Correspondence

A Triploid Fetus Further Expands Etiological Heterogeneity in Holoprosencephaly-Diencephalic Hamartoblastoma

Marco Castori,[1]* Evelina Silvestri,[2,3] Josè Nunnari,[3] Paola Grammatico,[4] and Bruno Dallapiccola[5,6]

[1]Laboratory of Molecular and Cell Biology, IDI-IRCCS, Rome, Italy
[2]Division of Anatomopathology, San Giovanni Addolorata Hospital, Rome, Italy
[3]Division of Anatomopathology, S. Camillo-Forlanini Hospital, Rome, Italy
[4]Department of Experimental Medicine, Medical Genetics, University "La Sapienza", S. Camillo-Forlanini Hospital, Rome, Italy
[5]IRCCS-C.S.S. San Giovanni Rotondo and C.S.S.-Mendel Institute, Rome, Italy
[6]Department of Experimental Medicine, University "La Sapienza", Rome, Italy

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To the Editor:

Our group recently described a 23-week fetus with the association of holoprosencephaly-diencephalic hamortoblastoma (HDH) and reviewed the literature, identifying 19 additional patients with similar features. Both clinical and etiological heterogeneity were outlined, thus suggesting that HDH could indeed represent an overlapping phenotype of separate conditions, perhaps within a common morphogenetic pathway. In pathogenetic perspective, we hypothesized that the cause(s) for HDH may act early in gestation, probably during blastogenesis [Castori et al., 2007].

We had an opportunity to evaluate an additional fetus with HDH, born to a G1P0 36-year-old woman and a 33-year-old man. Family history was unremarkable. Following ultrasound detection of alobar holoprosencephaly (HPE) and severe IUGR, transabdominal amniocentesis performed at 17 weeks demonstrated a 69,XXX fetal karyotype. Pregnancy was terminated at 19 weeks. Physical examination showed a female fetus with a weight of 108 g (<3rd centile); crown-rump length, 13 cm; crown-heel length, 19 cm (<3rd centile); and head circumference, 13 cm (<3rd centile), suggestive of apparently symmetric growth restriction. Facial abnormalities included upslanting palpebral fissures, apparently low-set ears, premaxillary agenesis, ankyloglossia, retrognathia, and mild nuchal edema (Fig. 1A,B). Bilateral III–IV finger and II–V toe syndactyly, stubby great toe on the left, and sandal gap of the right foot were also evident (Fig. 1C–E). Necropsy findings comprised ostium secundum type interatrial septal defect, ventricular septal defect, "horseshoe" kidneys with cystic dysplastic disease of the fused inferior poles, and hypoplastic adrenal glands. The placenta was small (29 g, <3rd centile) with multiple calcifications and had no sign of hydatiform degeneration. Brain dissection showed alobar HPE with a single ventricle and the absence of the falx cerebri, corpus callosum, septum pellucidum, and olfactory tracts and bulbs. Both thalami were substituted by a mass extending over the optic chiasm and the right optic nerve (Fig. 2A). Microscopically, this mass was composed of disorganized relatively mature neurons, glial cells, ependymal elements, and vessels, without any cytological atypia (Fig. 2B,C). These findings were consistent with hypothalamic hamartoma (HH). The eyes were normally formed and histologic examination showed bilateral retinal dysplasia, manifested by numerous rosettes and minimal gliosis (Fig. 2D). Neuronal migration defects and other histological abnormalities were excluded. A radiographic survey confirmed limb anomalies and

*Correspondence to: Dr. Marco Castori, Laboratory of Molecular and Cell Biology, Isituto Dermopatico dell'Immacolata, IRCCS, Via dei Monti di Creta, 104, 00168 Rome, Italy. E-mail: m.castori@idi.it
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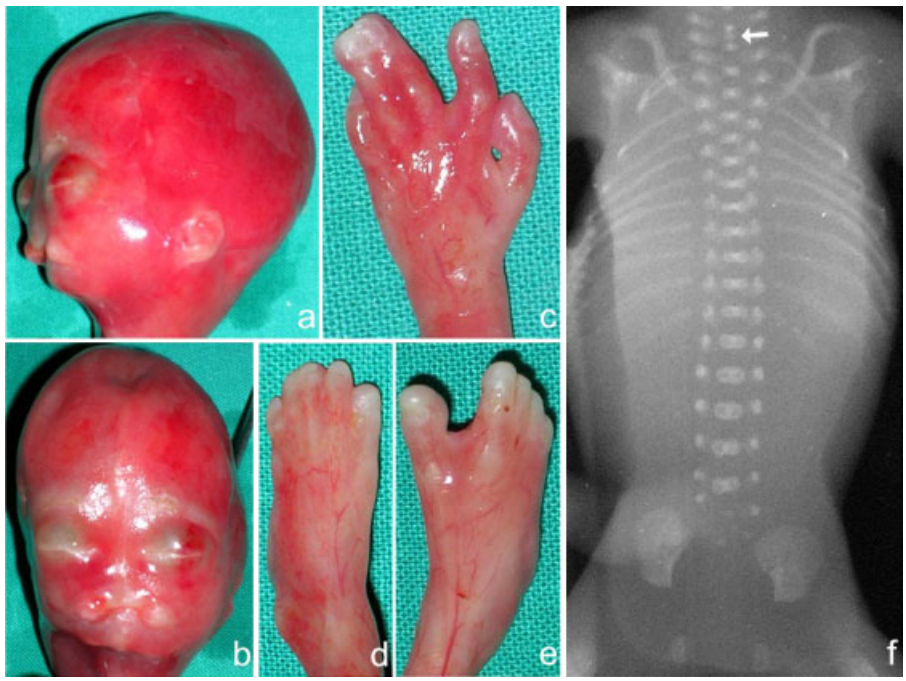

FIG. 1. Clinical and radiographic findings. Upslanting palpebral fissures, apparently low-set and malformed ears, premaxillary agenesis, retrognathia, and mild nuchal edema (**a,b**). III–IV finger and II–V toe syndactyly (**c–e**). Note stubby great toe on the left and sandal gap of the right foot (**d,e**). Eleven pairs of ribs, distal fusion of the first two right ribs, C6–C7 vertebral fusion (white arrow), non-specific sagittal clefts of the thoracic and lumbar segments, and delayed ossification of the sacral metameres (**f**). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

disclosed multiple defects of the axial skeleton, including 11 pairs of ribs, distal fusion of the first two right ribs, C6–C7 fusion, non-specific sagittal clefts of the thoracic and lumbar segments, and delayed ossification of the sacral metameres (Fig. 1F). The 69,XXX triploid karyotype was confirmed on cultured fibroblasts. Although fetal and placental anomalies were indicative of digynic triploidy, this suggestion was not molecularly confirmed, as the couple was lost to follow-up.

To the best of our knowledge, this fetus is the first instance of triploidy in HDH, further expanding the etiological heterogeneity of this condition; it supports the hypothesis that HDH may be a developmental field defect (DFD). HPE is not an unusual finding in triploidy and its frequency is age dependant. In fact, HPE is extremely common in first trimester triploid fetuses (22.2%), but rarer during the second trimester (3.1%), probably because the malformation is subject to an early demise [Jauniaux et al., 1996; Jauniaux et al., 1997]. However, neuropathological details in several of these cases are scarce. Thus, it is not possible to estimate the true frequency of HDH among triploid cases with HPE. It should be noted that triploidy is not the unique chromosome abnormality in reported cases of HDH because at least one HDH patient has been described with 7q36 terminal deletion [Kuller et al., 1992]. Therefore, meticulous neuropathological/radiological examination is indicated in HPE with chromosomal anomalies to exclude HH.

HH is observed in a wide spectrum of clinical entities [Verloes et al., 1992; Castori et al., 2007]. Nevertheless, while this feature has been reported occasionally in Bardet–Biedl syndrome, Waardenburg anophthalmia, orofaciodigital syndromes, and unclassified skeletal dysplasias [Somer et al., 1986; Munke et al., 1990; Diaz et al., 1991; Hingorani et al., 1991; Encha-Razavi et al., 1992; Sener, 1998], it has emerged that HDH is the most common form of "syndromal" HH, with 21 patients published to date (including the present case), second only to Pallister–Hall syndrome. Differential diagnosis between these two conditions is primarily based clinically on the absence of holoprosencephalic features and the presence of central polydactyly in the latter. Unlike Pallister–Hall syndrome in which molecular diagnosis is available, the wide etiological heterogeneity indicates a more difficult recurrence risk estimate in HDH. Although the risk may be as high as 50%, it seems to be very low in most cases, according to the DFD theory. However, genetic counseling entails investigating the possibility of parental consanguinity, teratogenic exposure (e.g., alcohol), and chromosomal anomalies, perhaps including subtelomeric rearrangement analysis in the affected individual. Moreover, as the diagnosis of HH usually requires specific training in fetal pathology, a second look at the histological material obtained from a previous malformed fetus/child could be useful in case of a positive family history.

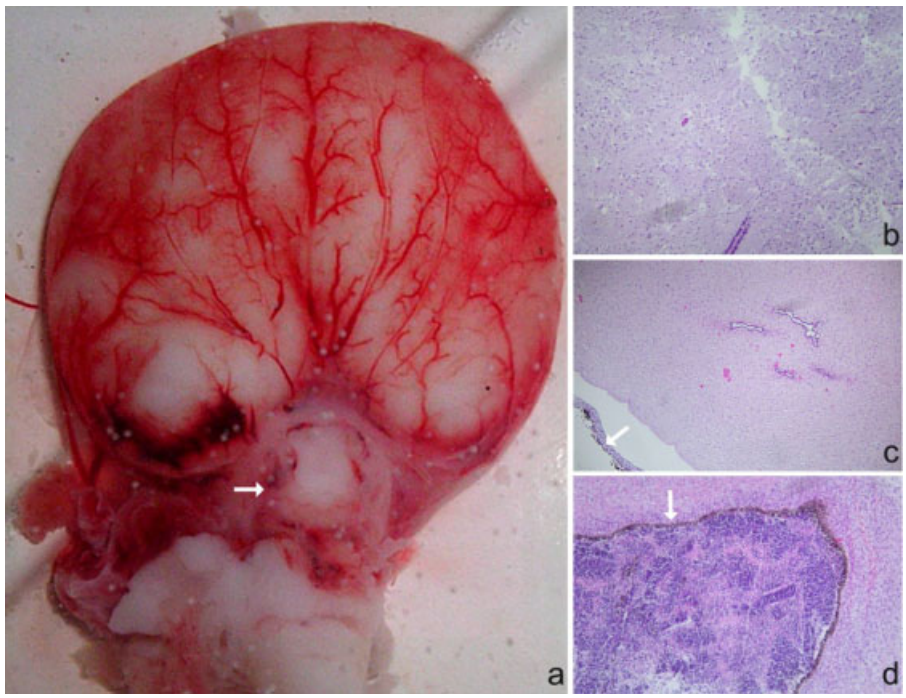

FIG. 2. Neuropathological findings. External appearance of the cerebrum showing alobar holoprosencephaly (HPE) and a hypothalamic hamartoma (HH) (arrow) extending over the optic chiasm (**a**). Disorganized relatively mature neurons, glial cells, and ependymal elements without any cytological atypia in the hypothalamic (**b**) and right optic nerve (**c**) regions (hematoxylin and eosin staining, original magnification 40×). Retinal dysplasia of the left eye (**d**; hematoxylin and eosin staining, original magnification 40×). Retinal epithelium is indicated by an arrow in (c) and (d). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

In the future, the identification of specific gene mutations could help in genetic counseling of HDH patients without a defined cause (e.g., chromosome abnormality or teratogenic exposure). Thus, in addition to *SHH*, which maps to 7q36, and was deleted in a case of HDH [Kuller et al., 1992], a possible candidate gene may be *SOX2*, which was recently reported as being mutated in a patient with HH, unilateral microphthalmia, and hypoplastic anterior hypophysis and corpus callosum [Kelberman et al., 2006].

REFERENCES

Castori M, Douzgou S, Silvestri E, Encha-Razavi F, Dallapiccola B. 2007. Reassessment of holoprosencephaly-diencephalic hamartoblastoma (HDH) association. Am J Med Genet Part A 143A:277–284.

Diaz L, Grech K, Prados M. 1991. Hypothalamic hamartoma associated with Laurence-Moon-Biedl syndrome. Case report and review of the literature. Pediatr Neurosurg 17:30–33.

Encha-Razavi F, Larroche JC, Roume J, Migne G, Delezoide AL, Gonzales M, Mulliez N. 1992. Congenital hypothalamic hamartoma syndrome: Nosological discussion and minimum diagnostic criteria of a possibly familial form. Am J Med Genet 42:44–50.

Hingorani SR, Pagon RA, Shepard TH, Kapur RP. 1991. Twin fetuses with abnormalities that overlap with three midline malformation complexes. Am J Med Genet 41:230–235.

Jauniaux E, Brown R, Rodeck C, Nicolaides KH. 1996. Prenatal diagnosis of triploidy during the second trimester of pregnancy. Obstet Gynecol 88:983–989.

Jauniaux E, Brown R, Snijders RJ, Noble P, Nicolaides KH. 1997. Early prenatal diagnosis of triploidy. Am J Obstet Gynecol 176:550–554.

Kelberman D, Rizzoti K, Avilion A, Bitner-Glindzicz M, Cianfarani S, Collins J, Chong WK, Kirk JM, Achermann JC, Ross R, Carmignac D, Lovell-Badge R, Robinson IC, Dattani MT. 2006. Mutations within Sox2/SOX2 are associated with abnormalities in the hypothalamo-pituitary-gonadal axis in mice and humans. J Clin Invest 116:2442–2455.

Kuller JA, Cox VA, Schonberg SA, Golabi M. 1992. Pallister-Hall syndrome associated with an unbalanced chromosome translocation. Am J Med Genet 43:647–650.

Munke M, McDonald DM, Cronister A, Stewart JM, Gorlin RJ, Zackai EH. 1990. Oral-facial-digital syndrome type VI (Varadi syndrome): Further clinical delineation. Am J Med Genet 35:360–369.

Sener RN. 1998. Cranial MR imaging findings in Waardenburg syndrome: anophthalmia, and hypothalamic hamartoma. Comput Med Imaging Graph 22:409–411.

Somer M, Lindahl E, Perheentupa J. 1986. Precocious puberty associated with oral-facial-digital syndrome type I. Acta Paediatr Scand 75:672–675.

Verloes A, Gillerot Y, Langhendries JP, Fryns JP, Koulischer L. 1992. Variability versus heterogeneity in syndromal hypothalamic hamartoblastoma and related disorders: Review and delineation of the cerebro-acro-visceral early lethality (CAVE) multiplex syndrome. Am J Med Genet 43:669–677.