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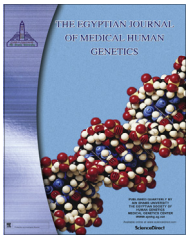

CASE REPORT

Opitz C syndrome: Trigonocephaly, mental retardation and craniofacial dysmorphism

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KEYWORDS

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Abstract We describe a 4-year-old female child with a dysmorphic and neurological syndrome of trigonocephaly, mental and psychomotor retardation and dysmorphic facial features. The anomalies of the face were the following: slight upward palpebral fissures, ocular hypertelorism, depressed nasal bridge, hypoplastic nasal root, short nose with anteverted nares; small low set ears, smooth broad philtrum and thin upper lip. The patient had important cerebral anomalies with diffuse alterations in white matter that caused developmental delay with verbal and nonverbal disabilities and severe learning difficulties. This clinical presentation is compatible with the diagnosis of the Opitz C syndrome, a heterogeneous disease of multiple neurological and craniofacial abnormalities. The physical sign more detectable and notorious is the trigonocephaly that is manifested by a prominent metopic suture, but also can be distinguished the other minor facial anomalies that are found in the eyes, nose, mouth and ears that constitute the phenotype of the disorder. The neurological development was altered by the compression of the cerebral frontal lobes with narrowing of this cerebral area, producing hypotonia with muscle weakness, epileptic episodes manifested by seizures, and neurobehavioral and neurocognitive disorders. This syndrome is a very rare genetic disorder with autosomal recessive inheritance trait; our patient had no chromosomal abnormality in the usual karyotype but the fluorescence in situ hybridization (FISH technique) showed a balanced translocation between the chromosomes two and eleven: t(2:11) (q32.2/q24).
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1. Introduction

The trigonocephaly is the manifestation from an abnormal synostosis in the metopic suture, it is a triangular shaped forehead as seen from top view. This is a sporadic condition in the majority of nonsyndromic cases, but that can be seen like the most important sign along other genetic syndromes [1] and this cranial characteristic is the main phenotypic feature of Opitz C syndrome. This was first described in 1969 when Opitz evaluated an affected family: one brother and one sister with trigonocephaly, unusual faces and severe mental retardation; both patients showed trigonocephaly by the

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prominent metopic suture by abnormal craniosynostosis [2]. the name with the "C" originated from the surname of this family, hence the eponymous name "Opitz C syndrome". Fewer than 60 cases have been reported in the worldwide literature [3]. Since almost all the patients have genetic etiology from de novo mutations in sporadic cases, it is suggested that the syndrome may be cytogenetically undetectable in the usual karyotype because the existence of a small microdeletion is only observed with the fluorescence in situ hybridization (FISH technique).

The premature closure of the metopic suture results in a growth restriction of the frontal bones, which leads to a skull malformation known as trigonocephaly [4]. There is insufficient knowledge about the genes that affect the formation of the base of the skull, the premature fusion of the metopic suture leads to the deformation of the anterior calvarium causing keel shaped deformity of the forehead, dysmorphic facial features, variable mental retardation and other somatic and cerebral congenital anomalies [5]. The unusual face present at birth includes eyes with upslanting palpebral fissures and ocular hypertelorism, nose with depressed nasal bridge and long philtrum; mouth with thin upper lip, and frequently the ears are in a low position [6]. The inheritance has been assumed to be autosomal recessive; then the syndrome is considered heterogeneous genetic disorder, predominantly sporadic but with sufficient familial cases [7] that may suggest dominant mutations with a rate of germinal mosaicism, or the presence of a recessive genocopy [8].

2. Case report

We report a 4-year-old girl with the main manifestations of Opitz C syndrome: mild motor and mental retardation, trigonocephaly and craniofacial dysmorphic features; that are the principal criteria for diagnosis. The family history was unremarkable; the marriage was non-consanguineous, the paternal age was 45, the maternal age was 36; the patient had other two siblings: an elder brother 18-year-old and a sister 11-year-old, all the family members were apparently healthy. The mother reported no exposure to teratogens and she did not drink any alcohol during the pregnancy. The newborn was obtained from 38 weeks of gestation, by cesarean section because of severe neonatal hypoxia before and during birth. The baby was considered small for her gestational age, the birth weight was 2525 g (7th percentile), length 41 cm (3rd percentile), and head circumference 32 cm (3rd percentile), the Apgar scores were 8 and 9. At birth was detected cranial anomaly with middle frontal protuberance with a triangular shaped forehead, it was diagnosed as congenital trigonocephaly. She had a mild delay in psychomotor development, including speech delay and early motor development retarded; she rolled over at age 7 months, had the head control at 9 months, and learned to sit independently at the age of 1, she stood momentarily without support at the age of 2; but the patient cannot walk. The speech development had a severe delay with the patient saying her first words like "mama" and "dada" at the age of 10; at age 20 months she had several single words, and now she occasionally can use 2 words together.

At the age of 2, the patient began with convulsive manifestations of infantile spasms, a neurologist diagnosed epilepsy that was corroborated by an electroencephalogram (EEG) pattern showing hypsarrhythmia with high disorganized and chaotic brain-wave; it was prescribed anticonvulsant medication: vigabatrin and valproate to obtain the control of the seizures. A cranial CT scan demonstrated a sharp angle and keel shape on the fronto-orbital area, leukodystrophy, demyelination and hypodense lesions at the subcortical areas in both hemispheres but mainly at occipital lobe and external capsule of basal ganglia; and there was significant hypomyelination of the periventricular white matter (Fig. 1).

Today the patient is 4-years-old, and now the physical examination reveals proportionate short stature with the following measures: height 75 cm (> 3rd percentile), weight 9.6 kg (> 3rd percentile) and head circumference 46 cm (> 3rd percentile) with prominent forehead and relative microcephaly. Her face shows a peculiar dysmorphism with the following features: a round face with prominent forehead, ocular area with arched eyebrows, slight upward palpebral fissures and widely spaced eyes; nasal area with wide and depressed nasal bridge, short and bulbous nose with anteverted nares, and broad smooth philtrum (Fig. 2); the ears have a low position, the mouth has a thin upper lip with tented vermillion and a broad lower lip; the jaw is narrow and there is a small chin (Fig. 3). The neurological examination detected a mild generalized hypotonia, clumsiness and awkward movements, global developmental delay with verbal and nonverbal disabilities. Her phenotype is a mild form of the syndrome with no severe visceral anomalies but has limb abnormalities like the small hands 8.5 cm (3rd percentile) with shortening of metacarpals and phalanges, and camptodactyly (cannot be extended) and clinodactyly (curved in the plane of the palm) of bilateral fifth fingers; she has small feet with measure of 11 cm (10th percentile) and there is an overlapping toe in the right foot, the fourth toe is dorsally positioned over the third (Fig. 4). The cytogenetic analysis using standard technique with banded metaphase chromosomes at the 500–750 band resolution was 46,XX karyotype; but FISH analysis showed balanced translocation between chromosomes two and eleven: t(2:11) (q32.2/q24).

3. Discussion

The C Opitz syndrome is a cerebral and craniofacial disorder, a very rare genetic disease and still under-recognized, the reviewed clinical criteria for diagnosis comprise: trigonocephaly with dysmorphic face, in patients with cerebral defects that have severe mental retardation [9]; the main dysmorphic features are the upward slanting palpebral fissures, ocular hypertelorism; depressed nasal bridge with hypoplasy of the nasal root, short nose with anteverted nares; smooth and broad philtrum, small ears in low position, and mouth with thin upper lip [10]. The syndrome has no chromosomal abnormality defined in the usual karyotype suggesting that this disorder may be a microdeletion syndrome which is cytogenetically detectable only with fluorescence in situ hybridization (FISH) that can show in some cases a genetic alteration by subtelomeric deletion in the long arm of different chromosomes like 3, 9 and 11 [11,12]; our case shows translocation at the chromosome 11 like other previous cases reported [13]. The syndrome has a complex phenotype due to the haploinsufficiency of one or more genes, in some patients was found that the CD96 gene is disrupted, identifying a missense

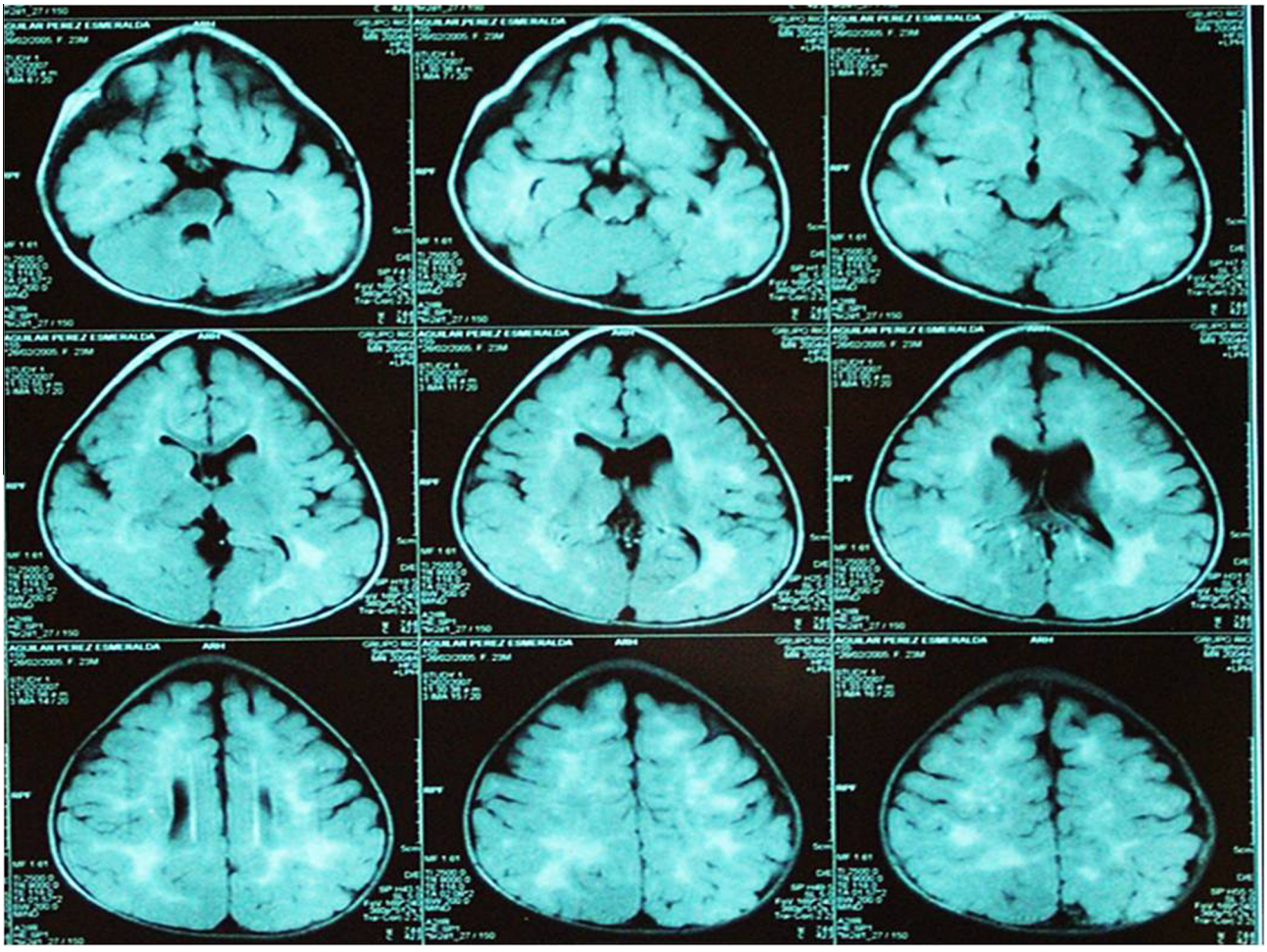

Figure 1 CT demonstrated cranial sharp angle and keel shape, hypodense lesions in the subcortical area and significant hypomyelination in white matter.

Figure 2 Dismorphic upper facial appearance: trigonocephaly, slight upslanted palpebral fissures, ocular hypertelorism, depressed nasal bridge and small nose.

mutation [14]; these mutations may cause a disease by interfering with adhesion and growth of the cells; recently were found some CD96 aberrations caused by genetic translocation [15]; the disorder is a heterogeneous genetic disease which occurs mainly sporadically, although there are some rare cases of familial occurrence that have been described; if the chromosome analysis performed in both parents is normal, this condition indicates that the translocation occurred for the first time by a new mutation. In our case, the parents and the siblings of the patient, all of them have normal stature and there are no craniofacial dysmorphic features, actually these parents no longer wish for new children and they rejected their cytogenetic studies; therefore it is not known if one of them is carrier of a genetic anomaly, if both parents were normal, the recurrence risk was low at 1%.

The trigonocephaly has been observed also as part of several chromosomal syndromes, the differential diagnosis of this case was performed with Jacobsen syndrome, a rare disorder with multiple dysmorphic features, caused by the terminal deletion of chromosome 11q, with cardiac defects and thrombocytopenia [16]; the Say–Meyer syndrome, X linked disease of trigonocephaly with short stature, developmental delay and ocular hypotelorism [17], and Frydman syndrome of

Figure 3 Dismorphic lower face: short and bulbous nose with anteverted nares; small low set ears, smooth broad philtrum, thin upper lip and mild micrognathia.

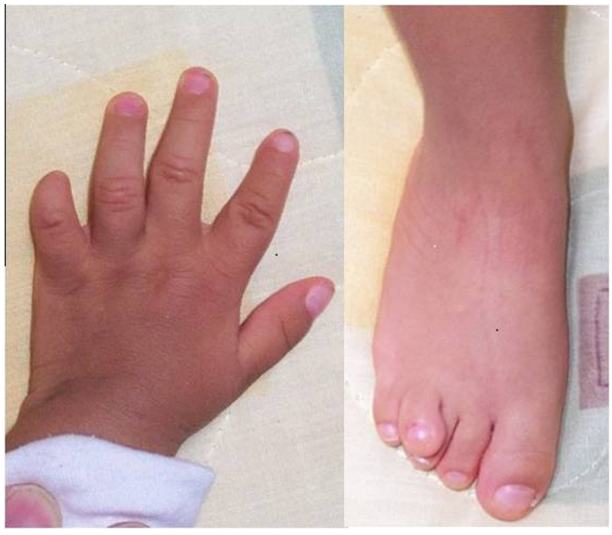

Figure 4 Small hands with camptodactyly and clinodactyly at the fifth finger; right foot with the fourth toe overlapping the third.

isolated trigonocephaly with normal psychomotor development, caused by heterozygous mutation in the FGFR1 gene [18].

The neurological defects of the C Opitz syndrome are usually important, with cerebral malformations and midline brain anomalies [19] like agenesis of the corpus callosum [20]. The trigonocephaly is associated with a remarkable incidence of intracranial abnormalities and the patient with neuropathology must be referred to pediatric neurology [21], and pediatric neurosurgery should be considered only if there are significant neurologic changes because of the craniosynostosis [22]. The patient's history of retarded mental and motor developmental delay is consistent with this syndrome [23]. Today she has regular monitoring of growth and receives speech therapy, her cognitive development is severely affected and needs extensive interdisciplinary rehabilitation; the infantile spasms disease is treated with appropriate anticonvulsant medications and has good control of seizures. All of her clinical and paraclinical features are consistent with the diagnosis of Opitz C syndrome.

Authors' contributions

All the authors JAAF and DAHA drafted the manuscript, performed the analysis and interpretation of data and revised the manuscript and made substantial scientific contributions. All authors have read and approved the final version of the manuscript.

Conflict of interest

The authors declare that they have no competing interests.

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