

C Syndrome in an Egyptian infant with dilated brain ventricles and heterotopia

Rabah M. Shawky¹ and Doaa I. Sadik²

¹Pediatric Department, ²Medical Genetics Center, Ain Shams University

ABSTRACT

C syndrome is an autosomal recessive disorder characterized by trigonocephaly, partial or complete obliteration of the metopic suture which is characteristic, and short limbs. In this paper we describe an Egyptian boy affected with this syndrome, with no exophthalmos and with dilated brain ventricles and heterotopia.

Key Words:

C syndrome, trigonocephaly, cutaneous syndactyly, metopic suture.

Corresponding Author:

Dr: Rabah M. Shawky
E-mail: : shawkyrabah@yahoo.com

INTRODUCTION

The C (Opitz trigonocephaly) syndrome (MIM 211750) is a malformation syndrome of unknown cause, and its mode of inheritance has been suggested to be an autosomal recessive. The syndrome comprises trigonocephaly and associated anomalies, such as unusual facies, wide alveolar ridges, multiple buccal frenula, limb defects, visceral anomalies, redundant skin, psychomotor retardation, and hypotonia^{1,2}. Recently^{3,4} suggested the delineation or existence of a severe form of the C syndrome (the C-like syndrome, or Bohring-Opitz syndrome [MIM 605039]). More recently Osaki et al.⁵ reported on a newborn infant who had many clinical features similar to those of the C-like syndrome but did not have exophthalmoses, which has been regarded as a hallmark of the C-like syndrome.

They suggested that the manifestations in this patient are a further indication of overlap between the C-like syndrome and the C syndrome. In addition, various chromosomal abnormalities, especially those that include chromosome 3, have been reported in patients originally described as having the C syndrome². These include 3p monosomy⁶ distal 3p trisomy⁷ 3q trisomy⁸ distal 3q trisomy with deletion of distal 3p⁹, and inversion in chromosome 3¹⁰. Although these cases might be removed from the C syndrome because they involve chromosome abnormalities, it is possible that there could be putative genes (or multiple loci) related to trigonocephaly and, even further, to pathogenesis of the C syndrome in chromosome 3.^{2,10}

Case report:

We encountered a 1 year old boy, the second in order of birth of a consanguineous marriage. He was born at full term and the pregnancy was uneventful, and weighted at birth 1.5 Kg, and there was history of failure to thrive. Pedigree analysis revealed one female sibling died suddenly during infancy from severe anemia at age 3 months without knowing the etiology of this anemia, and no other affected family members.

On examination, the patient had delayed motor and mental developmental milestones. His skull circumference was 42.5 cm (at the 5th centile), anterior fontanelle 1x1 cm, and his weight was 6.450 Kg (below 3rd centile). He had Midline forehead ridging (Figure 1a), mild trigonocephaly, supraorbital recession. His facial anomalies include bilateral upslanting palpebral fissures, epicanthal folds, convergent squint, and large cornea. He had low set posteriorly angulated ears (Figure 1b), wide alveolar ridges, and abnormal oral frenula, wide spaced teeth, high arched palate, upturned nares, thin upper and lower lips, long philtrum, and short neck (Figure 1c). Also he had significantly short limbs, fingers and toes with partial cutaneous syndactyly between the 3rd and 4th fingers and between the 2nd, and 3rd toes (Figure 2 a, b), abnormal dermatoglyphics in both hands in form of single crease in the fingers, rocker bottom feet and hypotonia in both upper limbs and lower limbs. Also he had rudimentary wide spaced nipples. Heart and abdominal examination were clinically free.

X-ray skull showed metopic fusions resulting in a trigone-shaped skull with bossing of the parietooccipital region (Figure 3).

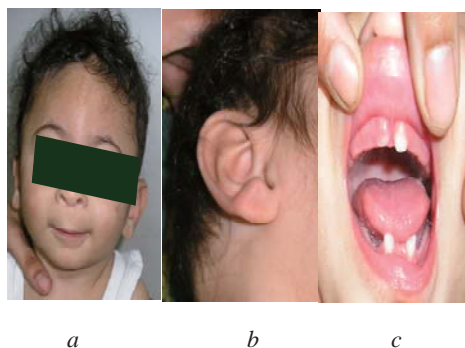


Fig. 1: Clinical features of C syndrome (a) Facial view showing forehead ridging, bilateral upslanting palpebral fissures, epicanthal folds, convergent squint, and large cornea (b) posteriorly angulated ears. (c) wide spaced teeth



Fig. 2: (a) Hand of the case showing fingers with partial cutaneous syndactyly between the 3rd and 4th fingers. (b) Foot of the case showing partial cutaneous syndactyly between the 2nd, and 3rd toes.

CT showed mild dilatation of the ventricular system especially the left lateral ventricle denoting mild atrophied brain changes with irregular ventricular margin with possible associated heterotopia (Figure 4).

Echocardiography showed no apparent significant cardiac lesion and patent foramen oval without significant left to right shunt. Abdominal ultrasound was normal. Cytogenetic analysis revealed normal male karyotype.



Fig. 3: X-ray skull showing metopic fusion resulting in a trigone-shaped skull with bossing of the parieto-occipital region.

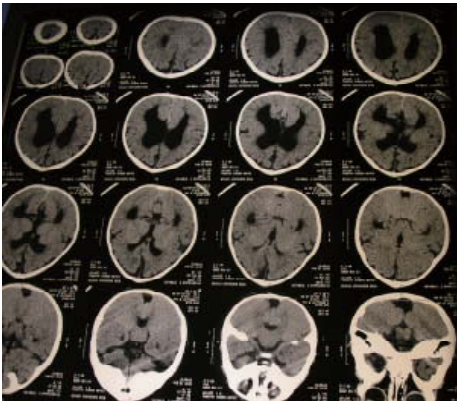


Fig. 4: Brain CT showing mild dilatation of the ventricular system and associated heterotopia.

DISCUSSION

Our patient had characteristic features of C syndrome. He had midline forehead ridging, mild trigonocephaly, upslanting palpebral fissures epicanthal folds, wide alveolar ridges, abnormal oral frenula, short limbs and fingers, with partial cutaneous syndactyly between the 3rd and 4th fingers and between the 2nd, and 3rd toes. There is enormous confusion in the delineation of C syndrome due to over reporting of a large number of cases whose only common feature is trigonocephaly. Anyone considering this diagnosis should refer back to the original paper of Opitz et al.¹. This reports a brother and sister

with an extremely specific malformation syndrome of which one of the least interesting features is trigonocephaly. Indeed trigonocephaly is not mentioned in the title, the abstract or anywhere in the article. Both sibs had loose skin, significantly short limbs, short fingers and toes and cutaneous syndactyly up to the end of the proximal phalanges in the hands and complete between the 2nd, 3rd and 4th toes. The palpebral fissures were upslanting and there were prominent epicanthic folds, a broad nose with anteverted nares, a wide mouth, thick alveolar ridges and multiple oral frenulae. They also reported hypermobile joints, a haemangioma of the forehead and a frontal cowlick, and internal malformations included an anomalous mesenteric attachment of the intestine, hepatomegaly, and a patent ductus arteriosus, and these findings are not present in our case. A skull radiograph in one sib was described as showing incomplete fusion of the inferior halves of the frontal bones, an osseous defect between orbits, (and) prominent ridging of metopic suture. Preus et al.¹¹ described 2 similar patients who were unrelated. Sargent et al.⁸ presented 12 cases of trigonocephaly of which 6 were associated with other malformations. Partial or complete obliteration of the metopic suture is characteristic. The forehead is narrow and pointed, often associated with biparietal widening and a triangular shape of the skull when viewed from above.

The phenotype in our case is a mild form with mild developmental delay and no severe visceral anomalies. Osaki et al.⁵, reported that there is controversial whether there is (1) a gradient of spectrum in the C syndrome, from the mild form (C syndrome), from the mild form (C syndrome) to the severe form (C-like syndrome), or (2) genetic

heterogeneity among the patients with the C syndrome.

Our case lacked exophthalmos which is characteristic of C like syndrome. Bohring et al.³, presented 4 unrelated cases of a syndrome resembling Opitz trigonocephaly (C) syndrome (211750). These cases differed from C syndrome on the basis of intrauterine growth retardation, cleft lip/palate, exophthalmos which is the hallmark of this syndrome, retinal involvement, flexion deformities of the upper limbs, dislocation of radial heads, and forehead hirsutism. Also Bohring et al.⁴, reported 4 additional unrelated cases of C like syndrome (Bohring-Opitz syndrome is alternative title) with the highly characteristic phenotype of facial anomalies including bulging forehead, frontal nevus flammeus, retrognathia, exophthalmos, hypertelorism, upslanting palpebral fissures, and cleft/lip palate. All showed severe failure to thrive, lack of development, brain abnormalities, and flexion deformities of upper limbs. Other features included hirsutism and possible hearing loss.

In our case, there is manifestations not recorded in the previously published patients, as wide spaced teeth, and mild dilatation of the ventricular system with possible associated heterotopia. Another neurological manifestations have been reported by Omren et al.¹³, who described a probable case of C syndrome in a patient who presented at the age of 12 years with symptoms of raised intracranial pressure due to medulloblastoma. Also Zampino et al.¹², described a child with trigonocephaly, strabismus, upslanting palpebral fissures, nasal bridge hypoplasia, hypertrophic alveolar ridges and large gingivolabial frenula, short neck, hip "dysplasia,"

equinovarus deformities, cryptorchidism, atrial septal defect ostium secundum, and severe mental retardation, findings consistent with C syndrome. The patient also had a Dandy-Walker malformation, complete callosal agenesis, and occipital meningocele. They reported that these structural defects are independent of the premature closure of the metopic suture, and confirm that midline brain anomalies are part of C syndrome. The hypothesis that the basic developmental defect in this syndrome primarily affects the midline field is supported by the concomitance of other anomalies, such as conotruncal heart defects, omphalocele, and genital anomalies.

The original report and other reports of affected sibs with the C syndrome suggested that the syndrome is inherited in an autosomal recessive fashion.¹⁴

Our case is an offspring of consanguineous parents and this favour the autosomal recessive inheritance. Normal chromosomes in most patients, unaffected parents with multiaffected offsprings, the equal sex ratio of affected individuals, and consanguineous matings^{1,2,8}. All support autosomal recessive inheritance. Meanwhile, many other patients have sporadic disease², and recurrence risk may be estimated to be 10%⁸, which suggests the possibility of dominant inheritance or germline mosaicism^{2,8,10}. These findings imply that the C syndrome is genetically heterogeneous, and its inheritance mode is in debate.³

In an individual with the C syndrome who harbors a balanced chromosomal translocation, t (3;18) (q13.13;q12.1) Kaname et al.¹⁴, Discovered that the TACTILE gene for CD96, a member of

the immunoglobulin superfamily, was disrupted at the 3q13.3 breakpoint. In mutation analysis of nine karyotype normal patients given diagnoses of the C or C-like syndrome, they identified a missense mutation (839C-->T, T280M) in exon 6 of the CD96 gene in one patient with the C-like syndrome. The missense mutation was not found among 420 unaffected Japanese individuals. Cells with mutated CD96 protein (T280M) lost adhesion and growth activities in vitro. These findings indicate that CD96 mutations may cause a form of the C syndrome by interfering with cell adhesion and growth.

CD96 was identified as a human T-cell-activated antigen in long-term culture and is known to interact with the poliovirus receptor, CD155, to recognize targets for natural killer (NK) cells.¹⁵ CD96 was found to be localized in the cytoplasm and cell-adhesion sites of the cell. The human CD96 gene is strongly expressed in the adult lung, spleen, and thymus and is moderately expressed in the adult spinal cord, kidney, trachea, digestive tissues, prostate, placenta, bone, fetal brain and liver. In 10-d-postcoitum mouse (dpc) embryos, Cd96 is expressed in the forebrain and in a front part of the head tissues, cardiac jelly, endothelial cells, pharynx, and blood cells. These expression patterns are consistent with organs and tissues involved in the abnormalities of the C syndrome that is trigonocephaly, redundant nuchal skin, and cardiovascular abnormalities.³

REFERENCES

1. Opitz JM, Johnson RC, McCreddie SR, Smith DW. The C syndrome of multiple congenital anomalies. *Birth Defects Orig.Art.Ser.* 1969; 5 (2): 161-6.
2. Gorlin RJ, Cohen MM, Hennekam RCM. *Syndromes of the head and neck.* 4th ed. USA: Oxford University Press; 2001.
3. Bohring A, Silengo M, Lerone M, Superneau DW, Spaich C, Braddock SR, et al. Severe end of Opitz trigonocephaly (C) syndrome or new syndrome? *Am.J. Med.Genet.* 1999 27; 85 (5): 438-46.
4. Bohring A, Oudesluijs GG, Grange DK, Zampino G, Thierry P. New cases of Bohring-Opitz syndrome, update and critical review of the literature. *Am.J.Med. Genet.A.* 2006 15; 140 (12): 1257-63.
5. Osaki M, Makita Y, Miura J, Abe N, Noguchi S, Miyamoto A. A Japanese boy with apparent Bohring-Opitz or "C-like" syndrome. *Am.J.Med. Genet.A.* 2006 15; 140 (8): 897-9.
6. Schwyzer U, Binkert F, Caffisch U, Baumgartner B, Schinzel A. Terminal deletion of the short arm of chromosome 3, del(3pter-p25): A recognizable syndrome. *Helv.Paediatr.Acta* 1987; 42 (4): 309-15.
7. McGaughan J, Aftimos S, Oei P. Trisomy of 3pter in a patient with apparent C (trigonocephaly) syndrome. *Am.J.Med.Genet.* 2000 2; 94 (4): 311-5.
8. Sargent C, Burn J, Baraitser M, Pembrey ME. Trigonocephaly and the Opitz C syndrome. *J.Med. Genet.* 1985; 22 (1): 39-45.
9. Preus M, Vekemans M, Kaplan P. Diagnosis of chromosome 3 duplication q23→qter, deletion p25→pter in a patient with the C (trigonocephaly) syndrome. *Am.J.Med.*

- Genet. 1986 ; 23 (4): 935-43.
10. Opitz JM, Putnam AR, Comstock JM, Chin S, Byrne JL, Kennedy A, et al. Mortality and pathological findings in C (Opitz trigonocephaly) syndrome. *Fetal. Pediatr. Pathol.* 2006; 25(4): 211-31.
 11. Preus M, Alexander WJ, Fraser FC. The C syndrome. *Birth Defects Orig. Artic. Ser.* 1975; 11(2): 58-62.
 12. Zampino G, Di Rocco C, Butera G, Balducci F, Colosimo C, Torrioli MG, et al. Opitz C trigonocephaly syndrome and midline brain anomalies. *Am.J.Med. Genet.* 1997. 31; 73 (4): 484-8.
 13. Omran H, Hildebrandt F, Korrinthenberg R, Brandis M. Probable Opitz trigonocephaly C syndrome with medulloblastoma. *Am.J.Med. Genet.* 1997 14; 69(4): 395-9.
 14. Kaname T, Yanagi K, Chinen Y, Makita Y, Okamoto N, Maehara H, et al. Mutations in CD96, a member of the immunoglobulin superfamily, cause a form of the C (Opitz trigonocephaly) syndrome. *Am.J.Hum. Genet.* 2007; 81 (4): 835-41.
 15. Fuchs A, Cella M, Giurisato E, Shaw AS, Colonna M. Cutting edge: CD96 (tactile) promotes NK cell-target cell adhesion by interacting with the poliovirus receptor (CD155). *J. Immunol.* 2004 1;172 (7): 3994-8.