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Original Article

Radiology Section

Multiparametric Cranial Ultrasound Evaluation of Normal Neonatal Cerebral Ventricular Dimensions to Establish Nomograms in the Eastern Indian Population: A Cross-sectional Study

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ABSTRACT

Introduction: Cerebrospinal Fluid (CSF) filled ventricles and their connecting foramina make up the brain's ventricular system. Ventricles hold around a fifth of an adult's CSF volume, approximately 20-25 mL. Two lateral ventricles and midline third and fourth ventricles make up the ventricular system.

Aim: To study normal neonatal cerebral ventricular dimensions to develop reference ranges in the Eastern Indian population.

Materials and Methods: This was a hospital-based observational cross-sectional study carried out on 189 neonate in the Department of Radiodiagnosis in collaboration with the Department of Neonatology, IMS and SUM Hospital, Bhubaneswar, Odisha, India. Measurement of ventricular size is of prime importance in diagnosing posthaemorrhagic ventricular dilatation and evaluating the need for intervention. Authors have studied Frontal Horn Width (FHW), Thalamo-Occipital Distance (TOD), Third Ventricle Width (TVW), Ventriculo-Hemispheric Ratio (VHR) and Levene index to establish nomograms showing normal reference range. Linear regression model was used for correlation.

Results: The FHW in present study showed a linear increase in the size with a corresponding increase in the gestational age, from 1.38 mm at 33 weeks to 1.59 mm at 40 weeks of gestation with a weak positive correlation. The TOD showed negligible change with increasing gestational age, from 17.24 mm at 33 weeks to 17.17 mm at 40 weeks. The TVW study showed a slight increase in width with increasing age, from 1.20 mm at 33 weeks to 1.45 mm at 40 weeks gestation. The VHR showed a negligible change with increasing gestational age, from 0.120 at 33 weeks to 0.100 at 40 weeks. The Levene index showed a slight increase, from 10.30 at 33 weeks to 11.64 at 40 weeks of gestation.

Conclusion: Neurosonogram has valid implications for measurement of ventricular size in diagnosing pathologic ventricular dilatation and for evaluating the need for intervention. Nomograms for different parameters (FHW, TOD, TVW, VHR and Levene index) as well as corresponding reference ranges are established for normal preterm and term neonates.

Keywords: Cranial ultrasound nomogram, Frontal horn width, Levene index, Thalamo-occipital distance, Third ventricular width, Ventriculo-hemispheric ratio

INTRODUCTION

The CSF filled ventricles and their connecting foramina make up the brain's ventricular system. The ependymal cells that border the ventricular system generate CSF, which flows from lateral ventricles to third ventricle through the foramen of Monro, from third ventricle to fourth ventricle via the Sylvius aqueduct, bilaterally into the cerebellopontine angle cisterns through the foramen of Luschka, and into the cisterna magna through the foramen of Magendie. Ventricles hold around a fifth of an adult's CSF volume, approximately 20-25 mL [1]. Two lateral ventricles, a midline third ventricle, and a fourth ventricle make up the ventricular system. Any dilatation of ventricles is considered as ventriculomegaly. Hydrocephalus refers to ventriculomegaly of the obstructive cause or enlarged ventricles associated with increased intracranial pressure. There are many causes of ventricular dilatation or hydrocephalus: subarachnoid haemorrhage, infective meningitis, normal pressure hydrocephalus, choroid plexus papilloma, ex-vacuo hydrocephalus, posthaemorrhagic ventricular dilatation. Hydrocephalus is also associated with various congenital anomalies in newborns with adverse clinical outcomes and has a prevalence of approximately 0.3-22 per 1,000 live births [2-4].

Periventricular Haemorrhage (PVH) is most common in premature infants and usually occurs in the first week of life. From various studies, it is hypothesised as secondary to hypoxic-ischaemic reperfusion injury of the germinal matrix [5,6]. In premature infants, the germinal matrix is richly perfused with fragile vessels, vulnerable to ischaemic insult, and reperfusion leads to haemorrhage. The incidence of PVH decreases with increasing gestational age. PVH appears to be rare after 34 weeks of gestation. The reason for the decrease is due to the involution of the vascular germinal matrix. Other factors may influence the incidence of PVH, like the birth weight <1500 grams. Many infants are asymptomatic and only found on regular neurosonogram. PVH, when large, can extend into the ventricles and obstruct drainage, causing posthaemorrhagic dilatation. Venous haemorrhagic infarct is an impending outcome without early recognition in these cases. Posthaemorrhagic ventricular dilatation represents the major threat in preterm infants. Following a significant germinal matrix-intraventricular haemorrhage, about 75% of premature babies have posthaemorrhagic ventricular dilatation. In infants with progressive ventricular dilatation, cerebral haemodynamics, oxygenation and prevention of further brain injury has been proven to be achieved by drainage of CSF [6,7].

Measurement of ventricular size is of prime importance in diagnosing posthaemorrhagic ventricular dilatation and evaluating the need for intervention [8-10]. Neurosonogram avails measurement of the lateral ventricles, in addition to diagnosing ex-vacuo dilatation of ventricles

in preterm infants due to periventricular white matter atrophy. Therefore, transcranial ultrasound (neurosonogram) since its clinical introduction in the 1970's, has been widely used and has become indispensable in neonatal intensive care units for screening preterm infants for intracranial haemorrhage, congenital and acquired brain lesions [11-14]. Transcranial ultrasound is the only choice in case of a bedside, critically ill infants, in spite of advances like Computed Tomography (CT) and Magnetic Resonance Imaging (MRI), reason being, transcranial ultrasound does not produce any ionising radiation, also does not require sedation, unlike CT and MRI, which has the risk of producing ionising radiation and require sedation for uncompromised imaging [15,16]. Quality of transcranial ultrasound has improved with time leading to high resolution, faster imaging and delineation of important brain structures, digital display and backup. The detailed structural assessment requires magnification of selected areas with higher resolution megahertz adjustments [17,18]. The main aim here was to study normal neonatal cerebral ventricular dimensions to develop reference ranges in the Eastern Indian population.

MATERIALS AND METHODS

This was a hospital-based observational cross-sectional study carried out in the Department of Radiodiagnosis in collaboration with the Department of Neonatology, IMS and SUM Hospital, Bhubaneswar, Odisha, India, from September 2018 to September 2020. The study was approved by the Institutional Ethics Committee (IEC) with reference number DRI/IMS.SH/SOA/180453.

Inclusion criteria: The study population of 189 normal cases comprising of 101 preterm (33-36 weeks gestation) and 88 term (37-40 weeks gestation) neonates were included.

Exclusion criteria: A neonate with an open wound or recent surgical incision near the area being imaged, neonate with changes in blood flow pattern due to heart disease or irregular heart rhythms, case of hydrocephalus, periventricular leukomalacia, intracranial haemorrhage were excluded.

Study Procedure

Transducer used: A 7.5-MHz or higher transducer in a premature infant; 5-MHz transducer necessary to allow for adequate sound penetration of a larger infant head; High-frequency transducers (up to 5-12 MHz) to provide high-quality images for scanning of near-field pathology. The approach was generally via the anterior fontanel in both coronal and sagittal planes. Other approaches done were posterior fontanel, mastoid fontanel and temporal fontanel. For ventricular size assessment, five parameters were measured to establish a normal reference range. These were FHW, TOD, TVW, VHR and Levene index.

The FHW is defined as the diagonal width of the frontal horns measured at the widest point in the coronal plane. In present study, the frontal horn was approached via anterior fontanelle and width was measured in the coronal plane in all the infants [19]. TOD is the thalamus's distance to the dorsal horn's tip (posterior horn/occipital horn). This measurement is most sensitive to mild dilatation of ventricles as ventricular dilatation is first noted in the occipital horns. The Thalamus and posterior horn were approached via a temporal window. The distance was measured in the sagittal plane in all the infants [19]. TVW is defined as the distance between the inner boundaries of the third ventricle when both the boundaries are displayed strictly parallel. It was identified as a hypoechoic space in front of the pineal gland and between basal ganglia structures. The third ventricle was approached via anterior fontanels. The distance was measured in the axial plane in all the infants [19]. VHR is defined as the ratio between falx cerebri to the limit of the frontal horn of lateral ventricle and falx cerebri to the inner table of skull measured at the same level. In present study, falx cerebri and lateral limit of the both lateral ventricles were assessed via anterior fontanelle and distance was measured in the coronal plane in all the infants [19]. Levene index is the distance between the falx and the lateral wall of the anterior horn of the lateral ventricle in the coronal plane at the level of the third ventricle. The lateral ventricles were assessed through the anterior fontanelle. Measurement of the ventricular system was done in an easy reproducible sonographic plane. A coronal section was chosen in which the lateral ventricles were observed and measured in a location slightly posterior to the foramen of monro [20].

STATISTICAL ANALYSIS

Herein, gestational age was taken as an independent variable; whereas FHW, TOD, TVW, VHR and Levene index were taken as dependent variables. Linear regression model was used for correlation. The Statistical Package for the Social Science (SPSS) for Windows, version 20.0 was used for all statistical analysis (IBM-SPSS Inc., Chicago, IL, USA).

RESULTS

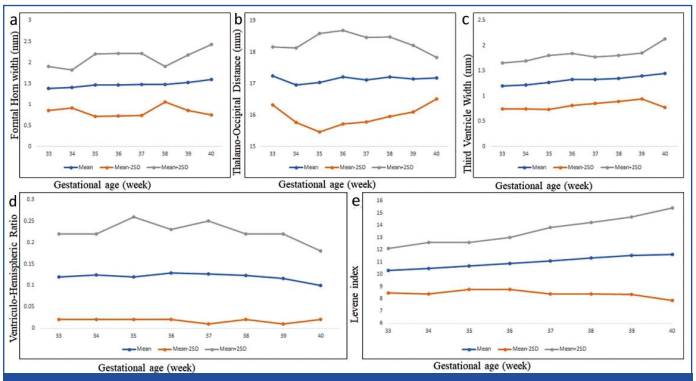
A total of 189 normal preterm and term neonate's transcranial ultrasound was performed in present study including 89 (47.1%) male and 100 (52.9%) female neonates across all gestational ages without any gender predominance. Present study included 18 (9.5%) neonates of 33 weeks gestational age, 25 (13.2%) neonates of 34 weeks gestational age, 36 (19.0%) neonates of 35 weeks gestational age, 22 (11.6%) neonates of 36 weeks gestational age, 22 (11.6%) neonates of 37 weeks gestational age, 23 (12.2%) neonates of 38 weeks gestational age, 23 (12.2%) neonates of 39 weeks gestational age, 20 (10.6%) neonates of 40 weeks gestational age. The youngest neonate was of 33 weeks gestational age and the oldest neonate was of 40 weeks with a mean gestational age of (36.4±2.1) weeks. The gestational age of neonates in present study skewed with maximum neonates from 33-36 weeks gestational age.

For a particular gestational age, the average value of right and left FHW, TOD and VHR was calculated, which was taken as Mean, and Standard Deviation (SD) values for that gestational age was also calculated from the pooled data [Table/Fig-1]. Then the means were plotted against the gestational age and the linear regression model of the graph was developed. Mean FHW of 1.47±0.33 with 95% confidence interval ranging from 1.32-2.21 mm. TOD showed Mean of 17.12±0.52 with 95% confidence interval ranging from 16.57-17.52 mm; it showed a linear increase in the size of the FHW and negligible change in TOD and VHR with the corresponding increase in gestational age [Table/Fig-2a,b,d]. Same was also done for mean value of other two parameters (TVW and Levene index). Mean TVW of 1.31±0.26 mm showing 95% Confidence interval ranging from 1.15-2.13 mm. There was linear increase in Levene index in correspondence to increase in gestational age [Table/Fig-2c,e]. Reference ranges for normal values of all parameters were calculated as mean plus or minus two standard deviations [Table/Fig-3]. The correlation was estimated as Gestational age taken as

Weeks		FHW (mm) Mean±SD	TOD (mm) Mean±SD	TVW (mm) Mean±SD	VHR Mean±SD	Levene index Mean±SD
Preterm (n=101)	33	1.38±0.26	17.24±0.46	1.20±0.23	0.120±0.05	10.30±0.90
	34	1.40±0.24	16.95±0.59	1.22±0.24	0.124±0.05	10.50±1.06
	35	1.46±0.37	17.03±0.78	1.27±0.27	0.120±0.07	10.69±0.96
	36	1.47±0.37	17.20±0.74	1.33±0.26	0.129±0.05	10.88±1.06
Term (n=88)	37	1.48±0.37	17.12±0.67	1.33±0.24	0.127±0.06	11.11±1.36
	38	1.48±0.21	17.21±0.63	1.35±0.23	0.123±0.05	11.32±1.45
	39	1.52±0.33	17.15±0.53	1.40±0.23	0.116±0.05	11.52±1.58
	40	1.59±0.42	17.17±0.33	1.45±0.34	0.100±0.04	11.64±1.89

[Table/Fig-1]: Normal dimension of ventricular parameters.
FHW: Frontal horn width; TOD: Thalamo-occipital distance; TVW: Third ventricle width; VHR: Ventriculo-hemispheric ratio

an independent variable and other variables (FHW, TOD, TVW, VHR, Levene index) taken as dependent variables [Table/Fig-4]. All the parameters except TOD and VHR showed p-value <0.05, which was significant.



[Table/Fig-2]: Linear regression model of (a) FHW, (b) TOD, (c) TVW, (d) VHR, (e) Levene index.

Weeks		FHW	TOD	TVW	VHR	Levene index
Preterm	33	0.86-1.90	16.32-18.16	0.74-1.66	0.02-0.22	8.50-12.10
	34	0.92-1.82	15.77-18.13	0.74-1.7	0.02-0.22	8.38-12.62
	35	0.72-2.20	15.47-18.59	0.73-1.81	0.02-0.26	8.77-12.61
	36	0.73-2.21	15.72-18.68	0.81-1.85	0.02-0.23	8.76-13.00
Term	37	0.74-2.22	15.78-18.46	0.85-1.78	0.01-0.25	8.39-13.83
	38	1.06-1.90	15.95-18.47	0.89-1.81	0.02-0.22	8.42-14.22
	39	0.86-2.18	16.09-18.21	0.94-1.86	0.01-0.22	8.36-14.68
	40	0.75-2.43	16.51-17.83	0.77-2.13	0.02-0.18	7.86-15.42

[Table/Fig-3]: Reference range of ventricular parameters.

Parameters	Coefficient of correlation (R)	Coefficient of determination (R2)	p-value
FHW	0.161	0.026	0.027
TOD	0.073	0.005	0.319
TVW	0.278	0.077	0.001
VHR	0.051	0.003	0.496
Levene index	0.416	0.173	0.001

[Table/Fig-4]: Correlation of coefficient (R) and correlation of determination (R2).

DISCUSSION

Ventricular dilatation is a major threat to preterm and term neonates. Transcranial ultrasound has become indispensable for detecting ventriculomegaly, thus helping to exclude other associated cerebral pathologies. Wide variations of ventricular indices are reported from previous studies for assessing the normal ventricular size [19,21]. Most of the studies established nomograms 30 years ago, which are still in use and these studies did not look into the racial cranial profile into consideration [22,23]. In present study, authors tried to establish cross-sectional reference ranges for normal values of FHW, TOD, TVW, VHR and Levene Index, among eastern Indian neonates of 33-40 weeks gestation. These nomograms have valid implications in day to day clinical practice.

The mean age of the neonates in present study was 36.4±2.1 gestational weeks. According to Sondhi V et al., among the 1483 neonates studied with various modes of delivery (caesarean or normal vaginal delivery or assisted delivery), newborn ventricle sizes did not alter much. So, the delivery mode was not considered a factor impacting the ventricular size [19]. Previous study showed a concordance of ventricular indices with sex distribution [23]. To avoid any significant impact of this concordance, authors tried to match the male to female neonates in the study as close as possible to check the confounding effect of the sex in correlation with ventricular indices. In present study, percentage of male neonates was 47% and female was 53%.

Previous study also highlighted variability in sizes of bilateral ventricular dimensions, which is a normal presentation without any pathological significance. According to Sondhi V et al., this difference was insignificant with a median difference of 0.2 mm for FHW [19]. Present study, tried to consider this important aspect and the mean of bilateral FHWs were achieved. This explained that if one dimension appeared smaller than the other, when a mean was achieved, it was not that significantly varied with the mean value of the dimension. This also held true for other dimensions like TOD and VHR. Therefore, the data was the mean data of the bilateral dimensions in present study.

In present study, the FHW increased from 1.38 mm at 33 weeks to 1.59 mm at 40 weeks. The linear regression model showed a linear increase in the size with a corresponding increase in gestational age, showing a positive correlation of 0.161 (p-value 0.027) which was significant. In a study by Perry RNW et al., the upper limit of FHW was 3 mm for infants from 26-42 gestational weeks. In their study, FHW showed no change from 26-42 gestational weeks [24]. Present study has a minimum measurement of FHW of 1.27 mm to a maximum of 3.34 mm, mean of 1.47±0.33 with 95% confidence interval ranging from 1.32 mm to 2.21 mm, in concordance with Davies MW et al., and Perry RNW et al., showing mean less than 1.7 mm (upper limit of 2.9 mm), and also with Sondhi V et al., and Karamimgham S et al., showing mean less than 1.8 mm [19,23-25].

The linear regression model showed almost no change in TOD with a corresponding increase in gestational age and no correlation with the gestational age (r=0.073, p=0.319). TOD remained constant in neonates of 23-33 gestational weeks with a reference range of 8.7-24.7 mm [18]. In a study by Sondhi V et al., TOD showed miniscule increase in size with advanced gestational age in neonates from 25-42 gestational weeks' (means ranging from 6.1-12 mm, 95% CI ranging from 7 mm to 17 mm) with a coefficient of determination (R2) 88%, which was highly significant [19]. In a study by Karamimagham S et al., 2017, mean TOD was 15±2.7 mm in neonates from 26-35 gestational weeks (minimum=8.4 mm, maximum=22 mm). TOD in this study did not show any correlation with gestational age (r=-0.07, p=0.35) [25]. Present study has a minimum measurement of TOD of 16.09 mm to a maximum of 20.53 mm, mean of 17.12±0.52 with 95% confidence interval ranging from 16.57-17.52 mm. Present study had a mean higher than Karamimagham S et al., (15±2.7 mm) and Sondhi V et al., with a narrow reference range [19,25]. Present study also showed no correlation with gestational age, similar to other study [24]. This higher mean could be explained by the high gestational ages of neonates in present study.

The TVW in present study showed a slight increase with increasing age from 1.20 mm at 33 weeks to 1.45 mm at 40 weeks of gestation. The linear regression model showed a linear increase in the size of the third ventricle with a corresponding increase in gestational age, showing a weak positive correlation of 0.278 with the gestational age and at a significance <0.001. In a study by Soni JP et al., TVW slightly increased from 3.69±1.2 mm at 33-37 weeks to 4.13±1.4 mm for greater than 38 weeks [26]. In a study by Lombroso CT et al., the TVW ranged from 4-7 mm in newborns and up to one year of age [27]. The reference range of TVW was 0-2.6 mm in a study by Davies MW et al., in neonates 23-33 gestational weeks [23]. In a study by Sondhi V et al., TVW in neonates from 25-42 gestational weeks (means ranging from 1.25-2.0 mm) showed a coefficient of determination (R2) as 66%, which was highly significant [19]. Present study has a minimum measurement of TVW as 1.14 mm to a maximum of 2.92 mm, with a mean of 1.31±0.26 mm showing 95% confidence interval ranging from 1.15-2.13 mm. The mean TVW in present study was smaller than studies by Soni JP et al., and Lombroso CT et al., [26,27], but was in range compared to studies by Sondhi V et al., and Davies MW et al., present study also showed a weak positive correlation with the gestational age [19,23]. The VHR decreased from 0.120±0.05 at 33 weeks to 0.100±0.04 at

40 weeks of gestation. Johnson ML et al., from their study observed that the mean value of VHR ranged between 0.24-0.34 in preterm and 0.24-0.30 in term neonates [28]. Soni JP et al., reported this ratio as 0.32±0.3 in preterm and 0.3±0.3 in term neonates [29].

Levene index measurements showed an increase with maturation, ranging from (Mean±2SD) 10.30±1.80 at 33 weeks to (Mean±2SD) 11.64±3.78 at 40 weeks. The reference intervals presented in present study are nearly similar to the curve published by Levene 30 years ago [20]. Liao MF et al., reported slightly higher values for the preterm infants [8]. The lower transducer resolution in the 1980s and fewer extremely premature infants may have accounted for the differences between the previous and present reference values.

Limitation(s)

Ultrasound examination is a motion-sensitive technique hence an active or crying neonate may hinder the examination process by making it difficult, resulting in inaccurate measurements. Study was a single centre study, so the results cannot be generalised to the whole population.

CONCLUSION(S)

Nomograms for different parameters (FHW, TOD, TVW, VHR and Levene index) and corresponding reference ranges are established for assessment of normal preterm and term neonatal ventricular size by using cranial ultrasound in Eastern Indian population. The FHW shows a linear increase in size with a corresponding increase in gestation, having a strong positive correlation with gestational age. The TOD and VHR show a negligible change with increasing gestational age. The TVW shows negligible increase and the Levene index shows linear increase with the gestational age.

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