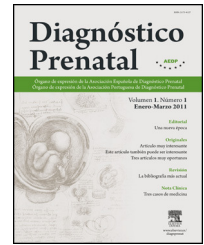




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Original Article

Neurological morbidity of monochorionic twins

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ABSTRACT

Monochorionic twins (MC) are at increased risk for morbidity. The unique placenta with vascular anastomoses may create imbalance with either acute or chronic hypotension or cardiac insufficiency that will eventually affect the fetal brain. It appears that these characteristics of the MC placenta add to the already higher frequency of brain anomalies observed among MZ twins.

TOPS, TAPS, and TTTS require not only inter-twin anastomoses but also two live twins with an unbalanced shunt of blood. The death of the co-twin may prompt a sudden hypotension in the surviving twin with the consequent brain lesions. The more frequently occurring velamentous cord insertion in this kind of pregnancies is related to severe selective intrauterine growth restriction that may cause cerebral compromise. Finally, the preterm birth rate among MC twins is ten times higher than in singletons, and prematurity is a key factor for neurological morbidity as well.

In this paper the various aspects of neurological morbidity in MC twins will be discussed.

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Morbilidad neurológica en gemelos monocoriónicos

RESUMEN

Los gemelos monocoriónicos (MC) poseen mayor riesgo de presentar un mal pronóstico, especialmente en la morbilidad neurológica. La existencia de una única placenta con anastomosis vascular crea un desequilibrio hemodinámico que causa hipotensión aguda o crónica, o insuficiencia cardíaca, lo que eventualmente afectará al cerebro fetal. Parece que estas características de la placenta MC se suman a la ya mayor frecuencia de anomalías cerebrales observadas entre los gemelos MZ.

La secuencia oligodramnio y polidramnio (TOPS), las secuencias anemia-policitemia (SAP) y el síndrome de transfusión fetal-fetal (STFF) requieren no solo anastomosis intergemelar, sino que además deben existir 2 gemelos vivos con un desequilibrio en el intercambio sanguíneo. La muerte de uno de los cogemelos puede provocar una hipotensión brusca en el gemelo superviviente con las consiguientes lesiones cerebrales. La inserción velamentosa del cordón, que ocurre con mayor frecuencia en este tipo de embarazos, está relacionada con una restricción grave del crecimiento intrauterino selectivo que puede comprometer

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la función cerebral. Por último, la tasa de nacimientos prematuros entre gemelos MC es 10 veces superior a la de los embarazos simples, y la prematuridad también es un factor clave para la morbilidad neurológica.

En este artículo se examinarán los distintos aspectos de la morbilidad neurológica en los gemelos MC.

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Introduction

Zygotic splitting is a formidable embryological event whereby an embryo that would otherwise develop into a singleton undergoes some unknown changes that lead to an embryological accident. This accident splits the early embryo and is responsible for the numerous malformations seen in these so-called monozygotic (MZ) twins.¹ It is assumed (never proven) that if this embryological event occurs soon after fertilization, the placenta also splits and the pregnancy becomes a bichorionic (BC) twin gestation. However, when the insult is somewhat delayed, the placenta is not spared and the resultant monochorionic (MC) pregnancy demonstrates severe placental malformations never seen in any other pregnancy.

The placental malformations include 3 elements. First, the placental territory that supplies each fetus is rarely equal. That said, unequal or discordant placental sharing is the rule rather than the exception, and some degree of discordant growth related to the unequal placental territory is common. In severe disproportion between the placental shares, selective intrauterine growth restriction (sIUGR) develops.

The second placental malformation in MC twins is the existence of inter-twin vascular connections (anastomoses). These come in various forms (veno-venous, arterio-arterial, arterio-venous) and calibers. In a very simplified version, this construct might lead to an imbalance shift of blood (transfusion) between the two twins involving deep arterio-venous anastomoses. At the end, a net twin-twin blood transfusion may occur (TTTS) which initiates a series of cardiac events in the overloaded recipient which develops polyhydramnios, hormonal messages from the recipient to the hypovolemic donor which develops oligohydramnios, forming the twin oligo-polyhydramnion sequence (TOPS)—the first stage and hallmark of TTTS. Major changes in the definition, diagnosis and treatment of TTTS were observed in the last 25 years. Primarily,² the diagnosis changed from a postnatal to an antenatal diagnosis. Next, better understanding of the pathogenesis as well as improved imaging led to establishing new stages of TTTS and, finally, various treatment modalities were examined. TTTS is a serious complication, and if remained untreated, may lead to single or double deaths.

The intertwin anastomoses—invariably present in the MC placenta—may also cause discordant hemoglobin levels once believed to be a criterion for TTTS. This anemia-polycythemia sequence (TAPS) may be seen with or without TTTS, and not infrequently after laser photocoagulation treatment of TTTS.

Transfusion through intertwin anastomoses does not necessarily have a bad connotation. For example, some small twins in the setting of TTTS survive in utero only because

the larger twin supplies its growth restricted twin by a A-A anastomosis (the so-called 'rescue' anastomosis).

TOPS, TAPS, and TTTS require not only inter-twin anastomoses but also two live twins. In the case of single fetal demise it was once believed that the dead twin may transfuse thromboplastin-like emboli through the vascular connections, leading to end-organ damage in the survivor. This mechanism was termed twin embolization syndrome irrespective of the fact that emboli were not found. Further research found that instead of embolization from the dead twin to the survivor, the shift of blood is from the survivor (normal blood pressure) to the dead (low blood pressure) twin via the anastomoses. In this scenario, the loss of blood may cause death of the survivor soon after its dead co-twin, or in less significant blood loss, hypovolemic damage to susceptible organs like the brain, kidney, adrenals, etc. Minor blood loss would result in an intact survivor.

The third placental malformation is the pathological insertion of the umbilical cord, usually to the placental side—the so-called velamentous cord insertion. It appears that this malformation is associated with both TTTS and sIUGR.

It appears that these characteristics of the MC placenta add to the already higher frequency of brain anomalies observed among MZ twins. Nevertheless, the major neurological threat to a MC pregnancy is not only being a twin pregnancy with an inherent higher risk of prematurity compared to singletons but also being a MC twin pregnancy with an inherent higher risk of prematurity compared to DC twins.

In this paper the various aspects of neurological morbidity in MC twins will be discussed.

Being a twin

Twinning is associated with increased risk of cerebral palsy (CP) with an average prevalence of 7.4% twins among CP cases. The prevalence of CP was roughly 6 times higher than that in singletons.³ It goes without saying that the most significant contributor to this increased rate is over-representation of twins among low and very low birth weight (LBW/VLBW) and among preterm and very preterm infants.

However, when stratifying the prevalence of CP in twins and singletons according to birth weight and gestational age, the data suggest that multiple and singleton pregnancies have similar risks for CP until around 36–37 weeks. It follows that although LBW/VLBW and preterm birth are the most significant risk factors for CP, the disadvantage of twins is apparent near term when the risk for singletons is extremely low. This conclusion may imply that 'term' occurs earlier in twins, and supports the recommendation to deliver all twins by 38 weeks gestation.

Being a MZ twin

Regrettably, there is lack of accurate zygosity or chorionicity testing and therefore, the risk of CP has been calculated based on rough estimates by comparing like-sex (all MZ twins + 50% of DZ twins) to unlike-sex ('pure' DZ) pairs. Studies have found similar prevalence of CP in like- and unlike-sex pairs and in MZ and DZ pairs using zygosity estimates.³ In contrast, data from 11 other studies compiled by Javier Laplaza et al.⁴ documented more same-sex twins among CP cases series.

A potential explanation for the discrepant figures is the extremely unreliable clinical assessment of zygosity. This unfortunate reality results from the fact that early sonography and postpartum examination of the placenta can prove zygosity in unlike-sex twins (all DZ) and in MC twins (all MZ), but clinical measures are blind to the zygosity of all same-sex DZ twins (with a DC placenta) and all (same-sex) MZ twins with a DC placenta. Thus, zygosity cannot be determined in about 45% (1/2 of DZs + 1/3 of MZs) in spontaneous conceptions. This problem is magnified in a mixed population of spontaneous and iatrogenic pregnancies where inference about zygosity from mathematical calculations using the Hardy–Weinberg rule are far from being accurate.

Being a MC twin

In the MC subset of MZ twins, the contribution of chorionicity becomes more apparent. In a study of 167 consecutive non-malformed infants, 22 (13%) showed signs of CP, including 10 with severe disability. MC placentation constituted the highest (6-fold increased) risk for disability.⁵ More recently, Hack et al.⁶ reached an opposite conclusion whereby 4/182 MC infants had CP (2.2%) compared to 1/189 DC infants. The authors concluded that there are no significant differences in CP rates as well as neurodevelopmental outcomes between MC and DC twins. Importantly, the authors maintained that outcome of MC twins in terms of neurodevelopment seems favorable in the absence of co-twin death or TTTS.

A study of the Leuven (B) group⁷ documented the neurodevelopmental outcome in MC twin pregnancies. The group followed a cohort of 136 MC twins from the first trimester until infancy. A total of 122 (90%) pregnancies resulted in 2 survivors, 6 (4%) in 1 survivor and 8 (6%) in no survivor. Neurodevelopmental impairment was present in 22 (10%) infants of the 230 (92%) of 250 surviving infants that were assessed at a mean age of 24 months. Either death or impairment of 1 or both infants occurred in 28 (22%) of 126 pregnancies. Put simply, an optimistic view is that a MC twin pregnancy has 90% chance of good outcome. The pessimistic view is that in 10% of these pregnancies, affected by TTTS or sIUGR, either death or neurodevelopmental impairment will affect 1 or both twins.

Preterm birth is the common denominator of most adverse outcomes related to twinning in general and to MC twins in particular. Therefore, the source of many of the adverse outcomes associated with MC twins might, in fact, be a result of preterm birth. For example, the risk of CP might well be a result of the preterm birth complicating TTTS rather than the shunt of blood from the donor to the recipient twin.

Moreover, preterm birth may be spontaneous or be a result of an indicated premature termination of pregnancy due to fetal–maternal reasons. Regrettably, the exact frequencies of spontaneous or indicated preterm births are not known and therefore one cannot establish the net effect of chorionicity on preterm birth.

Being a MC twin with co-twin death

The mechanism of brain damage following single fetal death is fairly established. Ong et al.⁸ performed a literature analysis to determine the incidence of co-twin death, neurological abnormality and preterm delivery for the surviving co-twin following single twin death after 14 weeks of gestation. The pulled data from 28 studies that met the inclusion criteria indicated that following the death of one twin, the risk of MC and DC co-twin demise was 12% and 4%, respectively. Importantly, the risk of neurological abnormality in the surviving MC and DC co-twin was 18% and 1%, respectively. The risk of preterm delivery was 68% and 57%, respectively. The pulled odds of MC co-twin intrauterine death and neurological abnormality were 6-times and 4-times that of DC twins, respectively.

A very intriguing finding was observed by Pharoah⁹ who compared, in same-sex and different-sex twins, birth weight specific neonatal death rates and CP prevalence rates in the surviving twin when the co-twin has died in infancy. The author found that the prevalence of CP in the ELBW group (<1000 g) was marginally higher in same-sex than different-sex twin survivors, suggesting that in this birth weight group zygosity/chorionicity has a relatively minor effect on outcome. However, in the birth weight group 1000–1999 g, same-sex twin survivors were at a significantly higher risk of CP than different-sex twin survivors. Additional English data¹⁰ showed that in children who survived infancy after fetal death of the co-twin, the CP prevalence was 93 per 1000 infant survivors, and much more common in like-sex compared with unlike-sex pairs. Interestingly, the same trend was also found in liveborn twin pairs in which one twin died in infancy: the CP prevalence of the survivors in like-sex pairs was much higher compared with unlike-sex survivors, for an overall prevalence of neurodevelopmental morbidity of 246 per 1000. This 'post-partum effect' was corroborated by Scher et al.¹¹ It could be intriguingly postulated that in MC twins blood might be shunted repeatedly from twin A to twin B and backwards. These shunts might affect the twins differently—it may cause fetal or neonatal death in one twin while it would cause brain damage from a significant backward shunt away from the second twin. Simply put, brain damage in MC twins might develop merely because of the existing anastomoses.

Pharoah and Cooke¹² used the clear-cut relationship between sIUFD and brain damage in the survivor of a MC set to hypothesize that the 'vanishing' twin syndrome (i.e., spontaneous reduction in number of embryos or fetuses, the natural counterpart of iatrogenic multifetal pregnancy reduction, MFPR) may be similarly implicated in the etiology of spastic CP. This exciting hypothesis suggests that some singletons with CP but without apparent complications during pregnancy and delivery might be survivors of an unrecognized 'vanishing' twin syndrome and are likely to be affected from

the demise of the co-embryo.¹³ The theory has been criticized mainly because the 'classical' sonographic image of the vanishing twin syndrome is of a DC placenta that lacks the necessary anastomoses.¹⁴

It is quite impossible to accurately assess this hypothesis in the absence of complete registration of embryonic and fetal losses in twins. However, more complete registries exist for assisted reproduction technology (ART) conceptions. Pinborg et al.¹⁵ assessed the incidence rates of the 'vanishing' twin syndrome in in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) twin gestations and compared short- and long-term morbidity in survivors of a vanishing co-twin with singletons and liveborn twins. Of all IVF singletons born, 10.4% come from a twin gestation in early pregnancy (i.e., survivors of the 'vanishing' twin syndrome). After adjustments, survivors of the 'vanishing' twin syndrome were more frequently born preterm and had low birth weight. However, no excess risk of neurological complications in survivors of a vanishing co-twin compared to the singleton cohort was found. Similar results were obtained from an underpowered case-control study of maternities with evidence of a 'vanishing' twin on ultrasound.¹⁶

Whereas guidelines exist for the management of single fetal demise in MC twins, based on the risks calculated by Ong et al.,⁸ no evidence exists for such risks occurring in early pregnancy. In other words, it is unknown at which stage of a MC gestation do the anastomoses form or become functional. Inference from observations of very early TTTS may suggest that anastomoses are expected to be functional as early as 8 weeks' gestation. Of note, such early embryonic demise in MC twins is implicated in the formation of the twin reversed arterial perfusion (TRAP) sequence (also known as the acardiac-acephalic twin).

Being a MC twin with TTTS

Whereas the vascular communications in MC placentas seem to explain the mechanism of neurological morbidity in cases of single fetal death, the risk of CP in TTTS may be unrelated to fetal death, and as strange as it may sound – CP may be related to the methods of treatment.¹⁷ Indeed, therapy for TTTS appears to be primarily related to the gestational age when the syndrome develops and to the severity of the syndrome.¹⁷ The major change in management protocols emerged from the interim results of the EUROFETUS trial, comparing outcomes of amnioreduction and laser therapy and showing an advantage for laser therapy in terms of CP of the survivor of TTTS. Since then, data continue to accumulate regarding the neurological morbidity following treatment of TTTS. Rossi et al.¹⁸ performed a systematic review of the literature regarding the occurrence of neurologic morbidity, neurologic impairment, or neurologic morbidity and impairment of patients treated with laser therapy for TTTS. From 15 articles, the incidence of neurologic morbidity at birth was 55 out of 895 (6.1%), regardless of being a donor or recipient (7.6% compared with 5.8%). At follow-up, the incidence of neurologic impairment was 11.1%, with cerebral palsy the most frequent (39.7%), and again regardless of being a donor or recipient and irrespective of single IUID. More recently, an

Australian study¹⁹ evaluated survivors of TTTS cases treated with laser at 2 years corrected for prematurity. The perinatal survival rate was 79.3%, CP rate was 4.4% and cognitive impairment was 8%, with a neurodevelopmental disability rate of 12.4%. The only risk factor neurodevelopmental disability was Quintero stage of TTTS. Interestingly, Rossi et al.¹⁸ considered 11.1% neurologic impairment as a small proportion whereas Gray et al.¹⁹ maintained that 12.4% of neurodevelopmental disability is considerable.

Being an anemic MC twin

The sequence of anemia in the donor twin and polycythemia in the recipient (TAPS) was a hallmark of fetal-neonatal morbidity in MC twins, included in the criteria of TTTS. Eventually it became clear the TAPS and TTTS are two chronic but distinct features of the shift of blood via anastomoses of the MC placenta.²⁰ TAPS is characterized by large discordant intertwin hemoglobin level in the absence of TOPS occurring spontaneously (5% of MC twins) but more often after incomplete laser treatment (3–18%). In the latter event, TAPS means treatment failure if the aim of laser surgery was complete dichorionization of the placenta, leaving behind very tiny (<1 mm) anastomoses.

At present, it is possible to establish fetal anemia using Doppler studies of the middle cerebral artery (MCA-PSV). When severe fetal anemia is suspected treatment by intrauterine transfusion might be offered. After birth, when a discordant hemoglobin value (>8 g/dL) is found, blood transfusion and exchange transfusion might be required to alleviate TAPS. Not infrequently, intervention in the form of laser ablation might be required.

TAPS is a relatively new entity and is probably heterogeneous. Hence, outcome may range from birth of two healthy twins (except of being discordant for hemoglobin) and double IUIDs. It is unknown to which extent does TAPS affect the developing brain and the potential risk of neurological morbidity.

Being a growth restricted MC twin

The human female is programmed by nature for mono-fetal development. It follows that pregnancies with more than one fetus overwhelm the uterine capacity to adequately nurture the multiple fetuses, and exhibit a wide range of growth aberrations such as absolute intrauterine growth restriction (IUGR) or relative (discordant) growth restriction. This statement is true irrespective of chorionicity.

Growth discordance per se, however, is not of concern unless significant (over 25% difference) and/or when the smaller twin is small for gestational age. Obviously, both twins might be growth restricted (and concordant). In a study of over 1200 twin pairs with 3-tier placental examination we found that the incidence of 1 small for gestational age (SGA) infant was twice higher in MC gestations compared to DC (fused or separate placentas) pregnancies (13.7% vs. 7.3%). This was true also for the frequency of two SGAs.²¹

It is clear now that being growth restricted, by itself and irrespective of plurality and chorionicity, is implicated with intrauterine brain damage and death. Thus, twins do not escape this risk. Whereas single IUGR in DC twins does not affect the surviving co-twin, the interest in recent years in single (or selective) IUGR in a MC gestation was primarily to avoid sudden death of the sIUGR twin and death or brain damage in the survivor.

Selective IUGR may develop with or without TTTS, but has nothing to do with the unbalanced intertwin blood flow that initiates TTTS. Because sIUGR is a serious complication, such cases need extensive follow-up by serial Doppler studies because it was found that absent or reversed end diastolic velocities in MC twins with sIUGR identifies a subgroup of twins with an increased risk of intrauterine death of the smaller twin.²² Interestingly, an increased risk of neurological damage in the larger twin was noted irrespective of whether the smaller twin died or not.²²

Conflict of interest

The author declares no conflict of interest.

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