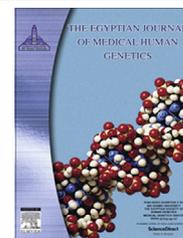




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CASE REPORT

C syndrome with skeletal anomalies, mental retardation, eyelid chalazion, Bitot's spots and agenesis of the corpus callosum in an Egyptian child



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KEYWORDS

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Agenesis of corpus callosum

Abstract We report a 2.5 year old female child, third in order of birth of healthy non consanguineous Egyptian parents with C syndrome. The patient had moderate mental retardation, trigonocephaly, protruding forehead, low anterior hair line, wide upslanted palpebral fissures, depressed nasal bridge, broad nose, high arched palate, microretrognathia, low set ears, short neck, scoliosis, hypertrichosis over the back, talipes equinovarus as well as interatrial septal defect. The patient had in addition chalazion in left lower eyelid as well as bilateral Bitot's spots most probably due to vitamin A deficiency. MRI brain revealed agenesis of the corpus callosum.

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1. Introduction

C syndrome, also known as Opitz trigonocephaly syndrome (OTCS), is a rare and heterogeneous malformation syndrome characterized by trigonocephaly, variable mental retardation, hypotonia, variable cardiac defects, redundant skin, and dysmorphic facial features, including upslanted palpebral fissures, epicanthal folds, depressed nasal bridge, and low-set, posteriorly rotated ears [1]. The premature closure of the metopic suture results in a growth restriction of the frontal bones and trigonocephaly [2]. Morbidity and mortality are very high in this syndrome [3]. OTCS is a heterogeneous genetic disorder which occurs sporadically, although familial cases have also been reported [4].

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

2. Case report

A 2.5 year old female child, third in order of birth of healthy non consanguineous Egyptian parents. The patient was delivered at full term by vaginal delivery after uncomplicated pregnancy. The patient was referred to the Genetics Clinic, Pediatric Hospital, Ain Shams University complaining of developmental delay and abnormal skull shape.

The condition started since birth when her mother noticed that her baby had abnormal skull shape. At the age of 2 months, she developed focal convulsions (twitches in the eyes) and was given Tiratam for 6 months. The convulsions stopped at the age of 1 year and the patient stopped having

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anticonvulsant drug. At the age of 1 year, she had repeated chest infections and was admitted to the hospital twice. At the age of 2 years, she developed chalazion in the right eye then in the left eye. Then she sought medical advice at our Genetics Clinic.

Family history was unremarkable. Both parents were normal.

On examination, the patient had moderate mental retardation, her weight was 6 kg (below 3rd percentile), her length was 80 cm (below 3rd percentile), and her skull circumference was 46.5 cm (15th percentile).

The patient had trigonocephaly, protruding forehead, low anterior hair line, wide upslanted palpebral fissures, chalazion in the left lower lid, bilateral Bitot's spots, depressed nasal bridge, broad nose, high arched palate, microretrognathia, low set ears, short neck, scoliosis and hypertrichosis over the back (Figs. 1–3). She also had talipes equinovarus (Fig. 4).

Cardiac examination was apparently normal. Abdominal examination revealed small umbilical hernia (Fig. 5). Genital and neurologic examinations were normal.

Abdomino-pelvic ultrasonography was normal. ECHO cardiography revealed interatrial septal defect. Extended metabolic screen, serum lactate and serum ammonium were normal. Karyotype was also normal. MRI brain revealed complete agenesis corpus callosum (Fig. 6), premature closure of metopic suture. Ophthalmology examination revealed lower eyelid chalazion, dryness and Bitot's spots in both eyes (Fig. 2). Fundus examination was normal.

3. Discussion

We report a 2.5 year old female child with Opitz trigonocephaly C syndrome (OTCS) with trigonocephaly, protruding forehead, low anterior hair line, wide palpebral fissures, chalazion in the left lower lid, depressed nasal bridge, broad nose, high arched palate, microretrognathia, low set ears, short neck, scoliosis, hypertrichosis over the back and talipes equinovarus.

Opitz trigonocephaly C syndrome (OTCS) is a rare and heterogeneous genetic disorder characterized by synostosis of metopic suture, dysmorphic facial features, variable mental



Figure 2 Facial features after surgery for craniosynostosis and bilateral Bitot's spots.



Figure 3 Hypertrichosis over the back.



Figure 1 Trigonocephaly, protruding forehead, low anterior hair line, wide upslanted palpebral fissures, chalazion in the left lower eye lid, depressed nasal bridge, broad nose, microretrognathia, low set ears and short neck.



Figure 4 Talipes equinovarus.



Figure 5 Small umbilical hernia.

retardation and cerebral anomalies. Fewer than 60 cases have been reported in the literature [3]. OTCS was first described in 1969 by Opitz [5]. Opitz et al. [5] described a brother and sister with a malformation syndrome that included unusual facies, polydactyly, cardiac abnormality and in boys cryptorchidism. Given the eponym C syndrome after the family name possibly with recessive inheritance.

Bohring et al. suggested the delineation or existence of a severe form of the C syndrome (the C-like syndrome, or Bohring-Opitz syndrome) [6,7]. C syndrome shows phenotypic overlap with Bohring-Opitz syndrome, or C-like syndrome, a disorder with more severe features than C syndrome, caused by heterozygous mutation in the ASXL1 gene on chromosome 20q11 [7].

Variable cardiac anomalies were described in the C syndrome including [8] patent foramen oval, atrial septal defect [9], ventricular septal defect with pulmonary hypertension, persistent ductus arteriosus and tetralogy of Fallot [10]. Our patient had interatrial septal defect.

Our patient also had small umbilical hernia. Lalatta et al. [11] reported a patient with a large omphalocele. Also Cabral de Almeida et al. [12] reported another example of large omphalocele with the C syndrome.

Our patient had normal genitalia. Shawky et al. reported a patient with C syndrome with hypoplastic scrotum with bilateral undescended testes [9].

Many cases with C syndrome showed variable skeletal anomalies; including flexion deformities of the upper limbs,

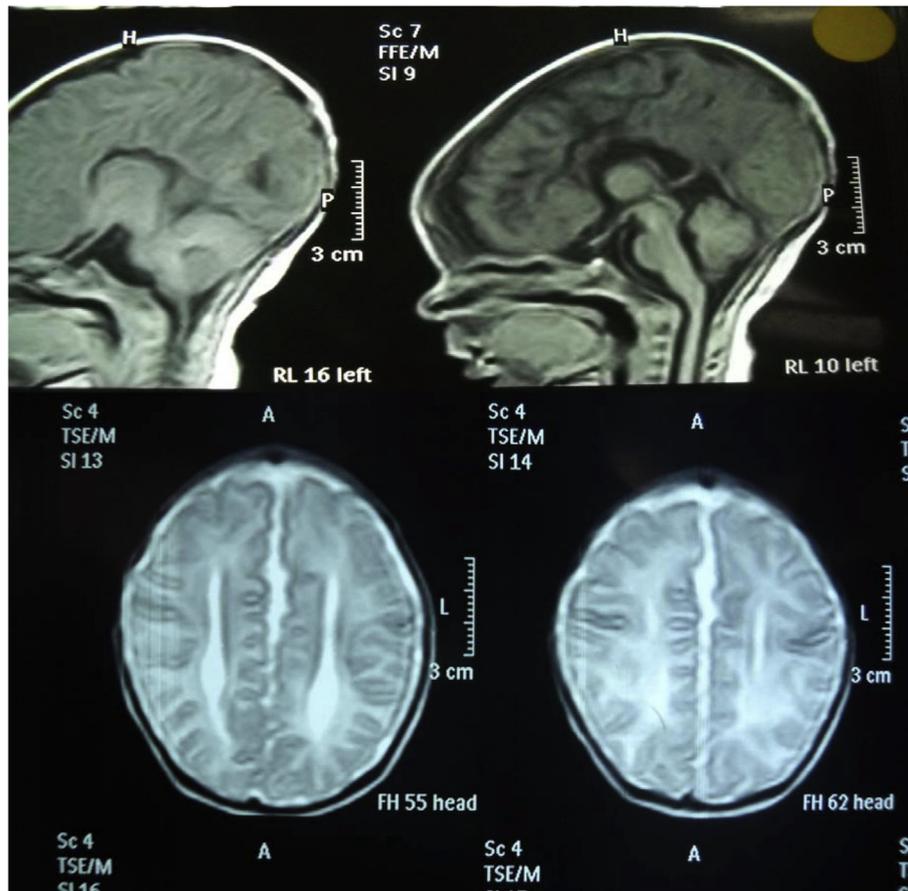


Figure 6 MRI brain revealed complete agenesis of corpus callosum.

dislocation of radial heads, short rhizo- and acromelic limb segments, hypermobile elbows with crepitus, polydactyly (usually postaxial), syndactyly, deformed chest, sacral dimple and varus or equinovarus deformities [6]. Our patient had scoliosis and talipes equinovarus.

Exophthalmos and retinal involvement were described in patients with C syndrome [6]. Our patient had lower eyelid chalazion, Bitot's spots and dry eyes which weren't reported before. Bitot's spots are the buildup of keratin located superficially in the conjunctiva, as a sign of vitamin A deficiency and are associated with conjunctival xerosis as reported in our patient [13].

Our patient had moderate mental retardation. However, Stratton et al. [14] reported a case with apparently normal development. Seizures are common in these patients with OTCS [1]. Our patient suffered from seizures at the age of 2 months, which stopped at the age of 1 year.

MRI brain scan of our patient demonstrated complete agenesis of corpus callosum and premature closure of metopic suture. Glickstein et al. [15] reported a girl who, in addition to typical manifestations of the C syndrome, had agenesis of the corpus callosum. Other brain anomalies reported in OTCS were not detected in our patient included dilation of the lateral and third ventricles, and absence of the cerebellar vermis [16]. Shawky et al. reported two cases of C syndrome with mild dilatation of the ventricular system with possible associated heterotopia and Dandy walker variant [8,9].

Our patient had a normal karyotype. Various chromosomal abnormalities, especially those that include chromosome 3, have been reported in patients originally described as having C syndrome [17]. These include 3p monosomy, [18] distal 3p trisomy [19], 3q trisomy [16], distal 3q trisomy with deletion of distal 3p [20], and inversion in chromosome 3 [21]. Chinen et al. [22] described a patient with a severe Opitz trigonocephaly C syndrome phenotype and balanced reciprocal translocation t(3; 18) (q13.13; q12.1).

C syndrome is inherited in an autosomal recessive fashion [5]. However, many other patients represent sporadic cases [17], with the recurrence risk being estimated at 10% which suggests the possibility of germline mosaicism [16,17]. The parents of our patient are not consanguineous, although consanguinity is high in Egypt [23], suggesting that our patient is most probably a sporadic case.

Opitz trigonocephaly syndrome can be caused by the disruption of the CD96 gene [24], which encodes a member of the immunoglobulin superfamily, on chromosome 3q13. Cells with mutated CD96 protein of the T280M type lost adhesion and growth activities in vitro. The findings indicated that CD96 mutations may cause a form of C syndrome by interfering with cell adhesion and growth [25].

A very high mortality rate has been described: almost 50% of patients with OTCS die within the first year of life [21]; however, some patients may have a good quality of life [11]. Our patient underwent surgery to correct the craniosynostosis. Some cases with OTCS died [21] after surgery for craniosynostosis repair.

To conclude: C syndrome is a rare syndrome characterized by trigonocephaly and metopic suture synostosis, dysmorphic facial features, short neck, skeletal anomalies, and variable intellectual disability. We reported a patient with the typical features of OTC syndrome who has in addition eyelid chalazion and Bitot's spots which were not reported before.

Conflict of interest

The authors declare no conflict of interest.

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