■ ANNOTATION

Twins and locomotor disorder in children

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Several locomotor disorders in children that come to the attention of orthopaedic surgeons have their origin in fetal life and present as congenital anomalies. These include cerebral palsy (which may be considered as a congenital anomaly as, in the majority of cases, the impairment is prepartum in timing), club foot and arthrogryposis. Alternatively, conditions that present as locomotor disorders may arise from impairments that have occurred intra-partum or in early childhood. Cerebral palsy also features strongly in this group. This annotation will consider the role of twinning in the pathogenesis of locomotor disorders and will focus on cerebral palsy, but will also consider the possible role of twinning in other congenital anomalies.

Pathogenic mechanisms of impairment in twins

Crucial to the pathogenesis of many abnormalities in twins is the zygosity and chorionicity of the conception. The fertilisation of two ova produces dizygous twins which are dichorionic and have separate placental circulations. Division of a single fertilised ovum leads to monozygotic (identical) twins and the timing of the division determines chorionicity. Early division leads to dichorionic twins, later division to monochorionic twins and very late division to incomplete separation or conjoined twins. Concerns arise with monochorionic twinning owing to placental vascular anastomoses that are present. Chronic haemodynamic instability between fetuses results in the fetofetal transfusion syndromes. These anastomoses are also a channel for other mechanisms which may damage the fetus.

A proposed hypothesis is that thromboemboli or thromboplastin, released from the dead fetus, produce ischaemic damage in the co-twin.¹ However, emboli or disseminated intravascular coagulation from thromboplastin release have rarely been demonstrated. An alternate hypothesis is that the dead fetus acts as a low resistance vascular sump with shunt-

ing of blood from the live to it leading to ischaemic damage in the survivor.² Both hypotheses demand the death of one fetus as crucial to the pathogenesis of abnormalities in the co-twin. However, occasionally both twins survive with a congenital anomaly or cerebral palsy. When both twins are affected they are usually discordant for the anomaly. More frequently, one twin has a congenital anomaly and the co-twin is normal. To account for this, a third hypothesis suggests that haemodynamic instability between monochorionic twins causes episodes of acute fetofetal transfusion which result in ischaemic damage to either or both twins.^{3,4} Occasionally the damage to one twin is lethal and the surviving co-twin suffers from a congenital anomaly or cerebral palsy. Trueta⁵ recognised the role of prenatal ischaemic damage when he stated "In the human embryo, from the time circulation is established, development goes on according to both the amount and the quality of blood distributed through its tissues and organs. Any substantial alteration of either one or both of these factors may cause damage to the embryo, which will be directly proportional to the intensity of vascular abnormality".

The poor prognosis for fetal and infant death and severe morbidity in monochorionic twins has long been a recognised hazard of obstetric practice. Numerically, however, most congenital anomalies or cerebral palsy are found among singletons and this requires explanation. Two important sources of error occur in the recording of twin births. One arises from the failure to register a fetal death. For such a death to be registered as a stillbirth, international definition depends not on the gestational age at death but on the age at which it is delivered. This leads to varying practice among obstetricians in informing parents of the presence of a dead fetus and gives rise to confusion as to whether or not a fetus papyraceous should be registered.⁶⁻¹⁰ Failure to register the fetal death of one twin erroneously leads to the assumption that the surviving twin

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is a singleton. This is extremely important when the pathogenesis of cerebral palsy in singletons is considered. In six of 18 cases of cerebral palsy where fetal death of the co-twin was noted in the hospital obstetric records, only a singleton had been registered at birth.⁷ Another misapprehension of a singleton birth may arise when there is very early loss of one twin in the first trimester of pregnancy. Twin conceptions are much more frequent than twin births because one conceptus in a multiple pregnancy may be lost very early in gestation. The development of ultrasound examination and its routine use in early pregnancy has led to the recognition of the 'vanishing' twin phenomenon.¹¹ The question of registration of a 'vanishing' twin does not arise because of lack of its physical evidence at birth. Nevertheless, the survivor is the product of a twin conception. This has led to the proposal that a significant proportion of cases of spastic cerebral palsy in apparent singletons is attributable to ischaemic cerebral impairment in a twin conception in which the co-twin suffered very early loss as a 'vanishing' twin.¹²

The double jeopardy of cerebral palsy in twins compared with singletons is largely limited to the subgroup of monochorionic within monozygotic twins. To the consequences of placental haemodynamic instability in monochorionic twins, should be added the additional risk in monozygotic compared to dizygotic twins of being born preterm. Estimates from national birth registrations in England and Wales show that 25% of twins of birthweight ≥ 3000 g, but almost 50% of birthweight < 1000 g, are monozygous. This difference is probably attributable to monochorionicity, as 7.5% of monochorionic compared to 1.7% of dichorionic twins are below the fifth percentile.¹³ This highlights the importance of always recording zygosity and chorionicity in multiple births.

The escalation of the proportion of multiple births arising from techniques of assisted reproduction inevitably raises questions as to whether there are adverse implications for the prevalence of congenital anomalies and cerebral palsy. A degree of complacency is acceptable, as these techniques result in dizygous and, therefore, dichorionic conceptions. There is a caveat, however, since monozygous splitting may occur in 10% to 15% of assisted reproduction techniques conceptions.^{14,15}

Cerebral palsy and twins

Cerebral palsy is not a single nosological entity and more than one pathogenic mechanism may result in cerebral impairment which presents as cerebral palsy. The impairment may occur prepartum during fetal development, peripartum or post-peripartum. The prevalence of cerebral palsy is between 2 and 2.5 per 1000¹⁶ of which about 10% occur post-peripartum due to head injury, cerebral infection and severe hypoxia.^{17,18} Twins are at no greater risk than singletons in this group. Peripartum impairment, generally attributable to hypoxic-ischaemic episodes, accounts for between 10% and 15% of cerebral palsy.^{19,20} Infants of

Table 1. Birthweight specific prevalence of cerebral palsy in twins and singletons^{29,38}

Birthweight	Prevalence of cerebral palsy per 1000	
	Twins	Singletons
< 1500 g	60.0	60.4
1500 to 2499 g	10.6	10.6
≥ 2500 g	4.9	1.5
All	11.1	2.3

low birthweight have an increased risk of peripartum impairment and twins a greater risk than singletons because of the greater probability of preterm birth. There remains between 70% and 80% of cerebral palsy where the cerebral impairment occurs prenatally and the risk for twins in this group is of particular interest.

The increased risk of cerebral palsy in twins compared with singletons was recognised over a century ago by Freud.²¹ Twins comprise 5% to 10% of children with cerebral palsy but only 1.6% of all births.²² The risk of cerebral palsy increases inversely with birthweight and it is pertinent to compare the birthweight specific prevalence of cerebral palsy in twins and singletons (Table 1). There is no significant difference in the prevalence of cerebral palsy in twins compared with singletons for those of low birthweight (< 1500 g and 1500 to 2499 g). However, twins of normal birthweight (≥ 2500 g) have a threefold increased risk of cerebral palsy. Thus, the overall fivefold increased risk of cerebral palsy in twins compared with singletons is attributable to twins suffering a double jeopardy, a higher proportion are of low birthweight and those of normal birthweight are at increased risk.

Here it is relevant to consider why twins of normal birthweight are at an increased risk of cerebral palsy. A greater variety of abnormalities of the central nervous system such as polymicrogyria, multicystic encephalopathy, porencephaly and cortical atrophy which present as cerebral palsy and other neurological syndromes, occurs in a twin whose co-twin has died in utero.²³⁻²⁷ These observations are confirmed in population-based cerebral palsy registers and in a national survey of surviving twins. In such cases, the risk of cerebral palsy in the surviving twin is extraordinarily high at one in ten²⁸⁻³⁰ indicating the circulatory risks to the fetus in twin pregnancy. Case reports invariably note that the risk is specific to monochorionic twins.

Other locomotor disorders associated with twinning

While cerebral palsy predominates among the locomotor disorders attributable to twinning, it is entirely plausible that other congenital anomalies with locomotor manifestations may result from fetal ischaemic damage. Although monozygous compared with dizygous twins show greater concordance for congenital anomalies, nevertheless, both monozygous and dizygous twins are more likely to be discordant.³¹ The lack of concordance for many congenital

anomalies indicates that a genetic aetiology is unlikely and other pathogenic mechanisms must be considered.

The aetiology of talipes equinovarus is largely unknown and is probably multifactorial with genetic and environmental factors. Undoubtedly there is a genetic component as a higher risk is associated with first, second and third-degree relatives of the proband. There is also a higher risk of both twins being affected if they are monozygotic than if dizygotic.³² However, among monozygotic twins, the concordance for talipes is not high and environmental factors must enter the equation. Current opinion is that although there is a genetic component in congenital club foot, non-genetic factors play a dominant role.³³ The question that arises is whether the pathogenesis of congenital club foot is consistent with prenatal ischaemic impairment. If it is, club foot, even in singletons, could be attributable to monochorionic twinning in which one twin was lost early in gestation. It is pertinent that the anterior tibial vascular tree is poorly developed in children with club foot.³⁴

Arthrogryposis multiplex congenita presents with many congenital joint contractures with clubfoot being particularly refractory to correction. The condition may present in association with other congenital anomalies, in particular with neuronal migration disorders characterised by polymicrogyria on MRI scanning and presenting with pseudobulbar palsy, epilepsy and cognitive disability.^{35,36} Neuronal migrational disorders have often been reported in monochorionic twins and are considered to have an ischaemic pathogenesis during early fetal development.^{23,25} Of particular interest is the case report of arthrogryposis and polymicrogyria in which one twin was lost before the 12th week of gestation.³⁷ This suggests that the damage to the surviving twin occurred in the first trimester, a period when the loss of one twin is most likely.

Loss of one conceptus in a multiple pregnancy, either as a vanishing twin in the first trimester or as a fetus papyraceous from death in the second, is frequently not recognised and, when recognised, may not be registered. It is generally assumed that the loss of a twin in early gestation is not of relevance to the surviving co-twin. This assumption may be wrong. Many disorders of locomotor function that present to orthopaedic surgeons have their origin in early fetal life. If the pathology of the disorder is consistent with fetal ischaemic damage affecting one or more organs, the possibility of early loss of a twin must be considered. The problem that should now be tackled by specialists in fetal medicine, is to determine what can be done to prevent these disorders.

References

1. Benirschke K. Twin placental in perinatal mortality. *New York State J Med* 1961;61: 1499-508.
2. Fusi L, McParland P, Fisk N, Nicolini U, Wigglesworth J. Acute twin-twin transfusion: a possible mechanism for brain-damaged survivors after intrauterine death of a monochorionic twin. *Obstet Gynecol* 1991;78:517-20.
3. Larroche J Cl, Droulle P, Delezoide AL, Narcy F, Nessmann C. Brain damage in monozygous twins. *Biol Neonate* 1990;57:261-78.
4. Gonen R. The origin of brain lesions in survivors of twin gestations complicated by fetal death. *Am J Obstet Gynecol* 1991;161:1897-8.
5. Trueta J. *Studies of the development and decay of the human frame*. London: Heine-mann, 1968:89.
6. Heys RF. Selective abortion: dead fetuses might have to be registered as stillbirths. *BMJ* 1996;313:1004.
7. Pharoah PO, Cooke RW. Registering a fetus papyraceus: registration is important for research into cerebral palsy. *BMJ* 1997;314:441-2.
8. Heys RF. Regulations on registration of a fetus papyraceus need to be revised. *BMJ* 1997;314:1352-3.
9. Griffiths M. Registering a fetus papyraceus: health professionals can exercise discretion. *BMJ* 1997;314:442.
10. Gompels MJ, Davies D. Fetus papyraceus is being registered increasingly in Wes-sex. *BMJ* 1999;319:1271.
11. Landy HJ, Keith L, Keith D. The vanishing twin. *Acta Genet Med Gemmelol* 1982; 31:179-84.
12. Pharoah PO, Cooke RW. A hypothesis for the aetiology of spastic cerebral palsy: the vanishing twin. *Dev Med Child Neurol* 1997;39:292-6.
13. Sebire NJ, Snijders RJM, Hughes K, Sepulveda W, Nicolaides KH. The hidden mortality of monochorionic twin pregnancies. *Br J Obstet Gynaecol* 1997;104:1203-7.
14. Wenstrom KD, Syrop CH, Hammitt DG, van Voorhuis BJ. Increased risk of monochorionic twinning associated with assisted reproduction. *Fertil Steril* 1993;60:510-14.
15. Platt MJ, Marshall A, Pharoah PO. The effects of assisted reproduction on the trends and zygosity of multiple births in England and Wales. *Twin Res* 2001;4:417-21.
16. Pharoah POD, Cooke T, Johnson MA, King R, Mutch L. Epidemiology of cerebral palsy in England and Scotland, 1984-9. *Arch Dis Child Fetal Neonatal Ed* 1998;79:21-5.
17. Paneth N, Kiely J. The frequency of cerebral palsy: a review of population studies in industrialised nations since 1950. *Clin Dev Med* 1984;87:46-56.
18. Stanley F, Blair E. Postnatal risk factors in the cerebral palsies. *Clin Dev Med* 1984; 87:135-49.
19. Nelson KB, Ellenberg JH. Antecedents of cerebral palsy: multivariate analysis of risk. *N Engl J Med* 1986;315:81-6.
20. Blair E, Stanley F. Intrapartum asphyxia: a rare cause of cerebral palsy. *J Pediatr* 1988;112:515-19.
21. Freud S. *Infantile Cerebrallähmung*. Nothnagels specielle pathologie und therapie. 1897. In: Holder Wein A, ed. *Infantile cerebral paralysis*. Miami: University of Miami Press, 1968.
22. Laplaza FJ, Root L, Tassanawipas A, Cervera P. Cerebral palsy in twins. *Dev Med Child Neurol* 1992;34:1053-63.
23. Bordarier C, Robain O. Microgyric and necrotic cortical lesions in twin fetuses: original cerebral damage consecutive to twinning? *Brain Dev* 1992;14:174-8.
24. Van Bogaert P, Donner C, David P, et al. Congenital bilateral perisylvian syndrome in a monozygotic twin with intra-uterine death of the co-twin. *Dev Med Child Neurol* 1996;38:166-70.
25. Larroche JCl, Girard N, Narcy F, Fallet C. Abnormal cortical plate (polymicrogyria), heterotopias and brain damage in monozygous twins. *Biol Neonate* 1994;65:343-52.
26. Anderson RL, Golbus MS, Curry CJR, Callen PW, Hastrup WH. Central nervous system damage and other anomalies in surviving fetus following second trimester antenatal death of co-twin. *Prenat Diagn* 1990;10:513-18.
27. Weig SG, Marshall PC, Abrams IF, Gauthier NS. Patterns of cerebral injury and clinical presentation in the vascular disruptive syndrome in monozygotic twins. *Pediatr Neurol* 1995;13:279-85.
28. Grether JK, Nelson KB, Cummins CK. Twinning and cerebral palsy: experience in four Northern Californian counties, births 1983 through 1985. *Pediatrics* 1993;92:854-8.
29. Pharoah POD, Cooke T. Cerebral palsy and multiple births. *Arch Dis Child Fetal Neonatal Ed* 1996;75:174-7.
30. Pharoah POD, Adi Y. Consequences of in-utero death in a twin pregnancy. *Lancet* 2000;355:1597-602.
31. Little J, Bryant EM. Congenital anomalies. In: MacGillivray I, Campbell DM, Thompson B, eds. *Twinning and twins*. Chichester: John Wiley & Sons, 1988.
32. Idleberger K. Die zwillingspathologie des klumpfusses. *Z Orthop* 1939;(Suppl 69).
33. Engell V, Damborg F, Andersen M, Kyvik KO, Thomsen K. Clubfoot: a twin study. *J Bone Joint Surg [Br]* 2006;88-B:374-6.
34. Muir L, Laliotis N, Kuty S, Klenerman L. Absence of the dorsalis pedis pulse in the parents of children with club foot. *J Bone Joint Surg [Br]* 1995;77:114-16.
35. Brodtkorb E, Torbgsen T, Nakken KO, et al. Epileptic seizures, arthrogryposis, and migrational disorders: a syndrome? *Acta Neurol Scand* 1994;90:232-40.
36. Kuzniecky R, Andermann F, Guerrini R. Congenital bilateral perisylvian syndrome: study of 31 patients. *Lancet* 1993;341:608-12.
37. Baker EM, Khorasgani MG, Gardner-Medwin D, Gholkar A, Griffiths PD. Arthrogryposis multiplex congenita and bilateral parietal polymicrogyria in association with the intrauterine death of a twin. *Neuropediatr* 1996;27:54-6.
38. Watson L, Stanley F. Report of the Western Australian Cerebral Palsy Register. Perth, Western Australia: TVW Telethon Institute for Child Health Research, 1999.