neuroblastoma may provide new opportunities for therapy of aggressive neuroblastoma.

Recent evidence has revealed a substantial role of microRNAs (miRNAs) in multidrug resistance in various cancer types. MicroRNAs are small (18–24 nucleotides) non-coding RNA molecules that regulate the expression of genes at the post-transcriptional level by either direct cleavage of target mRNAs or repression of translation. Several studies indicate that deviant expression of certain miRNAs correlate with poor clinical outcome in neuroblastoma. However, the role of miRNAs in neuroblastoma cell resistance to chemotherapeutic drugs is poorly understood.

Methods To explore the role of miRNAs in the resistance of neuroblastoma cells to anticancer drugs, we generated miRNA cDNA libraries from six isogenic human neuroblastoma cell line pairs established from the same patients at the time of initial diagnosis and relapse following therapy. To analyse expression patterns of miRNAs, a deep sequencing analysis (SOLiD sequencing) was performed using the miRNA cDNA libraries.

Results Deep sequencing analysis (SOLiD sequencing) revealed differential expression patterns of miRNAs before and after treatment. Systematic analysis of these miRNA expression patterns identified potential alterations in pathways associated with drug resistance suggesting that dysregulation of miRNAs might influence sensitivity to therapy.

Conclusion We anticipate that our findings will provide new insights into the molecular mechanisms of drug resistance in neuroblastoma.

O-090 FOXO3 IS ACTIVATED IN HIGH-RISK NEUROBLASTOMA AND CONTRIBUTES TO CHEMOTHERAPY-RESISTANCE AND ANGIOGENESIS

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10.1136/archdischild-2014-307384.158

Background FOXO transcription factors control programmed cell death, stress resistance and longevity in normal and malignant cells. We investigated the expression, subcellular localization and phosphorylation of FOXO3 in tumour sections of *post* chemotherapy neuroblastoma (NB) patients and analysed the effects of FOXO3 in cultured NB cells.

Methods Paraffin-embedded sections from patients were analysed for FOXO3 expression, localization and phosphorylation. Effects of chemotherapeutics on FOXO3 subcellular shuttling were assessed by live cell fluorescence imaging in ECFP-FOXO3 transgenic cells. To study how FOXO3 modulates survival we generated cell lines expressing a conditional PKB-independent FOXO3 allele (FOXO3(A3)ERtm) that can be activated by 4OH-tamoxifen and studied the effects of FOXO3-activation *in vitro* by clonagenic survival and propidium iodide FACS-analyses and *in vivo* by xenograft transplantation into nude mice.

Results We found that FOXO3 was localised in the nucleus in tumour sections from high-risk NB patients. FOXO3 nuclear localization and phosphorylation significantly correlated with reduced patient survival. The chemotherapeutics etoposide and doxorubicin led to rapid nuclear accumulation and increased phosphorylation of FOXO3. After low activation of FOXO3 increased clonagenic survival was observed in NB8/FOXO3 cells in combination with chemotherapeutic drugs whereas NB15/FOXO3 cells underwent spontaneous apoptosis. When transplanting NB15/FOXO cells into nude mice, basal FOXO3 activity induced angiogenesis of NB tumours *in vivo*, whereas full activation eradicated the tumour.

Conclusions The combined data suggest that FOXO3 is activated in high risk NB tumours and depending on the level of its activation, contributes to chemotherapy resistance and tumour angiogenesis or acts as a tumour suppressor.

O-091 WITHDRAWN

O-092 WITHDRAWN

O-092a LEFT VENTRICULAR FUNCTION IN CHILDREN WITH ACUTE LEUKAEMIA RECEIVING HEMATOPOIETIC STEM CELL TRANSPLANTATION

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10.1136/archdischild-2014-307384.159

Hematopoietic stem cell transplantation (HSCT) is a curable therapy for paediatric cancer. Cardiovascular complications are the leading cause of late morbidity and mortality in long-term childhood cancer survivors. However, cardiac function in children after HSCT is not well known. We assessed left-ventricular (LV) function in children after HSCT for acute leukaemia by using tissue Doppler imaging (TDI) and speckle tracking echocardiography (STE). Forty consecutive patients (median 11.9 years) who had HSCT for acute leukaemia between 2011 and 2014 had undergone an echocardiographic assessment before and after (median 9.2 month) HSCT. LV function parameters, including conventional, TDI, and STE data, were collected from patients' echocardiographic data, and were compared with those of controls (n = 39, median age 9 years). All patients had anthracycline as a pre-HSCT chemotherapy. At post-HSCT, patients had decreased LV ejection fraction ($p = 0.06$), rate-corrected velocity of fibre shortening ($p = 0.04$), and mitral septal annular E' velocity ($p = 0.03$) compared with controls. STE parameters also decreased in patients; mid LV global circumferential strain ($p < 0.01$), and mid LV global circumferential systolic strain rate (SR, $p = 0.01$). There was no significant change in LV function parameters after HSCT compared with pre-HSCT study. Patients with anthracycline cumulative dose > 400 mg/m^2 showed significantly lower mid LV global circumferential strain ($p < 0.05$) and mid LV global circumferential diastolic SR ($p < 0.05$). Patients who received HSCT for acute leukaemia had subclinical cardiac dysfunction, which may be associated with pre-HSCT anthracycline exposure with little effect of conditioning regimens. Serial monitoring of cardiac function is mandatory in all children following HSCT.

O-093 ENERGY EXPENDITURE IN WHITE ADIPOSE TISSUE IS ACTIVATED IN RESPONSE TO BRAIN TUMOUR GROWTH

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10.1136/archdischild-2014-307384.160

Background and aims The PI3K pathway is frequently activated during tumourigenesis through deletion of the tumour suppressor PTEN. In contrast, increased PTEN expression in adipose tissue results in an increase in UCP1 expression and provides metabolic protection from tumourigenesis. This intrinsic protection normally arises from interscapular brown adipose tissue (iBAT) but may also arise from 'beiging' of inguinal white adipose tissue (iWAT). The aim of this study was to see if an association existed between UCP1 expression in adipose tissue and paediatric brain tumour growth through elevated PTEN levels.
Methods Two types of medulloblastoma (WNT and group 4) and ependymoma tumour cells were orthotopically xenografted into mice. iBAT and iWAT samples were extracted from tumour and non-tumour bearing mice to examine UCP1 and PTEN expression through QRT-PCR and Western blotting. Haematoxylin and eosin staining and UCP1 antibody immunohistochemistry (IHC) was also used to determine BAT activity in adipose tissue. Thermogenic activity of the adipose tissue was indirectly measured by thermal imaging of mice.
Results iWAT from ependymoma tumour-bearing mice had evidence of beiging and increased UCP1 expression through histology and IHC, while UCP1 expression in iBAT remained high in all mice. An increase in UCP1 gene expression and thermogenesis was observed with spinal metastasis. PTEN expression did not relate to UCP1 expression.
Conclusion Our data indicated mice implanted with aggressive tumours had increased UCP1 expression in iWAT. In conclusion, this pilot study suggests rapidly growing and metastatic brain tumours stimulate metabolic protection via an increase UCP1 expression in iWAT.

Paediatric Emergency Medicine II

O-094 DIAGNOSTIC USEFULNESS OF BIOMARKERS IN THE MANAGEMENT OF CHILDREN WITH FEVER AT RISK OF SERIOUS BACTERIAL INFECTIONS AT THE EMERGENCY DEPARTMENT: PROSPECTIVE DIAGNOSTIC STUDY

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10.1136/archdischild-2014-307384.161

Background and aims To evaluate the diagnostic usefulness of biomarkers in the management of children with fever at risk of serious bacterial infections (SBI) at the emergency department (ED).
Methods In this prospective observational study previously healthy children with fever, aged 1 month to 16 years, attending the EDs of a university hospital and a teaching hospital (Rotterdam, the Netherlands) between 2009 and 2012 were included. Standardised information on clinical signs and symptoms, C-reactive protein (CRP), procalcitonin (PCT), neutrophil CD64 expression and urinalysis were collected prospectively. Logistic multivariable regression analysis was used to assess diagnostic performance.
Results 1,084 children were included, median age was 1.6 years (interquartile range: 0.8–3.5), 170 children (16%) had SBI. CRP (receiver operating characteristic curve (ROC-area) 0.77 (95% confidence interval (CI) 0.69–0.85)) and PCT (ROC-area 0.75 (95% CI 0.67–0.83)) were both strong predictors of SBI. CD64 lacked diagnostic strength (ROC-area 0.62 (95% CI 0.54–0.70)). A score containing PCT and CRP together with urinalysis, the Lab-score, performed well (ROC-area 0.79 (95% CI 0.72–0.87)), but thresholds performed similar to often used cut-offs of single biomarkers. Combined with clinical signs and symptoms both CRP and PCT were useful; additional PCT to CRP did not improve diagnostic performance substantially.
Conclusions CRP and PCT were equally useful in the diagnostic evaluation of the febrile child, whereas CD64 wasn't useful. Performing both CRP and PCT is often not indicated in a general population of febrile children. Our findings contrast previous studies suggesting PCT outperforming CRP and superior value of CD64 in specific settings.

O-095 INFANTS WITH FRACTURES IN THE PAEDIATRIC EMERGENCY DEPARTMENT: ARE WE CONSIDERING CHILD PHYSICAL ABUSE?

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10.1136/archdischild-2014-307384.162

Background Recognition of child physical abuse (PA) is important to avoid further morbidity and mortality. There is limited knowledge regarding how frequently paediatric emergency department (PED) clinicians consider child abuse in infants with fractures.
Objective Estimate the percentage of infants with fractures for whom PA was considered, and to examine characteristics that are associated with consideration of PA.
Methods We reviewed the electronic medical record (EMR) of all patients ≤ 1 year with fractures in a PED between 2008–2012. We used a multivariable logistic regression model to examine associations of patient and physician characteristics with our

Abstract O-095 Table 1

Patient characteristics	
Age, in weeks[a]	27 [12.1, 38.7]
Gender, Male[b]	282 (53)
Race[b]	
Caucasian	372 (75)
African American	92 (19)
Hispanic	21 (4)
Physician characteristics	
Male[b]	282 (53)
PEM fellowship trained[b,c]	308 (58)[c]

a. Median [IQR]
b. n (%)
c. All others EM-trained except 1 paediatrics-trained