Head size at birth in neonates with transposition of great arteries and hypoplastic left heart syndrome

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ABSTRACT

Objective: Appropriate fetal brain growth depends upon the cerebral blood flow (CBF). Different congenital heart defects (CHDs), due to the difference in anatomy and physiology, alter the intrauterine CBF. Thus, variable brain growth is expected in different CHDs that is reflected by variability in the head circumference (HC) at birth. The present study was carried out to compare the HC of babies born with transposition of great arteries (TGA) and hypoplastic left heart syndrome (HLHS) in comparison to normal control.

Methods: The data on the HC of neonates with TGA and HLHS were extracted from the computer database then compared with the control group. During the period from January 1996 to December 2003, a total of 7396 neonates were admitted, out of which 639 (8.6%) were admitted with the diagnosis of the CHD. After correcting for gestational age and non-availability of HC measurements, 236 infants were excluded. Out of the remaining 403 term appropriate for gestational age (AGA) infants, 46 had TGA while 28 had HLHS. The control group comprised of a total of 74 term AGA infants.

Results: The mean HC for the control group was noted to be 34.4 ± 1.7 centimeters (cms), 33.7 ± 1.5 cms for TGA while it was 32.9 ± 1.3 cms for HLHS. The head size at birth for newborn with HLHS was significantly smaller than the TGA (p=0.03) and control group (p=0.001). Similarly, HC of TGA group was significantly smaller than the control group (p=0.02).

Conclusion: The newborns with TGA and HLHS are found to have significantly small head size at birth. The clinical significance of this finding with respect to the neurodevelopmental outcome and value of early antenatal intervention to repair these defects remains to be evaluated in further studies.

Saudi Med J 2005; Vol. 26 (3): 453-456

The appropriate fetal brain growth depends upon the adequate oxygen supply continuously maintained through the auto regulation of cerebral blood flow (CBF). Abnormalities of CBF heralds stunting in fetal brain growth. The congenital heart defects (CHD) affect fetal CBF by altering the blood flow pattern in the distal circulatory beds. The CBF could be objectively measured by Doppler ultrasound as cerebral-to-placental resistance ratio (CPR).[1] A CPR of 1 or greater promises good brain perfusion and vice versa. The CPR has shown to be affected in fetuses with growth restriction and CHD. The flow through the cerebral vessels varies according to the heart lesions. Transposition of great arteries (TGA) and hypoplastic left heart syndrome (HLHS) are the 2 heart lesions with wide variation in the CPR. In TGA, the CPR was reported to be >1 in 80% of the cases while in HLHS the CPR of >1 was observed only in 52% of

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Received 31st July 2004. Accepted for publication in final form 30th November 2004.

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Table 1 - Summary of the results.

Diagnostic group	No. of cases	Head circumference	*p* value
TGA group	46	33.7 ± 1.5	
Control group	74	34.4 ± 1.7	0.02*
HLHS group	28	32.9 ± 1.3	
Control group	74	34.4 ± 1.7	0.001*
TGA group	46	33.7 ± 1.5	
HLHS group	28	32.9 ± 1.3	0.03*

TGA - Transposition of great arteries,
HLHS - Hypoplastic left heart syndrome
* $p<0.05$ is statistical significant
Results expressed as mean ± standard deviation

Table 2 - Comparative variables between TGA and HLHS.

Variable	TGA		HLHS		*p* value
	n	(%)	n	(%)	
Weight (grams)	3136 ± 561		28.58 ± 512		0.03*
Sex					
Male	33	(71)	17	(60)	
Female	13	(29)	11	(40)	0.30
Outcome					
Died	6	(13)	17	(60)	
Survival to discharge	40	(87)	11	(40)	0.0001*
Place of birth					
Inborn	5	(11)	8	(29)	
Outborn	41	(89)	20	(71)	0.052

TGA - Transposition of great arteries,
HLHS - Hypoplastic left heart syndrome
* $p<0.05$ is statistical significant
Results expressed as mean ± standard deviation

the cases.[2] The difference in the cerebral flow may lead to inappropriate brain growth in these 2 congenital lesions of the heart. It has been shown earlier that fetal blood flow significantly correlates with head circumference (HC).[3] Similarly, it has been shown that HC is a direct reflection of the brain volume.[4,5] Basing on these facts, we planned this study to look at the birth HC in neonates with TGA and HLHS.

Methods. The study was conducted at the Neonatal Intensive Care Unit (NICU) at the Royal Hospital in Muscat, Sultanate of Oman. The NICU has 30 beds and provides level III-IV care for all high-risk neonates including general and cardiac surgery. It is the main tertiary center of the region with birth rate of 5,000 annually. In the NICU, the details of all the admissions and discharges/deaths are kept both as case files in the Medical Records Department and on the computer database using Visual Dbase Program. For this study, the data was extracted from the computer database, which was maintained since January 1996. A limited search was performed using the query module of the database from January 1996 to December 2003. The selected fields were the identification number, birth weight, HC, gestational age, gender, malformation [cardiovascular system (CVS)], final diagnosis and procedure performed. Only term appropriate for gestational age infants were analyzed. The babies with multi-organ congenital malformation, chromosomal disorders and syndromes and with microcephaly were excluded from final analysis. The measurement of length and weight for corresponding HC measurement for the individual cases were noted down.

The echocardiograms confirming the diagnosis of CHD were performed by one of the on-call pediatric cardiologist using Agilent Sonos 4500 ECHO machine. Head circumference measurements were taken by the admitting nurse using the measuring tape. The control group for the study was selected with one case corresponding to each CHD. These controls were term newborn who were admitted during the same period of study with the diagnosis of transient tachypnea of newborn (TTNB).

As the study did not require any intervention on the infants and no extra sampling, informed parental consent and formal approval from the Institution Review Committee was not considered. No external or internal funding was used for the study. The Statistical Package for Social Sciences version 7.5 for windows and Epi Info version 6 were used for statistical analysis. Student's t-test was used for comparison of numeric parameters and Chi-square test of qualitative parameters of the study. Statistical significance be taken at $p<0.05$ level of significance.

Results. The total numbers of neonates admitted during the study period of 8 years were 7396, which corresponded to 925 admissions annually or 77 monthly. Out of the 7396 admissions, 639 (8.6%) were admitted with the diagnosis of the CVS malformation. After correcting for gestational age and non-availability for HC measurements, 236 infants were excluded from the study. Out of the remaining 403 term appropriate for gestational age (AGA) infants, 46 neonates had TGA while 28 had HLHS. The control group comprised of a total of 74 term AGA infants, 46 for TGA and 28 for HLHS.

The mean HC for the control group was noted to be 34.4 ± 1.7 centimeters (cms) while that for the TGA and HLHS were 33.7 ± 1.5 and 32.9 ± 1.3 cms, respectively. The head size at birth for newborn with HLHS were significantly small than the TGA and control group (p=0.03 and p=0.001). Similarly, HC of TGA group was significantly smaller than control group (p=0.02) (**Table 1**). Basing on the birth weight, the newborns with TGA were noted to be heavier than the HLHS, 3136 ± 561 and 2858 ± 512 (p=0.03). The majority of the cases were males (67%) and 82% were referred from other hospitals. The mortality was significantly higher among HLHS infants as compared to TGA, 60% (17/28) versus 13% (6/46), p=0.0001 (**Table 2**). Out of 46 TGA, 41 were operated (balloon atrial septostomy, arterial switch), 2 were critically sick and died prior to intervention, while 3 were not operated (parents denied consent). Out of 28 HLHS, only 3 were operated (Norwood procedure, all died), 14 died without operation, 11 were sent home and to the nearest hospital (parental request, outcome not known).

Discussion. The incidence, male to female ratio and the mortality pattern of CHD, noted in the present study, was similar to the previously reported statistics.[6-8] The finding of lower HC in HLHS than TGA was in agreement to the finding of Rosenthal.[9] The reason for this difference could be explained by the fact that in HLHS the CBF is impeded by the hypoplastic aortic isthmus as compared to TGA where there is no antegrade obstruction to the CBF.[2] Thus, in TGA adequate blood supply to the developing brain for appropriate growth is maintained preserving normal brain volume. The other reasons for significant small head size in HLHS could be associated congenital brain anomalies, as described earlier.[10]

The clinical relevance of small head size at birth in neonates with CHD lies in the associated risk of neurodevelopmental delay. It has been shown earlier by Limperopoulos et al[11] that neurodevelopmental abnormalities are common in infants with CHDs. However, relating neurodevelopmental outcome with brain size at birth is not as simple. Recent studies have clearly shown that there is no relation between the IQ and measurement of head size at birth suggesting that the postnatal brain growth rather than the head size at birth is more important detrimental factor for cognitive function in later life.[12,13] Nevertheless, follow up studies in infants with CHD have shown persistence of growth retardation in such infants, which could be responsible for causing general and neurological disabilities observed in such infants.[14-16]

The main limitation of the study is its small size due to non-availability of data in few cases. The measurements of HC in all the CVS malformation and analyzing them separately would be ideal but only TGA and HLHS were studied, as further subdivision would lead to sample size reduction making statistical computation difficult. As depicted in **Table 2**, the birth weight of neonate with HLHS was significantly lower than the neonates with TGA, thus, it could be argued that the difference noted in the HC between the corresponding group may be due to their size only. The birth weights and lengths alone were not taken into account, however, cases were matched for term gestation. Thus, there may be some cases of intrauterine growth retardation, but we expect it to be small in number. This and the issue of standardizing the HC measurement could be controlled in further prospective study.

The innate variability of HC measurements is difficult to control appropriately, as there is no 'gold standard'. However, measurement of HC is still considered to be the most reliable assessment in clinical practice with sensitivity of 91% and specificity of 97%.[17] Further, HC standards are difficult to set,[18] thus, we selected a control group from the same population to eliminate the chance of wide variability in comparison. As subdivision into male and female HC references will result in further reduction of the sample size, the suggested gender specified HC measurements was not considered.[19] The fetal brain growth and development depends on many factors including history of maternal smoking and stress, use of steroids and cocaine.[20-23] No control for these confounding variables was performed. However, in future prospective studies these points should be considered.

The present study clearly indicates that performing postnatal cardiac surgery could be too late to influence the neurodevelopmental outcome in neonates with TGA and HLHS. The damage has already been done in utero. This inference is further supported by the findings of Limperopoulos et al.[11] They studied 56 newborns that underwent cardiac surgery for CHDs and found that greater than 50% of the newborns had neurobehavioral abnormalities even before the surgery. So, the best strategy is to perform prenatal intervention, which is still in the research and experimental phase.[24,25] With the on going advancement in the Doppler and fetal echocardiographic techniques,[25,26] a rapid growth in the technique of fetal interventional cardiology is expected. This prospect is studied in fetal lamb model, a well correlated model with the human fetal cardiac development.[27] In the same model, fetal cardiac intervention has shown to be effective and 42% long-term survival has been reported.[28] Similarly, the influence of *in utero* cardiac intervention on fetal guinea pig myocardial development has been shown.[29] Despite these promising reports, intrauterine cardiac intervention

still remains a challenging endeavor, especially for TGA and HLHS. Many factors have to be taken into account including ethics, maternal risk and outcome, feasibility of the complex procedure and issue regarding maternal and fetal anesthesia.[30] Keeping in view these difficulties and lack of available data on fetal cardiac surgery, the alternative in the prenatally confirmed TGA and HLHS is to offer early delivery and immediate neonatal intervention.[31,32] The effect of which on developing brain and its growth remains to be determined.

In conclusion, babies born with TGA and HLHS are found to have significantly small head size at birth. The clinical significance of this finding with respect to the neurodevelopmental outcome and value of early antenatal intervention has to be evaluated in further studies.

Acknowledgment. We would like to extend our thanks to the Pediatric Cardiology and Cardiothoracic and Vascular Surgery team of the Royal Hospital, Muscat, Oman for providing their expertise in managing the infants with cardiac defects.

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