Hydatidiform mole: parental chromosome aberrations in partial and complete moles

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SUMMARY The relationship between parental constitutional chromosome abnormalities and the development of hydatidiform mole was evaluated in series from four institutions. Karyotype analysis was performed on blood samples from 237 patients with a pathological diagnosis of complete mole and 217 of their spouses. One patient was found to have a constitutional balanced translocation, t(11;18), while one spouse was found to have a balanced translocation, t(4;20). Among 125 patients with partial mole and 106 of their spouses, one male was found to be a translocation carrier, t(13;14). No significant increase in the frequency of translocations in the parents of complete moles was found in any of the series considered separately or together. Data from the combined series show no evidence of constitutional parental chromosome aberrations as an aetiological factor in the development of molar pregnancies.

Hydatidiform moles are of interest because of their potential to progress to trophoblastic tumours. Pathologically and genetically there are two types of hydatidiform moles, complete and partial, the former having the more malignant potential.

Demonstration of diploid androgenesis in complete moles by Kajii and Ohama¹ and Wake *et al*² raised the question of the mechanism of origin. The most likely mode of origin suggested is that of fertilisation of an anucleated egg, in which the chromosomes are inactivated or expelled as a polar body, by a haploid sperm whose chromosomes are duplicated.³⁻⁵

Structural chromosome aberrations in women who produce complete moles have been reported to be more frequent than in the general population. Kajii and Ohama¹ described two patients who were translocation carriers, t(7;8) and t(3;22), among 35 couples with molar pregnancies. Lawler *et al*⁵ observed one translocation carrier t(11;18) among 26 women karyotyped in an investigation of 50 complete moles. Based on these observations, it was suggested that structural chromosome aberrations in women might interfere with meiosis, thus increasing

the number of anucleated eggs and providing an increased risk for molar pregnancy.

We have compiled data from parental chromosome examinations in four centres investigating cytogenetic markers in molar pregnancies. The aim of this collaboration was to perform a reliable statistical analysis of the relationship between parental chromosome aberrations and the risk of developing a molar pregnancy.

Material and methods

At The John F Kennedy Institute (JFK), the Royal Marsden Hospital (RMH), Magee-Womens Hospital (MWH), and Hokkaido University (HU), chromosome data were obtained during prospective studies on the genetics of molar pregnancies. Morphological diagnoses of complete (CHM) and partial (PHM) hydatidiform mole were ascertained according to the criteria stated by Szulman and Surti.⁶ Chromosome analysis was performed in 237 couples after the diagnosis of a complete mole. In 20 cases, the paternal karyotype was not available. Similarly, 125 couples with a partial mole were karyotyped. Among these, 19 paternal karyotypes were not investigated. The distribution of cases among the participating centres is presented in table 1.

Received for publication 18 June 1986.

Revised version accepted for publication 11 July 1986.

TABLE 1 Chromosome analysis of couples with hydatidiform mole.

	RMH		MWH		JFK		HU		Total	
	CHM	PHM	CHM	PHM	CHM	PHM	CHM	PHM	CHM	PHM
Patient and spouse karyotypically normal	72	26	46	76	41	3	56	0	215	105
Patient normal, spouse not examined	8	2	10	16	1	1	1		20	19
Patient normal, spouse aberration	1			1					1	1
Spouse normal, patient aberration	1								1	
No of molar pregnancies	82	28	56	93	42	4	57	0	237	125

RMH: the Royal Marsden Hospital; MWH: Magee-Womens Hospital; JFK: The John F Kennedy Institute; HU: Hokkaido University. CHM: complete mole; PHM: partial mole.

TABLE 2 Parental chromosome aberrations in 362 cases of molar pregnancy.

Karyotype	
46,XX,t(11;18)(q21;p11)	CHM: patient
46,XY,t(4;20)(q21;q13-2)	CHM: spouse
45,XY,t(13q;14q)	PHM: spouse

CHM: complete mole. PHM: partial mole.

In all cases, peripheral blood lymphocytes were stimulated in culture by phytohaemagglutinin. Cells were arrested in metaphase by the addition of colcemid. Slides were made from acetic alcohol fixed material and metaphases stained using standard G banding or QM banding techniques. In each case a minimum of 10 metaphases were analysed.

For statistical calculation a binomial distribution was assumed and the exact 95% confidence limits calculated.

Results

Three cases were found to have balanced translocations (table 2). In 237 women with a complete mole, only one had an abnormal karyotype, a balanced translocation, t(11;18)(q21;p11). This case has been previously described.³ The incidence of women with a balanced translocation in the RMH series was thus 1 in 82 (1.22% (0.03 to 6.61%)) and in the combined series 1 in 237 (0.42% (0.01 to 2.35%)). Among the corresponding 217 spouses investigated, one had an abnormal karyotype, 46,XY,t(4;20)(q21;q13-2). The incidence in the RMH series was thus 1 in 74 (1.35% (0.03 to 7.30%)) and in the combined series 1 in 217 (0.46% (0.01 to 2.57%)).

The risk of being a translocation carrier for either the woman or the spouse in couples with CHM was 2 in 74 (2.70% (0.33 to 9.42%)) in the RMH series and in the combined series 2 in 217 (0.92% (0.11 to 3.33%)). The incidence for the general population reported by Buckton *et al*⁷ is 1.2% ($((0.006 \times 0.994 \times 2) + 0.006^2) \times 100$).

A total of 125 women with a diagnosis of partial mole showed no chromosome aberrations. In these couples one male partner out of 106 karyotyped (0.9% (0.02 to 5.19%)) was a carrier of a balanced Robertsonian translocation of chromosomes 13 and 14.

Chromosome variants including inv(9), fragile sites, and single cell aberrations were not included in this analysis.

Discussion

The observation of diploid androgenesis in complete¹⁻⁵ and paternally derived triploidy in partial moles^{8,9} suggested that genetic factors were involved in the development of molar pregnancies and led to further studies on the genetics of molar pregnancies, including examination of parents for constitutional chromosome aberrations. Balanced translocations may interfere with female meiosis and consequently produce eggs with absent or inactivated nuclei. The frequency of translocation carriers among patients with molar pregnancy has been previously reported as 6%¹ or 4.6%,⁵ considerably higher than that cited for the general population.^{7,10}

The incidence of translocation carriers in women with CHM in the RMH series alone (1.22% (0.03 to 6.61%)) and in the combined series (0.42% (0.01 to 2.35%)) was within 95% confidence limits for the incidence in the normal population. Neither was the chance of being a translocation carrier for either the woman or the spouse increased in the RMH series considered alone (2.70% (0.33 to 9.42%)) or in the combined series (0.92% (0.11 to 3.33%)), when compared to the incidence of 1.2% calculated for couples in the general population.

The incidence of moles varies considerably among different regions. In spite of recent advances in research, this is not readily explained. Since genetic mechanisms are involved in molar conceptions, differences in incidence may reflect different genetic constitutions in the populations observed. Population based studies indicate a higher rate of hydatidi-

form moles in Japan compared with USA and western Europe.¹¹ However, in the present study the chromosome aberrations were observed in areas with a low incidence of molar pregnancies.

Three couples where one partner had an abnormal karyotype were observed among the 323 couples studied. In all three, different chromosomes were involved in the translocations. Although the proportion of CHM to PHM varies in the different series, constitutional abnormalities occurred in couples with both CHM and PHM. Translocations were found in both patients and their spouses. If translocations were important to the development of ova with absent or inactivated nuclei, one might expect the incidence of translocations to be highest in the mothers of complete moles.

Chromosome variants and fragile sites have been considered in relation to recurrent pregnancy losses.¹² However, they have not been evaluated in this study and their significance in couples with molar conceptions remains to be investigated.

Results from the present collaborative study indicate that the incidence of constitutional structural chromosome aberrations in couples with PHM or CHM did not differ significantly from the incidence in the general population. Thus, the morphological diagnosis of hydatidiform mole is not necessarily an indication for parental chromosome examination. However, analysis of parental markers is essential for differentiation between homozygous and heterozygous androgenesis, two cell lines having identical karyotypes with different heteromorphisms, exclusion of maternal cells contaminating cell culture, and determination of the origin of additional chromosomes or chromosome complements.

In view of the low incidence of translocations observed in couples with molar conceptions, the fact that they occur in couples with both complete and partial moles and in both maternal and paternal chromosomes, and that they are not localised to any part of the genome, there appears to be little evidence that constitutional abnormalities in the parents have an aetiological role in the development of molar pregnancies.

In the Danish study the cooperation of the medical staff at the gynaecological and obstetric departments throughout the country is gratefully acknowledged. Thanks are due to the pathologists at the local pathological departments and at Aarhus Municipal Hospital for the histopathological evaluation. The

cytogenetic investigations were supported by the Danish Medical Research Council, grants no 12-4514, 12-5302, and 12-5580. In the British study we should like to thank the many obstetricians who collaborated in our studies. The work was supported by a Medical Research Council grant to the Fetal Tissue Bank and the Joint Medical Research Council/Cancer Research Campaign funding of the Section of Human Genetics. The study at MWH was supported by NIH grant No HD17572, March of Dimes grant No 6-283, and the Magee-Women's Hospital Research Fund. The technical assistance of Ms Kathleen Wagner and Ms Shubha Mullick and the cooperation of the medical staff at MWH is gratefully acknowledged. We want to thank Ib Jarle Christensen for the statistical evaluations.

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