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Review Article

Clinical and genetic-epignetic aspects of recurrent hydatidiform mole: A review of literature

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ABSTRACT

Hydatidiform Mole (HM) is the most common form of Gestational Trophoblastic Disease (GTD), defined by hyper-proliferation of trophoblastic cells. HM is typified as abnormal proliferation of extraembryonic trophoblastic (placental) tissues and failure of embryonic tissues development and is the only GTD with Mendelian inheritance, which can reoccur in different pregnancies. Moles are categorized into Complete Hydatidiform Moles (CHM) or Partial Hydatidiform Moles (PHM) and a rare familial trait, which forms a CHM and despite having androgenetic pattern, shows normal biparental inheritance, conceived from one sperm and egg. Recessive maternal-effect mutations in *NLRP7* (NACHT, leucine rich repeat and PYD containing 7) and *KHDC3L* (KH Domain Containing 3-Like) genes have been shown to be responsible for Recurrent Hydatidiform Moles (HYDM1 MIM# 231090 when is caused by mutation in the *NLRP7* gene and HYDM2 MIM#614293 when is caused by mutation in the *KHDC3L* gene). Methylation aberration in multiple maternally imprinted genes is introduced as the cause of Recurrent HYDM pathology. The current article reviews the histopathology, risk factors, and genetic and epigenetic characteristics of Recurrent HYDMs.

Epidemiology and risk factors

Incidence

The incidence of gestational trophoblastic disease is both geographic and ethnic-related. Due to high incidence of molar pregnancy in some populations, studies have associated low socio economic status with high incidence of GTD [1]. GTD incidence is three to four times higher in Asia, Africa and Latin America than in North America and Europe. GTD incidence has remained relatively constant at 1 to 2 per 1000 deliveries in Europe and in United States [2]. However, despite substantial economic achievements over the recent years, Japan yet shows a relatively high frequency (3 in 2000 deliveries in 2000 and 1/500 pregnancies in 2003) of molar pregnancy. On the other hand, GTD occurs in a rate of 28 per 1000, 8.5 per 1000, 9.8 per 1000 and 2 per 1000 in Pakistan, Brazil, Finland and Sweden respectively [2,3]. As documented, Hispanics and Native Americans residing in the United States and certain population groups in South East Asia show a higher incidence of molar pregnancy compared to the rest of the population living in the same countries 8 [4]. Considering the global statistics, genetic, nutritional and environmental factors also seem to play roles in GTD development [3]. The incidence of Hydatidiform Mole in Hamadan in west of Iran was estimated 3.34 per 1000 pregnancies between 1997 and 2006. Among the cases with mole, 53.29% were complete and 46.71% were partial mole [5].

Risk factors

Clinical studies have been carried out to identify risk factors for molar pregnancy and discover whether factors differ in CHM or PHM. Maternal age at upper and lower extremes, i.e. teenage women and those aged over 35 have 2–3 fold increased risk of

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developing complete molar pregnancy [2]. This risk escalates up to 7 fold for women older than 40 years, which could be attributed to higher susceptibility of ovum from old women to abnormal fertilization. Old paternal age, history of spontaneous abortion or previous gestational trophoblastic disease, low dietary intake of carotene and vitamin A deficiency [6], certain ABO blood groups and smoking have been reported to carry a higher risk of CHM development. On the other hand, there is limited knowledge concerning risk factors for partial molar pregnancy. Oral contraceptive use and history of irregular menstruation have been linked to increased risk of PHM development. However, no association between maternal or dietary intake with partial mole has been reported [6]. Recurrent HYDM is a sub-class of CHM and clearly mentioned risk factors, threaten women to develop also this form. However One most significant risk factor associated with recurrent HYDM is maternal homozygous and compound mutations in maternal effect genes, *NLRP7* and C6ORF221, further discussed below [7]. Moreover, other factors including previous molar pregnancy either partial or complete, family history of molar pregnancy and maternal age over 40 has also been mentioned [1].

Clinical presentation and diagnosis

Due to current routine use of para clinical technology, the clinical presentation of molar pregnancy has been transformed drastically over the past few decades. Serum β-hCG measurement and transvaginal ultrasonography have reduced the mean gestational age of complete molar diagnosis from 16 to 17 weeks in 1960s and 1970s to 12 weeks, today. A significant feature of molar pregnancies is their overproduction of β-hCG as the consequence of trophoblastic overgrowth, resulting in markedly high levels of serum β-hCG in excess of that expected for the gestational age [8]. However, first trimester serum β-hCG levels may not always be elevated, in which cases sonography has proved to be a more useful tool for molar pregnancy diagnosis [9,10]. Sonographic appearance of CHM reveals a diffuse intrauterine complex echogenic mass with tiny cystic spaces and absent fetal tissue [9]. On the contrary PHM sonographic feature is characterized by a thickened hydropic placenta with a concomitant fetus [10].

Histopathology

Trophoblastic diseases are characterized by aberrant histological changes within placenta. Being the most common form of gestational trophoblastic disease, hydatidiform mole specifically is characterized with abnormal or absence of fetal development, excessive trophoblastic overgrowth and hydropic villous degeneration [11]. In microscopic evaluation, CHM, which represents approximately 75% of molar pregnancies involves diffuse edematous villi and trophoblastic hyperplasia in the entire placenta [12]. Macroscopically, no fetal tissue or amnion development is observed. As apparent from the term partial HM, the extent of villous edema, trophoblastic proliferation and signs and symptoms are comparatively lower than that of CHM. Furthermore, partial moles contain fetal tissue and amnion in addition to placental tissue.

Hematoxylin & eosin (H&E) staining of sections of chorionic villi from CHMs reveals the presence of excessive circumferential trophoblastic proliferation around most CVs with no embryonic tissue of inner cell mass origin such as fetal membrane, cord or nucleated blood cells. That is completely in contrast to H&E stained sections of PHMs in which mild or focal trophoblastic proliferation of some CVs along with fetal tissues and sometimes even abnormal or normal complete fetus are displayed [13].

Recurrent HYDM is a familial pathology defined by the occurrence of at least two moles in the same patient and affects 1.5–9.3% of women with a prior HM [14]. Recurrent HYDMs mostly are CHM. Although some PHM have been described and in the rare cases the woman also had live-born offspring [13,15]. They are phenotypically like CHM of androgenetic origins (AnCHM) wherein both genomes being paternally derived. It means both parents contribute equally their genome to the formation of this kind of mole. Biparental HYDMs have familial property and can recur more times in the same individual. Clearly recurrent pattern in the case of single pregnancy is senseless and so the best candidate nomination for Recurrent HYDM is Biparental HM (BiHM) [11,12]. The absence of bias for one of two genomes in these moles and the phenotype of HMs in the same time, indicate that this pathology is linked to any deregulation in imprinted genes expression.

Genetic basis of recurrent HYDMs and responsible genes

Genetically, CHMs have diploid karyotypes, 85% of which are result of androgenesis. In androgenesis a chromosomally inactivated or enucleated ovum is fertilized by a haploid sperm, which then duplicates via meiosis producing 46XX karyotype with complete paternal origin [16] (Fig. 1-A, Modified from Williams and colleagues, 2010 [12]). In the remaining, dispermic fertilization of a single ovum results in 46XY paternal karyotype (Fig. 1-B, Modified from Williams and colleagues, 2010 [12]). Apparently 46YY karyotype never survives. PHMs in contrast, show triploid karyotypes. Most PHMs are reported to develop from dispermic fertilization of an egg showing 69XXX or less occasionally 69XYY (Fig. 1-D, Modified from Williams and colleagues, 2010 [12]). However, 69XYY also less commonly arises from fertilization of an egg by a single diploid sperm [12].

Recurrent HYDM is a sub group of CHM and despite having androgenetic phenotype shows normal biparental inheritance, conceived from one sperm and egg (Fig. 1-C, Modified from Williams and colleagues, 2010 [12]). The karyotype of these moles is 46XX or 46XY. Recessive maternal-effect mutations in *NLRP7* and *KHDC3L* (also known as C6ORF221) genes have been shown to be responsible for Recurrent HYDM [1,17]. The best method to differentiate this form of moles is genetic testing [18]. In most of women with Recurrent HYDM, homozygote or compound heterozygote mutations have been seen in *NLRP7* or *KHDC3L* genes [19].

NLRP7

Initially linkage analysis has shown that in most families the gene responsible for Recurrent HYDM is located on 1.1 Mb region on chromosome 19q13.4. Mutations in this gene result in imprinting dysregulation in the female germ line with abnormal development of both embryonic and extraembryonic tissues [20]. As women continued to have recurrent molar pregnancies with more than one partner, autosomal recessive pattern was suggested in women themselves responsible for disrupting normal oocyte fertilization with no paternal genomic involvement [12,21]. In 2006 Murdoch and colleagues identified *NLRP7* (NOD-like receptor pyrin domain (PYD)- containing 7) as the candidate maternal-effect gene responsible for Recurrent HYDM and reproductive wastage such as spontaneous abortions and stillbirths [22]. *NLRP7* is located on 19q13.42 and encodes for a protein of 1037 amino acids. *NLRP7* belongs to the CATERPILLER family of proteins and contains four conserved and functional domains consists of a N-terminal pyrine domain, 9–10 leucine-rich repeats (LRRs) depending on splice isoforms in C-terminal domain, NACHT-associated domain (NAD) (physical mediator for oligomeric assembly) and a NACHT region in the middle of the protein (this domain contain Walker A/Ploop motif which is a binding site for ATP) (Fig. 2) [23,24]. Unlike LRR and pyrine domains on *NLRP7*, which are involved in protein–protein