudinal ridging of the nail plate and dysplasia, in addition to micronychia. Nail abnormalities may be present in 89% of the patients. We found seven patients (87%) with nail abnormality.

A Western series showed that the most common orthopedic findings in patients with FDH are syndactyly (68%) and ectrodactyly (68%) followed by leg length discrepancy (57%) and reduction defects of long bones (52%). In consonance with this report, syndactyly and ectrodactyly were the most common bony defect noted in the present series. Apart from the above-mentioned defects, one of our patients had kyphoscoliosis which is probably a hitherto unreported condition. Approximately 20% of the cases with FDH may have longitudinal linear striations in the metaphyses of the long bones (osteopathia striata) seen on radiography. However, none of our patients had similar picture.

Dental anomalies are highly prevailing in FDH. Western data showed that 68% of patients with FDH demonstrated vertical enamel grooving, 52% had peg-shaped tooth deformities and 78% had enamel hypoplasia with or without discoloration. Cleft lip and cleft palate were noted in 15% of the patients. Other findings may include intraoral lipoma or papilloma with no site predilection. Dental malocclusions may be present in approximately 63% of FDH. Patients may have speech problems or difficulty with chewing.

Deidrick et al. showed that intellectual impairment may occur in 15%–18% of persons with FDH. Behavioral or emotional problems may also occur in patients with Goltz syndrome. Withdrawn behavior was reported by 65% of parents. These findings suggest that clinicians should routinely assess persons with FDH to rule out cognitive and emotional/behavioral problems and recommend timely treatment. Future research should focus on identifying risk factors for psychoeducational problems in this population.

Structural abnormalities of kidneys and urinary system that may lead to recurrent urinary tract infections and urinary reflux may include, hypoplastic kidney, cystic renal dysplasia, hydronephrosis, and fused/horseshoe kidney. Unilateral agenesis of the kidney with multiple cortical cysts of the contralateral kidney was a notable finding in one of our patients. We could find only one previous report of unilateral absent kidney in PubMed database. In the present series, we found only one male patient who had bilateral undescended testis which was probably an unreported occurrence. The presence of dermal sinus over the sacral region was another unusual feature in one of our patient. Neurological manifestations in the form of myelomeningocele, Arnold–Chiari malformation, and hydrocephalus have been reported in association with FDH. Approximately 40% of cases with Goltz syndrome may have ocular abnormalities in the form of coloboma, microphthalmia, and recurrent papillomas arising from the conjunctiva and lid margins. Aniridia, as seen in our patient, is an extremely rare ocular finding of Goltz syndrome.

Recently, Bostwick et al. proposed a diagnostic criteria of Goltz syndrome. They proposed that the characteristic skin findings should include congenital patchy skin aplasia, congenital nodular fat herniation,
congenital hyper-/hypo-pigmentation in Blaschko linear distribution, telangiectasia, and congenital ridged dysplastic nails. On the other hand, characteristic bony abnormalities include split hand/foot (ectrodactyly), transverse limb defects, syndactyly, oligodactyly, and marked long bone reduction. Clinical diagnosis of FDH needs three or more characteristic skin findings and one or more characteristic limb malformation. All of the patients of the patient series fulfilled these criteria.

Bostwick et al. reported that the occurrence was similar (67%) for papilloma, fat deposits, and nail hypoplasia. Our case series also showed six out of the eight patients (75%) had papilloma. Although fat deposits and nail hypoplasia were included in their diagnostic criteria, papilloma was not considered to be a part of it.[2] In view of this fact, we think that raspberry-like papilloma should also be incorporated into the clinical diagnostic criteria of FDH due to its distinctive appearance and more or less similar occurrence with other cutaneous criteria.

We have searched the PubMed and MEDLINE database with the search terms “FDH,” “Goltz syndrome,” and “India.” We could not find any previous case series of Goltz syndrome in Indian population in these databases. To the best of our effort, we could found 12 previously reported cases of Goltz syndrome in Indian population. Apart from the typical and common features of Goltz syndrome, a few rare and interesting features have been described in Indian population. Sarkar et al. reported a case of FDH with the presence of bilateral hydronephrosis and hydroureter which regressed within 3 months and absence of the fibula and all other bones distal to it.[14] Abdominal dehiscence was reported by Sarma et al. in two patients with this syndrome.[15] Srinivas and Hiremagalore reported a patient with supernumerary nipples.[10] Genetic analysis was not done in most of these reported cases from India. However, a novel splice site mutation of PORCN gene was reported by Kapoor et al.[18]

History of parental consanguinity,[4] association of mild aortic regurgitation,[19] and association of porencephalic cyst in the brain[20] were other notable features. Psychological assessment was rarely done in these cases. However, Riyaz et al. reported a girl with IQ of around 60–70, indicative of mild mental retardation.[19]

Limitations

Due to institutional nonavailability, we could not perform genetic analysis of our patients which remained a limitation of our report. However, genetic defects or the mutations in the PORCN gene are not specific for Goltz syndrome. Mutations or deletions of this gene were also reported in other conditions (e.g., angioma serpiginosum, the pentalogy of Cantrell and Limb-body wall complex).[21] Moreover, genetic analysis was not considered to be a component of the recently proposed diagnostic criteria (5) of FDH.

The common differential diagnoses for FDH are microphthalmia, dermal aplasia, and sclerocornea syndrome, incontinentia pigmenti, and Rothmund–Thomson syndrome among others. However, the characteristic clinical and histological features have ruled out these possibilities in the present series.[8]

Treatment of FDH is mainly supportive, with an emphasis on genetic counseling. Reconstructive surgery can also be an imperative treatment option. The use of a flashlamp-pumped pulsed dye laser to flatten lesions and to decrease pruritus and erythema was anecdotally reported. In another report, cryotherapy was used to treat giant trunk and extremity papillomas. Fortunately, patients with FDH generally have a normal lifespan and are able to live productive lives.[8]

Conclusions

The present study highlighted the different typical as well as unfamiliar features of Goltz syndrome. In this study we have also emphasized the importance of detail systemic examination to find out underlying organ involvement.

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Nil.

Conflicts of interest

There are no conflicts of interest.

What is new?

• The present study highlighted the patterns of mucocutaneous manifestations in a group of patients with Goltz syndrome from Eastern India
• Our case series showed a few unusual or extremely rare manifestations such as undescended testes, dermal sinus, kyphoscoliosis, aniridia, unilateral kidney agenesis, and renal cortical cysts among others.

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