HYDATIDIFORM MOLE - A LITERATURE REVIEW

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ABSTRACT

Hydatidiform moles are intriguing pathologic entities representing abnormal placental villous tissue with unique genetic profiles and a wide spectrum of morphologic features, which makes accurate diagnosis challenging. Over representation of the paternal genome in sporadic hydatidiform moles (purely androgenetic in complete hydatidiform moles and triploid in partial hydatidiform moles) is a fundamental genetic event leading to global alteration of imprinting gene expression in the molar trophoblast. Rare familial biparental hydatidiform moles (due to *NLRP7* or *KHDC3L* mutations) share such global imprinting alterations, implying a common end point of pathogenesis. Despite being the cornerstone of diagnosis, routine morphologic assessment of hydatidiform moles continues to suffer from interobserver diagnostic variability, emphasizing the need for new diagnostic modalities. Analyses of p57 expression by immunohistochemistry and polymerase chain reaction–based DNA genotyping have emerged as powerful diagnostic methods for accurate classification of hydatidiform moles.

Keywords

- Genetic basis,
- Hydatidiform mole,
- p57,
- Precision diagnosis,
- Genotyping

BACKGROUND OF DATA

Hydatiform mole (also known as molar pregnancy) is a subcategory of diseases under gestational trophoblastic disease (GTD), which originates from the placenta and can metastasize. It is unique because the tumor originates from gestational tissue rather than from maternal tissue. Other forms of gestational trophoblastic disease include gestational choriocarcinoma (which can be extremely malignant and invasive) and placental site trophoblastic tumors. Hydatiform mole (HM) is categorized as a complete and partial mole and is usually considered the noninvasive form of gestational trophoblastic disease. Although hydatiform moles are usually considered benign, they are premalignant and do have the potential to become malignant and invasive.

ETIOLOGY

Hydatiform moles are divided into complete and partial moles. Complete mole is the most common type and does not contain fetal parts, whereas in a partial mole there might be identifiable fetal residues. Complete moles are typically diploid, whereas partial moles are triploid. Complete moles tend to cause higher levels of the human chorionic gonadotropin (hCG), which is one of the main clinical features of this process. In complete moles, the karyotype is 46, XX 90% of the time and 46, XY 10% of the time. It arises when an enucleated egg is fertilized either by two sperms or by a haploid sperm that then duplicates and therefore, only paternal DNA is expressed. On the other hand, in partial moles, the karyotype is 90% of the time triploid and either 69, XXX or

69, XXY. This karyotype arises when a normal sperm subsequently fertilizes haploid ovum duplicates and or when two sperms fertilize a haploid ovum. In partial moles, both maternal and paternal DNA is expressed.

INCIDENCE OF HYDATIDIFORM MOLES

The incidence of GTD is generally reported in relation to the total number of pregnancies or deliveries in a study cohort rather than in the total population. It is worth noting that epidemiological data curated from CHMs are far more accurate than those that also include PHMs, as significant diagnostic problems exist in the routine evaluation of the latter. The highest incidence of hydatidiform mole per 1,000 pregnancies is seen in Southeast Asia, with rates of 13.0 in Indonesia, 8.0 in Taiwan, 5.0 in the Philippines and China, and 1.9–4.9 in Japan. North America, Europe, and Oceania have the lowest incidence, with approximately 0.5–1.84 per 1,000 pregnancies. A few African nations have documentation in English of the incidence of the disease, which is close to 5.0 per 1,000 pregnancies. Data from South America is also limited, with reported incidence ranging from 0.2 to 0.3 per 1,000 pregnancies. Recent reports showed a significant reduction in the incidence of GTD in Korea, where the rate has fallen from 4.4 per 1,000 pregnancies in the 1960s to 2.3 per 1,000 pregnancies in the 1990s and in Japan, where a reduction in the incidence of hydatidiform mole from 4.9 to 1.9 per 1,000,000 cases in the general population was reported. Saudi Arabia and Taiwan reported a similar trend. The most recent population-based data from the Netherlands, however, indicate that the incidence of hydatidiform moles has kept steady between 1.2 and 1.6 per 1,000 deliveries over the past 20 years.

EPIDEMIOLOGY

There is a very low frequency of hydatiform moles. In North America and Europe, the frequency has been described as 60 to 120/100,000 pregnancies for hydatiform moles. The frequency has been shown to be higher in other countries of the world. Certain risk factors increase the prevalence of molar pregnancies:

- Extremes of maternal age:
    - Greater than 35 years old carries a five to ten-fold increased risk.
    - Early teenage years, usually less than 20 years old
- Previous molar pregnancy increases the risk 1% to 2% for future pregnancies
- Women with previous spontaneous abortions or infertilities
- Dietary factors including patients that have diets deficient in carotene (vitamin A precursor) and animal fats
- Smoking

GENETIC BASIS OF HYDATIDIFORM MOLES

Androgenetic Nature of Sporadic Hydatidiform Moles

Karyotyping and genetic investigations in the 1970s were crucial to the elucidation of the genetic requirement for the pathogenesis of hydatidiform moles. Using direct chromosomal preparations of fresh chorionic villi from molar samples and Q- or R-banding techniques, investigators repeatedly observed paternal homozygosity of the homologous chromosomes in CHMs. In all sporadic CHMs, the cellular components inherit an androgenic-only nuclear genome and a maternal-only mitochondrial DNA; most commonly, the karyotype is 46, XX and homozygous (80–90%), but some are either 46, XX or 46, XY heterozygous (10–20%). The mechanism by which the ovum loses its maternal haploid genome remains largely unclear. Initially, it was thought that CHMs are the result of fertilization of an ovum in which the maternal nucleus is either eliminated or inactivated as a polar body. The current prevailing hypothesis indicates that the pathogenesis of CHM involves fertilization of an empty ovum (null genome) by a haploid sperm with duplication of the sperm DNA to reconstitute a diploid genome in the majority of the homozygous cases or by a diploid sperm resulting from failure of the second meiotic division . However, the finding of rare CHMs with some retained maternal chromosomes indicates that the ovum is not necessarily devoid of all maternal DNA in all examples . The remaining heterozygous CHMs arise from fertilization of an empty ovum (null genome) by two independent haploid sperm . Diploidization of a triploid ovum after abnormal fertilization is another proposed mechanism for the development of sporadic CHMs.

SIGNS AND SYMPTOMS

Symptoms of a molar pregnancy may include:

- Abnormal growth of the uterus, either bigger or smaller than usual
- Severe nausea and vomiting
- Vaginal bleeding during the first 3 months of pregnancy
- Symptoms of hyperthyroidism, including heat intolerance, loose stools, rapid heart rate, restlessness or nervousness, warm and moist skin, trembling hands, or unexplained weight loss
- Symptoms similar to preeclampsia that occur in the first trimester or early second trimester, including high blood pressure and swelling in the feet, ankles, and legs (this is almost always a sign of a hydatidiform mole, because preeclampsia is extremely rare this early in a normal pregnancy)

DIAGNOSIS

A pregnancy ultrasound will show a snowstorm appearance with an abnormal placenta, with or without some development of a baby.

Tests done may include: hCG (or HCG, both quantitative) blood test Abdominal or vaginal ultrasound of the pelvis, Chest x-ray, CT or MRI of the abdomen (imaging tests), Complete blood count (CBC), Blood clotting tests, Kidney and liver function tests.

TREATMENT

If there are signs of symptoms of eclampsia (late stage of pre-eclampsia), including seizures, one should initiate appropriate management, including benzodiazepines and magnesium sulfate administration. If the patient has signs of pre-eclampsia, urgent blood pressure control is necessary with medications such as hydralazine and labetalol. If there are signs and symptoms of hyperthyroidism, practitioners should initiate proper treatment, including beta-blockers, and monitor for thyroid storm. If severe anemia is present, the clinician should consider a blood transfusion. As discussed earlier, if a patient is Rh(D) negative, the physician should administer the anti-D immunoglobulin.

Once the patient is stabilized, an emergent obstetrics consultation is necessary for the likely need for dilation and curettage (D and C). In patients with advanced maternal age typically greater than 40 years old and those who have completed childbearing, hysterectomy is often performed instead of a D and C. Hysterectomy, however, does not completely eliminate the risk of metastatic disease. After the evacuation of the molar pregnancy, the hCG levels should be monitored; if remain elevated, there is evidence of persistent or invasive disease requiring at times chemotherapy. A gynecological oncologist consultation is usually necessary in these cases to guide therapy.

CONCLUSIONS

Although the androgenetic nature of hydatidiform moles has been well established for the past four decades, global imprinting alteration leading to preferential expression of paternally imprinted genes in villous trophoblast has only been recently hypothesized. Without any doubt, mutations of *NRLP7* and *KHDC3L* genes are causal events in the development of FBCHM, and follow-up investigations into the consequences of *NRLP7* gene alterations may hold the key to unlock the mystery of how altered genomic imprinting and related gene expression result in the molar phenotype.

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