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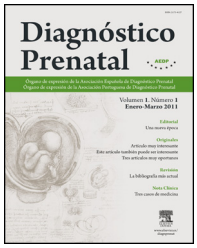

Original Article

Monozygotic twins: Ten reasons to be different

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ABSTRACT

MZ twins, though arising primarily from a single zygote and considered genetically identical, will not ever be absolutely the same. Post-fertilization events such as chromosomal mosaicism, skewed X-inactivation and imprinting mechanisms, as well as other epigenetic mechanisms are responsible for the putative differences between MZ twins. Numerous discordant MZ twins have been reported in the literature, including discordance for malformations or genetic diseases, lateral asymmetry, discrepant growth and intrauterine death of the co-twin. This discrepancy for the disorder may be valuable in the analysis of the effect of a disease upon gene expression or on phenotype variation, and have long-term implications. With today's whole-genome sequencing technologies and increasing evidence for genetic and epigenetic differences in some MZ twins, the understanding of these differences is a whole new field of research.

We reviewed the genotypic and phenotypic differences between MZ twins and discuss ten main reasons for being different.

Gemelos monocigóticos: 10 razones para ser diferentes

Palabras clave:
Gemelos homocigóticos
Genotipo
Fenotipo
Proceso epigenético

RESUMEN

Si bien se considera que los gemelos monocigóticos surgen de un solo cigoto y son genéticamente idénticos, nunca lo son absolutamente. Ciertos procesos posfecundación, como el mosaicismo cromosómico, los mecanismos de inactivación sesgada del cromosoma X e impronta genética, así como otros mecanismos epigenéticos son responsables de las supuestas diferencias entre los gemelos monocigóticos. En la literatura se han publicado numerosos ejemplos de gemelos monocigóticos «discordantes». Esta discrepancia puede resultar valiosa en el análisis del efecto de una enfermedad sobre la expresión genética o la variación fenotípica, y tener implicaciones a largo plazo. Con las tecnologías de secuenciación genómica actuales y el creciente cuerpo de evidencia sobre las diferencias genéticas y epigenéticas en algunos monocigóticos gemelos, la comprensión de estas diferencias se ha convertido en un nuevo campo de investigación.

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Revisamos las diferencias genotípicas y fenotípicas existentes entre gemelos monocigóticos y examinamos las 10 razones principales para ser diferente.

Introduction

Monozygotic (MZ) twins are indeed very much alike but almost never "identical". However, genotypic as well as phenotypic differences between MZ twins have been poorly explained by measurable genetic or environmental discordance.[1–3]

Therefore, the new paradigm is not one of 'nature versus nurture', but of a complex and dynamic interaction between genetic, epigenetic and environmental factors that act in concert to establish the final phenotype.[4] The purpose of this review is to describe the ten reasons that make each MZ twin both phenotypically and/or genetically different.

Understanding the origin of monozygotic twinning

Zygosity is the one that reflects the type of conception, i.e., whether twins arise from one or two fertilized eggs (MZ or dizygotic (DZ), respectively), whereas chorionicity refers to the type of placentation. Why MZ twinning does occur in humans is not clear.[5] According to Machin[2] post-zygotic events would not only precede the twinning event, but may actually trigger it. If two different cell clones exist within one early zygote, the differences between the clones may be sufficient to cause mutual 'recognition and repulsion', resulting in the 'splitting' into two embryos.[6] Another exciting theory is the one proposed by Boklage: he suggests that monozygotic and dizygotic twinning events arise from the same embryogenic mechanism, which is completely innovative since previous theories attribute totally different mechanisms for producing MZ (origin in a single zygote) or DZ twins (origin in two ova fertilized by two spermatozoa).[7]

MZ twins comprise about a third of all spontaneous twins. According to Corrner' hypothesis which was never proven, since no such evidence exists of a split in observations from in vitro fertilization, dichorionic diamniotic MZ twins (18–36%) have separate membranes and placentas and result from abnormal splitting at the 2 cell stage to morula (day 0–3); monochorionic diamniotic twins (~80%) separate at the inner cell mass, after the chorion was formed (day 4–7); monochorionic monoamniotic twins (2–4%) are believed to split at the late blastocyst stage (day 7–14) and conjoined twins (2/10,000) are assumed to split around day 14 resulting in the incomplete division of the embryonic disk.[8,9]

The recognition of zygosity in dichorionic MZ twins is based on physical similarities what may prove inaccurate.[8,10] In liked-sex dichorionic twins, we are blind to zygosity in about 44% of the twins. Despite observations of DZ monochorionic twins, the current belief is that all monochorionic twins are MZ. Biochemical characteristics such as blood type, enzyme polymorphisms and HLA types have also been used to classify zygosity. Nevertheless, DNA "fingerprinting" (quantitative fluorescence polymerase chain reaction (QF-PCR) is the gold standard for defining zygosity. However, we must bear in mind that due to vascular placental connections in the placenta of MC twins DNA may be exchanged (chimerism).[8]

Mechanisms of discordance

There are several mechanisms of phenotypic discordance in MZ twins available in the literature (Table 1).

Chromosomal mosaicism

MZ twins may have a different chromosomal composition (heterokaryotypic twins). All possible combinations of karyotypes observed in twins can be attributed to the unequal allocation of the abnormal cells to each twin: abnormal/normal, mosaic/mosaic, abnormal/mosaic, and normal/mosaic,[11,12] including discordant sex phenotype with mosaicism 46XY/45X, Turner's syndrome in female twins with mosaicism 46XX/45X, trisomy 21 and trisomy 13. There are a few case reports of MZ twins with discordant phenotype and rare partial chromosomal anomalies including 22q11 deletion,[13] 7q syndrome,[14] monosomy 21[15] and partial trisomy 1. Trisomy 11p has already been reported, either associated with a non-specific clinical pattern or with the Beckwith–Wiedemann syndrome (BWS) when the additional region cause paternal disomy. MZ pairs discordant for 45X emerging from 47XXY, 47XXX, 46XY and 46XX zygotes have also been reported.

If the mitotic error occurs before the twinning event, a mosaic will be present in both fetuses with different distribution of the two cell lines between the twins; if the mitotic error occurs after the twinning event, the mosaic will be present in only one twin.[11] Blood mosaicism may also be present in normal twins, as a result of interfetal anastomoses, and therefore, karyotyping in MZ twins that are discordant for some fetal abnormality should be performed in amniocytes rather than in fetal blood.[11]

Table 1 – (Epi)genetic mechanisms that may cause MZ twin discordance.

Mechanisms
1. Chromosomal mosaicism (pre- and post-twinning event)
2. Post-zygotic (dominant and recessive gene) mutation
3. Differential DNA methylation (epigenetics)
4. Skewed X-inactivation
5. Genomic imprinting
6. Unequal distribution or mutations of mitochrondrial DNA
7. Different triplet repeat expansion
8. Unequal placental territoriality
9. Death of a co-twin
10. Discrepant malformations/disruptions/deformations