Factors Associated with Thymic Size at Birth among Low and Normal Birth-Weight Infants

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Objective To study the effect of gestational and perinatal exposures on thymic size in 366 normal birth weight and 426 low birth weight (LBW) neonates in Guinea-Bissau in West Africa.

Study design In a cross-sectional study, thymic size was measured at birth by the use of ultrasound. Information on possible determinants was collected from pregnancy cards, hospital records, and interviews with the mother. We used the log-transformed thymic index and thymus/weight index as outcome measures. Data were analyzed with adjusted linear regression models providing geometric mean ratios (GMRs) with 95% CI.

Results Determinants of thymic size among normal birth weight infants were pathologic amniotic fluid (adjusted GMR for thymic index: 0.84 [0.74-0.96]) and male sex (GMR: 1.13 [1.06-1.22]). Among LBW infants, birth season (1.11 [1.01-1.22]), maternal body temperature (0.89 [0.79-0.98]), antibiotic treatment at the time of labor (0.84 [0.70-1.00]), number of pregnancy consultations (1.03 [1.00-1.05]), maternal age (0.91 [0.84-0.98]), Apgar score (1.06 [1.03-1.10]), and infant convulsions (0.44 [0.29-0.65]) were all independent determinants of thymic index but not all were determinants of thymus/weight index. Pathologic amniotic fluid and cesarean delivery were associated with thymus/weight index among LBW infants (0.85 [0.75-0.95] and 0.80 [0.67-0.96]) but were only borderline significant for thymic index.

Conclusion Exposures mainly related to stress and infections were associated with a smaller thymus, mainly in LBW infants. *(J Pediatr 2014;165:713-21)*.

The thymus gland is a key organ in the development of the cellular immune system and the human T-cell repertoire.[1] In Guinea-Bissau, thymic size at birth is strongly correlated to survival the first year of life.[2] The mechanism is unknown, but a possible explanation could be improved cellular immune function, leading to decreased susceptibility or reduced severity of infectious diseases. Thymic size at birth is most likely determined by a combination of genetic factors and gestational and perinatal environmental exposures. Malnutrition,[3] infectious diseases,[4] toxic exposures,[5] and stress[6] all have been associated with a small thymus. The stress hormone cortisol often mediates this effect and can cause acute thymic involution with extensive cell death of the developing T-lymphocytes in the thymic cortex.[6] Acute thymic involution during infection and malnutrition can have long-term influence on the cellular immune function.[7]

In Guinea-Bissau approximately 14% of infants are low birth weight (LBW; <2500 g; unpublished data, Aaby P), and LBW neonates have a high mortality in particular from infectious diseases.[8] Because thymic size is strongly associated with weight,[2] LBW infants have a smaller absolute thymic size, which could contribute to increased mortality. Whether LBW infants also have a smaller thymic size relative to weight has not been studied. Common causes of LBW in low-income countries include infection and poor maternal nutrition, factors also associated with a decreased thymic size. Understanding what causes a small thymus at birth, in particular in the vulnerable LBW infants, could help identify interventions that possibly could improve thymic size and immunologic competence and ultimately reduce mortality. We aimed to assess absolute and relative thymic size in newborns in a normal birth weight (NBW) and a LBW cohort in Guinea-Bissau and to study the influence of gestational and perinatal exposures on thymic size in the 2 cohorts.

BHP	Bandim Health Project
GMR	Geometric mean ratio
LBW	Low birth weight
MUAC	Mid–upper-arm circumference
NBW	Normal birth weight
PROM	Premature rupture of membranes
RCT	Randomized controlled trial

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Methods

The study was conducted at the Bandim Health Project (BHP), a health and demographic surveillance system site in Guinea-Bissau, covering approximately 102 000 individuals in the capital Bissau. All births are registered in the BHP study area and at the maternity ward at the national hospital, and all mothers are interviewed after birth about exposures during pregnancy and delivery. Mothers whose infants were eligible for enrollment into the present thymus study were given both a written and an oral explanation of the study and signed the informed consent with a signature or with a fingerprint. Both the 2 trials and this study were approved by the ethics committee in Guinea-Bissau, and the Danish Central Ethical gave its consultative approval.

Using a cross-sectional design, we studied newborns who were being enrolled into 2 randomized controlled trials (RCTs) at the maternity ward. Cohort A consisted of NBW neonates from the BHP study area enrolled into a RCT examining the effect on infant mortality of not providing oral polio vaccine at birth. Cohort B consisted of LBW neonates from all suburbs of Bissau who were enrolled in a RCT in which investigators examined the effect on neonatal mortality of providing the Bacille Calmette-Guérin vaccination at birth. The enrollment criteria for both trials were absence of severe malformations and readiness for discharge from the hospital. At the day of enrollment, the infant was weighed on an electronic Seca scale (model 336; Seca, Hamburg, Germany) to determine NBW cohort (≥2.5 kg) or LBW cohort (<2.5 kg) status. Infants were enrolled in the present thymus study only if their mothers had already accepted participation in 1 of the 2 trials. After informed consent was obtained, the ultrasound examination of the thymus was performed before vaccine randomization.[9]

Assessment of Thymic Size

All ultrasound examinations were performed by the same medical doctor trained in the procedure (H.E.). Thymic size was estimated by use of the method described by Hasselbalch et al.[10] Examining the infant in supine position, the largest transverse diameter of the gland was measured twice. Perpendicular to the diameter, the largest sagittal area of the largest lobe was measured. If measurements differed more than 15%, both were repeated. The average diameter and average area were multiplied to estimate the thymic index. The thymic size relative to weight, the "thymus/weight index" was estimated as the thymic index divided by infant weight in kilograms. A Sonosite MicroMaxx transportable ultrasound scanner (Sonosite, Bellshill, Scotland) with an 8-5 MHz C11e transducer, manufactured by Secma (Skævinge, Denmark), was used for the examination. The assessment of thymic size may be more difficult if the infant is crying, sleeping, or not lying in an exact supine position (eg, lying on the mothers arm); we therefore registered this information at each examination. We also registered whether the examiner considered the examination to be difficult.

Information on Determinants

Data on possible determinants of thymic size were collected from labor charts and birth records, maternal pregnancy cards, BHPs standard birth interview, and from an interview designed for this study. From labor charts and birth records, we collected information on the sex of the infant, twin status, Apgar score, pathologic amniotic fluid, cesarean delivery, and birth weight. Birth in the rainy season was defined as birth from June to November (included). All mothers who gave birth at the hospital were offered an HIV antibody test free of charge before giving birth. A local nongovernmental organization took care of HIV-positive mothers and their infants and provided medical treatment. Because of periodic shortages of HIV tests in the country, not all participants were tested. At enrollment, the mother was interviewed about alcohol consumption, fever episodes in pregnancy, premature rupture of membranes (PROM), antibiotic treatment during labor, and medical consultations and hospitalization during pregnancy. This information was obtained from the mother and not from hospital records, because these were scarce, often nonexistent, and rarely included this information. From the pregnancy card, we gathered information on the number of pregnancy consultations, the number of tetanus vaccinations in pregnancy, and maternal blood pressure at consultations; maternal blood pressure also was obtained from hospital records, if available.

We defined preeclampsia as a registered systolic blood pressure greater than 140 mmHg or a diastolic blood pressure greater than 90 mm Hg before or at the time of admission. From the BHP's standard birth interview, we obtained information regarding ethnicity, maternal age, previous births, maternal schooling, and 2 socioeconomic markers: indoor or outdoor toilet and electricity in the house. The mother was asked whether she judged her infant to be well, if the infant was able to breastfeed, and whether she had observed any convulsions in the infant. Observation of the newborn in the maternity ward is dependent almost exclusively on the mother, due to lack of staff. After the interview we measured maternal mid–upper-arm circumference (MUAC) and axillary temperature. A trained nurse conducted a standard neonatal examination to screen for congenital illness or malformations and estimated gestational age via Ballard score[11] in the LBW cohort; Ballard score was not estimated for NBW infants. After the ultrasound examination, infant length, head, and abdominal circumference, MUAC, and axillary temperature were measured.

Statistical Analyses

All analyses were conducted using STATA 11/SE (StataCorp Lp, College Station, Texas). Differences in background characteristics between the 2 cohorts were examined using a χ^2-test, a 2-sample t-test, or a Kruskal-Wallis test. To obtain a normal distribution of the 2 outcomes, we log transformed the thymic index and thymus/weight index. The crude association between the possible determinants and thymic size was calculated using linear regression models providing geometric mean ratios (GMRs) with 95% CIs. The interpretation of a GMR between 2 groups of, eg, 1.20 is that one of the groups has 20% larger thymic index compared with the other group.