Oncology and Haematology

INVESTIGATION OF MYC GENE AMPLIFICATION IN PAEDIATRIC BRAIN TUMOURS
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Background: Brain tumours are the second most common malignancy in childhood, and carry a poor prognosis. Identification of tumour-specific genetic changes may provide insights into novel therapies. Myc oncogenes are involved in regulation of gene transcription, and activation of these genes has been implicated in tumourigenesis.

Aims: To demonstrate amplification of the C-myc and N-myc oncogenes, located on 8q and 2p respectively in 14 paediatric brain tumours.

Methods: Four high grade astrocytomas, seven ependymomas and three medulloblastomas were selected as demonstrating gains at 8p and/or 2p by Comparative Genomic Hybridisation analysis. Interphase Fluorescence In Situ Hybridisation utilising markers for N-myc and centromere 2 and C-myc and centromere 8 was used to determine amplification and identify the copy number of these oncogenes.

Results: Ten tumours demonstrated amplification of the myc oncogenes. Amplification of the N-myc gene alone occurred in 3 ependymomas. Amplification of the C-myc gene alone occurred in 1 high grade astrocytoma, 1 medulloblastoma and 3 ependymomas. In 2 high grade astrocytomas there was amplification of both the C-myc and N-myc oncogenes. Five tumours demonstrated sub-populations of cells with triploidy of chromosome 2, and 6 tumours demonstrated triploidy of chromosome 8. One tumour (a medulloblastoma) demonstrated an increased copy number of chromosome 8 without amplification of C-myc.

Conclusions: N-myc and C-myc amplifications occur in high grade astrocytomas, medulloblastomas and ependymomas in the paediatric population. The pattern of amplification varied within and between the tumours studied. Further study is needed to correlate these tumour-specific genetic changes with phenotype.

STATISTICAL ANALYSES PROVIDE SUPPORT FOR TWO INFECTIOUS MECHANISMS IN THE AETIOLOGY OF CHILDHOOD BRAIN TUMOURS
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Aims: (i) To use Manchester Children's Tumour Registry data (1954–1998) to test predictions of space-time clustering patterns which might arise as a result of environmental exposures. (ii) To distinguish between hypotheses relating to post-natal exposures or pre-natal events by using locations and dates of birth as well as at diagnosis.

Methods: Knox tests for space-time interactions between cases were applied with fixed thresholds of close in space, <3km, and close in time, <1 year apart. Both places and times of birth and diagnosis were utilised. Tests were repeated replacing geographical distance with distance to the Nth nearest neighbour (Nearest Neighbour [NN] threshold analysis). N was chosen such that the mean distance was 3km. Data were also examined by a second order procedure based on K-functions. Analyses were applied to 15 diagnostic subgroups.

Results: Diagnostic subgroups involving astrocytoma and ependymoma showed significant evidence of space-time clustering at place and time of diagnosis. Two diagnostic sub-groups involving pilocytic astrocytoma and ependymoma showed significant evidence of space-time clustering at place and time of birth.

Conclusions: The results are consistent with a role for infections or other localised environmental causes involving two different mechanisms, one acting around the time of birth, with a variable latent period, for cases of pilocytic astrocytoma and ependymoma, and the other acting around the time of diagnosis, with a short constant latent period, for older cases (aged 5–14 years) of astrocytoma and ependymoma.

GEOGRAPHIC MOBILITY FOLLOWING CANCER TREATMENT IN YORKSHIRE
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Maximising re-integration into society is a major goal of childhood cancer units. Geographic mobility has been used as an objective proxy for this and here we present the first population-based study.

Data was extracted from the Yorkshire Specialist Register of Cancer in Children & Young People, where changes of address are updated biennially. Eligible cases were diagnosed with a malignancy whilst living in the former Yorkshire Regional Health Authority, aged<15 years and greater than 5 years post-diagnosis or relapse. Validated addresses and postcodes were examined. Mobility was defined as any address different to that at diagnosis. Migration was regressed against age, sex, socio-economic status, treatment with a bone-marrow transplant (BMT) or cranial irradiation.

Analysis of 4 main diagnostic groups (267 leukemias, 154 lymphomas, 166 brain and 344 solid tumours) revealed no significant difference in mobility. Those currently aged 18 or over were more likely to move than those under 18 (58% vs. 41%). For all cancers, girls were 20% more likely to move than boys; increasing to 71% for acute lymphoblastic leukaemia (P<0.06). Children living in less affluent areas were more likely to move, particularly those with leukaemia. Cranial irradiation had no effect on mobility of survivors of brain tumours. Relapse did not alter mobility. Following BMT, children with leukaemia/lymphoma were 12% less likely to have moved.

Trends in overall burden of morbidity have been identified and support some subjective theories. Normative data (unavailable in UK) would enhance interpretation. Assessment of geographic mobility provides an objective proxy for the long-term impact of cancer survival on life quality.

CHIMERAPLASTY AS A METHOD OF GENE THERAPY IN SICKLE CELL DISEASE
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Chimeraplasty (CPY) is an exciting new approach of in situ gene repair utilizing the cells own DNA repair machinery. It avoids problems associated with viral mediated gene transfer for correction of hemoglobinopathies such as low transduction efficiency and transgene silencing. CPY has successfully been applied to plants and animal cells including liver and renal tubular cells. Sickle cell disease (SCD) is an ideal candidate for CPY as it is caused by a single base substitution. Studies have shown that CPY can induce gene correction in committed progenitors, but corrections have not persisted long-term, suggesting that the corrections were not made in HSCs. This could be caused by inability to introduce the chimera in the cell, inability to enter the nucleus, or lack of the repair proteins to induce the base pair exchange. These hypotheses were tested using cord blood CD34+ cells, K562 and KG1a cell lines. Using Western blot, we detected the DNA-repair enzymes, hMSH2 and hMLH1, known to be involved in chimeraplasty in CD34+ cells. We then tested several methods to introduce chimeras into the target cells. 15% of CD34+ cells were transfected by lipofection with cationic lipids but 60±15% of cells were transfected by electroporation. To determine the fate of the chimera in the cells, we stained the cells with DII, a cyttoplasmic dye and analysed the cells by confocal microscopy. Following electroporation, the chimera was located within the nuclei of CD34+ cells with the brightest fluorescence at 18 to 24 hours. Finally, we tested, thus far only in cell lines, whether the chimera can induce point mutations in the Hb gene. Following chimeraplasty, 4% of the Hb gene was found to have a Val→Glu mutation.
Mobilized peripheral blood (MPB) has almost completely replaced the use of bone marrow (BM) for patients undergoing autografting. Time to engraftment is largely dependent on the CD34+ cell dose. CD34+ cells contain both committed as well primitive progenitors. Estimation of human primitive progenitors can be done using xenogeneic transplantation or in vitro assays. Punzel et al (Blood; 1999) showed that CD34+ cell when transplanted in vivo (BM) differentiate into long-term hematopoietic progenitors. ML-IC are therefore closely related to hematopoietic stem cells. To assess how different cytokine schemes affect mobilization of primitive progenitors, we compared the frequency of ML-IC in PB collections of lymphoma patients (mobilized with 10mcg/kg each G-CSF+SCF), with that of PB collections from normal donors mobilized with 5mcg/kg G-CSF (n=9), as well as that of normal BM and cord blood (CB). PB collections were done on day 6, CD34+/CD38-Lin- cells were selected by FACS. Single CD34+/CD38-Lin- cells were deposited on AFT024 feeders and cultures maintained under ML-IC conditions for 5–7 weeks as published. A ML-IC was a cell that gave rise to at least 1 LTC-IC and 1 NK-IC. Overall frequencies were compared using analysis of variance Mann-Whitney U tests. The ML-IC frequency was lowest in G-CSF MPB (2.8±1.5%), followed by steady state BM (3.8±1.6%), but significantly higher (p=0.05) in G-CSF+SCF MPB (4.5±2.1%) and UCB (4.7±2.8%). The ability of a single ML-IC to generate 2 LTC-IC and 2 NK-IC in G-CSF+SCF MPB was 3.8±1.0%. 5.7±3.4% of ML-IC in G-CSF+SCF MPB could generate CD19+ B cells. We conclude that SCF combined with G-CSF mobilizes significantly more ML-IC in the PB than G-CSF alone. Furthermore, ML-IC in G-CSF+SCF MPB have significantly greater generative potential (ie can generate more than 1 LTC-IC and 1 NK-IC) than those in G-CSF MPB.

CD34+ PROGENITORS CAN BE CONSISTENTLY GENERATED FROM FROM CORD BLOOD, MOBILISED PERIPHERAL BLOOD AND NORMAL BONE MARROW CD34+/CD38-Lin- CELLS EX Vivo

Until recently it was thought that human hematopoietic stem cells (HSC) were all CD34+. However there is a growing body of evidence that cells with HSC characteristics also reside in the CD34- fraction and acquisition of CD34 expression is influenced by culture conditions. We compared conditions needed for generating CD34+ from CD34-. CD34- and Lin- cells in mobilized peripheral blood (MPB), bone marrow (BM) and cord blood (CB). Using the ML-IC assay we also assessed the functional characteristics of CD34+ cells generated from CD34- cells. BM, MPB or CB CD34+/CD38-Lin- cells were selected by MACS and FACS and CD34+/CD38-Lin- by StemSep lineage depletion and FACS. 500–5000 cells were plated for 14 days in transwells, with GCSF, IL3, IL6, IL7 and varying concentrations of Flt3L, Tpo and SCF (0–300ng/ml). On day 14 CD34+/CD38-Lin- cells were reselected by FACS and single cells deposited onto AFT024 feeders and cultured in ML-IC conditions. ML-IC frequencies were compared on day zero and 14 and CD34+ creation/ expansion was calculated for each condition. No ML-IC was generated from day zero CD34- cells while 4.3±2.7% 2.1±1.3%, 3.7±1.6% ML-IC were present in CD34+ from CB, MPB and BM, resp. Optimal conditions for expansion of CD34+ Lin- cells as well as the generation of CD34+ cells and ML-IC from CD34+ cells differed for the three sources. Maximal CB CD34+ Lin- cell and ML-IC creation (3.9±1.5% of reselected CD34+ Lin- cells) was seen in AFT024-SNC cultures with 300ng/ml Flt3-L+Tpo and SCF 200ng/ml. Maximal BM or CB CD34+Lin- cell (MPB: 3.8±1.1 and BM:8±1.1) and ML-IC creation (MPB: 3.1±1.1% and BM: 3.1±1.1% of reselected CD34+ Lin- cells) was seen in AFT024-SC cultures with 300ng/ml SCF+Flt3-L but without Tpo. Thus, generation of CD34+ cells and ML-IC from CB CD34- cells or similar cells from MPB did not differ significantly with respect for the need of direct contact with stromal cells and the type of cytokines added.

STEM CELL FACTOR (SCF) ADMINISTRATION AS A METHOD IF INCREASING MOBILISATION OF PRIMITIVE PROGENITORS IN TRANSPLANT PATIENTS

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Aims: To establish current practice in both regional and shared care paediatric oncology centers which routinely carry out painful procedures in children with cancer and to compare this to accepted standards set out by the American Academy of Pediatrics.

Methods: A questionnaire was sent to the lead clinicians for Paediatric oncology in tertiary referral and shared care centers in England, Scotland, and Wales. If no reply was obtained a telephone enquiry was made. Information was collected between May 1999 and March 2000.

Results: Responses were obtained from 17 regional and 24 shared care centers. 26 centres in total use general anaesthesia for routine painful procedures. 15 centres use deep sedation. 6 of these 15 centres use maximum drug doses above those recommended in the RCPCH “Medicines For Children.” Only 1 of the 15 centres provided adequate monitoring during the sedation. In total 4 centres had insufficient personnel present to insure that one member of staff has sole responsibility for observing vital signs and monitoring the airway.

Conclusion: This survey raises important issues about the safety of current practices for the deep sedation of children undergoing routine painful procedures in oncology. We recommend that the guidelines set out by the American Academy of Pediatrics should be issued to and followed by all centres involved in the management of children with cancer.

A survey of the sedation and Anaesthetic practice used for routine painful procedures in Paediatric oncology

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Aims: To establish current practice in both regional and shared care paediatric oncology centers which routinely carry out painful procedures in children with cancer and to compare this to accepted standards set out by the American Academy of Pediatrics.

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RENAL FUNCTION FOLLOWING LIVER TRANSPLANTATION FOR UNRESECTABLE HEPATOBLASTOMA

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Aim: To determine whether children undergoing liver transplantation (LT) for hepatoblastoma (HB) were at increased risk of nephrotoxicity.

Methods: Retrospective review of all children undergoing LT for HB, from February 1991 to April 2000. Three cases, age- and sex-matched for each of HB, and transplanted for biliary atresia (BA) were selected as control. Pre- and post-LT renal function, change of immunosuppression due to nephrotoxicity and post-LT hypertension, were studied. Renal function was determined by serial plasma creatinine and estimated glomerular filtration rate (cGFR) derived from Schwartz’s formula.1

Results: 10 children (5 boys, 5 girls) underwent LT for HB at a mean age of 47 months. The mean age at LT for controls was 34 months (p<0.01). See table for cGFR.

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cGFR (ml/min/1.73m²) HB (n=10) BA (n=10) P value
(mean ±SD)

Before OLT 102±36 145±40 0.03
5 months post-OLT 64±16 84±23 0.02
6 months 64±18 88±29 0.02
12 months 59±18 83±23 0.01
24 months 60±8 82±23 0.05
36 months 55±5 92±25 0.04

Conclusions: Children underwent LT for HB had renal impairment pre-LT. The percentage of reduction in renal dysfunction post-LT was similar to controls, but there was no improvement with reduction in immunosuppression compared with controls. Different immunosuppression regime for children undergoing LT for HB may be necessary.

G73  
POPULATION-BASED SURVEY OF THE MORTALITY AND MORBIDITY OF INFANTS WITH RHEUSIS ISOIMMUNIZATION

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Background: Introduction of anti-D prophylaxis to prevent sensitization of women lacking rhesus antigens resulted in a marked reduction in Rh haemolytic disease (RhD) and associated mortality and morbidity. It is controversial, however, whether additionally giving antenatal prophylaxis at 28 weeks of gestation would be cost-effective—that debate requires accurate information on the present occurrence of infants with RhD.

Objective: To provide population-based data on the mortality and morbidity of infants with RhD.

Methods: A paediatrician was identified in each of 29 hospitals in South Thames (West and East) in which 81,119 deliveries occurred from February 1999 to January 2000 inclusive. Additional information was obtained from obstetricians/midwives. Every month each hospital sent back a postcard indicating whether or not an infant with RhD had been admitted to their NICU/SCBU. Antenatal and postnatal information was then requested for all those with positive responses. Within the year, late responders were chased and at the end of the year each hospital was given a summary of their results to confirm their accuracy.

Results: During the one-year study period 26 infants with RhD required admission to NICU/SCBU. Their median duration of phototherapy was 5 days (range 1–12 days). Seven infants required at least one exchange transfusion (2 required 2 exchanges). No RhD infant died.

Conclusion: The current mortality and morbidity from RhD is low.

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THE EFFECT OF DIFFERENT UKALL XI CHEMOTHERAPY RANDOMISATIONS, IN TREATMENT FOR CHILDHOOD ACUTE LYMPHOBlastic LEUKAEMIA, ON GROWTH AND OBESITY

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Method: A retrospective cohort study of 100 patients treated on UKALL XI MRC trial for acute lymphoblastic leukaemia (ALL) was undertaken to determine the effects of chemotherapy on height and body mass index (BMI), during treatment and for 2 years post-treatment. Knemometry, to measure short-term growth, was carried out on a sub-group.

Results: Height standard deviation score (SDS) fell by 0.3 (p = 0.000) in the first 6 months, which persisted throughout treatment. Reductions in lower leg length velocity of the sub-group correlated with neutropenia (p = 0.0001), steroid courses (p = 0.000), severe infection (p = 0.02) and intensification blocks (p = 0.05). Mean height SDS returned to pre-treatment levels within the first year after treatment. Patients who received high dose methotrexate (HDMTX) had significantly greater loss in height SDS (-0.38 vs -0.14 without HDMTX) by completion of treatment (p = 0.05).

BMI increased by a mean of 0.5 SDS (p = 0.000) in the first 6 months of therapy, which did not fall significantly during or after treatment. Percentage of overweight (≥85th percentile BMI) and obese (≥95th percentile BMI) children increased from 21% and 9% at diagnosis to 28.6% and 16.7% respectively, at the end of the study. Percentage of obese children who received ≥3rd intensification increased, but not significantly, from 10% to 18.8% during the study period in contrast to a fall in the percentage of obese children who did not receive the 3rd block.

Conclusion: Treatment for ALL, without radiotherapy, has significant effects on both growth and body composition which is more marked in those receiving more intensive chemotherapy.

G75  
IMPORTANCE OF ETHNIC-SPECIFIC REFERENCE RANGES IN ASSESSING THE IMPACT OF SICKLE CELL DISEASE IN CHILDREN

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Background: Children with Sickle Cell Disease (SCD) in Jamaica and the USA have been reported to be lighter and have lower standing height than healthy children. Comparison, however, has often been made to ethnically-mixed, but largely Caucasian, controls and not undertaken in the UK.

Aims: To compare results of SCD children to those of healthy African/Caribbean (AC) children and both groups’ results to reference ranges established from Caucasian children (1) and thus determine if any differences detected were explained by ethnic origin or disease status.

Patients: 63 SCD and 50 healthy AC children (AC controls); both groups had similar ages with a median of 7.3 years (range 3–12 years).

Methods: Children with SCD were recruited from two specialist clinics. Siblings and school peers were recruited as AC controls. Standing and sitting height were measured using a Holtain stadiometer, and weight by Avery scales. Body Mass Index (BMI) was calculated as weight (kg) divided by height (m)².

Results: SCD children did not differ significantly with regard to their height, weight or BMI to similarly aged Caucasian children. The SCD children, however, had lower BMI than the AC controls (p = 0.001). The AC controls were of greater weight (p = 0.003) and had higher BMI (p = 0.001) than similarly aged Caucasian children.

Conclusions: To assess the effect of disease status it is essential to use ethnic specific reference ranges.


G76  

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Fanconi anemia is a life threatening genetic disease that results in bone marrow failure at an early age. In older patients leukemia and cancers of the head and neck are common complications. To date, bone marrow transplantation is the only therapy that can reverse the bone marrow failure and prevent the development of leukemia. Unfortunately, extreme sensitivity to radiation and chemotherapy and an exceptionally high risk of rejection and infection have been major obstacles to the successful use of bone marrow transplantation. Over the past five years, investigators at the University of Minnesota have improved the success rate of unrelated donor bone marrow transplantation in patients with Fanconi anemia. Adjustments to the preparative therapy and manipulation of stem cells have moved cure rates from 20% in 1995 to 50% in 2000. In a series of phase 1–11 trials, we have shown that the addition of fludarabine to the regimen of cyclophosphamide and total body irradiation virtually eliminates the risk of graft rejection that was previously observed in up to 35% of patients. The use of umbilical cord blood or T cell depleted marrow has virtually eliminated the risk of severe graft-versus-host disease. Although these achievements have resulted in improved cure rates, infection and cancers of the head and neck continue to be important areas of investigation. New investigations include better screening for hidden infections, use of antibiotics and anti-fungal agents prophylactically, and methods of early cancer detection. We are also exploring the potential of bone marrow transplantation without prior radiation therapy, gene therapy (where the correction of a single stem cell could be sufficient for reversing the bone marrow failure) and preimplantation genetic diagnosis (PGD) in an attempt to further increase the chance of cure and improve the quality of life for patients with Fanconi anemia.

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INCIDENCE OF OBESITY IN CHILDREN FOLLOWING TREATMENT FOR ACUTE LYMPHOBlastic LEUKAEMIA (ALL) WITHOUT CRANIAL IRRADIATION (XRT)

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Obesity is well recognised in adults and children following treatment for ALL which included multi-agent chemotherapy and XRT.
Furthermore, direct assessment of body composition in these patients demonstrated increased fat mass and raised serum leptin which was dependent on their growth hormone status. Since 1992 the majority of children with ALL do not receive XRT and are likely to have a normal growth hormone status. We therefore assessed body mass index (BMI), in 96 children (54 male, mean age at diagnosis 5.6 years, range 1.2–16 years) treated for ALL without XRT with UKALL XI protocol, at diagnosis and then yearly for a total of 4 years. We also assessed the effect of gender and chemotherapy on any observed changes. BMI was converted to standard deviation scores (SDS) using the reference curves for the United Kingdom. The mean BMI SDS at diagnosis and at yearly intervals for 4 years was 0.36, 0.54, 0.71, 0.75 and 0.78 respectively. Although there was an increase in BMI SDS with time, this was not significant (p=0.4). There was no difference in BMI SDS between males and females at the end of treatment and 2 years later (p=0.3, and p=0.94 respectively) and between treatment groups—group 1 intrathecal methotrexate only, group 2 intrathecal methotrexate and third intensification, group 3 high dose methotrexate only and group 4 high dose methotrexate and third intensification—(p=0.99 at cessation of treatment and p=0.27 two years later). The percentage of children who were clinically obese (BMI, SDS >2) at diagnosis and then yearly for 4 years were 11%, 9%, 14%, 15% and 13% respectively. In conclusion, the BMI of children treated for ALL without XRT does not significantly increase with time within the period of 4 years from diagnosis. There is no effect of gender or treatment on their BMI SDS.

Aims: To survey clinical practice in the United Kingdom Children’s Cancer Study Group (UKCCSG) centres relating to the immunisation of patients during and following completion of chemotherapy.

Methods: A postal questionnaire was sent to the 22 UKCCSG centres asking them for their policy regarding active and passive immunisation of patients during and following completion of chemotherapy. Specific questions were asked relating to vaccines recommended as routine in the National immunisation schedule and also those that are not routinely recommended at present such as pneumococcal and influenza vaccines. Questions were also asked relating to prophylaxis following exposure to varicella and measles.

Results: Fifteen of the 22 centres responded. Although all centres withheld active immunisation during chemotherapy, there was otherwise wide variation in clinical practice. The time to reinstate any immunisation varied from 6 months to over 12 months following completion of chemotherapy. One centre routinely repeated the entire course while 2 centres repeated them on an “ad hoc” basis. Two centres gave booster vaccines. Ten centres did not repeat any vaccines. There was also no consensus on the passive immunisation of these patients following exposure to measles and varicella.

Conclusion: The widely varying practices recorded in this survey indicate a need for formal, evidence-based recommendations for the active and passive immunisation of these patients during and following completion of treatment.

Aims: As Late-HDN is a preventable condition and is not uncommon in this region, this study was conducted to evaluate the risk factors, clinical profile and outcome.

Methods: Study was conducted in a tertiary care teaching hospital over a period of 2.5 years. Vitamin K deficiency bleeding was diagnosed on the basis of prolongation of prothrombin time index and activated partial thromboplastin time (INR>1.2) in a bleeding infant beyond 7 days age, having normal peripheral blood film and platelet counts. The infants whose PTI & APTT returned to normal along with cessation of bleeding after injection vitamin K were included in the study.

Results: There were 28 cases constituting 2.2% of all infant admissions. 68% were in the age group of 4–8 weeks. All were term babies on exclusive breast-feeding, had not received vitamin K at birth and were healthy prior to the episode. 50% of them were hospital born. Pallor and bleeding were seen in 64% and 57% patients respectively. 71% patients had clinical evidence of intracranial hemorrhage, which was confirmed on CT scan. Of these, 65% had hemorrhage at more than one site. Intracerebral hemorrhage was the commonest followed by subarachnoid (SAH) and subdural hemorrhage (SDH). Mortality rate was 7%, all related to ICH.

Conclusions: Even babies delivered by doctors are not given vitamin K routinely. ICH (71%) is common among babies with Late-HDN and mortality is significant. The need for routine vitamin K administration at birth requires further evaluation.