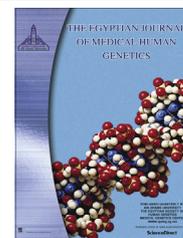




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CASE REPORT

Christ-Siemens-Touraine syndrome with cleft palate, absent nipples, gallstones and mild mental retardation in an Egyptian child



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KEYWORDS

Christ-Siemens-Touraine syndrome;
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Abstract We report a 6 year old child, second in order of birth of non consanguineous Egyptian parents with typical characteristics of Christ-Siemens-Touraine syndrome. The patient had sparse light hair over the scalp, scanty eyebrows and eyelashes, a high arched cleft palate, decayed oligodontic teeth, hyperpigmentation all over the body more marked in cheeks, perioral area, chin, neck, axillae and back of both knees, fragile dry skin, hyperextensibility of the metacarpophalangeal joints, dysplastic nails and absent nipples. Our patient had also gallstones which were not reported previously and mild mental retardation. His mother had mild teeth abnormalities.

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1. Introduction

Ectodermal dysplasia (ED) syndromes comprise a group of genetic disorders characterized by deficient function of at least 2 ectodermal derivatives such as skin, hair, teeth and sweat glands [1,2]. Although more than 170 different subtypes of ectodermal dysplasia have been identified, these disorders are considered to be relatively rare with an estimated incidence of 1 case per 100,000 [3,4].

Ectodermal dysplasia is divided into two types based on the number and function of sweat glands: hidrotic ectodermal dysplasia (Clouston syndrome) and hypohidrotic (anhidrotic) ectodermal dysplasia (HED) (Christ-Siemens-Touraine syndrome) [5].

The Christ-Siemens-Touraine syndrome (CST syndrome) is the rare an- or hypohidrotic form of the ectodermal dysplasia

[6]. It was first described in 1848 by Thurnam [7] and later by Darwin [8]. In 1913, Christ characterized it as a congenital ectodermal defect, Siemens confirmed the X-linked nature of inheritance in 1921 and in 1936, and Touraine published works on the wide range of features. It is characterized by sparse hair, heat intolerance, excessively dry skin due to the absence of sweat glands and abnormal spiky or absent teeth [9].

We report a case with the typical features of the CST syndrome who had in addition some unreported features after taking the consent of parents.

2. Case report

We report a 6 year old male child, second in order of birth of healthy non consanguineous Egyptian parents. The patient was delivered at full term by cesarean section. His birth weight was 3 kg. No problems were noted by the mother during

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pregnancy. The patient was referred to the Genetics Clinic, Pediatric Hospital, Ain Shams University complaining of abnormal features since birth.

The patient was admitted to neonatal intensive care unit (NICU) since birth for meconium aspiration. He had scaling of the skin during the neonatal period which was treated with moisturizing creams. The mother noticed that her son had scanty hair, cleft palate, tie tongue, abnormalities of nails and teeth. His mother also noticed that her child had recurrent episodes of unexplained hyperpyrexia; he was not able to sweat, and she had to protect him from overheating during warm weather.

At the age of 3 months, he had tongue-tie surgery. At the age of 8 months he was admitted to hospital for gastroenteritis. He had an attack of gastroenteritis every month for 8 months. He had cleft palate repair operation at the age of 1 year. At the age of 2 years he had gastroenteritis and dehydration which necessitated admission to hospital. During admission, multiple gall bladder stones were discovered on abdominal ultrasound and he had a cholecystectomy operation. Then he was referred to our genetics clinic.

The patient had mild mental retardation. Family history was unremarkable. He had two healthy sibs.

On examination, his weight was 20 kg (50th percentiles), his height was 114 cm (50th percentiles), and his skull circumference was 52 cm (75th percentiles).

He had sparse, thin hair over the scalp, scanty eyebrows and eyelashes, frontal bossing, prominent supraorbital ridges, depressed nasal bridge, saddle nose, dry lips, angular stomatitis, high arched palate and decayed oligodontic teeth (Figs. 1 and 2).

He had absent nipples and hyperpigmentation all over the body mainly in cheeks, perioral area, chin, neck, axillae and the back of both knees (Figs. 1, 3 and 4). He also had fragile skin.

He had hyperextensibility of the metacarpophalangeal joints, dysplastic nails, left partial simian crease and partial syndactyly between 2nd and 3rd toes (Fig. 5).



Figure 1 Sparse, thin dry hair over the scalp, scanty eyebrows and eyelashes, frontal bossing, prominent supraorbital ridges, depressed nasal bridge, saddle nose, dry lips and marked hyperpigmentation over the cheeks, perioral area, chin and neck.

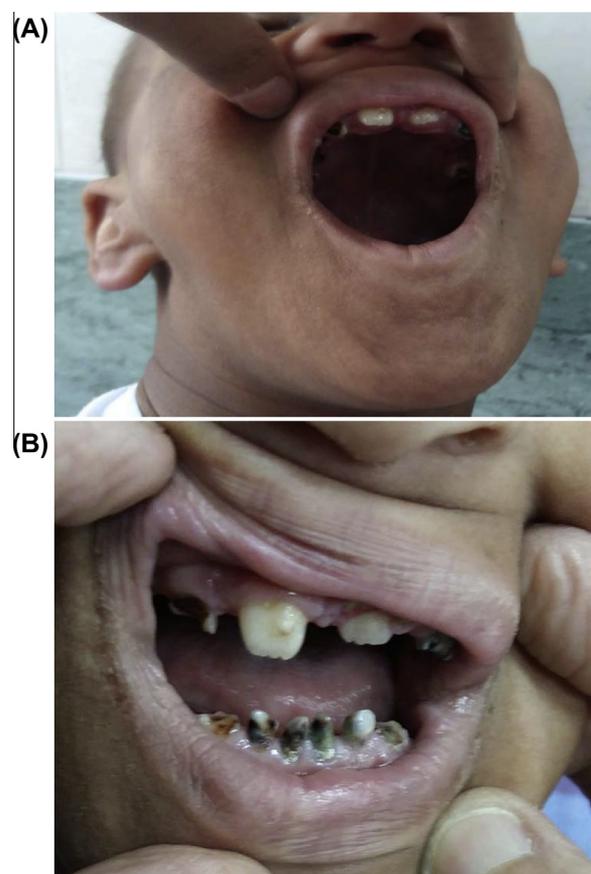


Figure 2 (A) High arched palate, dry lips and angular stomatitis. (B) Decayed oligodontic teeth.

Abdominal examination revealed the scar of the cholecystectomy operation. The back, cardiac and neurological examinations were apparently normal. The genitalia were also normal.



Figure 3 Absent nipples and hyperpigmentation all over the body more marked on the back of the neck.



Figure 4 Hyperpigmentation in axilla.

Abdomino-pelvic ultrasonography and ECHO cardiography were normal.

Hemoglobin was 12 mg/dl. Serum IgA, IgM and IgG levels were normal.

Panoramic X-ray showed partial anodontia in permanent dentition (absent lateral incisors, absent 1st premolar of right side, no buds of lower premolars bilaterally, absent 2nd and 3rd molar buds bilaterally) (Fig. 6). Fundus examination was normal. Audiological evaluation revealed normal hearing. IQ test was 69.

Both parents were normal apart from slight abnormality in mother's teeth (Fig. 7).

3. Discussion

We report a 6 year old child with typical characteristics of Christ-Siemens-Touraine syndrome who presented with sparse, thin, light hair over the scalp, scanty eyebrows and



Figure 5 Dysplastic nails and partial cutaneous syndactyly between 2nd and 3rd toes.

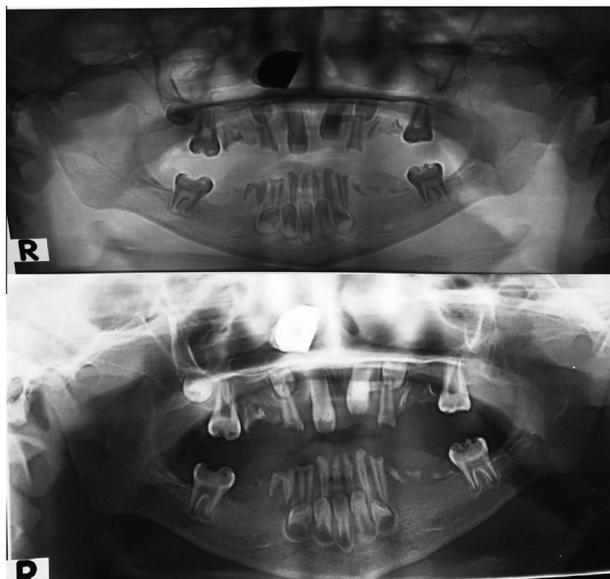


Figure 6 Panoramic radiograph showing partial anodontia.

eyelashes, frontal bossing, prominent supraorbital ridges, depressed nasal bridge, saddle nose, dry lips, angular stomatitis, high arched repaired cleft palate, decayed oligodontic teeth, hyperpigmentation all over the body mainly in cheeks, perioral area, chin, neck, axillae and back of both knees, fragile dry skin, hyperextensibility of the metacarpophalangeal joints, dysplastic nails, left partial simian crease, partial syndactyly between 2nd and 3rd toes and absent nipples.

Main clinical feature of the CST syndrome is sparse or absent eccrine glands as well as hypotrichosis and oligodontia. Our patient had sparse, thin, light hair over the scalp, scanty eyebrows and eyelashes. Some individuals with the CST syndrome are completely bald by their middle teens, whereas other individuals have normal amounts of scalp hair with abnormal texture [10]. Generally scalp hair grows very slowly and is often dry due to lack of sebaceous glands in the scalp [11].

Most individuals show decreased body hair, pubic hair and/or axillary hair, however, beard and moustache hair are normal [10]. The apparent slow growth of the scalp hair may result from the excessive fragility of the shafts, which break easily with the usual wear and tear of childhood [12].



Figure 7 The mother's teeth showing a wide space between her teeth with a difference in size (smaller) of similar teeth in both sides of the upper and lower jaws.

Our patient had recurrent episodes of unexplained hyperpyrexia and he was not able to sweat. The absence or diminished activity of sweat glands results in patients having more chances of developing hyperthermia with minimal exertion and recurrent fever as present in our case [13]. The hyperthermia may also lead to brain damage, and is probably the cause of the rare cases of EDA reported with mental retardation as detected in our case [10]. It also has been associated with sudden infant death [13]. There is substantial mortality and morbidity in male infants, with about 30% dying in the first two years of life, because of fever or a chest infection [14].

Oral manifestations of the CST syndrome include conical or peg-shaped teeth, hypodontia or complete anodontia in both deciduous and permanent dentition, malformation of the present teeth, generalized spacing, delayed eruption of permanent teeth, and underdeveloped or asymmetric development of the alveolar ridge [15]. Besides the delay in teething, the teeth appear radiographically abnormal in shape [10]. An average of nine permanent teeth develops in individuals with classic HED, typically the canines and first molars [16].

Our patient had partial anodontia with decayed teeth. Analysis of the saliva in patients with the CST syndrome has revealed a reduced buffer capacity and an increased number of bacterial cultures susceptible to dental caries as detected in our patient [17]. Dental implants in the anterior portion of the mandibular arch have proven successful only in children aged seven years and older [18].

The association of the cleft palate with ED is known in the literature with only few cases reported so far [19]. More et al. did a retrospective study of 19 cases of ED and found 94.74% had partial anodontia, 84.21% had conical shaped teeth, 05.26% had complete anodontia, 100% had thin alveolar bone; and in one case (05.26%) cleft lip and cleft palate [20]. Our patient had a high arched corrected cleft palate.

Patients with the CST syndrome have a characteristic facies with frontal bossing, prominent supraorbital ridges, depressed nasal bridge, saddle nose, and dry lips, [13] as detected in our case. The men have an easily recognizable facies as an 'old man' facies [10] as detected in our patient. The chin may be pointed and the lips everted and protuberant [21] which were not detected in our patient.

Sunken cheeks (malar hypoplasia) and micrognathia (mandibular hypoplasia) were detected in patients with the CST syndrome [22].

In addition our patient had hyperextensibility of the metacarpophalangeal joints, left partial simian crease, partial syndactyly between 2nd and 3rd toes, dysplastic nails and absent nipples. About half of the affected individuals exhibit mild fingernail abnormalities and nail dystrophy [13].

Our patient had also absent nipples. Over one third of the boys have abnormalities of the breast, including absent or accessory nipples [23].

Absence or underdevelopment of the nipples and mammary glands in women with the CST syndrome cause difficulties to breast feed [11].

Typical clinical manifestations also include dryness of the skin due to the defective development of several exocrine glands as detected in our patient [24].

Additional cutaneous features of HED include scaling of the skin during the neonatal period which was detected in our patient, periorbital hyperpigmentation and wrinkles, and eczematous dermatitis [13]. The skin may be covered with a

glue-like membrane (collodion baby) at birth [11]. Our patient had hyperpigmentation all over the body mainly in cheeks, perioral area, chin, neck, axillae and back of both knees. He also had dry fragile skin with no eczematous dermatitis. Affected individuals have a smooth skin that is "thinner" than expected for age as detected in our patient owing to the absence of sebaceous (oil-producing) glands and the reduced number of sweat glands [10]. Lack of dermal ridges was detected in some patients [12].

Histologically, the epidermis is thin and flattened, the eccrine sweat glands are absent or rudimentary. The dermal connective tissue is grossly normal but elastic and collagen fibers may be sparse or fragmented [25].

Hypoplasia of salivary glands and the absence of oral accessory glands were also present and resulted in xerostomia and dry cracked lips [5,16]. Our patient had dry lips with angular stomatitis.

Patients with the CST syndrome may present with deficient nasal cilia with subsequent chronic infections, epistaxis, dysphagia, and bronchitis [26]. Abnormal mucous glands result in extremely thick nasal secretions and a propensity to develop respiratory tract infections [27] which were not detected in our patient.

Our patient had repeated gastroenteritis and dehydration which necessitated admission to hospital. He also had gallstones and underwent cholecystectomy which was not reported previously. HED variably affects the mucous lining of gastrointestinal tract and the mucous glands may be absent, reduced in number or may not function normally [22].

CST syndrome may be associated with decreased function of certain components of the immune system [22], potentially causing an increased susceptibility to recurrent nasal and respiratory infections which was not detected in our case.

Voice changes in the CST syndrome are due to atrophic rhinitis, hypoplastic alae nasi, laryngeal mucous hyposecretion and vocal cord palsy [28], which were not detected in our patient.

HED primarily presents with features of dry eyes, corneal vascularisation, corneal scarring, ulcers and perforation caused by the combined effect of dysplasia, tear deficiency and eye infection [22] which were not detected in our patient. Dry eye symptoms are due to abnormal Meibomian glands [29]. Lid abnormalities as recurrent inflammation of lid margins, trichiasis and loss of eyelashes and eyebrows are also present [30]. Our patient had scanty eyelashes and eyebrows.

Ear wax is often thick and sticky in patients with the CST syndrome, as detected in our patient, and the hearing can be affected if wax accumulates in the ear or the auditory tube becomes blocked while the ear is inflamed. There is also an increased risk of developing infections of the middle ear [11].

If a person with hypohidrotic ectodermal dysplasia is about to undergo general anesthesia it is important that the anesthesiologist is informed about the patient's poor temperature regulation, dry, sensitive mucous membranes in the throat and nose.

However our patient had mild mental retardation, which probably can be explained by hyperthermia causing brain damage. Physical growth and psychomotor development are otherwise within normal limits in patients with the CST syndrome [12].

The family history is very important for adequate genetic counseling and other members of the family must be examined for signs of this syndrome.

HED can be inherited in an X-linked recessive (XLHED). The parents of our patient are not consanguineous, although consanguinity is high in Egypt [31]. So most probably our patient has an X-linked recessive inheritance, especially as the mother has slight teeth anomalies.

Clinical analyses of the families with XLHED are useful for checking carrier status and also provide information for diagnosis of other affected members.

However signs of EDA are found in about 70% of obligate carriers [10], no signs of EDA are found in a substantial number of carriers. The mother of our patient had wide spaces between her teeth with difference in size (smaller) of similar teeth in both sides of upper and lower jaws. In a female heterozygous for the XLHED gene, the presence of two different cell lines due to random inactivation (lyonization) of one of the two X chromosomes during embryogenesis results in much variability in the degree of clinical expression of the disorder which explains that some heterozygous females may show minor symptoms or no clinical evidence of the disorder [14].

The most significant finding in obligate carriers is hypodontia, which is easily recognized. There is also a greater tendency for abnormal crown form and smaller tooth size in carrier females [10]. The mapping of a gene for X-linked EDA has given new possibilities for the detection of carriers of XLHED by molecular genetics with a high degree of accuracy.

The autosomal dominant and autosomal recessive inheritance EDA are extremely rare conditions [10]. The clinical features are quite similar in both conditions but due to the different modes of inheritance. AR-HED affects both males and females and the heterozygotes have no signs at all.

Four genes (EDA1, EDAR, EDARADD, and WNT10A) account for 90% of hypohidrotic/anhidrotic ectodermal dysplasia cases [24]. EDA is the only gene in which pathogenic variants are known to cause X-linked HED.

Mutant EDA affects cell signaling transduction or cell migration during the epithelial-mesenchymal inductive process [32].

The EDA, EDAR and EDARADD genes provide instructions for making proteins that work together during embryonic development which form part of a signaling pathway that is critical for the interaction between two cell layers, the ectoderm and the mesoderm. So mutations in the EDA, EDAR or EDARADD genes prevent normal interactions between the ectoderm and the mesoderm and impair the normal development of hair, sweat glands and teeth [22].

The EDAR protein plays an important role in embryogenesis. It is activated by its ligand EDA and uses EDARADD as an adaptor to build an intracellular NF- κ B signal-transducing complex which is necessary for normal development of ectodermal organs in humans [33,34].

Autosomal dominant (AD) forms of HED have been linked to mutations in the ectodysplasin 1 anhidrotic receptor (EDAR) protein but mutations in the EDAR gene are also associated with recessive forms of ED [35,36]. Mutations in EDAR have been reported to account for 25 per cent of non-EDA1 HED cases [37].

Prenatal diagnosis of EDA has been made on fetal skin biopsy, obtained by fetoscopy by 20 weeks gestation after determination of the sex of the fetus [38] with a procedure which implies a considerable risk to the pregnancy.

The use of linked markers on DNA from chorionic villi has greatly improved the safety of prenatal diagnosis of X-linked

EDA and permits the diagnosis to be made earlier with less risk to the pregnancy than the fetoscopy and multiple skin biopsies [10]. The identification of mutations in the family will further improve the accuracy of prenatal diagnosis [39].

During hot weather, affected individuals need access to an adequate supply of water and a cool environment [40]. Special hair care formulas for sparse, dry hair may be required [40].

Tooth agenesis of these patients and its secondary effects on growth and development of the jaws is often the most significant clinical problem. The course of the treatment is to restore the function of the teeth. There are published cases of early implant placement in toothless EDA patients, however the success has been variable [38]. Saliva substitutes and optimal fluoride exposure may be helpful in preventing dental caries in those individuals having a marked reduction in salivary flow [40].

Regular visits with an ENT physician may be necessary for management of the nasal and aural concretions. Nasal and aural concretions must be removed and recommendations made about humidification of the ambient air to prevent their formation [41].

The treatment may range from use of lubricants for treatment of dry eyes to surgical management with its complications [22].

To conclude: Christ-Siemens-Touraine syndrome has severe problems for affected individuals at early ages. Thus early clinical diagnosis and treatment planning of this disease is of great importance and prevent complications owing to overheating. Periodic check-up is an essential step in treating these patients. Multidisciplinary team comprising of dermatologist, psychiatrist and dentists have responsibility to rehabilitate these patients. Our patient has the typical features of the CST syndrome who has in addition some unreported features, so increased awareness of this disorder is important and the family members must be assessed for signs of this syndrome and offered genetic counseling.

Conflict of interest

We have no conflict of interest to declare.

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