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N-Terminal Pro-brain Natriuretic Peptide and Cardiovascular Adaptations in Monochorionic Diamniotic Twins

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Abstract

Monochorionic diamniotic pregnancies are associated with adverse perinatal outcomes, including neonatal death and handicaps. Additionally, postnatal circulatory collapse has been suggested to be associated with a poor perinatal outcome, but this has not been fully investigated. We have assessed postnatal cardiac adaptations of monochorionic diamniotic twins by measuring N-terminal pro-brain natriuretic peptide, a precursor of brain natriuretic peptide. We observed the following findings. First, monochorionic diamniotic twins with twin-to-twin transfusion syndrome show an increased cardiac load at birth, and they require complete intensive care for both twins for postnatal circulatory collapse, which is alleviated by fetoscopic laser photocoagulation. Second, monochorionic diamniotic twins with selective intrauterine growth restriction show mildly increased cardiac load at birth compared with twin-to-twin transfusion syndrome, and most require intensive care for both twins because of poor cardiovascular adaptations. Third, the reason for the increased cardiac load in these monochorionic diamniotic twins is unbalanced blood transfusion via intertwin vascular anastomoses, as shown by a comparative study between monochorionic diamniotic and dichorionic diamniotic twins with selective intrauterine growth restriction. Further study is necessary to determine other high risk monochorionic diamniotic twin groups. Additionally, a novel therapeutic strategy, including fetal therapy, is mandatory to prevent postnatal cardiovascular collapse in monochorionic diamniotic twins.

Introduction

Twin pregnancies are associated with adverse perinatal outcomes, including neonatal death and handicaps [1]. With respect to chorionicity, monochorionic twin pregnancies are less frequent than dichorionic twin pregnancies, and are associated with higher morbidity and mortality [2,3]. Monochorionic Diamniotic (MD) twins have placental vascular anastomoses, but this is not found in Dichorionic Diamniotic (DD) twins, which can cause intertwin blood transfer to different degrees [4-7]. Twin-to-Twin Transfusion Syndrome (TTTS), the severest complication of MD pregnancies, occurs from a disrupted balance of intertwin blood transfer, or unidirectional twin-to-twin blood transfusion [8-10]. TTTS occurs in approximately 15% of MD pregnancies and has a poor fetal prognosis, which leads to hypervolemia, polyuria, and polyhydramnios in the recipient, and hypovolemia, oliguria, and oligohydramnios in the donor [6,9,11]. Fetal cardiac dysfunction in recipients of TTTS has been studied, and has mainly been assessed by fetal echocardiography [12-15] or amniotic Brain Natriuretic Peptide (BNP) concentrations [16-18]. An association between fetal cardiac dysfunction and poor perinatal outcome has been suggested [19,20]. In particular, we have observed MD twins with TTTS frequently developed postnatal circulatory collapse, which required intensive treatment [10]. However, this situation has not been thoroughly investigated by others. The pathophysiology of this cardiovascular disturbance in MD twins with TTTS has not been fully clarified, but renin-angiotensin-aldosterone system involvement has been proposed by Mahieu-Caputo et al. [21].

They found that both MD twin pairs with TTTS have high renin cord blood levels. In donor twins, circulatory volume is reduced by shunt flow to the recipient, which induces renin upregulation. Additionally, in the recipient twin, circulatory volume is increased by shunt flow from the donor, which induces renin downregulation. Furthermore, hyper-secreted renin is transferred from donor to recipient via placental anastomoses, and then the recipient suffers from high renin levels in spite of volume overload, aggravating congestive heart failure [21,22]. However, this mechanism is not sufficient to completely explain the poor postnatal cardiac adaptations in both MD twins with TTTS, especially for the donor twin. Some other possible mechanisms for postnatal cardiovascular disturbance in donor twins have been proposed, such as pressure overload induced by renin-angiotensin-aldosterone activation [6], hypoxemia resulting from hypovolemia that could affect cardiac function [23], intrauterine growth restriction in the smaller twin that is associated with increased cardiac load [24], and fetal anemia caused by intertwin blood transfusion, which also induces cardiac workload due to the hyperdynamic state [25].

Recently, a couple of specific MD twin groups, who did not meet Quintero's criteria of TTTS, but had poor perinatal outcomes, were described, including selective Intrauterine Growth Restriction (sIUGR) [26,27], twin anemia polycythemia syndrome [28,29],

and acute peripartum twin-twin transfusion syndrome [30,31]. We previously reported an unusual case of preterm MD twins who did not meet the criteria of the above three entities [32]. They suffered from circulatory collapse soon after birth and needed intensive treatment. Intraventricular hemorrhage and severe retinopathy of prematurity with retinal detachment in both twins occurred [32]. Among these non-TTTS MD twins, an increasing number of studies have shown a significant association between sIUGR and adverse perinatal outcomes [26,33,34], and cardiac complications were suggested as the cause of these adverse outcomes [27]. However, the postnatal cardiovascular adaptations of these patients have not been fully investigated, because most of the MD pregnancies researches were done by obstetrician, not neonatologists who were engaged in neonatal circulatory management.

We are interested in postnatal cardiac adaptations of MD twins and have attempted to assess cardiac function by using N-terminal pro-Brain Natriuretic Peptide (NT-proBNP) measurements in combination with other diagnostic modalities. NT-proBNP is a precursor of BNP, and is a convenient and objective diagnostic marker of cardiac dysfunction in neonates, as well as in adults and children [35,36]. Interestingly, an increase in serum NT-proBNP levels in the late stage of twin pregnancy was reported [37]. Preferably, NT-proBNP is derived from the fetus itself, and does not reflect transplacental exchange of maternal NT-proBNP [38]. Moriichi et al. showed that high BNP levels in the umbilical cord blood and amniotic fluid are a predictive factor for cardiac dysfunction and hypotension soon after birth in singleton neonates [39]. Therefore, we propose that NT-proBNP levels at birth would reflect intrauterine cardiac load and be a predictive marker for postnatal circulatory collapse in MD twins. Echocardiography is the most frequently used technique to evaluate cardiac function in high risk MD pregnancies, but the accuracy of assessment may depend on the examiner's experience and the fetal position [40]. Therefore, we adopted serum NT-proBNP as a conventional biomarker of cardiac load in clinical practice in combination with echocardiography as a complementary method.

Kobe Children's Hospital is a tertiary center in Hyogo Prefecture and manages more than 100 complicated twin pregnancies per year. In this hospital, we have used NT-pro BNP as a neonatal cardiac biomarker for premature and complicated newborns for years. In addition, when we attempted brief literature review to identify articles relating cardiovascular adaptations in MD twins and NT-pro BNP, only a couple of literatures were found except ours [18,37,41]. In this narrative review, we briefly describe the postnatal circulatory status in MD twins based on our recent observations.

Neonatal Nt-Pro BNP Levels in MD Twins with TTTS

The fact that MD twins with TTTS have a poor pregnancy outcome is well known, but there are few reports regarding postnatal cardiac adaptations. With regard to assessment of NT-pro BNP, there is a positive correlation between TTTS staging and amniotic NT-proBNP levels [41], as well as a correlation between the severity of cardiomyopathy in TTTS recipients and amniotic NT-proBNP levels [18]. However, no reports have assessed postnatal cardiac function in MD twins with TTTS using NT-proBNP, except for our previous study [10]. In our previous study, we found increased levels of NT-pro BNP at birth in recipient and donor twins of TTTS, using MD twins with TTTS treated by Fetoscopic Laser Photocoagulation (FLP) as controls [10]. Theoretically, MD twins with TTTS treated by FLP have similar intrauterine hemodynamics to DD twins, because DD twins do not have intertwin vascular anastomoses. We found the serum NT-proBNP levels at birth in MD twins with TTTS were significantly higher than those in MD twins with TTTS treated by FLP (29,900 pg/ml [range, 7300-77,900 pg/ml] vs. 1425 pg/ml [range, 466-9560 pg/ml], P<0.001, Figure 1A). Additionally, serum NT-proBNP levels between larger and smaller co-twins were significantly correlated (r=0.75, P=0.03, Figure 2A). This suggests that both donor and recipient MD twins with TTTS suffer from significant cardiac load soon after birth. Eliminating the vascular anastomoses by FLP turned out to be efficacious, even for reducing the postnatal cardiac load of MD twins with TTTS, which is consistent with reports evaluating the effect of FLP on postnatal outcomes [42,43].
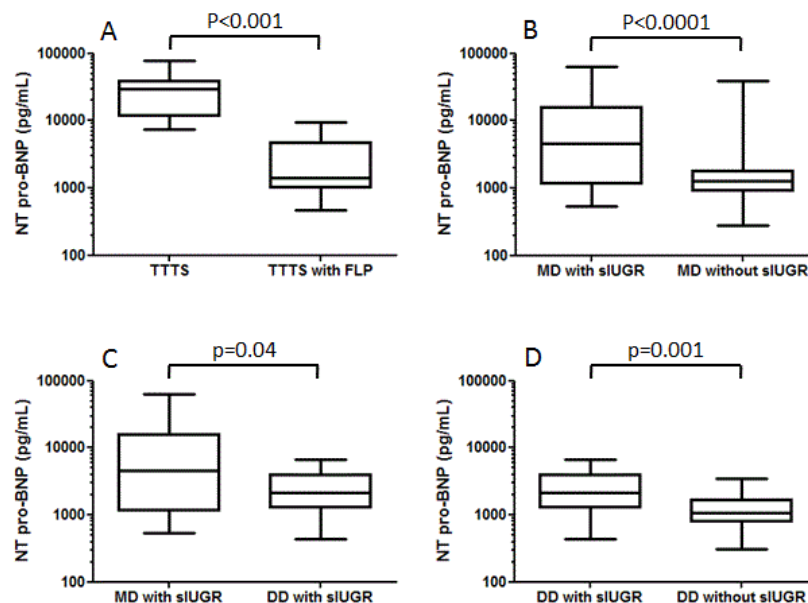
Neonatal Nt-ProBNP Levels in MD Twins with sIUGR

Selective intrauterine growth restriction is a newly recognized complication in MD twins accompanied by poor fetal outcome, where only one of the twins develops intrauterine growth restriction. The definition of sIUGR proposed by Gratacos was recently accepted, that estimated fetal weight is below the 10th percentile in the smaller twin at 18 to 26 weeks and does not meet the criteria of TTTS [26]. The incidence of sIUGR is approximately 11-14% in all monochorionic twin pregnancies, and this is associated with a poor pregnancy outcome, including perinatal death or neurological morbidity for both twins [26,33,34]. We and others have proposed that postnatal cardiac complications are a cause of such adverse outcomes in monochorionic twin pregnancies with sIUGR [6,27,44,45]. For the purpose of clarifying postnatal cardiovascular adaptations of sIUGR, we carried out an observational study of NT-proBNP levels at birth, comparing MD twins with sIUGR and those without. Consequently, we found that the serum NT-proBNP levels at birth in MD twins with sIUGR were significantly higher than those in MD twins without sIUGR (4520 pg/ml [range, 529-62,400 pg/ml] vs. 1270 pg/ml [range, 274-38,700 pg/ml], P<0.0001, Figure 1B).

In addition, the incidence of cardiac dysfunction was significantly higher in the sIUGR group than in the control group. In addition, serum NT-proBNP levels between smaller and larger co-twins were significantly correlated (r=0.87, P<0.0001, Figure 2B). These significant correlations were found in the sIUGR group (r=0.85, P<0.0001) and the control group (r=0.84, P<0.0001). Most importantly, sIUGR was independently associated with NT-proBNP levels at birth after multivariate linear regression analysis [46]. According to these observations, we currently consider that even MD twins without TTTS should be monitored carefully for circulatory collapse soon after birth, if they show specific phenotypes during the fetal period.

Effect of Vascular Anastomoses on Neonatal Nt-ProBNP levels

Imbalance of intertwin blood transfusion via vascular anastomoses in MD twins with sIUGR should be a powerful contributor to cardiac load and increased NT-proBNP levels, as well as to the mechanisms in TTTS. However, other factors could affect BNP or NT-proBNP levels, including prematurity [47], asphyxia [48], fetal anemia [25], and IUGR [24], as mentioned above. In particular, IUGR causes redistribution of circulation, diverting oxygenated blood from other tissues to sustain growth of the brain, by shifting cardiac flow [49]. Leipala et al. reported that IUGR is associated with an alteration in early hemodynamic adaptation in low birth weight infant [24]. By consideration of their result, it was necessary to use twins with sIUGR, but without vascular anastomoses, as a negative control. This was necessary to determine the effect of vascular anastomoses on NT-proBNP levels in MD twins with sIUGR. Following this study, we planned to compare NT-

Figure 1: Comparison of NT-pro BNP levels at birth. NT-pro BNP levels at birth were compared between (A) MD twins with TTTS and MD twins with TTTS treated by FLP, (B) MD twins with and without sIUGR, (C) MD twins with sIUGR and DD twins with sIUGR, and (D) DD twins with and without sIUGR. Modified from previous papers by Fujioka et al. [10,46,50].
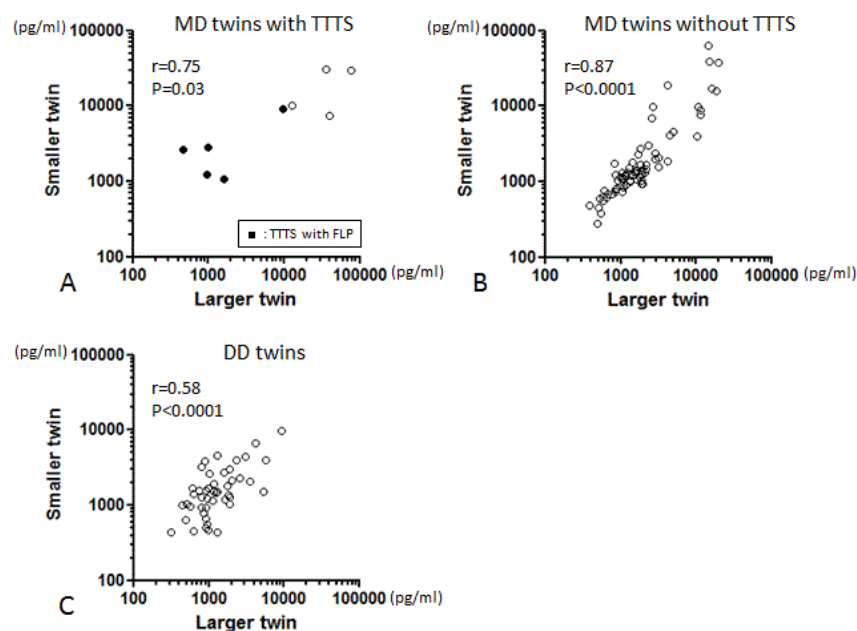
Figure 2: Correlation of NT-pro BNP levels at birth. NT-pro BNP levels at birth were correlated between larger and smaller co-twins in (A) MD twins with TTTS, (B) MD twins without TTTS, and (C) DD twins. Modified from previous papers by Fujioka et al [10,46,50].

proBNP levels at birth in MD twins with sIUGR and DD twins with sIUGR in whom we adapted the same criteria as MD twins [50]. In that comparative study, we found that serum NT-proBNP levels at birth were significantly higher in MD twins with sIUGR than in DD twins with sIUGR (4520 pg/ml [range, 529-62,400 pg/ml] vs. 2115 pg/ml [range, 443-6590 pg/ml], P=0.04, Figure 1C). In addition, serum NT-pro BNP levels at birth were significantly higher in the DD twins with sIUGR than in the DD twins without sIUGR (2115 pg/ml [range, 443-6590 pg/ml] vs. 1080 pg/ml [range, 313-3470 pg/ml], P=0.001, Figure 1D), indicating an effect of IUGR on cardiac load [50]. Furthermore, a significant correlation in serum NT-proBNP levels between smaller and larger co-twins was found in DD twins (r=0.58, P<0.0001, Figure 2C), but this was weaker than that in MD twins. Based on these findings, we consider imbalanced feto-fetal transfusion via placental anastomoses

to be a potential primary cause of postnatal cardiovascular disturbance in MD twins. This implies that the fetal therapy target can be potentially expanded, which is in agreement with the results of a clinical trial with a favorable outcome for sIUGR treated by FLP [51].

Future Directions

Because we have determined the potential effect of placental vascular anastomoses for postnatal cardiovascular adaptations in non-TTTS MD twins, it is important to determine high risk MD twins without TTTS. In our studies, we have examined MD twins who did not meet the criteria of both TTTS and sIUGR as controls; however, that was not sufficient to eliminate high risk cases from the controls. Since these studies, we have experienced two MD twin cases with severe postnatal circulatory collapse, both requiring intensive treatment. Those cases were assigned to the control group in the previous study [46]. Both of those twins showed a significantly increased intertwin hemoglobin difference (>8 g/dL) and increased NT-proBNP levels (1st larger twin: 2580 pg/ml, smaller twin: 6870 pg/ml, 2nd larger twin: 14,900 pg/ml, smaller twin: 38,700 pg/ml), suggesting twin anemia polycythemia syndrome [28] or acute peripartum TTTS [31] (unpublished data). We consider that these newly proposed entities should be assessed for postnatal cardiovascular adaptations; however their incidence is low and the definition of acute peripartum TTTS is still controversial. Therefore, a multicenter prospective study using an identical definition is desirable to identify other high risk MD twins without TTTS.

Summary

Based on our observations, we believe the following: (1) MD twins with TTTS show an increased cardiac load at birth and require complete intensive care for both twins for postnatal circulatory collapse, but this is not required for MD twins with TTTS post FLP; (2) MD twins with sIUGR also show mildly increased cardiac load at birth compared with TTTS, and most of them require intensive care for both twins because of poor cardiovascular adaptations; and (3) the reason for an increase in cardiac load in these MD twins could be unbalanced blood transfusion via intertwin vascular anastomoses. Further study is necessary to determine the other high risk MD twin groups, and a novel therapeutic strategy, including fetal therapy, is mandatory to prevent postnatal cardiovascular collapse.

Acknowledgements

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