Growth and Neurodevelopmental Outcome of VLBW Infants at 1 Year Corrected Age

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Objectives: To evaluate growth and neurodevelopmental outcome of very low birth weight infants (VLBW) and compare with term normal birth weight infants (NBW) till 12 months corrected age.

Design: A prospective cohort study

Setting: Tertiary care neonatal unit in northern India

Subjects: 37 VLBW infants and 35 NBW infants born between January 2007 and December 2007.

Interventions: Anthropometric measurements were recorded and Z-scores were computed serially at birth, discharge, 40 weeks post menstrual age (PMA), and at 1, 3, 6 and 12 months of corrected age. Developmental quotient (DQ) at 12 months corrected age was assessed.

Results: Z-scores for weight, length and head circumference (HC) at birth were -1.21(±0.92), -0.98(±1.32) and -0.70(±1.14), respectively for VLBW infants and -0.37(±0.72), -0.11(±0.96) and 0.05(±0.73) respectively for NBW infants. VLBW infants had a significant drop in all Z-scores by discharge (P<0.001). There was a catch up to birth scores by 12 month age. VLBW infants had significantly lower Z-scores for weight, length and HC at one year corrected age as compared to NBW infants (P =0.01, 0.04 and 0.001, respectively). DQ at 12 months was significantly lower in VLBW infants (91.5±7.8) than NBW infants (97.5±5.3) (P <0.001). DQ of small for gestational age (SGA) and appropriate for gestational age (AGA) VLBW infants was comparable.

Conclusion: VLBW infants falter in their growth during NICU stay with a catch-up later during infancy. In comparison to NBW infants, they continue to lag in their physical growth and neurodevelopment at 1 year of corrected age.

Key words: Development, Neonate, Outcome, Very low birth weight.

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Very low birth weight (VLBW) infants are at higher risk of poor growth and neurodevelopmental outcomes, due to associated adverse perinatal risk factors and postnatal morbidities. Several studies have reported high incidence of growth failure and poor neurological outcome during infancy and childhood [1-3]. There have been a few studies from India, reporting growth and neurodevelopment of low birth weight infants [4-6]. However, there is paucity of data on these outcomes of VLBW infants. Recently, Mukhopadhyay, *et al.* [7] have reported neurodevelopmental outcome of VLBW infants from northern India.

We planned this study with an objective to evaluate growth and neurodevelopmental outcome of VLBW infants at 12 months of corrected age and compare it with term, normal birth weight (NBW) infants.

METHODS

All VLBW infants, admitted to our NICU from January 2007 to December 2007 were enrolled and prospectively followed till one year corrected age. Gross congenital malformation was an exclusion criteria. This study was approved by the Institutional Review Board and Hospital Ethics Committee. Parental consent was obtained at the time of enrolment. Gestational age was recorded as per obstetrical estimates based on first trimester ultrasonography or if not available, by date of last menstrual period. Weight was taken at birth, on electronic weighing scale with accuracy of ± 5 gram, with baby being unclothed. Length and head circumference (HC) were taken first at 12-24 hrs of age using standard techniques. Subsequently, measurements were repeated at discharge and then at 40 weeks, 1, 3, 6, and 12 months of corrected age. To improve follow up, periodic reminders were sent to parents through telephonic calls and postal mails.

All VLBW infants were started on enteral feeds as soon as possible after birth. Parenteral nutrition (PN) was initiated on first day of life, if infant was not receiving total enetral feeds. Most infants with birth weight <1250 grams and all with a birth weight <1000 grams received partial parenteral nutrition along with incremental enteral feeds. As per the unit practice during the study period, PN was initiated with protein and lipid at 1 gm/kg with daily increments by 1 gm/kg to maximum protein 3.5-4 gm/kg and lipid 3 gm/kg. Target calorie through PN was 70-90 Cal/kg/day. PN was continued till feed volume reached 100 ml/kg/day. Enteral feeds were increased gradually to a volume of 180 mL/kg/day. Human milk was preferred; where not available, LBW formula was used. Once infant reached 100 mL/kg/day of enteral feeds, expressed breast milk was fortified with human milk fortifier to make caloric content of 80 Cal/100 mL, to achieve a target calories 110-130 cal/kg/day. Developmentally supportive care was routinely provided to all the neonates. Special care was taken for environment including noise level, light, positioning and nesting. Kangaroo mother care was offered, once infants were hemodynamically stable. Early stimulation and intervention, tailored to the infant's need was provided during NICU stay and during follow up. A cohort of term, birth weight (≥2500 grams) infants born during same period, who had uneventful antenatal and postnatal course, was enrolled for comparison. Their anthropometric measurements were taken at birth and then at 1, 3, 6 and 12 months of chronological age.

Z-scores for each anthropometric parameter before 40 wks Post menstrual age (PMA) were computed using Fenton's reference [8]. Infants below 10th centile were categorized as small for gestational age (SGA). For term gestation and beyond, Z-scores were computed using new WHO growth standard [9]. Neurodevelopmental assessment was done at 1 yr of corrected age, by a single developmental pediatrician, using Developmental Assessment Scale for Indian Infants (DASII). Motor index, mental index and combined developmental quotient (DQ) were computed. We used revised version of the original Baroda norms [10]. A comparison between VLBW and NBW infants was made for each anthropometric parameter and development quotients, at corresponding age.

Statistical analysis was done using SPSS version 17.0. Comparisons were made using independent *t* test, paired *t* test and repeated measure ANOVA, as applicable.

RESULTS

Flow chart of study infants is shown in ***Fig.* 1**. Baseline characteristics and morbidity profile of VLBW infants is depicted in ***Table* I**. The mean birthweight and gestational age of the enrolled VLBW infants were 1238 ± 176 grams and 31.2 ± 2.2 weeks, respectively. Mean birth weight and gestational age of NBW infants were 3378 ± 598 grams and 38.5 ± 1.2 weeks, respectively.

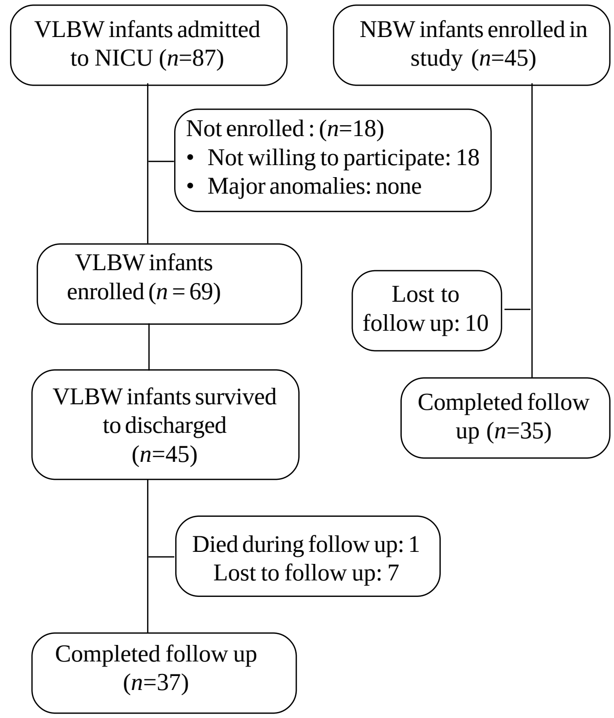

FIG. 1 *Study flow chart.*

Anthropometric parameters of VLBW and NBW infants are depicted in ***Web Table* I**. Among VLBW infants, there was a significant decline in all three anthropometric parameters from birth to discharge (*P* <0.001). Thereafter, there was an increase in all Z-scores during infancy (***Fig.* 2**). After 40 wks PMA, the difference of each anthropometric Z-score from respective birth Z-scores was insignificant. However, all anthropometric Z-scores of VLBW infants continued to be significantly lower than NBW infants, throughout infancy (*P*<0.05).

Developmental indices of enrolled infants are displayed in ***Table* II**. Developmental indices of VLBW infants were significantly lower than that of NBW infant (*P*<0.01). A DQ <85 was observed in 22% of VLBW

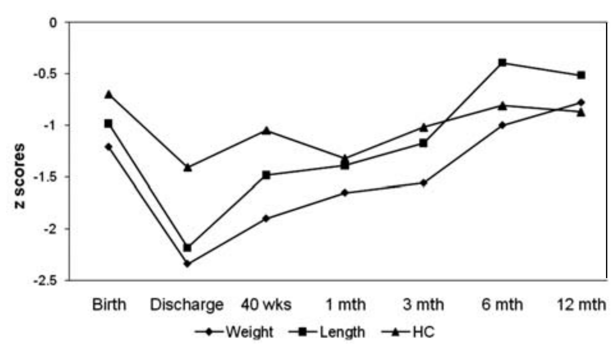

Fig. 2 *Growth pattern of VLBW infants from birth to 12 months.*

TABLE I CHARACTERISTICS OF THE VLBW INFANTS

Characteristics	*N = 37*
Birth weight (g)*	1238 (176)
Gestational age (wk)*	31.2 (2.2)
SGA	17 (46)
PIH	12 (32)
Need for Ventilation	26 (70)
CPAP	10 (27)
SIMV	16 (43)
Duration of ventilation (days)#	4 (0; 8.5)
CPAP days	3 (0; 5.5)
SIMV days	0 (0; 2)
Surfactant	9 (24)
Patent ductus arteriosus requiring treatment	2 (5)
Intraventricular hemorrhage Grade I-II	3 (8)
Cystic periventricular leucomalacia	1 (3)
Culture proven Sepsis	13 (35)
Necrotizing enterocolitis stage II or more	2 (5)
ROP Any stage	2 (5)

**Values expressed as mean (SD); #values expressed as median (IQR)Other values expressed as n (%); No neonate has chronic lung disease or grade III-IV intraventricular hemorrhage.*

infants. Developmental indices in AGA and SGA VLBW infants were comparable. Developmental quotient was significantly lower in VLBW infants with 12 months head size below -1SD than those with head size above -1SD (P<0.05) (***Web Table* II**).

DISCUSSION

Majority of VLBW infants are born smaller for their respective gestation as compared to their NBW counterparts [1,11]. We observed that VLBW infants at birth had lower Z-scores for weight, length and HC as compared to NBW controls. This suggests that most VLBW infants suffer intrauterine growth failure, possibly due to adverse perinatal factors. Amongst these infants, about 20-25% have been reported to be small for gestational age [1,12]. The incidence of growth restriction was higher in our cohort, with 47% of VLBW infants being SGA, which is similar to other reports in Indian infants [6,13]. This could be due to differences in socio-economic factors, ethnic variation or perinatal morbidities in our cohort.

It has been suggested that the postnatal growth of VLBW infants should match intrauterine growth rates during third trimester [14]. However, most VLBW infants experience a growth lag during NICU stay [1,13,15]. This extra-uterine growth failure is possibly due to neonatal morbidities, inappropriate nutritional management or unfavourable NICU environment. Our VLBW infants had a decline in Z-scores, from birth to discharge, by approximately 1 unit for weight and length and 0.7 unit for head circumference. This pattern is similar to other observations of postnatal growth of VLBW infants during initial hospitalization [1,15,16].

After early growth failure, VLBW infants experience a catch up in growth beyond infancy through adolescence [1,13,16,17]. We observed a steady improvement in all anthropometric parameters of VLBW infants from discharge to 12 months. This growth pattern is consistent with findings of other authors, who reported a similar magnitude of improvement in anthropometric Z-scores [1,16]. Despite a catch up to their birth scores by 12 months age, our VLBW infants remained significantly smaller and lighter than NBW infants. Considering the risk of metabolic syndromes, it is debatable whether VLBW infants should catch up to their NBW counterparts or continue to grow along their birth centiles. A larger cohort with long term follow up is required to address this issue.

VLBW infants have been observed to have poor long-term neurodevelopmental outcomes [3,18]. Mean DQ at 12 months in our VLBW cohort was 6 points lower than that of NBW infants. Developmental quotients in our cohort were approximately 10-12 points higher than previous observations [7,18]. In the study by Procianoy, *et al*. [2], mean mental and motor indices, at 1 year of age ranged from approximately 78 to 80. Higher DQs in our infants are possibly related to higher gestation and lower neonatal morbidities, or a difference in assessment tools used. The mean gestation of VLBW infants in our study

TABLE II DEVELOPMENTAL INDICES OF VLBW AND NBW INFANTS AT 12 MONTHS

	VLBW infants (n=37)	*NBW infants (n=35)*	*Mean difference (95% CI)*	*P value*
DQ	91.5(7.8)	97.5(5.3)	-6.0 (-9.3 to -2.6)	0.001
Motor index	90.1(9.6)	96.6 (5.8)	-6.4 (-10.5 to -2.4)	0.002
Mental index	92.9 (8.0)	98.4 (6.1)	-5.5 (-9.0 to -2.0)	0.003

Data are expressed as mean (SD).

WHAT IS ALREADY KNOWN?

- VLBW infants suffer a growth lag during early infancy with a catch up during childhood and adolescence. They have poor neurodevelopment outcome as compared to normal birth weight infants.

WHAT THIS STUDY ADDS?

- This study highlights growth pattern and neuro-developmental outcome of Indian VLBW infants during infancy.

was also significantly higher than the cohort reported by Pracianoy, *et al*. [2]. Mukhopadhyay, *et al*. [7] reported mean mental and motor quotients at 18 months, 80.4 (±10.7) and 77.2 (±13.3), respectively. The conspicuous difference in developmental indices of our cohort could be related to lower incidence of IVH and other morbidities (ROP, BPD, etc.) in our cohort. Further, earlier age at assessment in our study might have missed subtle motor and cognitive deficits, which could unmask subsequently. For more appropriate inferences, there is a need to evaluate long-term neurological outcome of our VLBW cohort at a later age.

There are contradictory reports about neuro-devlopmental outcomes of SGA infants [19-21]. We did not find a significant difference in either motor or mental developmental index in SGA VLBW infants, compared to AGA VLBW infants. The mean gestation of SGA infants in our cohort was 32.8 (±1.5) weeks as compared to 29.8 (±1.70) weeks in AGA infants. The morbidities associated to lower gestation, would possibly offset any potential benefit of AGA status of these infants. Comparison of gestation matched AGA and SGA might disclose any potential difference. This comparison was not possible in our study due to smaller number of subjects.

Poor head growth has been linked to poor neurological outcome [22,23]. To explore association of head growth and neuro-developmental outcome, we categorized VLBW infants into two groups, with HC at 12 month below and above -1SD. During design phase of the study, it was decided to compare infants with HC below or above-2SD. However due to smaller number of subjects below -2 SD, a post hoc analysis was done with a cut off of -1SD. DQ at 12 months was significantly lower for VLBW infants with a head size below -1SD. This observation reiterates the association of head growth to neurological outcome.

Ours was a prospective cohort study, comparing the outcomes of VLBW infants with a simultaneously enrolled normal birth weight cohort. In this study, we assessed both physical growth as well as neurodevelopmental outcome of VLBW infants. Neuro-developmental outcome was assessed using DASII, which has been validated for Indian infants. However, the number of infants enrolled in the study was small. There was 18% follow up loss in this study. Age at final assessment in our study was also early wherein we may have missed minor neurological deficit, as longer follow up duration is required to assess subtle cognitive deficits, behavioral disorders and scholastic performance.

To summarize, our study shows that VLBW infants catch up to their birth Z scores by infancy; however, they continue to remain smaller and lighter as compared to normal birth weight infants. Neurodevelopmental indices of the VLBW infants at 1 year are lower as compared to the NBW infants. Despite advances in neonatal care, growth and neurodevelopment of VLBW infants during initial hospitalization and infancy remains a challenge. A multipronged approach is required to improve growth and development of these infants.

Contributors: MM and SS conceived the idea and designed the study. MM, BA and KA were responsible for data collection and analysis. AS and PG helped in editing manuscript. SP and MM performed the neurodevelopment assessment. NK supervised the study and helped in editing the manuscript. All authors approved the final content of the manuscript.
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REFERENCES

1. Hack M, Schluchter M, Cartar L, Rahman M, Cuttler L, Borawski E. Growth of very low birth weight infants to age 20 years. Pediatrics. 2003;112:30-8.
2. Ho JJ, Amar HS, Mohan AJ, Hon TH. Neurodevelopmental outcome of very low birth weight babies admitted to a Malaysian nursery. J Pediatr Child Health. 1999;35:175–80.
3. Boo NY, Ong LC, Lye MS, Chandran V, Teoh SL, Zamratol S, *et al*. Comparison of morbidities in very low birthweight and normal birthweight infants during the first year of life in a developing country. J Paediatr Child Health. 1996;32:439-44.
4. Chaudhari S, Otiv M, Chitale A, Pandit A, Hoge M. Pune Low Birth Weight Study – Cognitive abilities and educational performance at twelve years. Indian Pediatr. 2004;41: 121-8.
5. Bhargava SK, Ramji S, Srivastava S, Sachdev HPS, Kapani V, Datta V, *et al*. Growth and sexual maturation of low birth weight children: a 14 year follow up. Indian Pediatr.

1995;32: 963-70.

6. Bavdekar AR, Vaidya UV, Bhave SA, Pandit AN. Catch up growth and its determinants in low birth weight babies: a study using Z scores. Indian Pediatr. 1994;31:1483-90.
7. Mukhopadhyay K, Malhi P, Mahajan R, Narang A. Neurodevelopmental and behavioral outcome of very low birth weight babies at corrected age of 2 years. Indian J Pediatr. 2010;77: 963-7.
8. Fenton TR. Preterm Growth Chart 2003calculations. Available from: URL: http://members. shaw.ca/ growthchart/Fenton Growth Chart calculations.xls. Accessed on 10 February, 2009.
9. New WHO growth charts. Available from:URL: http:// www.who.int/nutgrowthdb/software/en/ Accessed on 10 February 2009.
10. Misra N, Pathak P. Developmental assessment scales for Indian Infants (DASII): Manual, Baroda, M.S. University of Baroda, 1996.
11. Westerberg A C, Henriksen C, Ellingvåg A, Veierød MB, Júlíusson PB, Nakstad B. First year growth among very low birth weight infants. Acta Pædiatrica. 2010;99:556-62.
12. Ehrenkranz RA, Younes N, Lemons JA, Fanaroff AA, Donovan EF, Wright LL. Longitudinal growth of hospitalized very low birth weight infants. Pediatrics. 1999;104:280-9.
13. Saluja S, Modi M, Kaur A, Batra A, Soni A, Garg P, *et al*. Growth of very low birth weight infants during hospital stay. Indian Pediatr. 2010;47:851-6
14. American Academy of Pediatrics, Committee on Nutrition. Nutritional needs of low-birth-weight infants. Pediatrics. 1977;60:519-30.
15. Marks KA, Reichman B, Lusky A, Zmora E; Israel Neonatal Network. Fetal growth and postnatal growth failure in very-low-birthweight infants. Acta Paediatr. 2006;95:236-42.
16. Mackay CA, Ballot DE, Cooper PA. Growth of a cohort of very low birth weight infants in Johannesburg, South Africa. BMC Pediatrics. 2011;11:50-5.
17. Saigal S, Stoskopf B, Streiner D, Paneth N, Pinelli J, Boyle M. Growth trajectories of extremely low birth weight infants from birth to young adulthood: A longitudinal, population-based study. Pediatr Res. 2006;60:751-8.
18. Procianoy RS, Koch MS, Silveira RC. Neuro-developmental outcome of appropriate and small for gestational age very low birth weight infants. J Child Neurol. 2009;24:788-94.
19. Larroque B, Bertrais S, Czernichow P, Leger J. School difficulties in 20-year-olds who were born small for gestational age at term in a regional cohort study. Pediatrics. 2001;108:111-5.
20. Gutbrod T, Wolke D, Soehne B, Ohrt B, Riegel K. Effects of gestation and birth weight on the growth and development of very low birthweight small for gestational age infants: a matched group comparison. Arch Dis Child (Fetal Neonatal Ed). 2000;82:F208-14.
21. Latal-Hajnal B, von Siebenthal K, Kovari H, Bucher HU, Largo RH. Postnatal growth in VLBW infants: significant association with neurodevelopmental outcome. J Pediatr. 2003; 143:163–70.
22. Hack M, Breslau N, Weissman B, Aram D, Klein N, Borawski E. Effect of very low birth weight and subnormal head size on cognitive abilities at school age. N Engl J Med. 1991; 325:231-7.
23. Gross SJ, Oehler JM, Eckerman.CO. Head growth and developmental outcome in very low birthweight infants. Pediatrics. 1983;71:70-5.